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Thirty-day outcomes in patients with proximal deep vein thrombosis who discontinued anticoagulant therapy prematurely

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Title: Thirty-day Outcomes in Patients with Proximal Deep Vein Thrombosis who Discontinued Anticoagulant Therapy Prematurely.

Running title: **Early Discontinuation of Anticoagulants for DVT**

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Abstract

Introduction: In patients receiving anticoagulation for deep vein thrombosis (DVT), a variety of reasons (including active bleeding or high-risk for bleeding) may lead into premature discontinuation of therapy (prior to completing 90 days). The relative frequency and clinical consequences of premature discontinuation in contemporary patients remain unknown.

Methods: We used the data from RIETE, an international registry of patients with venous thromboembolism (VTE), to identify patients with proximal (above knee) lower limb DVT who prematurely discontinued anticoagulation. We assessed the incidence of the composite outcome: pulmonary embolism (PE)-related death, sudden death, or recurrent VTE within the subsequent 30 days after discontinuation and compared the risk of these events vs. the risk in patients without premature discontinuation, once adjusted for demographics and clinical factors.

Results: Of 26,335 patients with proximal DVT recruited from 2001 to 2018, 1,322 (5.02%) prematurely discontinued anticoagulation. Thirty days after discontinuation, 12 (0.91%) patients suffered fatal PE (n=8) or sudden death (n=4) and 33 (2.50%) had non-fatal recurrent VTE (PE=15; recurrent DVT=18). In patients with premature discontinuation, the 30-day incidence of the composite outcome was 1.62 per 1,000 patient-days (95%CI: 0.00-3.80). During the first week after discontinuation, the incidence rate was 4.09 per 1,000 patient-days (95%CI: 0.65-7.52). The adjusted odds of the composite outcome was 7.88 times (95%CI: 6.39-9.72) higher in patients who discontinued prematurely than in those without premature discontinuation.

Conclusion: Premature discontinuation of anticoagulation occurred in 5% of patients with proximal DVT, and was associated an 8-fold increased odds for the composite outcome.

Keywords: Anticoagulants; Deep vein thrombosis; Outcome studies; Pulmonary embolism; Venous thromboembolism.

Introduction

Anticoagulant therapy modifies the natural history of patients with proximal deep vein thrombosis (DVT), and anticoagulation has been considered the mainstay of treatment for at least 3 months (1). In routine daily practice however, some patients with DVT may discontinue (temporarily or permanently) anticoagulant therapy mainly due to urgent need for surgery, active bleeding, high bleeding risk (e.g. severe thrombocytopenia) or advanced co-morbid conditions, among others. These patients may be exposed to an increased risk for recurrent venous thromboembolism (VTE), including pulmonary embolism (PE), or recurrent DVT. Accurate information on the incidence of complications during the days after premature discontinuation of anticoagulation would assist physicians to better weigh the potential benefits and harms of withholding anticoagulation. However, there are no contemporary studies that estimate the risk of thrombotic events after premature discontinuation of anticoagulation in patients with proximal DVT. The existing natural history studies were conducted decades ago and may not be relevant to contemporary patient populations (2-6).

The RIETE (Registro Informatizado Enfermedad TromboEmbólica) registry is an ongoing, multicenter, international registry of consecutive patients with objectively confirmed acute VTE (7). In the current study, we aimed to identify all patients included in the registry with proximal lower limb DVT who had premature (less than 90 days) discontinuation of anticoagulant therapy, and to assess the incidence of symptomatic VTE recurrences appearing during the first

30 days after discontinuation. In addition, we compared these outcomes against patients who did not undergo premature discontinuation of anticoagulation.

Methods

We used the data from patients enrolled in the RIETE registry with acute symptomatic proximal DVT in the lower limbs confirmed by objective tests (ultrasonography, contrast venography, or computed tomography). Previous publications have described the design and conduct of the RIETE registry (7). Briefly, RIETE has been prospectively enrolling consecutive patients with VTE from 24 countries. Patients were excluded if they were participating in a therapeutic clinical trial with a blinded therapy. All patients (or healthcare decision-makers) provided written or oral informed consent to their participation in the registry, in accordance with local Ethics Committee requirements. Main IRB Committee name, Comite de Etica de Investigacion Clinica, Hospital Germans Trias i Pujol. Project approval number, PI-17-053. RIETE is registered at Clinicaltrials.gov (NCT: 02832245).

Patients

In this study, we included patients who were enrolled in the RIETE registry from March 2001 to December 2018 due to symptomatic proximal (above knee) DVT in the lower limbs who received anticoagulation but terminated it prematurely and did not re-initiate it during the study period. “Early discontinuation” was defined when the time interval between initiation of anticoagulant therapy and last dose of administered anticoagulant therapy was less than 90 days.

We excluded patients who underwent vena cava (IVC) filter placement, those who developed VTE recurrences or died during the same day of discontinuation of anticoagulation, and those who died during the day of DVT diagnosis. The last exclusions were made to establish a wash out period of one day without anticoagulants and to avoid inclusion of patients who had an immediately fatal PE, thereby not having time to receive effective anticoagulation at all (Figure 1).

Outcomes

The study period was the time interval (without anticoagulant therapy) between the date of the last dose of anticoagulant and the date of the last follow-up. We assessed the events that occurred during the 30-day period following the last anticoagulant treatment (i.e. within 30 days after "early discontinuation").

The main outcome was the composite of fatal PE, sudden unexpected death (8) or symptomatic recurrent non-fatal VTE (either symptomatic PE or DVT), appearing during the first 30 days after discontinuing anticoagulant therapy. The rate of the composite outcome in patients discontinuing prematurely was compared with the rates of the composite outcome in those patients that did not discontinue during the same time intervals.

Fatal PE, in the absence of autopsy, was defined as any death appearing shortly after (within 10 days) an objectively confirmed recurrent event, in the absence of any alternative cause of death. Recurrent VTE was diagnosed by lung scanning, helical-CT scan, pulmonary angiography, compression ultrasonography or contrast venography, as appropriate, in patients with DVT or PE symptoms. VTE recurrences presenting as superficial- or upper-extremity vein thrombosis were not included in this analysis. Outcomes were classified as reported by site investigators. However, if staff at the RIETE coordinating center were uncertain on how to classify a reported outcome, that event was reviewed by a central adjudicating committee (less than 10% of events).

Other definitions

Recent surgery was defined as a surgical intervention in the 2 months prior to VTE. Immobilization was defined as total bed rest with bathroom privileges for medical patients for ≥4 days in the 2-month period prior to VTE. Recent bleeding was defined as a major bleeding episode appearing <30 days prior to VTE. Bleeding events were classified as 'major' if they were overt and required a transfusion of two units or more of blood, or were retroperitoneal, spinal or intracranial, or when they were fatal (7).

Statistical analysis

We reported median with interquartile range for quantitative variables and reported the categorical variables with frequency counts and percentages and compared them using the Chi-squared test or the Fisher exact test, when appropriate. We avoided reporting on numerous pairwise statistical comparisons. However, to explore the potential impact of time of discontinuation on the event rates, the entire group of patients with premature discontinuation was divides into 3 pre-specified subgroups (discontinuing in days 1 to 7, days 8 to 30, or days 31 to 89 after the index VTE event). We reported the rate of the primary outcome per 1,000 patient-days. We used logistic regression to compare the odds of the primary outcome in patients with- (n=1,322) versus those without (n=23,424) premature discontinuation, after adjusting for demographics and clinical risk factors (a list of co-variates is shown in the Appendix Table S1). Analyses per categories were also performed, by comparing the number of events after discontinuation in the pre-specified subgroups with those occurring in equivalent time intervals in full anticoagulated patients (for example, if a patient underwent premature discontinuation on day 30, the outcomes were assessed between days 31-60. The control patients included those who continued receiving anticoagulation over 90 days and their outcomes were assessed between days 31-60. The same approach was implemented for all patients). Survival curves were built according to the Kaplan-Meier method. SPSS software (version 20, SPSS Inc., Chicago, Illinois) was used for the statistical analysis and a two-sided $p<0.05$ was considered as statistically significant.

Role of the funding source

The sponsors of RIETE had no role in study design, data collection, data analysis, data interpretation, or writing of the report. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of the study, all study analysis, the drafting and editing of the paper and its final contents.

Results

From March 2001 to December 2018, 36,087 patients with acute symptomatic DVT were enrolled in RIETE. Of these, 3,592 (9.95%) had upper limb, cerebral, retinal or splanchnic vein thrombosis, 5,385 (14.9%) initially presented with only distal DVT, 761 (2.11%) underwent a vena cava filter placement and 14 (0.04%)

died during the same day of DVT diagnosis with no time to receive any therapy. (Figure 1). These patients were not included in the study. Among the 26,335 remaining patients with proximal DVT in the lower limbs, 1,322 (5.02%) received anticoagulant therapy for less than 90 days and then were considered to have discontinued anticoagulation prematurely.

The clinical characteristics of the patients discontinuing prematurely compared to those treated for at least 90 days are depicted in Table 1. Among 1,322 patients who received therapy for <90 days (median duration, 45 days; IQR: 24-78 days), 8 (0.61%) were actively bleeding at baseline, 34 (2.6%) had recent major bleeding prior to the index DVT event (intracranial 6, gastrointestinal 11, genitourinary 10, haemoptysis 3, hematoma 1, other 3), 331 (25%) had metastatic cancer, 201 (16%) had severe renal insufficiency and 16 (1.2%) had platelet counts <50,000 platelets/µL at baseline. Additionally, 184 patients (14%) developed major bleeding (intracranial 28, retroperitoneal 12, gastrointestinal 80, hematoma 23, genitourinary 22) during the first 90 days of anticoagulant therapy, and anticoagulation was immediately discontinued. Sixty-one patients had more than one of these factors.

During the first 30 days after discontinuation of therapy, 431 patients (33%) died: 8 (1.9%) died of PE, 4 (0.93%) had a sudden and unexplained death. Moreover, 190 patients (44%) died of disseminated malignancy, 55 (13%) died of bleeding and 36 (8.4%) died of infection. The median time elapsed from DVT diagnosis to death was 35 days (interquartile range [IQR]: 19-58 days) and from discontinuation of therapy to death 3 days (IQR, 1-8 days). Fatal bleeding occurred within a median of 3 days (IQR, 2-6 days) after discontinuation, and sudden death or fatal PE occurred after a median of 5 days (IQR, 1-8 days). Additionally, 47 patients (3.6%) suffered from major non-fatal bleeding, 15 (1.14%) had non-fatal PE recurrences and 18 (1.36%) presented with recurrent DVT. Non-fatal VTE recurrences occurred after a median of 5 days (IQR 1-12.5 days). Overall, 27 of the 45 events (60%) occurring during the 30 days following discontinuation were fatal PE or sudden deaths. Most PE recurrences (17 of 23, 74%) and DVT recurrences (11 of 18, 61%) appeared during the first week after discontinuing anticoagulation. The time course of the events is presented in Figure 2. The type of event varied depending on the duration of anticoagulation: PE or sudden death occurred in patients treated after a median of 27 days (IQR, 19-40 days), while recurrent DVT appeared after a median of 72 days (IQR 41-86 days).

In a post-hoc assessment, patients who had premature discontinuation and developed the composite outcome were significantly younger than those who did not develop it despite premature discontinuation. We did not find other specific clinical characteristics that were different between those with- or without the composite outcome (Appendix Table S2). Patients who died due to PE or sudden death were in the lower age range (median, 53 years) and did not suffer from specific co-morbidities other than cancer (6 patients) and anemia (9 patients) (Appendix Table S3).

The proportion of patients with premature discontinuation who developed the composite outcome was 3.40% (Figure 3A). PE or sudden death were the only outcomes in the subgroup of patients treated 1-7 days, and recurrent DVT most frequently occurred in patients treated during more than 1 week.

Overall, the daily incidence of events during the 30 days without anticoagulation was 1.62 per 1,000 patient-years (95% CI, 0.00-3.80). However, these rates varied according to the duration of anticoagulation showing a unimodal pattern with a peak of incidence in the subgroup of patients treated during 8-30 days (Figure 3B). In the subgroups of patients treated with anticoagulants during less than 30 days, the incidence of events (2.61 per 1,000 patient-days; 95% CI 0.00-7.47) doubled that of the patients treated 31 to 89 days (1.28 per 1,000 patient-days; 95% CI 0.00-3.61) ($p<0.001$).

During the first week after discontinuation, the incidence of events was particularly high: 4.09 per 1,000 patient-days (95% CI, 0.65-7.52%), (Figure 3B). Again, the subgroups of patients treated with anticoagulants for less than 30 days had higher rates of VTE events (mean, 6.04 per 1,000 patient-days) than patients treated for 31 to 89 days (3.31 per 1,000 patient-days) ($p<0.001$).

The event rates of the study cohort were compared to those occurring in patients who received anticoagulant therapy for at least 90 days (Table 2) during equivalent follow-up times. Overall, patients that prematurely discontinued anticoagulation had an 8-fold increase in the odds for events (adjusted OR: 7.88; 95%CI: 6.39-9.72) during the first 120 days since enrolment; the risk varied depending on the duration of anticoagulation: It was highest in the subgroup of patients anticoagulated during 8-30 days (Table 2).

Discussion

In routine clinical practice, anticoagulation may be prematurely discontinued in some patients with proximal DVT for a number of reasons. Our findings reveal that in a large multinational registry, one in every 20 (5.0%) patients with proximal DVT discontinued anticoagulant therapy before the minimum recommended duration of 90 days. Overall, patients undergoing premature discontinuation had an 8-fold increase in the odds for 30-day PE-related death, sudden death, or recurrent VTE within the subsequent 30 days, compared to those without premature discontinuation. Despite recruiting 26,349 proximal DVTs, the number of events (n, 45) and of fatalities (n, 14) was relatively few, which may have affected the point estimates. However, there is 95% confidence that the true adjusted odds of adverse outcomes was between 6.4 and 9.7 times higher in patients with early discontinuation, compared with the rest of patients. The incidence of symptomatic events was highest during the first week after discontinuation, a time period when roughly two third of VTE events (including three quarter of PEs) had occurred. This pattern is similar to what has been observed in a similar study including patients with PE having premature discontinuation of anticoagulation (8).

To our knowledge, there are no other contemporary studies to report on the natural history of DVT patients who have premature discontinuation of anticoagulant therapy. Kelly et al. reviewed pooled data from small studies performed decades ago, and reported a 16% overall incidence of fatal PE in untreated patients with DVT and a 16% of recurrent non-fatal PE (3). Our findings differ from this study in several ways. First, we did not include completely untreated patients. Second, our data reflect findings from prospectively collected data from a large multinational multicentre registry. Third, unlike studies using aggregate data from previous publications, we were able to use homogenous definitions across patients enrolled at various centers and over time. Fourth, and most importantly, our data reflect contemporary practice patterns and outcomes. Although we observed worse outcomes associated with premature discontinuation, similar to those reported by Kelly et al, we observed a lower absolute magnitude of risk. This may –at least in part– be due to differences in (early) case identification, and presence of effective ancillary supportive care measures in contemporary practice. In another study, Hull et al (4), reported a symptomatic 3-month recurrence rate of 31.6% in 19 patients with proximal DVT treated with unfractionated intravenous heparin during 10 days and then with subcutaneous low-dose. Most of the recurrences occurred during the first week of the low-dose period. Other studies reported rates of 4.35% in one month (5) and 8.6% in 2 months in patients treated for 4 weeks (6).

In a prior study, we reported the outcomes after early discontinuation of anticoagulation in patients with acute PE (8). Our findings clearly suggested that there was an inverse logarithmic relationship between the duration of anticoagulation and the risk for the composite of fatal PE, sudden death or recurrent VTE after PE diagnosis. In the current investigation of patients with proximal DVT, although we similarly observed a relationship between duration of anticoagulation and outcomes, the magnitude of association was quantitatively less intense. Nevertheless, the duration of anticoagulant therapy, and the time since its cessation may have important implications on subsequent outcomes and should be assessed when discontinuation of anticoagulants is considered an option in a particular clinical setting.

Prior studies (9,10) have suggested that recurrent DVTs are more frequent in patients with DVT than subsequent PEs. Among our patients with premature discontinuation however, we observed more episodes of PE recurrences than DVT recurrences, mostly in patients treated for less than 30 days. However, this was post-hoc observation. One possible explanation is a low sensitivity assessment for DVT recurrence or progression because in RIETE only symptomatic events were recorded. Earlier trials showed that 4 of 9 patients with objectively documented early recurrent VTE after proximal DVT were asymptomatic (4), and asymptomatic progression of proximal DVT occurred even in 6.7% of fully anticoagulated patients if a programmed venography is carried out by the first week (11). In addition, early recurrences as PE may be more symptomatic and clinically evident (2). In patients with proximal DVT treated with heparin-warfarin, there were more VTE recurrences presenting as PE (4 out of 5) during the first week after heparin discontinuation (2).

We hypothesize that when anticoagulants were discontinued in the first days, many patients probably had still symptoms of the index proximal DVT, and even in case of progression of the thrombosis, the symptoms would be closely similar. Therefore, delays in improvement or even slight worsening of symptoms would be not registered as recurrent VTE, unless symptomatic PE or sudden death appeared. We assume that some cases of proximal progression of DVT or asymptomatic PE could have been missed out. That probably explains the low incidence of events in patients treated less than one week after VTE diagnosis and that the benefit of anticoagulation in the multivariable analysis was significant only after 7 days of treatment. To properly assess the occult effect of anticoagulant discontinuation on the thrombus growth, other parameters more sensitive to this phenomenon should be used.

The study has limitations that should be acknowledged. First, the study population was composed of patients at increased risk for bleeding and with clinical characteristics different to the remaining patients with proximal DVT (Table 1). Patients with temporary discontinuation of anticoagulation (e.g. a few days) that re-started later were not included in the main group of the study and the results cannot be extrapolated to them. Also, patients with proximal DVT who had a vena cava filter inserted were excluded, since the goal of the current study was to reflect on the natural history of patients who undergo premature discontinuation. Therefore, the incidence of VTE-related complications should not be extrapolated directly to all patients with DVT. However, the data from the current study provide a contemporary estimate of the natural history of VTE for partially treated patients and share insights for clinicians about the risk for early symptomatic complications.

Second, in our study, bleeding or high risk for bleeding was the most likely reason for premature discontinuation in many cases, although the exact cause was not available for some patients in the database. In fact, one in every 7 patients (184 of 1,322; 14%) had an episode of major bleeding during anticoagulation (a proportion similar to that observed in our prior study on PE patients (8)). Major high risk procedures, non-elective surgery or terminal diseases might also be a reason for discontinuation in other cases. Irrespective of the reason for discontinuation, our findings reveal that early discontinuation was associated to an increased risk for fatal and non-fatal symptomatic VTE, a risk that progressively declined over time.

Third, RIETE, by design, ensures follow-up for a minimum of 90 days or until death, although the majority of patients have longer follow-up available. Therefore, for the subset of patients with premature discontinuation until day 60, there were no missing data (all reached 30-day follow-up or death). However, for the subset that discontinued anticoagulation between days 61-90 (and their controls), a minority (n=58, 4.4% of patients with early discontinuation and n=3,758, 16% of controls) were lost to follow-up during the month after discontinuation (days 91-120). It is unlikely that this small rate of dropouts has made a substantive impact on the main findings of this study. As any other observational study, we cannot exclude the possibility that unmeasured confounders, not assessed in RIETE, may have influenced the observed outcomes.

Fourth, we would have preferred to identify the characteristics of patients who suffered from the composite outcome, but even in RIETE –the largest VTE-registry in the world, the number of events were prohibitively low, not allowing us to sufficiently explore this. Fifth and finally, the inclusion of sudden death episodes in the composite outcome may lead to overestimate the rate of fatal PE. Nevertheless, the findings were materially similar after excluding sudden death.

In conclusion, our study provides quantitative evidence of the risk for the composite of fatal PE, sudden death or recurrent VTE after premature discontinuation of anticoagulant therapy for proximal DVT. These findings do not question the indication already established in the 1990s with respect to a minimum of 3 months of anticoagulation in patients with acute VTE. Rather, they supplement the knowledge about the natural history of DVT by showing the magnitude of the risk of the early interruption of anticoagulation in contemporary patients. This information could be of help in decision making when unexpected complications (i.e. bleeding or surgery) challenge the use of anticoagulant therapy in early stages of DVT.

Conflict of interest disclosures

Authors do not have any conflict of interest regarding this study.

The sponsors of RIETE had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. Dr. Bikdeli was supported by the National Heart, Lung, and Boos Institute, National Institutes of Health (NIH), through grant number T32 HL007854. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Dr. Bikdeli reports that he has been a consulting expert (on behalf f the plaintiff) for litigation related to a specific type of IVC filters. The current study is the idea of the investigators and has not been performed at the request of a third party.

Addendum

JA Nieto and D Mora take responsibility for the content of the manuscript, including the data and analysis. All authors had full access to all the data, revised critically the text and provided final approval of the version to be published. JA Nieto and M Monreal take responsibility for the integrity of the data and contributed substantially to the study design. JA Nieto, M Monreal and B Bikdeli contributed substantially to the interpretation of the data and the writing of the manuscript.

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APPENDIX

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Table 1. Clinical characteristics at time of DVT diagnosis according to duration of anticoagulant therapy.

	Premature Discontinuation	*No Premature Discontinuation*	OR (95% CI)
Patients, N	***1.322 (5%)***	***25.013 (95%)***	
Clinical characteristics,			
Male gender	622 (47%)†	12.873 (52%)	0.84 (0.75-0.94)
Age >80 years	356 (27%)‡	5.009 (20%)	1.47 (1.30-1.67)
Body weight <50 kg	77 (5.8%)‡	636 (2.5%)	2.37 (1.86-3.02)
SBP levels <90 mm Hg	15 (1.1%)	221 (0.9%)	1.29 (0.76-2.18)
Heart rate >110 beats per minute	65 (4.9%)†	819 (3.3%)	1.53 (1.18-1.98)
Chronic lung disease	122 (9.2%)	2.160 (8.6%)	1.08 (0.89-1.30)
Chronic heart disease	82 (6.2%)‡	1.004 (4.0%)	1.58 (1.25-2.00)
Cancer	538 (41%)‡	5.189 (21%)	2.63 (2.34-2.94)
Immobilization	419 (32%)‡	6.059 (24%)	1.45 (1.29-1.64)
Abnormal mental status	48 (5.5%)‡	424 (3.1%)	1.84 (1.36-2.50)
Risk for bleeding,			
History of peptic ulcer	21 (1.6%)‡	142 (0.6%)	2.82 (1.78-4.48)
Angiodysplasia	0	6 (0.0%)	----
Hiatal hernia	22 (1.7%)	318 (1.3%)	1.31 (0.85-2.03)
Esophageal varices	5 (0.4%)*	29 (0.1%)	3.27 (1.26-8.48)
Liver cirrhosis	14 (1.1%)‡	71 (0.3%)	3.76 (2.11-6.67)
High risk for bleeding,			
Recent major bleeding	34 (2.6%)‡	363 (1.5%)	1.79 (1.26-2.56)
Active bleeding at baseline	8 (0.6%)*	60 (0.2%)	2.53 (1.21-5.31)
Metastatic cancer	331 (25%)‡	2.164 (8.7%)	3.53 (3.09-4.02)
Anemia	742 (56%)‡	8.539 (34%)	2.48 (2.22-2.77)
Platelet count <50,000/µL	16 (1.2%)‡	81 (0.3%)	2.48 (2.22-6.48)
Abnormal prothrombin time	144 (11%)‡	1.329 (5.3%)	2.18 (1.82-2.61)
CrCl levels <30 ml/min	201 (16%)‡	1.668 (6.9%)	2.50 (2.14-2.93)
Any of the above	927 (70%)‡	10.458 (42%)	3.29 (2.92-3.72)
VTE characteristics ,			
Asymptomatic PE	66 (5.0)*	1.674 (6.7%)	0.73 (0.57-0.94)
Anticoagulant therapy,			
Duration (median days, IQR)	45 (24-78)	≥90	
Initial therapy			
Low-molecular-weight heparin	1.184 (90%)‡	23.378 (93%)	0.60 (0.50-0.72)
Unfractionated heparin	57 (4.3%)‡	542 (2.2%)	2.03 (1.54-2.69)
Thrombolytics	2 (0.2%)	14 (0.1%)	

Abbreviations: SBP: Systolic blood pressure. VTE, venous thromboembolism; PE pulmonary embolism; DVT, deep vein thrombosis; CrCl, creatinine clearance; LMWH, low molecular weight heparin.

* *p<0,05 ;* † p<0,01; ‡ p<0,001

Table 2. Thirty-day Composite Clinical Outcome in Patients with and without Premature Discontinuation

	Premature discontinuation		No premature discontinuation		Follow-up* (days)	OR	95% CI	OR adjusted	95% CI
Time on anticoagulants	N	Episodes	N	Episodes					
1-7 days	99	2	23,424	158	2-37	3.04	0.74-12.4	1.60	0.38-6.84
8-30 days	326	17	23,408	180	8-60	7.10	4.26-11.8	4.89	2.84-8.40
31-89 days	897	26	23,391	195	31-120	3.55	2.34-5.38	2.84	1.85-4.36
1-89 days	1,322	164	23,424	340	2-120	9.62	7.91-11.7	7.88	6.39-9.72

*Days of observation after VTE diagnosis in both cohorts.
OR, Odds risk; CI, confidence interval.

Figure 1. Flow Diagram of Patient Selection.

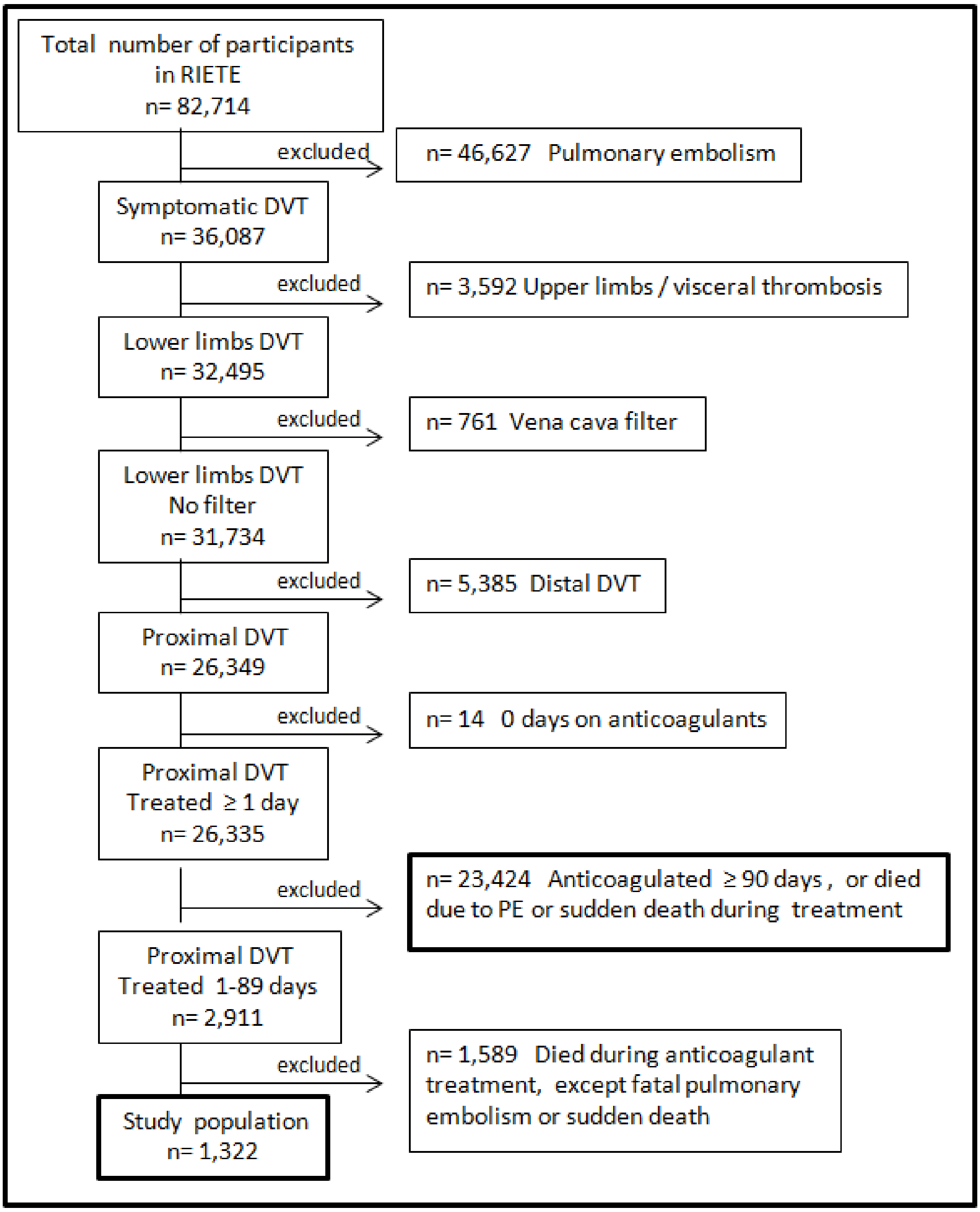
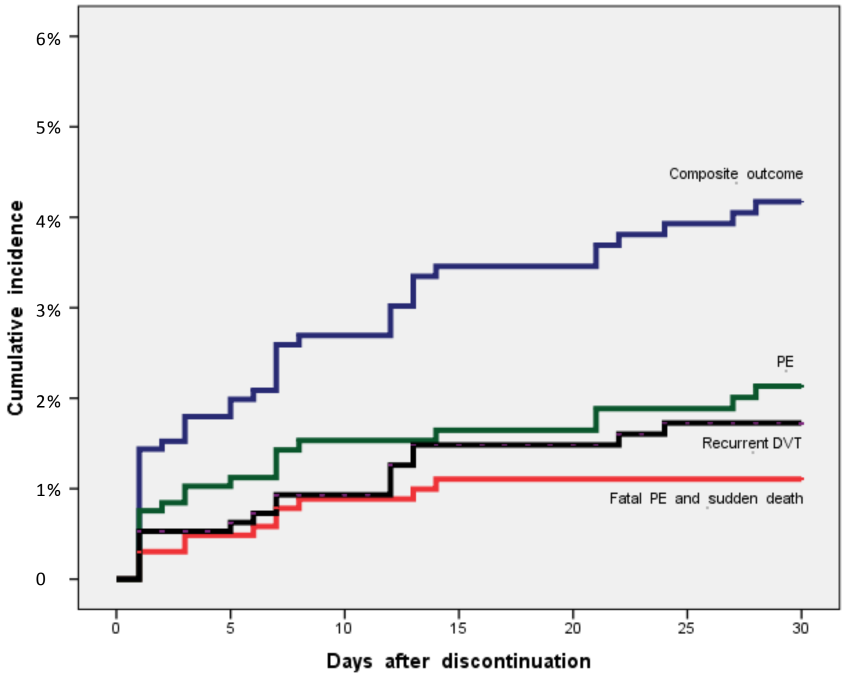
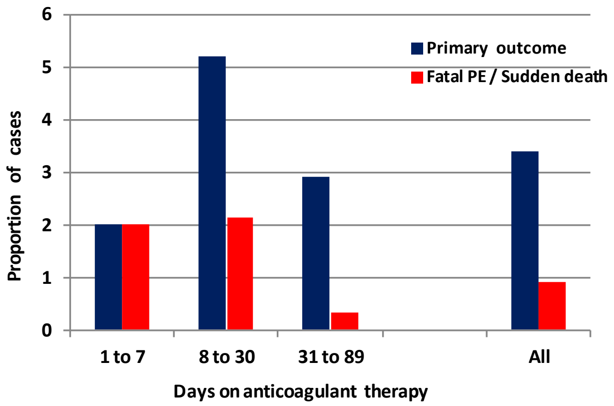


Figure 2. Time course of outcomes (fatal PE and sudden death, recurrent non-fatal VTE, and the composite of both) after discontinuation of anticoagulant therapy.



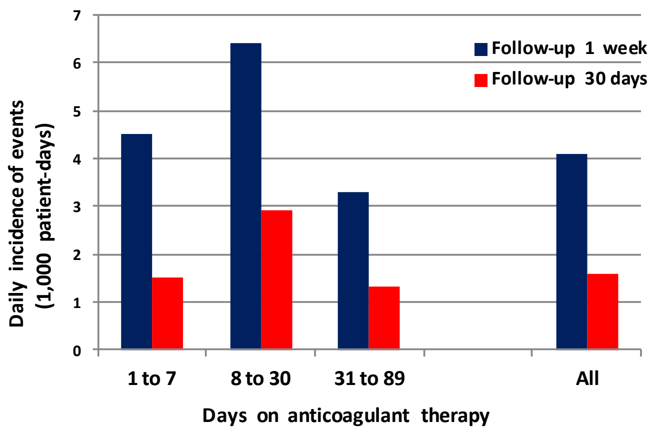
Days after discontinuation	1-5	6-10	11-15	16-20	21-25	26-30
Patients at risk	1322	994	907	855	823	794
Composite outcome	25	7	7	0	4	2
Fatal PE / sudden death	7	3	2	0	0	0
Pulmonary embolism	14	4	1	0	2	2
Recurrent DVT	8	3	5	0	2	0
Deaths, any cause	283	70	33	19	12	14
Loss to follow-up	0	20	10	12	3	13

Figure 3A. Proportion of patients with adverse outcomes during 30 days after discontinuing anticoagulation, classified in accordance to the duration of therapy.

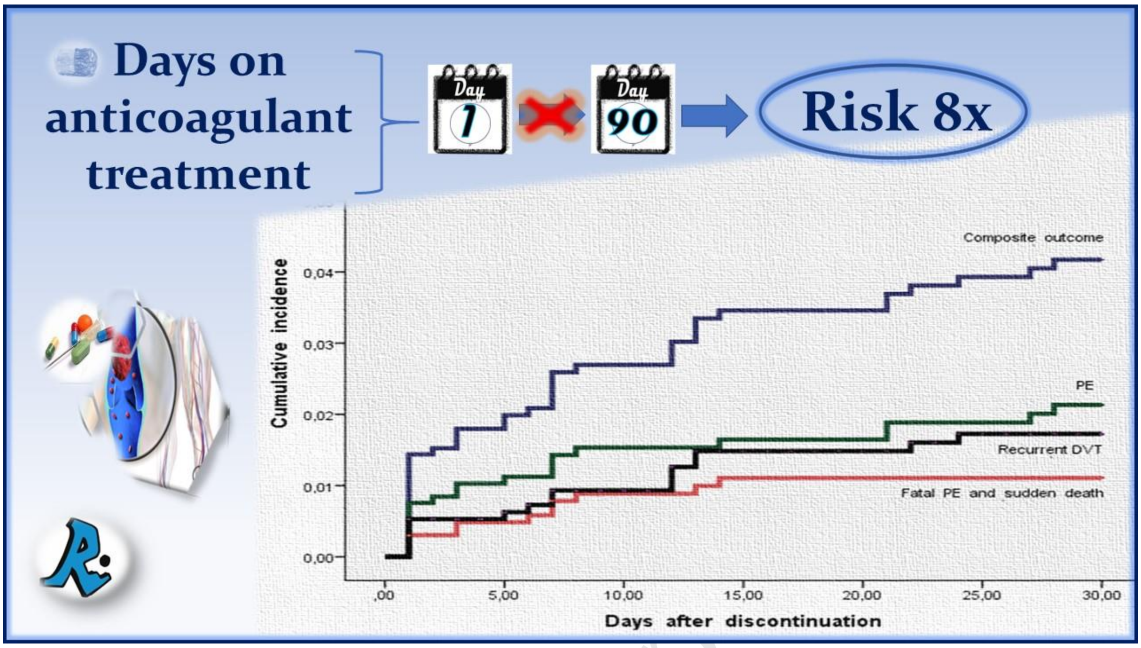


Days on therapy	1-7	8-30	31-89	All
Patients (n)	99	326	897	1322
Median days (IQR)	5 (3-6)	19 (13-25)	69 (49-83)	45(24-78)
Primary outcome (n)	2	17	26	45
Fatal PE / sudden death (n)	2	7	3	12
PE (n)	1	12	10	23
DVT (n)	0	3	15	18

Figure 3B. Daily incidence of fatal PE, sudden death or recurrent VTE during an observation period of 1 week (blue columns) or 1 month (red columns) after premature discontinuation of anticoagulant treatment.



Days of follow-up after discontinuation	Days on anticoagulant therapy			
	1-7	8-30	31-89	All
Days 1 to 7 (‰ patient-days) (95% CI)	4.50 0.0-17.7	6.43 0.0-15.1	3.32 0.0-7.07	4.09 0.65-7.52
Days 1 to 30 (‰ patient-days) (95% CI)	1.49 0.0-9.07	2.87 0.0-8.67	1.28 0.0-3.61	1.62 0.0-3.80



Graphical abstract

Highlights

1. 5% of patients with DVT were treated with anticoagulation for less than 90 days.

2. The incidence of complications after discontinuation was studied in 1.322 patients.

3. Post-treatment incidence of VTE-related events was 4.09 ‰ pt-days in the first week.

4. The risk of 30-day VTE-related events increased 8 times without anticoagulation.