REVIEW ARTICLE

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 do 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-

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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 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

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.[7] A fixed-effects or a random-effects model was used depending on whether heterogeneity was present (Cochran Q χ^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/).[8]

RESULTS

LITERATURE SEARCH

The literature search yielded 1089 references, from which 15 articles

were eligible for the analysis.[2-6,9-18] Details about the study selection procedure are given in **Figure 1**. Thirteen[2-6,9,10,12-16,18] of the 15 studies reported data for the 0- to 12-month interval and 11[4-6,9-11,14-18] reported data for the 0- to 24-month interval. Seven studies[2,3,6,9-12] reported raw numbers of recurrent VTE events, and we estimated these data in 8 studies.[4,5,13-18] Additional details are given in **Table 1**.

PATIENT CHARACTERISTICS

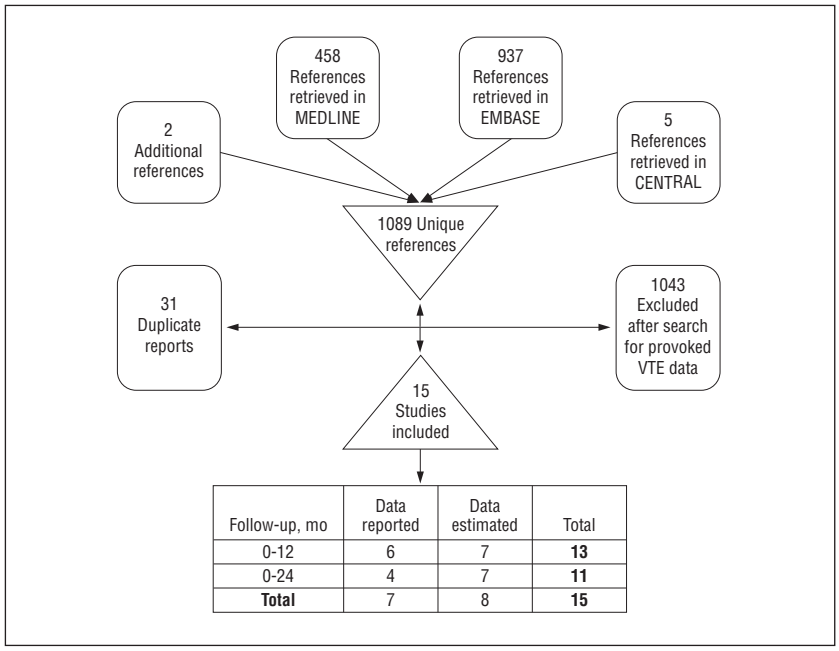
Table 1 provides the categories of patients enrolled in each study; **Table 2** lists the definitions of surgical and nonsurgical trigger events as reported in the source studies.

CHARACTERISTICS OF THE QUALIFYING VTE

Venous thromboembolism was symptomatic in all the studies. One study[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[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[2-6,9,10,12-16,18]) 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 2**A). During the 0- to 24-month interval after stopping anticoagulant therapy, there were 150 recurrent VTEs in 2268 patients (4186 patient-years; 11 studies[4-6,9-11,14-18]) who had an in-



Follow-up, mo	Data reported	Data estimated	Total
0-12	6	7	**13**
0-24	4	7	**11**
Total	7	8	**15**

Figure 1. Flowchart of the study selection procedure showing the number of references at each stage. The embedded table lists the number of studies providing data (reported or estimable) at the 2 follow-up lengths analyzed.

Table 1. Study and Patient Characteristics[a]

Source	Design	No. of Patients: Provoked VTE	No. of Patients: Unprovoked VTE	VKAs Duration, mo	Nonsurgical Risk Factors: Surgery	Trauma	Plaster	Medical Bed Rest	Pregnancy	Puerperium	OC/HRT	Outcome: At 12 mo	At 24 mo	Proportion Female
Schulman et al,[9] 1985	RCT	10	35	3-60	E	E	NA	NA	E	NA	NA	E	R	R	NA
BTS,[2] 1992	RCT	56	298	3	R	NA	NA	NA	NA	NA	NA	NA	R	NA	0.49
Schulman et al,[4] 1995	RCT	167	287	6	NA	NA	NA	NA	NA	NA	NA	NA	E	E	0.43
Levine et al,[3] 1995	RCT	84	NA	3	E	NA	NA	NA	E	NA	NA	NA	R	NA	0.45
Hansson et al,[5] 2000	Obs	195	NA	6	R	NA	NA	NA	R	R	NA	NA	E	E	0.53
Palareti et al,[10] 2002	Obs	185	166	5	R	R	R	NA	R	R	NA	R	R	R	0.50
Prandoni et al,[11] 2002	Obs	109	124	3-12	E	E	E	NA	NA	E	NA	E	NA	R	0.53
Baglin et al,[6] 2003	Obs	377	193	3	R	NA	R	R	R	R	R	R	R	R	0.56
Kearon et al,[12] 2004	RCT	81	NA	3	E	NA	E	NA	E	NA	NA	NA	R	NA	0.47
Cushman et al,[13] 2004	Obs	82	116	NA	NA	NA	NA	NA	NA	NA	NA	NA	R	NA	0.52
Christiansen et al,[14] 2005	Obs	215	256	3-96	E	E	E	NA	E	E	E	E	E	E	0.57
García-Fuster et al,[15] 2005	Obs	43	NA	6	E	NA	NA	NA	E	NA	NA	E	E	E	0.49
Prandoni et al,[16] 2007	Obs	762	864	3-36	E	E	E	E	NA	E	NA	E	R	E	0.55
Poli et al,[17] 2007	Obs	75	107	7	NA	NA	NA	NA	NA	NA	NA	NA	NA	E	0.43
Baglin et al,[18] 2008	Obs	130	142	6	NA	E	E	E	E	NA	NA	E	NA	E	0.48

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.

[a] "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.

dex 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[2,5,6]) with 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[5,6,10]) 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 $I^2=10\%$ 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[5,6]) 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 $I^2=0\%$ 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[5,6,10]) 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 $I^2=0\%$ 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, 0.9-15.5, fixed-effects model; Cochran Q, $P=.45$ and $I^2=0\%$ for heterogeneity) at 1 year (2 studies[5,6]) 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[5,6,10]).

Table 2. Definition of Provoked and Unprovoked Index VTE Events in the Source Studies

Surgical Provoking Factors
Orthopedic, general, urologic, or gynecologic surgery[3]
Abdominal, orthopedic, or other major surgery within 3 mo[5]
Surgery within 3 mo[11,14]
Surgery in the previous 6 wk[6]
Surgery with general anesthesia >30 minutes within 8 wk[12]
Having had VTE associated with surgery without describing the type of surgery and the interval between surgery and when VTE was diagnosed[2,4,9,10,13,15-18]
Nonsurgical Provoking Factors
Various forms of immobilization within 7 d before a DVT diagnosis (trauma, traveling, plaster on a leg, bedridden because of acute infectious disease), pregnancy, post partum[5]
Pregnancy or childbirth, estrogen use for contraception or hormone therapy (ongoing or interrupted for <1 mo), recent trauma, fracture within 3 mo[11]
Pregnancy, postpartum events up to 2 mo after delivery, fracture, plaster cast, estrogen-containing oral contraceptive use, immobilization, nonspecific transient illness, history of travel[6]
Fracture or plaster casting of a lower limb, hospitalization with confinement to bed for 3 consecutive days within 8 wk[12]
Major trauma, marked immobility within 90 d[13]
Pregnancy, puerperium, use of an oral contraceptive within 30 d, or trauma, immobilization, or use of a plaster cast within 3 mo[14]
Pregnancy or having given birth in the previous 3 mo, estrogen use, recent (< 3 mo) leg trauma, fracture, or bedridden for >1 wk because of a chronic medical illness[16]
Fracture, application of a plaster cast, use of estrogen-containing oral contraceptives, immobilization (≥3 d), nonspecific transient illness with immobilization for ≥3 d, or history of travel (>6 h continuous air flight or road travel within 1 wk of onset of symptoms)[18]
Having had VTE associated with a nonsurgical illness without describing the type of illness and how long it occurred before diagnosis[2-4,9,10,15,17]

Abbreviations: DVT, deep venous thrombosis; VTE, venous thromboembolism.

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.[3,10,13,14] 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 $I^2=52\%$ 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 $I^2=2\%$ 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[5,6,10,11,13-18] and 5 where randomized controlled trials.[2-4,9,12] 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 $I^2=44\%$ 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

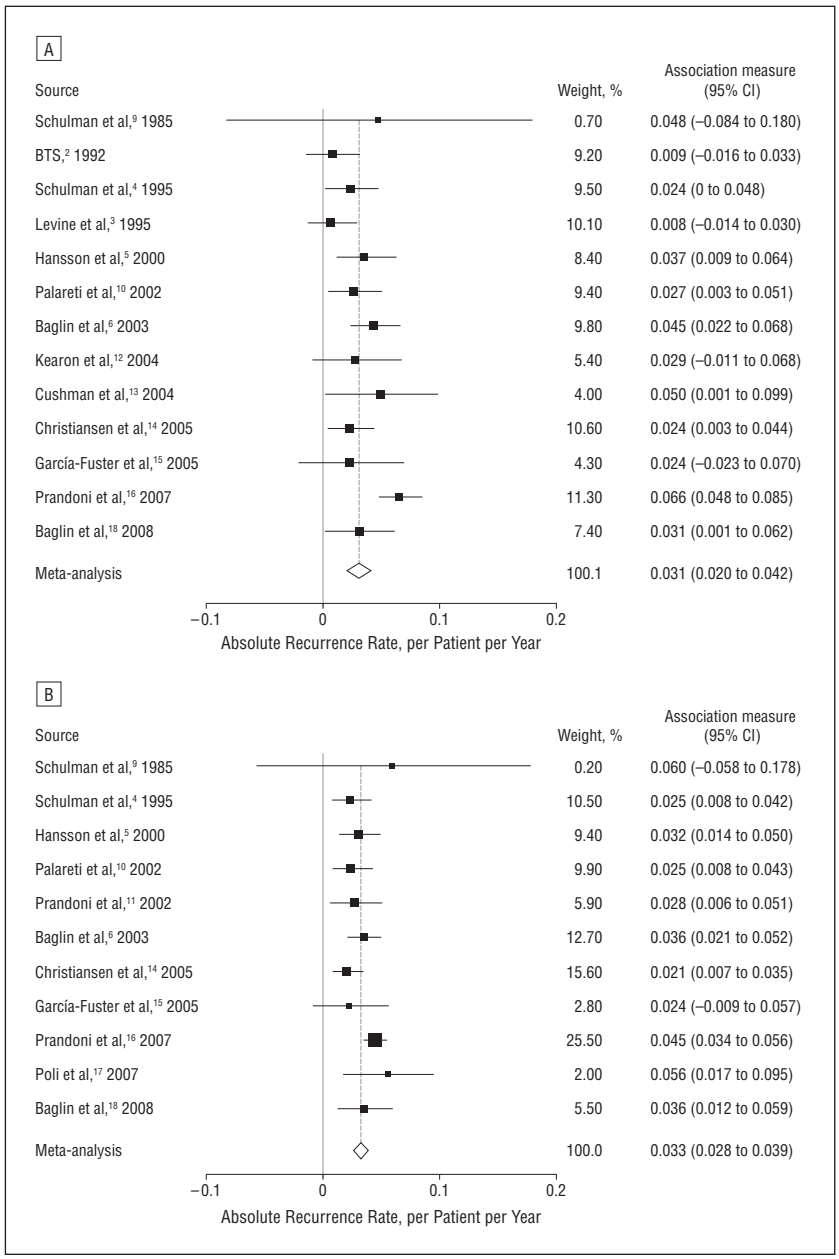


Figure 2. Recurrence rates of venous thromboembolism during the first year (A) and the first 2 years (B) after stopping anticoagulant therapy in all patients with an index venous thromboembolism provoked by a transient risk factor. Recurrence rates are calculated for individual studies and are pooled across studies. Recurrence rates are per patient per year (ie, 0.1 corresponds to 10% of patients per year). BTS indicates Research Committee of the British Thoracic Society; CI, confidence interval; diamonds, pooled recurrence rate; dashed line, mean pooled recurrence rate.

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 $I^2=22\%$ 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 $I^2=0\%$ 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[2,4,6,9,10,13,14,16,18]) 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 $I^2=84\%$ 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[4,6,9-11,14,16-18]), 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 $I^2=76\%$ 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 $I^2=0\%$ for heterogeneity) (9 studies[2,4,6,9,10,13,14,16,18]) at 1 year and 2.3 (95% CI, 1.9-2.8; Cochrane Q, $P=.93$ and $I^2=0\%$ for heterogeneity) (9 studies[4,6,9-11,14,16-18]) at 2 years; (2) patients with a VTE provoked by surgery was 7.9 (95% CI, 2.2-28.7) at 1 year (1 study[6]) and 10.6 (95% CI, 3.4-32.5) at 2 years (2 studies[6,10]); and (3) patients with VTE provoked by a nonsurgical risk factor was 1.4 (95% CI, 0.9-2.2) at 1 year (1 study[6]) and 1.8 (95% CI, 1.2-2.5) at 2 years (2 studies[6,10]).

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 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 pro-

voked by surgery, and 1.5-fold that of patients with VTE provoked by a nonsurgical 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 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 detected by screening after surgery). Weaknesses include that (1) the definitions of provoked and unprovoked VTE differed among studies; (2) many studies did not subdivide provoked VTE into surgical and nonsurgical groups and, consequently, the precision of the estimates for these subgroups is reduced; moreover, patients in the nonsurgical group are expected to be heterogenous (eg, minor trauma, medical illness), and the risk of recurrence may differ among these patients; (3) many studies[2-4,9] did not enroll consecutive patients with provoked VTE, and, consequently, the patients in this analysis may not be fully representative. The observation that some recurrence rates differed according to whether the qualifying episode of VTE was prospectively rather than retrospectively categorized as being due to a transient risk factor, and in observational studies compared with randomized trials, suggests that differences in study design may have contributed to heterogeneity of findings among studies. Because we did not include studies of patients with unprovoked VTE that did not also include patients with VTE provoked by a transient risk factor, the estimate for the rate of recurrence in patients with unprovoked VTE may be less reliable. Evidence suggests that factors such as patient sex, presence of postthrombotic syndrome, and D-dimer levels after stopping anticoagulant therapy may help predict an individual patient's risk of recurrent VTE after stopping therapy.[19,20] 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 unprovoked VTE and not in those with provoked thrombosis.[18,21]

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.[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, 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.[22]

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.

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.

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