New concepts in optimal management of anticoagulant therapy for extended treatment of venous thromboembolism

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Summary
Recent trials on secondary prophylaxis after venous thromboembolism (VTE) have provided a wealth of data on the risk factors for recurrence and, to some extent, also for bleeding. Some of the results are consistent across the studies, but there are also conflicting data. Certain risk factors, such as pulmonary embolism versus deep vein thrombosis or presence of cardiolipin antibodies, have a more pronounced influence on the risk early in the course of disease. Others, such as hereditary thrombophilic defects, seem to gain importance over many years of follow-up. Therefore, it can be difficult to make decisions on an individual patient basis. In this article, data from important and illustrative trials have been extracted and compared and controversies highlighted. The conclusions drawn should help clinicians make balanced decisions on the optimal duration of anticoagulation after an episode of VTE.

Keywords
Venous thromboembolism, risk factors, recurrence, bleeding

Introduction
Venous thromboembolism (VTE) is an acute disease that can have variable outcomes. At one end of the spectrum is the patient who develops distal deep vein thrombosis (DVT) after surgery or a fracture. Such a patient is unlikely to have recurrent events. Pulmonary embolism (PE) is unusual and the risk of venous insufficiency is almost nil. At the other end of the spectrum are patients with proximal DVT without any obvious precipitating risk factor. Such patients are not only prone to recurrence after discontinuation of anticoagulant treatment, but also are likely to develop the post-thrombotic syndrome (PTS) years later, with chronic swelling of the leg, telangiectasia around the medial malleolus, hyperpigmentation, lipodermatosclerosis and, finally, a venous ulcer. Another worst-case scenario is a young patient with proximal DVT and PE after a questionable triggering factor, such as travel by car for four hours, who presents years later with increasing shortness of breath. Echocardiographic investigation reveals increased pulmonary artery pressure, and perfusion lung scan shows new defects. Thrombophilia screening shows high titer cardiolipin antibodies of the IgG subtype in combination with the factor V Leiden mutation in heterozygous form.

General risk estimates
A large number of cohort studies and randomized controlled trials (RCTs) on the treatment of VTE have provided us with ample data on risk factors for recurrence of VTE. It is becoming increasingly important to utilize this information to select the optimal duration of anticoagulation for the individual patient. RCTs typically generate relative risk estimates that may be helpful to assess the strengths of relationships with risk factors, but are less useful for clinical guidance. Cohort studies and some RCTs, whenever it is possible to extrapolate study terms to the general population, allow expression of assessment of risk in absolute terms. However, it is not sufficient to inform patients with a first VTE that the risk of recurrence over the next eight years is 30%, as demonstrated in cohort studies (1, 2) and recently confirmed in an RCT with a 10-year follow-up period (3). Instead, with increased knowledge of the variation of risks according to specific risk factors, it should be possible to provide a more individualized assessment. Recurrent DVT in the same leg is the strongest risk factor for development of PTS, with a hazard ratio of 6.4 (1). Recurrent events in other anatomical sites also appear to aggravate the development of PTS in the leg of the initial DVT (3). This finding may reflect an underlying hypercoagulable state.
with asymptomatic ipsilateral recurrent DVT. Recurrent PE is an even stronger risk factor for the development of chronic thromboembolic pulmonary hypertension (CTPH), with an odds ratio (OR) of 19 (4).

Are DVT and PE the same disease?

There is firm evidence that these entities often occur concurrently. Thus, asymptomatic PE is verified by ventilation–perfusion lung scan in 30–50% of patients with venographically documented DVT (5, 6). Conversely, up to 70% of patients with PE also have DVT (7). The treatment of DVT and PE is essentially the same. It is interesting to note that the risk of recurrence in patients with proximal DVT is initially lower than that in patients with PE, with a cumulative incidence 12.4% versus 18% after 18 months in THRIVE III (8), and 22.1% versus 29.9% in DURAC I after four years (unpublished data). However, in the long-term follow-up this difference disappeared [cumulative incidence 32.5 and 35.5 at 10 years in the DURAC I trial and even earlier than that in a meta-analysis on individual data from 2,474 patients in five RCTs (9)]. The only statistically significant increase in the incidence of recurrence was in patients with PE during the first six months after stopping anticoagulant therapy. Between month 6 and 48, the hazard ratio for recurrence after PE versus DVT was 1.3 (95% confidence interval [CI] 0.9–1.9). It is important to note that patients whose index event was a PE were more likely to have recurrent PE rather than DVT (81% vs. 19%), whereas those whose index event was a DVT recurred more often with DVT than with PE (79% vs. 21%), as reported by Douketis et al. (10) and more recently supported by Murin et al. (11). Moreover, Douketis et al. reported in a meta-analysis that the incidences of fatal PE during anticoagulant therapy in patients with initial DVT or initial PE were 0.4% (95% CI 0.2–0.4) and 1.5% (95% CI 0.9–2.2), respectively (10). Therefore, despite similar risks of recurrence, the consequences appear to differ. Consequently, clinicians may treat patients with PE with a longer duration of anticoagulant therapy than those with DVT.

In this paper, the impact of various factors on the risk of recurrent VTE will be discussed. We have chosen to present data from a number of illustrative studies that show the influence of different risk factors on the risk of recurrence and also indicate the controversies in this field. It is the hope of the authors that the data extracted can be of some support in the risk estimates for individual cases.

Nature of the triggering risk factor

The risk of recurrence is higher, and increases more over time, when triggering risk factors are absent or persistent compared with risk factors that are well documented and treated. Transient risk factors include surgery, trauma, intercurrent disease with immobilization, travel and treatment or substitution with estrogen. The pattern is consistent across many different trials (Fig. 1). The absolute difference in risk between these two subsets is approximately 10% the first two years and from three to 10 years it stabilized at about 13% in the DURAC I trial (unpublished data). Building on this observation, two RCTs only included patients with idiopathic VTE (13, 14). Baglin et al. suggested that risk factors should be classified into three groups; temporary, idiopathic (not identified) and non-removable (15). In these groups, the investigators reported an incidence of recurrence of 4.3%, 11.7% and 23.7%, respectively, after 2.4 years of follow-up. Based on 10-year follow-up in the DURAC I trial, patients with venous insufficiency prior to VTE diagnosis had the highest risk of recurrence (55% at 10 years, 95% CI 37–73) (3). This may reflect the fact that these patients have had previous, asymptomatic episodes of DVT. With the nature of the triggering risk factor being such a consistent determinant of the risk of recurrence, this must always be taken into account in the decision on duration of anticoagulation.

Number of episodes of VTE

The guidelines of the American College of Chest Physicians (ACCP) from 2004 recommend secondary prophylaxis of in-

Location of the thromboembolism

Data extracted from the 10-year follow-up of the DURAC I trial show consistent differences in the risk of recurrence between distal and proximal DVT with an absolute difference of approximately 9% from three years and onwards. The incidence of recurrence is initially even higher in patients with PE. In the DOTAVK trial, patients with distal DVT were randomized to six or 12 weeks of anticoagulant treatment, whereas patients with proximal DVT or PE received three or six months of therapy. The overall incidence of recurrence after one year was approximately 2.6% and 17%, respectively (12). The explanation for the larger difference in this study compared with the DURAC I trial is unclear, since both studies included patients with a variety of risk factors. Anyhow, it is obvious that many patients with distal DVT can have the anticoagulant therapy discontinued after 6–12 weeks, particularly if there has been a removable risk factor, as discussed below.
definite duration for patients with two or more VTE events (16). This recommendation is only based on data from a single RCT (17) that included 227 patients with a second episode of VTE. Patients were assigned to six months’ or indefinite treatment with a vitamin K antagonist (VKA), and data were analyzed after four years of follow-up. A comparison between patients with one and two episodes of VTE, treated according to the same protocol, i.e. the six-month treatment arms in DURAC 1 (18) and DURAC 2 (17), respectively, shows a progressively higher recurrence rate in the latter group, albeit without reaching statistical significance. The placebo group in the THRIVE III study (8) and both the placebo group and the low-intensity warfarin group in the PREVENT trial (19) showed a similar difference. However, in these studies patients with multiple previous events were lumped together, so that the risk of recurrence with exactly two episodes of VTE cannot be discerned. Further support can be derived from the Olmsted County inception cohort, where the hazard ratio for recurrent VTE after multiple previous episodes was 2.11 (95% CI 1.62–2.74) (2). It is not evident that all patients with two episodes of VTE should be treated indefinitely, since for example a patient with one distal DVT in each leg, especially after a transient risk factor, still could benefit more from a limited period of treatment. For patients with signs of chronic sequelae, i.e. post-thrombotic syndrome or pulmonary hypertension, indefinite anticoagulation should be strongly considered.

Sex and age

It is well known that there is a preponderance of women among patients who develop VTE at a young age. This is due to the increased risks associated with combined oral contraceptives or pregnancy. Overall, the incidence is similar among men and women, with a small excess in one or the other direction in different studies (20). In a large Swedish population-based autopsy cohort, PE was more common in women (OR 1.32, 95% CI 1.25–1.41) (21). Recurrent VTE, however, appears to be more common in men, a consistent finding in most studies, except in LAFIT (14), which reported a higher overall recurrence rate than the other trials. The absolute increase in risk for men is about 5% after the first year and in studies with longer follow-up there was a progressive increase in this difference to 11% (18, 22) and to more than 20% in Kyrlé’s cohort study (23). In the RIETE registry, which includes data on more than 6,000 patients followed for three months after an event, there was also an increased risk of recurrence in men with an adjusted OR of 1.43 (95% CI 1.04–1.97) (23). It is peculiar that in an Italian population the difference was insignificant with an odds ratio of 1.3 (24) compared to a highly significant difference in an Austrian population with odds ratio of 4.6, both after five years of follow-up (23). This difference is not explained by the location of the VTE, and the mechanism for this effect is unclear and requires further studies.

The mean age at the time of VTE was 4.5 years higher among females than males in the Swedish autopsy study (21), with no difference between cases with and without PE (Fig. 2). The increase in PE risk was 22% (95% CI 19–25) per 10-year increment in age. Age had no effect on the risk of recurrence in the PREVENT trial (19). However, Heit et al. described a 17% increase in risk of recurrence per 10-year increase in age (2). In the meta-analysis of five RCTs based on individual data, Böttigie et al. described an increase in the risk of recurrence up to age 70, with no significant increase thereafter (9). Thus, in young patients a shorter treatment may be justified, but old age should not indiscriminately lead to a decision on indefinite duration of anticoagulation.

Obesity

Recently, obesity has been identified as a risk factor for VTE. Obesity and overweight have mainly been studied in terms of body mass index (BMI), and risks were commonly expressed in relation to a BMI >30 kg/m². In studies of risk of PE, an age-adjusted relative risk in obesity of 3.2 (95% CI 1.7–6.0) was found in the Nurses’ Health Study cohort (26). Similar associations have been reported in autopsy studies (27–29).

Subsequent studies of VTE in various populations have led to disparate results. An excess risk in obese patients has been reported in the SIRIUS case-control study of medical outpatients (OR 2.4, 95% CI 1.5–3.9) (30), in a Dutch case-control study (OR 2.3, 95% CI 1.5–3.4) (31) and in the population-based Italian VITA study (OR 2.9, 95% CI 1.4–6.2) (32). In other studies, such as the Swedish ‘Men born in 1913’ cohort (33), the Copenhagen City Heart Study (34) and a medical inpatient case-control study (35), obesity did not increase the risk of VTE. In contrast, Heit et al. reported an increase in the risk of recurrence with increasing BMI (2), whereas the rate of recurrence in the placebo group in the THRIVE III trial was 12.2% and 11.1% for patients with a body weight <80 kg and ≥80 kg, respectively, after 1.5 years (8).

The mechanism by which obesity may promote thrombosis is incompletely understood, but is likely to be multifactorial. Apart
from possible compression effects, abdominal obesity can lead to liver metabolic changes that may increase the levels of procoagulant factors and depress fibrinolysis (36). Relative immobility as a consequence of more sedentary behavior may also play a part. Moderate overweight might also lead to an increased risk, as indicated by studies evaluating the entire BMI range (26, 32). Unfortunately, BMI provides a poor estimation of body fat and is a blunt instrument for assessment of regional fat distribution. Waist–hip ratio has commonly been used as proxy for abdominal obesity, and in one study the waist circumference – but not BMI – was shown to be a risk factor for VTE in middle-aged men (33). Among patients with proximal DVT in a Swedish autopsy cohort, subcutaneous fat thickness, as well as BMI, were independent risk factors for PE (21).

**Thrombophilia**

The value of investigation for thrombophilic defects is controversial. Several studies have indicated that the most prevalent defects have a clear association with the first episode of VTE, but not with recurrence. These defects include the factor V Leiden and prothrombin G20210A mutations and hyperhomocysteinemia. The results from three prospective cohort studies suggest that the effect of thrombophilic defects on the risk of recurrence is relatively small (absolute increase of risk 1–5%) and does not increase over time (15, 37, 38). Although the hazard ratio for recurrence in patients with at least one thrombophilic defect versus those without was 1.4 (95% CI 0.9–2.2), it was 2.7 (95% CI 1.8–4.2) for men versus women and 1.9 (95% CI 1.2–2.9) for idiopathic versus secondary VTE (38). These findings suggest that it is more important to determine whether the VTE was provoked or unprovoked than it is to perform detailed investigations for thrombophilia.

**Factor V Leiden**

Most studies show a higher risk of recurrence in patients with the factor V Leiden mutation, an effect that is more pronounced in those homozygous for the mutation compared with those who are heterozygous (39, 40). However, several studies failed to demonstrate any effect of this mutation (19, 38, 41, 42) in the heterozygous form. It is interesting to note that in the DURAC trial, the effect of the heterozygous form became more apparent over time. Thus, at four years, the risk of recurrence was not significantly increased (40), but after 10 years, the risk was higher (p = 0.028 for heterozygous form and p = 0.030 for homozygous form in a multivariate analysis) (3).

**Prothrombin gene mutation**

In most studies, this mutation in the heterozygous form has little or no effect on the risk of recurrence (3, 43, 44). The exception is the cohort study of Simioni et al. (45), where patients with the mutation had a cumulative incidence of recurrence of 61.3% over 10 years compared to 23.1% in the group without identified mutations. The number of patients with the mutation was, however, quite small. It is remarkable that this mutation is both more prevalent and has a greater effect in the Italian population than in other, more northern European populations.

**Combined factor V Leiden and prothrombin polymorphisms**

In two studies, patients heterozygous for both the factor V Leiden and prothrombin mutations had a higher risk of recurrence than those without any defect or with either one alone (42, 44). It should be noted, however, that the 100% rate of recurrence in the study of Miles et al. constituted only three patients (44).

**Elevated factor VIII level**

Although the normal range of factor VIII (FVIII) is 0.5–1.5 IU/ml, only levels above the 90th percentile in the study population have been strongly associated with an increased risk of recurrence (45). The studies of Kyrle et al. and Legnani et al. are consistent and show more than a doubling of the risk of recurrence in patients with elevated FVIII levels (45, 46) (Fig. 3). In the Italian study, a large difference between the groups was not only evident in patients with idiopathic VTE (relative risk 5.43 [95% CI 1.76–16.8]), but there was also a weak effect in those with a transient risk factor (relative risk 2.62 [95% CI 0.34–19.9]) (46). In the Leiden Thrombophilia Study (LETS), a weaker effect of high FVIII levels was observed, with an adjusted hazard ratio of 1.3 (95% CI 0.8–2.1) (38). Elevated FVIII levels also have been reported to be a risk factor for poor outcome after VTE in children, including recurrence (47).

**Other thrombophilic defects**

In the LAFIT study, patients randomized to the placebo group had a relative risk of 3.5 for recurrence (67% vs. 19%) if they had cardiolipin antibodies and/or a lupus anticoagulant after a mean follow-up of 10 months (14). In the DURAC trial, patients with VTE treated for six months with warfarin and who tested positive for cardiolipin antibodies at the time warfarin was stopped had a two-fold higher risk of recurrence (29% vs. 14%) after four years (48). Furthermore, mortality during this follow-up period was 2.5-fold higher in those with antibodies (15% vs. 6%). This difference was mainly ascribed to an increase in arterial and ve-
nous thromboembolic causes of death. At the final 10-year follow-up, initial presence of cardiolipin antibodies was no longer an independent risk factor for recurrence (3).

In meta-analyses, hyperhomocysteinemia (levels above the 95th percentile) was associated with an increased risk of VTE, with a pooled OR of 2.5–2.9 (49,50). In a cohort study, the rate of recurrence after two years was 19.2% with hyperhomocysteinemia and 6.3% in those without this finding (51). By contrast, in the LETS cohort, hyperhomocysteinemia had no effect on the risk of recurrence, with an adjusted OR of 0.9 (95% CI 0.5–1.6) (37).

Cancer

Three cohort studies demonstrated consistently that patients with VTE in combination with cancer have a tripling of the risk of recurrent VTE after one year compared with those without cancer (Fig. 4) (52–54). In the study of Prandoni et al., it was also evident that the risk increased with the severity of the malignancy, from 14.5% per year for limited cancer to 44% and 54% for moderate and very extensive disease, respectively (52). It should be noted that these high rates of recurrence occur despite anticoagulant therapy. Heit et al. reported that the hazard ratio for recurrence in patients with cancer compared with those without was 3.5 or 2.5, depending on whether or not they were receiving chemotherapy (2). Another expression of the association between VTE and cancer, and reflecting the often insidious development of malignancies, is the demonstrated increased incidence of subsequent cancer in patients with recurrent VTE (55).

Elevated D-dimer

During secondary prophylaxis, D-dimer levels are low, and only about 15% of the patients will have increased levels at the time of discontinuation of treatment (56). One and three months thereafter, this proportion increases to 40% and 46%, respectively (56). Therefore, a time point of one month after stopping treatment has been used for blood sampling in several studies. An increased level of D-dimer appears to be associated with a consistent and progressive increase in the risk of recurrence (Fig. 5). This effect is more pronounced in cases of unprovoked (idiopathic) VTE or in the presence of thrombophilic defects (37, 57, 58). Evidently, some recurrences will occur during the month between cessation of drug and blood sampling, and patients who test positive will have to be restarted on anticoagulants. However, D-dimer testing may become a useful test to determine whether or not to extend anticoagulation.

Residual thrombosis

The significance of residual thrombus in the leg veins as a determinant of the optimal duration of anticoagulation was addressed early on by Levine et al., using impedance plethysmography (59). More recently, compression ultrasound (CUS) of the leg veins has been evaluated as a predictor of recurrence. The number of compression points, as well as the criteria for residual thrombus (e.g. 20% or 40% of the vein area, or 2–3 mm), has varied between studies, which may explain the disparate results. In addition, CUS has usually been performed at the end of anticoagulant treatment and then repeated at different time intervals, and the rate of recurrence was reported as that among the patients still with residual thrombus, but this proportion decreased with time. Cosmi et al. found a rate of recurrence two years after cessation of anticoagulation of 15.5% in those with normal CUS and 18.2% in those with residual abnormalities (adjusted hazard ratio 1.2, 95% CI 0.72–2.07) (57). The information from the CUS did not improve the predictive value of D-dimer testing. Conversely, Prandoni et al. found a hazard ratio of 2.4 (95% CI 1.3–4.4) and Young et al. of 2.1 (p = 0.02) for recurrence in those with residual abnormalities (60, 61). Until a simplified CUS protocol has been established at one time point, and better consensus on the definition of residual thrombus has been reached, this tool is not very useful for predicting the risk of recurrence.
Risk of bleeding

Whereas the risk of recurrent VTE has been well described in many studies, the risk of bleeding has not been as clearly defined. This is partly due to the fact that many studies have a long follow-up after cessation of anticoagulation. Indeed, some of the studies only start the protocol at this point. Secondly, the risk of bleeding seems to decrease with time, and several trials included patients who had received at least three months of anticoagulant therapy. Thirdly, the definition of major bleeding has varied among studies, and fatal bleeding has occasionally been reported among deaths but not as bleeding. A recently published recommendation from the International Society on Thrombosis and Haemostasis on the definition of major hemorrhage is aimed at correcting these issues (62).

The risk of bleeding during anticoagulant therapy is influenced by age. A slow but steady increase from 1% per year at age 20 up to 2% at the age of 70 years, reaching 3.5% at age 90, was shown in a meta-analysis of RCTs based on individual data (9). It is also increased by comorbid conditions, including hypertension, cerebrovascular disease, ischemic stroke, renal insufficiency, serious heart disease and a history of peptic ulcer disease (63). Patients with cancer also have a higher bleeding risk (Fig. 4) during anticoagulant therapy, for several reasons. The cancer causes vascular lesions, and accordingly, hemorrhages typically occur at the site of the tumor or metastases. In addition, cancer patients are thrombocytopenic and/or have a consumptive coagulopathy.

In trials where patients were randomized to different intensities of anticoagulation (19, 64) and followed for at least two years, the risk of bleeding was much lower than in trials randomizing the patients at a maximum of three months after the index event (13, 14, 17–19, 64, 65) (Fig. 6). The most plausible reason is that the patients with a high propensity to bleed had already had an event and were discontinued from anticoagulation before the study.

![Figure 6: Risk of major bleeding per year, arranged along the y-axis, according to when during the course of anticoagulant therapy the patients were observed (13, 14, 17–19, 64, 65).](image)

![Figure 7: Risk factors to balance for a decision on duration of anticoagulation in the majority of patients with VTE.](image)

Duration of anticoagulation

**Proximal DVT and permanent risk or PE**

<table>
<thead>
<tr>
<th>Bleeding, Poor compliance</th>
<th>Old age Needs ASA Female?</th>
<th>Mild thrombophilic defect / Second VTE</th>
<th>Third VTE or more, Severe thrombophilia, Severe venous insuff., Pulmonary hypertension</th>
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<td>3 m</td>
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Patient preferences
Weighing the risk of recurrence versus the risk of bleeding

Recurrent VTE may require a brief hospital stay but will often result in a decision to maintain the patient on long-term anticoagulation therapy. A major hemorrhage also results in hospitalization and may cause significant sequelae. Douketis et al. reviewed trials with VKA for patients with VTE and found a case fatality rate for recurrent VTE of 8.8% (95% CI 5.0–14.1) during treatment and 5.1% (95% CI 1.4–12.5) after cessation of treatment (10). The high rate during treatment may reflect the aggressive prothrombotic effect of disseminated cancer, which is more likely to manifest itself early after the VTE diagnosis (66). For patients with PE as the index event, the case fatality rate was as high as 26.4% (95% CI 16.7–38.1) (9). Against this, a literature review by Linkins et al. reported a case fatality rate from all bleeding of 13.4% (95% CI 9.4–17.4) (67), and Punthakee et al. observed a case fatality rate from intracranial hemorrhage of 45% (68). It is thus important to take into account the risk of bleeding, and in cases where the decision as to whether to extend anticoagulation is challenging, a prediction score for bleeding may render some support (69).

Two additional aspects of great importance are i) the fact that no study to date has shown that extended secondary prophylaxis against VTE reduces mortality, and ii) the burden of long-term anticoagulation with vitamin K antagonists, which requires frequent monitoring and dose adjustments.

Conclusion: Balancing the risks in practice

It is obviously difficult to determine whether the risk of recurrence from stopping anticoagulation or the risk of hemorrhage from continuing the treatment weighs heavier. Instead, for every patient, a careful decision has to be made, taking the different risk factors into account. Frequently, the decision will have to wait until the full picture emerges. An important component is the compliance of the patient with treatment. In those whose VKA treatment is difficult to stabilize, it may be safer to discontinue treatment because of the high risk of bleeding (70). Finally, the preferences of the patient need to be taken into account, especially if they are strongly in favor of or against the treatment.

For some patients, the decision is relatively straightforward. Those with distal DVT, especially after a transient risk factor, need only 6–12 weeks of anticoagulation. Conversely, in the presence of active cancer, long-term secondary prophylaxis is indicated. Although the risk of bleeding is increased, the risk of recurrence is even higher. The preferred anticoagulant for these patients is low-molecular-weight heparin, at least for the initial 3–6 months (16). For patients with proximal DVT or PE, especially when there is no identified or a permanent risk factor, the illustration in Figure 7 may be helpful. In Table 1 some typical scenarios and recommended duration of anticoagulation are presented.

Patients with life-threatening VTE in combination with one or several thrombophilic defects, patients with any type of VTE in combination with congenital deficiency of antithrombin, the homozygous form of factor V Leiden mutation or multiple defects, or with two or more recurrences have a strong indication for extended prophylaxis for many years. However, without evidence of reduced mortality by extended anticoagulation, and with the burden that most patients perceive long-term treatment with VKA, 6–12 months of anticoagulation should be considered optimal for the majority of cases. Investigation for thrombophilia should not be performed without selection and is questionable in patients for whom the result will not influence the choice of duration of anticoagulation.

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