Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: systematic review and meta-analysis

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ABSTRACT

OBJECTIVES
To determine the rate of a first recurrent venous thromboembolism (VTE) event after discontinuation of anticoagulant treatment in patients with a first episode of unprovoked VTE, and the cumulative incidence for recurrent VTE up to 10 years.

DESIGN
Systematic review and meta-analysis.

DATA SOURCES
Medline, Embase, and the Cochrane Central Register of Controlled Trials (from inception to 15 March 2019).

STUDY SELECTION
Randomised controlled trials and prospective cohort studies reporting symptomatic recurrent VTE after discontinuation of anticoagulant treatment in patients with a first unprovoked VTE event who had completed at least three months of treatment.

DATA EXTRACTION AND SYNTHESIS
Two investigators independently screened studies, extracted data, and appraised risk of bias. Data clarifications were sought from authors of eligible studies. Recurrent VTE events and person years of follow-up after discontinuation of anticoagulant treatment were used to calculate rates for individual studies, and data were pooled using random effects meta-analysis. Sex and site of initial VTE were investigated as potential sources of between study heterogeneity.

RESULTS
18 studies involving 7515 patients were included in the analysis. The pooled rate of recurrent VTE per 100 person years after discontinuation of anticoagulant treatment was 10.3 events (95% confidence interval 8.6 to 12.1) in the first year, 6.3 (5.1 to 7.7) in the second year, 3.8 events/year (95% confidence interval 3.2 to 4.5) in years 3-5, and 3.1 events/year (1.7 to 4.9) in years 6-10. The cumulative incidence for recurrent VTE was 16% (95% confidence interval 13% to 19%) at 2 years, 25% (21% to 29%) at 5 years, and 36% (28% to 45%) at 10 years. The pooled rate of recurrent VTE per 100 person years in the first year was 11.9 events (9.6 to 14.4) for men and 8.9 events (6.8 to 11.3) for women, with a cumulative incidence for recurrent VTE of 41% (28% to 56%) and 29% (20% to 38%), respectively, at 10 years. Compared to patients with isolated pulmonary embolism, the rate of recurrent VTE was higher in patients with proximal deep vein thrombosis (rate ratio 1.4, 95% confidence interval 1.1 to 1.7) and in patients with pulmonary embolism plus deep vein thrombosis (1.5, 1.1 to 1.9). In patients with distal deep vein thrombosis, the pooled rate of recurrent VTE per 100 person years was 1.9 events (95% confidence interval 0.5 to 4.3) in the first year after anticoagulation had stopped. The case fatality rate for recurrent VTE was 4% (95% confidence interval 2% to 6%).

CONCLUSIONS
In patients with a first episode of unprovoked VTE who completed at least three months of anticoagulant treatment, the risk of recurrent VTE was 10% in the first year after treatment, 16% at two years, 25% at five years, and 36% at 10 years, with 4% of recurrent VTE events resulting in death. These estimates should inform clinical practice guidelines, enhance confidence in counselling patients of their prognosis, and help guide decision making about long term management of unprovoked VTE.

SYSTEMATIC REVIEW REGISTRATION
PROSPERO CRD42017056309.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Anticoagulant treatment is highly effective at reducing the risk of recurrent venous thromboembolism (VTE) after a first episode of unprovoked VTE, but this clinical benefit is not maintained once anticoagulation is discontinued

Deciding whether patients with a first unprovoked VTE should stop or continue anticoagulation indefinitely requires balancing the long term risks of recurrent VTE if anticoagulation is stopped and major bleeding if treatment is continued

The long term risk of recurrent VTE after discontinuing anticoagulation in patients with first unprovoked VTE is uncertain

WHAT THIS STUDY ADDS

In this meta-analysis of 18 studies involving 7515 patients with a first unprovoked VTE, the risk of recurrent VTE after discontinuing anticoagulation was 10% in the first year, 16% at two years, 25% at five years, and 36% at 10 years, with 4% of recurrent events resulting in death

These findings provide patients, clinicians, and policymakers with reliable estimates for the long term risks and consequences of recurrent VTE to help guide decision making about long term management of unprovoked VTE

Introduction

For patients with unprovoked venous thromboembolism (VTE), comprising deep vein thrombosis and pulmonary embolism, the optimal duration of anticoagulant treatment is uncertain. After three to six months of initial anticoagulation, extended treatment is highly effective at reducing the risk of recurrent VTE,[1] but this clinical benefit is not maintained when anticoagulation is stopped.[2] After discontinuation of anticoagulant treatment, patients with a first unprovoked VTE have a much higher risk of recurrence compared with patients with VTE provoked by a major transient risk factor.[3-5] Consequently, anticoagulant treatment is discontinued after three to six months in patients with VTE due to a major transient provoking factor, whereas current guidelines suggest extended (ie, indefinite) anticoagulation in patients with unprovoked proximal deep vein thrombosis or pulmonary embolism who have a non-high bleeding risk.[6-8] This is, however, a weak (grade 2B) recommendation, in large part as a result of uncertainty in estimates of the long term risk of major bleeding if treatment is continued, and, importantly, the long term risk of recurrent VTE if anticoagulation is discontinued. Thus deciding whether patients with a first episode of unprovoked VTE should receive indefinite anticoagulation or can stop treatment after the initial three to six months, remains an important challenge.

A previous individual patient data meta-analysis[5] of 1732 patients with unprovoked VTE from six randomised trials, reported an overall risk of recurrent VTE of about 10% per year in the first two years after discontinuation of anticoagulation. That analysis did not assess the risk of recurrent VTE in men and women separately or in patients with isolated pulmonary embolism, and it only followed patients for 24 months. Furthermore, trials in that analysis were published before 2004, whereas since then additional prospective studies have reported on the risk for recurrent VTE after discontinuation of anticoagulant treatment in patients with a first episode of unprovoked VTE, with several of these studies having followed patients beyond 24 months and some up to 10 years.[9-13] This offers an opportunity to obtain reliable estimates of the long term risk of recurrent VTE and to assess how the risk varies over time—knowledge that is crucial for deciding the need for indefinite anticoagulation, as well as defining the burden of illness in this common patient population.

Methods

We formed the Meta-Analysis of the long term Risk of recurrent Venous thromboEmboLism after stopping anticOagulation for acute Unprovoked venous thromboemboliSm (MARVELOUS) collaboration to undertake a systematic review and meta-analysis to determine the rate of a first recurrent VTE event in the first year, in the second year, in years 3-5, and in years 6-10 after discontinuation of anticoagulant treatment for a first episode of unprovoked VTE, as well as the cumulative incidence for recurrent VTE at 2, 5, and 10 years.

The study protocol was developed using guidance from the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) statement,[14] registered in PROSPERO and published.[15] This systematic review and meta-analysis is reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[16]

Search strategy and study selection

In conjunction with a medical librarian, we conducted a comprehensive systematic search (from inception to 15 March 2019) of Embase, Medline, and the Cochrane Central Register of Controlled Trials. For these searches, we combined terms related to VTE and anticoagulant treatment with those related to study design, without language restrictions (Appendix table 1 shows the systematic search strategy used for Embase). We supplemented the electronic searches by hand searching reference lists of relevant review articles, and without consideration of grey literature. Two authors (FK, AR) independently screened titles, abstracts, and full text publications, and a third author (MAR) resolved discrepancies.

Randomised controlled trials and prospective observational cohort studies were included if they were published in a peer reviewed journal; they enrolled patients with a first episode of objectively confirmed, symptomatic VTE that was either unprovoked or associated with minor transient risk factors, as defined according to the International Society on Thrombosis and Haemostasis guidance (see box 1)[17]; patients had completed at least three months of initial anticoagulation before stopping treatment, and the decision to stop anticoagulation was not influenced by stratification of the risk of VTE recurrence (eg, negative D dimer test result, clinical decision rules); patients were followed-up for at least nine months after discontinuation of anticoagulant treatment; and symptomatic recurrent VTE (as defined in individual studies) events were reported during follow-up after discontinuation of anticoagulant treatment. When more than one article included the same population of patients (ie, duplication), we included the publication with the longest follow-up.

Data extraction and quality assessment

Using a standardised form, two authors (FK, AR) independently extracted data, with clarifications requested from the study's authors when necessary. Data were extracted on study design; number of eligible patients; average age of patients; percentage of men; number of eligible patients with isolated distal deep vein thrombosis (ie, in deep veins of the calf), proximal deep vein thrombosis (ie, in the popliteal, femoral, or iliac veins), and pulmonary embolism (with or without deep vein thrombosis); and the definition of unprovoked VTE. For the calculation of event rates, we requested the following from the authors: aggregate data on the number of recurrent VTE events (any

Box 1: International Society on Thrombosis and Haemostasis definition of unprovoked venous thromboembolism

VTE is defined as unprovoked if the following provoking risk factors are absent:

Persistent

Active cancer, defined as:
- cancer that has not received potentially curative treatment, or
- treatment is ongoing, or
- evidence that treatment has not been curative

Major transient

Surgery with general anaesthesia for more than 30 minutes

Confined to bed (only "bathroom privileges") for at least three days with an acute illness

Caesarean section

Minor transient

Surgery with general anaesthesia for less than 30 minutes

Admission to hospital for fewer than three days with an acute illness

Oestrogen treatment

Pregnancy or puerperium

Confined to bed out of hospital for at least three days with an acute illness

Leg injury associated with reduced mobility for at least three days

VTE, and subtypes deep vein thrombosis, pulmonary embolism, pulmonary embolism plus deep vein thrombosis, and fatal pulmonary embolism), and the total number of person years of follow-up during each of the specified intervals (to ensure appropriate censoring of deaths, patients lost to follow-up and those withdrawn from study). Patients who did not satisfy our eligibility criteria (eg, those with cancer or a second unprovoked VTE event) were not included in those aggregate data.

The same two authors independently assessed the risk of bias of studies. Since our objective was to establish pooled event rates after discontinuation of anticoagulant treatment, we evaluated all studies, including each arm of a randomised trial, as an independent observational cohort. As such, the risk of bias for each observational cohort was assessed using a modified version of the Newcastle-Ottawa scale score[18] based on three selection criteria and three outcome criteria only (criteria assessing comparability were considered irrelevant in the context of this systematic review and meta-analysis). Given data clarifications obtained from the authors of all included studies, we judged the risk of bias assessment not only at the published study level but also based on authors' clarifications. Following quality assessment standards of a previous meta-analysis,[19] we considered studies in our meta-analysis that met four or more of these Newcastle-Ottawa scale criteria to be of higher quality. A third author (MAR) resolved discrepancies.

Data synthesis and analysis

For each study cohort we calculated the rates of recurrent VTE, expressed as number of events per 100 person years, from the number of first recurrent VTE events divided by the person years of follow-up obtained from the authors of original studies and categorised by four time intervals after discontinuation of anticoagulant treatment when a first recurrence of VTE occurred: year 1 (0-12 months), year 2 (12-24 months), years 3-5, and years 6-10. We used random effects meta-analyses to pool rates from each study cohort, with cohorts weighted according to their inverse variance.[20] Given that we calculated rates of recurrent VTE in our analysis based on person time at risk accounting for deaths and other patient losses to follow-up, obtained from the authors of the included studies, during each of the studied intervals, we calculated the cumulative incidence for recurrent VTE at 2, 5, and 10 years after discontinuation of anticoagulation. To do this, we first determined the proportion of patients who did not experience recurrent VTE based on event rates during each of the intervals we studied. Then we determined the proportion of patients who did experience a recurrent VTE by multiplying the proportion of patients, in each year under consideration, who did not experience a recurrent VTE. For example, if the rate of recurrent VTE (per 100 person years) was 10 events in year 1, five events in year 2, and four events/year in years 3-5, then the proportion of patients who did not experience a recurrent VTE within five years=90.0% (year 1)×95.0% (year 2)×(96.0%)^3 (years 3, 4, and 5)=75.6%, resulting in a cumulative incidence for recurrent VTE of 24.4% five years after discontinuation of anticoagulant treatment.

We determined the upper and lower limits of the 95% confidence interval for cumulative incidence by performing the calculations described on the upper and lower limits of the 95% confidence interval of the event rates, respectively. For example, if the rate of recurrent VTE (per 100 person years) was 10.0 events (95% confidence interval 9.0 to 11.0) in year 1 and 5.0 events (4.0 to 6.0) in year 2, resulting in a two year cumulative incidence of 14.5%, then the 95% confidence interval of the cumulative incidence was calculated as follows: using the lower bound 95% confidence intervals of 9.0 events (year 1) and 4.0 events (year 2), the proportion of patients who did not experience a recurrent VTE within two years=91.0% (year 1)×96.0% (year 2)=87.4%, resulting in a lower bound 95% confidence interval for the cumulative incidence of 12.6%. Using the upper bound 95% confidence interval of 11.0 events (year 1) and 6.0 events (year 2), the proportion of patients who did not experience a recurrent VTE within two years=89.0% (year 1)×94.0% (year 2)=83.7%, resulting in an upper bound 95% confidence interval for the cumulative incidence of 16.3%.

Lastly, to measure the clinical impact of disease recurrence after discontinuation of anticoagulant treatment, we determined the case fatality rate of recurrent VTE from the total number of fatal recurrent pulmonary embolism events divided by the total number of recurrent VTE events.

Heterogeneity between studies was assessed using the I^2 statistic, with values of 75% or greater indicating substantial heterogeneity. All meta-analyses (with a requirement for at least three cohorts of patients)

were performed using StatsDirect Version 3 (Cheshire, UK).[21]

We performed sensitivity and subgroup analyses to investigate several potential sources of between study heterogeneity: cohorts with event rates that were outliers, cohorts randomised to receive aspirin after completing initial anticoagulant treatment, cohorts derived from randomised trials versus prospective observational studies, sex, and site of initial VTE.

Patient and public involvement
Patients were not involved in the design or conduct of the study. Patient partners in the CanVECTOR network (www.canvector.ca) will be involved in dissemination or knowledge translation activities, or both.

Results
Search results
Of the 1034 records identified by the literature search, 604 remained after removal of duplicates. Of these, 512 were excluded after screening of titles and abstracts, leaving 92 articles for full text screening. A further 68 articles were excluded after full text screening because they were neither a randomised controlled trial nor prospective cohort study, did not include patients with unprovoked VTE, did not systematically stop anticoagulation, did not have patient follow-up lasting for a minimum of nine months after discontinuation of anticoagulation, did not report on recurrent VTE after anticoagulation, or included duplicate patients from other included studies. Thus, 24 studies were identified as eligible for inclusion in the meta-analysis (fig 1). We requested data clarifications for person years of follow-up and recurrent VTE events during follow-up from the authors of the 24 eligible studies. Data clarifications were obtained for 18 of the studies. The remaining six studies[22-27] were excluded because the published manuscript did not provide the data required for our analysis.

Characteristics of included studies
Eighteen studies[2 9-13 28-39] with a total of 7515 patients were included in the analysis (fig 1). Four of the 18 studies were prospective observational cohort studies[11-13 31] and 14 were randomised controlled trials[2 9 28-30 32-39] (table 1). Fifteen studies[2 10-13 28-34 36 38 39] met the criteria for the International Society on Thrombosis and Haemostasis definition of unprovoked VTE or VTE associated with minor transient risk factors (table 1). All 18 studies with 24 independent observational cohorts followed patients for one year after discontinuation of anticoagulant treatment. Thirteen studies[2 9 10-13 28 31-33 35 36 39] (18 cohorts and 5078 patients) followed patients for two years, four studies[10 11 12 13] (four cohorts and 2638 patients) followed patients for five years, three studies[10 11 13] (three cohorts and 1975 patients) followed patients for 10 years after discontinuation of anticoagulation (table 1). All studies were of high quality according to the Newcastle-Ottawa scale (table 1). Appendix table 2 presents the components of the Newcastle-Ottawa scale score for all studies.

Recurrent VTE after anticoagulation
Table 2 presents the pooled person years of follow-up, number of events for recurrent VTE, deep vein thrombosis, pulmonary embolism, pulmonary embolism plus deep vein thrombosis, and fatal pulmonary embolism, as well as the corresponding rates and cumulative incidence for these outcomes. Appendix tables 3, 6, and 7 provide the results from individual study cohorts.

In the first year after discontinuation of anticoagulation, the pooled rate of recurrent VTE per 100 person years was 10.3 events (95% confidence interval 8.6 to 12.1; I^2=81%). The rate of recurrent VTE events per 100 person years for deep vein thrombosis was 6.2 (95% confidence interval 4.8 to 7.7; I^2=79%), for pulmonary embolism was 3.3 (2.4 to 4.2; I^2=68%), and for pulmonary embolism plus deep vein thrombosis was 0.3 (0.1 to 0.5; I^2=44%) (table 2).

In the second year after discontinuation of treatment, the pooled rate of recurrent VTE events per 100 person years was 6.3 (95% confidence interval 5.1 to 7.7; I^2=56%). The rate of recurrent VTE events per 100 person years for deep vein thrombosis was 3.7 (2.8 to 4.7; I^2=55%), for pulmonary embolism was 2.0 (1.4 to 2.6; I^2=36%), and for pulmonary embolism plus deep vein thrombosis was 0.2 (0.1 to 0.4; I^2=0%) (table 2).

In years 3-5 after discontinuation of treatment, the pooled rate of recurrent VTE per 100 person years was 3.8 events/year (95% confidence interval 3.2 to 4.5; I^2=24%). The recurrent VTE events annually per 100 person years for deep vein thrombosis was 2.5 (95% confidence interval 2.0 to 2.9; I^2=0%), for pulmonary embolism was 1.0 (0.4 to 1.8; I^2=83%), and for pulmonary embolism plus deep vein thrombosis was 0.1 (0.0 to 0.3; I^2=71%) (table 2).

During years 6-10 after discontinuation of treatment, the pooled rate of recurrent VTE per 100 person years was 3.1 events/year (95% confidence interval 1.7 to 4.9; I^2=84%). The recurrent VTE events annually per 100 person years for deep vein thrombosis was 2.2 (95% confidence interval 1.0 to 3.8; I^2=86%), for pulmonary embolism was 0.7 (0.2 to 1.6; I^2=79%), and 0.0 for pulmonary embolism plus deep vein thrombosis was 0.0 (0.0 to 0.1; I^2=0%) (table 2).

The cumulative incidence for recurrent VTE was 16.0% (95% confidence interval 13.3% to 18.8%) at 2 years, 25.2% (21.3% to 29.3%) at 5 years, and 36.1% (27.8% to 45.0%) at 10 years after discontinuation of anticoagulant treatment. The corresponding values for recurrent deep vein thrombosis were 9.7% (95% confidence interval 7.5% to 12.0%), 16.3% (12.9% to 19.5%), and 25.1% (17.2% to 33.7%), for recurrent pulmonary embolism were 5.2% (3.7% to 6.7%), 8.0% (4.0% to 11.6%), and 11.2% (5.9% to 18.4%), and for recurrent pulmonary embolism plus deep vein thrombosis were 0.5% (0.2% to 0.9%), 0.8% (0.2% to 1.8%), and 0.8% (0.2% to 2.3%) after discontinuation of anticoagulation (table 2).
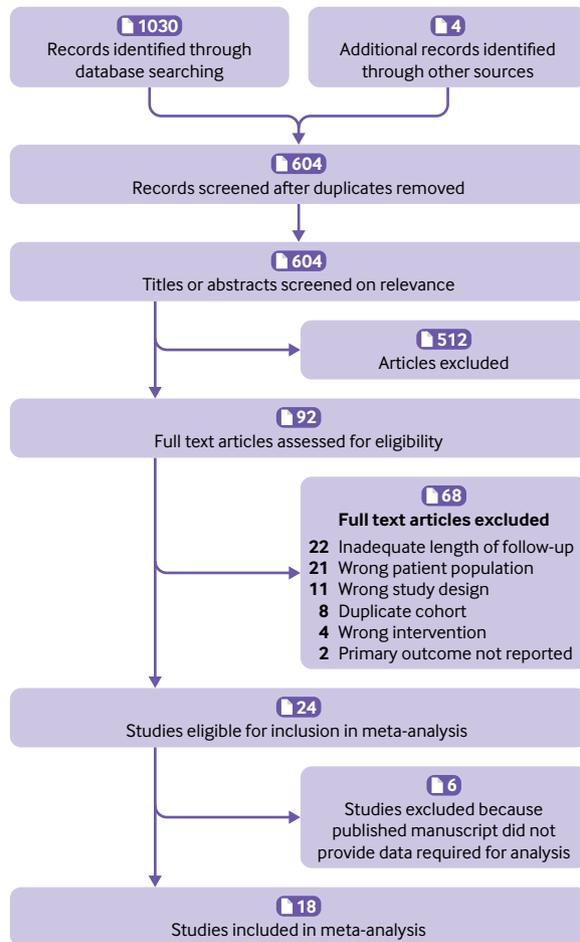
Fig 1 | Flow diagram of study identification and selection

The flow diagram contains the following boxes:

- 1030 Records identified through database searching
- 4 Additional records identified through other sources
- 604 Records screened after duplicates removed
- 604 Titles or abstracts screened on relevance
- 512 Articles excluded
- 92 Full text articles assessed for eligibility
- 68 Full text articles excluded
  - 22 Inadequate length of follow-up
  - 21 Wrong patient population
  - 11 Wrong study design
  - 8 Duplicate cohort
  - 4 Wrong intervention
  - 2 Primary outcome not reported
- 24 Studies eligible for inclusion in meta-analysis
- 6 Studies excluded because published manuscript did not provide data required for analysis
- 18 Studies included in meta-analysis

Fatal recurrent pulmonary embolism and case fatality rate of recurrent VTE

After discontinuation of anticoagulation, the pooled rate of fatal recurrent pulmonary embolism events per 100 person years was 0.4 (95% confidence interval 0.2 to 0.7; I^2=57%) in the first year, 0.3 (0.2 to 0.6; I^2=10%) in the second year, and 0.1 (95% confidence interval 0.0 to 0.3) in both years 3-5 (I^2=53%) and years 6-10 (I^2=0%) (table 2). The cumulative incidence for fatal recurrent pulmonary embolism was 0.7% (95% confidence interval 0.4% to 1.3%) at 2 years, 1.0% (0.4% to 2.2%) at 5 years, and 1.5% (0.4% to 3.6%) at 10 years (table 2).

Based on 17 studies involving 6864 patients with information available on both fatal recurrent pulmonary embolism (n=49) and recurrent VTE (n=1145), the pooled case fatality rate of recurrent VTE after discontinuation of anticoagulation was 3.8% (95% confidence interval 2.0% to 6.1%; I^2=59%) (fig 2), which remained constant over time (Appendix table 5).

Recurrent VTE according to sex

Among men with a first unprovoked VTE, the pooled rate of recurrent VTE per 100 person years after discontinuation of anticoagulation was 11.9 events (95% confidence interval 9.6 to 14.4; I^2=76%) in the first year, 7.3 events (5.3 to 9.5; I^2=63%) in the second year, 4.4 events/year (95% confidence interval 3.2 to 5.7; I^2=60%) in years 3-5, and 3.8 events/year (1.6 to 6.9; I^2=89%) in years 6-10 (table 3). The cumulative incidence for recurrent VTE in men was 18.3% (95% confidence interval 14.4% to 22.5%) at 2 years, 28.6% (22.3% to 35.0%) at 5 years, and 41.2% (28.4% to 55.6%) at 10 years (table 3).

Among women with a first unprovoked VTE, the pooled rate of recurrent VTE per 100 person years after discontinuation of anticoagulation was 8.9 events (95% confidence interval 6.8 to 11.3; I^2=72%) in the first year, 5.2 events (3.6 to 7.0; I^2=57%) in the second year, 3.0 events/year (95% confidence interval 1.6 to 4.7; I^2=74%) in years 3-5, and 2.0 events/year (1.3 to 2.9; I^2=0%) in years 6-10 (table 3). The cumulative incidence for recurrent VTE in women was 13.6% (95% confidence interval 10.1% to17.5%) at 2 years, 21.2% (14.4% to 28.6%) at 5 years, and 28.8% (19.8% to 38.4%) at 10 years (table 3).

Overall, men had 1.4 times the rate of recurrent VTE compared with women (rate ratio 1.4, 95% confidence interval 1.3 to 1.6, P<0.001) (see table 5).

Recurrent VTE according to site of initial VTE

In patients with a first unprovoked distal deep vein thrombosis, the pooled rate of recurrent VTE in the first year after discontinuation of anticoagulation was 1.9 events per 100 person years (95% confidence interval 0.5 to 4.3; I^2=0%) (table 4).

Among patients with a first unprovoked proximal deep vein thrombosis, the pooled rate of recurrent VTE in the first year after discontinuation of anticoagulation was10.6 events per 100 person years (8.1 to 13.3; I^2=73%). In the second year after treatment had stopped, the rate was 6.5 events per 100 person years (5.2 to 7.8; I^2=0%) (table 4). The cumulative two year incidence for recurrent VTE was 16.4% (95% confidence interval 12.9% to 20.1%) (table 4).

In patients with a first unprovoked isolated pulmonary embolism, the pooled rate of recurrent VTE in the first year after discontinuation of anticoagulation was 7.7 events per 100 person years (95% confidence interval 5.6 to 10.2; I^2=49%). In the second year after treatment had stopped, the rate was 4.5 events per 100 person years (2.6 to 6.8; I^2=45%) (table 4). The cumulative two year incidence for recurrent VTE was 11.9% (8.1% to 16.3%) (table 4).

Among those with pulmonary embolism plus deep vein thrombosis as the initial unprovoked VTE, the pooled rate of recurrent VTE in the first year after discontinuation of anticoagulation was 10.2 events per 100 person years (6.7 to 14.2; I^2=59%). In the second year after treatment had stopped, the rate was 7.6 events per 100 person years (4.7 to 11.2; I^2=23%) (table 4). The cumulative two year incidence for recurrent VTE was 17.0% (95% confidence interval 11.1% to 23.8%) (table 4).

Overall, patients with distal deep vein thrombosis had a lower rate of recurrent VTE compared to patients

Table 1 | Characteristics of studies included in meta-analysis

Source (year)	Study design	No of patients (n=7515)	Men (%)	Age (range or SD) (years)	No and site of initial VTE	Definition of unprovoked VTE (minor transient risk factors included)	Follow-up (years)*	Independent adjudication of outcomes	Overall Newcastle-Ottawa scale score (out of 6)
LAFIT: Kearon et al[28]	RCT	83	53.0	58 (16)	61 proximal DVT; 22 PE with or without DVT	International Society on Thrombosis and Haemostasis	2	Yes	6
WODIT-DVT: Agnelli et al[29]	RCT	133	61.2	67.7 (7.3)	133 proximal DVT	International Society on Thrombosis and Haemostasis	1	Yes	6
DOTAVK: Pinede et al[30]:	RCT	308			53 distal DVT; 145 proximal DVT; 18 PE; 92 PE plus DVT	International Society on Thrombosis and Haemostasis		Yes	6
Arm 1		161	47.6	58.2 (1.0)	30 distal DVT; 79 proximal DVT; 8 PE; 44 PE plus DVT		1		
Arm 2		147	47.0	58.9 (0.9)	23 distal DVT; 66 proximal DVT; 10 PE; 48 PE plus DVT		1		
Palareti et al[31]	Cohort	166	50.0	67 (12-91)	4 distal DVT; 137 proximal DVT; 25 PE plus DVT	International Society on Thrombosis and Haemostasis	2	Yes	6
WODIT-PE: Agnelli et al[32]	RCT	181			72 PE; 109 PE plus DVT	International Society on Thrombosis and Haemostasis		Yes	6
Arm 1		91	41.6	61.0 (15.5)	37 PE; 54 PE plus DVT		2		
Arm 2		90	39.4	62.9 (16.3)	35 PE; 55 PE plus DVT		2		
PREVENT: Ridker et al[9]	RCT	160	52.9	67.7 (7.3)	20 distal DVT with or without PE; 100 proximal DVT with or without PE; 40 unspecified VTE	Unprovoked VTE events were defined as those that did not occur within 90 days after surgery or trauma	2	Yes	6
DURAC I: Schulman et al[10]	RCT	272	61.4	60.6 (15.4)	234 DVT with or without PE; 38 PE	International Society on Thrombosis and Haemostasis	10	Yes	6
Prandoni et al[11]	Cohort	864	45.2	66.0 (16-96)	735 DVT with or without PE; 129 PE	International Society on Thrombosis and Haemostasis	10	Yes	6
AESOPUS: Prandoni et al[33]	RCT	151	57.6	69.0 (21-89)	151 proximal DVT	International Society on Thrombosis and Haemostasis	2	Yes	6
EINSTEIN-Extension: Bauersachs et al[34]	RCT	465	58.5	57.6 (16.2)	267 DVT; 144 PE; 46 PE plus DVT	International Society on Thrombosis and Haemostasis (oestrogen treatment; pregnancy and puerperium; leg trauma with transient impairment of mobility)	1	Yes	6
WARFASA: Becattini et al[35]	RCT	402			252 proximal DVT; 55 PE; 95 PE plus DVT			Yes	6
Arm 1		197	61.9	62.1 (15.1)	130 proximal DVT; 18 PE; 49 PE plus DVT	Unprovoked VTE events were defined as those that occurred in the absence of any known persistent or temporary risk factors for VTE	2		
Arm 2		205	65.8	61.9 (15.3)	122 proximal DVT; 37 PE; 46 PE plus DVT		2		
ASPIRE: Brighton et al[36]	RCT	822			468 proximal DVT; 231 PE; 114 PE plus DVT	International Society on Thrombosis and Haemostasis		Yes	6
Arm 1		411	54	54 (15.8)	232 proximal DVT; 119 PE; 59 PE plus DVT		2		
Arm 2		411	55	55 (16)	236 proximal DVT; 112 PE; 56 PE plus DVT		2		
RE-SONATE: Schulman et al[37]†	RCT	651	42.4	56.1 (15.5)	Not available	Patients were initially treated for more than 10 months	1	Yes	6
PADIS-PE: Couturaud et al[2]	RCT	371			259 PE; 112 PE plus DVT	International Society on Thrombosis and Haemostasis (oestrogen treatment)		Yes	6

Table 1 | Characteristics of studies included in meta-analysis

Source (year)	Study design	No of patients (n=7515)	Men (%)	Age (range or SD) (years)	No and site of initial VTE	Definition of unprovoked VTE (minor transient risk factors included)	Follow-up (years)*	Independent adjudication of outcomes	Overall Newcastle-Ottawa scale score (out of 6)
Arm 1		187	55.1	57.3 (17.4)	131 PE; 56 PE plus DVT		2		
Arm 2		184	42.5	58.7 (16)	128 PE; 56 PE plus DVT		2		
REVERSE I: Rodger et al[11]	Cohort	663	51.4	53.2 (18-95)	346 proximal DVT; 194 PE; 123 PE plus DVT	International Society on Thrombosis and Haemostasis (oestrogen treatment)	5	Yes	6
AUREC: Kyrle et al[12]	Cohort	839	66.0	53 (14)	154 distal DVT; 349 proximal DVT; 336 PE with or without DVT	International Society on Thrombosis and Haemostasis	10	Yes	6
EINSTEIN-Choice: Weitz et al[38]	RCT	880	56.7	58.4 (15.0)	442 proximal DVT; 295 PE; 139 PE plus DVT	International Society on Thrombosis and Haemostasis (oestrogen treatment; pregnancy and puerperium; lower limb trauma with transient impairment of mobility)	1	Yes	6
PADIS-DVT: Couturaud et al[39]	RCT	104			104 proximal DVT	International Society on Thrombosis and Haemostasis (oestrogen treatment)		Yes	6
Arm 1		54	72.2	61.5 (14.5)			2		
Arm 2		50	62.0	59.0 (17.2)			2		

DVT=deep vein thrombosis; PE=pulmonary embolism; RCT=randomised controlled trial.
*Duration of follow-up as applicable to intervals of 1, 2, 5, and 10 years after discontinuation of anticoagulation used in analysis.
†Data corresponds to post-treatment follow-up in dabigatran arm. Data during 12 months of follow-up in placebo arm of trial were not accessible.

with proximal deep vein thrombosis (rate ratio 0.2, 95% confidence interval 0.04 to 0.5, P<0.001), isolated pulmonary embolism (0.2, 0.05 to 0.7, P=0.009), as well as pulmonary embolism plus deep vein thrombosis (0.2, 0.03 to 0.5, P<0.001). Patients with proximal deep vein thrombosis had 1.4 times the rate of recurrent VTE of patients with isolated pulmonary embolism (1.4, 1.1 to 1.7, P=0.004), and 0.9 times the rate of recurrent VTE of patients with pulmonary embolism plus deep vein thrombosis (0.9, 0.7 to 1.2, P=0.47). Patients with pulmonary embolism plus deep vein thrombosis had 1.5 times the rate of recurrent VTE of patients with isolated pulmonary embolism (1.5, 1.1 to 1.9, P=0.005) (table 5).

Sensitivity analyses

Estimates of the rate of recurrent VTE events were not different in the overall and subgroup analyses excluding outliers or cohorts among included trials with participants randomised to receive aspirin after completing initial antaicoagulant treatment, as well as in cohorts derived from either randomised trials or prospective observational studies (Appendix tables 3, 4, 6, and 7).

Discussion

In this meta-analysis of 7515 patients with a first unprovoked venous thromboembolism (VTE) event who had completed at least three months of

Table 2 | Risk of recurrent venous thromboembolism (VTE) after discontinuation of anticoagulation in patients with a first unprovoked VTE event

Interval after anticoagulation	Person years of follow-up	Recurrent events					Event rate per 100 person years*				
		VTE	DVT	PE	PE+DVT	Fatal PE	VTE	DVT	PE	PE+DVT	Fatal PE
1st year	6678.0	644	350	194	20	28	10.3 (8.6 to 12.1); 81, <0.001	6.2 (4.8 to 7.7); 79, <0.001	3.3 (2.4 to 4.2); 68, <0.001	0.3 (0.1 to 0.5); 44, 0.008	0.4 (0.2 to 0.7); 57, <0.001
2nd year	3906.0	262	151	82	7	12	6.3 (5.1 to 7.7); 56, 0.002	3.7 (2.8 to 4.7); 55, 0.003	2.0 (1.4 to 2.6); 36, 0.07	0.2 (0.1 to 0.4); 0, 0.63	0.3 (0.2 to 0.6); 10, 0.34
2 year cumulative incidence, % (95% CI)							16.0 (13.3 to 18.8)	9.7 (7.5 to 12.0)	5.2 (3.7 to 6.7)	0.5 (0.2 to 0.9)	0.7 (0.4 to 1.3)
Years 3-5	4772.0	182	116	54	5	6	3.8 (3.2 to 4.5); 24, 0.27	2.5 (2.0 to 2.9); 0, 0.59	1.0 (0.4 to 1.8); 83, <0.001	0.1 (0.0 to 0.3); 71, 0.02	0.1 (0.0 to 0.3); 53, 0.09
5 year cumulative incidence, % (95% CI)							25.2 (21.3 to 29.3)	16.3 (12.9 to 19.5)	8.0 (4.0 to 11.6)	0.8 (0.2 to 1.8)	1.0 (0.4 to 2.2)
Years 6-10	3023.4	99	67	27	0	3	3.1 (1.7 to 4.9); 84, <0.001	2.2 (1.0 to 3.8); 86, <0.001	0.7 (0.2 to 1.6); 79, 0.009	0.0 (0.0 to 0.1); 0, 1.00	0.1 (0.0 to 0.3); 0, 0.37
10 year cumulative incidence, % (95% CI)							36.1 (27.8 to 45.0)	25.1 (17.2 to 33.7)	11.2 (5.9 to 18.4)	0.8 (0.2 to 2.3)	1.5 (0.4 to 3.6)

DVT=deep vein thrombosis; PE=pulmonary embolism.
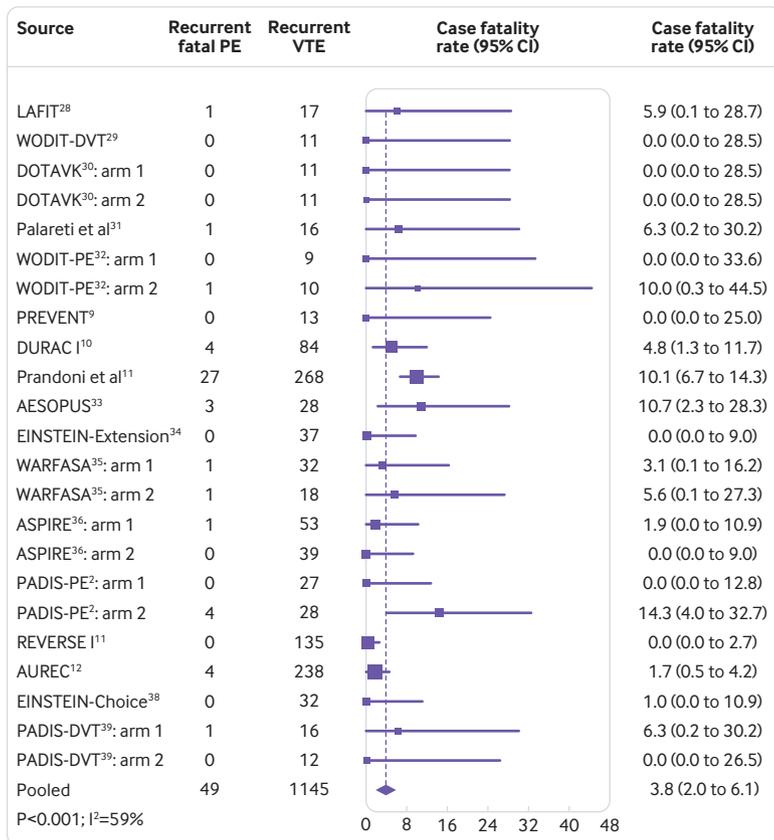*Data are event rate (95% CI); I^2 (%), P value unless stated otherwise. P value is for heterogeneity.

Source	Recurrent fatal PE	Recurrent VTE	Case fatality rate (95% CI)	Case fatality rate (95% CI)
LAFIT[28]	1	17		5.9 (0.1 to 28.7)
WODIT-DVT[29]	0	11		0.0 (0.0 to 28.5)
DOTAVK[30]: arm 1	0	11		0.0 (0.0 to 28.5)
DOTAVK[30]: arm 2	0	11		0.0 (0.0 to 28.5)
Palareti et al[31]	1	16		6.3 (0.2 to 30.2)
WODIT-PE[32]: arm 1	0	9		0.0 (0.0 to 33.6)
WODIT-PE[32]: arm 2	1	10		10.0 (0.3 to 44.5)
PREVENT[9]	0	13		0.0 (0.0 to 25.0)
DURAC I[10]	4	84		4.8 (1.3 to 11.7)
Prandoni et al[11]	27	268		10.1 (6.7 to 14.3)
AESOPUS[33]	3	28		10.7 (2.3 to 28.3)
EINSTEIN-Extension[34]	0	37		0.0 (0.0 to 9.0)
WARFASA[35]: arm 1	1	32		3.1 (0.1 to 16.2)
WARFASA[35]: arm 2	1	18		5.6 (0.1 to 27.3)
ASPIRE[36]: arm 1	1	53		1.9 (0.0 to 10.9)
ASPIRE[36]: arm 2	0	39		0.0 (0.0 to 9.0)
PADIS-PE[2]: arm 1	0	27		0.0 (0.0 to 12.8)
PADIS-PE[2]: arm 2	4	28		14.3 (4.0 to 32.7)
REVERSE I[11]	0	135		0.0 (0.0 to 2.7)
AUREC[12]	4	238		1.7 (0.5 to 4.2)
EINSTEIN-Choice[38]	0	32		1.0 (0.0 to 10.9)
PADIS-DVT[39]: arm 1	1	16		6.3 (0.2 to 30.2)
PADIS-DVT[39]: arm 2	0	12		0.0 (0.0 to 26.5)
Pooled	49	1145		3.8 (2.0 to 6.1)
P<0.001; I²=59%				

Fig 2 | Case fatality rate of recurrent venous thromboembolism (VTE) after discontinuation of anticoagulant treatment in patients with a first unprovoked VTE event. P value is for heterogeneity

anticoagulant treatment, we found that the long term risk for recurrent VTE was substantial. The risk reached 10.3% in the first year after discontinuation of treatment, with a cumulative incidence of 16% at 2 years, 25% at 5 years, and 36% at 10 years.

Our observed rate of recurrent VTE in the year after discontinuation of anticoagulation is consistent with that of 9.8 events per 100 person years (95% confidence interval 8.7 to 11.2) reported in a previous individual patient data meta-analysis,[5] but our study provides precise estimates for the risk of symptomatic recurrent VTE up to 10 years. Thus our findings extend the knowledge for the prognosis of unprovoked VTE. Our results indicate that after diagnosis of a first unprovoked VTE, 36% of patients will experience a recurrent VTE within 10 years after discontinuation

of anticoagulant treatment, underscoring that unprovoked VTE is a chronic disease imposing a substantial long term burden.

To measure the clinical impact of VTE recurrence in this patient population, we determined the case fatality rate of recurrent VTE after discontinuation of anticoagulant treatment. Our analysis showed that after treatment for a first unprovoked VTE, 3.8% (95% confidence interval 2.0% to 6.1%) of recurrent VTE events are fatal. This case fatality rate is similar to the reported 3.6% (1.9% to 5.7%) in a previous study of patients with VTE.[40]

Clinicians, patients, and policymakers currently lack clear guidance on decision making about duration of anticoagulation for unprovoked VTE. To date, no randomised trial has compared the risk after 3-6 months of initial treatment with that of continuing treatment indefinitely. Furthermore, no trial that has compared durations of anticoagulant treatment for VTE has been powered to detect differences in mortality. Consequently, we must rely on indirect evidence to project absolute long term rates of recurrent VTE and major bleeding, and combine these rates with surrogate measure of mortality (ie, case fatality rate) to balance the risks and benefits of anticoagulant treatment.

Our results provide clinicians, patients, and policymakers with rigorous benchmarks as well as a management framework in which to consider the long term risks and consequences of recurrent VTE if anticoagulation is stopped. When weighed against current best estimates for risks and consequences of major bleeding if anticoagulation is continued, our results could be used to decide whether to consider indefinite anticoagulation for unprovoked VTE. For example, in a typical patient with a first episode of unprovoked VTE with a risk for recurrent VTE of 36% at 10 years, combined with a case fatality rate for recurrent VTE of 4% as determined by our analysis, the risk of death from a first recurrent VTE after discontinuation of anticoagulant treatment would be about 1.44% by 10 years. Indeed, our pooled results showed a cumulative risk of recurrent fatal VTE of 1.5% at 10 years after discontinuation of treatment. For the same patient, the annual risk for major bleeding if treatment is continued is estimated at 1.2%,[1] translating to a 10 year risk for major bleeding of 12%. When combined with the case fatality rate for major bleeding of 11%,[40] the risk of death from major bleeding if anticoagulation is continued would

Table 3 | Risk of recurrent venous thromboembolism (VTE) after discontinuation of anticoagulation in patients with first unprovoked VTE event according to sex

Interval after anticoagulation	Person years of follow-up		Recurrent VTE		Event rate per 100 person years*	
	Men	Women	Men	Women	Men	Women
1st year	3273.8	2528.1	377	205	11.9 (9.6 to 14.4); 76, <0.001	8.9 (6.8 to 11.3); 72, <0.001
2nd year	2026.8	1738.1	160	97	7.3 (5.3 to 9.5); 63, <0.001	5.2 (3.6 to 7.0); 57, 0.003
2 year cumulative incidence, % (95% CI)					18.3 (14.4 to 22.5)	13.6 (10.1 to 17.5)
Years 3-5	2880.6	1891.7	125	57	4.4 (3.2 to 5.7); 60, 0.06	3.0 (1.6 to 4.7); 74, 0.01
5 year cumulative incidence, % (95% CI)					28.6 (22.3 to 35.0)	21.2 (14.4 to 28.6)
Years 6-10	1820.6	1202.4	76	23	3.8 (1.6 to 6.9); 89, <0.001	2.0 (1.3 to 2.9); 0, 1.02
10 year cumulative incidence, % (95% CI)					41.2 (28.4 to 55.6)	28.8 (19.8 to 38.4)

*Data are event rate (95% CI); I² (%), P value unless stated otherwise. P value is for heterogeneity.

Table 4 | Risk of recurrent venous thromboembolism (VTE) after discontinuation of anticoagulation in patients with a first unprovoked VTE event according to site of initial event

Interval after anticoagulation	Site of initial VTE			
	Distal DVT	Proximal DVT	Isolated PE	PE+DVT
1st year				
Total person years of follow-up	198.0	2387.4	1200.5	638.9
Total recurrent VTE events	3	233	86	66
Event rate per 100 person years (95% CI); I^2 (%), P value*	1.9 (0.5 to 4.3); 0, 0.56	10.6 (8.1 to 13.3); 73, <0.001	7.7 (5.6 to 10.2); 49, 0.02	10.2 (6.7 to 14.2); 59, 0.005
2nd year				
Total person years of follow-up	NA	1417.1	763.5	347.9
Total recurrent VTE events	NA	89	36	25
Event rate per 100 person years (95% CI); I^2 (%), P value*	NA	6.5 (5.2 to 7.8); 0, 0.55	4.5 (2.6 to 6.8); 45, 0.07	7.6 (4.7 to 11.2); 23, 0.24
2 year cumulative incidence, % (95% CI)	NA	16.4 (12.9 to 20.1)	11.9 (8.1 to 16.3)	17.0 (11.1 to 23.8)

DVT=deep vein thrombosis; PE=pulmonary embolism; NA=not available.
*P is for heterogeneity.

be about 1.32% at 10 years. Hence, over a 10 year horizon, patients with a first unprovoked VTE might be expected to derive a small net long term mortality benefit from continuing anticoagulation, consistent with current guidelines that suggest considering indefinite anticoagulation in patients with unprovoked proximal deep vein thrombosis or pulmonary embolism who are not at high risk for bleeding.[6-8] Nevertheless, our estimation of the net mortality benefit is limited owing to the uncertainty in estimates of the long term risk of major bleeding and case fatality rate of major bleeding during extended anticoagulation in patients with a first unprovoked VTE event, which should be the focus of future research.

Because the overall reduction in mortality with indefinite anticoagulation is small, other factors that affect the risk of recurrence (eg, sex, site of initial VTE) and the risk of bleeding, as well as patient preferences, could influence decisions about whether to continue or stop treatment. We found that the cumulative risk of recurrent VTE at 10 years after discontinuation of anticoagulation was 41% in men and 29% in women with a first unprovoked VTE event. Estimating the long term mortality risks over a 10 year horizon shows that a net long term mortality benefit from continuing anticoagulation might be expected in men (1.64% risk of fatal recurrent VTE versus 1.32% risk of fatal major bleeding) but not in women (1.16% risk of fatal recurrent VTE versus 1.32% risk of fatal major bleeding). Consequently, our findings affirm the importance of considering a patient's sex in deciding the optimal

duration of treatment, suggesting that there might be a stronger argument for indefinite anticoagulation in men with a first unprovoked VTE than in women. However, given the closely balanced risks of mortality from recurrent VTE and major bleeding, as well as the lack of precise sex specific estimates of the risks for major bleeding during extended anticoagulation in this patient population, the need for an individualised, patient centred approach in the long term management of unprovoked VTE is emphasised.

Certainly, risk stratification approaches enable individualised management of unprovoked VTE. Although there appears to be no clear subgroup of men who can be identified as having low risk of recurrent VTE[41 42] the prospectively validated HERDOO2 (Hyperpigmentation, Edema, or Redness in either leg; D-dimer level ≥250 µg/L; Obesity with body mass index ≥30; or Older age, ≥65 years) clinical decision rule[43] allows about 50% of women with a first unprovoked VTE to be classified as having a low risk of recurrent VTE (3% in the year after discontinuing treatment), with a long term risk of recurrent VTE of less than 10% at eight years after discontinuing anticoagulation.[11] On the other hand, as suggested by current guidelines,[6 7] it is unlikely that patients with a major bleeding risk that exceeds 3% a year would ever experience a net long term mortality benefit from indefinite anticoagulation. Currently, however, there are no validated prediction tools to identify subgroups of patients with VTE at high risk of major bleeding.

Additional findings from our study are noteworthy. Firstly, our results show that it is unlikely that patients with a first unprovoked distal deep vein thrombosis will benefit from indefinite anticoagulation given the low rate of recurrent VTE (1.9%, 95% confidence interval 0.5% to 4.3%) in the year after discontinuation of treatment. Secondly, a cohort study[44] suggested that patients with a first unprovoked pulmonary embolism have a higher rate of recurrent VTE after discontinuation of anticoagulation is discontinued than patients with a first unprovoked proximal deep vein thrombosis, whereas another cohort study suggested the opposite.[45] Our meta-analysis shows that the rate of recurrent VTE after discontinuation

Table 5 | Comparison of rate of recurrent venous thromboembolism (VTE) after discontinuation of anticoagulation in subgroups of patients with a first unprovoked VTE event

Patient subgroups	Recurrent VTE rate ratio (95% CI)	P value
Men versus women	1.4 (1.3 to 1.6)	<0.001
Distal DVT versus proximal DVT	0.2 (0.04 to 0.5)	<0.001
Distal DVT versus isolated PE	0.2 (0.05 to 0.7)	0.009
Distal DVT versus PE+DVT	0.2 (0.03 to 0.5)	<0.001
Proximal DVT versus isolated PE	1.4 (1.1 to 1.7)	0.004
Proximal DVT versus PE+DVT	0.9 (0.7 to 1.2)	0.47
PE+DVT versus isolated PE	1.5 (1.1 to 1.9)	0.005

DVT=deep vein thrombosis; PE=pulmonary embolism.

of anticoagulation in patients with a first unprovoked proximal deep vein thrombosis is 1.4-fold higher than in patients with a first unprovoked isolated pulmonary embolism and is comparable to the rate of recurrent VTE in patients with pulmonary embolism plus deep vein thrombosis. Thirdly, our study establishes that the absolute risk of recurrent VTE in patients with a first unprovoked VTE varies considerably over time—it is highest in the first year after treatment, reaching 10.3% (95% confidence interval 8.6% to 12.1%), declines in the second year after treatment to 6.3% (5.1% to 7.7%), and then significantly drops to an average of 3.1% to 3.8% (95% confidence interval 1.7% to 4.9%) per year in the subsequent eight years. Given current guideline recommendations on treatment duration for unprovoked VTE, this finding might help clinicians counsel patients who have already stopped treatment and want advice about resuming anticoagulation. Our results suggest that patients who have not experienced a recurrence within two years of discontinuing anticoagulant treatment are unlikely to experience a net long term mortality benefit from restarting anticoagulation.

Strengths and limitations of this study

This study has several strengths. Firstly, despite a heterogeneous population of patients with VTE in studies included in our analysis, we were able to obtain and pool data from a large number of patients specifically with a first episode of unprovoked VTE who were prospectively followed for recurrent VTE after stopping anticoagulant treatment. Secondly, with the help of data clarifications from authors of included studies, we were able to capture accurately the time varying risk for recurrent VTE by standardising the varying durations of follow-up across patient cohorts, as well as compare the rates of recurrent VTE in six relevant subgroups of patients with unprovoked VTE.

Limitations of our study include the finding of moderate to high statistical heterogeneity in the primary analyses. However, the extent of heterogeneity as measured by the I^2 statistic tends to be larger for meta-analyses of proportions.[46] We were unable to fully explain between study heterogeneity through subgroup and sensitivity analyses, which could potentially be explored better with a meta-analysis of individual patient data. Secondly, owing to the lack of individual patient data, we could not account for death from causes other than pulmonary embolism as a competing event for recurrent VTE, adjust for other potentially confounding variables such as patient's age, and explore the potential effect of an age-sex interaction on the differences in the risk of recurrent VTE observed between men and women. Lastly, we did not assess the risk of major bleeding during extended anticoagulant treatment, as well as other long term consequences of recurrent VTE that should also be considered in weighing the long term risk and benefits of anticoagulation, including the risk for post-thrombotic syndrome, chronic thromboembolic pulmonary hypertension, and quality of life.

Conclusion

In patients with a first episode of unprovoked VTE who have completed at least three months of anticoagulant treatment, the risk of recurrent VTE after discontinuing anticoagulation reached 10% in the first year, 16% at 2 years, 25% at 5 years, and 36% at 10 years, with 4% of recurrent VTE events resulting in death. These findings provide rigorous benchmarks of the long term risks and consequences of recurrent VTE that should inform clinical practice guidelines, enhance confidence in counselling patients of their prognosis, and help guide decision making about long term management of unprovoked VTE.

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Supplementary information: additional tables 1-7