The risk of recurrent venous thromboembolism after discontinuation of anticoagulant therapy in patients with cancer-associated thrombosis: a systematic review and meta-analysis

Marte A. M. van Hylckama Vlieg,[a,*] Kazem Nasserinejad,[b,c] Chantal Visser,[b] Wichor M. Bramer,[d] Aneel A. Ashrani,[e] Jean-Luc Bosson,[f] Daniel J. Crusan,[g] Andrea D'Alessio,[h] Meg E. Fluharty,[i] Valdis Ģibietis,[j] Per-Olof Hansson,[k,l] Nobuhiro Hara,[m] Luis Jara-Palomares,[n,o] Noémie Kraaijpoel,[p] Isabelle Mahé,[q] Andrea Marshall,[r] Yutaka Ogino,[s] Remedios Otero,[n,o] Jorie Versmissen,[t] Frederikus A. Klok,[u] Marieke J. H. A. Kruip,[b] Carin C. D. van der Rijt,[a] and Eric C. T. Geijteman[a]

[a]Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands
[b]Department of Haematology, Erasmus MC, University Medical Center, Rotterdam, the Netherlands
[c]Innovative Statistical Consulting, Therapeutics Development Team, Cytel Inc., Massachusetts, USA
[d]Medical Library, Erasmus MC, University Medical Center, Rotterdam, the Netherlands
[e]Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA
[f]Department of Public Health, Grenoble-Alpes University Hospital and TIMC-IMAG, Grenoble, France
[g]Division of Clinical Trials and Biostatistics, Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN, USA
[h]Department of Medical Oncology and Internal Medicine, Policlinico San Marco, Istituti Ospedalieri Bergamaschi, Bergamo, Italy
[i]Thrombosis Research Institute, London, United Kingdom
[j]Department of Internal Diseases, Riga Stradiņš University, Riga, Latvia
[k]Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[l]Department of Medicine, Geriatrics and Emergency Medicine, Sahlgrenska University Hospital/Östra, Gothenburg, Region Västra Götaland, Sweden
[m]Department of Cardiology, IMS Katsushika Heart Center, Tokyo, Japan
[n]Medical Surgical Unit of Respiratory Diseases, Hospital Universitario Virgen del Rocío, Seville, Spain
[o]CIBERES, ISCIII, Madrid, Spain
[p]Department of Vascular Medicine, Amsterdam UMC/University of Amsterdam, Amsterdam, the Netherlands
[q]Université Paris Cité, Hôpital Louis Mourier, Assistance Publique des Hôpitaux de Paris, INSERM, UMR_ S1140 Innovative Therapies in Haemostasis, Paris, France
[r]Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK
[s]Department of Cardiology, Yokohama City University Medical Center, Yokohama, Japan
[t]Division of Vascular Medicine and Pharmacology, Department of Internal Medicine and Department of Hospital Pharmacy, Erasmus MC, University Medical Center, Rotterdam, the Netherlands
[u]Department of Medicine – Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands

Summary

Background The optimal duration of anticoagulation in patients with active cancer and venous thromboembolism (VTE) is unknown. Current clinical guidelines advocate anticoagulant therapy for 3–6 months and to continue anticoagulant therapy for as long as the cancer is active. However, an adequate systematic review on the rate of recurrent VTE after discontinuation of anticoagulant therapy has not been performed.

Methods For this systemic review and meta-analysis, we searched Embase.com, Medline (Ovid), Web of Science, Cochrane Library, and Google Scholar, from database inception to February 16, 2023, for studies on anticoagulant therapy in patients with cancer and the recurrence of venous thromboembolism after discontinuation of this therapy. We included randomised controlled trials and cohort studies published in English that reported on patients who met the following: cancer and a first VTE, completed at least 3 months of anticoagulant therapy, were followed after discontinuation of anticoagulant therapy, and with symptomatic recurrent VTE as an outcome during follow-up. Study-level data were requested from study authors. The primary outcome was the rate of recurrent VTE after discontinuation of anticoagulant therapy. A Bayesian random-effects meta-analysis was used to estimate the rate of recurrent VTE per 100 person-years for the pooled studies at different time intervals after

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*Corresponding author. Department of Medical Oncology, Erasmus MC Cancer Institute, P.O. Box 2040, 3000 CA, Rotterdam, the Netherlands.
E-mail address: m.vanhylckamavlieg@erasmusmc.nl (M.A.M. van Hylckama Vlieg).

discontinuation of anticoagulation therapy. We also calculated the cumulative VTE recurrence rate at different time intervals. Forest plots were mapped and the results were summarized by the median and 95% credible interval (CIs). This study was registered with PROSPERO, CRD42021249060.

Findings Of 3856 studies identified in our search, 33 studies were identified for inclusion. After requesting study-level data, 14 studies involving 1922 patients with cancer-associated thrombosis were included. The pooled rate of recurrent VTE per 100 person-years after discontinuation of anticoagulant therapy was 14.6 events (95% credible interval 6.5–22.8) in the first three months, decreasing to 1.1 events (95% CI 0.3–2.1) in year 2–3, and 2.2 events (95% CI 0.0–4.4) in year 3–5 after discontinuation of anticoagulant therapy. The cumulative VTE recurrence rate was 28.3% (95% CI 15.6–39.6%) at 1 year; 31.1% (95% CI 16.5–43.8%) at 2 years; 31.9% (95% CI 16.8–45.0%) at 3 years; and 35.0% (95% CI 16.8–47.4%) at 5 years after discontinuation of anticoagulant therapy.

Interpretation This meta-analysis demonstrates a high rate of recurrent VTE over time after discontinuation of anticoagulant therapy in patients with cancer-associated thrombosis. Our results support the current clinical guidelines to continue anticoagulant therapy in patients with active cancer.

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Keywords: Anticoagulants; Neoplasms; Venous thrombosis; Deprescriptions; Duration of therapy

Research in context

Evidence before this study

The optimal duration of anticoagulation in patients with active cancer and venous thromboembolism (VTE) is unknown. Current clinical guidelines advocate anticoagulant therapy for 3–6 months and to continue anticoagulant therapy for as long as the cancer is active. However, there is limited information about the benefits of anticoagulation therapy beyond 3–6 months in patients with cancer-associated thrombosis. The rate of recurrent VTE after discontinuation of anticoagulant therapy in this population has not been studied systematically. Consequently, the level of evidence for anticoagulation therapy beyond 6 months is (very) low, and recommendations in guidelines, therefore, are especially based on expert opinion. The panel of the American Society of Hematology 2021 guidelines for management of VTE identified this as an important knowledge gap for which additional data are needed.

Added value of this study

To the best of our knowledge, this is the first meta-analysis that provides a comprehensive overview of the current literature and provides a robust estimate of the rate of recurrent VTE after discontinuation of anticoagulant therapy in patients with cancer-associated thrombosis. We calculated the recurrent VTE rates per 100 person-years for predetermined time intervals (0–3 months, 3–6 months, 6–12 months, 1–2 years, 2–3 years and 3–5 years) after discontinuation of anticoagulant therapy. Using published data from 14 randomised trials or cohort studies, that includes more than 1900 patients with several types of cancer, we demonstrated that the percentage of patients with cancer-associated thrombosis developing recurrent VTE after discontinuation of anticoagulant therapy over time is considerable with a final cumulative VTE recurrence rate of 35.0% 5 years after discontinuation of anticoagulant therapy.

Implications of all the available evidence

Our meta-analysis confirms the current clinical guidelines and strengthen the recommendation to continue anticoagulant therapy in patients with active cancer.

Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis, and pulmonary embolism, is a frequent complication in patients with cancer.[1] In patients with cancer the risk of VTE is approximately ten to twelve times higher compared to patients without cancer.[2] This risk is especially high among patients with specific cancer types (including pancreatic, brain, lung, and ovarian cancer), immobile hospitalized patients with cancer, patients undergoing antineoplastic therapy and patients with metastatic disease.[2–6] The recommended therapy for cancer-associated thrombosis is anticoagulant therapy, as in patients without cancer. International guidelines suggest to use Factor Xa inhibitors (apixaban, edoxaban and rivaroxaban) or low-molecular-weight heparin (LMWH) for 3–6 months and to continue with anticoagulant therapy for as long as the cancer is active and the bleeding risk

is acceptable.[7–13] However, the risk of recurrent VTE may change over time and side effects of anticoagulant therapy, such as bleeding, may prevail. There is scarce amount of available data regarding the rate of recurrent VTE after discontinuation of anticoagulant therapy in patients with cancer-associated thrombosis. Current guidance on anticoagulant therapy beyond 3–6 months is based on low quality of evidence.[7,8,11,12] Consequently, the optimal duration of anticoagulant therapy for patients with cancer-associated thrombosis is unknown.

Several studies have described the rate of recurrent VTE after discontinuation of anticoagulant therapy in the general population.[14–20] A recently published systematic review and meta-analysis of patients with a first episode of unprovoked VTE who had completed at least 3 months of anticoagulant therapy, demonstrated that the rate of recurrent VTE was 10% in the first year after anticoagulant therapy was discontinued. The cumulative VTE recurrence rate after discontinuation of anticoagulant therapy was 16% at two years, 25% at five years, and 36% at 10 years, respectively.[21]

However, the rate of recurrent VTE after discontinuation of anticoagulant therapy has been inadequately studied in patients with cancer-associated thrombosis. It has been clearly demonstrated that patients with cancer receiving anticoagulant therapy are at higher risk of recurrent VTE compared with patients without cancer receiving anticoagulant therapy.[19,22,23] A recently published systematic review provided a structured summary of available data on the rate of recurrent VTE between 6 and 12 months after diagnosis of cancer-associated thrombosis.[24] Rates of recurrent VTE in the first 6 months after discontinuation of an initial course of anticoagulant therapy varied between 1.9% and 14.6% across the studies.[24–27] Nonetheless, this study only focussed on one time interval (6–12 months after diagnosis of cancer-associated thrombosis) and cannot be extrapolated to other time intervals.

Accurate data on the rate of recurrent VTE at different time intervals after discontinuation of anticoagulant therapy in patients with cancer-associated thrombosis may improve current clinical decision making. Therefore, we performed a systematic review and meta-analysis to assess the recurrent VTE rate and cumulative VTE recurrence rate in patients with cancer-associated thrombosis who completed an initial course of anticoagulant therapy.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[28] The research protocol was developed using guidance from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement.[29] The research protocol was registered with PROSPERO (CRD42021249060).

In conjunction with a biomedical information specialist of the Erasmus MC medical library (WB), we conducted a comprehensive systematic search strategy for Embase.com. Subsequently, we adapted it for Medline ALL (Ovid), Web of Science Core Collection, Cochrane Central Register of Controlled Trials (Wiley) and Google Scholar (date last searched: 16 February 2023). The searches combined terms for cancer OR neoplasms with anticoagulants OR blood clotting inhibitor; venous thromboembolism OR extremity thrombosis, and recurrence OR disease-free survival. Conference abstracts published before 2019, animal-only studies, and studies in languages other than English were excluded in our search strategy. The complete search strategy is listed in Supplementary material S1. Beyond the search of bibliographic databases, the references of the selected articles were also screened manually.

After removing duplicates, two reviewers (MH and EG) independently and separately screened the studies for eligibility, initially based on the title and abstract and subsequently on the full text.[30] Randomised controlled trials, prospective cohort studies and retrospective cohort studies were selected if the studies included patients (age ≥18) with any solid or haematological cancer with a first/incident VTE event, who had completed at least 3 months of anticoagulant therapy (low-molecular-weight heparin (LMWH), Vitamin K antagonist (VKA) or Factor Xa inhibitors) before its discontinuation, and were followed-up thereafter for at least 3 months, and if symptomatic recurrent VTE events (deep vein thrombosis or pulmonary embolism, diagnosed with objective testing) were reported during follow-up period after the discontinuation of anticoagulant therapy.

We excluded case–control studies, cross-sectional studies, case series, case reports or opinion reports. Additionally, we excluded articles where initial VTE events included isolated portal vein, splanchnic vein, retinal vein and cerebral vein thrombosis. There was no restriction on the number of patients included per study. Conflicts in screening were resolved through discussion between the two reviewers.

Data analysis

Data extraction

The primary outcome was the rate of recurrent VTE, defined as distal or proximal DVT and/or pulmonary embolism, during different time intervals after discontinuation of anticoagulant therapy in patients with cancer-associated thrombosis who have completed at least three months of anticoagulant therapy. A secondary outcome was the cumulative VTE recurrence rate at 6 months, 1 year, 2 years, 3 years, and 5 years after discontinuation of anticoagulant therapy.

Data pertaining to the purpose of this study were independently extracted by two reviewers (MH and EG) from all the included studies. The following data (study characteristics) were extracted from eligible studies: first author, year of publication, study design, and follow-up period after discontinuation of anticoagulant therapy. We needed data per specific time interval after discontinuation of anticoagulant therapy, either by extracting from the published manuscript or to be provided by the authors of the eligible studies. Therefore, an extraction roadmap on how to extract specific study-level data and a standard data extraction form was sent to the authors of all the included studies to meet our specific criteria. Therefore, the number of eligible patients may differ between those mentioned in the original manuscript of the included study and ones with data extracted for the current study. We requested for the following patient characteristics: percentage of men, mean age, percentage of the various cancer types, and stage of disease (locally advanced/metastatic). Locally advanced cancer was defined as advanced cancer without distant metastases. Metastatic cancer was defined as advanced cancer with distant metastases. The potential overlap of patients between studies from the same research group was evaluated. In cases of potential overlap, we asked the respective study authors to include and extract data on duplicate patients only once.

Risk of bias assessment

Two reviewers (MH and EG) independently assessed the methodological quality and risk of bias of all eligible studies. We evaluated all studies as an independent observational cohort, by using a modified version of the Newcastle-Ottawa Scale (NOS) for observational studies.[31] The modified NOS includes quality criteria that are categorized in two groups (e.g. selection and outcome) instead of three groups. The category comparability was deemed as irrelevant in this systematic review and meta-analysis. Based on quality assessment standards of previous meta-analysis,[21,32] we considered studies in our meta-analysis that met four or more of these Newcastle-Ottawa scale criteria to be of high quality. Disagreement was resolved by consensus.

Data analysis

For the calculation of the rate of recurrent VTE per 100 person-years, we requested the following data from the authors in addition to the number of eligible patients at the start of follow-up: the total number of person-months of follow-up, the number of recurrent VTE and death events, as well as the number of patients lost to follow-up during each time interval. We asked the authors to calculate the number of available patients at the beginning of each predetermined time interval by subtracting the number of patients from the previous time interval who died, were lost to follow-up/end of study or experienced a recurrent VTE from the available patients in the start of that previous time interval. We converted the total number of person-months of follow up to total person-years of follow up. The total person-years of follow up was defined as the sum of maximum follow up period of each person for that specific time interval. The date of anticoagulation discontinuation was used as the index date. We calculated the rate of recurrent VTE per 100 person-years ensuring appropriate censoring of deaths, patients lost to follow-up, patients who reached the end of follow-up, patients withdrawn from the study and those patients who had a recurrent VTE.

Statistical analysis

For each included cohort, we calculated the rates of recurrent VTE per 100 person-years for each predetermined time interval (0–3 months, 3–6 months, 6–12 months, 1–2 years, 2–3 years and 3–5 years after discontinuation of anticoagulant therapy). A Bayesian random-effects meta-analysis was used to estimate the overall rate of recurrent VTE per 100 person-years at different time intervals, which were summarised by the median and 95% credible intervals (Cis). Forest plots were also mapped. We also calculated the cumulative VTE recurrence rate per 100 person-years at 6 months and 1, 2, 3, and 5 years after discontinuation of anticoagulation therapy. Relatively non-informative priors were used for all variables. All computations and graphics were performed with R program language version 4.2.0, and the Bayesian computations were performed using the Markov chain Monte Carlo (MCMC) sampler through Jags version 4.3.1 interface in R. See Supplementary S2 for a detailed overview of our statistical analysis.

Our model employed random-effects to account for the inherent heterogeneity between the studies. The standard deviation (SD) of the random effects (Tau) were reported as the heterogeneity index. The Egger test and funnel plot was used to check the publication bias.

We conducted a sensitivity analysis which aimed to assess the impact of variations of information implemented into the analytical model. The sensitivity analysis was performed using only studies in which the decision to stop anticoagulant therapy was not influenced by stratification of the risk of VTE recurrence (e.g. clinical decision rules, negative D-dimer test, or absence of residual deep vein thrombosis on compression ultrasound).

Role of the funding source

The funder had no role in the study design, conduct of the study, data collection, data management, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. The corresponding authors (MH and EG) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In total, 7090 studies were identified by the literature search. Duplicates were removed, rendering a total of 3856 studies (Supplementary Table S1). After reviewing the titles and abstracts from these 3856 studies, the full texts of 77 studies were examined. Of these studies, 33 fulfilled the inclusion criteria. Manually searching the bibliographies of the selected articles identified no additional papers. Fig. 1 shows the study selection process and reasons for exclusion.

We requested the authors of the 33 eligible studies to extract the needed data. Study-level data were obtained from 14 of the 33 eligible studies. The remaining 19 studies were excluded because the authors could or did not provide the data that were required for our analysis. Supplementary Table S2 gives an overview of the 19 excluded studies, specifying why they were excluded for the meta-analysis. Six of the nineteen excluded studies were prospective observational studies, twelve were retrospective cohort studies, and one was a randomised controlled trial.

Fourteen studies[3,25,33–44] with a total of 1922 patients were included in the analysis (Fig. 1). Eight of the fourteen studies were prospective observational cohort studies,[33–36,38,39,43,44] five were retrospective cohort studies[3,37,40–42] and one was a randomised controlled trial where two cohorts were included.[25] All fourteen studies with a total of fifteen observational cohorts followed patients at least three months after discontinuation of anticoagulant therapy; fourteen studies[3,25,33–43] had 6 month follow-up data on 1375 patients, and five studies[3,33,36,37,40,41] had 5-year follow-up data on 128 patients after discontinuation of anticoagulant therapy. The characteristics of the included original studies are shown in Table 1. The general characteristics of the included patients in the separate cohorts are shown in Table 2. The number of patients extracted from each study ranged between 2 and 355. Of the total 1922 patients included, 983 (51%) were male. The median age of patients ranged from 57 to 72 years across all studies. The percentage of metastatic cancer ranged between 17.8% and 75.9%, and the percentage of (high

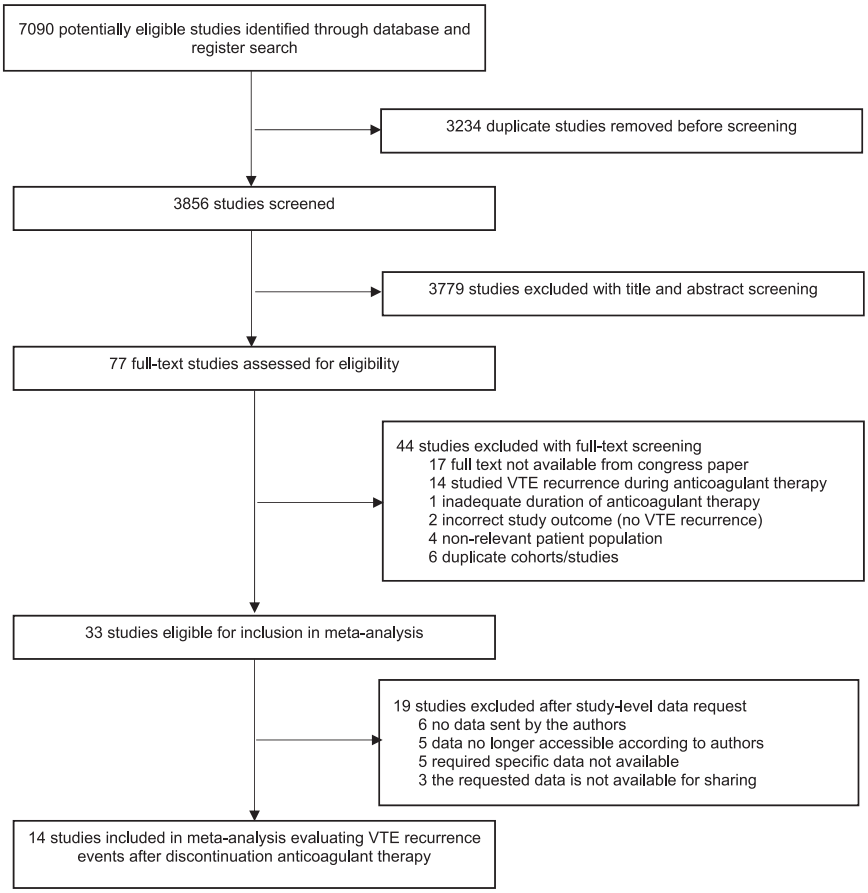

***Fig. 1:* Study selection**. Full details on included and excluded studies (and reason for exclusion) after study-level data request are provided in Table 1 and 2 and in the Supplementary Table S2.

Study	Study design	N original study	N cohort	Purpose of original study
Chee (2014)[3]	R	477	175[a]	A population-based historical cohort study of patients with active cancer and incident VTE to estimate VTE recurrence, estimate bleeding while receiving anticoagulation therapy, estimate survival after VTE recurrence and bleeding, and test baseline cancer and non-cancer characteristics and secondary prophylaxis as potential predictors of VTE recurrence and bleeding.
D'Alessio (2017)[33]	P	62	26	A prospective, observational study to evaluate, in a group of patients under treatment for metastatic cancer and diagnosed with a first episode of acute VTE, the values of TG and D-Dimer, at baseline, during anticoagulation with LMWH, and after its discontinuation.
Galanaud (2017)[34]	P	368	45	An observational, prospective multicentre study to compare, at 3 years, the incidences of death, VTE recurrence and major bleeding in patients with cancer-related iDDVT with those in cancer patients with isolated proximal DVT (matched 1:1 on age and sex) and patients with iDDVT without cancer.
GARFIELD-VTE (2023)[44]	P	10,679	594	A prospective, non-interventional observational study of real-world treatment practices to capture the 36-month clinical outcomes of patients with objectively confirmed VTE.
Ģībietis (2019)[35]	P	219	4	A single-center cohort study to assess the risk factors for VTE recurrences, as well as the effect of treatment strategies on the recurrence rate.
Hansson (2000)[36]	P	738	57	A follow-up study to estimate the cumulative incidence of recurrent venous thromboembolic events after a first or a second DVT and to identify possible risk factors for recurrent venous thromboembolism.
Hara (2022)[40]	R	893	58	A retrospective, single-center cohort study to compare the safety and outcomes of DOACs and warfarin therapies for VTE treatment, and to investigate VTE recurrence after completion of anticoagulation treatment.
Heit (2015)[37]	R	1262	2[a]	A population-based case-cohort study to identify predictors of VTE recurrence, adjusted for treatments and interim exposures.
Jara- Palomares (2018)[38]	P	114	114	A prospective, multicenter study to evaluate cancer-associated thrombosis with ≥3 months of anticoagulation that was subsequently discontinued and to examine the clinical relevance of D-dimer and hs-CRP levels for predicting VTE recurrence among patients with CAT.
Kraaijpoel (2019)[39]	P	695	180	A prospective, observational cohort study to assess the current treatment strategies for incidental PE in patients with cancer and associated risks of recurrent VTE, major bleeding, and mortality.
Mahé (2020)[42]	R	432	355	A retrospective non-interventional study to document patient management and outcomes beyond 6 months and up to 12 months in CAT patients initially treated for 6 months with tinzaparin.
Marshall (2020)[25]	RCT	127		A second randomisation study to assess VTE recurrence and bleeding, with anticoagulation or not, beyond 6 months.
Placebo[b]		46	46	
No residual VTE[b]		35	30	
Ogino (2021)[41]	R	200	79	A retrospective study to evaluate bleeding and recurrent complication of patients with cancer-associated isolated deep vein thrombosis who received DOAC therapy, and to validate the safety and efficacy of prolonged DOAC therapy in routine clinical practice.
Otero (2022)[43]	P	166	157	A prospective multicenter study in CAT patients with more than 6 months of anticoagulant treatment to predict the risk of VTE recurrence after anticoagulation discontinuation.

N original study = number of patients in the original study from which the cohort was extracted; N cohort = number of patients with active cancer extracted from the included study for the current meta-analysis; R = retrospective cohort study; P = prospective cohort study; RCT = randomised controlled trial. [a]Non-overlapping patients from the same longitudinal data (Chee and Heit). [b]In the SELECT-D trial, after 6 months of trial treatment for VTE, patients with active cancer and residual deep vein thrombosis (RDVT) or index pulmonary embolism (PE) were eligible for randomization to a further 6 months of rivaroxaban or placebo. Patients with no RDVT were not eligible for the second randomization and were mandated to discontinue anticoagulant therapy at 6 months. Patients with no RDVT were also followed-up to 24 months.

Table 1: **Characteristics of original studies in meta-analysis.**

thrombotic risk) upper gastrointestinal cancer ranged between 2% and 29% across all cohorts.

The definition of active cancer differed per included study. Supplementary Table S3 provides an overview of the definition of active cancer per study. For this meta-analysis, our goal was to include only studies with patients with cancer who had experienced a first VTE event. However, a limited number of patients with cancer with a second VTE event may have been included, because the inclusion criteria of some of the individual studies did not clarify it.[36,41–43] All studies were of high quality according to the Modified Newcastle-Ottawa Scale. The Supplementary material (Table S4) presents the quality assessments results per study.

Table 3 shows the pooled number of patients available at the beginning of each specified time interval, the total person-years of follow-up, the number of recurrent VTE events, the corresponding recurrent VTE events per 100 person-years, and patients who were lost to follow-up/end of follow-up in each predetermined time interval. In the first three months after discontinuation of anticoagulant therapy for cancer-associated thrombosis, the pooled rate of recurrent VTE per 100 person-years based on the Bayesian random effects model was 14.6 events (95% CI 6.5–22.8) (Fig. 2). The rate of recurrent VTE per 100 person-years was 10.3 events (95% CI 6.9–13.6) between 3 and 6 months after discontinuation of anticoagulant therapy (Fig. 3); 6.4 events (95% CI 3.1–9.4) between 6 and 12 months; 4.0 events (95% CI 1.1–7.0) between 12 and 24 months; 1.1 events (95% CI 0.3–2.1) between 24 and 36 months; and 2.2 events (95% CI 0.0–4.4) during years 3–5 after discontinuation of anticoagulant therapy. See Supplementary Figure S1 and S2 for all forest plots and graphs.

Egger test and visual assessment of funnel plots evaluating the rate of recurrent VTE per 100 person-years in each predetermined time interval after

Study	N Cohort	Men (%)	Age, mean (SD)	Cancer type (n, %)								Stage of disease (n,%)			Type of AC	Follow-up (years)[e]
				Breast	CRC	Upper gastro intestinal[b]	Gynaecologic	Lung	Urogenital[c]	Hematologic	Other[d]	Locally advanced	Metastatic	NA		
Chee (2014)[3]	175[a]	53.1	67.0 (13.9)	26 (14.9%)	25 (14.3%)	3 (1.7%)	10 (5.7%)	11 (6.3%)	48 (24.7%)	36 (20.6%)	16 (9.1%)	95 (54.3%)	32 (18.3%)	48 (27.4%)	VKA, LMWH	5
D'Alessio (2017)[33]	26	57.7	69.0 (11.2)	3 (11.5%)	9 (34.6%)	5 (19.2%)	0	3 (11.5%)	2 (7.6%)	2 (7.6%)	2 (6.6%)	15 (57.7%)	11 (42.3%)	0	LMWH	5
Galanaud (2017)[34]	45	46.7	65.9 (NA)	0	0	13 (28.9%)	12 (26.7%)	4 (8.9%)	12 (26.7%)	3 (6.7%)	1 (2.2%)	26 (57.8%)	8 (17.8%)	11 (34.2%)	VKA, LMWH	3
GARFIELD-VTE (2023)[44]	594	48.7	63.0 (13.2)	66 (11.1%)	72 (12.1%)	44 (7.4%)	64 (10.8%)	81 (13.6%)	75 (12.6%)	100 (16.8%)	92 (15.5%)	NA	NA	594 (100%)	LMWH, VKA, fXa inhibitors	3
Ghibetis (2019)[35]	4	50.0	72.0 (10.0)	0	2 (50.0%)	0	0	1 (25.0%)	0	0	1 (25.0%)	1 (25.0%)	3 (75.0%)	0	LMWH, VKA, fXa inhibitors	1
Hansson (2000)[36]	57	36.8	70.3 (10.3)	14 (24.6%)	8 (14.0%)	1 (1.7%)	8 (14.0%)	3 (5.3%)	10 (17.5%)	8 (14.0%)	5 (8.8%)	NA	NA	57 (100%)	VKA, LMWH	5
Hara (2022)[40]	58	44.8	69.4 (11.5)	0	13 (22.4%)	11 (19.0%)	24 (41.4%)	8 (13.8%)	0	0	2 (3.4%)	14 (24.1%)	44 (75.9%)	0	VKA, fXa inhibitors	5
Heit (2015)[37]	2[a]	100.0	57.3 (8.2)	0	1 (50.0%)	0	0	0	1 (50.0%)	0	0	0	1 (50.0%)	1 (50.0%)	VKA, LMWH	5
Jara-Palomares (2018)[38]	114	50.8	61.7 (13.7)	20 (17.5%)	20 (17.5%)	4 (3.5%)	5 (4.4%)	12 (10.5%)	17 (14.9%)	16 (14.0%)	20 (17.5%)	69 (60.5%)	45 (39.5%)	0	LMWH	1
Kraaijpoel (2019)[39]	180	61.1	64.8 (12.7)	9 (5.0%)	39 (21.7%)	30 (16.7%)	18 (10.0%)	24 (13.3%)	20 (11.1%)	6 (3.3%)	34 (18.9%)	85 (47.2%)	83 (46.1%)	2 (1.1%)	LMWH, VKA, fXa inhibitors	2
Mahé (2020)[42]	355	48.4	66.6 (12.8)	57 (16.1%)	66 (18.6%)	33 (9.3%)	35 (9.9%)	62 (17.5%)	39 (11.0%)	0	63 (17.7%)	NA	NA	355 (100%)	LMWH, VKA, fXa inhibitors	6
Marshall (2020)[25]															LMWH, fXa inhibitors	3
Placebo	46	60.9	66.0 (12.0)	9 (19.6%)	6 (13.0%)	8 (17.4%)	8 (17.4%)	3 (6.5%)	3 (6.5%)	5 (10.9%)	4 (8.7%)	24 (52.2%)	21 (45.6%)	1 (2.2%)		
No residual VTE	30	50.0	63.0 (10.0)	4 (13.3%)	14 (44.7%)	2 (6.7%)	2 (6.7%)	1 (3.3%)	1 (3.3%)	2 (6.7%)	4 (13.3%)	23 (77.0%)	7 (23.0%)	0		
Ogino (2021)[41]	79	57.0	71.1 (10.0)	3 (3.8%)	20 (25.3%)	29 (36.7%)	10 (12.7%)	6 (7.6%)	3 (3.8%)	5 (6.3%)	3 (3.8%)	53 (67.1%)	26 (32.9%)	0	VKA, fXa inhibitors	5
Otero (2022)[43]	157	54.8	62.3 (13.6)	26 (16.6%)	30 (19.1%)	6 (3.8%)	10 (6.4%)	17 (10.8%)	23 (14.6%)	25 (15.9%)	20 (12.7%)	96 (61.1%)	61 (38.8%)	0	LMWH	0,5

N cohort = number of patients with active cancer extracted from the included study for the current meta-analysis; CRC = colorectal cancer; NA = not available; AC = anticoagulant therapy; VKA = Vitamin K antagonist; LMWH = low-molecular-weight heparin; fXa inhibitors = Factor Xa inhibitors. [a]Non-overlapping patients from the same longitudinal data (Chee and Heit). [b]Excluding colorectal cancer. [c]Excluding kidney cancer. [d]Including kidney, brain, bone, melanoma, non-melanoma skin, sarcoma, head and neck, (A)CUP, thyroid, adrenal, mediastinal and thymoma. [e]Duration of follow up as applicable to time intervals of 0.5, 1, 2, 3 and 5 years after discontinuation of anticoagulation therapy.

Table 2: **Characteristics of cohorts in meta-analysis.**

Time	No. of patients at risk	Person- years of follow-up	Recurrent VTE events	Event rate per 100 person-years	95% CI	Heterogeneity standard deviation	No. of deaths	No. lost to FU/end of study	Based on how many studies
0–3 months	1922	367.8	63	14.6	6.5–22.8	0.69	223	261	15
3–6 months	1375	617.1	69	10.3	6.9–13.6	0.16	100	102	15
6–12 months	888	727.3	57	6.4	3.1–9.4	0.36	122	94	13
12–24 months	615	949.9	60	4.0	1.1–7.0	0.66	113	76	11
24–36 months	366	867.1	10	1.1	0.3–2.1	0.22	45	59	9
3–5 years	128	363.7	10	2.2	0.0–4.4	0.40	14	40	5

Table 3: **Rate of recurrent venous thromboembolism (VTE) after discontinuation of anticoagulant therapy in patients with cancer-associated VTE.**

discontinuation of anticoagulant therapy did not show any evidence of publication bias (Supplementary Figure S3).

Table 4 and Fig. 4 show the cumulative VTE recurrence rate. The cumulative VTE recurrence rate was 28.3% (95% CI 15.6–39.6%) at 1 year; 31.1% (95% CI 16.5–43.8%) at 2 years; 31.9% (95% CI 16.8–45.0%) at 3 years; and 35.0% (95% CI 16.8–47.4%) at 5 years after discontinuation of anticoagulant therapy.

The sensitivity analysis based on studies in which the decision to stop anticoagulant therapy was not influenced by stratification of the risk of VTE recurrence (i.e. absence of residual deep vein thrombosis on compression ultrasound) showed similar results to the main analysis. See See Supplementary Figure S4, Tables S5 and S6.

Discussion

In this systematic review and meta-analysis of 1922 patients with cancer-associated thrombosis who had completed at least three months of anticoagulant therapy, we found that a considerable percentage of patients develop recurrent VTE after discontinuation of anticoagulant therapy. One in seven patients with cancer-associated thrombosis developed recurrent VTE in the first 3 months after discontinuation of anticoagulant therapy, and more than one-third of the patients with cancer-associated thrombosis developed recurrent VTE within 5 years after discontinuation of anticoagulant therapy.

Our observed rate of recurrent VTE in the first 6 months after discontinuation of anticoagulant therapy is almost 2-fold higher compared to the reported rate of recurrent VTE of patients without cancer with a provoked or unprovoked VTE (12.2 events per 100 person-years, 95% CI 10.5–14.2).[14] Our results demonstrate a high rate of recurrent VTE in the first few months after discontinuation of anticoagulation therapy, after which the rate of recurrent VTE per time-interval decreases, similar to the trend seen in VTE patients without cancer.[14,19,20] Similar results are seen when comparing our observed cumulative VTE recurrence rates to the ones reported for patients without cancer.[17,19,45]

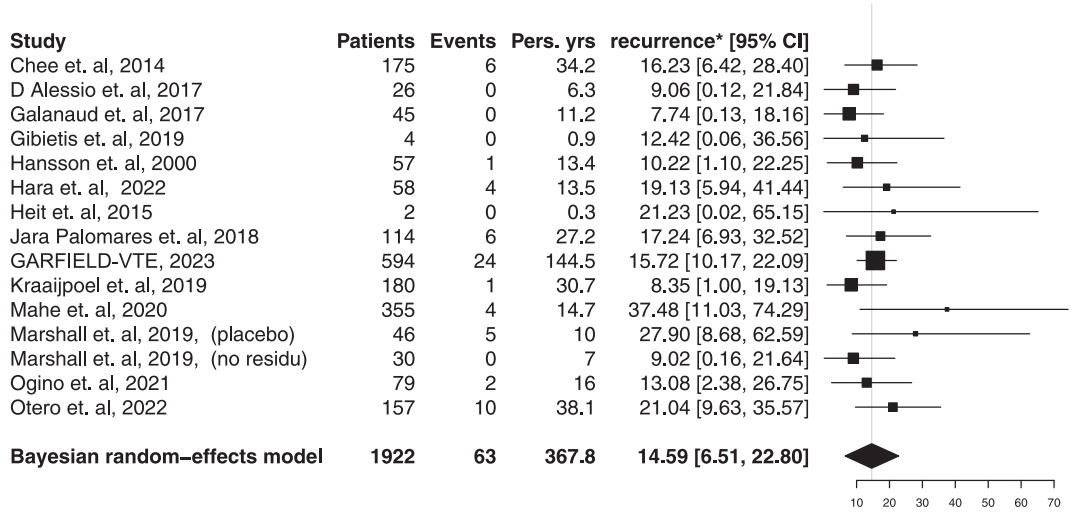

Fig. 2: **Forest plot for rate of recurrent VTE per 100 person-years between 0 and 3 months after discontinuation of anticoagulant therapy.** * Shrunken estimates using the estimates of the random effects. Results are rounded. Heterogeneity: $\sigma = 0.69$.

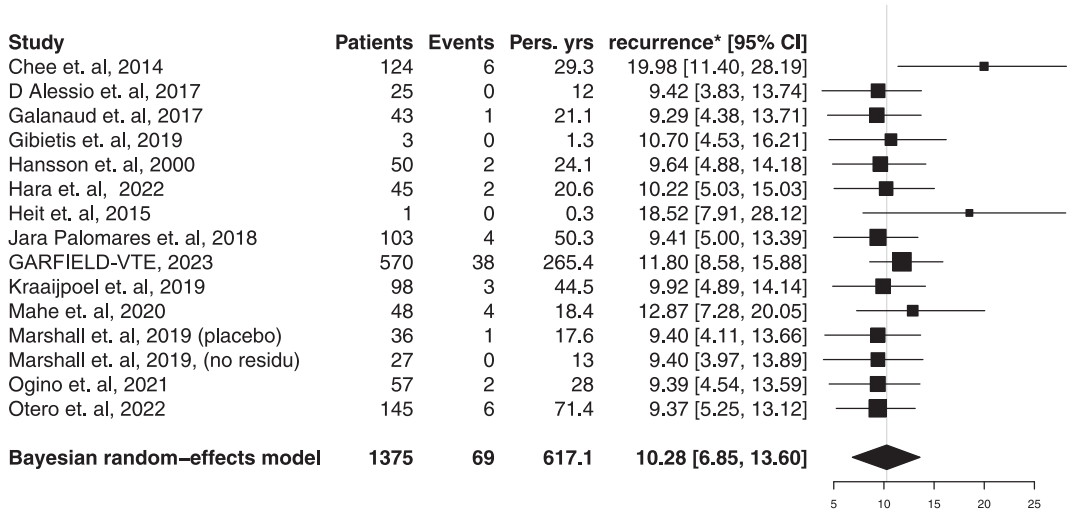

Fig. 3: **Forest plot for rate of recurrent VTE per 100 person-years between 3 and 6 months after discontinuation of anticoagulant therapy**. * Shrunken estimates using the estimates of the random effects. Results are rounded. Heterogeneity: $\sigma = 0.16$.

This study showed that the rate of recurrent VTE after discontinuation of anticoagulant therapy decreased over time. However, the percentage of patients with cancer-associated thrombosis developing recurrent VTE over time is considerable with a final cumulative VTE recurrence rate of 35.0% 5 years after discontinuation of anticoagulant therapy. This notable cumulative VTE recurrence rate is not seen in patients without cancer.[14,17,19,21] We should be cautious to compare our observed cumulative VTE recurrence rates to the reported cumulative VTE recurrence rates of patients without cancer in the literature because of different duration of anticoagulation and different anticoagulation therapies chosen. However, the difference between the cumulative VTE recurrence rates of patients with and without cancer-associated thrombosis after discontinuation does seem to be larger compared to the difference in cumulative VTE recurrence rates during anticoagulant therapy described in prior publications.[22,23,46] Based on the available literature, guidelines for cancer-associated thrombosis suggest continuing anticoagulant therapy for as long as the cancer is active, and the side effects of therapy are acceptable.[47–50] Our results provide additional strength to this recommendation of current guidelines.

Time	Cumulative VTE recurrence rate, %	95% CI
6 months	23.4	12.9–33.3
1 year	28.3	15.6–39.6
2 year	31.1	16.5–43.8
3 year	31.9	16.8–45.0
5 year	35.0	16.8–47.4

Table 4: **The cumulative VTE recurrence rate after discontinuation of anticoagulant therapy.**

Clinicians need to weigh the risk of recurrent VTE after discontinuation of anticoagulant therapy with the risk of bleeding complications during anticoagulant therapy to decide on long-term management in patients with cancer-associated thrombosis. In our current study, we could not estimate the short- and long-term bleeding risks, as it was not feasible to incorporate bleeding risk during anticoagulant therapy in our systematic search strategy. In the literature, the short-term major bleeding rates range from 1.7% to 16%, and clinically relevant bleeding rates range from 2.0% to 23.2%,[51–56] depending on type and stage of cancer, and type of anticoagulation. Extrapolation of the short-term bleeding risks to the daily clinical setting and different subpopulations remains challenging because of the strict selection criteria of most randomised control trials and the contrasting reported results regarding an increased bleeding risk in patients allocated to factor Xa inhibitors.[55–59] The long-term major bleeding rates summarized by a recent systematic review range from 2% to 5% between 6 and 12 months after starting anticoagulant therapy.[24] Of note, these bleeding rates might be higher since sampling and survival bias might be present and a proportion of the patients discontinued anticoagulant therapy.[24] However, as the cumulative VTE recurrence rate 6 months after discontinuation lies between 12.9% and 33.3% in patients with cancer-associated thrombosis, continuing anticoagulation therapy seems to outweigh these long-term bleeding risks, especially in patients with high thrombotic risk cancers.

An alternative long-term strategy to reduce bleeding complications and VTE recurrence might be secondary prophylaxis with low-dose factor Xa inhibitors after an

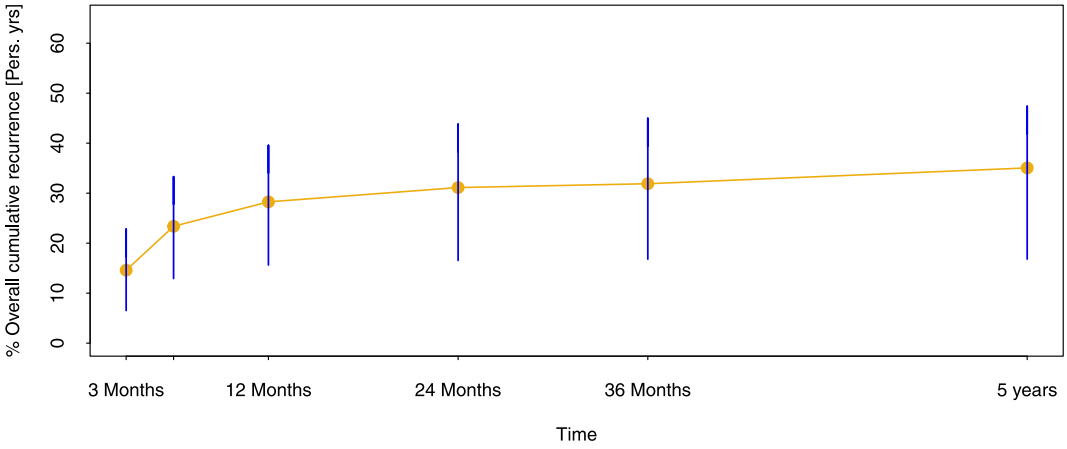

***Fig. 4:* The cumulative VTE recurrence rate after discontinuation of anticoagulant therapy**. Bars represent 95% credible intervals.

initial period of full-dose factor Xa inhibitors. Low-dose factor Xa inhibitors as secondary prophylaxis have been shown to reduce recurrent VTE without increasing the rate of major bleeding in VTE patients.[60,61] These trials only included a small proportion of patients with active cancer. A recent observational study of patients with active cancer demonstrated a substantial decrease in major bleedings and a slight increase in VTE recurrence when low dose apixaban was compared to the full dose apixaban as secondary prophylaxis.[62] Two randomised studies, the EVE trial[63] and the API-CAT study,[64] were set up to assess the optimal long-term strategy in patients with active cancer by comparing low-dose and full-dose apixaban after at least 6 months of full-dose anticoagulant therapy. First results of the EVE trial were recently presented. The investigators showed that apixaban 2.5 mg twice daily resulted in similar rates of bleeding compared to apixaban 5 mg twice daily without increasing thrombotic outcomes.[65] Publications of both the EVE and the API-CAT studies are awaited before final conclusions about the use of low-dose factor Xa inhibitors after an initial period of full-dose factor Xa inhibitors can be drawn.

This study has several strengths. First, this is a systematic review, which provides a comprehensive overview of all available data on the rate of recurrent VTE after discontinuation of anticoagulant therapy in patients with cancer-associated thrombosis thus far. Second, this is a study-level meta-analysis in which we have derived extracted data from all included studies in a uniform way with strict selection criteria, through which we have gained more insight from the raw data of all available studies on this problem. Third, most included studies were observational practice-based studies without strict selection criteria applicable to randomised controlled trials. That would suggest that, despite the heterogeneity between patients with cancer, the external validity of the study's findings should be good.

This study has several limitations. First, only half of the eligible studies were included in the final meta-analysis as data of the other studies were not available (Supplementary Table S2). This unintended selection bias could lead to a less accurate estimate of the rate of recurrent VTE. However, the study characteristics of the excluded studies were similar to the included studies. In addition, the Egger test and visual assessment of funnel plots did not show any evidence of publication bias. Second, there is clinical and methodological heterogeneity between included studies. For example, the definition of patients with active cancer differed among the included studies, which entails heterogeneity between included patients with active cancer. In our meta-analysis, two studies did not clearly define active cancer,[36,43] and four studies included patients who may have already finished their anticancer treatment on inclusion and thus may have a history of cancer rather than active disease.[25,35,38,39] Due to the lack of individual patient-level data, we do not know if, and when, patients successfully completed curative anticancer treatment. The inclusion of cured patients, combined with sampling and survival bias, might dilute our estimates resulting in an underestimation of VTE recurrence, as the recurrence rate is lower in patients who are cured or in remission.[54,66,67] In addition, owing to the lack of individual patient-level data, we could not account for causes of death, although we took the number of deaths into account when calculating the recurrence rate. It is possible that patients have died as a result of recurrent VTE, so our VTE recurrence rate may be an underestimation of the actual percentage. Moreover, due to the inclusion of retrospective cohort studies and the lack of individual patient-level data, the decision to stop anticoagulant therapy is not always known. In some cases, this could mean that anticoagulant therapy was discontinued because the risk of VTE recurrence was estimated as low. Consequently, our VTE recurrence rate may be an

underestimation. Third, we included studies in which the decision to stop anticoagulant therapy was influenced by stratification of the risk of VTE recurrence (i.e. absence of residual deep vein thrombosis on compression ultrasound).[25,38] However, the sensitivity analysis, based on studies in which the decision to stop anticoagulant therapy was not influenced by stratification of the risk of recurrent VTE, showed the same results as the main analysis. Fourth, because of lack of patient-level data, we could not distinguish between the risk of recurrent VTE in locally advanced cancer and metastatic cancer group. Fifth, due to the limited available extracted data, outcomes related to the type of cancer, type of VTE (pulmonary embolism or deep vein thrombosis; acute symptomatic or incidental), type of anticoagulant therapy, and total duration of anticoagulant therapy could not be evaluated. Sixth, we were not able to assess the risk of major bleeding during extended anticoagulant therapy.

Despite these limitations, this is the first meta-analysis which provides a comprehensive overview of the available literature and estimates a more accurate rate of recurrent VTE after discontinuation of anticoagulant therapy in patients with cancer-associated thrombosis.

In summary, the results of this meta-analysis show that a considerable percentage of patients with cancer-associated thrombosis develop recurrent VTE after discontinuation of anticoagulant therapy. This high rate of recurrent VTE over time implies that it is advisable to continue anticoagulant therapy in patients with active cancer.

Contributors

Conceptualisation: MH, EG, KN; Methodology: MH, EG, KN, CV, JV, FK, MK, CR; Performing extended search: WB; Literature search: MH, EG; Risk of bias assessment: MH, EG; Resources: AA, JB, DC, AD, MF, VG, PH, NH, LJ, NK, IM, AM, YO, RO; Writing-original draft: MH, EG, KN; Data collection: MH, EG; Data verification: MH, EG; Formal analysis: KN; Data analysis: MH, EG; Writing—original draft, review and editing: MH, EG, KN, CV, WB, AA, JB, DC, AD, MF, VG, PH, NH, LJ, NK, IM, AM, YO, RO, JV, FK, MK, CR.

All co-authors were not precluded from accessing data in the study, and they accept responsibility to submit for publication. The corresponding authors (MH and EG) have accessed and verified the underlying data, and had final responsibility for the decision to submit for publication.

Data sharing statement

This meta-analysis used extracted data from published studies; researchers interested in obtaining data not provided in the manuscript and supplementary material, can contact the corresponding authors. All extracted data are available on request from the corresponding authors.

Declaration of interests

All authors have completed the ICMJE uniform disclosure form. Luis Jara-Palomares: has received support for the present manuscript from MSD; grants from Leo Pharma; honoraria from Actelion Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Leo Pharma, MSD, Pfizer, ROVI, and Bristol-Myers Squibb. Isabelle Mahé: has received grants from BMS Pfizer; honoraria from BMS Pfizer, Leo Pharma, and Sanofi; support for attending meetings/travel from BMS Pfizer and Leo Pharma. Andrea Marshall: my institution received unrestricted educational grant from Bayer AG for the select-D trial. Remedios Otero Candelera: LEO-PHARMA was partially involved in the financial support to Hispalis Study without interfering in the intellectual conception, design and data analysis; received financial support for attendance to congresses and scientific meetings, payment to conferences or advisory board from BAYER HISPANIA, MSD, LEO-PHARMA and ROV; participated on a Data Safety Monitoring Board or Advisory Board. Frederikus Klok: has received research support from Bayer, Bristol-Myers Squibb, Actelion, Boston Scientific, Leo Pharma, PharmX, The Netherlands Organisation for Health Research and Development, The Dutch Thrombosis Association, The Dutch Heart Foundation and the Horizon Europe program, all outside this work and paid to his institution. Marieke Kruip: has received an unrestricted research grant from Sobi; research grants from Netherlands Thrombosis Foundation and the Netherlands Organization for Health Research and Development; speakers fee from Sobi, Roche, and BMS; all grants and fees are paid to her institution (Erasmus MC). Carin van der Rijt: has received a payment to the institution from the Netherlands Organization for Health Research and Development for a project on deprescription of medication at the end of life; is Chair of the Dutch Association for Professional Palliative Care (unpaid); is member of the Supervisory Board of the Foundation Roparun (attendance fee is paid). Eric Geijteman: has received an internal grant from the Erasmus MC (50.000 euro). This is a payment to finance this study (together with an interview- and questionnaire study about the perspectives of patient, caregivers and healthcare professionals on anticoagulation therapy). All other authors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102194.

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