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.1

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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.2–6 For this reason, patients with VTE provoked by a transient risk factor are usually treated with anticoagulant agents for 3 months,1 whereas patients with VTE that was not associated with a transient risk factor are often treated long-term.1 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.6

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.

**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 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**

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.

**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. A fixed-effects or a random-effects model was used depending on whether heterogeneity was present (Cochran Q $\chi^2$ with $P>.05$ or $I^2<50%$), 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/).

**RESULTS**

**LITERATURE SEARCH**

The literature search yielded 1089 references, from which 15 articles...
were eligible for the analysis.\textsuperscript{2,6,9-18} Details about the study selection procedure are given in Figure 1. Thirteen\textsuperscript{2,6,9,10,12-16,18} of the 15 studies reported data for the 0- to 12-month interval and 11\textsuperscript{4-6,9-11,14-18} reported data for the 0- to 24-month interval. Seven studies\textsuperscript{2,3,6,9-12} reported raw interval and 11\textsuperscript{4-6,9-11,14-18} reported data for the 0- to 12-month studies.\textsuperscript{4,5,13-18} 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.

CHARACTERISTICS OF THE QUALIFYING VTE

Venous thromboembolism was symptomatic in all the studies. One study\textsuperscript{12} 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\textsuperscript{2,3,9,12} 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\textsuperscript{4-6,9,10,12-16,18}) 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 $I^2=51\%$ 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\textsuperscript{4-6,9,11,13-18}) who had an...
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 I²=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 studies5,6,10) 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 I²=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 studies5,6,10) 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 I²=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 studies5,6) 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 I²=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 studies5,6,10) 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 I²=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 I²=0% for heterogeneity) at 1 year (2 studies5,6) and 3.0 (95% CI, 1.1-8.1, fixed-effects model; Cochran Q, P = .50 and I²=0% for heterogeneity) at 2 years (3 studies5,6,10).

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 studies2,4,6,9,11,12,15-18 prospectively categorized the qualifying VTE as provoked or unprovoked, whereas this categorization was done retrospectively in 4 studies.5,10,13,14 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 I²=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 I²=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 I²=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 I²=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 studies5,6,10,11,13,18 and 5 where randomized controlled trials2,4,9,12 At 12 months, the recurrence rate after VTE provoked by a transient risk factor was 4.1% per patient-year (95% CI, 3.2%-5.0% per patient-year, fixed-effects model; Cochran Q, P = .08 and I²=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 I²=0% for heterogeneity) for randomized controlled trials. The Cochran Q test for heterogeneity between studies of different design was not significant (P=.15).
COMMENT

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 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 studies6,9,10,11,14,16-18), 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 studies6,9,10,11,14,16-18) at 1 year and 2.3 (95% CI, 1.9-2.8; Cochran Q, P = .93 and I² = 0% for heterogeneity) (9 studies6,9,10,11,14,16-18) at 2 years; (2) patients with a VTE provoked by surgery was 7.9 (95% CI, 2.2-28.7) at 1 year (1 study6) and 10.6 (95% CI, 3.4-32.5) at 2 years (2 studies6,10); and (3) patients with VTE provoked by a nonsurgical risk factor was 1.4 (95% CI, 0.9-2.2) at 1 year (1 study6) and 1.8 (95% CI, 1.2-2.5) at 2 years (2 studies6,10).

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 studies6,9,10,11,14,16-18) 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 studies6,9,10,11,14,16-18), 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 studies6,9,10,11,14,16-18) at 1 year and 2.3 (95% CI, 1.9-2.8; Cochran Q, P = .93 and I² = 0% for heterogeneity) (9 studies6,9,10,11,14,16-18) at 2 years; (2) patients with a VTE provoked by surgery was 7.9 (95% CI, 2.2-28.7) at 1 year (1 study6) and 10.6 (95% CI, 3.4-32.5) at 2 years (2 studies6,10); and (3) patients with VTE provoked by a nonsurgical risk factor was 1.4 (95% CI, 0.9-2.2) at 1 year (1 study6) and 1.8 (95% CI, 1.2-2.5) at 2 years (2 studies6,10).
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 analy-
sis; only prospective studies that had
satisfied predefined methodological
criteria were included; data were in-
dependently extracted by 2 of us (A.I.
and E.F.), which reduced the risk of
errors; data from individual studies
were combined using appropriate
meta-analytic techniques; and the
analysis includes only patients who
had symptomatic VTE (ie, it does not
include asymptomatic DVT de-
tected by screening after surgery).
Weaknesses include that (1) the defi-
nitions of provoked and unpro-
voked VTE differed among studies;
(2) many studies did not subdivide
provoked VTE into surgical and non-
surgical groups and, consequently, the
precision of the estimates for these
subgroups is reduced; moreover, pa-
tients in the nonsurgical group are
expected to be heterogeneous (eg, mi-
nor trauma, medical illness), and the
risk of recurrence may differ among
these patients; (3) many studies did not enroll consecutive patients with
provoked VTE, and, consequently, the
patients in this analysis may not be
fully representative. The observa-
tion that some recurrence rates dif-
fered according to whether the qual-
ifying episode of VTE was pro-
spectively rather than retrospec-
tively categorized as being due to a
temporary risk factor, and in observa-
tional studies compared with ran-
donized trials, suggests that differ-
ences in study design may have
contributed to heterogeneity of find-
ings among studies. Because we did
not include studies of patients with
unprovoked VTE that did not also in-
clude patients with VTE provoked by
a transient risk factor, the estimate for
the rate of recurrence in patients with
unprovoked VTE may be less reli-
able. Evidence suggests that factors
such as patient sex, presence of post-
thrombotic syndrome, and D-dimer
levels after stopping anticoagulant
therapy may help predict an indi-
nual patient’s risk of recurrent VTE
after stopping therapy.10,20 We did not
assess the effect of these factors in the
present analysis; however, we note
that an association between such risk
factors and risk of recurrence has been
observed in patients with unpro-
voked VTE and not in those with pro-
voked thrombosis.18,21

Current recommendations are to
treat patients with VTE provoked by
a transient risk factor, including
those with VTE provoked by a non-
surgical trigger, for 3 months.1 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, al-
though 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 un-
provoked VTE.22

We suggest that whether using
clinical or laboratory markers, it was
possible to identify subgroups of pa-
tients with unprovoked proximal
DVT or PE with a risk of recur-
rence that was similar to, or less
than, that in patients with VTE pro-
voked 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 treat-
ment. However, we acknowledge that
the risk of recurrence after stop-
ning anticoagulant therapy is only
one factor that needs to be consid-
ered when deciding on the dura-
tion of anticoagulant therapy for
VTE; the risk of bleeding during ant-
icoagulant therapy, cost of therapy,
and individual patient preferences
(ie, burden of therapy and fear of re-
currence or bleeding) also affect this
decision.

In conclusion, we confirm that
there is a low risk of recurrence af-
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 sur-
gery. Although the risk of recur-
rence was higher if VTE was asso-
ciated 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 jus-
tify stopping anticoagulant therapy
at 3 months in most such patients.

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REFERENCES

GE, Comerota AJ; American College of Chest Physi-
cians. Antithrombotic therapy for venous throm-
boembolic disease: American College of Chest
Physicians Evidence-Based Clinical Practice Guide-
WWW.ARCHINTERNMED.COM

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