Clinical Investigation

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Clinical Investigation

Title: Thirty-day outcomes in patients with acute pulmonary embolism who discontinued anticoagulant therapy before 90 days.

Running title: **Early discontinuation of anticoagulant therapy**

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Abstract

Background. The contemporary natural history of patients with acute pulmonary embolism (PE) not receiving (or early discontinuing) anticoagulant therapy has not been consistently evaluated.

Objective. To assess the rate of the composite outcome of PE-related death, sudden death, or recurrent thromboembolism (VTE) within 30 days in all PE patients in whom anticoagulation was not administered or discontinued prematurely (< 90 days of anticoagulation).

Methods: We used the RIETE database to assess the incidence rates (per 100 person-days) of the composite outcome within the subsequent 30 days. The risk of these events was compared to PE patients who were anticoagulated for ≥90 days.

Results. Of 34,447 PE recruited from 2001 to 2017, 47 (0.14%) did not receive anticoagulants and 1,348 (3.91%) discontinued it before 90 days. Fatal PE developed in 25 (53%) of those without any anticoagulation and in 45 (3.33%) with premature discontinuations. Sudden death or non-fatal recurrent VTE occurred in 6 (0.45%) and 24 (1.48%) patients, respectively. The incidence of the primary outcome declined logarithmically from 6.36 per 100 patient-days in untreated patients to 0.32-0.13 in those treated for 8-90 days. During the first week of follow-up, the incidence rate was 13.9 and 0.60-0.31 per 100 patient-days, respectively. The adjusted odds of the primary outcome was 27 fold higher in untreated than in treated patients, and progressively decreased to 2.5-7 fold higher in patients treated for at least 7 days.

Conclusion. The incidence of the composite outcome was highest during the first week, and inversely and logarithmically correlated with the duration of anticoagulant therapy.

Keywords. Pulmonary embolism, anticoagulation, outcomes.

Introduction

Anticoagulant therapy dramatically modifies the natural history of patients with acute pulmonary embolism (PE). Anticoagulation has been considered the mainstay of treatment for PE (1). In daily practice however, some patients with PE may not receive anticoagulant therapy for a number of reasons: active bleeding, urgent need for surgery, reasonable doubts about the diagnosis, patient's objections to anticoagulation or contraindications to anticoagulant therapy. Other patients may face complications, competing morbidities, or choices based on preference that may lead to early discontinuation (prior to a minimum of 3 months) of anticoagulation after acute PE.

Natural history studies would be enlightening to help inform clinical choices and future research related to these patient subgroups. However, the existing natural history studies were conducted decades ago (2,3). Since then, the clinical presentation, constellation of co-morbidities, method of diagnosis, and ancillary in-hospital care has gone through major changes. Yet, there are no contemporary updates about the natural history and outcomes of patients with PE who do not receive anticoagulant therapy or those who undergo early discontinuation.

The RIETE (Registro Informatizado Enfermedad TromboEmbólica) registry is an ongoing, multicenter, international observational registry of consecutive patients with objectively confirmed acute venous thromboembolism (VTE). Data from this registry have been used to evaluate outcomes after acute VTE, such as the frequency of recurrent VTE, bleeding and mortality, and risk factors for these outcomes (4-7).In the current study, we aimed to assess the rate of the

composite outcome of fatal PE, sudden unexpected death or symptomatic VTE recurrences appearing during the first 30 days in patients not receiving or early discontinuing anticoagulant therapy.

Methods

We used the data from patients enrolled in the RIETE registry with acute symptomatic PE confirmed by objective tests (pulmonary angiography, lung scintigraphy, or helical computed tomography). Previous publications have described the design and conduct of the RIETE registry (7). Briefly, RIETE registry prospectively enrols consecutive patients with VTE from 24 countries. Data were recorded on to a computer-based case report form at each participating hospital and submitted to a centralized coordinating centre through a secure website. Patients were excluded if they were currently participating in a therapeutic clinical trial with a blinded therapy. All patients (or healthcare decision-makers) provided written or oral consent to their participation in the registry, in accordance with local Ethics Committee requirements. 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 March 2017 and did not receive any anticoagulation at all after an acute PE (Cohort A), or those who received anticoagulation but terminated it prematurely (prior to a minimum of 90 days) (Cohort B). We excluded patients who underwent vena cava (IVC) filter placement, those who developed VTE recurrences or died the same day of discontinuation, and those who died on the

day of PE 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 anticoagulation at all.

Outcomes

The main outcome was the composite of fatal PE, sudden unexpected death or recurrent non-fatal VTE (either symptomatic PE or deep vein thrombosis [DVT]), appearing during the first 30 days without anticoagulant therapy (8).

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 thromboses were not included in this analysis. Outcomes were classified as reported by site investigators. However, if staff at the coordinating centre were uncertain 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.

Statistical analysis

We reported median with inter-quartile range for quantitative variables. We compared the frequencies of categorical variables using the Chi-squared test or the Fisher's exact test, where appropriate. We used logistic regression analysis to determine whether the duration of anticoagulant therapy is a factor associated with development of fatal PE or VTE recurrences, after adjusting for demographics and clinical risk factors (a list of co-variates is shown in the footer of Table 3). In this analysis, we considered the duration of anticoagulant therapy as a categorical variable with 6 levels (0, 1 to 7, 8 to 14, 15 to 30, 31 to 60, and 61 to 90 days), and patients treated for 61-90 days as the reference group.

In a separate analysis, we compared the event rates of the study cohort (n, 1,395) with those appearing in PE patients who received anticoagulation for at least 90 days (n, 31,901) and we used a separate logistic regression model to compare the risks for fatal PE or VTE recurrences between groups (a list of co-variates is shown in the footer of Table 4). Survival curves were built according to the Kaplan-Meier method. The rates of different outcomes were reported as events per 100 patient-days to standardize for different durations of follow-up. SPSS software (version 20, SPSS Inc., Chicago, Illinois) was used for the statistical analysis and a two-sided $p<0.05$ was considered to be 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 March 2017, 34,447 patients with acute PE were enrolled in RIETE. Of these, 1,015 (2.95%) underwent a vena cava filter placement, 82 (0.24%) died during the same day of PE diagnosis with no time to receive any therapy and 54 (0.16%) developed VTE recurrences the same day of discontinuation. These patients were not included in the study. Among the 33,296 remaining patients, 47 (0.14% of the whole series) did not receive anticoagulation at all (and survived the first 24 hours; Cohort A)) and 1,348 (3.91%) received anticoagulant therapy for less than 90 days and then stopped anticoagulation (Cohort B).

Among the 47 patients (Cohort A) who did not receive any anticoagulant therapy, 6 (13%) were actively bleeding at baseline, 11 (23%) had recent (< 30 days before) major bleeding (including 5 with intracranial bleeding), 15 (32%) had metastatic cancer, 10 (21%) had severe renal insufficiency and 5 (11%) were thrombocytopenic (platelet count <50,000 platelets/μL) (Table 1).

During the first 30 days of follow-up, 41of the 47 patients (87%) not receiving anticoagulation died: 25 of PE, 3 of bleeding and 13 of other reasons. Additionally, 6 patients (13%) suffered from non-fatal major bleeding. Median time elapsed from PE diagnosis to death was 3 days (inter-quartile range [IQR]: 1-6 days).

Among the 1,348 patients (Cohort B) that received therapy for less than 90 days(median duration, 37 days; IQR: 15-68 days), 10 (0.74%) were actively bleeding at baseline, 53 (3.9%) had recent major bleeding (intracranial 13), 369 (27%) metastatic cancer, 148 (11%) severe renal insufficiency and 13 (1.0%) were thrombocytopenic (platelet count <50,000 platelets/μL). Additionally, 210 patients (16%) had major bleeding (intracranial 38, retroperitoneal 19) during the course of anticoagulant therapy.

During the first 30 days of follow-up, 586 of the 1,348 patients (44%) died: 45 (3.3%) died of PE, 6 (0.5%) had a sudden, unexplained death and 70 (5.2%) died of bleeding. The median time elapsed from PE diagnosis to death was 29 days (IQR: 15-50 days). Additionally, 126 patients (9.4%) suffered from major non-fatal bleeding, 13 (1.0%) had non-fatal PE recurrences and 11 (0.8%) presented with DVT.

Combining all the patients who received no anticoagulation as well as those who discontinued it prematurely (Cohorts A and B),100 of the 1,395 (7.2%) had the composite outcome during the first 30 days: fatal PE in 70 patients, sudden unexpected death in 6, non-fatal recurrent PE in 13 and DVT in 11. Patients developing the composite outcome were more likely to have recent or active

bleeding at baseline, abnormal prothrombin time, renal insufficiency or at least one risk factor for bleeding than those not developing the composite outcome (Table 2). Fatal PE or sudden death accounted for 76% of the events, and appeared early (median, one day; IQR 1-3 days). Non-fatal VTE recurrences increased more slowly over time (median 7 days; IQR 3-15 days), as shown in Figure 1. The proportion of patients developing the composite outcome inversely correlated with the duration of therapy, ranging from 53% in untreated patients to 2.8% in those receiving therapy for 61-90 days (Figure 2). The cumulative rate of fatal PE or recurrent VTE according to the duration of anticoagulant therapy is shown in Figure 3.

On multivariable analysis, adjusted for demographics and clinical factors, absence of anticoagulation at all (odds ratio [OR]: 39.2, 95% confidence interval [CI]: 17.4-88.2), and use of anticoagulation for 1-7 days (OR 10.2, 95% CI 5.12-20.3) were associated with an increased odds of the composite outcome. Patients receiving anticoagulant therapy for 8-60 days were at a non-significantly higher risk (Table 3).

Overall, the incidence of events inversely correlated with the time on therapy (Figure 4) in a logarithmic relation (R square between composite outcome and Log duration of treatment as a continuous variable, 0.511; p<0,001). The fitting curve equation was:

Incidence (% patient-days) = 3.37 – 0.82 Ln (days on AC treatment).

During the first month without anticoagulation, the daily incidence of the composite outcome was 0.41% (95% CI: 0.08-0.75). However, this rate largely varied according to the duration of anticoagulation, ranging from 6.36% (95% CI: 0-13.3) in patients not receiving anticoagulants to 0.13% (95% CI: 0-0.47) in those treated for 61 to 90 days. Also, the incidence showed an inverse relation to the time elapsed since discontinuation of anticoagulant therapy (Figure 4). The daily incidence of events during the first week was more than twice as high as during the following weeks (Figure 4).

Finally, we compared the event rates of the study cohorts with patients who received anticoagulant therapy for at least 90 days (Table 4). The risk of the composite outcome was significantly higher in the study subgroups compared to those receiving therapy for at least 90 days. It was highest in untreated patients (adjusted OR: 27.3; 95%CI: 14.4-53.2); and decreased to 2.5-8 times in the rest of the patients.

Discussion

Our data, obtained from a large series of patients with PE, reveal that one in every 732 patients (0.14%) did not receive anticoagulant therapy at all, and one in every 25 (3.91%) received anticoagulation only for less than 90 days. Consistent with our *a priori* hypothesis, these patients had a higher rate of the composite outcome of PE-related death or recurrent VTE than those receiving therapy for over 90 days. The risk of events was highest during the first week, and declined thereafter. Of note, the risk diminished logarithmically with

anticoagulation and was markedly lower in patients who successfully completed at least 1 week of treatment. Complementary data obtained after comparing the rate of the composite outcome in patients treated for over 90 days confirm this inverse correlation and the greatly increased risk that we observed over the first week without anticoagulation.

The highest rate of PE-related deaths appeared in the subgroup of 47 patients who did not receive anticoagulation. Over half of them died of PE, mostly within the first few days. Kelly et al. based on studies performed decades ago, calculated a 26.6% overall risk of fatal PE in untreated patients and a 12.8% of recurrent non-fatal PE (9).Our large-scale investigation provides contemporary updates about outcomes in patients with PE who did not receive any anticoagulation. The higher rates in our study might be attributed to differences in the clinical characteristics of these untreated populations. Inability to receive anticoagulant therapy at all is a relatively uncommon, but clinically-important situation. Although the evidence base for overall use of inferior vena cava (IVC) filters is slim, the finite available evidence may suggest that IVC filters could be considered in these patients (10-12).

Duration of anticoagulant therapy, as well as time since its cessation may have important implications on subsequent outcomes. Studies in the past decades have provided some evidence that in short-term treated patients with VTE, the rate of recurrences inversely correlated to the duration of therapy, ranging from 26% in patients treated during 10 days (13) to 8.6% in patients treated for 4 weeks (14).This study confirms that there is an inverse correlation between

duration of therapy and the risk of events, and highlight the importance of administering treatment at least for few days. Kearon et al. estimated the overall rates of recurrent VTE without anticoagulant therapy as 40% during the first month, with a 1.0 percent absolute increase in the risk of recurrences every day without anticoagulant therapy (15).Our data suggest that the risk varies broadly over time and the estimates should be adapted to the duration of anticoagulant therapy and to the time elapsed since discontinuation.

In a large nested case-control study, Martinez et al. found a 2-fold higher risk of VTE recurrences in the first 60 days after discontinuing vitamin K antagonists than in patients continuing on anticoagulant therapy (rate ratio 2.23; 95%CI, 1.71-2.91) (16).In our cohort, anticoagulant therapy reduced the risk of the composite outcome by 2.5 to 7 fold in patients treated for over one week following discontinuation.

This study has several limitations. First, we do not know the precise reasons for anticoagulation discontinuation in some patients. One in every 7 patients (210 of 1,395; 15%) had to discontinue therapy probably because of major bleeding. Of these, 15 patients died of PE or had VTE recurrences. Subsegmental PE is considered a low risk category suitable to left untreated if there is no concomitant proximal DVT in high bleeding risk scenarios (17,18). Although in our study, sub-segmental PEs were associated with a non-significant lower risk of VTE related complications (OR, 0.33; Table 2), such patients represented only 3% of the cohort and due to small numbers we cannot provide conclusive evidence. It has been suggested (19) that PE developing in patients with

adequate cardiorespiratory reserve and without concomitant proximal VTE could be also a low-risk subgroup, because if left untreated, they have a low incidence of PE recurrences (3-month incidence of fatal PE: 1%, and non-fatal PE: 3%). We found 702 (50%) undertreated patients with similar characteristics and they have a proportion of events (6.7%) similar to the rest of the group. Renal failure was significantly represented in the untreated population, probably as a co-morbidity marker. Although renal failure is associated with increased bleeding risk, it is not, in isolation, a contraindication to anticoagulation. Future studies are warranted to explore the reasons behind undertreatment in these patients. Major high risk procedures, non-elective surgery or terminal diseases might also be a reason for discontinuation in other cases. Irrespectively of the reason, however, we show that lack of anticoagulant therapy or early discontinuation indicates higher risk of fatal and non-fatal VTE, a risk that drastically declines with each day of anticoagulation. Our findings may have important implications for future strategies to help to improve tailored antithrombotic therapies.

We urge for caution for extrapolation of our results to all patients with PE. It is likely that our studied cohort had an inherent selection bias, being medically disadvantaged or sicker, thereby not receiving anticoagulation. Therefore, the observed high rate of mortality is unlikely in an average PE patient left untreated. However, we found that PE is an important cause of death in this select minority of contemporary patients with PE, and that only a few days on anticoagulants may change the outcomes rate.

Second, loss for follow-up is a potential source of bias in our study. We cannot quantify the direction or the magnitude of the effect but it was probably low: Participating centres were requested to enrol consecutive patients to minimize this flaw, an issue that has been vetted in prior investigations (7,20). Further, many patients included in this study constitute an “exception” to routine practice, i.e. antithrombotic therapy for VTE. As such, we hypothesize that were usually closely observed. Lack of independent adjudication of events is another limitation, similar to other large-scale registries. However, RIETE has had frequent entry-level audits by the staff to improve the data quality and there is constant day-to-day feedback and communication between the RIETE staff and site investigators who enter the data. Further, periodic site visits by the RIETE coordinating team have not demonstrated sizeable flaws in critical variables entered by the site investigators. Relevant parameters regarding the severity of PE (i.e. troponin and NT-proBNP levels, right ventricular dysfunction or pulmonary vascular obstruction index) were not systematically recorded and were not evaluated. Finally, the inclusion of sudden death episodes in the composite outcome may lead to overestimate the rate of fatal PE. Nevertheless, the size of the effect would be light and the findings were materially similar after excluding sudden death.

In conclusion, our study provides contemporary evidence of the inverse relationship between the duration of anticoagulation and the risk for the composite of fatal PE, sudden death or recurrent VTE after PE diagnosis. These data 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 PE.

Role of the funding source and 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 is 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.

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JAN takes 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. JAN and MM take responsibility for the integrity of the data and contributed substantially to the study design. JAN, MM and BB contributed substantially to the interpretation of the data and the writing of the manuscript.

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APPENDIX

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References

1.- Barrit DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. Lancet 1960;1:1309–1312.

2.- Dalen JE, Alpert JS. Natural history of pulmonary embolism. Prog Cardiovasc Dis.1975; 17: 257-270.

3.- Carson JL, Kelley MA, Duff A, Weg JG, Fulkerson WJ, Palevsky HI et al. The clinical course of pulmonary embolism. N Engl J Med 1992; 326:1240-1245.

4.-Laporte S, Mismetti P, Decousus H,Urresandi F, Otero R, Lobo JL, et al. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry. Circulation 2008; 117:1711-1716.

5- Lecumberri R, Soler S, Del Toro J, Barba R, Rosa V, Ciammaichela MM, et al. Effect of the time of diagnosis on outcome in patients with acute venous thromboembolism. Findings from the RIETE Registry. Thromb Haemost. 2011;105:45-51.

6.- Jiménez D, de Miguel-Diez J, Guijarro R, Trujillo-Santos J, Otero R, Barba R, et al. Trends in the management and outcomes of acute pulmonary embolism: Analysis from the RIETE Registry. J Am Coll Cardiol. 2016; 67:162-70.

7.- Bikdeli B, Jimenez D, Hawkins M, Ortíz S, Prandoni P, Brenner B, et al. Rationale, Design and Methodology of the Computerized Registry of Patients with Venous Thromboembolism (RIETE). Thromb Haemost. 2018; 118(1):214-224.

8.- Douketis JD, Gu CS, Schulman S, Ghirarduzzi A, Pengo V, Prandoni P. The risk for fatal pulmonary embolism after discontinuing anticoagulant therapy for venous thromboembolism. Ann Intern Med. 2007; 147:766-74.

9.-Kelly J, Hunt BJ, Lewis RR, Rudd A. Anticoagulation or inferior vena cava filter placement for patients with primary intracerebral hemorrhage developing venous thromboembolism?. Stroke 2003; 34:2999-3005.

10.- Bikdeli B, Chatterjee S, Desai NR, Kirtane AJ, Desai MM, Bracken MB, et al. Inferior Vena Cava Filters to Prevent Pulmonary Embolism: Systematic Review and Meta-Analysis.J Am Coll Cardiol. 2017; 70:1587-1597.

11.- Muriel A, Jiménez D, Aujesky D, Bertoletti L, Decousus H, Laporte S, et al. Survival effects of inferior vena cava filter in patients with acute symptomatic venous thromboembolism and a significant bleeding risk. J Am Coll Cardiol. 2014; 63:1675-83.

12- Bikdeli B, Ross JS, Krumholz HM. Data Desert for Inferior Vena Caval Filters: Limited Evidence, Supervision, and Research. JAMA Cardiol. 2017; 2:3-4.

13.- Hull R, Delmore T, Genton E, Hirsh J, Gent M, Sackett D, et al. Warfarin sodium versus low-dose heparin in the long-term treatment of venous thrombosis. N Engl J Med 1979; 301:855-858.

14.- Levine MN, Hirsh J, Gent M, Turpie AG, Weitz J, Ginsberg J, et al.Optimal duration of oral anticoagulant therapy: a randomized trial comparing four weeks with three months of warfarin in patients with proximal deep vein thrombosis. ThrombHaemost.1995; 74:606-611.

15.-Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. N Engl J Med 1997; 336:1506-1511.

16.- Martinez C, Katholing A, Folkerts K, Cohen AT.Risk of recurrent venous thromboembolism after discontinuation of vitamin K antagonist treatment: A nested case-control study. J Thromb Haemost. 2016; 14: 1374-1383.

17.- Carrier M, Righini M, Wells PS, Perrier A, Anderson DR, Rodger MA, et al. Subsegmental pulmonary embolism diagnosed by computed tomography: incidence and clinical implications. A systematic review and meta-analysis of the management outcome studies. J Thromb Haemost. 2010; 8:1716-1722.

18.- Kearon C, Akl EA, Ornelas J, Blaivas A, Jiménez D, Bounameaux H, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016; 149:315-352.

19.-Stein PD, Hull RD, Raskob GE. Withholding treatment in patients with acute pulmonary embolism who have a high risk of bleeding and negative serial noninvasive leg tests. Am J Med. 2000; 109:301-306.

20.-Guijarro R, Montes J, Sanroman C, Monreal M, for the RIETE investigators. Venous thromboembolism in Spain. Comparison between an administrative database and RIETE Registry. Eur J Intern Med. 2008; 19:443-446.

Table 1. Clinical characteristics at diagnosis of patients with PE, according to duration of anticoagulant therapy[π].

	Therapy ≥90 days	No therapy	Therapy <90 days
Patients, N	***31,901***	***47***	***1,348***
Clinical characteristics,			
Male gender	14,910 (47%)	24 (51%)	606 (45%)
Age >85 years	3,158 (9.9%)	9 (19%)	227 (17%)[‡]
Body weight <50 kg	684 (2.1%)	2 (4.3%)	66 (4.9%)[‡]
High risk for fatal PE,			
SBP levels <90 mm Hg	1,080 (3.4%)	8 (17%)[‡]	49 (3.6%)
Sat O_2levels <90% (N=21,100)	5,952 (19%)	17 (65%)[†]	281 (34%)[*]
Heart rate >110 beats per minute	6,434 (20%)	20 (44%)[‡]	284 (22%)
Chronic lung disease	4,565 (14%)	9 (19%)	206 (15%)
Chronic heart disease	2,888 (9.0%)	8 (17%)	187 (14%)[‡]
Abnormal mental status	1,338 (4.2%)	6 (13%)[*]	22 (1.6%)[‡]
Cancer	6,658 (21%)	19 (40%)	577 (43%)[‡]
sPESIscore <1 points (N= 21.093)	5,735 (18%)	2 (7.7%)[*]	109 (13%)[‡]
Right ventricular hypokinesis (n, 12,204)	2,770 (23%)	5 (71%)[‡]	81 (22%)
High risk for bleeding,			
Recent major bleeding	586 (1.8%)	11 (23%)[‡]	53(3.9%)[‡]
Active bleeding at baseline	107 (0.3%)	6 (13%)[‡]	10 (0.7%)[*]
Major bleeding during therapy	404 (1.3%)	3 (6.4%)[*]	210 (16%)[‡]
Metastatic cancer	2,660 (8.3%)	15 (32%)[‡]	369 (27%)[‡]
Anemia	10,087 (32%)	30 (64%)[‡]	641 (48%)[‡]
Platelet count <50,000/µL	65 (0.2%)	5 (11%)[‡]	13 (1.0%)[‡]
Abnormal prothrombin time	2,687 (8.4%)	17 (36%)[‡]	183 (14%)[‡]
CrCl levels <30 ml/min	2,002 (6.3%)	10 (21%)[‡]	148 (11%)[‡]
Any of the above	13,734 (43%)	43 (92%)[‡]	936 (69%)[‡]
VTE characteristics ,			
Subsegmental PE	663 (2.1%)	1 (2.1%)	39 (2.9%)[*]
Concomitant proximal DVT	10,321 (32%)	6 (13%)[‡]	380 (28%)[‡]
Anticoagulant therapy,			
Duration (median days, IQR)	≥90	-	37 (15-68)
Initial therapy			
Low-molecular-weight heparin	27,105 (85%)	-	1,192 (88%)
Unfractionated heparin	3,101 (9.7%)	-	107 (7.9%)[*]
Thrombolytics	666 (2.1%)	-	16 (1.2%)[*]
DOACs	358 (1.1%)	-	7 (0.5%)
Fondaparinux	564 (1.8%)	-	22 (1.6%)

*p <0.05; [†]p <0.01; [‡]p <0.001.[π]Comparisons were done with patients treated ≥90 days as the reference group.

Abbreviations: SBP: Systolic blood pressure. VTE, venous thromboembolism; PE pulmonary embolism; DVT, deep vein thrombosis; CrCl, creatinine clearance; LMWH, low molecular weight heparin; DOACs, Direct oral anticoagulants; PESIs, Pulmonary Embolism Severity Index simplified.

Table 2. Clinical characteristics and treatment of PE patients not receiving anticoagulant therapy (n, 1395) according to the composite outcome of fatal PE, sudden death or VTE recurrences.

	Composite outcome	No composite outcome	Odds ratio (95% CI)
Patients, N	***100***	***1,295***	
Clinical characteristics,			
Male gender	42 (42%)	588 (45%)	0.87 (0.58-1.31)
Age >85 years	25 (25%	246 (19%)	1.42 (0.89-2.28)
Body weight <50 kg	5 (5%)	63 (4.9%)	1.03 (0.40-2.60)
High risk for fatal PE,			
SBP levels <90 mm Hg	8 (8%)	49 (3.8%)	2.21 (1.02-4.81)
Sat O2 <90% (n,856)	38 (53%)	260 (33%)	2.25 (1.39-3.66)
Heart rate >110 bpm	29 (29%)	275 (22%)	1.51 (0.96-2.38)
Chronic lung disease	11 (11%)	204 (16%)	0.66 (0.35-1.26)
Chronic heart disease	12 (12%)	183 (14%)	0.83 (0.44-1.55)
Abnormal mental status	10 (10%)	118 (9.1%)	1.11 (0.56-2.19)
Cancer	40 (40%)	556 (43%)	0.89 (0.59-1.34)
sPESI, mean score (SD) (n, 849)	1.97 (1.11)	1.72 (1.11)	-
sPESI score <1 point	6 (8.5%)	105 (14%)	0.52 (0.25-1.40)
Right ventricular hypokinesis (n, 372)	11 (13%)	14 (4.9%)	2.84 (1.24-6.54)
High risk for bleeding,			
Recent (<30 days before) major bleeding	11 (11%)	53 (4.1%)	2.90 (1.46-5.74)
Active bleeding at baseline	5 (5.0%)	11 (0.85%)	6.14 (1.82-19.6)
Major bleeding during therapy	14 (14%)	199 (15%)	0.90 (0.50-1.61)
Metastatic cancer	29 (29%)	355 (27%)	1.08 (0.67-1.73)
Anemia	50 (50)	621 (48%)	1.01 (0.72-1.63)
Platelet count <50,000/µL	2 (2.0%)	16 (1.2%)	1.63 (0.37-7.20)
Abnormal prothrombin time	27 (27)	173 (13.4)	2.28 (1.42-3.68)
CrCl levels <30 ml/min	19 (19)	139 (10.7)	1.95 (1.15-3.31)
Any of them	81 (81%)	898 (69%)	1.89 (1.13-3.15)
VTE characteristics ,			
Subsegmental PE	1 (1.0%)	39 (3.0%)	0.33 (0.04-2.39)
Concomitant proximal DVT	29 (29%)	357 (28%)	1.07 (0.69-1.68)
Anticoagulant therapy,			
Duration (median days, IQR)	6 (2-29)	38 (15-69)	-
0 days	25 (25%)	22 (1.7%)	19.3 (10.4-35.8)
1-7 days	34 (34%)	115 (8.9%)	5.29 (3.35-8.34)
8-14 days	7 (7%)	177 (14%)	0.48 (0.22-1.04)
15-30 days	12 (12%)	234 (18%)	0.62 (0.33-1.15)
31-60 days	10 (10%)	333 (26%)	0.32 (1.65-0.62)
61-90 days	12 (12%)	414 (32%)	0.29 (1.56-0.54)

Abbreviations:PE pulmonary embolism; VTE, venous thromboembolism; bpm, beats per minute; Sat O_2, Saturation of oxygen; SBP, systolic blood pressure; sPESI, simplified Pulmonary Embolism Severity Index; SD, standard deviation; CrCl, creatinine clearance; DVT, deep vein thrombosis; IQR, inter-quartile range; CI, confidence intervals.

Table 3. Adjusted risks for the composite outcome of fatal PE, sudden death or VTE recurrences according to the duration of anticoagulant treatment in PE patients in whom anticoagulation was not administered or discontinued before 90 days.

	OR (95% CI)	**p value**
Anticoagulation time 0 days	39.2 (17.4-88.2)	<0.001
Anticoagulation time 1-7 days	10.2 (5.12-20.3)	<0.001
Anticoagulation time 8-14 days	1.36 (0.53-3.52)	0.52
Anticoagulation time 15-30 days	1.77 (0.78-4.00)	0.17
Anticoagulation time 31-60 days	1.04 (0.44-2.43)	0.94
Anticoagulation time 61-90 days[π]	1.00	-----

[π]The reference category for comparisons was of the patients anticoagulated 61-90 days.

Multivariable analysis was performed by adjusting the proportion of events to age (years), gender, recent bleeding, metastatic cancer, concomitant proximal DVT, presentation as subsegmental PE, abnormal prothrombin time, chronic lung disease, chronic heart disease, active bleeding at baseline, SBP levels <90 mm Hg, CrCl levels <30 ml/min, anemia, platelet count <50,000/µL, recent surgery, unprovoked VTE, immobilization and duration of anticoagulation (6 levels).

Table 4. Episodes of recurrent VTE, fatal PE or sudden death in the study cohort (n, 1,395) compared to those reported inpatients that received anticoagulation for ≥90 days (n, 31,901) during equivalent follow-up times.

	Early discontinued		Anticoagulated >90 days		Follow-up* (days)	OR	95% CI	OR adjusted	95% CI
Time onanticoagulants	N	Episodes	N	Episodes					
0days	47	25	31,901	584	1-30	60.9	33.0-112.8	27.2	14.4-53.2
1-7 days	149	34	31,901	612	1-37	15.1	10.0-22.7	8.32	5.40-12-8
8-14 days	184	7	31,283	262	8-44	4.68	2.00-10.4	2.58	1.17-5.68
15-30 days	246	12	30,913	171	15-60	9.22	4.82-17.3	5.40	2.87-10.2
31-60 days	343	10	30,433	142	31-90	6.41	3.15-12.6	4.47	2.28-8.79
61-90 days	426	12	29,926	102	61-120	8.47	4.40-16.0	6.85	3.68-12.8

*Days of observation after VTE diagnosis in both cohorts.

Crude ORs were adjusted for age (years), gender, recent bleeding, metastatic cancer, concomitant proximal DVT, presentation as subsegmental PE, abnormal prothrombin time, chronic lung disease, chronic heart disease, active bleeding at baseline, SBP levels <90 mm Hg, CrCl levels <30 ml/min, anemia, platelet count <50,000/μL, recent surgery, unprovoked VTE and immobilization.

OR, Odds risk; CI, confidence interval.

Figure legends

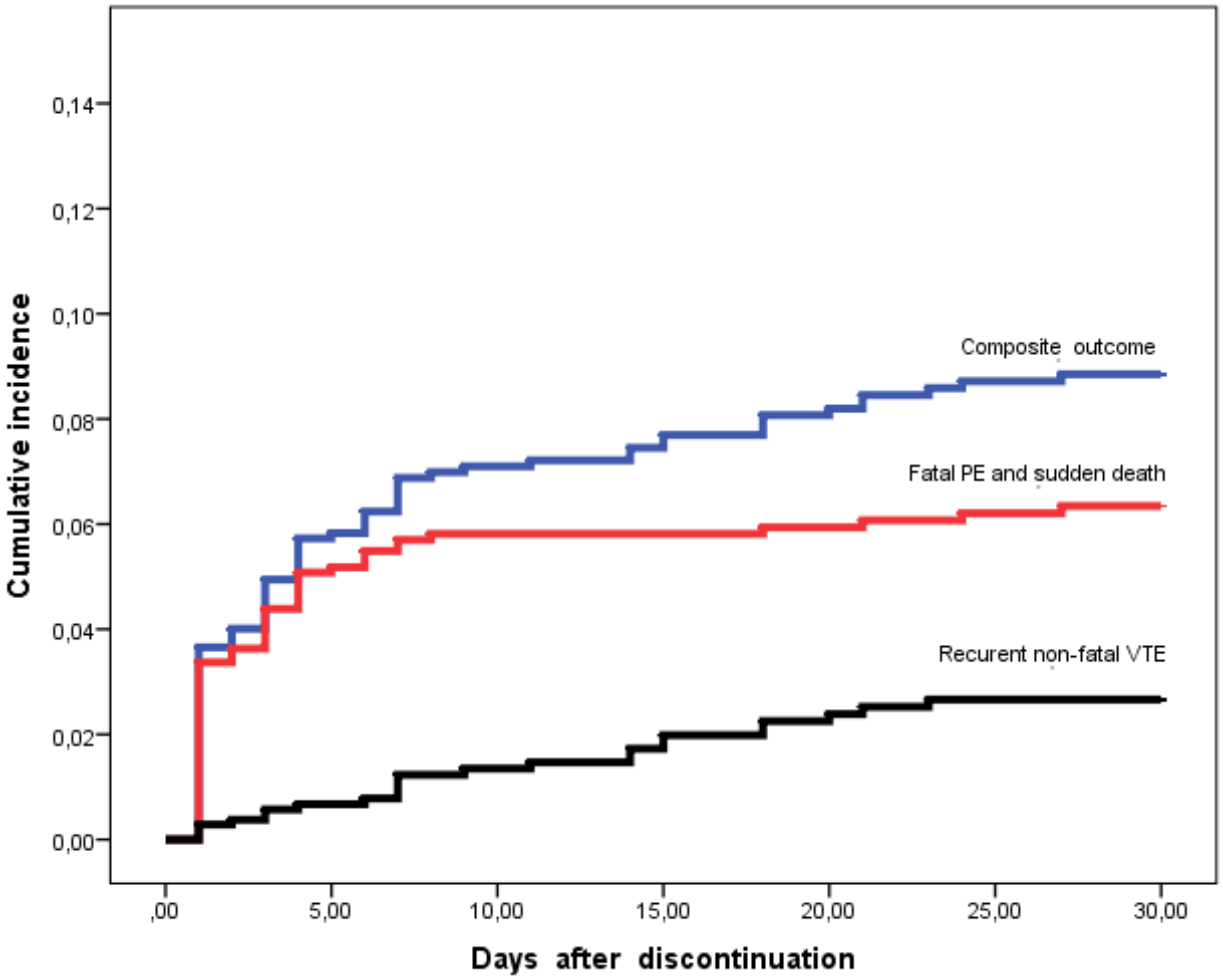
Figure 1. Time course of outcomes (fatal PE and sudden death, recurrent non-fatal VTE, and the composite of both) after discontinuation of anticoagulant therapy.

Figure 2. Outcomes during 30 days after discontinuing anticoagulation, classified in accordance to the duration of therapy.

Figure 3. Cumulative incidence of fatal PE or recurrent VTE during the month following discontinuation of anticoagulant treatment.

Figure 4. 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 discontinuation of anticoagulant treatment.

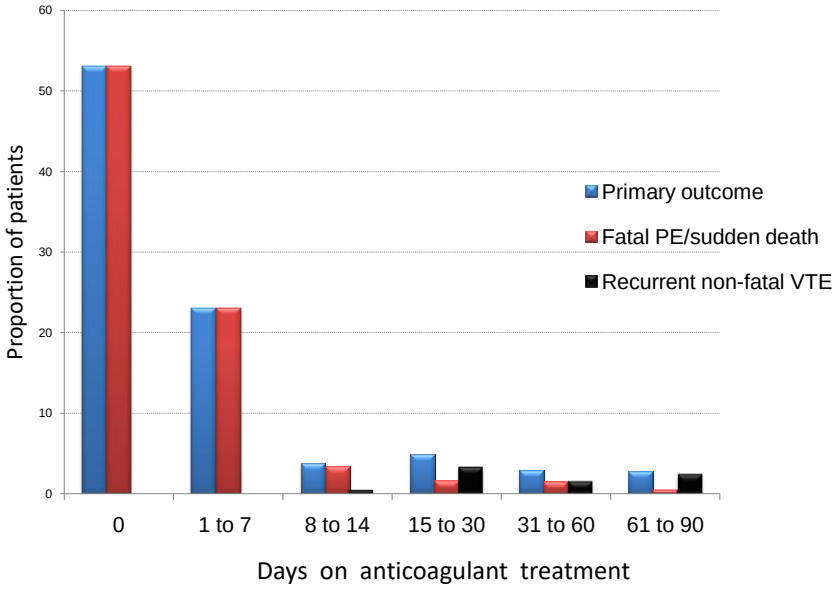
Figure 1. Time course of outcomes (fatal PE and sudden death, recurrent non-fatal VTE, and the composite of both) after discontinuation of anticoagulant therapy.



Days after discontinuation	1-5	6-10	11-15	16-20	21-25	26-30
Patients at risk	1,395	942	807	751	714	680
Composite outcome	74	12	5	4	4	1
Fatal PE / sudden death	66	6	0	1	2	1
Recurrent non-fatal ETV	8	6	5	3	2	0

PE pulmonary embolism; VTE, venous thromboembolism

Figure 2. Outcomes during 30 days after discontinuing anticoagulation, classified in accordance to the duration of therapy.



Days on therapy	0	1-7	8-14	15-30	31-60	61-90
Patients (n)	47	149	184	246	343	426
Median days (IQR)	0	4 (3-6)	11 (9-13)	22 (18-26)	43 (36-50)	79 (70-86)
Primary outcome (n)	25	34	7	12	10	12
Fatal PE / sudden death (n)	25	34	6	4	5	2
Recurrent ETV (n)	0	0	1	8	5	10

Abbreviations: IQR, interquartile range; PE, pulmonary embolism; ETV, Thromboembolic disease. n, number of patients

Figure 3. Cumulative incidence of fatal PE or recurrent VTE during the month following discontinuation of anticoagulant treatment.

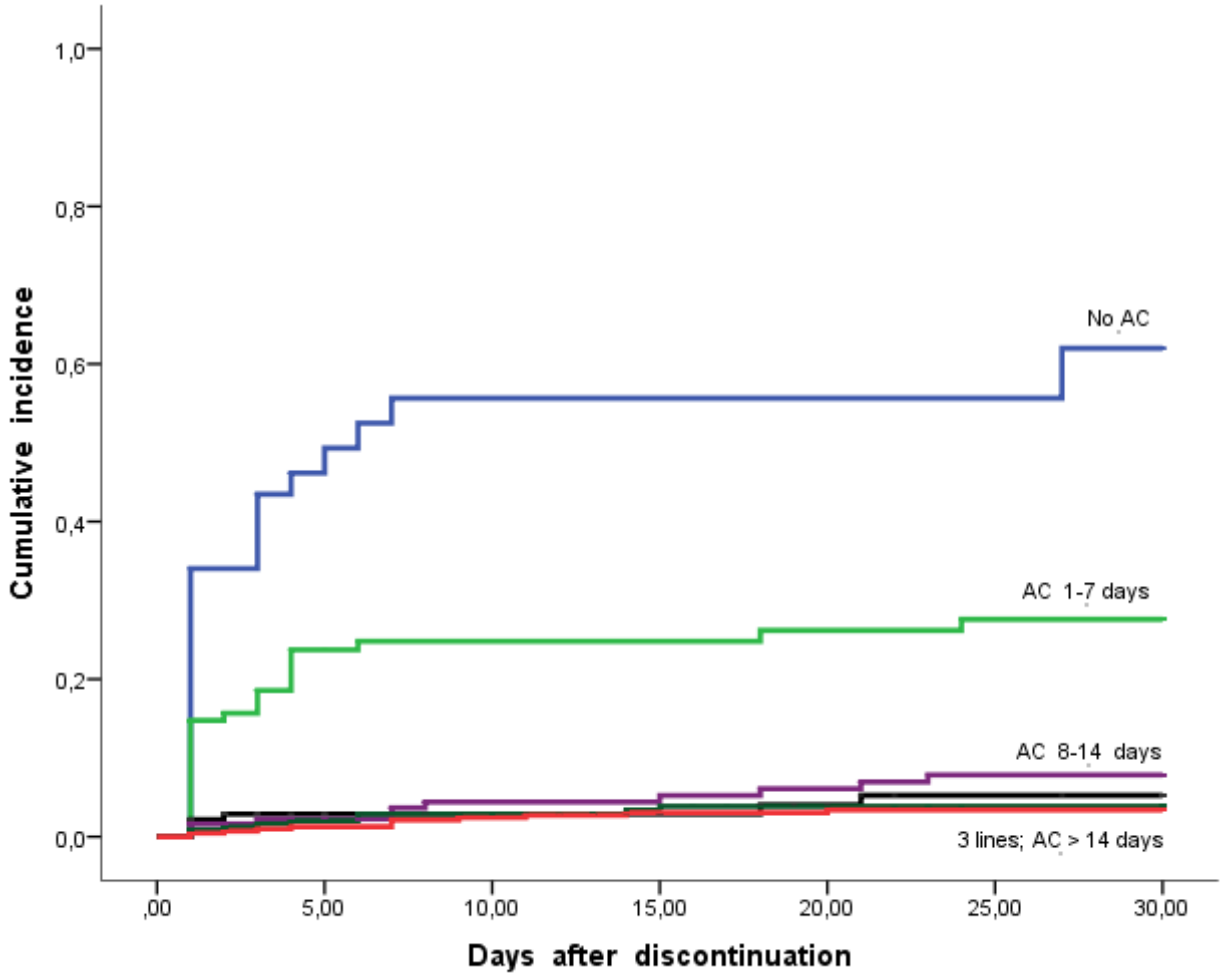
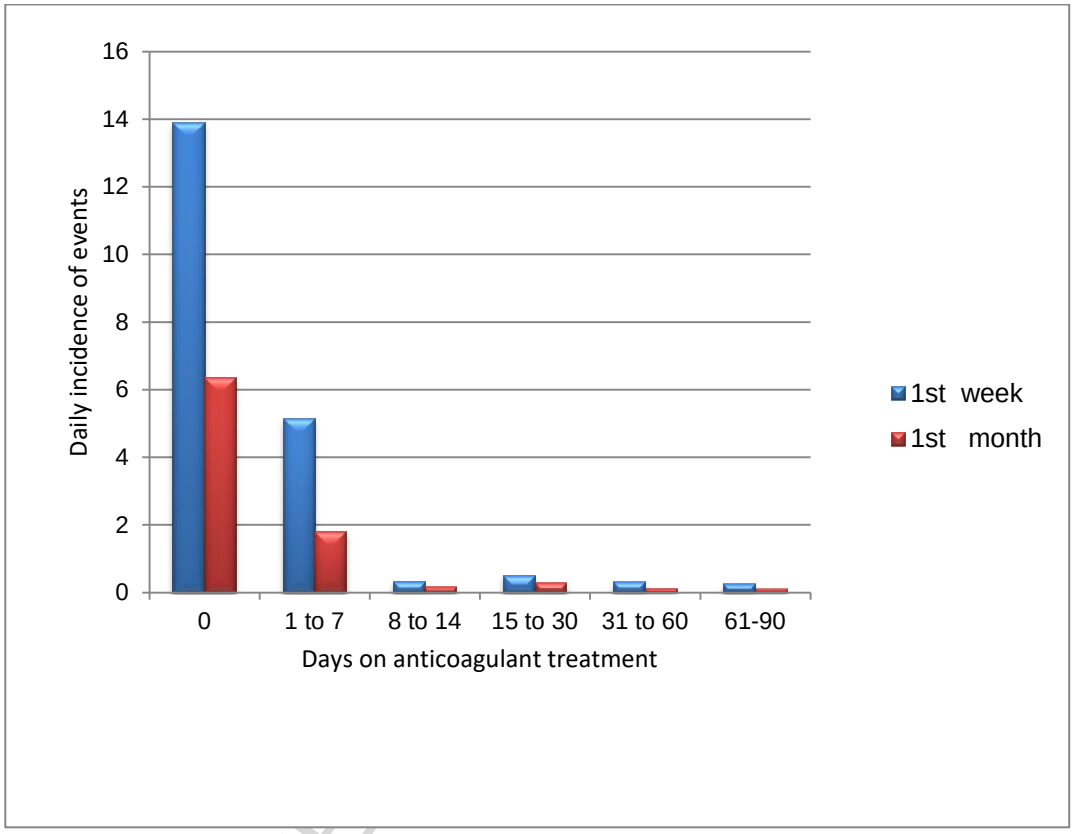


Figure 4. Daily incidence of fatal PE, sudden death or recurrent VTE during an observation period of 1 week (blue columns) or 1 month (red columns) after discontinuation of anticoagulant treatment.



Days on treatment	**0**	**1-7**	**8-14**	**15-30**	**31-60**	**61-90**
1st week % patient-days 95% CI	13.9 3.99-23.8	5.15 1.60-8.69	0.57 0-1.65	0.60 0-1.57	0.44 0-1.15	0.31 0-0.83
1st month % patient-days 95% CI	6.36 0-13.3	1.80 0-3.94	0.25 0-0.98	0.32 0-1.03	0.16 0-0.58	0.13 0-0.47

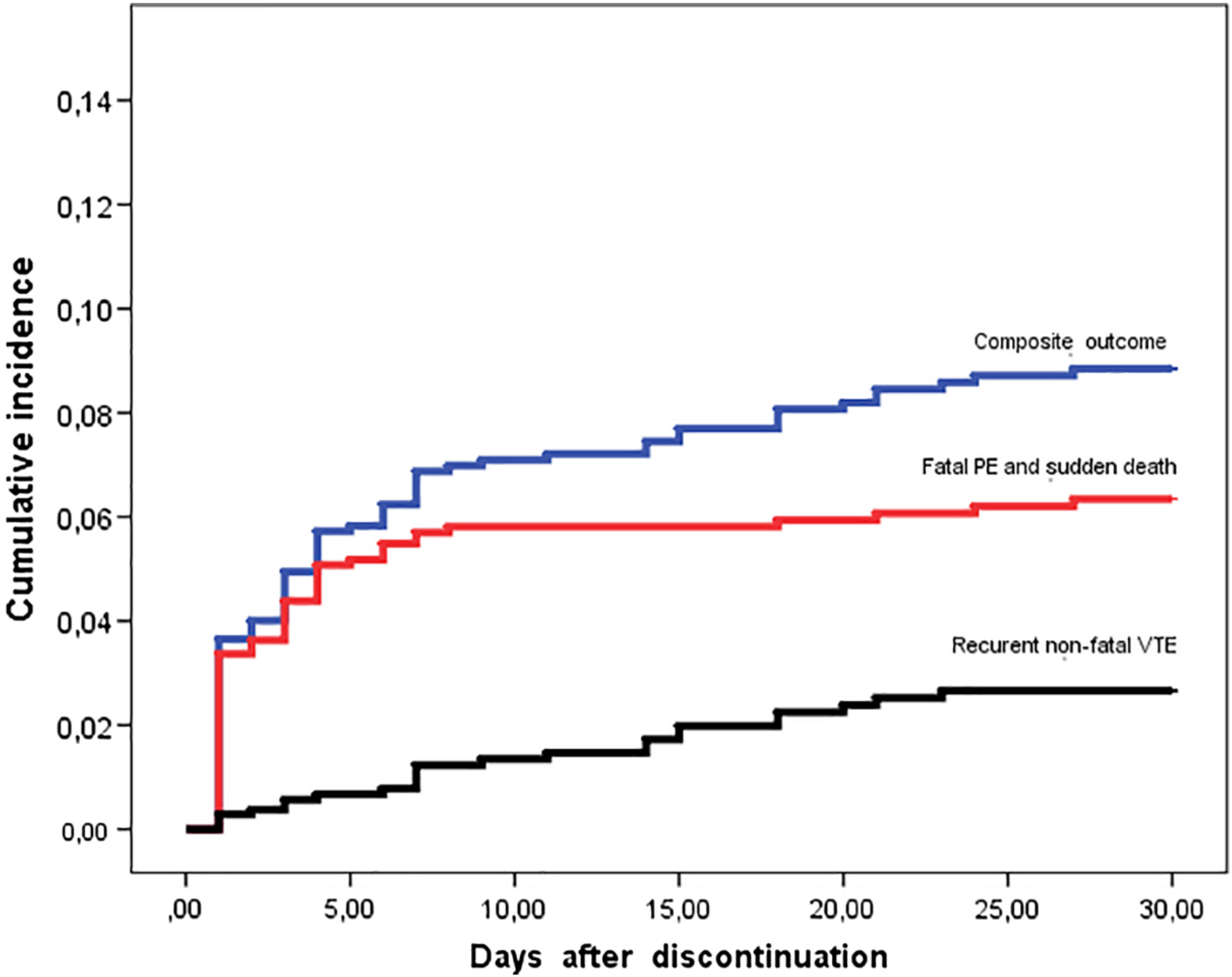

Cumulative incidence
0,14
0,12
0,10
0,08
0,06
0,04
0,02
0,00
Composite outcome
Fatal PE and sudden death
Recurent non-fatal VTE
,00
5,00
10,00
15,00
20,00
25,00
30,00
Days after discontinuation

Figure 1

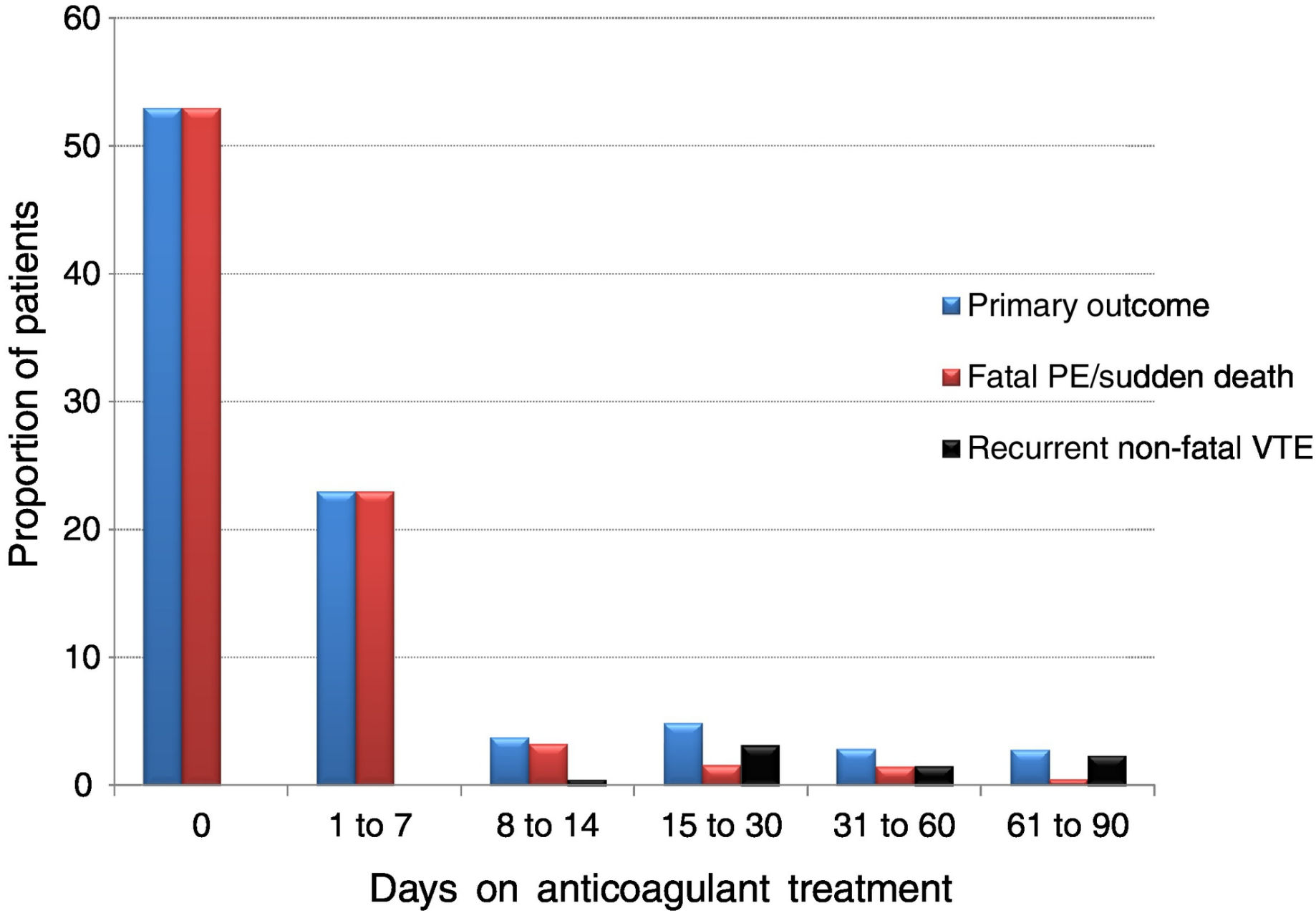

60
50
40
30
20
10
0
Proportion of patients
Primary outcome
Fatal PE/sudden death
Recurrent non-fatal VTE
0
1 to 7
8 to 14
15 to 30
31 to 60
61 to 90
Days on anticoagulant treatment

Figure 2

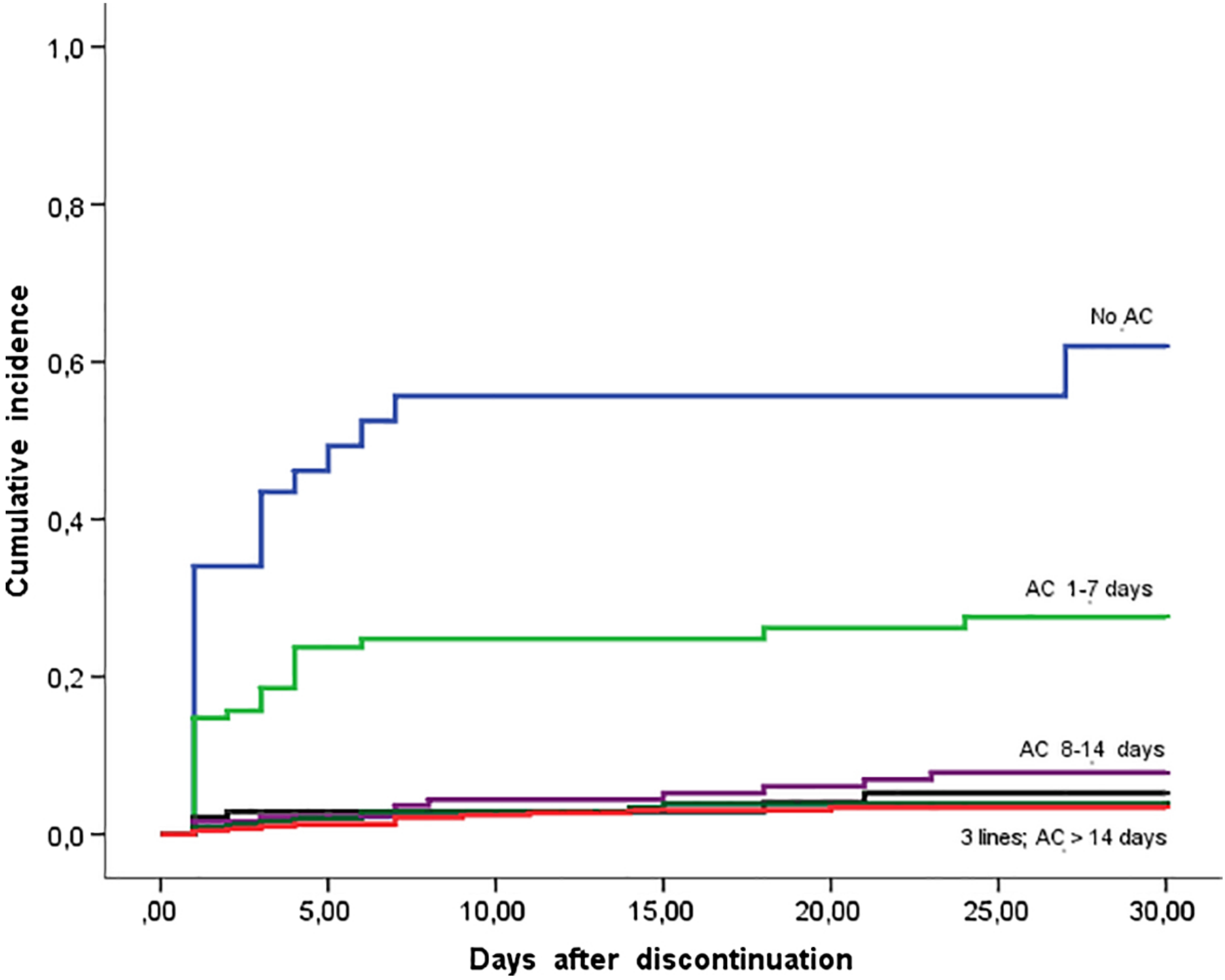

1,0
0,8
0,6
0,4
0,2
0,0
Cumulative incidence
No AC
AC 1-7 days
AC 8-14 days
3 lines; AC > 14 days
,00
5,00
10,00
15,00
20,00
25,00
30,00
Days after discontinuation

Figure 3

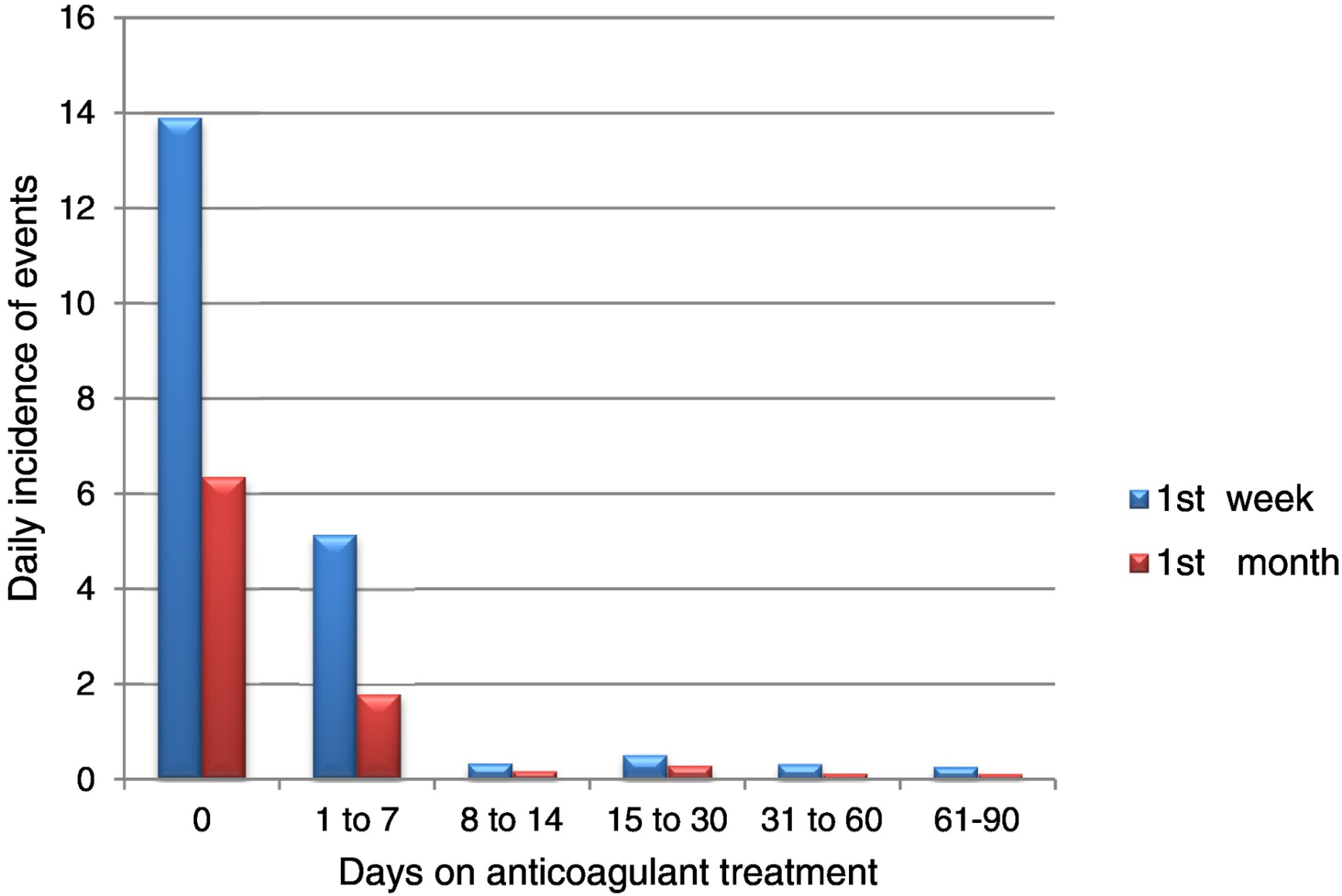

16
14
12
10
8
6
4
2
0
Daily incidence of events
0
1 to 7
8 to 14
15 to 30
31 to 60
61-90
Days on anticoagulant treatment
1st week
1st month

Figure 4