Risk of Recurrence After a First Episode of Symptomatic Venous Thromboembolism Provoked by a Transient Risk Factor

A Systematic Review

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Background: We aimed to determine the risk of recurrence for symptomatic venous thromboembolism (VTE) provoked by different transient risk factors.

Data Sources: MEDLINE, EMBASE, and Cochrane Collaboration Registry of Randomized Trials databases were searched.

Study Selection: Prospective cohort studies and randomized trials of patients with a first episode of symptomatic VTE provoked by a transient risk factor and treated for at least 3 months were identified.

Data Extraction: Number of patients and recurrent VTE during the 0- to 12-month and 0- to 24-month intervals after stopping therapy, study design, and provoking risk factor characteristics were extracted.

Data Synthesis: Annualized recurrence rates were calculated and pooled across studies. At 24 months, the rate of recurrence was 3.3% per patient-year (11 studies, 2268 patients) for all patients with a transient risk factor, 0.7% per patient-year (3 studies, 248 patients) in the subgroup with a surgical factor, and 4.2% per patient-year (3 studies, 509 patients) in the subgroup with a nonsurgical factor. In the same studies, the rate of recurrence after unprovoked VTE was 7.4% per patient-year. The rate ratio for a nonsurgical compared with a surgical factor was 3.0 and for unprovoked thrombosis compared with a nonsurgical factor was 1.8 at 24 months.

Conclusions: The risk of recurrence is low if VTE is provoked by surgery, intermediate if provoked by a nonsurgical risk factor, and high if unprovoked. These risks affect whether patients with VTE should undergo short-term vs indefinite treatment.

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Venous thromboembolism (VTE) is associated with diverse risk factors, some of which are transient, such as recent surgery and pregnancy, and others of which are persistent, such as cancer. When VTE is associated with an acquired risk factor, either transient or persistent, it is called provoked. When there is no apparent clinical risk factor, it is called unprovoked or idiopathic.

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It has recently been recognized that the presence or absence of a transient, or reversible, risk factor at the time of VTE strongly affects the risk of recurrence after anticoagulant therapy is stopped. Patients with VTE provoked by a transient risk factor have a low risk of recurrence compared with patients with either VTE provoked by a persistent risk factor or unprovoked VTE. For this reason, patients with VTE provoked by a transient risk factor are usually treated with anticoagulant agents for 3 months, whereas patients with VTE that was not associated with a transient risk factor are often treated long-term. Although it is widely accepted that the risk of recurrence in patients with VTE provoked by a transient risk factor is low enough to justify stopping anticoagulant therapy after 3 months, this recurrence risk is not well quantified. Furthermore, the risk of recurrence may not be the same in all patients with VTE provoked by a transient risk factor; those with VTE provoked by recent surgery seem to have a lower risk of recurrence than those with VTE provoked by a nonsurgical risk factor, such as a medical illness.

We performed a systematic review of the literature to quantify the risk of recur-
rence after stopping anticoagulant therapy in patients with a first episode of symptomatic VTE (index VTE) that was provoked by any reversible risk factor and to compare the risk of recurrence according to whether VTE was associated with recent surgery or with a transient nonsurgical risk factor. We considered it important to identify the risk of recurrence in the subgroup of patients with VTE provoked by a nonsurgical transient risk factor because it remains unclear whether these patients should be treated in a similar manner as those with surgically provoked events (ie, short-term anticoagulation) or whether their risk of recurrence is high enough to justify long-term anticoagulation.

The primary objective of this systematic review was to determine rates of first recurrent VTE after stopping anticoagulant therapy in patients who had completed 3 or more months of treatment for an index VTE provoked by (1) any transient risk factor, (2) surgery, or (3) a nonsurgical factor. Secondary objectives were to determine whether study design and quality (ie, randomized controlled trial vs observational cohort study and prospective vs retrospective categorization of patients as having a reversible risk factor) affected these rates and to compare rates of recurrence in patients with index VTE provoked by a transient risk factor with rates of recurrence in patients with unprovoked index VTE enrolled in the same studies.

STUDY SELECTION

Two reviewers (A.I. and E.F.) independently screened all articles using a standard form, and disagreements were resolved by a third person (M.M.). For studies to be eligible for the present analysis, they had to satisfy all the following criteria: (1) enrolled patients (all patients or a subgroup) had a first episode of objectively confirmed VTE (deep venous thrombosis [DVT] or pulmonary embolism [PE]) provoked by a transient risk factor, and the definition of a transient risk factor was provided (patients with cancer are not included, even if they had VTE provoked by an additional transient risk factor); (2) patients were treated for at least 3 months with oral anticoagulant agents; (3) patients were observed prospectively after stopping anticoagulant therapy; (4) first recurrent VTE was systematically assessed during follow-up and diagnosed using objective testing; and (5) the recurrence rate was reported in the article or data were reported that enabled its calculation or estimation.

DATA EXTRACTION AND QUALITY ASSESSMENT

The following data were extracted from eligible studies: (1) the number of patients with index VTE provoked by a transient risk factor, subcategorized as provoked by a surgical or a nonsurgical factor, when this information was available; (2) whether patients with unprovoked index VTE were also included in the study, and the number of such patients; (3) the number of first episodes of recurrent VTE after stopping anticoagulant therapy for each group of patients, subcategorized as during follow-up from 0 to 12 months and 0 to 24 months (follow-up beyond 24 months after stopping anticoagulant therapy was excluded from this analysis); (4) the number of patient-years of follow-up after stopping anticoagulant drug therapy for each group of patients, subcategorized as during follow-up from 0 to 12 months and 0 to 24 months; (5) the criteria used to categorize patients as having index VTE provoked by a transient risk factor; (6) the proportion of patients in each subgroup who were female; (7) whether the patients were enrolled in a randomized trial or a prospective cohort study; and (8) whether classification of the patients as having a provoked or unprovoked index VTE was performed prospectively or retrospectively.

METHODS

DATA SOURCES AND SEARCHES

The following databases were searched: MEDLINE (PubMed, 1966 to June 2008), EMBASE (http://www.embase.com, 1980 to June 2008), and Cochrane Collaboration Registry of Randomized Trials (CENTRAL, Wiley 2008 edition). No methodological filters and language or date restrictions were applied. Searches included the following text words and index terms: anticoagulant, anticoagulation, warfarin, Coumadin, coumarin, venous thromboembolism, pulmonary embolism incidence, pulmonary embolism recurrence, pulmonary embolism epidemiology, venous thrombosis complications, venous thrombosis drug therapy, venous thrombosis epidemiology, venous thrombosis prevention, and control. The references of retrieved articles, including related guidelines and systematic reviews, were scanned for additional relevant studies.

STUDY SELECTION

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DATA EXTRACTION AND QUALITY ASSESSMENT

The following data were extracted from eligible studies: (1) the number of patients with index VTE provoked by a transient risk factor, subcategorized as provoked by a surgical or a nonsurgical factor, when this information was available; (2) whether patients with unprovoked index VTE were also included in the study, and the number of such patients; (3) the number of first episodes of recurrent VTE after stopping anticoagulant therapy for each group of patients, subcategorized as during follow-up from 0 to 12 months and 0 to 24 months (follow-up beyond 24 months after stopping anticoagulant therapy was excluded from this analysis); (4) the number of patient-years of follow-up after stopping anticoagulant drug therapy for each group of patients, subcategorized as during follow-up from 0 to 12 months and 0 to 24 months; (5) the criteria used to categorize patients as having index VTE provoked by a transient risk factor; (6) the proportion of patients in each subgroup who were female; (7) whether the patients were enrolled in a randomized trial or a prospective cohort study; and (8) whether classification of the patients as having a provoked or unprovoked index VTE was performed prospectively or retrospectively.

DATA SYNTHESIS AND ANALYSIS

The rate of recurrence, with its 95% confidence interval (CI), was calculated for each group in each study from the number of episodes of VTE that occurred during the corresponding total number of patient-years of follow-up and is expressed as an annualized percentage probability of events (eg, 6 episodes in 400 patient-years corresponds to a rate of 1.5% per patient-year). Whenever possible, the annualized rate was calculated for the first year and for the first 2 years (includes the first year) after anticoagulant therapy was stopped. If these data were not reported directly, they were estimated from the data that were provided, with the assumption that patients who did not complete a follow-up period (eg, died or were lost to follow-up) were observed for half of that interval. Annualized recurrence rates in individual studies were combined to obtain pooled estimates of recurrence rates using the method of Laird and Mosteller.7 A fixed-effects or a random-effects model was used depending on whether heterogeneity was present (Cochran Q χ² with P > .05 or I² > 50%), with inverse variance weighting. In the comparison of 2 populations of patients, provided data were available for the 2 populations in at least 3 studies; rate ratios (with their 95% CIs) were calculated in each study and then combined. If only 2 studies were available, the number of events and the number of patient-years of follow-up in each subgroup were directly combined to estimate overall event rates in the relevant population; these rates were then used to estimate rate ratios between subgroups. Calculations were produced using Comprehensive Meta-Analysis version 2.0 (Biostat, Englewood, New Jersey) and forest plots using MIX version 1.7 (http://www.meta-analysis-made-easy.com/).8

RESULTS

LITERATURE SEARCH

The literature search yielded 1089 references, from which 15 articles...
were eligible for the analysis. Details about the study selection procedure are given in Figure 1. Thirty-four of the 15 studies reported data for the 0- to 12-month interval and six for the 0- to 24-month interval. Seven studies reported raw data for the 0- to 24-month interval and 11 for the 0- to 12-month interval. Additional details are given in Table 1.

**PATIENT CHARACTERISTICS**

Table 1 provides the categories of patients enrolled in each study; Table 2 lists the definitions of surgical and nonsurgical trigger events as reported in the source studies. Additional information is given in Table 1.

Additional details are given in Table 1.

**CHARACTERISTICS OF THE QUALIFYING VTE**

Venous thromboembolism was symptomatic in all the studies. One study also included a small proportion (9%) of patients with asymptomatic DVT diagnosed by means of venographic screening after orthopedic surgery. The mode of presentation (eg, DVT or PE) of the index VTE was usually reported for the whole population in a study rather than for each subgroup of patients. In 4 studies that included 569 index VTEs provoked by a transient risk factor, 29% were proximal DVT, 5% were distal DVT, 33% were DVT of unspecified extent, 22% were PE without symptomatic DVT, and 11% were PE with symptomatic DVT.

**VTE PROVOKED BY ANY TRANSIENT RISK FACTOR**

During the first 12 months after stopping anticoagulant therapy, there were 96 recurrent VTEs in 2387 patients (2273 patient-years; 13 studies) who had an index VTE provoked by any transient risk factor, corresponding to an annualized event rate of 3.1% per patient-year (95% CI, 2.0%-4.2% per patient-year, random-effects model; Cochran Q, P = .02 and I² = 51% for heterogeneity) (Figure 2A). During the 0- to 24-month interval after stopping anticoagulant therapy, there were 150 recurrent VTEs in 2268 patients (4186 patient-years; 11 studies) who had an in-

### Table 1. Study and Patient Characteristics

<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>No. of Patients</th>
<th>VKAs Duration, mo</th>
<th>Nonsurgical Risk Factors</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schulman et al.1985</td>
<td>RCT</td>
<td>10</td>
<td>35</td>
<td>E E NA NA NA E NA NA NA E R R R NA</td>
<td></td>
</tr>
<tr>
<td>BTS,² 1992</td>
<td>RCT</td>
<td>56</td>
<td>298</td>
<td>3 R NA NA NA NA NA NA NA NA NA HA E E E 0.49</td>
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</tr>
<tr>
<td>Schulman et al.1995</td>
<td>RCT</td>
<td>167</td>
<td>287</td>
<td>6 NA NA NA NA NA NA NA NA NA NA NA NA NA E 0.43</td>
<td></td>
</tr>
<tr>
<td>Levine et al.1995</td>
<td>RCT</td>
<td>84</td>
<td>NA</td>
<td>3 E NA NA NA E NA NA NA NA NA NA NA NA NA 0.46</td>
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<tr>
<td>Hansson et al.2000</td>
<td>Obs</td>
<td>195</td>
<td>NA</td>
<td>6 R NA NA NA NA NA NA NA NA NA NA NA NA NA 0.53</td>
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</tr>
<tr>
<td>Palareti et al.2002</td>
<td>Obs</td>
<td>185</td>
<td>166</td>
<td>5 R R R NA NA NA NA NA NA NA NA NA R R R 0.50</td>
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<tr>
<td>Prandoni et al.2002</td>
<td>Obs</td>
<td>109</td>
<td>124</td>
<td>3-12 E E E NA NA E NA NA NA NA NA NA NA NA 0.53</td>
<td></td>
</tr>
<tr>
<td>Baglin et al.2003</td>
<td>Obs</td>
<td>377</td>
<td>193</td>
<td>3 R NA R R R R R R R R R R R R 0.56</td>
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<tr>
<td>Kearon et al.2004</td>
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<td>256</td>
<td>3-96 E E E NA E E E E E E 0.57</td>
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<tr>
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<td>75</td>
<td>107</td>
<td>7 NA NA NA NA NA NA NA NA NA NA NA NA NA 0.43</td>
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<td>Obs</td>
<td>130</td>
<td>142</td>
<td>6 NA E E E E E NA NA E NA NA NA 0.48</td>
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</tr>
</tbody>
</table>

Abbreviations: BTS, Research Committee of the British Thoracic Society; Obs, observational; OC/HRT, oral contraceptive/hormone therapy; RCT, randomized controlled trial; VKAs, vitamin K antagonists; VTE, venous thromboembolism.

R indicates that outcomes for subset data, or overall outcomes at 12 or 24 months, are directly reported; E, that outcomes for subset data, or overall outcomes at 12 and 24 months, are estimated from the reported data as detailed in the “Methods” subsection of the main text; and NA, that subset data or outcomes at 12 or 24 months were not available.

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VTE provoked by any transient risk factor, corresponding to an annualized event rate of 3.3% per patient-year (95% CI, 2.8%-3.9%) per patient-year, fixed-effects model; Cochran Q, P = .32 and I^2 = 13% for heterogeneity) (Figure 2B).

VTE PROVOKED BY SURGERY

During the first 12 months after stopping anticoagulant therapy, there were 2 recurrent VTEs in 243 patients (234 patient-years; 3 studies) with an index VTE provoked by surgery, corresponding to an annualized event rate of 1.0% per patient-year (95% CI, 0%-2.3% per patient-year, fixed-effects model; Cochran Q, P = .67 and I^2 = 0% for heterogeneity). During the 0- to 24-month interval after stopping anticoagulant therapy, there were 5 recurrent VTEs in 248 patients (443 patient-years; 3 studies) with an index VTE provoked by surgery, corresponding to an annualized event rate of 0.7% per patient-year (95% CI, 0%-1.5% per patient-year, fixed-effects model; Cochran Q, P = .33 and I^2 = 10% for heterogeneity).

VTE PROVOKED BY A NONSURGICAL FACTOR

During the first 12 months after stopping anticoagulant therapy, there were 20 recurrent VTEs in 385 patients (347 patient-years; 2 studies) with an index VTE provoked by a nonsurgical factor, corresponding to an annualized event rate of 5.8% per patient-year (95% CI, 3.2%-8.3% per patient-year, fixed-effects model; Cochran Q, P = .89 and I^2 = 0% for heterogeneity). During the 0- to 24-month interval after stopping anticoagulant therapy, there were 36 episodes of recurrent VTE in 509 patients (833 patient-years; 3 studies) with an index VTE provoked by a nonsurgical factor, corresponding to an annualized event rate of 4.2% per patient-year (95% CI, 2.8%-5.6% per patient-year, fixed-effects model; Cochran Q, P = .68 and I^2 = 0% for heterogeneity). The rate ratio for the recurrence of VTE provoked by a nonsurgical trigger compared with that provoked by recent surgery was 3.7 (95% CI, 0.9-15.3, fixed-effects model; Cochran Q, P = .45 and I^2 = 0% for heterogeneity) at 1 year (2 studies) and 3.0 (95% CI, 1.1-8.1, fixed-effects model; Cochran Q, P = .50 and I^2 = 0% for heterogeneity) at 2 years (3 studies).

STUDY DESIGN AND QUALITY

Analyses were performed to assess whether differences in study design and quality affected study findings and accounted for heterogeneity among studies. Eleven studies (2,4,6,9,11,12,15-18) prospectively categorized the qualifying VTE as provoked or unprovoked, whereas this categorization was done retrospectively in 4 studies. At 12 months, the recurrence rate after VTE provoked by a transient risk factor was 3.5% per patient-year (95% CI, 2.1%-4.9% per patient-year, random-effects model; Cochran Q, P = .03 and I^2 = 52% for heterogeneity) for prospective studies and 2.1% per patient-year (95% CI, 0.9%-3.4% per patient-year, fixed-effects model; Cochran Q, P = .38 and F = 2% for heterogeneity) for retrospective studies. The Cochran Q test for heterogeneity between studies of different design was not significant (P = .15). At 24 months, the annualized recurrence rate was 3.7% per patient-year (95% CI, 3.0%-4.3% per patient-year; Cochran Q, P = .55 and I^2 = 0% for heterogeneity) for prospective studies and 2.3% per patient-year (95% CI, 1.2%-3.4% per patient-year; Cochran Q, P = .73 and I^2 = 0% for heterogeneity) for retrospective studies. The Cochran Q test for heterogeneity between studies of different design was significant (P = .03).

Ten of the studies were prospective observational studies and 5 where randomized controlled trials. At 12 months, the recurrence rate after VTE provoked by a transient risk factor was 4.1% per patient-year (95% CI, 3.2%-5.6% per patient-year, fixed-effects model; Cochran Q, P = .08 and I^2 = 44% for heterogeneity) for observational studies and 1.5% per patient-year (95% CI, 0.3%-2.8% per patient-year, fixed-effects model; Cochran Q, P = .75 and I^2 = 0% for heterogeneity) for randomized controlled trials. The Cochran Q test for heterogeneity between studies of different design was not significant (P = .15). At 24 months, the annualized recurrence rate was 3.6% per patient-year (95% CI, 3.0%-4.0% per patient-year; Cochran Q, P = .52 and I^2 = 0% for heterogeneity) for prospective studies and 2.3% per patient-year (95% CI, 1.5%-3.0% per patient-year; Cochran Q, P = .66 and I^2 = 0% for heterogeneity) for retrospective studies. The Cochran Q test for heterogeneity between studies of different design was significant (P = .01).
heterogeneity between studies of different design was significant (P = .009). At 24 months, the annualized recurrence rate was 3.4% per patient-year (95% CI, 2.8%-4.0% per patient-year; Cochran Q, P = .25 and I² = 22% for heterogeneity) for observational studies and 2.5% per patient-year (95% CI, 0.8%-4.2% per patient-year; Cochran Q, P = .56 and I² = 0% for heterogeneity) for randomized controlled trials. The Cochran Q test for heterogeneity between studies of different design was not significant (P = .38).

UNPROVOKED VTE

Patients with unprovoked VTE were enrolled in 11 of the 15 studies (Table 1). During the first 12 months after stopping anticoagulant therapy, there were 216 recurrent VTEs in 2357 patients (2228 patient-years; 9 studies) with unprovoked VTE, corresponding to an annualized event rate of 7.9% per patient-year (95% CI, 4.9%-10.9% per patient-year, random-effects model; Cochran Q, P < .001 and I² = 84% for heterogeneity). During the 0- to 24-month interval after stopping anticoagulant therapy, there were 321 recurrent VTEs in 2174 patients (3899 patient-years; 9 studies) corresponding to an annualized event rate of 7.4% per patient-year (95% CI, 6.5%-8.2% per patient-year, random-effects model; Cochran Q, P < .001 and I² = 76% for heterogeneity). The recurrence rate was 8.2% per patient-year in studies that prospectively categorized patients as having unprovoked VTE and 4.9% per patient-year in studies that did this retrospectively (Cochran Q, P = .04). The rate ratio of recurrence after unprovoked VTE compared with (1) all patients with VTE provoked by a transient risk factor was 2.5 (95% CI, 2.0-3.2, fixed-effects model; Cochran Q, P = .99 and I² = 0% for heterogeneity) (9 studies) at 1 year and 2.3 (95% CI, 1.9-2.8; Cochran Q, P < .001 and I² = 76% for heterogeneity) at 2 years; (2) patients with a VTE provoked by surgery was 7.9 (95% CI, 2.2-28.7) at 1 year (1 study) and 10.6 (95% CI, 3.4-32.5) at 2 years (2 studies); and (3) patients with VTE provoked by a nonsurgical risk factor was 1.4 (95% CI, 0.9-2.2) at 1 year (1 study) and 1.8 (95% CI, 1.2-2.5) at 2 years (2 studies).

This analysis estimated that the rate of recurrence after stopping treatment in patients with symptomatic index VTE provoked by a transient risk factor was 3.3% during the first year and 6.6% during the first 2 years. In patients with index VTE provoked by a transient risk factor, the risk of recurrence was much lower (about one third) if VTE was provoked by surgery than if it was provoked by a nonsurgical factor. The highest risk of recurrence was in patients with unprovoked VTE, who had a risk of recurrence that was approximately 2.5-fold that of all patients with VTE provoked by a transient risk factor, 7-fold that of patients with VTE provoked by a transient risk factor.
voked by surgery, and 1.5-fold that of patients with VTE provoked by a non-surgical trigger.

This analysis has strengths and weaknesses. Strengths include that a thorough literature search was performed to ensure that all relevant studies were included in the analysis; only prospective studies that had satisfied predefined methodological criteria were included; data were independently extracted by 2 of us (A.I. and E.F.), which reduced the risk of error; and individual patient preferences were considered when deciding on the duration of anticoagulant therapy for VTE; the risk of recurrence during anticoagulant therapy, cost of therapy, and individual patient preferences (ie, burden of therapy and fear of recurrence or bleeding) also affect this decision.

In conclusion, we confirm that there is a low risk of recurrence after stopping anticoagulant therapy in patients with symptomatic VTE provoked by a reversible risk factor and a low risk of recurrence when VTE was provoked by recent surgery. Although the risk of recurrence was higher if VTE was associated with a nonsurgical risk factor than if it was associated with recent surgery, this risk was lower than in patients with unprovoked VTE and still seems to be low enough to justify stopping anticoagulant therapy at 3 months in most such patients.

Author Contributions: Study concept and design: Iorio, Kearon, and Palareti. Acquisition of data: Iorio, Filippucci, Macura, and Palareti. Analysis and interpretation of data: Iorio, Kearon, Marcucci, Pengo, Siragusa, and Palareti. Drafting of the manuscript: Iorio, Kearon, Macura, and Palareti. Critical revision of the manuscript for important intellectual content: Iorio, Kearon, Filippucci, Macura, Pengo, Siragusa, and Palareti. Statistical analysis: Iorio and Marcucci. Administrative, technical, and material support: Filippucci, Macura, Pengo, and Palareti. Study supervision: Iorio, Kearon, and Siragusa.

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Current recommendations are to treat patients with VTE provoked by a transient risk factor, including those with VTE provoked by a nonsurgical trigger, for 3 months. The rate of recurrence of 5.7% in the first year and 8.4% in the first 2 years in patients with VTE provoked by a transient nonsurgical factor, although substantially higher than the rate in patients with VTE provoked by surgery, is still supportive of this practice. The findings from this analysis may also be helpful in the management of patients with unprovoked VTE.

We suggest that whether using clinical or laboratory markers, it was possible to identify subgroups of patients with unprovoked proximal DVT or PE with a risk of recurrence that was similar to, or less than, that in patients with VTE provoked by a nonsurgical factor (eg, approximately 5% after 1 year and 8% after 2 years); anticoagulant therapy could also be stopped in these patients after 3 months of treatment. However, we acknowledge that the risk of recurrence after stopping anticoagulant therapy is only one factor that needs to be considered when deciding on the duration of anticoagulant therapy for VTE; the risk of bleeding during anticoagulant therapy, cost of therapy, and individual patient preferences (ie, burden of therapy and fear of recurrence or bleeding) also affect this decision.


