Fatal recurrent VTE after anticoagulant treatment for unprovoked VTE – a systematic review

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Take home message: The rate of fatal recurrent VTE rate after anticoagulation cessation for unprovoked VTE was 0.173 per 100 patient-years, with a case-fatality rate of 2.0%
Abstract

Current guidelines recommend long-term anticoagulant therapy in patients with unprovoked venous thromboembolism (VTE). The risk of fatal recurrent VTE after treatment discontinuation (versus that of fatal bleeding during anticoagulation) is of particular relevance in the decision to continue or stop anticoagulation during long-term treatment after the first three months. Our primary aim was to provide a point-estimate of the yearly rate of fatal recurrent VTE and VTE-case-fatality rate in patients with unprovoked VTE after anticoagulation cessation in studies with low to moderate bias. Data were extracted from both randomized controlled trials and observational studies of all publications published before May 1st 2017. The pooled fatality rates were calculated using a random-effects model. Twenty-four Eighteen studies with low to moderate bias were included in the primary analysis, totaling 8914 6758 patients with a median follow up duration of 2.5 years (range 1-5.7 years). After anticoagulation cessation, the weighted pooled rate of VTE recurrence was 6.32 (95% CI 5.4-7.32, \( I^2 = 72.6 \)%) per 100 patient-years and the weighted pooled rate of fatal recurrent VTE was 0.172 (95% CI 0.172-0.252, \( I^2 = 88.5 \)%) per 100 patient-years, for a case-fatality rate of 2.66% (95% CI 1.86-5.09, \( I^2 = 66.6 \)%). These numbers are a solid benchmark for comparison to the risks associated with long-term anticoagulation treatment for the decision on the optimal duration of treatment of patients with unprovoked VTE.
Introduction

The risk of recurrent venous thromboembolism (VTE), which includes recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE), persists after cessation of anticoagulant treatment and is particularly high among patients with unprovoked VTE [1-3]. Consequently, recent treatment guidelines recommend continuation of anticoagulant therapy beyond the first three months in patients with unprovoked VTE without high risk for major bleeding [4-6]. This recommendation is based on weighing the risk of recurrent VTE after anticoagulant treatment cessation against the risk of major bleeding during ongoing treatment. For the individual patient, the risk of fatal recurrent VTE versus that of fatal bleeding is of particular relevance when deciding on the therapeutic management making the decision to prolong treatment or not.

The case-fatality rate of major bleeding events during long-term vitamin K antagonist (VKA) treatment has been estimated to be as high as 9%-13%, with a yearly rate of fatal bleeding varying between 0.2% and 1.5% [7, 8]. Importantly, this bleeding risk was found to decrease considerably with the introduction of direct oral anticoagulants (DOACs) that are associated with lower rates of intracranial and fatal bleeding than VKA, while non-inferiority was shown with regard to risk of venous thromboembolic risk recurrent VTE [9]. Long-term follow-up of current ongoing large practice-based cohort studies including VTE patients treated with DOACs are necessary to confirm these findings.

The case-fatality rate of recurrent VTE after cessation of anticoagulant therapy has previously been shown to vary between 3.6% and 5.1% in a mixed cohort of patients with both provoked and unprovoked VTE, for with a yearly risk of fatal recurrence rate of ranging between 0.4% and 0.5% [7, 10]. To date, these exact numbers are unknown for patients with unprovoked VTE, although even though this knowledge is especially valuable for this specific patient category because of the recommendation for indefinite treatment duration this is the patient category for whom this knowledge is most relevant [4, 5]. Therefore, we conducted a systematic review and meta-analysis of the literature to provide an accurate point-estimate of the case-fatality rate of
recurrent VTE as well as a yearly rate of fatal recurrences after anticoagulation cessation in patients with a first unprovoked VTE.
Methods

Data sources and literature search

A systematic literature search was conducted for all relevant publications in PubMed, Embase, Web of Science and Cochrane in May 2017. The Subject Headings and/or keywords of our search strategy comprised ‘Venous Thromboembolism’, ‘Pulmonary Embolism’, ‘Deep Venous Thrombosis’, ‘Anticoagulation’ and ‘Recurrence’ and were database-specifically translated (Supplementary Appendix).

Study selection and data extraction

Initial results were screened for relevant titles and abstracts by two independent reviewers (S.J. and L.M.). This process was performed in duplicate and disagreements were independently resolved by consensus or by a third reviewer (F.A.). Studies were included if: i) consecutive patients with objectively confirmed symptomatic DVT or PE were prospectively enrolled (proximal DVT diagnosed in case of evidence of thrombosis in the popliteal or more proximal veins on compression ultrasonography or contrast venography and a diagnosis of PE based on at least one subsegmental filling defect on computed tomography pulmonary angiography (CTPA), high-probability ventilation perfusion lung scan (V/Q) or abnormal pulmonary angiography, (ii) patients were dedicatedly followed for symptomatic recurrent VTE and such events were objectively and symptomatically confirmed, (iii) the initial anticoagulation treatment (with VKA or DOAC) was continued for at least three months and the follow-up period extended for at least three months after the anticoagulation therapy was discontinued, (iv) fatal VTE events during follow-up after treatment cessation were reported (PE and/or DVT) and (v) at least 100 patients were included. Only full-text publications in the English language were reviewed for potential inclusion. There was no restriction on publication year.
After selection of all relevant articles, two reviewers (S.J. and L.M.) independently extracted data on first author’s name, year of publication, design (prospective/retrospective), number of patients included, age, initial anticoagulation treatment, the total duration of follow up after cessation of treatment, proportion of unprovoked VTE at baseline (PE/DVT), case-fatality rate of recurrent VTE during follow-up after anticoagulant discontinuation (PE/DVT) and finally overall mortality during follow-up, as reported by the authors. The authors of publications with missing data were approached by email at least two times on two weeks apart. The PRISMA statement for reporting systematic reviews and meta-analysis was used for this study [12].

**Study objectives**

The primary objective was to determine the case-fatality rate of recurrent VTE after anticoagulation cessation following a first unprovoked VTE diagnosis, as well as the yearly rate of fatal VTE recurrences in selected studies with low to moderate bias. The secondary aims were to determine the overall rate of fatal VTE for all available studies, including those with a high risk of bias and to determine overall fatal rates for all studies, including those with a high risk of bias. Moreover, we differentiated between: i) enrolment periods, comparing studies that started enrolment before and after the 1st of January 2000 (if reported) patients who initially presented with unprovoked DVT and unprovoked PE, ii) enrolment periods, comparing studies that started enrolment before and after the 1st of January 2000 (if reported), iii) cohort studies and RCTs, and iv) studies with a follow-up duration that was shorter versus longer than 2.5 years, iv) patients who initially presented with DVT versus unprovoked PE and v) In addition, since uniform criteria for the different definitions of fatal VTE are lacking, we elaborated on potential differences in primary outcomes that were applied. Sensitivity analyses were performed in selected studies with low or moderate risk of bias, excluding studies with a high risk of bias.
Study outcomes and definitions

Recurrent PE was predefined as a new intraluminal filling defect on pulmonary angiography or CTPA, a new high probability perfusion defect on V/Q scan or any new defects after earlier normalisation of the scan [11]. Recurrent DVT was defined as new non-compressibility by ultrasonography of the common femoral and/or popliteal vein, non-compressibility of a previously normalised vein segment, or a pronounced increase in vein diameter (≥ 4 mm) of a previously non-compressible venous segment [11]. Patients with both index DVT and PE were classified as patients with PE when fatal rates were reported separately for this subgroup. Fatal recurrent VTE was predefined as PE diagnosed by autopsy, high-probability V/Q scan, a new intraluminal filling defect detected on pulmonary angiography, computed tomography (CTPA) or venography prior to death, or a high clinical suspicion as judged by the investigators of the individual studies. For each study, the definition of unprovoked VTE was evaluated post-hoc predefined according and compared to criteria provided by the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis [13].

Risk of bias

Two authors (S.J. and L.M.) independently evaluated the risk of bias at a study level in accordance with the Cochrane Collaboration’s tool for assessing risk of bias and the PRISMA statement [12, 14]. We focused on the following criteria: 1) pre-specified protocol, 2) clear description of inclusion and exclusion criteria, 3) adequate anticoagulation treatment prior to cessation according to international standards, 4) clear description of follow-up after anticoagulation cessation, 5) clear definitions provided of unprovoked and fatal VTE, 6) loss to follow up, 7) adjudication of outcomes, and 8) assessment of primary endpoint in all patients. Disagreements were resolved through discussion with a third author (F.A.).
Statistical analyses

Case-fatality rates of each study were calculated by dividing the number of recurrent fatal VTEs by all recurrent VTEs. The case-fatality rates were pooled after Freeman-Tukey double arcsine transformation to stabilize variances, using a random effects model according to the method of DerSimonian and Laird [15, 16]. Pooled case-fatality rates were reported with corresponding 95% confidence intervals (CIs). Subsequently, we estimated the rate of recurrent VTE and fatal recurrent VTE per 100 patient-years. We evaluated differences across subgroups under the null hypothesis of no differences ($\chi^2$ distribution with $S$ [number of subgroups] minus 1 degrees of freedom). We assessed statistic heterogeneity of exposure effects across the various cohort studies by calculating the $I^2$ statistic, which depicts the variance of results from study to study beyond (or rather than) chance. Heterogeneity was considered low when $I^2$ was <25%, intermediate when $I^2$ was 25–75% and high when $I^2$ was >75% [17]. Heterogeneity was explored using meta-regression. We evaluated differences across subgroups under the null hypothesis of no differences ($\chi^2$ distribution with $S$ [number of subgroups] minus 1 degrees of freedom). All analyses were performed using Stata 14.0 (Stata Corp., College Station, TX, USA).

Results

Literature search and study selection

The initial search yielded 7647 potentially relevant articles; 586 in Cochrane, 2839 in EMBASE, 2307 in PubMed and 1915 in Web of Science (Figure 1). After the first screening of title and abstract, 7540 records were excluded, leaving 107 unique articles for detailed assessment. An additional 83 articles were excluded after full review for the following reasons: 28 were abstracts only, with insufficient information, 27 comprised studies of duplicate patients with other reports, eight did not clarify if fatal events were on or off anticoagulation treatment, eight had fewer than 100 patients, four did not distinguish between provoked and unprovoked VTE and authors did not comply with our data
request after at least two attempts, and eight were excluded for other reasons. The remaining 24 articles all satisfied our predetermined methodological criteria [18-41].

Included studies

Table 1 shows the characteristics of the included studies. Fifteen were cohort studies [21, 23-26, 28, 29, 32, 33, 35, 37-41] and nine were RCTs [18-20, 22, 27, 30, 31, 34, 36]. The 24 articles were published between 1995 and 2017 and included a total of 8914 patients with unprovoked VTE (range 117-914 patients per study). The median follow-up duration after treatment cessation was 2.5 years (range 1-7.7 years). The evaluation of the presence of bias is shown in Table 2. Of the 24 studies, 18 were considered to be at low or moderate risk of bias and were included in the primary analysis. Five studies did not involve an independent adjudication committee [24, 28, 32, 33, 40]. Most studies did not meet all the criteria of our predefined definition of unprovoked VTE [20, 21, 24, 26, 28-30, 32, 34-39, 41]. One study did not provide a definition of unprovoked VTE at all [22].

Primary outcome: rate of fatal recurrent VTE in studies with low or moderate risk of bias

These 18 studies with low or moderate risk of bias enrolled a total of 6758 patients with a median follow up of 2.2 years (range 133-914). Table 3 shows the rates of recurrent VTE and fatal recurrent VTE per subgroup. In 19 studies, fatal recurrent VTE could be distinguished for patients initially presenting with DVT versus PE [13, 18, 19, 23-25, 27-39, 41]. The evaluation of the presence of bias is shown in Table 2. Five studies did not involve an independent adjudication committee [24, 28, 32, 33, 40]. Most studies did not meet all criteria of our predefined definition of unprovoked VTE [20, 21, 24, 26, 28-30, 32, 34-39, 41]. One study did not provide a definition of unprovoked VTE [22]. The definition of fatal VTE varied widely across studies (Supplementary Appendix, Table S1). Only twelve studies [54%] reported a definition of fatal VTE [18, 19, 22, 24, 25, 27, 30, 31, 34, 36-38], of which eleven (92%) included autopsy and/or clinical suspicion [18, 19, 22, 24, 25, 27, 30, 31, 36-38] and five (42%) involved ‘sudden unexplained death’ [25, 27, 34, 36, 37]. Table 3 shows the rates of recurrent
VTE and fatal recurrent VTE per subgroup. The overall weighted pooled rate of recurrent VTE recurrence in studies with low or moderate risk of bias was 6.32 (95% CI 5.4-7.23; I²=72.68%) per 100 patient-years and the rate of fatal recurrent VTE was 0.17 (95% CI 0.067-0.33; I²=66.66%) per 100 patient-years, for a case-fatality rate of 2.60% (95% CI 0.86-5.03; I²: 66.66% (Figure 2). The weighted pooled recurrent fatal VTE rate was numerically higher in patients presenting with DVT than with PE (0.18, 95% CI 0.22-0.33; I²=72.8% versus 0.0611, 95% CI 0.0-0.2811 per 100 patient-years; I²=51.38%; P=0.86 for interaction). This was consistent with a case-fatality rate of 2.73% (95% CI 0.50-6.14; I²=63.53%) in DVT patients and 1.60.13% (95% CI 0.57-1.8; I²=48.43%) in PE patients (P=0.6657 for interaction; Supplementary Appendix, Figure S1). These estimates remained similar in sensitivity analyses restricted to studies with low or moderate risk of bias (Supplementary Appendix, Figure S1).

Secondary outcomes
The overall weighted pooled rate of VTE recurrence among all 24 studies was 6.2 (95% CI 5.4-7.2; I²=86.8%) per 100 patient-years and the rate of fatal recurrent VTE was 0.13 (95% CI 0.036-0.25; I²=72.7%) per 100 patient-years, for a case-fatality rate of 2.0% (95% CI 0.69-3.8; I²: 65.2%: Supplementary Appendix Figure S1). In 19 studies, fatal recurrent VTE could be distinguished for patients initially presenting with DVT versus PE [13, 18, 19, 23-25, 27-39, 41] Overall, the weighted pooled recurrent fatal VTE rate was numerical higher in patients presenting with DVT than with PE (0.18, 95% CI 0.22-0.33; I²=72.8% versus 0.011, 95% CI 0.0-0.11 per 100 patient-years; I²=38.7%; P=0.86 for interaction), which was consistent with a case-fatality rate of 2.3% (95% CI 0.63-4.9; I²=60.3%) in DVT patients and 0.12% (95% CI 0.1-0.24%) in PE patients (P=0.57 for interaction; Supplementary Appendix, Figure S2). Fatal recurrent rates for patients with both index DVT and PE could only be retrieved from three reports [31, 38, 41], comprising one fatal and 42 non-fatal.
recurrences (case-fatality rate 3.3%). These patients were classified as having index PE for the purpose of this study.

Studies that initiated enrolment before the year 2000 had a numerical higher but not significant different pooled rate of fatal VTE than studies that started inclusion within or after the year 2000 (0.27, 95%CI 0.038-0.59; \(I^2=83.1\%\) vs. 0.039, 95%CI 0.0028-0.1 per 100 patient-years; \(I^2=0\); \(P=0.70\) for interaction), as well as case-fatality rate (3.7%, 95%CI 0.95-7.6; \(I^2=76.5\%\) vs. 0.71%, 95%CI 0.063-1.8; \(I^2=0\); \(P=0.21\) for interaction; Supplementary Appendix, Figure S4). Notably, there were no differences between case-fatality rates between patients with index DVT or PE in both periods, with rates of 4.5% for patients with index DVT (95%CI 1.3-9.1) and 6.0% for patients with index PE (95%CI 0-26) in studies that started inclusion before 2000 (\(P=0.76\) for interaction), and 0.5% for patients with index DVT (95%CI 0-3.3) and 0% for patients with index PE (95%CI 0-0.5) in studies initiating enrolment after this period (\(P=0.94\) for interaction; Supplementary Appendix, Table S2). A significantly higher number of DVT patients were enrolled in studies that started inclusion before the analysis of the more recent studies showed good homogeneity (both \(I^2=0\)) while the results of earlier studies were quite heterogeneous (both \(I^2=84\%\) than within or after the year 2000 (46%; Odds Ratio 6.1, 95%CI 5.5-6.9).

The rate of fatal recurrent VTE rate was similar in cohort and RCT studies (0.11, 95% CI 0.009-0.29; \(I^2=79.5\%\) vs. 0.14 95% CI 0.021-0.33; \(I^2=49.7\%\) per 100 patient-years; \(P=0.96\) for interaction) and studies with short and longer than 2.5 years follow up duration (0.11, 95% CI 0.018; 0.27; \(I^2=52.4\%\) vs. 0.13, 95% CI 0.076-0.35; \(I^2=81.7\%\) per 100 patient-years; \(P=0.94\) for interaction). Likewise, the case-fatality rates did not differ for cohort and RCT studies (1.7%, 95% CI 0-4.2; \(I^2=74.6\%\) vs. 2.5%, 95% CI 0.69-5.0; \(I^2=26.8\%\); \(P=0.87\) for interaction) as well as for studies with shorter and longer than 2.5 years follow up duration (2.2%, 95% CI 0.22-5.4; \(I^2=76.6\%\) vs. 1.8%, 95% CI 0.46-3.8; \(I^2=34.9\%\); \(P=0.69\) for interaction).

In 19 studies, fatal recurrent VTE could be distinguished for patients initially presenting with DVT versus PE [13, 18, 19, 23-25, 27-39, 41]. The case-fatality rates of patients initially presenting
with DVT and PE were 2.3\% (95\% CI 0.52-4.8; $I^2=6.1\%$) and 0.12\% (95\% CI 0-1.8; $I^2=34.9\%$; $P=0.57$ for interaction; Supplementary Appendix, Figure S3). When focusing on studies with low or moderate risk of bias only, this numerically difference decreased considerably (2.7\% [95\% CI 0.50-6.1]; $I^2=63.52\%$) versus 1.6\% (95\% CI 0-5.7; $I^2=48.43\%$; $P=0.66$ for interaction; Supplementary Appendix, Figure S4).

The difference between the case-fatality rates of patients initially presenting with DVT and PE increased substantially when analysing all studies, including those with high risk of bias (2.3\% [95\% CI 0.52-4.8]; $I^2=60.39\%$) versus 0.12\% (95\% CI 0-1.8; $I^2=34.9\%$; $P=0.57$ for interaction; Sensitivity analysis restricted to studies with low- or moderate-risk of bias showed a less distinct difference with a case-fatality rate for patients initially presenting with DVT of 2.7\% (95\% CI 0.50-6.1; $I^2=63.52\%$) and 1.6\% (95\% CI 0-5.7; $I^2=48.43\%$; $P=0.66$ for interaction; Supplementary Appendix, Figure S3).

The fatal recurrent VTE rate was similar in cohort and RCT studies (0.11, 95\% CI 0.009-0.29; $I^2=79.5\%$ vs. 0.14, 95\% CI 0.021-0.33; $I^2=49.7\%$ per 100 patient-years; $P=0.96$ for interaction) and studies with short and longer than 2.5 years follow up duration (0.11, 95\% CI 0.018-0.37; $I^2=14\%$ vs. 0.13, 95\% CI 0.026-0.36; $I^2=61.7\%$ per 100 patient-years; $P=0.94$ for interaction). Likewise, the case-fatality rates did not differ for cohort and RCT studies (1.7\%, 95\% CI 0.19-4.3; $I^2=34.6\%$ vs. 2.5\%, 95\% CI 0.69-5.0; $I^2=76.8\%$; $P=0.87$ for interaction) as well as for studies with shorter and longer than 2.5 years follow up duration (2.2\%, 95\% CI 0.22-5.4; $I^2=36.6\%$ vs. 1.8\%, 95\% CI 0.46-3.8; $I^2=44.0\%$; $P=0.69$ for interaction).

**Fatal VTE definition**

The definition of fatal VTE varied widely across studies (Supplementary Appendix, Table S1). Only twelve studies (54\%) actually reported a definition of fatal VTE [18, 19, 22, 24, 25, 27, 30, 31, 34, 36-38], of which eleven (92\%) included autopsy and/or clinical suspicion [18, 19, 22, 24, 25, 27, 30, 31, 36-38] and five (42\%) involved ‘sudden unexplained death’ [25, 27, 34, 36, 37]. Studies including
'sudden unexplained death' in their fatal VTE definition were found to have the highest case-fatality rates (3.6%, 95% CI 0.018-11; I²= 81.15%), while studies without a clear definition of fatal recurrent VTE reported lowest rates (0.95%, 95% CI 0.067-2.5; I²= 27.06%; P=0.29 for interaction)

Supplementary Appendix, Table S2). This difference in case-fatality rates was observed in both index PE and index DVT patients.

Discussion

In this systematic review and meta-analysis, we determined the risk of fatal recurrent VTE in patients with unprovoked VTE after cessation of anticoagulation treatment. Overall, we observed a pooled rate of fatal recurrent VTE rate of 0.173 per 100 patient-years with a case-fatality rate of 2.60% in studies with low to moderate risk of bias. High heterogeneity was observed in both analyses. Remarkably, where most meta-analyses performed in our study showed high heterogeneity among the included studies, the secondary analysis focusing on more recent studies (patient enrolment after January 1st 2000, total of 4508 patients) showed good homogeneity. The heterogeneity showed a numerically lower pooled rate of fatal recurrence rate (0.039 per 100 patient-years) as well as a case-fatality rate (0.71%) compared to earlier studies (pooled fatal recurrence rate 0.27 per 100 patient-years and case-fatality rate 3.7%) with high heterogeneity found in this subanalysis may be explained by, although this difference did not reach statistical significance. This might be due to improved patient care over the years, earlier presentation at the hospital or detection of smaller and less dangerous PE blood clots by more advanced CTPA technology.

The present study revealed similar rates of fatal recurrent VTE in cohort studies compared to RCTs, thus supporting the external validity of our findings. The fatal rates of studies with longer and shorter follow-up durations did not differ as well, indicating that our main finding is valid for long-term follow-up (at least beyond the first 2 years after treatment continuation). Further, we use the
finding of a lower rate of fatal recurrent VTE in more recent studies as an argument to hypothesize
that the identified rates in our main analysis represent an overestimation of the ‘true’ risk rather
than an underestimation. Therefore, our findings provide clinicians, guidelines committees,
investigators and policymakers with a solid and valid benchmark of the mortality risk due to
recurrent VTE after cessation of treatment to be compared with the risks associated with long-term
anticoagulation treatment for patients with unprovoked VTE [4, 5]. Importantly, since risk of VTE
recurrence changes over time with the bulk of recurrences occurring in the first years, and the risk of
bleeding remains more stable, the ultimate answer to the question of the most optimal duration of
anticoagulation for unprovoked VTE is to be determined in future RCTs with long-term follow-up.

We found an non-significant higher risk of fatal recurrent VTE after an index DVT diagnosis
than after an index PE diagnosis which was Our meta-analysis may be subject to potential biases.
Notable differences were observed between the studies with regard to sample size, follow-up
duration, definitions of ‘unprovoked’ and fatal recurrent VTE, as well as rate of recurrent VTE, as
underlined by relevant heterogeneity observed in most of the analyses that were performed. This is
illustrated by the numerically higher fatal recurrent rates in patients with an index DVT diagnosis
than in patients with index PE diagnosis. This was unexpected since DVT is more likely to recur as
DVT and PE as PE, with PE being considered the ‘most lethal’ presentation of VTE [7, 10]. This
difference is mostly explained by biases of the data pooling due to major methodological differences
between the included studies increased substantially when including studies with high risk of bias.
The difference in fatal rates between patients with index DVT and those with index PE were clearly
less distinct in the sensitivity analyses that did not consider studies with high risk of bias (Figure S2).
Moreover, although no difference was observed, the comparison between enrolment periods
revealed that no difference was observed when comparing the two predefined different inclusion
periods. Early studies – reporting higher fatal VTE rates – were subject to high heterogeneity and
comprised mostly DVT patients (84%), whereas in contrast, recent studies – with lower rates of fatal
VTE – had no heterogeneity and included a higher number of PE patients (54%). On the other hand,
as has been noted in VTE epidemiology studies. Other explanations may be that, there has been a reduction in PE case fatality rates suggesting overdiagnosis of PE is often over diagnosed with time, likely secondary to adoption of more and more advanced CT technology for PE diagnosis. This could have led to a reduced risk of (fatal) recurrent VTE in index PE patients, but not of DVT patients. In addition, a selection of 'healthier' PE patients for whom anticoagulation discontinuation was deemed to be safe in observational studies could have contributed to the lower observed fatal rates of recurrent VTE. Moreover, a single DVT diagnosis without further evaluation on the presence of PE might also explain the higher rate of fatal recurrent VTE in patients with an index DVT. A DVT diagnosis is sufficient to introduce anticoagulation without further imaging tests for a PE diagnosis. Lastly, many of the patients with DVT may actually have had PE as well, although this was not objectively confirmed and therefore not reported in the original study publications.

The present study revealed similar rates of fatal recurrent VTE in cohort studies compared to RCTs, thus supporting the external validity of our findings. The fatal rates of studies with longer and shorter follow-up durations did not differ as well, indicating that our main finding is valid for long-term follow-up (at least beyond the first 2 years after treatment continuation). Our findings provide clinicians, guidelines committees, investigators and policymakers with a solid benchmark of the mortality risk due to recurrent VTE after cessation of treatment to be compared with the risks associated with long-term anticoagulation treatment for patients with unprovoked VTE [4, 5]. Importantly, since risk of VTE recurrence changes over time with the bulk of recurrences occurring in the first years, and the risk of bleeding remains more stable, the ultimate answer to the question of the most optimal duration of anticoagulation for unprovoked VTE is to be determined in future RCTs with long-term follow-up.

Remarkably, the reported rate of fatal recurrent VTE was largely dependent on the definition adopted across the various studies. Overall, studies without a clear definition reported the lowest rates, whilst studies in which unexplained death was adjudicated as recurrent VTE showed the highest rates. Half of the included studies did not report a definition of fatal VTE, whereas the
remaining studies used various definitions ranging from autopsy findings alone to ‘sudden unexplained death’. With no widely accepted definition of ‘fatal VTE’, it is impossible to rank these different definitions, although it seems reasonable to assume that studies focusing on autopsy findings may provide underestimated rates of fatal recurrent VTE, while the opposite is true for studies adjudicating all unexplained death as being provoked by recurrent VTE. Moreover, the adjudication process itself might also be difficult and could possibly lead to different rates of PE-related deaths among studies. Nonetheless, our findings again thus urgently call for an effort to standardize this definition for future studies in order to allow for valid inter-study comparisons [43].

When deciding on the duration of anticoagulation treatment, the risk of recurrent VTE should be balanced against the risk of major bleeding, with risks of fatal recurrence and/or bleeding as ultimate endpoints. In both trial circumstances and practice based data, we found a recurrent VTE fatal rate of 0.173% (95% CI 0.04-7.26-0.3325) per year, and in the most recent studies of 0.039 (95% CI 0.0028-0.1). During VKA treatment, the 0.2-1.48% yearly rate of fatal bleeding was shown to be considerably higher [7, 8]. Relevant high-quality data in the current DOAC era is yet unavailable for VTE cohorts. Nonetheless, until now, phase IV DOAC studies with only limited follow-up duration have reported few fatal major bleeding complications, or even none at all [44-47], supporting the current guideline recommendations to continue anticoagulant treatment in most patients. The best data available comes from the German Dresden registry describing the long-term follow-up of a combined cohort of patients with VTE or atrial fibrillation anticoagulated with a DOAC. The incidence rate of major bleeding was 3.4% (2.6-4.4), with a 5.1% (95% CI 0.0-10.7) 90-day case-fatality rate [44]. Importantly, this rate included the initial anticoagulation period as well, during which patients are known to have increased risk of major bleeding [8]. Moreover, the 90-day mortality after major bleeding may overestimate the true rate of death directly related to the major bleeding. Future ongoing DOAC studies with longer follow-up durations in VTE patients are urgently warranted to provide a robust anticoagulation-associated rate of fatal bleeding.
Current guideline recommendations with regard to extended duration of treatment after unprovoked VTE will be confirmed beyond doubt if these studies show that long-term treatment with DOACs is, indeed, associated with a yearly rate of fatal bleeding lower than 0.01736 - 0.3325%. Until then, anticoagulation duration should be individualised based on a patient-specific balance between bleeding and recurrent thrombotic risk. Valid bleeding and thrombotic risk tools have been developed and -although not validated in RCTs- could be helpful to assess these risks and thereby identify patients who may benefit from short or long-term anticoagulation treatment [48-51].

Strong points of this analysis include the strict selection criteria applied and the large number of patients studied. Source data were only derived from high-quality studies. Moreover, we were able to compare fatal rates in four relevant subgroups. Our study has several limitations in addition to the issue of varying definitions of fatal recurrent VTE. In particular, we did not have the availability of patient-level data, which would have allowed us to evaluate the prognostic role of risk factors such as age and gender. Also, although we performed rigorous inclusion criteria and focused only on high-quality studies, the meta-analyses presented were subject to relevant heterogeneity caused by several between-study differences, especially for those studies that enrolled patients before January 1st 2000.

**Conclusions**

This meta-analysis revealed a pooled rate of fatal recurrent VTE of 0.173 (95% CI 0.01730-0.3325) per 100 patient-years for patients with unprovoked VTE after discontinuation of anticoagulation therapy in studies with low to moderate risk of bias. This, which was consistent with a case-fatality rate of 2.05% (95% CI 0.86-5.0). Notably, we observed utilisation of varying fatal VTE definitions which was associated with moderate to high between-study heterogeneity, affecting the reported rates of fatal recurrent VTE. Current guideline recommendations on the duration of treatment of unprovoked VTE would be strengthened if future studies show that long-term anticoagulation treatment with DOACs is indeed associated with a rate of fatal bleeding lower than 0.3325% per year.
year, representing the upper limit of the 95% confidence interval the pooled incident rate of fatal recurrent VTE after anticoagulation discontinuation.

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**Conflict of interest**

Sake J. van der Wall, Liselotte M. van der Pol, Yvonne M. Ende-Verhaar, Suzanne C. Cannegieter, Sam Schulman, Paolo Prandoni and Marc Rodger have no conflicts to declare. Menno V. Huisman reports research grants from ZONMW, Pfizer-BMS, Boehringer-Ingelheim and Daiichi-Sankyo as well as fees for lectures from Pfizer-BMS, Boehringer-Ingelheim and Daiichi-Sankyo. Frederikus A. Klok reports research grants from Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, Daiichi-Sankyo, MSD and Actelion.

**Author contributions**

Sake J. van der Wall and Frederikus A. Klok were responsible for the concept and design of the study,
quality assessment, and interpretation of the results and writing of the manuscript. Liselotte M. van der Pol was responsible for data extraction, quality assessment and critical revision of the manuscript. Yvonne M. Ende-Verhaar was responsible for statistical analysis and critical revision of the manuscript. Sam Schulman, Paolo Prandoni, Marc Rodger, Suzanne C. Cannegieter and Menno V. Huisman were responsible for interpretation of the results, and critical revision of the manuscript.
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Figures

Figure 1. Flow-chart of the clinical search

Potentially relevant articles found with search strategy (n=7647)
- Cochrane: 586
- EMBASE: 2839
- PubMed: 2307
- Web of Science: 1915

Excluded (n=7540)
- Duplicates (n=2431)
- Not relevant based on title and abstract (n=5109)

Detailed assessment for eligibility (n=107)

Excluded (n=83)
- Abstracts without sufficient information (n=28)
- Duplicate patients (n=27)
- Unclear if fatal events were on or off treatment (n=8)
- Fewer than 100 patients included (n=8)
- No distinction between provoked and unprovoked VTE (n=4)
- Other reasons (n=8)

Included for analysis (n=24)
Figure 2. **Sensitivity analysis** of the case-fatality incidences after anticoagulant cessation in studies with low to moderate risk of bias. CFR=Case Fatality Rate, CI=Confidence Interval.

| Study                        | Overall CFR | CFR % (95% CI) | Weight (%) |
|------------------------------|-------------|-----------------|------------|
| Schulman et al., 1995 (18)  |             | 10 (3.6-25)    | 4.58       |
| Agnelli et al., 2001 (19)   |             | 0 (0-15)       | 3.96       |
| Ridker et al., 2003 (20)    |             | 5.4 (1.5-18)   | 5.23       |
| Baglin et al., 2003 (21)    |             | 0 (0-11)       | 4.91       |
| Schulman et al., 2003 (22)  |             | 4.2 (1.5-12)   | 6.59       |
| Cowan et al., 2005 (23)     |             | 6.7 (2.9-15)   | 6.59       |
| Prandoni et al., 2007 (25)  |             | 13 (9.2-17)    | 8.33       |
| Baglin et al., 2008 (26)    |             | 0 (0-12)       | 4.60       |
| Prandoni et al., 2009 (27)  |             | 8.3 (2.9-22)   | 5.17       |
| Siragusa et al., 2014 (29)  |             | 0 (0-12)       | 4.68       |
| Bocchini et al., 2014 (30)  |             | 2.3 (0.41-12)  | 5.56       |
| Brighton et al., 2012 (31)  |             | 1.4 (0.24-7.4) | 6.54       |
| Schulman et al., 2013 (32)  |             | 0 (0-10)       | 5.11       |
| Galanoud et al., 2014 (35)  |             | 11 (3.1-33)    | 3.52       |
| Couturaud et al., 2015 (36) |             | 0 (0-9.0)      | 5.35       |
| Kean et al., 2015 (37)      |             | 2.4 (0.42-12)  | 5.51       |
| Rodger et al., 2016 (38)    |             | 1.9 (0.84-5.3) | 7.83       |
| Rodger et al., 2017 (41)    |             | 0 (0-8.4)      | 5.51       |

**VTE low to moderate bias (P=0.60)**

CFR % 0 20 40
### Tables

**Table 1.** Characteristics and outcomes of the included studies. DVT=Deep Vein Thrombosis, PE=Pulmonary Embolism, VTE=Venous Thromboembolism, RCT=Randomised Controlled Trial, VKA=Vitamin K Antagonist, DOAC=Direct Oral Anticoagulant, NA=Not Applicable.

| Study, Year | Study type | Enrolment period | VTE patients included | DVT patients included | PE patients included | Secondary VTE at baseline, no (%) | Initial treatment, minimum (months) | Follow up after cessation, years | Recurrent PE | Recurrent VTE, no. (DVT/PE at presentation) | Fatal VTE, no. (DVT/PE at presentation) |
|-------------|------------|------------------|-----------------------|-----------------------|----------------------|----------------------------------|----------------------------------|----------------------------------|-------------|------------------------------------------|----------------------------------------|
| Schulman et al, 1995 [18] | RCT       | 1988-1991        | 289                   | 249                   | 40                   | 0                                | VKA, 6                           | 2                  | 5                                       | 29 (24/5)                              | 3 (2/1)      |
| Agnelli et al, 2001 [19] | RCT       | 1995-1998        | 133                   | 133                   | 0                    | 0                                | VKA, 3                           | 3.1                | 3                                       | 21 (21/0)                              | 0            |
| Ridker et al, 2003 [20] | RCT       | 1998-2002        | 253                   | -                     | -                    | 93 (37)                          | VKA, 3                           | 2.1*               | NA                                     | 37                                    | 2            |
| Baglin et al., 2003 [21] | Cohort    | 1997-2002        | 193                   | -                     | -                    | 0                                | VKA, 3                           | 2                  | NA                                     | 32                                    | 0            |
| Schulman et al., 2003 [22] | RCT       | 1999-2000        | 611                   | 389                   | 221                  | 98 (16)                          | VKA, 6                           | 1.5                | 23                                     | 71                                    | 3            |
| Cosmi et al., 2005 [23] | Cohort    | 1995-2004        | 400                   | 400                   | 0                    | 0                                | VKA, 6                           | 1.8*               | 15                                     | 75 (75/0)                             | 5 (5/0)      |
| Young et al, 2006 [24] | Cohort    | 1996-2002        | 103                   | 103                   | 0                    | Unclear                          | VKA, 3                           | 2.9*               | NA                                     | 26 (26/0)                             | 1 (1/0)      |
| Prandoni et al., 2007 [25] | Cohort    | 1991-2003        | 864                   | 733                   | 131                  | 0                                | VKA, 6                           | 4.2**              | NA                                     | 268 (240/28)                        | 34 (30/4)    |
| Baglin et | Cohort    | 2001-2003        | 142                   | -                     | -                    | 0                                | VKA, 6                           | 3.2*               | NA                                     | 28                                    | 0            |
| Study                          | Design  | Year   | Follow-up | # Thrombosis/LB | # ATE/LB | # Major Bleeding/LB | # Major Thromboembolic Event/LB | # Major Bleeding/All LB | # Major Thromboembolic Event/All LB |
|-------------------------------|---------|--------|-----------|-----------------|----------|---------------------|-----------------------------|-------------------------|-----------------------------------|
| Prandoni et al., 2009 [27]    | RCT     | 1999-2006 | 151       | 151             | 0        | 0                   | 2.8                         | 7                       | 36 (36/0)                        | 3 (3/0)                          |
| Poli et al., 2010 [28]        | Cohort  | Unclear | 161       | 0               | 161      | 0                   | VKA, 6                      | 3**                     | 11                                | 20 (0/20)                        | 0                                |
| Siragusa et al., 2011 [29]    | Cohort  | 1999-2007 | 409       | 409             | 0        | 0                   | VKA, 3                      | 1                       | NA                                | 29 (29/0)                        | 0                                |
| Becattini et al., 2012 [30]   | RCT     | 2004-2010 | 197       | 130             | 67       | 0                   | VKA, 6                      | 2*a                     | 14                                | 43 (27/16)                       | 1 (0/1)                          |
| Brighton et al., 2012 [31]    | RCT     | 2003-2011 | 411       | 232             | 175      | 0                   | VKA, 3                      | 3.1**                   | NA                                | 73 (40/33)                       | 1 (0/1)                          |
| Olie et al., 2012 [32]        | Cohort  | 2003-2009 | 583       | 175             | 421      | 0                   | VKA, 8 (mean)               | 2.2                     | NA                                | 74 (21/53)                       | 0                                |
| Ribeiro et al., 2013 [33]     | Cohort  | 2000-2011 | 117       | 88              | 29       | 0                   | VKA, 6                      | 3.6*                    | NA                                | 22 (20/2)                        | 0                                |
| Schulman et al., 2013 [34]    | RCT     | 2006-2010 | 662       | 441             | 213      | Unclear             | DOAC or VKA, 6              | 1.5                     | 13                                | 35 (22/13)                       | 0                                |
| Galanaud et al., 2014 [35]    | Cohort  | 2004-2006 | 173       | 173             | 0        | 0                   | DOAC or VKA, 3              | 3                       | NA                                | 18 (18/0)                        | 2 (2/0)                          |
| Couturaud et al., 2015 [36]   | RCT     | 2007-2012 | 187       | 0               | 187      | 0                   | VKA, 6                      | 3.4**                   | 31                                | 39 (0/39)                        | 0                                |
| Kearon et al., 2015 [37]      | Cohort  | 2008-2012 | 319       | 141             | 178      | 16 (5)              | VKA, 3                      | 2.2*                    | 17                                | 42 (20/22)                       | 1 (0/1)                          |
| Study                  | Cohort                  | n   | n   | n   | n   | n   | n   | n   | n   | n   | n   | n   | n   | n   |
|-----------------------|-------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----- |
| Rodger et al., 2016 [38] | 2001-2006               | 450 | 221 | 229 | 0   | DOAC or VKA, 5 | 5   | NA | 161 (105/56) | 3 (3/0) |
| Kyrle et al., 2016 [39]   | 1992-2008               | 839 | 503 | 336 | 0   | VKA, 7 (mean) | 7.7a | 116 | 259 (151/108) | 4 (3/1) |
| Moreno et al., 2016 [40]   | 2004-2013               | 353 | 83  | 270 | 0   | VKA, 3 | 1.8a | 43  | 65  | 1   |
| Rodger et al., 2017 [41]   | 2008-2015               | 914 | 260 | 654 | Unclear | DOAC or VKA, 5 | 1   | NA | 42 (10/32) | 0   |

* Comprises follow up of patients with provoked VTE
* Median follow up duration
Table 2. Evaluation of presence of bias for all 24 identified relevant studies. VTE=Venous Thromboembolism

| Article                  | Assessment of bias |          |          | Selective outcome reporting | Overall judgement |
|-------------------------|--------------------|----------|----------|-----------------------------|-------------------|
|                         | Representative study population | Incomplete outcome data | | | | |
|                         | Clear description in and exclusion criteria | Patient population | Adequate anticoagulation treatment prior to cessation | Clear follow up duration | Complete follow up >95% | Definition of unprovoked VTE | Definition of fatal VTE | Adjudication of outcomes | Bias in certain direction |
| Schulman et al., 1995 [18] | • | • | • | • | • | • | • | • | • |
| Agnelli et al., 2001 [19] | • | • | • | • | • | • | • | • | • |
| Ridker et al., 2003 [20] | • | • | • | • | • | • | • | • | • |
| Baglin et al., 2003 [21] | • | • | • | • | • | • | • | • | • |
| Schulman et al., 2003 [22] | • | • | • | • | • | • | • | • | • |
| Cosmi et al., 2005 [23] | • | • | • | • | • | • | • | • | • |
| Young et al., 2006 [24] | • | • | • | • | • | • | • | • | • |
| Prandoni et al., 2007 [25] | • | • | • | • | • | • | • | • | • |
| Baglin et al., 2008 [26] | • | • | • | • | • | • | • | • | • |
| Prandoni et al., 2009 | • | • | • | • | • | • | • | • | • |
| Reference                        | 2010 | 2011 | 2012 | 2012 | 2013 | 2013 | 2014 | 2015 | 2016 |
|---------------------------------|------|------|------|------|------|------|------|------|------|
| Poli et al., 2010               | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    |
| Siragusa et al., 2011           | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    |
| Becattini et al., 2012          | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    |
| Brighton et al., 2012           | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    |
| Olie et al., 2012               | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    |
| Ribeiro et al., 2013            | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    |
| Schulman et al., 2013           | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    |
| Galanaud et al., 2014           | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    |
| Couturaud et al., 2015          | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    |
| Kearon et al., 2015             | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    |
| Rodger et al., 2016             | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    |
| Kyrle et al., 2016              | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    |
| Moreno et al., 2016             | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    |
| Rodger et al., 2017             | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    | ●    |
Overall
- unknown or unclear
- no
- yes

Definition unprovoked/fatal VTE
- other than definitions in our study
- not present
- according to definitions in our study

Patient population: patient selection
- no distinction in follow up and baseline characteristics between provoked and unprovoked VTE
- no distinction in follow up or baseline characteristics between provoked and unprovoked VTE
- unprovoked VTE patients clearly identified

Overall risk of bias
- low risk
- moderate risk
- high risk
| Subgroup                                         | Studies included | Patients | Fatal recurrent VTE | Recurrent VTE | Pooled Case-fatality rate % (95%CI) | I² (%) | Pooled rate of recurrent fatal VTE (95%CI), events per 100 py | Pooled rate of recurrent VTE (95%CI), events per 100 py |
|-------------------------------------------------|------------------|----------|---------------------|--------------|-------------------------------------|--------|---------------------------------------------------------------|---------------------------------------------------------------|
| VTE at baseline in studies with low or moderate risk of bias |                  |          |                     |              |                                     |        |                                                               |                                                               |
| Unprovoked VTE                                  | 18               | 6758     | 58                  | 1079         | 2.6 (0.86-5.0)                      | 66.60  | 0.17 (0.047-0.33)                                             | 6.3 (5.42-7.3)                                                |
| Unprovoked DVT                                  | 13               | 3675     | 45                  | 669          | 2.7 (0.50-6.1)                      | 63.52  | 0.18 (0.025-0.43)                                             | 6.2 (4.6-8.0)                                                |
| Unprovoked PE                                   | 9                | 1783     | 8                   | 243          | 1.6 (0-5.7)                         | 48.43  | 0.060 (0-0.28)                                               | 5.6 (4.2-7.1)                                                |
| Any unprovoked VTE                             | 24               | 8914     | 64                  | 1545         | 2.0 (0.69-3.8)                      | 65.21  | 0.12 (0.036-0.25)                                             | 6.2 (5.4-7.2)                                                |
| Unprovoked DVT                                  | 17               | 4544     | 49                  | 887          | 2.3 (0.52-4.8)                      | 60.39  | 0.14 (0.022-0.33)                                             | 6.3 (5.0-7.6)                                                |
| Unprovoked PE                                   | 13               | 2230     | 9                   | 426          | 0.12 (0-1.8)                        | 34.90  | 0.011 (0-0.11)                                               | 4.9 (4.2-5.7)                                                |
| Other subgroups                                 |                  |          |                     |              |                                     |        |                                                               |                                                               |
| Overall VTE                                     | 24               | 8914     | 64                  | 1545         | 2.0 (0.69-3.8)                      | 65.21  | 0.13 (0.036-0.25)                                             | 6.2 (5.4-7.2)                                                |
| Overall DVT                                     | 17               | 4544     | 49                  | 887          | 2.3 (0.52-4.8)                      | 60.39  | 0.14 (0.022-0.33)                                             | 6.3 (5.0-7.6)                                                |
| Overall PE                                      | 13               | 2230     | 9                   | 426          | 0.12 (0-1.8)                        | 34.90  | 0.011 (0-0.11)                                               | 4.9 (4.2-5.7)                                                |
| Enrolment before 2000                           | 11               | 4245     | 55                  | 883          | 4.0 (1.3-7.8)                       | 76.46  | 0.27 (0.038-0.59)                                             | 6.8 (5.4-8.4)                                                |
| Enrolment after 1st of Jan 2000                 | 12               | 4508     | 9                   | 642          | 0.71 (0.063-1.8)                    | 0      | 0.039 (0.0028-0.1)                                            | 5.9 (0.47-7.2)                                                |
| Cohort                                          | 16               | 6020     | 51                  | 1161         | 1.7 (0.19-4.2)                      | 74.62  | 0.11 (0.009-0.29)                                             | 6.4 (5.3-7.6)                                                |
| RCT                                             | 9                | 2894     | 13                  | 384          | 2.5 (0.69-5.0)                      | 26.83  | 0.14 (0.021-0.33)                                             | 6.0 (4.6-7.6)                                                |
| FU ≤2.5 years                                   | 12               | 5183     | 16                  | 574          | 1.8 (0.46-3.8)                      | 34.85  | 0.11 (0.018-0.27)                                             | 6.7 (5.2-8.3)                                                |
| FU >2.5 years                                   | 12               | 3731     | 48                  | 971          | 2.2 (0.22-5.4)                      | 76.57  | 0.13 (0.076-0.35)                                             | 5.8 (4.8-7.0)                                                |

| Sensitivity analyses (only studies with low/moderate bias) |                  |          |                     |              |                                     |        |                                                               |                                                               |
| Unprovoked VTE                                  | 18               | 6758     | 58                  | 1079         | 2.6 (0.86-5.0)                      | 66.60  | 0.17 (0.047-0.33)                                             | 6.3 (5.42-7.3)                                                |
| Unprovoked DVT                                  | 13               | 3675     | 45                  | 669          | 2.7 (0.50-6.1)                      | 63.52  | 0.18 (0.025-0.43)                                             | 6.2 (4.6-8.0)                                                |
| Unprovoked PE                                   | 9                | 1783     | 8                   | 243          | 1.6 (0-5.7)                         | 48.43  | 0.060 (0-0.28)                                               | 5.6 (4.2-7.1)                                                |

Table 3. Fatal VTE rates per subgroup. VTE=Venous Thromboembolism, DVT=Deep Vein Thrombosis, PE=Pulmonary Embolism, RCT=Randomised Controlled Trial, FU=Follow Up, CI=Confidence Interval, py=patient years.
| Enrolment before 2000 | 9 | 2203 | 50 | 598 | 4.4 (1.3-8.4) | 66.7 | 0.3 (0.081-0.62) | 6.9 (5.9-8.1) |
|-----------------------|---|------|----|-----|---------------|------|-----------------|--------------|
| Enrolment after 1st of January 2000 | 9 | 2455 | 8 | 481 | 0.94 (0.01-2.3) | 0 | 0.05 (0.008-0.13) | 5.6 (4.3-7.1) |
| Cohort | 9 | 3864 | 45 | 695 | 2.6 (0.17-6.8) | 78.5 | 0.18 (0.011-0.47) | 6.6 (5.5-7.8) |
| RCT | 9 | 2894 | 13 | 384 | 2.5 (0.69-5.0) | 26.8 | 0.14 (0.021-0.33) | 6.0 (4.6-7.6) |
| FU<2.5 years | 10 | 4247 | 15 | 435 | 2.4 (0.73-4.7) | 26.6 | 0.14 (0.022-0.33) | 6.5 (4.9-8.3) |
| FU>2.5 years | 8 | 2511 | 43 | 644 | 3.0 (0.17-7.8) | 80.3 | 0.19 (0.009-0.52) | 6.3 (5.4-7.2) |
Supplementary Appendix

Literature search strategy:

**Pubmed**

("PE"[ti] OR "DVT"[ti] OR "Pulmonary Embolism"[Majr] OR "Venous Thromboembolism"[Majr] OR "Venous Thrombosis"[Majr] OR ("Embolism"[Majr:NoExp] OR "Embolism"[ti] OR "Thrombosis"[Mesh:NoExp] OR "Embolisms"[ti] OR "embolus"[ti] OR "emboli"[ti] OR "thromboembolism"[ti] OR "thromboembolisms"[ti]) AND ("Lung"[Majr] OR "lung"[ti] OR "lungs"[ti] OR "pulmonary"[ti] OR "venous"[ti] OR "deep vein"[ti] OR "deep-vein"[ti] OR "deep venous"[ti] OR "deep-venous"[ti])) AND ("Anticoagulants"[Mesh] OR "Anticoagulant"[tw] OR "Anticoagulants"[tw] OR "Anticoagulants" [Pharmacological Action] OR "Acenocoumarol"[tw] OR "apixaban"[tw] OR "antivitamins K"[tw] OR "vitamin K"[tw] OR "NOAC"[tiab] OR "NOACs"[tw] OR "DOACs"[tw] OR "DOAC"[tiab] OR "warfarin"[tw] OR "dabigatran"[tw] OR "edoxaban"[tw] OR "Rivaroxaban"[tw] OR "Factor Xa Inhibitors" [Pharmacological Action] OR "Antithrombins"[Mesh] OR "Antithrombins" [Pharmacological Action] OR "Heparin"[Mesh] OR "heparin"[tw]) AND ("recurrent"[tw] OR "recurrence"[tw]) AND english [la] NOT ("animals"[mesh] NOT "humans"[mesh])

NOT "Case Reports" [Publication Type]

**EMBASE**

("PE".ti. OR "DVT".ti. OR *lung embolism/ OR *exp venous thromboembolism/ OR *vein thrombosis/ OR (*embolism/ OR "Embolism".ti. OR "Embolism".ti. OR *thrombosis/ OR "Emboli".ti. OR *embolus/ OR "embolus".ti. OR "emboli/ OR "thromboembolism".ti. OR "thromboembolisms".ti.) AND (*lung/ OR "lung".ti. OR "lungs".ti. OR "pulmonary".ti. OR "venous".ti. OR "vein".ti. OR "deep vein".ti. OR "deep-vein".ti. OR "deep venous".ti.)) AND (exp anticoagulant agent/ OR "Anticoagulant".ti,ab. OR "Anticoagulants".ti,ab. OR acenocoumarol/ OR "Acenocoumarol".ti,ab. OR apixaban/ OR "apixaban".ti,ab. OR "antivitamins K".ti,ab. OR "vitamin K".ti,ab. OR "NOAC".ti,ab. OR "NOACs".ti,ab. OR "DOACs".ti,ab. OR "DOAC".ti,ab. OR "warfarin" OR "warfarin".ti,ab. OR "dabigatran" OR "dabigatran".ti,ab. OR edoxaban OR "edoxaban".ti,ab. OR rivaroxaban OR "Rivaroxaban".ti,ab. OR "Rivaroxaban".ti,ab.)
OR exp blood clotting factor 10a inhibitor/ OR "blood clotting factor 10a inhibitor".ti,ab. OR "blood clotting factor 10a inhibitors".ti,ab. OR antithrombin/ OR "Antithrombins".ti,ab. OR "anti-thrombins".ti,ab. OR "anti thrombins".ti,ab. OR heparin/ OR "heparin".ti,ab. AND
("recurrent".ti,ab. OR "recurrence".ti,ab.) NOT (animal/ NOT human/) NOT case report/

Web of Science
TI=("PE" OR "DVT" OR ("Embolism" OR "Embolisms" OR "embolus" OR "emboli" OR "thromboembolism" OR "thrombosis" OR "thromboembolisms") AND ("lung" OR "lungs" OR "pulmonary" OR "venous" OR "vein" OR "deep vein" OR "deep-vein"))) AND TS=("Anticoagulant" OR "Anticoagulants" OR "Acenocoumarol" OR "apixaban" OR "antivitamins K" OR "vitamin K" OR "NOAC" OR "NOACs" OR "DOACs" OR "DOAC" OR "warfarin" OR "dabigatran" OR "edoxaban" OR "Rivaroxaban" OR "Antithrombins" OR "heparin" OR "blood clotting factor 10a inhibitor" OR "blood clotting factor 10a inhibitors") AND TS=("recurrent" OR "recurrence") NOT TS=("animal" NOT "human") NOT TS="case report"

Cochrane
(PE" OR "DVT" OR ("Embolism" OR "Embolisms" OR "embolus" OR "emboli" OR "thromboembolism" OR "thrombosis" OR "thromboembolisms") AND ("lung" OR "lungs" OR "pulmonary" OR "venous" OR "vein" OR "deep vein" OR "deep-vein")) AND ("Anticoagulant" OR "Anticoagulants" OR "Acenocoumarol" OR "apixaban" OR "antivitamins K" OR "vitamin K" OR "NOAC" OR "NOACs" OR "DOACs" OR "DOAC" OR "warfarin" OR "dabigatran" OR "edoxaban" OR "Rivaroxaban" OR "Antithrombins" OR "heparin" OR "blood clotting factor 10a inhibitor" OR "blood clotting factor 10a inhibitors") AND ("recurrent" OR "recurrence")
Supplementary Figures

Figure S1. Meta-analysis of the case-fatality incidences after anticoagulant cessation in all studies. CFR=Case Fatality Rate, CI=Confidence Interval.

| Study                  | Overall CFR | CFR % (95%CI) | Weight (%) |
|------------------------|-------------|---------------|------------|
| Schulman et al, 1996   |             | 10 (3.6-26)  | 3.43       |
| Agnelli et al, 2001    |             | 0 (0-15)     | 2.87       |
| Rodier et al, 2003     |             | 5.4 (1.5-18) | 3.87       |
| Brgin et al, 2003      |             | 0 (0-11)     | 3.61       |
| Schulman et al, 2003   |             | 4.2 (1.5-12) | 4.98       |
| Gomes et al, 2005      |             | 6.7 (2.6-15) | 5.98       |
| Young et al, 2005      |             | 3.9 (0.6-19) | 3.24       |
| Prandini et al, 2007   |             | 13 (9.2-17)  | 6.68       |
| Brgin et al, 2008      |             | 0 (0-12)     | 3.37       |
| Prandini et al, 2006   |             | 8.3 (2.8-22) | 3.82       |
| Poli et al, 2010       |             | 0 (0.16)     | 2.79       |
| Srngaya et al, 2011    |             | 0 (0.12)     | 3.43       |
| Becattini et al, 2012  |             | 2.3 (0.41-12)| 4.14       |
| Brighton et al, 2012   |             | 1.4 (0.24-7.4)| 5.02      |
| Olie et al, 2012       |             | 0 (0-4.8)    | 5.04       |
| Ribero et al, 2013     |             | 0 (0-15)     | 2.95       |
| Schulman et al, 2013   |             | 0 (0-10)     | 3.77       |
| Galansau et al, 2014   |             | 11 (3.1-33)  | 2.61       |
| Couturaud et al, 2015  |             | 0 (0-0.9)    | 3.96       |
| Kearon et al, 2015     |             | 2.4 (0.42-12)| 4.10       |
| Rodger et al, 2016     |             | 1.5 (0.64-5.3)| 6.04     |
| Kykle et al, 2016      |             | 1.5 (0.60-3.9)| 6.46     |
| Moreno et al, 2016     |             | 1.5 (0.27-8.2)| 4.84     |
| Rodger et al, 2017     |             | 0 (0-4.1)    | 4.10       |

Overall VTE (P^2=65.21) | 2.0 (0.60-3.8) | 100

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Figure S2. Meta-analysis of case-fatality incidences after anticoagulant cessation for studies that started enrolment before and after the 1st of January 2000. CFR=Case Fatality Rate, CI=Confidence Interval, Jan=January
Figure S3. Meta-analysis of case-fatality incidences after anticoagulant cessation for initial unprovoked DVT and PE. DVT=Deep Vein Thrombosis, PE=Pulmonary Embolism, CFR=Case Fatality Rate, CI=Confidence Interval.
Figure S4. Meta-analysis of the case-fatality incidences after anticoagulant cessation for initial unprovoked DVT and PE in studies with low to moderate bias. DVT=Deep Vein Thrombosis, PE=Pulmonary Embolism, CFR=Case Fatality Rate, CI=Confidence Interval.

| Study                  | Overall CFR | CFR % (95% CI) | Weight (%) |
|------------------------|-------------|----------------|------------|
| **DVT**                |             |                |            |
| Schulman et al, 1995 (18) |             | 8.3 (2.3-26)  | 6.57       |
| Agnelli et al, 2001 (19)  |             | 0.0 (0-15)     | 6.22       |
| Cozzi et al, 2005 (23)    |             | 5.8 (2.9-15)   | 10.28      |
| Prandoni et al, 2007 (25)  |             | 13.8 (9.3-17)  | 12.51      |
| Prandoni et al, 2009 (27)  |             | 8.5 (5.29-22)  | 8.04       |
| Singla et al, 2011 (26)    |             | 0.0 (0-12)     | 7.31       |
| Becattini et al, 2012 (30)  |             | 0.0 (0-12)     | 7.07       |
| Brighton et al, 2012 (31)  |             | 0.0 (4-4.9)    | 8.39       |
| Schulman et al, 2013 (34)  |             | 0.0 (0-15)     | 6.37       |
| Catala et al, 2014 (35)    |             | 11.1 (3.1-33)  | 5.71       |
| Kearon et al, 2015 (37)    |             | 0.0 (0-15)     | 6.37       |
| Rodger et al, 2016 (38)    |             | 2.9 (0.98-6.1) | 11.10      |
| Rodger et al, 2017 (41)    |             | 0.0 (0-28)     | 3.94       |
| **DVT low to moderate bias (I²=63.52)** |             | 2.7 (1.5-6.1)  | 100        |
| **PE**                  |             |                |            |
| Schulman et al, 1995 (18) |             | 2.6 (0.6-6)    | 3.95       |
| Prandoni et al, 2007 (25)  |             | 1.14 (0.5-3.1) | 12.19      |
| Becattini et al, 2012 (30)  |             | 6.3 (1.1-28)   | 8.95       |
| Bright et al, 2012 (31)    |             | 3.1 (0.25-10)  | 12.96      |
| Schulman et al, 2013 (34)  |             | 0.0 (0-23)     | 7.85       |
| Couturaud et al, 2015 (36)  |             | 0.0 (0-9.9)    | 14.15      |
| Kearon et al, 2015 (37)    |             | 4.6 (0.81-22)  | 10.76      |
| Rodger et al, 2016 (38)    |             | 0.0 (0-6.4)    | 16.18      |
| Rodger et al, 2017 (41)    |             | 0.0 (0-11)     | 12.98      |
| **PE low to moderate bias (I²=48.43)** |             | 1.5 (0.5-7)    | 100        |
Supplementary Tables

Table S1. Fatal VTE definitions of 24 included studies. VTE=Venous Thromboembolism

| Study                    | Definition of fatal VTE | Adjudicated by central committee |
|--------------------------|-------------------------|---------------------------------|
| Schulman et al., 1995 [18] | Autopsy                | Yes                             |
| Agnelli et al., 2001 [19]  | Autopsy, clinically suspected | Yes                           |
| Ridker et al., 2003 [20]   | None provided           | Yes                             |
| Baglin et al., 2003 [21]   | None provided           | Yes                             |
| Schulman et al., 2003 [22] | Autopsy                | Yes                             |
| Cosmi et al., 2005 [23]    | None provided           | Yes                             |
| Young et al., 2006 [24]    | Autopsy, clinically suspected | No                            |
| Prandoni et al., 2007 [25] | Clinically suspected, unexplained death | Yes                        |
| Baglin et al., 2008 [26]   | None provided           | Yes                             |
| Prandoni et al., 2009 [27] | Autopsy, unexplained death | Yes                           |
| Poli et al., 2010 [28]     | None provided           | No                              |
| Siragusa et al., 2011 [29] | None provided           | Yes                             |
| Becattini et al., 2012 [30] | Autopsy, clinically suspected | Yes                       |
| Reference                        | Methodology                                            | Result |
|---------------------------------|--------------------------------------------------------|--------|
| Brighton et al., 2012 [31]      | Autopsy, clinically suspected                          | Yes    |
| Olie et al., 2012 [32]          | None provided                                          | No     |
| Ribeiro et al., 2013 [33]       | None provided                                          | No     |
| Schulman et al., 2013 [34]      | Clinically suspected, unexplained death                | Yes    |
| Galanaud et al., 2014 [35]      | None provided                                          | Yes    |
| Couturaud et al., 2015 [36]     | Autopsy, unexplained death                            | Yes    |
| Kearon et al., 2015 [37]        | Unexplained death                                      | Yes    |
| Rodger et al., 2016 [38]        | Autopsy                                               | Yes    |
| Kyrle et al., 2016 [39]         | None provided                                          | Yes    |
| Moreno et al., 2016 [40]        | None provided                                          | No     |
| Rogder et al., 2017 [41]        | None provided                                          | Yes    |
Table S2. Index VTE, DVT and PE fatality rates stratified by enrolment initiation before and after the 1st of January 2000 and fatal VTE definitions. Fatal rates stratified by different fatal VTE definitions. VTE=Venous Thromboembolism, DVT=Deep Vein Thrombosis, PE=Pulmonary Embolism, CI=Confidence Interval, py=patient years

| Subgroup | Studies included (n) | Patients included (n) | Fatal recurrent VTE (n) | Recurrent VTE (n) | Pooled Case-fatality rate % (95%CI) | I² (%) | Pooled rate of recurrent fatal VTE (95%CI), events per 100 py | Pooled rate of recurrent VTE (95%CI), events per 100 py |
|----------|---------------------|----------------------|------------------------|------------------|-----------------------------------|-------|-------------------------------------------------------------|-------------------------------------------------------------|
| **Enrolment before the year 2000** | | | | | | | | |
| Any unprovoked VTE | 11 | 4245 | 55 | 883 | 4.0 (1.3-7.8) | 26.46 | 0.27 (0.06-0.57) | 6.8 (5.4-8.4) |
| Any unprovoked DVT | 8 | 2681 | 44 | 602 | 4.5 (1.3-9.1) | 20.24 | 0.31 (0.047-0.74) | 6.8 (5-8.9) |
| Any unprovoked PE | 3 | 507 | 6 | 141 | 6.0 (0-26) | - | 0.27 (0-1.5) | 4.2 (3.5-4.9) |
| **Enrolment after 1st of Jan 2000** | | | | | | | | |
| Any unprovoked VTE | 12 | 4508 | 9 | 642 | 0.71 (0.063-1.8) | 0 | 0.039 (0.0028-0.1) | 5.9 (0.4-7.2) |
| Any unprovoked DVT | 9 | 3861 | 5 | 285 | 0.5 (0-2.2) | 0 | 0.14 (0.022-0.33) | 6.3 (5.0-7.6) |
| Any unprovoked PE | 9 | 2153 | 3 | 265 | 0 (0-0.51) | 0 | 0.12 (0.03-0.25) | 6.2 (5.4-7.2) |
### Fatal VTE definitions;

#### any VTE

|                | 12  | 3668 | 14  | 701 | 0.95 (0.067-2.5) | 27.06 | 0.057 (0-0.16) | 6.1 (4.8-7.4) |
|----------------|-----|------|-----|-----|-----------------|-------|----------------|---------------|
| Autopsy, clinically suspected | 7   | 2194 | 12  | 434 | 2.1 (0.73-4.0)  | 0     | 0.14 (0.045-0.26) | 6.6 (5.5-7.9) |
| Unexplained death | 5   | 1470 | 38  | 420 | 3.6 (0.018-11)  | 81.15 | 0.16 (0-0.56)  | 5.9 (3.8-8.4)  |

#### Unprovoked DVT

|                | 7   | 1748 | 10  | 324 | 1.6 (0.059-5.2) | 19.98 | 0.094 (0-0.30) | 5.6 (3.8-7.7) |
|----------------|-----|------|-----|-----|-----------------|-------|----------------|---------------|
| Autopsy, clinically suspected | 6   | 1068 | 6   | 243 | 1.5 (0.083-3.8) | 0.58  | 0.11 (0-0.29)  | 7.1 (5.3-9.2) |
| Unexplained death | 4   | 1468 | 33  | 320 | 4.7 (0.15-13)   | 70.48 | 0.28 (0-1.1)   | 6.2 (3.3-9.8)  |

#### Unprovoked PE

|                | 5   | 947  | 1   | 215 | 0 (0-0)  | 0     | 0 (0-0.026) | 4.5 (3.8-5.3) |
|----------------|-----|------|-----|-----|---------|-------|-------------|---------------|
| Autopsy, clinically suspected | 4   | 511  | 3   | 109 | 1.6 (0-9.9) | 53    | 0.077 (0-0.67) | 5.9 (3.8-8.4) |
| Unexplained death | 4   | 709  | 5   | 102 | 2.9 (0-12)   | 59.89 | 0.14 (0-0.59) | 5.0 (3.7-6.4)  |
