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Thrombosis and Haemostasis | Original Article

Long-term risk of major bleeding after discontinuing anticoagulation for unprovoked venous thromboembolism: a systematic review and meta-analysis

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What is known about this topic?

- In order to estimate the net clinical benefit of extended anticoagulant therapy and counsel patients with a first unprovoked venous thromboembolism (VTE) about the duration of treatment, clinicians require precise estimates for the long-term risks of recurrent VTE and major bleeding both with and without anticoagulation.
- Estimates of the long-term risk of major bleeding after discontinuing anticoagulation in patients with first unprovoked VTE are uncertain.

What does this paper add?

- In this meta-analysis of 20 studies and 8740 patients with a first unprovoked VTE, the overall risk of major bleeding after discontinuing anticoagulation was 0.4% per patient-year with a 5-year cumulative incidence of 1%.
- This information can help inform patient prognosis and estimate the incremental risk of major bleeding with extended anticoagulation to guide decision making about treatment duration for unprovoked VTE.

Abstract

Background: The long-term risk of major bleeding after discontinuing anticoagulant therapy for a first unprovoked venous thromboembolism (VTE) is uncertain.

Objectives: To determine the incidence of major bleeding up to 5 years after discontinuing anticoagulation for a first unprovoked VTE.

Methods: We searched MEDLINE, EMBASE, and Cochrane CENTRAL (from inception to January 2021) to identify relevant randomized controlled trials (RCTs) and prospective cohort studies reporting major bleeding after discontinuing anticoagulation in patients with a first unprovoked or weakly provoked VTE who had completed ≥3 months of initial treatment. Unpublished data on major bleeding events and person-years were obtained from authors of included studies to calculate study-level incidence rates. Random-effects meta-analysis was used to pool results across studies.

Results: Of 1123 records identified by the search, 20 studies (17 RCTs) and 8740 patients were included in the analysis. During 13 011 person-years of follow-up after discontinuing anticoagulation, the pooled incidence of major bleeding (n=41) and fatal bleeding (n=7) per 100 person-years was 0.35 (95% confidence interval [CI], 0.20-0.54) and 0.09 (95% CI, 0.05-0.15). The 5-year cumulative incidence of major bleeding was of 1.0% (95% CI, 0.4%-2.4%). The case-fatality rate of major bleeding after discontinuing anticoagulation was 19.9% (95% CI, 10.6%-31.1%).

Conclusions: The risk of major bleeding once anticoagulants are discontinued in patients with a first unprovoked VTE in not zero. Estimates from this study can help clinicians counsel patients about the incremental risk of major bleeding with extended anticoagulation to guide decision making about treatment duration for unprovoked VTE.

Keywords: anticoagulation, major bleeding, prognosis, thrombosis, venous thromboembolism,

INTRODUCTION

Venous thromboembolism (VTE) should be treated with anticoagulant therapy for at least 3 to 6 months.[1-3] Deciding whether to stop or continue anticoagulation beyond the initial 3 to 6 months of treatment (termed *extended anticoagulation*) remains a challenge particularly for patients with a first unprovoked VTE or VTE associated with minor transient risk factors (i.e., weakly provoked). To counsel these patients, clinicians require precise estimates for the *long-term* risks of recurrent VTE and major bleeding both with and without anticoagulation in order to estimate the net clinical benefit of extended treatment.

In three recent systematic reviews and meta-analyses, we determined the long-term risk of: 1) major bleeding during extended anticoagulation;[4] , 2) recurrent VTE during extended anticoagulation;[5], and 3) recurrent VTE after discontinuing anticoagulation[6] among patients with a first unprovoked or weakly provoked VTE. However, estimates for the long-term risk of major bleeding after discontinuing anticoagulation in this patient population are not well-established. Quantifying this risk is important to accurately estimate the incremental risk of major bleeding with extended anticoagulation, that is over and above the risk of major bleeding with no anticoagulant therapy (i.e. establish a baseline risk of major bleeding in patients with unprovoked/weakly provoked VTE).

A previous systematic review and meta-analysis of 11 randomized controlled trials (RCTs) reported a major bleeding incidence of 0.45 events per 100 person-years (95% confidence interval [CI], 0.29-0.64) after discontinuing anticoagulation in 3965 patients with VTE who did not receive extended treatment.[7] However, approximately 20% of all VTE patients included in this meta-analysis either had cancer, a history of prior VTE (i.e., not first event), or

VTE associated with strong provoking risk factors. Moreover, this meta-analysis did not examine the risk of major bleeding in men and women separately, or assess bleeding risk over time, and only included RCTs which were published up to February 2013.[7]

We performed a systematic review and meta-analysis of RCTs and prospective cohort studies to determine the annual and cumulative incidence of major bleeding up to 5 years after discontinuing anticoagulation in patients with a first episode of unprovoked or weakly provoked VTE that completed at least 3 months of initial treatment.

METHODS

The protocol for this study is registered in PROSPERO (CRD42017056309). This systematic review and meta-analysis is reported according to Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.[8]

Search strategy and study selection

An information specialist performed an electronic search in MEDLINE, EMBASE, and the Cochrane CENTRAL databases from inception to 1 January 2021, without language restrictions. Electronic searches were supplemented by hand searching bibliographies of relevant review articles to identify other potentially eligible studies. The systematic search strategy used for MEDLINE is provided in ***Supplementary Table S1***.

Two reviewers (F.K. and A.R.) independently screened titles, abstracts, and full-text publications using Covidence[9] (an online systematic review software program). Any disagreements were resolved through discussion or by consulting a third reviewer. Published RCTs and prospective cohort studies were eligible if they satisfied the following criteria: 1)

included patients with a first episode of objectively confirmed, symptomatic VTE that was either unprovoked or provoked by minor transient risk factors (as defined per International Society on Thrombosis and Haemostasis [ISTH] guidance on categorization of VTE[10] or per individual studies), 2) completed at least 3 months of initial anticoagulation before discontinuing treatment in eligible patients, and 3) reported major bleeding (as defined per ISTH criteria[11] or by individual studies) events during a minimum follow-up duration of 9 months after discontinuing anticoagulation. We included the publication with the longest follow-up when more than one article analyzed the same patients.

Data extraction and quality assessment

For each eligible study, two reviewers (F.K. and A.R) independently extracted the following data: study design; number of eligible patients; mean age, % men, definitions of unprovoked VTE and major bleeding, and duration of follow-up after discontinuing anticoagulation. For calculating incidence, we requested the following information from authors of every eligible study: aggregate data on the number of first major bleeding and fatal bleeding events, and person-years of follow-up (to ensure appropriate censoring of deaths, and patient losses to follow-up or withdrawals) after stopping anticoagulation among patients with a first unprovoked or weakly provoked VTE. To assess bleeding risk over time, we requested study authors to categorize these aggregate data into the following time intervals after discontinuing anticoagulation, as applicable to the duration of study follow-up: year 1, year 2, and years 3-5. Our request to study authors also ensured that major bleeding events during anticoagulant treatment, as well as patients with active cancer (as defined by the individual studies), a history of prior VTE, or strongly provoked VTE were excluded from those aggregate data.

Two reviewers (F.K. and A.R.) independently appraised risk of bias among the included studies using a modified version of the Newcastle-Ottawa Scale[12] based on 3 selection criteria and 3 outcome criteria – criteria assessing comparability were considered irrelevant in the context of our meta-analysis as we sought to determine the incidence of major bleeding during patient follow-up after discontinuing anticoagulation. Thus, we assessed all studies, including each arm of a RCT, as an independent observational cohort. Studies with ≥4 Newcastle-Ottawa Scale points were judged as having low risk of bias.[6]

Data synthesis and analysis

Incidence rate of major bleeding events per 100 person-years was calculated within each study cohort using the total number of first major bleeding events divided by the total person-years of follow-up. Results across study cohorts were pooled using DerSimonian–Laird random-effects meta-analysis, with cohorts weighted by the inverse of their variance.[13] Since we calculated the annual incidence rate using exact person-time at risk, we calculated the cumulative incidence of major bleeding at 2 and 5 years after discontinuing anticoagulation by 1) estimating the cumulative proportion of patients who *did not* experience major bleeding as the product of the proportion of patients who *did not* experience major bleeding during each of the specified time intervals, and then 2) estimating the cumulative proportion of patients that experienced major bleeding as the complement of the cumulative proportion of patients that *did not* experience major bleeding.[6] For example, the cumulative incidence of major bleeding at 5 years after discontinuing anticoagulation was calculated as follows:

> If the incidence rate of major bleeding events per 100 person-years was 1.0 in *year 1*, 0.8 in *year 2*, and 0.6 in *years 3-5*, then the cumulative proportion of patients that *did not*

experience major bleeding between years 1-5 was calculated as $(99.0\%_{year\ 1}) \times (99.2\%_{year\ 2}) \times ([99.4\%]^{3}_{years\ 3\text{-}5}) = 96.5\%$. The cumulative proportion of patients that experienced major bleeding between *years 1-5* was then estimated as $100\% - 96.5\% = 3.5\%$.

The calculation described above was repeated using the lower and upper limits of the 95% confidence intervals (CIs) associated with the incidence rates in order to estimate the lower and upper limits of the 95% CI for the cumulative incidences.

We also determined the case-fatality rate of major bleeding from the total number of fatal bleeding events divided by the total number of major bleeding events.

Subgroup analyses based on patient's sex and study design (RCTs vs. cohort studies) were performed to investigate potential sources of between-study heterogeneity. Incidence rate ratio [IRR] was computed to statistically compare major bleeding rates among subgroups. We also performed sensitivity analyses restricted to 1) studies that used the ISTH definition of major bleeding; and 2) excluding cohorts among included RCTs that were randomized to receive aspirin after completing initial anticoagulant therapy.

Between-study heterogeneity was quantified using the I^2 statistic with values of 25% defined as low, 50% as moderate, and 75% as high heterogeneity. All meta-analyses were performed using StatsDirect Version 3.3.5 (Merseyside, United Kingdom).[14]

RESULTS

Literature search and study characteristics

The systematic literature search identified a total of 1115 citations. After screening of titles and abstracts, 92 records were deemed eligible for full-text screening. After full-text screening, 18 studies (supplemented with 8 additional studies identified from other sources) were considered

eligible for inclusion in meta-analysis (**Figure 1**). After contacting the authors of these 26 studies for data clarifications in our target population, we acquired the requested data from 20 studies[15-34], while the remaining 6 studies[35-40] were excluded because information required for our analysis was unavailable or not provided.

A total of 17 RCTs[15-25, 28, 29, 31-34] and 3 prospective cohort studies[26, 27, 30] with 8740 patients with a first unprovoked or weakly provoked VTE were included in the analysis (**Table 1**). All 20 studies (27 independent study cohorts) contributed to the 'year 1' interval, 13 studies (19 cohorts) contributed to the 'year 2' interval, and 4 studies (6 cohorts) contributed to the 'years 3-5' interval of follow-up after discontinuing anticoagulation (**Table 1**). Eleven studies met the ISTH criteria for definition of major bleeding (**Table 1**). The overall risk of bias in individual studies was judged to be low (**Table 1**) – individual study scores for each Newcastle-Ottawa Scale criterion are provided in ***Supplementary Table S2***.

Major bleeding after discontinuing anticoagulation

During 13, 011 person-years of follow-up after discontinuing anticoagulation, there were a total of 41 major bleeding events (0.35 events per 100-person years; 95% CI, 0.20-0.54) and 7 fatal bleeding events (0.09 events per 100-person years; 95% CI, 0.05-0.15) (**Table 2**). Incidences of major and fatal bleeding events in individual study cohorts during each of the studied intervals of follow-up are provided in ***Supplementary Table S3***.

After discontinuing anticoagulation, the pooled incidence of major bleeding per 100 person-years was 0.44 (95% CI, 0.25-0.70) in year 1, 0.28 (95% CI, 0.14-0.48) in year 2, and 0.10 (95% CI, 0.0-0.42) in years 3-5, with a 5-year cumulative incidence of 1.0% (95% CI, 0.4%-2.4%) (**Table 2**). The pooled incidence of fatal bleeding per 100-person years was 0.15

(95% CI, 0.07-0.25) in year 1, and 0.13 (95% CI, 0.07-0.24) in year 2 – there were insufficient data to estimate the incidence of fatal bleeding beyond 2 years of follow-up (**Table 2**).

Based on 7 fatal bleeding and 41 major bleeding events, the pooled case-fatality rate of major bleeding after discontinuing anticoagulation was 19.9% (95% CI, 10.6%-31.1%) **(Figure 2).**

Subgroup analyses

Patient's sex. Information on major bleeding events after discontinuing anticoagulation in men and women separately was available from 17 studies (n=7775). The pooled incidence of major bleeding events per 100 person-years was 0.43 (95% CI, 0.21-0.74) in women and 0.28 (95% CI, 0.15-0.44) in men (IRR, 1.34; 95% CI, 0.75-2.47) (**Table 3**). The pooled incidence of fatal bleeding events per 100 person-years was 0.14 (95% CI, 0.06-0.26) in women and 0.12 (95% CI, 0.05-0.22) in men (**Table 3**).

Study design. There were 24 study cohorts (n=6697) from the 17 RCTs and 3 cohorts (n=2043) from the 3 prospective cohort studies included in this analysis (**Table 4**). Among study cohorts derived from RCTs, the pooled incidence of major and fatal bleeding events per 100 person-years was 0.39 (95% CI, 0.21-0.63) and 0.09 (95% CI, 0.04-0.16), respectively (**Table 4**). Among cohorts derived from prospective cohort studies, the pooled incidence of major and fatal bleeding events per 100 person-years was 0.19 (95% CI, 0.03-0.50) and 0.09% (95% CI, 0.02-0.22). The IRR for major bleeding among patients derived from RCTs vs. prospective cohort studies was 1.87 (95% CI, 0.78-5.47).

Sensitivity analyses

Estimates for the incidence of major bleeding in the primary analyses were similar in analyses restricted to 11 studies (n=5378) using the ISTH definition of major bleeding, and analyses excluding 3 study cohorts (n=1496) randomized to receive aspirin after completing initial anticoagulation (**sTable 3** in **Supplement 2).**

DISCUSSION

This large systematic review and meta-analysis establishes that the annual risk of major bleeding once anticoagulants are discontinued in patients with a first unprovoked or weakly provoked VTE who have competed at least 3 months of initial anticoagulant therapy is 0.4% (95% CI, 0.20 – 0.54), with a 5-year cumulative incidence of 1.0% (95% CI, 0.4%-2.4%).

The clinical implications of our findings are two-fold. First, our results can be used to advise patients about their prognosis after discontinuing anticoagulation for a first unprovoked or weakly provoked VTE. Estimates for the incidence rate of major and fatal bleeding synthesized in our study may inform patients that their prognosis after discontinuing anticoagulation is good, with a less than 0.5% risk for a future major or fatal bleeding event per year. At the same time, our results underscore that the risk of major bleeding after discontinuing anticoagulation is not zero and thus, clinicians and patients should be aware of this baseline bleeding risk when making treatment decision.

Second, estimates from our study can assist clinicians in more accurately estimating the incremental risk of major bleeding with extended anticoagulation required to determine the net clinical benefit of extended anticoagulation and guide treatment duration. In a recent systematic review and meta-analysis, we determined that the overall incidence of major bleeding events per 100 person-years among patients with first unprovoked or weakly provoked VTE receiving

extended anticoagulation was 1.74 events per 100 person-years (95% CI, 1.34-2.20) with vitamin K antagonists (VKA) and 1.12 events per 100 person-years (95% CI, 0.72-1.62) with direct oral anticoagulants (DOACs).[4] Using the overall incidence for major bleeding of 0.35 events (95% CI, 0.20-0.54) in patients with first unprovoked or weakly provoked VTE *not* receiving extended anticoagulation, determined in this meta-analysis, the incremental risk (per patient-year) of major bleeding during extended anticoagulant therapy would be estimated at 1.39% (95% CI, 0.99-1.85; number needed to harm, 72) with VKAs and 0.77% (95% CI, 0.37-1.27; number needed to harm, 130) with DOACs. When combined with incidences for recurrent VTE of 1.55 events per 100 person-years (95% CI, 1.01 – 2.20) with VKAs[5], 1.08 events per 100 person-years (95% CI, 0.77 – 1.44) with DOACs,[5] and 10.3 events per 100 person-years (95% CI, 8.6 – 12.1) without extended anticoagulation,[6] estimates from this meta-analysis could be used to balance the absolute VTE reduction benefits of extended anticoagulant therapy in shared decision making regarding long-term management of patients with a first unprovoked or weakly provoked VTE.

Strengths of our study include a comprehensive literature search and pooling of unpublished data from studies with an overall low risk of bias. With help from investigators of original studies, we combined data on more than 8500 patients specifically with a first unprovoked or weakly provoked VTE (as well as subgroups of men and women) who were prospectively followed for major bleeding after discontinuing anticoagulant therapy. Limitation of our study is that we did not perform an individual patient-level meta-analysis (owing to resource and time constraints as well as access to such data) which would have allowed us to calculate direct estimates for the cumulative incidence of major bleeding over time, and adjust estimates by various risk factors (and potential interactions between risk factors [e.g., age and sex]). Also, in the three prospective cohort studies included in our analysis[26, 27, 30], decisions

about discontinuing anticoagulant therapy were influenced by stratification of the risk of recurrent VTE (i.e., negative D dimer test result or a clinical decision rule). Consequently, certain patient factors (e.g., younger age) may have contributed to the potential lower risk of major bleeding observed among the prospective cohort studies included in our analysis. However, the overall point estimates for bleeding rates did not meaningfully change after exclusion of the three cohort studies.

CONCLUSION

The risk of major bleeding once anticoagulants are discontinued in patients with a first unprovoked VTE in not zero. Estimates from this study can help clinicians counsel patients on the incremental risk of major bleeding with extended anticoagulation to guide decision making about treatment duration for unprovoked VTE.

Author Contributions

Study concept and design: FK, AR, MR, DF. *Data acquisition:* All authors. *Statistical analysis:* FK. *Drafting of the manuscript:* FK, AR, MR, DF. *Critical revision of the manuscript for important intellectual content:* All authors. *Final approval of the manuscript:* All authors.

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Figure 1: Flow Diagram of Study Identification and Selection.

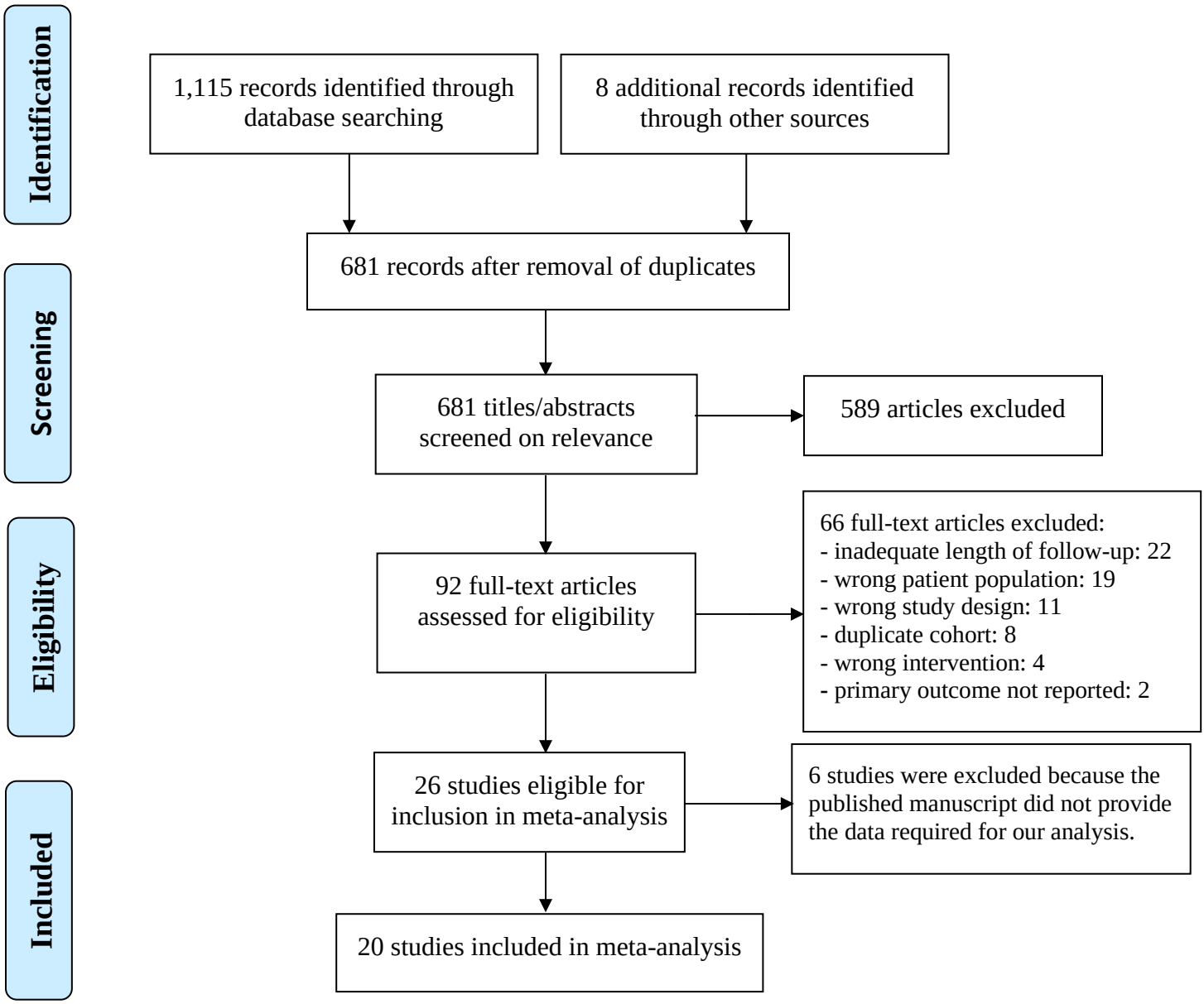


Table 1: Characteristics of included studies.

Source (year)	**Study Design**	**No. of patients with first unprovoked VTE**	**Men** (%)	**Age, years** (Range or SD)	**Unprovoked VTE Definition[a]** (minor transient risk factors included)	**Major Bleeding Definition**	***Follow-up Duration, years**	**Overall Risk of Bias**
LAFIT Kearon et al. (1999)[15]	RCT	83	53.0	58 (16)	ISTH	Overt bleeding and associated with a fall in hemoglobin of ≥2 g/dL; transfusion of ≥2 units of red cells; retroperitoneal or intracranial; warranting permanent discontinuation of study drug	2	Low
WODIT-DVT Agnelli et al. (2001)[16]	RCT	133	61.2	67.7 (7.3)	ISTH	Overt bleeding and associated with a fall in hemoglobin of ≥2 g/dL; transfusion of ≥2 units of red cells; retroperitoneal or intracranial; warranting permanent discontinuation of study drug	1	Low
DOTAVK Pinede et al. (2001)[17]	RCT	308			ISTH	Requiring hospitalization, transfusion, or treatment with blood products or vitamin K; when intracranial, intraocular, intraarticular, retroperitoneal; and/or when hemoglobin level fell by ≥2 g/dL.		Low
Arm 1		161	47.6	58.2 (1.0)			1	
Arm 2		147	47.0	58.9 (0.9)			1	
WODIT-PE Agnelli et al. (2003)[18]	RCT	181			ISTH	Overt bleeding and associated with a fall in hemoglobin of ≥2 g/dL; transfusion of ≥2 units of red cells; retroperitoneal or intracranial; warranting permanent		Low

						discontinuation of study drug or re-hospitalization.		
Arm 1		91	41.6	61.0 (15.5)			2	
Arm 2		90	39.4	62.9 (16.3)			2	
DURAC I Schulman et al. (2006)[19]	RCT	272	61.4	60.6 (15.4)	ISTH	Conditions requiring hospitalization, treatment with blood products or vitamin K, or both hospitalization and treatment.	5	Low
PROLONG Palareti et al. (2006)[20]	Cohort	505	41.7	68.2 (12.5)	ISTH	Overt bleeding and associated with a fall in hemoglobin of ≥2 g/dL; transfusion of ≥2 units of blood; retroperitoneal or intracranial; requiring surgery or invasive procedures to stop bleeding.	1	Low
AESOPUS Prandoni et al. (2009)[21]	RCT	151	57.6	69.0 (21-89)	ISTH	Overt bleeding and associated with a fall in hemoglobin of ≥20 g/L; transfusion of ≥2 units of red blood cells; retroperitoneal or intracranial.	2	Low
EINSTEIN-Extension Bauersachs et al. (2010)[22]	RCT	465	58.5	57.6 (16.2)	ISTH	ISTH	1	Low
WARFASA Becattini et al. (2012)[23]	RCT	402			ISTH	ISTH		Low
Arm 1		197	61.9	62.1 (15.1)			2	
Arm 2		205	65.8	61.9 (15.3)			2	
ASPIRE Brighton et al. (2012)[24]	RCT	822			ISTH	ISTH		Low
Arm 1		411	54	54 (15.8)			2	

Arm 2		411	55	55 (16)			2	
RE-SONATE Schulman et al. (2013)[25]	RCT	651	42.4	56.1 (15.5)	All patients were initially treated for >290 days	ISTH	1	Low
DULCIS Palareti et al. (2014)[26]	Cohort	637	54.5	63 (45-75)	ISTH (minor general surgery, pregnancy, puerperium, estrogen treatment, travel >6 hours, minor trauma, hospitalization for medical illness, reduced mobility)	ISTH	2	Low
DODS Kearon et al. (2015)[27]	Cohort	391	56.3	51 (14)	ISTH (exogenous estrogen)	ISTH	5	Low
PADIS-PE Couturaud et al. (2015)[28]	RCT	371			ISTH (exogenous estrogen)	ISTH		Low
Arm 1		187	55.1	57.3 (17.4)			3	
Arm 2		184	42.5	58.7 (16)			3	
SURVET Andreozzi et al. (2015)[29]	RCT	615			ISTH	Overt bleeding which was fatal, or occurred in a critical location, or required a transfusion of 2 or more units of whole blood or red cells.		Low
Arm 1		308	55.1	57.3 (17.4)			2	
Arm 2		307	42.5	58.7 (16)			2	
REVERSE II Rodger et al. (2017)[30]	Cohort	1015	51.4	53.2 (18-95)	ISTH (exogenous estrogen)	ISTH	1	6
EINSTEIN-Choice Weitz et al. (2017)[31]	RCT	880	56.7	58.4 (15.0)	ISTH	ISTH	1	6

PADIS-DVT Couturaud et al. (2019)[32]	RCT	104			ISTH (exogenous estrogen)	ISTH		
Arm 1		54	72.2	61.5 (14.5)			3	
Arm 2		50	62.0	59.0 (17.2)			3	
ExACT Bradbury et al. (2020)[33]	RCT	134	67.2	63.3 (12.7)	ISTH	ISTH	2	Low
VISTA Geersing et al. (2020)[34]	RCT	620	57.0	55.0 (14)	ISTH	Bleeding accompanied by a fall in hemoglobin of ≥20 g/L; transfusion of ≥2 units of blood; retroperitoneal or intracranial; requiring surgery or invasive procedures to stop bleeding	2	Low

ISTH, International Society on Thrombosis and Haemostasis; RCT, randomized controlled trial; SD, standard deviation; y, years.

[a] "ISTH" is listed for studies judged to have defined unprovoked VTE, as closely as possible, as VTE occurring in the absence of ISTH defined persistent or major transient provoking risk factors.[10] The minor transient risk factors included in the definition of unprovoked VTE are listed in brackets after "ISTH".

[b] As applicable to the studied intervals of year 1, year 2, and years 3-5.

Table 2: Risk of major bleeding after discontinuing anticoagulation.

Interval After Discontinuing Anticoagulation	**Person-Years of Follow-up**	**Total Events, n**		**Rate per 100 person-years** (95% CI)	
		Major Bleeding	**Fatal Bleeding**	**Major Bleeding**	**Fatal Bleeding**
Overall	13 011	41	7	0.35 (0.20 – 0.54); I^2 = 59%	0.09 (0.05 – 0.15); I^2 = 0%
Year 1	7715	32	6	0.44 (0.25 – 0.70); I^2 = 49%	0.15 (0.07 – 0.24); I^2 = 0%
Year 2	3776	8	1	0.28 (0.14 – 0.48); I^2 = 0%	0.13 (0.04 – 0.27); I^2 = 0%
2-Year Cumulative Incidence, (95% CI)				0.7% (0.4% – 1.2%)	0.3% (0.1% – 0.5%)
Years 3-5	1520	1	---	0.10 (0.0 – 0.42); I^2 = 24%	---
5-Year Cumulative Incidence, (95% CI)				1.0% (0.4% – 2.4%)	---

---, data were insufficient to estimate incidence.

Table 3: Risk of major bleeding after discontinuing anticoagulation according to sex.

Interval After Discontinuing Anticoagulation	Person-Years of Follow-up	Total Events, n		Event Rate per 100 person-years (95% CI)	
		Major Bleeding	Fatal Bleeding	Major Bleeding	Fatal Bleeding
Men					
Overall	6355	16	3	0.28 (0.15 – 0.44); I^2 = 16%	0.12 (0.05 – 0.22); I^2 = 0%
Year 1	3529	14	3	0.44 (0.23 – 0.72); I^2 = 13%	0.21 (0.09 – 0.39); I^2 = 0%
Year 2	1992	2	0	0.26 (0.09 – 0.53); I^2 = 0%	0.0 (0.0 – 0.19); I^2 = 0%
2-Year Cumulative Incidence, (95% CI)				0.7% (0.3% – 1.3%)	0.2% (0.1% – 0.6%)
Years 3-5	---	---	---	---	---
5-Year Cumulative Incidence, (95% CI)				---	---
Women					
Overall	5577	22	4	0.43 (0.21 – 0.74); I^2 = 51%	0.14 (0.06 – 0.26); I^2 = 0%
Year 1	3304	17	3	0.59 (0.16 – 0.97); I^2 = 38%	0.22 (0.09 – 0.40); I^2 = 0%
Year 2	1642	5	1	0.45 (0.18 – 0.83); I^2 = 0%	0.27 (0.08 – 0.57); I^2 = 0%
2-Year Cumulative Incidence, (95% CI)				1.0% (0.3% – 1.8%)	0.7% (0.2% – 1.0%)
Years 3-5	---	---	---	---	---
5-Year Cumulative Incidence, (95% CI)				---	---

---, data were insufficient to estimate incidence.

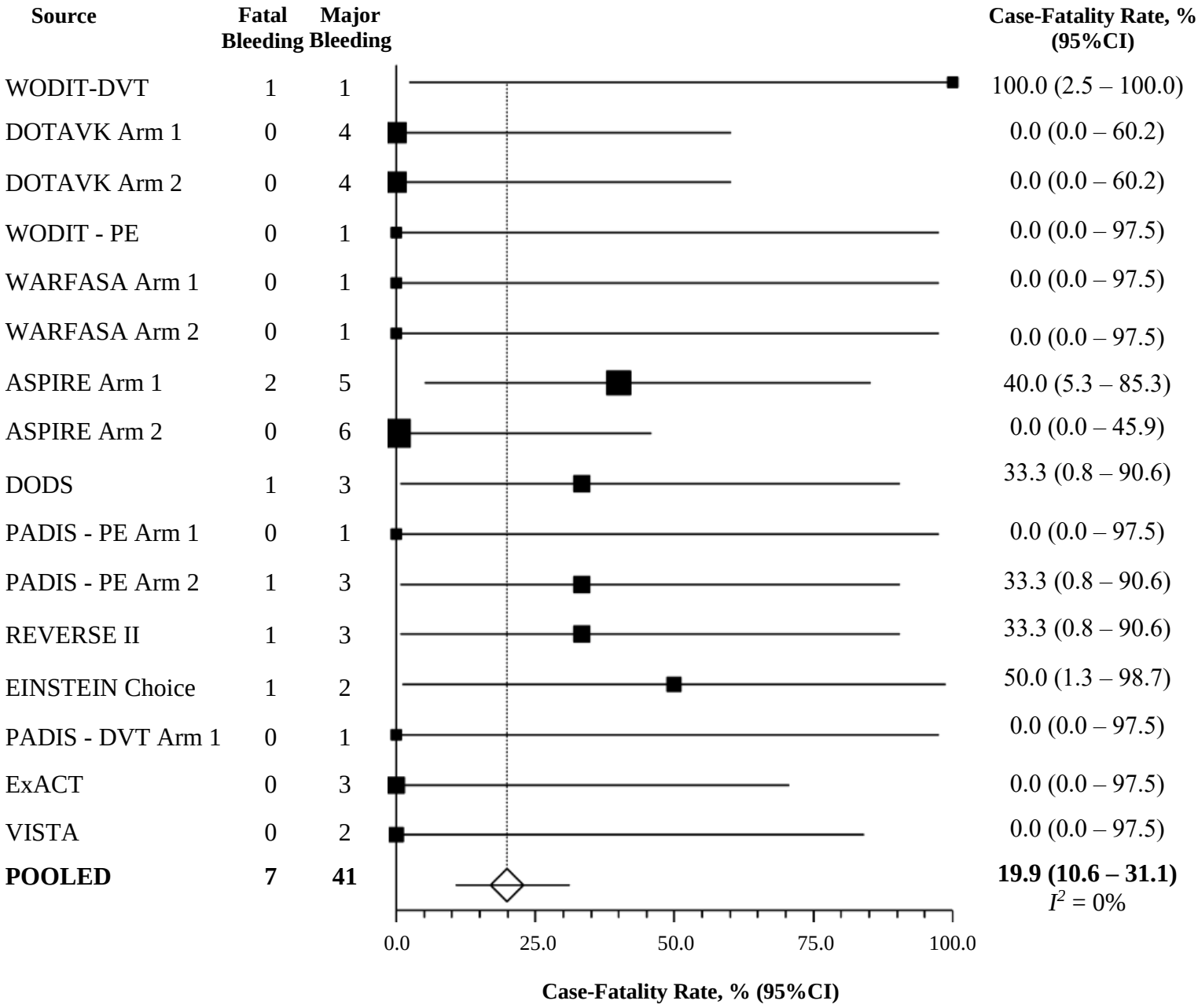
Information in men and women separately was available from 17 studies and 7775 patients.

Table 4: Risk of major bleeding after discontinuing anticoagulation according to study design.

Interval After Discontinuing Anticoagulation	Person-Years of Follow-up	Total Events, n		Event Rate per 100 person-years (95% CI)	
		Major Bleeding	Fatal Bleeding	Major Bleeding	Fatal Bleeding
Randomized Controlled Trials					
Overall	9840	35	5	0.39 (0.21 – 0.63); I^2 = 60%	0.09 (0.04 – 0.16); I^2 = 0%
Year 1	5941	27	4	0.48 (0.25 – 0.79); I^2 = 50%	0.14 (0.06 – 0.25); I^2 = 0%
Year 2	3067	7	1	0.31 (0.14 – 0.54); I^2 = 0%	0.15 (0.04 – 0.32); I^2 = 0%
2-Year Cumulative Incidence, (95% CI)				0.8% (0.4% – 1.3%)	0.3% (0.1% – 0.6%)
Years 3-5	832	1	---	0.26 (0.01 – 1.27); I^2 = 41%	---
5-Year Cumulative Incidence, (95% CI)				1.6% (0.4% – 5.0%)	---
Prospective Cohort Studies					
Overall	3171	6	2	0.19 (0.03 – 0.50); I^2 = 58%	0.09 (0.02– 0.22); I^2 = 0%
Year 1	1774	5	2	0.30 (0.04 – 0.82); I^2 = 55%	0.15 (0.02 – 0.39); I^2 = 0%
Year 2	709	1	0	0.20 (0.0 – 0.80); I^2 = 0%	0.0 (0.0 – 0.52); I^2 = 0%
2-Year Cumulative Incidence, (95% CI)				0.5% (0.0% – 1.7%)	0.2% (0.0% – 0.9%)
Years 3-5	---	---	---	---	---
5-Year Cumulative Incidence, (95% CI)				---	---

---, data were insufficient to estimate incidence.
There were 24 study cohorts (n=6697) from the 17 RCTs and 3 cohorts (n=2043) from the 3 prospective cohort studies included in this analysis.

Figure 2: Case-fatality rate of major bleeding after discontinuing anticoagulation.



SUPPLEMENTAL MATERIAL

Table S1: Literature Search Strategy for EMBASE

1. Venous Thromboembolism/
2. Venous Thrombosis/
3. Pulmonary Embolism/
4. ven* thrombos*.tw
5. ven* thromboe*.tw
6. pulmonary embol*.tw
7. DVP.mp
8. or/1-7
9. Anticoagulants/
10. Warfarin/
11. Rivaroxaban/
12. Dabigatran/
13. Heparin/
14. Heparin, Low-Molecular Weight/15. Factor Xa Inhibitors/
16. vitamin k antagonist.tw
17. VKA.tw
18. Aspirin/
19. ASA.tw
20. or/9-19
21. 8 and 20
22. Secondary Prevention/
23. Recurrence/
24. Randomized Controlled Trial/
25. Cohort Studies/
26. 24 or 25
27. 22 or 23
28. 21 and 27
29. 26 and 28
30. 21 and 26 and 27

Table S2: Modified Newcastle-Ottawa Scale Risk of Bias Assessment.

Scoring Guide:
+ indicates that the study satisfied the criteria
- indicates that the study did not satisfy the criteria
Total score ≥4 indicates an overall low risk of bias.

Study	Selection			Outcome			Total Score (out of 6)
	Was there a representative and well-defined sample of patients with a first unprovoked VTE?	Did patients complete a minimum of 3 months of anticoagulant treatment before start of follow-up?	Was there demonstration that no patient had major bleeding at start of follow-up?	Were objective and unbiased criteria used to assess major bleeding?	Was patient follow-up sufficiently long? (≥ 9 months)	Was patient follow-up sufficiently complete?	
Kearon et al. 1999	+	+	+	+	+	+	**6**
Agnelli et al. 2001	+	+	+	+	+	+	**6**
Pinede et al. 2001	+	+	+	+	+	+	**6**
Agnelli et al. 2003	+	+	+	+	+	+	**6**
Palareti et al. 2006	+	+	+	+	+	+	**6**
Schulman et al. 2006	+	+	+	+	+	+	**6**
Prandoni et al. 2009	+	+	+	+	+	+	**6**
Bauersachs et al. 2010	+	+	+	+	+	+	**6**
Becattini et al.2012	+	+	+	+	+	+	**6**
Brighton et al. 2012	+	+	+	+	+	+	**6**
Schulman et al. 2013	+	+	+	+	+	+	**6**
Palareti et al. 2014	+	+	+	+	+	+	**6**
Kearon et al. 2015	+	+	+	+	+	+	**6**
Couturaud et al. 2015	+	+	+	+	+	+	**6**
Andreozzi et al. 2015	+	+	+	+	+	+	**6**
Rodger et al. 2017	+	+	+	+	+	+	**6**
Weitz et al. 2017	+	+	+	+	+	+	**6**
Couturaud et al. 2019	+	+	+	+	+	+	**6**
Bradbury et al. 2020	+	+	+	+	+	+	**6**
Geersing et al. 2020	+	+	+	-	+	+	**5**

Table S3: Risk of Major Bleeding After Discontinuing Anticoagulation.

Source	Person-Years	Number of Events		Event Rate per 100 person-years (95% CI)	
		Major Bleeding	Fatal Bleeding	Major Bleeding	Fatal Bleeding
Year 1					
Kearon et al. 1999	43.1	0	0	0.0 (0.0 – 8.2)	0.0 (0.0 – 8.2)
Agnelli et al. 2001	89.4	1	1	1.1 (0.0 – 6.1)	1.1 (0.0 – 6.1)
Pinede et al. 2001					
Arm 1	153.1	4	0	2.6 (0.7 – 6.6)	0.0 (0.0 – 2.4)
Arm 2	106.1	4	0	3.8 (1.0 – 9.4)	0.0 (0.0 – 3.4)
Agnelli et al. 2003					
Arm 1	83.4	0	0	0.0 (0.0 – 4.3)	0.0 (0.0 – 4.3)
Arm 2	76.1	0	0	0.0 (0.0 – 4.7)	0.0 (0.0 – 4.7)
Schulman et al. 2006	256.0	0	0	0.0 (0.0 – 1.4)	0.0 (0.0 – 1.4)
Palareti et al. 2006	471.4	0	0	0.0 (0.0 – 0.8)	0.0 (0.0 – 0.8)
Prandoni et al. 2009	139.2	0	0	0.0 (0.0 – 2.6)	0.0 (0.0 – 2.6)
Bauersachs et al. 2010	261.5	0	0	0.0 (0.0 – 1.4)	0.0 (0.0 – 1.4)
Becattini et al. 2012					
Arm 1	169.2	1	0	0.6 (0.0 – 3.2)	0.0 (0.0 – 2.2)
Arm 2	181.9	0	0	0.0 (0.0 – 2.0)	0.0 (0.0 – 2.0)
Brighton et al. 2012					
Arm 1	376.5	4	1	1.1 (0.3 – 2.7)	0.3 (0.0 – 1.5)
Arm 2	393.6	4	0	1.0 (0.3 – 2.6)	0.0 (0.0 – 1.0)
Schulman et al. 2013	625.7	0	0	0.0 (0.0 – 0.6)	0.0 (0.0 – 0.6)
Palareti et al. 2014	585.5	0	0	0.0 (0.0 – 0.6)	0.0 (0.0 – 0.6)
Kearon et al. 2015	314.0	2	1	0.6 (0.08 – 2.3)	0.3 (0.0 – 1.8)
Couturaud et al. 2015					
Arm 1	184.8	0	0	0.0 (0.0 – 2.0)	0.0 (0.0 – 2.0)
Arm 2	180.5	2	1	1.1 (0.1 – 4.0)	0.3 (0.0 – 3.0)
Andreozzi et al. 2015					
Arm 1	287.4	0	0	0.0 (0.0 – 1.3)	0.0 (0.0 – 1.3)
Arm 2	287.1	0	0	0.0 (0.0 – 1.3)	0.0 (0.0 – 1.3)
Rodger et al. 2017	874.0	3	1	0.3 (0.1 – 1.0)	0.1 (0.0 – 0.6)
Weitz et al. 2017	733.9	2	1	0.3 (0.0 – 1.0)	0.1 (0.0 – 0.7)
Couturaud et al. 2019					
Arm 1	53.5	0	0	0.0 (0.0 – 6.7)	0.0 (0.0 – 6.7)
Arm 2	49.0	0	0	0.0 (0.0 – 7.3)	0.0 (0.0 – 7.3)
Bradbury et al. 2020	125	3	0	2.4 (0.5 – 6.9)	0.0 (0.0 – 2.9)
Geersing et al. 2020	614	2	0	0.3 (0.04 – 1.2)	0.0 (0.0 – 0.6)
Pooled					
Overall	**7714.7**	**32**	**6**	**0. 44 (0.25 – 0.70)**	**0.15 (0.07 – 0.24)**
Heterogeneity (I^2, %)				49%	0%
Excluding Aspirin/Sulodexide	**6118.1**	**26**	**5**	**0. 47 (0.24– 0.78)**	**0.15 (0.07 – 0.26)**
Heterogeneity (I^2, %)				51%	0%
Year 2					
Kearon et al. 1999	18.91	0	0	0.0 (0.0 – 17.7)	0.0 (0.0 – 17.7)
Agnelli et al. 2003					
Arm 1	67.1	1	0	1.5 (0.0 – 8.0)	0.0 (0.0 – 5.3)
Arm 2	57.6	0	0	0.0 (0.0 – 6.2)	0.0 (0.0 – 6.2)

Schulman et al. 2006	227.5	0	0	0.0 (0.0 – 1.6)	0.0 (0.0 – 1.6)
Prandoni et al. 2009	196.2	0	0	0.0 (0.0 – 1.9)	0.0 (0.0 – 1.9)
Becattini et al. 2012					
Arm 1	128.0	0	0	0.0 (0.0 – 2.8)	0.0 (0.0 – 2.8)
Arm 2	141.0	1	0	0.7 (0.0 – 3.9)	0.0 (0.0 – 2.6)
Brighton et al. 2012					
Arm 1	309.2	1	1	0.3 (0.0 – 1.8)	0.3 (0.0 – 1.8)
Arm 2	332.9	2	0	0.6 (0.1 – 2.2)	0.0 (0.0 – 1.1)
Palareti et al. 2014	414.4	0	0	0.0 (0.0 – 0.9)	0.0 (0.0 – 0.9)
Kearon et al. 2015	294.0	1	0	0.3 (0.0 – 1.9)	0.0 (0.0 – 1.2)
Couturaud et al. 2015					
Arm 1	183.0	1	0	0.6 (0.0 – 3.0)	0.0 (0.0 – 2.0)
Arm 2	149.6	1	0	0.7 (0.0 – 3.7)	0.0 (0.0 – 2.4)
Andreozzi et al. 2015					
Arm 1	204.4	0	0	0.0 (0.0 – 1.8)	0.0 (0.0 – 1.8)
Arm 2	230.1	0	0	0.0 (0.0 – 1.6)	0.0 (0.0 – 1.6)
Couturaud et al. 2019					
Arm 1	51.5	0	0	0.0 (0.0 – 6.9)	0.0 (0.0 – 6.9)
Arm 2	46.8	0	0	0.0 (0.0 – 7.6)	0.0 (0.0 – 7.6)
Bradbury et al. 2020	105	0	0	2.4 (0.5 – 6.9)	0.0 (0.0 – 2.9)
Geersing et al. 2020	619	0	0	0.3 (0.04 – 1.2)	0.0 (0.0 – 0.6)
Pooled					
Overall	**3776.0**	**8**	**1**	***0.28 (0.14– 0.48)***	***0.13 (0.04– 0.27)***
Heterogeneity (I^2, %)				0%	0%
Excluding Aspirin/Sulodexide	**3071.9**	**5**	**1**	**0.24 (0.09 – 0.44)**	**0.14 (0.04 – 0.30)**
Heterogeneity (I^2, %)				0%	0%
Years 3-5					
Schulman et al. 2006	581	0	0	0.0 (0.0 – 0.6)	0.0 (0.0 – 0.6)
Kearon et al. 2015	690.0	0	0	0.0 (0.0 – 0.5)	0.0 (0.0 – 0.5)
Couturaud et al. 2015					
Arm 1	173.0	0	0	0.0 (0.0 – 2.1)	0.0 (0.0 – 2.1)
Arm 2	20.4	0	0	0.0 (0.0 – 16.5)	0.0 (0.0 – 16.5)
Couturaud et al. 2019					
Arm 1	51.0	0	0	0.0 (0.0 – 7.0)	0.0 (0.0 – 7.0)
Arm 2	5.0	1	0	0.2 (0.5 – 71.6)	0.0 (0.0 – 52.1)
Pooled					
Overall	**1520**	**1**	**---**	***0.10 (0.0 – 0.42)***	**---**
Heterogeneity (I^2)				24%	0%

---, data were insufficient to estimate incidence.