Venous and arterial thrombotic complications. Solutions in clinical practice

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Chapter 2

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

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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 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. Data were extracted from both randomized controlled trials and observational studies published before May 1st 2017. The pooled fatality rates were calculated using a random-effects model. Eighteen studies with low to moderate bias were included in the primary analysis, totaling 6758 patients with a median follow up duration of 2.2 years (range 1-5 years). After anticoagulation cessation, the weighted pooled rate of VTE recurrence was 6.3 (95% CI 5.4-7.3) and the weighted pooled rate of fatal recurrent VTE was 0.17 (95% CI 0.047-0.33) per 100 patient-years, for a case-fatality rate of 2.6% (95% CI 0.86-5.0). 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 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 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 recurrent VTE (9).

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, with a yearly risk of fatal recurrence ranging between 0.4% and 0.5% (7, 10). To date, these exact numbers are unknown for patients with unprovoked VTE, although this is the patient category for which 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 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 from 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 differentiate between: i) enrolment periods, comparing studies that started enrolment before and after the 1st of January 2000 (if reported), ii) cohort studies and RCTs, iii) 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) different definitions of fatal VTE that were applied.

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 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 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

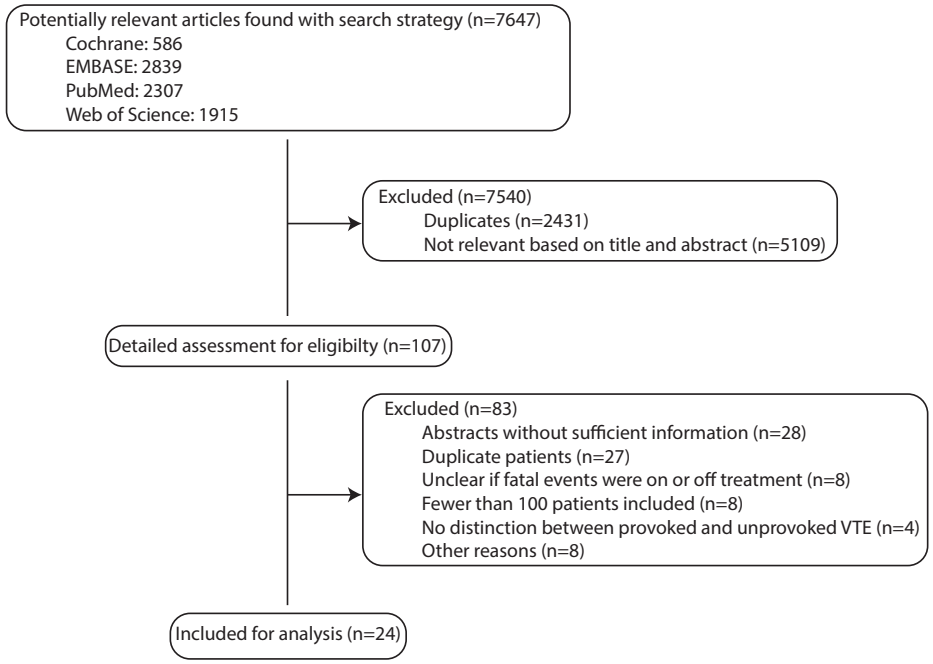
null hypothesis of no differences (χ^2 distribution with S (number of subgroups) minus 1 degree of freedom). All analyses were performed using Stata 14.0 (Stata Corp., College Station, TX, USA).

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).

Figure 1. Flow-chart of the clinical search



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 the criteria of the ISTH 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

The 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. The weighted pooled rate of recurrent VTE in studies with low or moderate risk of bias was 6.3 (95% CI 5.4-7.3; I^2=72.6%) per 100 patient-years and the rate of fatal recurrent VTE was 0.17 (95% CI 0.047-0.33; I^2=83.57%) per 100 patient-years, for a case-fatality rate of 2.6% (95% CI 0.86-5.0; I^2: 66.6%; **Figure 2**).

Secondary outcomes

The overall weighted pooled fatal rate of VTE recurrence among all 24 studies was 6.2 (95% CI 5.4-7.2; I^2=86.8%) per 100 patient-years and the rate of fatal recurrent VTE was 0.13 (95% CI 0.036-0.25; I^2=72.7%) per 100 patient-years, for a case-fatality rate of 2.0% (95% CI 0.69-3.8; I^2: 65.2%; **Supplementary Appendix, Figure S1**).

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 S2**). Notably, the analysis of the more recent studies showed good homogeneity (both I^2=0) while the results of earlier studies were quite heterogeneous (I^2>75). The rate of fatal recurrent VTE 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

Table 1. Characteristics and outcomes of the included studies.

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.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[a]	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*[a]	NA	268 (240/28)	34 (30/4)
Baglin et al., 2008 [26]	Cohort	2001-2003	142	-	-	0	VKA, 6	3.2[a]	NA	28	0
Prandoni et al., 2009 [27]	RCT	1999-2006	151	151	0	0	VKA, 6	2.8	7	36 (36/0)	3 (3/0)
Poli et al., 2010 [28]	Cohort	Unclear	161	0	161	0	VKA, 6	3*[a]	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*[a]	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[a]	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)
Rodger et al., 2016 [38]	Cohort	2001-2006	450	221	229	0	DOAC or VKA, 5	5	NA	161 (105/56)	3 (3/0)
Kyrle et al., 2016 [39]	Cohort	1992-2008	839	503	336	0	VKA, 7 (mean)	7.7[a]	116	259 (151/108)	4 (3/1)
Moreno et al., 2016 [40]	Cohort	2004-2013	353	83	270	0	VKA, 3	1.8[a]	43	65	1
Rodger et al., 2017 [41]	Cohort	2008-2015	914	260	654	Unclear	DOAC or VKA, 5	1	NA	42 (10/32)	0

Note: 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. * Comprises follow up of patients with provoked VTE. [a] Median follow up duration

Table 2. Evaluation of presence of bias for all 24 identified relevant studies.

	Assessment of bias								
	Representative study population			Incomplete outcome data		Selective outcome reporting			Overall judgement
Article	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 [27]	●	●	●	●	●	●	●	●	●
Poli et al., 2010 [28]	●	●	●	●	●	●	●	●	●
Siragusa et al., 2011 [29]	●	●	●	●	●	●	●	●	●
Becattini et al., 2012 [30]	●	●	●	●	●	●	●	●	●
Brighton et al., 2012 [31]	●	●	●	●	●	●	●	●	●
Olie et al., 2012 [32]	●	●	●	●	●	●	●	●	●
Ribeiro et al., 2013 [33]	●	●	●	●	●	●	●	●	●
Schulman et al., 2013 [34]	●	●	●	●	●	●	●	●	●
Galanaud et al., 2014 [35]	●	●	●	●	●	●	●	●	●
Couturaud et al., 2015 [36]	●	●	●	●	●	●	●	●	●
Kearon et al., 2015 [37]	●	●	●	●	●	●	●	●	●
Rodger et al., 2016 [38]	●	●	●	●	●	●	●	●	●
Kyrle et al., 2016 [39]	●	●	●	●	●	●	●	●	●
Moreno et al., 2016 [40]	●	●	●	●	●	●	●	●	●
Rodger et al., 2017 [41]	●	●	●	●	●	●	●	●	●

Note: VTE=Venous Thromboembolism

Overall
- ● unknown or unclear
- ● no
- ● yes

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

Overall risk of bias
- ● high risk
- ● moderate risk
- ● low risk

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

Table 3. Fatal VTE rates per subgroup.

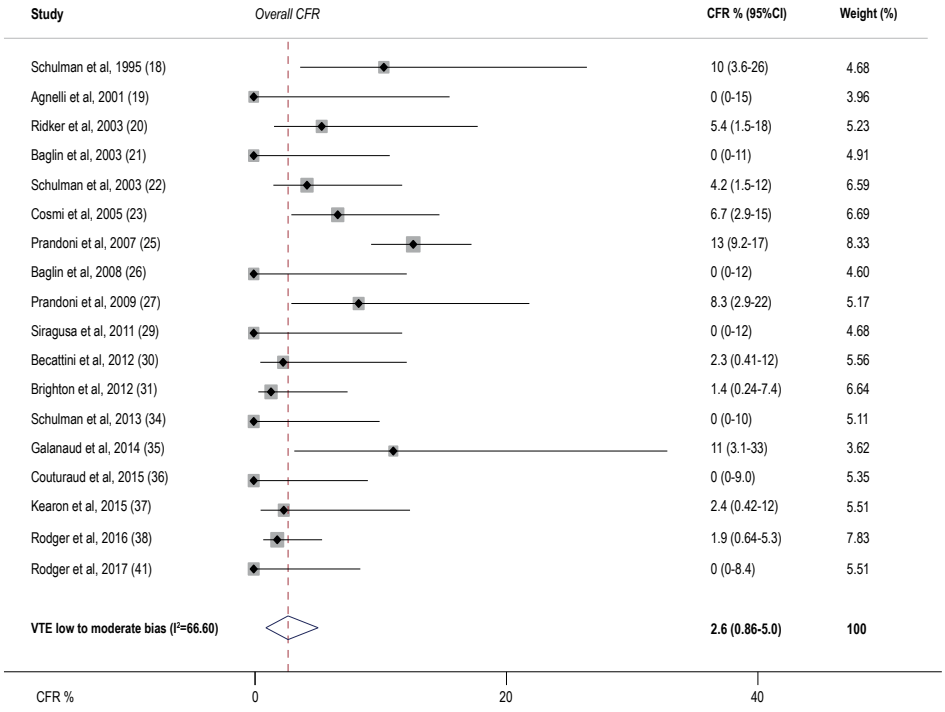
Subgroup	Studies included (n)	Patients (n)	Fatal recurrent VTE (n)	Recurrent VTE (n)	Pooled Case-fatality rate % (95%CI)	I^2 (%)	Pooled rate of recurrent fatal VTE (95%CI), events per 100 py	Pooled rate of recurrent VTE (95%CI), events per 100 py
VTE at baseline in studies with low or moderate risk of 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)
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	2730	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)

Note: VTE=Venous Thromboembolism, DVT=Deep Vein Thrombosis, PE=Pulmonary Embolism, RCT=Randomised Controlled Trial, FU=Follow Up, CI=Confidence Interval, py=patient years.

(1.7%, 95% CI 0.19-4.2; 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=60.39%) and 0.12% (95% CI 0-1.8; I^2=34.9%; P=0.57 for interaction; **Supplementary Appendix, Figure S3**). When focussing 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**).

Figure 2. Meta-analysis of the case-fatality incidences after anticoagulant cessation in studies with low to moderate risk of bias.



Note: CFR=Case Fatality Rate, CI=Confidence Interval.

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 sus-

picion (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; I^2= 81.15%), while studies without a clear definition of fatal recurrent VTE reported lowest rates (0.95%, 95% CI 0.067-2.5; I^2= 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. We observed a pooled rate of fatal recurrent VTE of 0.17 per 100 patient-years with a case-fatality rate of 2.6% in studies with low to moderate risk of bias. Where most meta-analyses performed in our study showed relevant heterogeneity among the included studies, the secondary analysis focussing on more recent studies (patient enrolment after January 1st 2000, total of 4508 patients) showed good homogeneity. The numerically lower pooled rate of fatal recurrence (0.039 per 100 patient-years) and case-fatality rate (0.71%) found in this subanalysis may be explained by 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 two 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 a non-significant higher risk of fatal recurrent VTE after an index DVT diagnosis than after an index PE diagnosis which was unexpected (7, 10). This difference is

mostly explained by biases of the data pooling due to major methodological differences between the included studies. Other explanations may be that PE is often over diagnosed due to adoption of more and more advanced CT technology (42). 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. Lastly, many of the patients with DVT may actually have had PE as well, although this was not objectively confirmed and therefore nor reported in the original study publications.

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 focussing 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. Our findings thus urgently call for an effort to standardize this definition for future studies in order to allow for valid inter-study comparisons (43).

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 0.047-0.33%. 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 (44-47).

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 0.17 (95% CI 0.047-0.33) per 100 patient-years for patients with unprovoked VTE after discontinuation of anticoagulation therapy in studies with low to moderate risk of bias. This was consistent with a case-fatality rate of 2.6% (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 0.33% per 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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