Journal of Thrombosis and Haemostasis, **11** (Suppl. 1): 151–160 DOI: 10.1111/jth.12234

INVITED REVIEW

Optimal treatment duration of venous thrombosis

W. AGENO, F. DENTALI, M. P. DONADINI and A. SQUIZZATO

**Department of Clinical and Experimental Medicine, Research Center on Thromboembolic Diseases and Antithrombotic Therapies, University of Insubria, Varese, Italy*

To cite this article: Ageno W, Dentali F, Donadini MP, Squizzato A. Optimal treatment duration of venous thrombosis. *J Thromb Haemost* 2013; **11** (Suppl. 1): 151–60.

Summary. Randomized controlled trials have shown that patients with venous thromboembolism benefit from a minimum of three months of anticoagulant therapy. After this period, it was suggested that patients with an expected annual recurrence rate of < 5% could safely discontinue treatment. Using a population-based approach for stratification, these patients are those with major transient risk factors, and represent the minority. For all other patients, including those with previous episodes of venous thromboembolism, cancer, or unprovoked events, this treatment duration may not be sufficiently protective. Because extending anticoagulation for additional three to nine months does not result in further, long-term reduction of recurrences, indefinite treatment duration should be considered. However, case-fatality rate for major bleeding in patients taking warfarin for more than three months is higher than case-fatality rate of recurrent venous thromboembolism. Thus, an individual patient approach to improve and increase the identification of those who can safely discontinue treatment at three months becomes necessary. Clinical prediction rules or management strategies based on D-dimer levels or residual vein thrombosis have been proposed and need further refinement and validation. Specific bleeding scores are lacking. Meanwhile, the oral direct inhibitors have been proposed as potential alternatives to the vitamin K antagonists, and aspirin may provide some benefit in selected patients who discontinue anticoagulation. Deep vein thrombosis in unusual sites is associated with less, but potentially more severe recurrences, in particular in patients with splanchnic vein thrombosis who also face an increased risk of bleeding complications while on treatment.

Keywords: anticoagulants, recurrence, risk assessment, secondary prevention, venous thromboembolism.

Correspondence: Walter Ageno, Department of Clinical and Experimental Medicine, University of Insubria, Via Guicciardini 9, Varese 21100, Italy.
Tel.: +39 0332 278831; fax +39 0332 393640.
E-mails: agewal@yahoo.com and walter.ageno@uninsubria.it

Introduction

Treatment of venous thromboembolism (VTE) is aimed to prevent thrombus extension and embolization and to reduce the risk of recurrence. Recurrent VTE may occur within the first few days or weeks, but also after several months or years. Because this risk varies according to patient characteristics and underlying risk factors, accurate patient selection is the first step in achieving optimal treatment duration. Anticoagulant drugs have been extensively studied for the prevention of secondary VTE and represent the current standard of treatment. We will review current evidence on the rates of recurrent VTE in usual as well as in some unusual sites, on risk stratification, on the efficacy and safety of older and newer anticoagulant drugs, and on the potential role of alternative treatment strategies.

Recurrence rates in real-world patients with proximal deep vein thrombosis and pulmonary embolism

The cumulative risk of recurrence after proximal deep vein thrombosis (DVT) of the lower limbs and pulmonary embolism (PE) has been assessed in a number of prospective observational cohort studies. In one of the largest and most recent studies, 1626 consecutive patients were followed up for a median of 50 months, and a maximum of 10 years [1]. Patients with cancer, with previous episodes of VTE, or with other indications for life-long anticoagulation were excluded from this cohort. VTE was defined as secondary in the presence of at least one of the following risk factors: pregnancy or recent delivery in the previous 3 months; leg trauma, fracture, or surgical intervention in the previous 3 months; and immobilization due to a chronic medical illness. In the absence of these risk factors, the event was defined as unprovoked. In this population, 53.1% of patients had unprovoked VTE. Anticoagulant treatment was administered for 3 months or less in about one-third of patients, and for 3 to 6 months in about half of patients, reflecting the standard

of practice in many European centers. After treatment discontinuation, the cumulative incidence of recurrent events was 11% after 1 year, 29.1% after 5 years, and 39.9% after 10 years, and it was higher if the index event was unprovoked: 15% vs. 6.6% in patients with a secondary VTE at 1 year, 40.5% and 16.1% at 5 years, and 52.5% and 22.5% at 10 years, respectively. In addition to the unprovoked nature of the event (adjusted hazard ratio (HR) 2.30; 95% confidence interval (CI) 1.82–2.90), the presence of thrombophilia (2.02; 1.52–2.69), a shorter (up to 6 months) duration of anticoagulation (1.39; 1.08–1.80), and age (1.14; 1.06–1.22) were also independently associated with VTE recurrence in the whole study population, as well as in patients with unprovoked VTE alone. Finally, patients presenting with PE as the first event were more likely to develop recurrent PE than patients with DVT as the index event. These observations raise a number of critical questions for the practicing clinician.

How do I assess the risk of recurrence for my patient?

To determine the risk of recurrence in a patient with VTE, clinicians may adopt a population-based or an individualized strategy [2].

Population-based approach

Patients are usually classified in three main groups: patients with major, permanent risk factors (e.g. cancer or previous episodes of VTE); patients with major, transient risk factors; and patients with unprovoked events. The first group is generally associated with a very high risk of recurrence: after 3 months of anticoagulant therapy, the incidence of recurrent VTE in patients with cancer was 3 times higher than in non-malignant patients in the study by Hutten *et al*. [3] (incidence of recurrence 27.1% and 9.0% patient-years, respectively). However, some heterogeneity in the risk of recurrence may be expected based on the type and site of cancer, the stage of disease, and the concomitant presence of additional provoking factors (e.g. chemotherapy, central vein catheters) at the time of the index VTE event.

The annualized recurrence rates after a 24-month follow-up in patients with a first VTE provoked by a transient risk factor were recently calculated [4]. The overall rate of recurrence was 3.3% per patient-year, but this figure ranged from 0.7% per patient-year for patients with a surgical risk factor to 4.2% per patient-year for patients with non-surgical risk factors, including pregnancy and puerperium, use of hormone therapy, trauma or fracture, and medical illness, among others. In the same study, the rate of recurrence after unprovoked events was 7.4% per patient-year. Thus, the risk of recurrence appears to be very low if VTE occurs after surgery, but not negligible in the presence of other transient provoking factors, suggesting the need for considering these two groups separately.

This population-based strategy is simple and has apparently good reproducibility, but it is imprecise and it may lead to incorrect treatment decisions. For example, the selection of provoking factors varied across studies. The definition of the type of surgery and of the time between the procedure and the diagnosis of VTE was not provided in most selected studies, and it was rather heterogeneous when provided [4]. The same occurred for the definition of non-surgical risk factors, suggesting that the enrolled populations were potentially different. As a consequence, heterogeneity across study populations also applies to patients with unprovoked VTE, resulting in proportions of unprovoked events ranging between 25% and 40% in large unselected cohorts of VTE patients [5,6]. This wide variation also depends on the inclusion or exclusion of weak to moderate risk factors, such as oral contraceptives, long-haul air flights or thrombophilia.

Individual patient approach

In light of these limitations and with the aim to pursue an ideal personalized treatment approach, research is moving toward individualized strategies. In addition to major, well-established risk factors for VTE (e.g. cancer, surgery, trauma or fracture, pregnancy and puerperium, acute medical illness) several minor to moderate risk factors have also been found to be associated with the risk of a first VTE event, including age [7], blood group [8], heterozygous Factor V Leiden or prothrombin gene mutations [9], infections and inflammatory disorders [10], cardiovascular risk factors [11], and endocrine disorders [12]. These risk factors are common and their coexistence and interaction might also play a role in the individual risk of recurrent events. Male sex [13], factor V Leiden mutation [9], prothrombin gene mutation [14], obesity [15], inflammatory bowel disease [16], and more proximal site of DVT [17] have all been associated with an increased risk of recurrence.

The detection of a positive D-dimer after stopping anticoagulant treatment in patients with unprovoked VTE was associated with an annualized risk of recurrence of 8.8% patient-years, as compared to 3.7% patient-years in patients with a negative D-dimer [18]. Subsequent studies showed that repeated testing for up to 3 months after treatment discontinuation in patients with initially negative D-dimer levels detects subsequent D-dimer changes which are also associated with an increased risk of recurrence [19]. Patients with residual vein obstruction detected on compression ultrasonography at the end of anticoagulant treatment also have a slightly increased risk of recurrence, although the predictive ability of this test in the subgroup of patients with unprovoked VTE remains uncertain [20]. The best definition of residual vein

obstruction, the optimal timing for the test, and its reproducibility remain open issues.

The combination of clinical and instrumental predictors of recurrent VTE has been finally assessed with the aim to produce clinical prediction rules (CPR) able to identify individual patients at low risk of recurrence who can safely withhold anticoagulant treatment. In the study by Rodger and colleagues, sex, age, signs of post-thrombotic syndrome, D-dimer, and obesity were identified as independent predictors and included in a CPR that was able to identify a subgroup of women (52% of the whole female population) with a very low risk of recurrence (1.6% per year) [21]. Recurrence rates in men were high (13.7% per year) and no combination of clinical predictors could identify a low-risk subgroup of men [21]. Eichinger and colleagues proposed a nomogram to calculate the individual risk of recurrence at 12 and 60 months, based on sex, extension of DVT, PE and D-dimer. A score of ≤ 180 points identified a low-risk population with an annualized risk of recurrence of 4.4% [22]. Finally, Tosetto *et al.* [23] proposed a CPR based on D-dimer, age, sex, and the use of hormonal therapy that identified about half of patients with unprovoked VTE with a low annualized recurrence risk (3.1%).

Each of the three proposed CPRs offers the possibility to identify individual patients with an acceptable annualized incidence of recurrence that could therefore safely discontinue anticoagulant treatment. However, these CPRs need, in our opinion, further validation and possibly some refinements before they can be definitively implemented in clinical practice.

How long is long enough for anticoagulant treatment with vitamin K antagonists?

Vitamin K antagonists (VKAs) have been the mainstay of treatment for the secondary prevention of VTE for many years. A number of randomized clinical trials have compared VKAs with no treatment or placebo after an initial course of anticoagulant therapy in patients with proximal DVT of the lower limbs and PE [24–29]. These studies, comparing a short-term treatment course (6 weeks to 3 months) with a longer-term course (6 months to 2 years) have helped to define the minimum duration of treatment and to identify those patients who can safely discontinue anticoagulation at the end of this period. No study has been sufficiently able to determine whether an optimal duration of extended treatment exists for patients at higher risk of recurrence. In all trials, patient subgroups have been defined using a population-based approach, with substantial heterogeneity between studies. In particular, separate data on patients with unprovoked VTE are available in three studies only [25–27], for a total sample of only 610 patients. Furthermore, some differences exist in the definition of unprovoked VTE between the LAFIT [25] and the WODIT studies [26,27]. For example, gender-specific risk factors such as pregnancy or the use of oral contraceptives were exclusion criteria in the WODIT studies, but not in the LAFIT study. Table 1 summarizes characteristics and main efficacy results of these randomized controlled trials.

Boutitie *et al.* [30] recently performed a pooled analysis of individual patients data from seven randomized controlled trials comparing different durations of VKAs treatment in patients with a first VTE and without cancer. Table 2 summarizes possible future treatment strategies for the secondary prevention of VTE in usual and unusual sites. This study concluded that the risk of recurrent VTE is higher in patients treated for less than three months than in patients treated for three months or longer; similar after DVT or after PE; and lower after VTE provoked by a transient risk factor than after unprovoked VTE. Of interest, high rates of recurrence seemed to be confined to the first six months after stopping treatment. Furthermore, when patients treated for three months were compared with patients treated for six months or longer, an increase in recurrent VTE of borderline statistical significance in the three-month group was observed (HR 1.57; 95% CI 0.94–2.61). Based on the results of the study, the authors concluded that patients with no indication to indefinite anticoagulant treatment (e.g. patients with VTE secondary to a transient risk factor) should stop VKAs at 3 months and that patients with unprovoked VTE may benefit from indefinite treatment because of their high risk of recurrence whenever treatment was stopped.

Is there an expected rate of events that I can consider acceptable to drive treatment duration for my patient?

It has been recently proposed by a statement of the International Society on Thrombosis and Haemostasis that a recurrence rate of 5% at one year and of 15% at five years after stopping anticoagulant therapy can be considered acceptable to justify discontinuation of VKAs, whereas a risk of 10% at one year and 30% at 5 years is unacceptably high [31]. Although this statement was proposed for studies rather than for individual patients, it well reflects physicians attitudes using current population-based stratifications, since the proposed cut-off to define low-risk patients corresponds to the expected recurrence rates in patients with VTE provoked by a non-surgical transient risk factor, who in most cases discontinue anticoagulant therapy.

However, additional drivers for treatment duration also include the severity of the recurrent event and the balance between risks and benefits of anticoagulant treatment. Thus, a patient with PE as the first event may be a better candidate for indefinite treatment duration than a patient with isolated DVT given their higher risk of having a new PE as the second event. On the other hand, the reported annual incidence of major bleeding in patients on warfa-

Table 1 Summary of the results of randomized controlled trials comparing different treatment durations with vitamin K antagonists in patients with proximal DVT or PE

Study	Population	Intervention	Control	Outcome
DURAC [23]	Temporary risk factors: surgery, trauma, temporary immobilization, travel, estrogens, infection, Baker's cyst, pregnancy	6 months (n:177)	6 weeks (n:167)	Cumulative incidence of recurrent VTE reduced from 8.6% to 4.8% after 2-year follow-up (OR 1.9, 95% CI 0.8–4.5)
DURAC [23]	Permanent risk factors: idiopathic VTE (absence of any temporary risk factor plus permanent paresis, cancer, deficiency of antithrombin, protein C, or protein S); systemic lupus erythematosus; venous insufficiency	6 months (n:287)	6 weeks (n:266)	Cumulative incidence of recurrent VTE reduced from 24.2% to 12.1% after 2-year follow-up (OR 2.3, 95% CI 1.5–3.6)
LAFIT [24]	Idiopathic VTE: absence of fracture or plaster casting of a lower limb, hospitalization with confinement to bed for 3 consecutive days, or use of general anesthesia, each within the previous 3 months; a known deficiency of antithrombin, protein C, or protein S; and cancer in the previous 5 years	24 months (n:79)	3 months (n:83)	Annualized incidence of recurrent VTE reduced from 27.4% patient-year after treatment discontinuation to 1.3% patient-year (this group was on treatment) after average follow-up 10 months (HR 0.05, 95% CI 0.01–0.37)
WODIT DVT [25]	Idiopathic DVT: absence of known cancer, known thrombophilia, prolonged immobilization (i.e. lasting more than 7 days) from any cause, recent trauma or surgery (i.e. within the previous 3 months), pregnancy, recent childbirth, or the use of oral contraceptives	12 months (n:134)	3 months (n:133)	Similar annualized incidence of recurrences after treatment discontinuation (5.0% patient-year and 5.1% patient-year, respectively) after average 3 years of follow-up
WODIT PE [26]	Idiopathic PE: absence of known cancer, known thrombophilia, or any transient risk factor	12 months (n:90)	3 months (n:91)	Similar annualized incidence of recurrences (4.2% patient-year and 4.6% patient-year, respectively) after average 32 and 35 months of follow-up, respectively (RR 0.99, 95% CI 0.45–2.16)
WODIT PE [26]	Transient risk factors: recent trauma with or without bone fracture, recent surgery or childbirth, or prolonged immobilization (that is, lasting > 7 days), or occurring during the use of oral contraceptives or pregnancy	6 months (n:75)	3 months (n:70)	Similar annualized incidence of recurrences (1.8% patient-year and 3.5% patient-year, respectively) after average follow-up 35 and 34 months, respectively (RR 0.53, 95% CI 0.16–1.74)
DOTAVK [27] *	Transient risk factors: surgery, immobilization, trauma, plaster cast, oral contraceptives, travel, infection Permanent risk factors: venous insufficiency, obesity, myocardial disease, hemiplegia Idiopathic: absence of above risk factors plus pregnancy, breast-feeding, cancer, known thrombophilia (exclusion criteria from the study)	6 months (n:269)	3 months (n:270)	Similar rate of recurrences (8.7% and 8.1%, respectively) after one-year follow-up including all patient subgroups (RR 0.93, 95% CI 0.53–1.65)
CAMPBELL [28]*	All VTE patients, with the following exclusion criteria: cancer within the previous 3 years; pregnancy; major thrombophilia; prolonged or continuous immobility or confinement to bed.	6 months (n:380)	3 months (n:369)	Similar rate of recurrences (8.0% in each group) after one-year follow-up including all patient subgroups

DVT, Deep vein thrombosis; PE pulmonary embolism; VTE, venous thromboembolism; OR, odds ratio; HR, hazard ratio; RR, relative risk; CI, confidence interval.
*It was not possible to obtain in the text separate data for patients with an idiopathic or a secondary event.

Table 2 Possible future scenarios in the secondary prevention of a first VTE*

At least 3 months of anticoagulant treatment	All patients with proximal DVT, PE, SVT, CVT
Treatment discontinuation at 3 months	Patients with all sites VTE secondary to surgical risk factors
Treatment discontinuation at 3 months	Patients with DVT or PE secondary to non-surgical, transient risk factors Comment: use of CPR and/or D-dimer measurement† may be advisable for higher-risk patients (e.g. VTE secondary to oral contraceptives) and in particular for patients with isolated PE to drive treatment duration. Validation of CPRs in all settings is required.
Treatment discontinuation at 3 months	Patients with unprovoked proximal DVT if RVO absent and D-dimer persistently negative Comment: ongoing studies are assessing this approach
Treatment discontinuation at 3 months	Patients with unprovoked proximal DVT and low probability CPR† Comment: prospective management studies are warranted to validate CPRs
Treatment discontinuation after 6–12 months	Patients with isolated unprovoked PE hemodynamically stable at presentation, no residual RVD, low probability CPR and a persistently negative D-dimer Comment: longer treatment duration based on common practice and on weak evidence of a lower risk of recurrence if treatment > 6 months
Treatment discontinuation after 6–12 months	Patients with CVT secondary to removable risk factors; patients with unprovoked CVT without RVO and residual neurological impairment Comment: longer treatment duration based on common practice; studies warranted to confirm this approach
Treatment with ASA after 3 months of anticoagulant therapy	Patients eligible for discontinuation of anticoagulant drugs (see above) and with increased cardiovascular risk (unless VTE occurred during antiplatelet treatment); patients with unprovoked DVT or PE and high probability CPR or positive D-dimer and persistent RVO who prefer to discontinue anticoagulant drugs Comment: studies are needed to better identify patients who can benefit from aspirin treatment.
Indefinite anticoagulant treatment (with periodic re-assessment of bleeding risk profile)	Patients with permanent major risk factors; patients with unprovoked VTE and high probability CPR; patients with unprovoked VTE, positive D-dimer and persistent RVO Comment: individual assessment of patients with permanent major risk factors (e.g. cancer or previous VTE) is also warranted
Indefinite anticoagulant treatment (with periodic re-assessment of bleeding risk profile)	Patients with unprovoked SVT; patients with SVT secondary to permanent risk factors; patients with Budd–Chiari syndrome; patients with unprovoked CVT with RVO and residual neurological impairment; patients with CVT secondary to permanent risk factors; patients with PE and chronic post-embolic pulmonary hypertension Comment: indefinite treatment duration in these patients is suggested considering the potential severity of a recurrent event.

DVT, deep vein thrombosis; PE, pulmonary embolism; CVT, cerebral vein thrombosis; SVT, splanchnic vein thrombosis; CPR, clinical prediction rule, CRNM, clinically relevant non-major bleeding; RVO, residual vein obstruction; TTR, time in therapeutic range; RVD, right ventricular dysfunction.

*Most suggested treatment strategies have not been validated and, thus, are not evidence based.

†D-dimer measurement is currently included in all available CPRs.

rin with an international normalized ratio (INR) range of 2.0–3.0 was estimated to be between 1.1% and 2.3% in selected patients [32–34], but these figures may be higher in unselected populations, as suggested by a recent nationwide registry reporting a 4.3% annual rate, although in a different setting of patients with myocardial infarction [35].

The case-fatality rate for major bleeding in patients taking warfarin for more than three months has been estimated to be 9.1% (95% CI 2.5–21.7%)[36]. On the other hand, the case-fatality rate for recurrent VTE after discontinuation of anticoagulant treatment was reported to be 3.6% (95% CI 1.9%–5.7%) [37]. Thus, although major bleeding during anticoagulant treatment is less common than recurrent VTE after treatment withdrawal, bleeding events seem to be associated with a higher risk of mortality that needs to be carefully taken into account when deciding treatment duration. For this reason, we favor the individual patient approach to minimize unneeded extended exposure to anticoagulant drugs in many VTE patients. This individual approach should also include a thorough assessment of bleeding risk factors. A number of bleeding risk scores have been proposed for patients on VKAs, but only two were assessed in patients with VTE and none is sufficiently validated [38,39].

Can I rely on D-dimer or on residual vein obstruction to determine the duration of anticoagulant treatment for my patient?

Management strategies using D-dimer measurement or residual vein obstruction have been assessed in clinical trials. In the PROLONG study, 619 patients with a first

unprovoked proximal DVT or PE who received VKA treatment for at least 3 months underwent D-dimer testing 1 month after the discontinuation of anticoagulation [40]. About one-third of patients had a positive D-dimer and were randomized to resume VKAs or to permanently discontinue treatment. After a mean follow-up of 1.4 years, the incidence of recurrences was 10.9% person-years in D-dimer positive patients randomized to stop treatment and 2.0% person-years in D-dimer positive patients who resumed treatment (HR 4.26, 95% CI 1.23–14.6). A negative D-dimer was associated with an incidence of recurrent VTE of 4.4% person-years without anticoagulant treatment. Of note, five patients experienced a recurrent event during the interval between treatment interruption and the one-month visit.

In the DACUS study, 258 patients with a first episode of DVT, both provoked and unprovoked, underwent compression ultrasonography to assess the presence of residual vein obstruction after three months of VKA treatment [41]. Residual vein obstruction was defined by the presence of a thrombus occupying more than 40% of the vein diameter and was detected in about two-thirds of the patients. Patients with residual vein obstruction were randomized to continue anticoagulants for additional nine months or to stop treatment. After a mean follow-up of two years, the incidence of recurrent VTE was 15.2% person-years in the extended treatment group and 10.1% person-years in the group treated for three months (HR 1.58, 95% CI 0.85–2.93). This incidence was 0.63% person-years in patients with no residual thrombosis. Finally, in the AESOPUS study 538 patients with a first episode of proximal DVT, both provoked and unprovoked, were assessed for residual vein obstruction after three months of anticoagulant treatment [42]. In this study, a residual obstruction was defined by a vein diameter of more than 2.0 mm in a single determination or more than 3.0 mm in two consecutive determinations. Patients were randomly assigned to a fixed-duration of anticoagulant treatment (a total of three months for provoked DVT and six months for unprovoked DVT) or to a flexible-duration based on the presence of residual vein obstruction (if present, treatment was continued for up to additional nine months for provoked DVT and twenty-one months for unprovoked DVT). After a total follow-up of three years, the incidence of recurrent events was 17.2% using the fixed-duration strategy and 11.9% using the flexible-duration strategy (HR 0.64, 95% CI 0.39–0.99). In patients with unprovoked DVT only, the HR was 0.61 (95% CI 0.36–1.02). Based on the results of these management studies, both strategies appear to have the potential to identify low-risk patients who may safely discontinue anticoagulant treatment. It seems less likely that these strategies may drive optimal treatment duration in patients at higher risk. Ongoing clinical trials are evaluating the accuracy of the combination of the two tests to improve the selection of low-risk patients.

Are the oral direct inhibitors a possible solution for patients requiring extended treatment?

The oral direct inhibitors (ODIs), including direct thrombin and direct factor Xa inhibitors, have been assessed in a number of clinical settings, there including the treatment of patients with VTE. The oral route of administration and the remarkable pharmacologic properties, such as the rapid onset and offset of action, the relatively short half-life, and the predictable anticoagulant effect, make these agents easy to use and, thus, ideal candidates for the secondary prevention of VTE, in particular in patients requiring indefinite treatment [43].

Dabigatran

Two studies have assessed the direct thrombin inhibitor dabigatran in the long-term secondary prevention of VTE. In the RE-SONATE study, 1343 patients with VTE who received 6–18 months of anticoagulant therapy were randomized to dabigatran 150 mg twice daily or to placebo for an additional 6 months [44]. The incidence of recurrent VTE was reduced from 5.6% in the placebo group to 0.4% in the dabigatran group (HR 0.08, 95% CI 0.02–0.25), with no difference in the incidence of major bleeding (0% and 0.3%, respectively, HR 1.0, 95% CI 0.00–1.00). Major or clinically relevant non-major bleeding events were significantly more frequent in the dabigatran group (5.3% and 1.8%, HR 2.92, 95% CI 1.52–5.60). In the RE-MEDY trial, dabigatran was compared with warfarin in 2856 patients with VTE for up to 36 months after an initial anticoagulant treatment of 3–12 months [44]. The incidence of recurrent VTE was similar between the two groups (1.8% in the dabigatran group and 1.3% in the warfarin group, HR 1.44, 95% CI 0.78–2.64), with no statistically significant difference in the rate of major bleeding events (0.9% vs. 1.8%, respectively, HR 0.52, 95% CI 0.27–1.02). The rate of major or clinically relevant bleeding events was significantly lower in the group treated with dabigatran than in the group treated with warfarin (HR 0.54, 95% CI 0.41–0.71), but an increased incidence of acute coronary syndromes in the dabigatran group (0.9% vs. 0.2%, $P = 0.02$) was also reported.

Rivaroxaban

In the EINSTEIN-EXTENSION study, 1196 patients with VTE who were treated with either rivaroxaban or VKAs for 6–12 months were randomized to rivaroxaban 20 mg daily or placebo for an additional 6 or 12 months [45]. Rivaroxaban significantly reduced the incidence of recurrent VTE (1.3% vs. 7.1%, HR 0.18, 95% CI 0.09–0.39), with no statistically significant difference in the rate of major bleeding events (0.7% vs. 0%, HR not reported, $P = 0.11$). Clinically relevant non-major

bleeding occurred more frequently in patients treated with rivaroxaban (5.4% and 1.2%, respectively, HR and *P*-value not reported).

Apixaban

In the AMPLIFY-EXTENSION study, two doses of apixaban, 2.5 mg and 5 mg twice daily, were compared with placebo for 12 months in 2482 patients with VTE treated with anticoagulants for 6 to 12 months [46]. Both doses of apixaban were highly effective in reducing the incidence of recurrent VTE, from 8.8% in the placebo group to 1.7% in both apixaban groups (relative risk [RR] for placebo vs. 2.5 mg 0.19, 95% CI 0.11–0.33; RR for placebo vs. 5 mg 0.20, 0.11–0.34). The rates of major bleeding were not different among the three groups: 0.5% in the placebo group, 0.2% in the apixaban 2.5 mg group (RR vs. placebo 0.49, 95% CI 0.09–2.64), and 0.1% in the apixaban 5 mg group (RR vs. placebo 0.25, 95% CI 0.03–2.24). The rates of clinically relevant non-major bleeding were also not different between the lower dose of apixaban and placebo, but significantly higher when the higher dose was compared with placebo: 2.3% in the placebo group, 3.0% in the apixaban 2.5 mg group (RR vs. placebo 1.29, 95% CI 0.72–2.33), and 4.2% in the apixaban 5 mg group (RR vs. placebo 1.82, 1.05–3.18).

Overall, the results of these trials confirm the efficacy of anticoagulant treatment in reducing the long-term risk of recurrent VTE, with an acceptable safety profile with the use of the ODIs. Nevertheless, only one clinical trial has thus far compared the ODIs with warfarin in this setting and there remains limited evidence from the literature with respect to the effectiveness of the ODIs in the 'real world' in unselected populations.

Are there alternative antithrombotic drugs that I could consider for my patient?

Recent studies have assessed the efficacy of aspirin for the secondary prevention of VTE after an initial course of anticoagulant therapy. In the WARFASA study, 402 patients with a first unprovoked VTE who completed six to eighteen months of oral anticoagulant treatment were randomized to aspirin 100 mg or placebo for two years [47]. The annual incidence of recurrent VTE in the placebo group was 11.2%, and it was reduced to 6.6% by the use of aspirin (HR 0.53, 95% CI 0.32–0.85), with no difference in major bleeding events (one in each group). In the ASPIRE study, 822 patients with a first unprovoked VTE who completed an initial course of anticoagulant therapy were also randomized to aspirin 100 mg or placebo for up to four years [48]. The annual incidence of recurrent VTE in the placebo group was lower than in the WARFASA study (6.5%), and the use of aspirin resulted in a non-significant reduction of VTE events (HR 0.74, 95% CI 0.52–1.05). The incidence of major bleeding was similar between the two groups, with 6 events occurring in patients receiving placebo and 8 in patients receiving aspirin. The pooled analysis of the two trials showed a statistically significant reduction in the incidence of recurrent VTE (HR 0.68, 95% CI 0.51–0.90), as well as in the incidence of major vascular events (arterial and venous thromboembolic events) (HR 0.66, 95% CI 0.51–0.86) with the use of aspirin [48].

The observed reduction in recurrent VTE obtained with aspirin is less striking than that obtained with either VKAs or ODIs. Which patients could be treated with aspirin remains to be established. Patients with previous cardiovascular disease, and thus with a concomitant indication for antiplatelet treatment, were excluded from both studies. Moreover, most of these patients likely had their index event while on antiplatelet therapy.

Should I use the same decisional approach for patients with DVT in unusual sites?

The long-term risk of recurrence and the optimal duration of secondary prevention in patients with DVT occurring in unusual sites have been less studied. In the absence of sufficient evidence, a decisional approach that is similar to that used for patients with proximal DVT of the lower limbs or PE is commonly adopted. However, the effects of recurrent DVT occurring in the cerebral or in the splanchnic veins are possibly different from the effects of recurrent DVT in a lower limb, as well as the risk of bleeding events, thus making the risk to benefit ratio of extended prophylaxis in these patients less predictable.

Cerebral vein thrombosis (CVT)

The recurrence rate of CVT seems to be relatively low. Pooling the results of 13 studies with follow-up duration ranging between 12 and 145 months, we found a recurrence rate of 2.8% [49]. The rate of VTE occurring in other sites (apart from CVT) was 3.7% [49]. In a single center study on 145 patients with a first CVT followed up for a median of six years after discontinuation of anticoagulant treatment, the annual recurrence rate for CVT was 0.5% person-years, and the annual rate of any VTE was 2.0% person-years [50]. The only independent risk factors for recurrence were male sex and severe thrombophilia. Median treatment duration was 12 months. In a multicenter study on 706 CVT patients followed up for a median of 40 months, the incidence of recurrent VTE after treatment discontinuation was 3.5% person-years [51]. Previous VTE was the only independent predictor of recurrence. Median duration of anticoagulant treatment was again 12 months.

Thus, the annual risk of recurrence after treatment discontinuation in patients with CVT is lower than that observed in patients with proximal DVT and PE. This

finding may be explained by the differences in both baseline characteristics and prevalence of temporary risk factors between these two populations. In patients with CVT, the mean age at presentation is 40 years, approximately 75% of patients are female, and, in women, more than 60% of events are secondary to hormonal therapy, pregnancy, or puerperium [51].

In these observational studies, the median duration of treatment was 12 months [51,52], a duration that is longer than that reported in patients with DVT and PE [1] and that is probably driven by a greater concern for recurrent thrombosis in the cerebral veins as compared to other sites. Unfortunately, there is no adequate information on case-fatality rates or impaired neurological outcome related to recurrent CVT. However, no study has found recurrent CVT as an independent predictor of a poor outcome [49]. There is also insufficient evidence to define the optimal minimum treatment duration in these patients. Finally, based on available data, there is no reason to believe that the risk of bleeding during treatment differs from that observed in patients with DVT in the lower limbs or PE.

Splanchnic vein thrombosis (SVT)

Few studies have provided information on the long-term risk of recurrences in patients with SVT. In a large retrospective cohort of 832 patients with portal, mesenteric, splenic, and hepatic vein thrombosis, the annual incidence of recurrent VTE after a mean follow-up of 27 months was 3.5% person-years and about half of the recurrent events occurred in the splanchnic veins [52]. Only 28% of patients received VKAs, which in 75% of cases were prescribed lifelong. The authors only found hormonal therapy to be independently associated with the risk of recurrence, while the use of VKAs was not protective. In another retrospective study enrolling 136 non-cirrhotic patients with portal vein thrombosis only, the incidence rate of thrombotic events after a median follow-up of 46 months was 5.5% person-years, but five of 38 events were arterial events [53]. Of the enrolled patients, 52 did not receive anticoagulant treatment, 54 continued on anticoagulants throughout the follow-up period, and in 30 the treatment was discontinued, but its duration was not reported. An 'underlying prothrombotic state' was the only independent predictor of recurrence, while the use of anticoagulant therapy was associated with a statistically significant reduction in recurrent events. Finally, the annual risk of recurrence in 77 patients with mesenteric vein thrombosis all treated with VKAs was found to be 4.6% person-years in the about 40% of patients who discontinued anticoagulant treatment [54].

As for patients with CVT, these data may suggest that recurrence rates in SVT patients are lower than in patients with proximal DVT or PE [1], but great caution should be taken before making any conclusion given the low quality of the available evidence. Furthermore, permanent risk factors are very common in these patients, since liver cirrhosis, solid cancer, and hematologic malignancies account for about two-thirds of all events [52], while transient risk factors are identified in at least one fourth of patients, thus leaving few patients classified as unprovoked. As for patients with CVT, there is insufficient information to define the optimal minimum duration of treatment. The effect of recurrences may be severe since in about one fourth of cases these occurred as hepatic, mesenteric, or splenic infarctions [53]. On the other hand, bleeding remains a major concern in SVT patients. In the study by Thatipelli and colleagues, major bleeding rates were 6.9% person-years, most commonly involving the gastrointestinal tract and were thus higher than the rates of recurrent VTE [53]. However, in the study on patients with mesenteric venous thrombosis only, case-fatality rate of thrombosis was significantly higher than that of gastrointestinal bleeding [54]. In all studies, the presence of esophageal varices resulted as an independent predictor of bleeding and adequate prophylaxis with beta-blockers or with endoscopic treatment should be considered when these patients require anticoagulant therapy. No adequate data are available in patients with liver cirrhosis, who are possibly at increased risk of both recurrence and bleeding. Indeed, when assessing the risks and benefits of anticoagulant therapy in SVT patients, the heterogeneity of this population according to the site of the event (in particular Budd-Chiari syndrome vs. other sites of thrombosis) and to the presence of underlying provoking disorders, needs to be carefully taken into account.

Disclosure of Conflict of Interest

Walter Ageno has received honoraria from Bayer, Boehringer Ingelheim, Pfizer/BMS, and Daiichi Sankio for participation in Advisory Boards and support for attendance at educational and scientific meetings.

References

1 Prandoni P, Noventa F, Ghirarduzzi A, Pengo V, Bernardi E, Pesavento R, Iotti M, Tormene D, Simioni P, Pagnan A. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. *Haematologica* 2007; **92**: 199–205.

2 Goldhaber SZ, Piazza G. Optimal duration of anticoagulation after venous thromboembolism. *Circulation* 2011; **123**: 664–7.

3 Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JG, Buller HR. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. *J Clin Oncol* 2000; **18**: 3078–83.

4 Iorio A, Kearon C, Filippucci E, Marcucci M, Macura A, Pengo V, Siragusa S, Palareti G. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor. *Arch Intern Med* 2010; **170**: 1710–6.

5 Heit JA, O'Fallon WM, Petterson TM, Lohse CM, Silverstein MD, Mohr DN, Melton LJ 3rd. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. *Arch Intern Med* 2002; **162**: 1245–8.

6 Ageno W, Agnelli G, Imberti D, Moia M, Palareti G, Pistelli R, Verso M. Prevalence of risk factors for venous thromboembolism in the Italian population: results of a cross-sectional study from the MASTER registry. *Intern Emerg Med* 2011. [Epub ahead of print].

7 Hansson PO, Welin L, Tibblin G, Erikkson H. Deep vein thrombosis and pulmonary embolism in the general population. The Study of Men Born in 1913. *Arch Intern Med* 1997; **157**: 1665–70.

8 Dentali F, Sironi AP, Ageno W, Turato S, Bonfanti C, Frattini F, Crestani S, Franchini M. Non-O blood type is the commonest genetic risk factor for VTE: results from a meta-analysis of the literature. *Semin Thromb Hemost* 2012; **38**: 535–48.

9 Segal JB, Brotman DJ, Necochea AJ, Emadi A, Samal L, Wilson LM, Crim MT, Bass EB. Predictive value of factor V Leiden and prothrombin G20210A in adults with venous thromboembolism and in family members of those with a mutation: a systematic review. *JAMA* 2009; **301**: 2472–85.

10 Tichelaar YIGV, Kluin-Nelemans HJ, Meijer K. Infections and inflammatory diseases as risk factors for venous thrombosis, a systematic review. *Thromb Haemost* 2012; **107**: 827–37.

11 Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. *Circulation* 2008; **117**: 93–102.

12 Squizzato A, Romualdi E, Büller HR, Gerdes VE. Clinical review: thyroid dysfunction and effects on coagulation and fibrinolysis: a systematic review. *J Clin Endocrinol Metab* 2007; **92**: 2415–20.

13 McRae S, Tran H, Schulman S, Ginsberg J, Kearon C. Effect of patient's sex on risk of recurrent venous thromboembolism: a meta-analysis. *Lancet* 2006; **368**: 371–8.

14 Ho WK, Hankey GJ, Quinlan DJ, Eikelboom JW. Risk of recurrent venous thromboembolism in patients with common thrombophilia: a systematic review. *Arch Intern Med* 2006; **166**: 729–36.

15 Eichinger S, Hron G, Bialonczyk C, Hirschl M, Minar E, Wagner O, Heinze G, Kyrle PA. Overweight, obesity, and the risk of recurrent venous thromboembolism. *Arch Intern Med* 2008; **168**: 1678–83.

16 Novacek G, Weltermann A, Sobala A, Tilg H, Petritsch W, Reinisch W, Mayer A, Haas T, Kaser A, Feichtenschlager T, Fuchssteiner H, Knoflach P, Vogelsang H, Miehsler W, Platzer R, Tillinger W, Jaritz B, Schmid A, Blaha B, Dejaco C, *et al.* Inflammatory bowel disease is a risk factor for recurrent venous thromboembolism. *Gastroenterology* 2010; **139**: 779–87.

17 Douketis JD, Crowther MA, Foster GA, Ginsberg JS. Does the location of thrombosis determine the risk of disease recurrence in patients with proximal deep vein thrombosis? *Am J Med* 2001; **110**: 515–9.

18 Douketis J, Tosetto A, Marcucci M, Baglin T, Cushman M, Eichinger S, Palareti G, Poli D, Campbell Tait R, Iorio A. Patient-level meta-analysis: effect of measurement timing, threshold, and patient age on ability of d-dimer testing to assess recurrence risk after unprovoked venous thromboembolism. *Ann Intern Med* 2010; **153**: 523–31.

19 Cosmi B, Legnani C, Tosetto A, Pengo V, Ghirarduzzi A, Testa S, Prisco D, Poli D, Tripodi A, Marongiu F, Palareti G. Usefulness of repeated D-dimer testing after stopping anticoagulation for a first episode of unprovoked venous thromboembolism: the PROLONG II prospective study. *Blood* 2010; **115**: 481–8.

20 Carrier M, Rodger MA, Wells PS, Righini M, Le Gal G. Residual vein obstruction to predict the risk of recurrent venous thromboembolism in patients with deep vein thrombosis: a systematic review and meta-analysis. *J Thromb Haemost* 2011; **9**: 1119–25.

21 Rodger MA, Kahn SR, Wells PS, Anderson DA, Chagnon I, Le Gal G, Solymoss S, Crowther M, Perrier A, White R, Vickars L, Ramsay T, Betancourt MT, Kovacs MJ. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. *CMAJ* 2008; **179**: 417–26.

22 Eichinger S, Heinze G, Jandeck LM, Kyrle PA. Risk assessment of recurrence in patients with unprovoked deep vein thrombosis or pulmonary embolism: the Vienna prediction model. *Circulation* 2010; **121**: 1630–6.

23 Tosetto A, Iorio A, Marcucci M, Baglin T, Cushman M, Eichinger S, Palareti G, Poli D, Campbell Tait R, Douketis J. Predicting disease recurrence in patients with previous unprovoked venous thromboembolism. A proposed prediction score (DASH). *J Thromb Haemost* 2012; **10**: 1019–25.

24 Schulman S, Rhedin AS, Lindmarker P, Carlsson A, Larfars G, Nicol P, Loogna E, Svensson E, Ljungberg B, Walter H, Viering S, Nordlander S, Leijd B, Jonsson KA, Hjorth M, Linder O, Boberg J. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. *N Engl J Med* 1995; **332**: 1661–5.

25 Kearon C, Gent M, Hirsh J, Weitz J, Kovacs MJ, Anderson DR, Turpie AG, Green D, Ginsberg JS, Wells P, MacKinnon B, Julian JA. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med* 1999; **340**: 901–7.

26 Agnelli G, Prandoni P, Santamaria MG, Bagatella P, Iorio A, Bazzan M, Moia M, Guazzaloca G, Bertoldi A, Tomasi C, Scannapieco G, Ageno W. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. *N Engl J Med* 2001; **345**: 165–9.

27 Agnelli G, Prandoni P, Becattini C, Silingardi M, Taliani MR, Miccio M, Imberti D, Poggio R, Ageno W, Pogliani E, Porro F, Zonzin P. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. *Ann Intern Med* 2003; **139**: 19–25.

28 Pinede L, Ninet J, Duhaut P, Chaubaud S, Demolombe-Rague S, Durieu I, Nony P, Sanson C, Boissel JP. Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis. *Circulation* 2001; **103**: 2453–60.

29 Campbell IA, Bentley DP, Prescott RJ, Routledge PA, Shett HGM, Williamson IJ. Anticoagulation for three versus six months in patients with deep vein thrombosis or pulmonary embolism, or both: randomised trial. *Br Med J* 2007; **334**: 674–7.

30 Boutitie F, Pinede L, Schulman S, Agnelli G, Raskob G, Julian J, Hirsh J, Kearon C. 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. *Br Med J* 2011; **342**: d3036.

31 Kearon C, Iorio A, Palareti G. Risk of recurrent after stopping treatment in cohort studies: recommendation for acceptable rates and standardized reporting. *J Thromb Haemost* 2010; **8**: 2313–5.

32 Ost D, Tepper J, Mihara H, Lander O, Heinzer R, Fein A. Duration of anticoagulation following venous thromboembolism: a meta-analysis. *JAMA* 2005; **294**: 76–715.

33 Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994; **154**: 1449–57.

34 Palareti G, Leali N, Coccheri S, Poggi M, Manotti C, D'Angelo A, Pengo V, Erba N, Moia M, Ciavarella N, Devoto G, Berrettini M, Musolesi S. Bleeding complication of anticoagulant treat-

ment: an inception-cohort, prospetive collaborative study (ISCOAT). *Lancet* 1996; **348**: 423–8.
35 Sørensen R, Hansen ML, Abildstrom SZ, Hvelplund A, Andersson C, Jørgensen C, Madsen JK, Hansen PR, Køber L, Torp-Pedersen C, Gislason GH. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. *Lancet* 2009; **374**: 1947–8.
36 Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. *Ann Intern Med* 2003; **139**: 893–900.
37 Carrier M, Le Gal G, Wells PS, Rodger MA. Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism. *Ann Intern Med* 2010; **152**: 578–89.
38 Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR; American College of Chest Physicians. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;**141**:e419S–94S.
39 Ruíz-Giménez N, Suárez C, González R, Nieto JA, Todolí JA, Samperiz AL, Monreal M, RIETE Investigators. Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism. Findings from the RIETE Registry. *Thromb Haemost* 2008; **100**: 26–31.
40 Palareti G, Cosmi B, Legnani C, Tosetto A, Brusi C, Iorio A, Pengo V, Ghirarduzzi A, Pattacini C, Testa S, Lensing AWA, Tripodi A. D-dimer testing to determine the duration of anticoagulation therapy. *N Engl J Med* 2006; **355**: 1780–9.
41 Siragusa S, Malato A, Anastasio R, Cigna V, Milio G, Amato C, Bellisi M, Attanzio MT, Cormaci O, Pellegrino M, Dolce A, Casuccio A, Bajardi G, Mariani G. Residual vein thrombosis to establish duration of anticoagulation after a first episode of deep vein thrombosis: the Duration of Anticoagulation based on Compression UltraSonography (DACUS) study. *Blood* 2008; **112**: 511–5.
42 Prandoni P, Prins MH, Lensing AWA, Ghirarduzzi A, Ageno W, Imberti D, Scannapieco G, Ambrosio GB, Pesavento R, Cuppini S, Quintavalla R, Agnelli G. Residual thrombosis on ultrasonography to guide the duration of anticoagulation in patients with deep venous thrombosis. *Ann Intern Med* 2009; **150**: 577–85.
43 Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141**: e44S–88S.
44 Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, Kvamme AM, Friedman J, Mismetti P, Goldhaber SZ, The RE-MEDY and the RE-SONATE Trials Investigators. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med* 2013; **368**: 709–18.
45 EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010; **363**: 2499–510.
46 Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Porcari A, Raskob GE, Weitz JI. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med* 2013; **368**: 699–708.
47 Becattini C, Agnelli G, Schenone A, Eichinger S, Bucherini E, Silingardi M, Bianchi M, Moia M, Ageno W, Vandelli MR, Grandone E, Prandoni P. Aspirin for preventing the recurrence of venous thromboembolism. *N Engl J Med* 2012; **366**: 1959–67.
48 Brighton TA, Eikelboom JW, Mann K, Mister R, Gallus A, Ockelford P, Gibbs H, Hague W, Xavier D, Diaz R, Kirby A, Simes J. Low-dose aspirin for preventing recurrent venous thromboembolism. *N Engl J Med* 2012; **367**: 1979–87.
49 Dentali F, Gianni M, Crowther MA, Ageno W. Natural history of cerebral vein thrombosis: a systematic review. *Blood* 2006; **108**: 1129–34.
50 Martinelli I, Bucciarelli P, Passamonti SM, Battaglioli T, Previtali E, Mannucci PM. Long-term evaluation of the risk of recurrence after cerebral sinus-venous thrombosis. *Circulation* 2010; **121**: 2740–6.
51 Dentali F, Poli D, Scoditti U, Di Minno MN, De Stefano V, Siragusa S, Kostal M, Palareti G, Sartori MT, Grandone E, Vedovati MC, Ageno W. Long-term outcomes of patients with cerebral vein thrombosis: a multicenter study. *J Thromb Haemost* 2012; **19**: 1297–302.
52 Thatipelli MR, McBane RD, Hodge DO, Wysokinski WE. Survival and Recurrence in Patients With Splanchnic Vein Thromboses. *Clin Gastroenterol Hepatol* 2010; **8**: 200–5.
53 Condat B, Pessione F, Hillaire S, Denninger MH, Guillin MC, Poliquin M, Hadengue A, Erlinger S. Current outcome of portal vein thrombosis in adults: risk and benefit of anticoagulant therapy. *Gastroenterology* 2001; **120**: 490–7.
54 Dentali F, Ageno W, Witt D, Malato A, Clark N, Garcia D, McCool K, Siragusa S, Dyke S, Crowther M. Natural history of mesenteric venous thrombosis in patients treated with vitamin K antagonists: a multi-centre, retrospective cohort study. *Thromb Haemost* 2009; **102**: 501–4.