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# Analysis of clinical factors affecting the rates of fatal pulmonary embolism and bleeding in cancer patients with venous thromboembolism

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## Abstract

**Background:** In cancer patients with symptomatic venous thromboembolism (VTE) (deep-vein thrombosis (DVT) and/or pulmonary embolism (PE)), clinical factors that influence the benefit-risk balance of anticoagulation need to be identified so treatment intensity and duration can be optimally adjusted for the individual patient.

**Methods:** Using clinical data for cancer patients with VTE obtained from the RIETE registry, we compared how rates of fatal PE and fatal bleeding during and after anticoagulation vary depending on patients' clinical characteristics.

**Results:** Data were analysed from the 10,962 cancer patients with VTE (5,740 with PE with or without DVT; 5,222 with DVT alone) in RIETE registry as of March 2016. Fatal PE occurred in 2.18% of patients, while fatal bleedings occurred in 1.55%. During the 12 months from initial VTE, fatal PE was the most common cause of death, after disseminating cancer, and bleeding the fourth most common. In patients initially presenting with PE, fatal PE during anticoagulation was 4-fold more frequent than fatal bleeding (204 vs 51 deaths) and occurred mostly during the first month of treatment (196/223, 88%). In patients initially presenting with DVT, fatal PE was 3-fold lower than fatal bleeding during (25 vs 85 deaths) and after anticoagulation treatment (8 vs 37 deaths). During the 12-month follow-up, other characteristics of cancer patients with VTE were identified as more common in fatal cases of PE and/or bleeding than in surviving cases.

**Interpretation:** Baseline clinical characteristics may determine anticoagulation outcomes in cancer patients with VTE and should be further investigated as possible factors for guiding changes in current practices of anticoagulation, such as adjusting anticoagulation intensity and duration in selected patients.

Keywords: Health Sciences, Medicine

## 1. Introduction

Venous thromboembolism (VTE) is a common condition and a major cause of morbidity and mortality in patients with cancer [1, 2]. In both Europe and the USA, large population-based studies and disease registry surveys have revealed that about 20% of patients with VTE have cancer [3, 4, 5, 6]. In an estimated 4,000 cancer patients per year in the UK, VTE is the registered cause of death and the mortality rate of cancer patients with VTE is >3-times greater than that for non-cancer patients with VTE [6, 7]. Several international clinical guidelines [1, 8, 9, 10, 11, 12] recommend, on the basis of data from randomized clinical trials [13, 14, 15] and meta-analyses [16], that cancer patients with VTE should receive initial therapy with low-molecular-weight heparin (LMWH), Fondaparinux or unfractionated heparin (UFH), followed by long-term treatment with LMWH.

However, it is generally accepted, based on the largest study in this setting, that cancer patients should received six months of LMWH treatment [14].

The therapeutic benefit of anticoagulant treatment needs to be balanced against the risk of bleeding. Continuing LMWH treatment beyond three or six months should depend on a benefit-risk assessment for the individual patient. The comparative risk of fatal PE (after anticoagulant withdrawal) or bleeding (due to continued anticoagulant treatment) needs to be determined. However, the determining risk factors still need to be defined. Clinical trial data are of limited value for determine the risk of VTE recurrence, because of the heterogeneity in design and patient population across trials, and their exclusion of certain sub-populations of cancer patients (such as with comorbidities, disseminated cancer, short-life expectancy or contraindications to anticoagulant therapy) that are of particularly relevance for assessing the risk-benefit of anticoagulant treatment [17]. Population-based, longitudinal data are needed, particularly when wanting to identify factors that may have been overlooked in those clinical trials that provide the evidence-base for treatment guidelines.

The ongoing RIETE (Registro Informatizado de Enfermedad TromboEmbólica) Registry provides a large prospective cohort of consecutive patients with symptomatic VTE (deep vein thrombosis (DVT) orpulmonary embolism (PE) or both), derived from multiple centres across several countries in Europe and in North and South America (its methodology is summarised in the Methods section and has been described elsewhere) [18, 19, 20]. So far, published analyses of data from the RIETE registry have provided valuable information on current outcomes of acute VTE, including the frequency of recurrent VTE and of major bleeding, mortality rates and risk factors [18, 19, 20]. In the study presented here, we took data from RIETE Registry in order to determine the frequency and time course of occurrence of fatal PE and of fatal bleeding in this large cohort of cancer patients with VTE. By comparing rates of fatal PE and of fatal bleeding with the overall mortality rate, we assessed how such fatal events may be influenced by the patients' clinical characteristics, such as the type and staging of the cancer, co-morbidities and the presence or absence of other VTE risk factors.

## 2. Methods

## 2.1. Registry design, patient collective and data collection

The RIETE registry is an ongoing, international, (Spain, Belgium, Canada, Czech Republic, Ecuador, France, Greece, Israel, Italy, Latvia, Portugal, Republic of Macedonia, Switzerland), multicenter, prospective collection of clinical data from consecutive patients presenting with symptomatic, acute VTE (DVT and/or PE) [18, 19, 20]. Clinical data were collected for patients presenting with symptomatic

VTE [21, 22]. The methodology of data collection has been described previously [18, 20] and is summarised in the following.

Consecutive patients with symptomatic acute VTE confirmed by objective tests (contrast venography or ultrasonography for suspected DVT, pulmonary angiography, lung scintigraphy or helical computed tomography scan for suspected PE) were enrolled in RIETE registry. The only patients excluded from the registry are those currently participating in a therapeutic clinical trial with a blinded therapy. All patients provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements. Participating physicians ensured that eligible patients were consecutively enrolled. Data recorded on a computer-based case report form at each participating hospital were submitted to a centralised coordinating center through a secure website. Data quality (including comparison of the data on medical records with the data that were transferred) was regularly monitored as previously described. This analysis was approved by the Ethics Committees of the UZ Gasthuisberg Hospital in Leuven, Belgium (B70721111790) and the Hospital Clinic of Barcelona, Spain (Reg. HCB/2015/0386).

## 2.2. Baseline variables

The following parameters are routinely recorded in RIETE registry: patient's baseline characteristics; clinical status including any coexisting or underlying conditions; recognized risk factors for VTE; laboratory data; treatment received upon VTE diagnosis (drugs, doses and duration); outcome during the course of anticoagulant therapy. Immobilized patients were defined as non-surgical patients having total bed rest for at least 4 days in the 2-month period prior to VTE diagnosis. Surgical patients were defined as those who underwent a surgical intervention within the two months prior to VTE. Recent bleeding was defined as a major bleeding episode within 30 days prior to VTE.

## 2.3. Treatment and follow-up

Patients were managed according to the clinical practice of each participating hospital; therefore, there was no standardization of choice of drug treatment, dose or treatment duration. The vast majority (77/10,962 were not taking anticoagulants) of patients were on anticoagulant treatment. Patients were followed-up for at least three months in the outpatient clinic. During each visit, any signs or symptoms suggesting symptomatic VTE recurrences or bleeding complications were noted. Each episode of clinically suspected recurrent VTE was investigated by repeat compression ultrasonography, lung scanning, helical-CT scan or pulmonary angiography as appropriate. Most outcomes were classified as reported by the

clinical centers but, if there was uncertainty, the event was reviewed by a central adjudicating committee (necessary for less than 10% of events).

## 2.4. Study design and outcomes

Cancer patients with newly diagnosed cancer (within the previous three months), with metastatic cancer or with cancer being treated by surgery, chemotherapy, radiotherapy, hormonal or support therapy were included in the analysis. Comparison was made of the following outcomes: alive, fatal PE, fatal bleeding, other fatal cause. The following factors were compared: initial presentation of VTE; patient's clinical characteristics; cancer site and staging; anticoagulant treatment; whether outcome was during or after anticoagulation. The primary outcomes were fatal PE and fatal bleeding. Fatal PE, in the absence of autopsy, was defined as any death appearing within the first 10 days after PE diagnosis (either the initial PE episode or recurrent PE), in the absence of any alternative cause of death. Fatal bleeding was defined as any death occurring within 10 days of a major bleeding episode, in the absence of an alternative cause of death. Bleeding complications were classified as 'major' if they were overt and required a transfusion of two units of blood or more, or were retroperitoneal, spinal or intracranial, or when they were fatal.

## 2.5. Statistical analysis

Categorical variables were reported as percentages and compared using the chi-square test (two-sided) and Fisher's exact Test as appropriate. Odds ratios and corresponding 95% confidence intervals were calculated, and a p-value of $<0.05$ was considered to be statistically significant. Continuous variables were compared with a Student t-test. Incidence rates were calculated as cumulative incidence (events/100 patient-years). The SPSS software (version 20, SPSS Inc. Chicago, Illinois) was used for the statistical management of the data.

## 3. Results

From March 2001 until March 2016, 10,962 (18%) of the 62,362 patients enrolled in the RIETE registry had active cancer. Of these, 5,740 patients initially presented with PE (with or without concomitant DVT) and 5,222 with DVT alone. During anticoagulation, 242 patients presented with symptomatic, objectively proven PE recurrences (4.36 per 100 patient years; 95% CI: 3.83–4.93), 257 had DVT recurrences (4.63 per 100 patient years; 95% CI: 4.09–5.22), 516 had major bleeding (9.29 per 100 patient years; 95% CI: 8.51–10.1) and 3,135 died (56.4 per 100 patient years; 95% CI: 54.5–58.4).

Table 1 lists the baseline demographic and clinical characteristics across four categories of patient outcome. During the 12-month follow-up, 239 (2.17%)

**Table 1.** Cancer Patients with VTE and ≥3 months anticoagulant treatment: Outcomes during 12-month Follow-up and Baseline Demographic and Clinical Characteristics.

| | N | Alive | Fatal PE | | Fatal bleeding | | Other fatalities | |
|---|---|---|---|---|---|---|---|---|
| | | | Number of patients with each outcome (percentage of outcome total) | | | | | |
| | 10,962 | 6,556 | 239 | | 171 | | 3,996 | |
| Clinical characteristics | | | | p-value* | | p-value* | | p-value* |
| Male gender | 5,894 | 3,450 (53%) | 126 (53%) | 0.977 | 99 (58%) | 0.173 | 2,219 (56%) | 0.004 |
| Age <50 years | 1,090 | 702 (11%) | 25 (11%) | 0.903 | 14 (8.2%) | 0.291 | 349 (8.7%) | 0.0010 |
| Underlying conditions | | | | | | | | |
| Chronic lung disease | 1,226 | 675 (10%) | 44 (18%) | 0.00006 | 26 (15%) | 0.038 | 481 (12%) | 0.005 |
| CrCl levels < 60 mL/min | 4,382 | 2,363 (36%) | 132 (56%) | 0.681 | 76 (44%) | 0.024 | 1,811 (45%) | <0.000001 |
| Recent major bleeding | 328 | 158 (2.4%) | 17 (7.1%) | 0.000007 | 12 (7.0%) | 0.00015 | 141 (3·5%) | 0.00078 |
| Anaemia | 6,773 | 3,740 (57%) | 146 (61%) | 0.215 | 121 (71%) | 0.0003 | 2,766 (69%) | <0.000001 |
| Abnormal platelet count | 1,311 | 656 (10%) | 50 (21%) | <0.000001 | 30 (18%) | 0.0013 | 575 (14%) | <0.000001 |
| Leukocyte count >11,000/µL | 3,157 | 1,468 (22%) | 122 (51%) | <0.000001 | 58 (34%) | 0.0004 | 1,509 (38%) | <0.000001 |
| Known Risk factors for VTE, | | | | | | | | |
| Surgery | 1,690 | 1,305 (20%) | 17 (7.1%) | <0.000001 | 13 (7.6%) | 0.00006 | 355 (8.9%) | <0.000001 |
| Immobility ≥4 days | 2,064 | 879 (13%) | 88 (37%) | <0.000001 | 49 (29%) | <0.000001 | 1,046 (26%) | <0.000001 |
| Estrogen use | 462 | 345 (5.3%) | 5 (2.1%) | 0.029 | 6 (3.5%) | 0.309 | 106 (2·7%) | <0.000001 |
| Prior VTE | 1,311 | 869 (13%) | 23 (9.6%) | 0.102 | 18 (11%) | 0.298 | 401 (10%) | 0.000001 |
| Initial VTE presentation, | | | | | | | | |
| Pulmonary embolism | 5,740 | 3,308 (51%) | 213 (89%) | <0.00001 | 82 (48%) | 0.518 | 2,137 (54%) | 0.003 |
| Proximal DVT alone | 3,641 | 2,200 (68%) | 22 (9.2%) | <0.00001 | 68 (40%) | 0.090 | 1,351 (34%) | 0.791 |
| Upper-extremity DVT alone | 827 | 557 (82%) | 4 (1.7%) | 0.00017 | 12 (7.0%) | 0.493 | 277 (7.0%) | 0.00006 |
| Time from VTE (days ± SD) | | 370 ± 476 | 17 ± 38 | <0.00001 | 118 ± 223 | <0.00001 | 152 ± 254 | <0.00001 |
| On therapy | – | – | 14 ± 26 | – | 89 ± 175 | – | 101 ± 194 | – |
| After therapy | – | – | 3 ± 23 | – | 28 ± 109 | – | 43 ± 154 | – |
| Anticoagulant therapy | | | | | | | | |
| On therapy | – | – | 228 (96%) | – | 150 (88%) | – | 2,820 (71%) | – |
| After therapy | – | – | 11 (4.6%) | – | 19 (11%) | – | 1,183 (29%) | – |

*For each baseline characteristic, the percentage of cases within each category of fatal outcome was compared with the corresponding percentage of "alive" cases.

developed fatal PE, mostly (96%) during anticoagulant treatment, while 170 (1.55%) had fatal bleeding, with 20 (12%) cases occurring after discontinuing anticoagulant treatment. Ten percent of the patients dying of PE and 8.1% of patients dying of bleeding were aged below 50 years. Most (87%) of the fatal PEs occurred in patients initially presenting with PE, while a half (52%) of the cases of

fatal bleeding presented with DVT alone. The proportion of patients within each category of fatal outcome exhibiting each of the listed baseline characteristics were compared with the proportion of surviving patients (Table 1). The proportion of fatal PE patients with reduced creatine clearance (57%) at baseline was significantly greater than the proportion of surviving patients (36%) (p < 0.001). This was also the case for recent major bleeding (7.4% vs 2.4%; p < 0.001), abnormal platelet count (21% vs 10%; p < 0.001), raised leucocyte count (51% vs 22%; p < 0.001), immobility for ≥4 days (36% vs 13%; p < 0.001), PE (87% vs 51%; p < 0.001), and upper-extremity DVT alone (57% vs 36%; p < 0.001). In contrast, the following baseline characteristics were significantly less represented among the cases of fatal PE than among surviving patients: recent surgery (6.6% vs 20%; p < 0.001), estrogen use (1.9% vs 5.3%; p < 0.05), proximal DVT alone (68% vs 11%; p < 0.001). For patients with fatal bleeding, the following baseline characteristic were significantly more represented than among surviving patients: chronic lung disease (15% vs 10%; p < 0.05), reduced creatine clearance (44% vs 36%; p < 0.05), recent major bleeding (7.0% vs 2.4%; p < 0.001), anaemia (71% vs 57%; p < 0.001), abnormal platelet count (18% vs 10%; p < 0.05), raised leucocyte count (34% vs 22%; p < 0.001), immobility for ≥4 days (29% vs 13%; p < 0.001), bilateral DVT alone (8.1% vs 5.2%; p < 0.001). Surgery was significantly less represented than among surviving patients (7.6% vs 20%; p < 0.001).

Table 2 compares fatal PE and fatal bleedings in regard to the stage and site of cancer and the patients' treatment. About one in four (24%) fatal PEs and 29% of fatal bleedings occurred in patients with non-metastatic cancer, while about one third of fatal PEs (35%) and of fatal bleedings (38%) occurred in patients who had their initial VTE within three months after cancer diagnosis. Generally, the incidence of fatal PEs tended to be greater than the incidence of fatal bleedings (238 [2.17%] vs 170 [1.51%]) but fatal bleeding was as frequent as fatal PE in patients with gastrointestinal cancer (49 vs 46). In cases of breast cancer, there were three cases of fatal bleeding compared to 23 cases of fatal PE.

The vast majority of patients received at least 3 months anticoagulant treatment and more than 50% of patients received at least 6 months anticoagulant treatment (data not shown). Table 3 compares fatal PE and fatal bleedings in regard to the chosen treatment strategy. There were more fatal bleedings than fatal PEs among patients treated with vitamin K antagonists. The large majority of patients received LMWH treatment for initial therapy while a smaller majority of patients received LMWH treatment for long-term treatment, with >20% receiving vitamin K antagonist. Fatal PE cases had a much shorter mean duration of anticoagulant treatment (16 days; median, 6 days) than cases of fatal bleedings had (86 days; median, 29 days). A more detailed analysis of the data relating to the duration and type of treatment is planned and will be submitted for publication as a separate report.

**Table 2.** Cancer Patients with VTE and ≥3 months antiocoagulant treatment: Patient Outcomes and Baseline Cancer Stage and Site, and Type of Treatment.

| | N | Alive | Fatal PE | | Fatal bleeding | | Other fatalities | |
|---|---|---|---|---|---|---|---|---|
| | | | number of patients with each outcome (percentage of outcome total) | | | | | |
| | 10,962 | 6,556 | 239 | | 171 | | 3,996 | |
| Stage of cancer | | | | p-value* | | p-value* | | p-value* |
| With metastases | 5,652 | 2,378 (36%) | 195 (76%) | <0.00001 | 122 (71%) | <0.000001 | 2,957 (74%) | <0.000001 |
| Diagnosis <3 months earlier | 4,086 | 2,346 (36%) | 84 (35%) | 0.840 | 65 (38%) | 0.549 | 1,591 (40%) | 0.00003 |
| Site of cancer | | | | | | | | |
| Lung | 1,676 | 637 (9.7%) | 61 (24%) | <0.00001 | 34 (20%) | 0.00001 | 948 (24%) | <0.000001 |
| Colorectal | 1,556 | 1,020 (16%) | 25 (10%) | 0.020 | 23 (14%) | 0.452 | 489 (12%) | 0.000002 |
| Breast | 1,355 | 1,103 (17%) | 21 (8.8%) | 0.0010 | 3 (1.8%) | <0.000001 | 228 (5.7%) | <0.000001 |
| Prostate | 1,027 | 816 (12%) | 17 (7.1%) | 0.014 | 9 (5.3%) | 0.005 | 185 (4.6%) | <0.000001 |
| Bladder | 590 | 345 (5.3%) | 11 (4.6%) | 0.653 | 12 (7.0%) | 0.312 | 222 (5.6%) | 0.517 |
| Haematologic | 559 | 334 (8.4%) | 18 (7.1%) | 0.288 | 6 (3.5%) | 0.011 | 202 (5.1%) | <0.000001 |
| CNS | 503 | 322 (4.9%) | 8 (3.3%) | 0.269 | 8 (4.7%) | 0.889 | 165 (4.1%) | 0.063 |
| Pancreas | 498 | 143 (2.2%) | 14 (5.9%) | 0.0002 | 7 (4.1%) | 0.095 | 334 (8.4%) | <0.000001 |
| Stomach | 447 | 198 (3.0%) | 15 (5.4%) | 0.034 | 13 (7.6%) | 0.0007 | 223 (5.6%) | <0.000001 |
| Uterine | 435 | 240 (3.7%) | 7 (4.2%) | 0.673 | 12 (7.0%) | 0.022 | 173 (4.3%) | 0.086 |
| Ovary | 366 | 211 (3.2%) | 6 (2.5%) | 0.541 | 3 (1.8%) | 0.282 | 146 (3.7%) | 0.230 |
| Unknown origin | 239 | 64 (1.0%) | 12 (5.0%) | <0.00001 | 11 (6.4%) | <0.000001 | 152 (3.8%) | <0.000001 |
| Kidney | 238 | 156 (2.4%) | 5 (2.1%) | 0.774 | 3 (1.8%) | 0.595 | 74 (1.9%) | 0.072 |
| EN | 184 | 128 (2.0%) | 0 | 0.029 | 4 (2.3%) | 0.719 | 52 (1.3%) | 0.012 |
| Biliary tract | 134 | 38 (0.6%) | 5 (2.1%) | 0.004 | 4 (2·3%) | 0.004 | 87 (2.2%) | <0.000001 |
| Oesophagus | 116 | 55 (0.8%) | 4 (1.6%) | 0.174 | 6 (3.5%) | 0.0003 | 51 (1.3%) | 0.029 |
| Liver | 87 | 40 (0.6%) | 3 (1.3%) | 0.217 | 5 (2.9%) | 0.0002 | 39 (1.0%) | 0.034 |
| Vulva | 38 | 14 (0.2%) | 1 (0.4%) | 0.507 | 1 (0.6%) | 0.310 | 22 (0.6%) | 0.004 |
| Other | 560 | 381 (5.8%) | 11 (4.6%) | 0.234 | 7 (4.1%) | 0.201 | 204 (5.1%) | 0.003 |

*For each baseline characteristic, the percentage of cases within each category of fatal outcome was compared with the corresponding percentage of "alive" cases; there were 55 patients who were not treated with anticoagulants: 10 received inferior vena cava filter, 19 antiplatelet therapy, 26 received neither anticoagulant therapy, antiplatelets nor underwent vena cava filter insertion.

Based on data in Table 4, the results of the Kaplan Meier analyses of fatalities are presented in Fig. 1 and Fig. 2 for patients initially presenting with PE or DVT only, respectively. Overall (summing the data listed in Fig. 1 and Fig. 2), PE was the second most frequent cause of death, followed by respiratory insufficiency, infection and then bleeding. For patients initially presenting with PE (Fig. 1), PE was the main cause of death after disseminating cancer, with more than twice the number of deaths due to infection and about 3-times the number of fatal bleedings.

**Table 3.** Patient Outcomes and Treatment Strategies.

| | Alive | Fatal PE | Fatal bleeding | Other Fatalities |
|---|---|---|---|---|
| | Number of patients with each outcome (percentage of outcome total)* | | | |
| | 6,556 | 239 | 171 | 3,976 |
| Initial therapy | | | | |
| Low-molecular-weight heparin (LMWH) | 5,924 (90%) | 189 (79%)‡ | 150 (88%) | 3,649 (92%)* |
| Mean dose of LMWH (IU/kg/day) | 174 ± 43 | 182 ± 43 | 174 ± 59 | 172 ± 47 |
| Unfractionated heparin | 374 (5.7%) | 41 (16%)‡ | 14 (8,2%) | 229 (5.8%) |
| Mean dose of UFH (IU/kg/day) | 368 ± 140 | 370 ± 100 | 350 ± 122 | 366 ± 141 |
| Fondaparinux | 95 (1.5%) | 0 | 1 (0.6%) | 36 (0.9%)* |
| Rivaroxaban | 25 (0.4%) | 0 | 0 | 0‡ |
| Thrombolytics | 52 (0.8%) | 9 (3.5%)‡ | 3 (1.8%) | 18 (0.5%)* |
| Vena cava filter | 124 (1.9%) | 2 (0.8%) | 3 (1.8%) | 82 (2.1%) |
| Long-term therapy | | | | |
| Vitamin K antagonists | 2,117 (32%) | 8 (7.3%)‡ | 28 (22%)† | 483 (14%)‡ |
| Low-molecular-weight heparin | 3,649 (56%) | 63 (58%) | 87 (67%)* | 2,556 (73%)‡ |
| Mean LMWH dose (IU/kg/day) | 151 ± 46 | 174 ± 39‡ | 156 ± 44 | 154 ± 46 |
| Rivaroxaban | 45 (0.7%) | 0 | 0 | 5 (0.1%)‡ |
| Duration of therapy | | | | |
| Mean days (±SD)* | 245 ± 335 | 14 ± 26‡ | 90 ± 178‡ | 109 ± 192‡ |
| Median days (range, IQR)* | 166 (161) | 6 (7)‡ | 28 (89)‡ | 56 (104)‡ |

For each baseline characteristic, the percentage of cases within each category of fatal outcome was compared with the corresponding percentage of "alive" cases: *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.

LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; IU, international units; SD, standard deviation; IQR, inter-quartile range; PE, pulmonary embolism.

Fatal PE occurs early after the initial event and mostly during the first month of anticoagulant treatment before reaching close to maximum at 3 months, after which very few cases occur. In contrast, cases of fatal bleeding occur throughout the 12 months, with just less than half of cases within the first month of treatment. For patients initially presenting with DVT only (Fig. 2), the pattern of fatality incidence is quite different than for patients initially presenting with PE. There are much fewer cases of fatal PE (33 compared to 223 cases during 12 months). Fatal bleeding and death due to infection are the main causes of death (excluding disseminating cancer), with almost three-times the number of cases of fatal PE. Again only a few cases of fatal PE occur after three months of treatment, whereas cases of fatal bleeding occur throughout the first 12 months. The Kaplan Meier analyses of fatalities were not significantly influenced by the presence or absence of metastatic cancer (see Fig. 3 and Fig. 4).

**Table 4.** Most frequent causes of death in patients (not including patients dying from disseminated cancer or unknown cause) initially presenting with pulmonary embolism and those presenting with deep vein thrombosis, at different time intervals during the 12 months following initial VTE diagnosis.

| Days | 2 | 10 | 30 | 90 | 180 | 270 | 365 |
|---|---|---|---|---|---|---|---|
| Patients initially presenting with pulmonary embolism | | | | | | | |
| Total number | 5,669 | 5,386 | 4,916 | 4,061 | 2,556 | 1,698 | 1,265 |
| Number of fatalities | 73 | 355 | 823 | 1,548 | 1,916 | 2,097 | 2,206 |
| Causes of fatality | | | | | | | |
| Pulmonary embolism | 52 | 176 | 196 | 217 | 221 | 223 | 223 |
| During therapy | 52 | 167 | 183 | 199 | 203 | 204 | 204 |
| After therapy | 0 | 9 | 13 | 18 | 18 | 19 | 19 |
| Respiratory insufficiency | 3 | 25 | 63 | 96 | 107 | 115 | 120 |
| Infection | 1 | 11 | 28 | 52 | 72 | 78 | 83 |
| Bleeding | 0 | 13 | 29 | 53 | 65 | 74 | 76 |
| During therapy | 0 | 11 | 24 | 37 | 44 | 49 | 51 |
| After therapy | 0 | 2 | 5 | 16 | 21 | 25 | 25 |
| Multiorgan failure | 1 | 8 | 23 | 37 | 42 | 48 | 50 |
| Heart failure | 4 | 6 | 9 | 22 | 25 | 28 | 28 |
| Bowel occlusion | 1 | 2 | 10 | 10 | 20 | 20 | 20 |
| Sudden, unexpected | 2 | 3 | 13 | 15 | 15 | 17 | 17 |
| Ischemic stroke | 0 | 5 | 5 | 13 | 15 | 16 | 16 |
| Bronchoaspiration | 1 | 3 | 7 | 12 | 14 | 16 | 16 |
| Renal insufficiency | 0 | 0 | 2 | 7 | 7 | 8 | 9 |
| Myocardial infarction | 0 | 1 | 2 | 5 | 5 | 5 | 6 |
| **Days** | **2** | **10** | **30** | **90** | **180** | **270** | **365** |
| Patients initially presenting with deep vein thrombosis | | | | | | | |
| Total number | 5,197 | 5,055 | 4,703 | 3,929 | 2,260 | 1,494 | 1,053 |
| Number of fatalities | 73 | 355 | 823 | 1,548 | 1,916 | 2,097 | 2,206 |
| Causes of fatalites | | | | | | | |
| Infection | 2 | 12 | 30 | 64 | 77 | 85 | 93 |
| Bleeding | 2 | 16 | 46 | 66 | 75 | 79 | 85 |
| During therapy | 2 | 14 | 34 | 42 | 46 | 47 | 48 |
| After therapy | 0 | 2 | 12 | 24 | 29 | 32 | 37 |
| Respiratory insufficiency | 2 | 11 | 26 | 42 | 53 | 58 | 60 |
| Multiorgan failure | 2 | 10 | 19 | 36 | 44 | 46 | 48 |
| Pulmonary embolism | 4 | 10 | 17 | 30 | 33 | 33 | 33 |
| During therapy | 3 | 8 | 13 | 23 | 25 | 25 | 25 |
| After therapy | 1 | 2 | 4 | 7 | 8 | 8 | 8 |

(*Continued*)

**Table 4**. (*Continued*)

| Days | 2 | 10 | 30 | 90 | 180 | 270 | 365 |
|---|---|---|---|---|---|---|---|
| Bowel occlusion | 0 | 0 | 5 | 12 | 20 | 23 | 28 |
| Bronchoaspiration | 0 | 2 | 7 | 15 | 18 | 19 | 19 |
| Ischemic stroke | 0 | 2 | 3 | 10 | 14 | 16 | 16 |
| Renal insufficiency | 0 | 3 | 6 | 9 | 11 | 13 | 14 |
| Heart failure | 0 | 0 | 2 | 7 | 9 | 11 | 11 |
| Sudden, unexpected | 0 | 3 | 7 | 9 | 10 | 11 | 11 |
| Myocardial infarction | 0 | 1 | 1 | 2 | 2 | 3 | 3 |
| Other causes | 0 | 2 | 17 | 31 | 42 | 45 | 46 |

## 4. Discussion

This large prospective, multicenter, cohort analysis of cancer patients with VTE and receiving at least three months of anticoagulant treatment provides important insight into the current, "real-life" benefit-risk balance of anticoagulant treatment in cancer patient with VTE. We provide evidence of how the fatality rates of the two main hazards of anticoagulation, PE and bleeding, are dependent on the clinical presentation of the initial VTE. These findings are important for efforts to improve treatment of cancer patients with VTE as they suggest that anticoagulant treatment should be adjusted to the clinical profile of the patient [23, 24, 25].
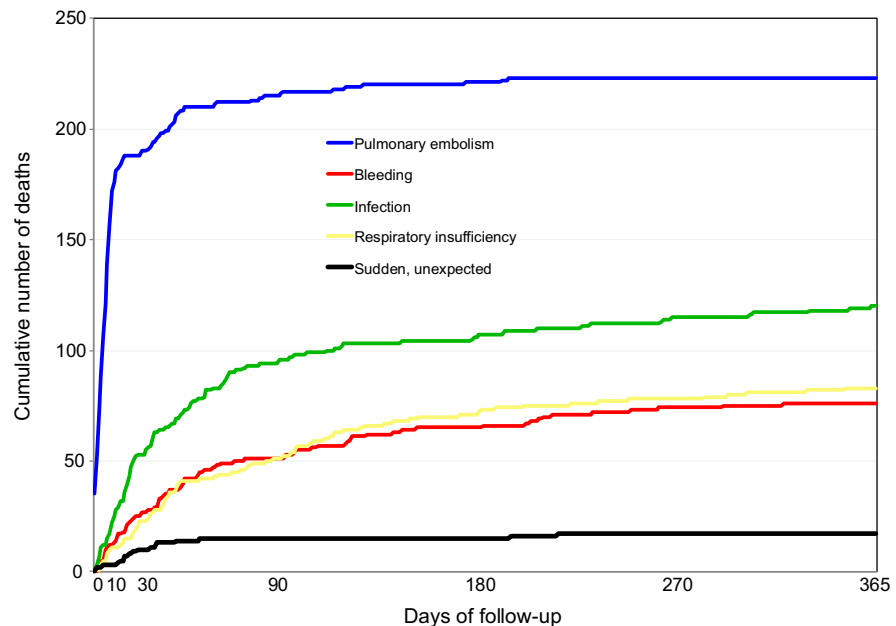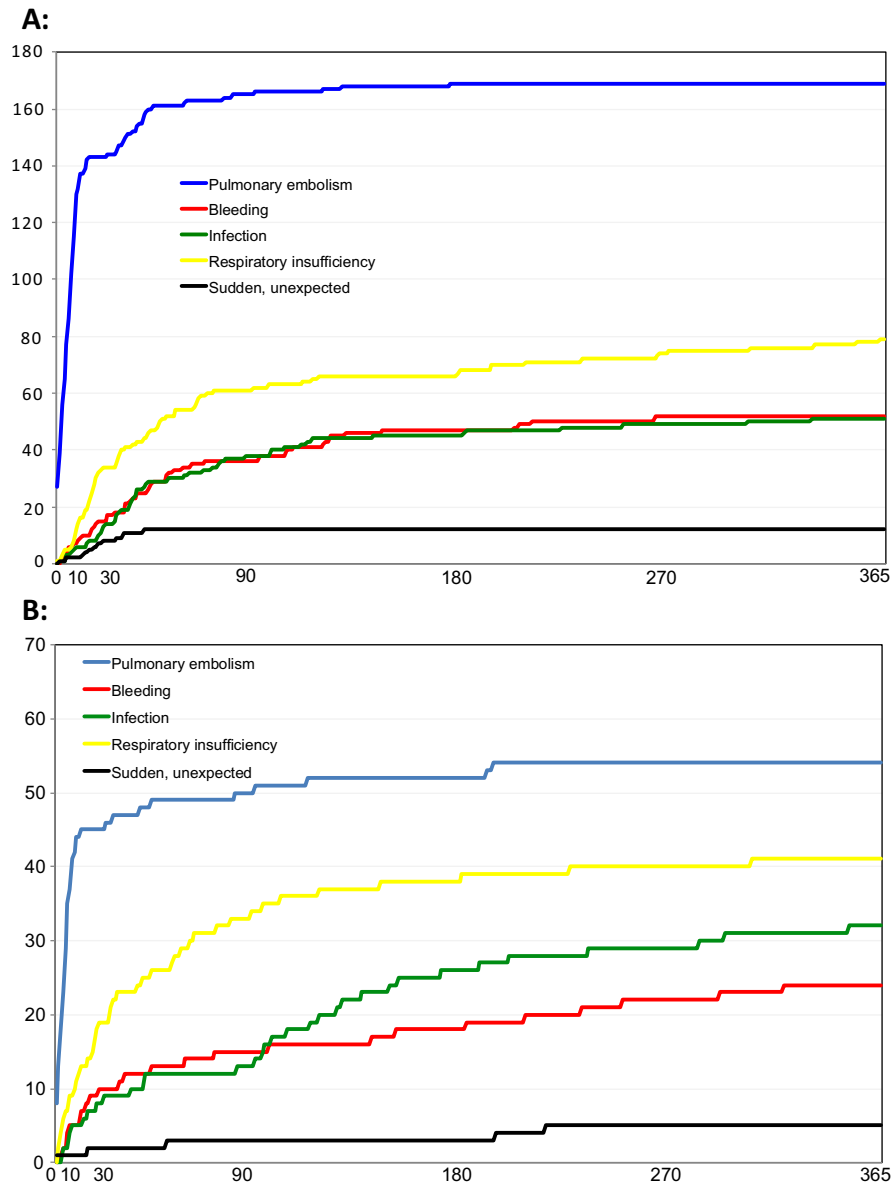


**Fig. 1.** Most frequent causes of death in patients initially presenting with PE: time-to-event data for the 12 months after initial PE (curve for patients dying from disseminated cancer not include).
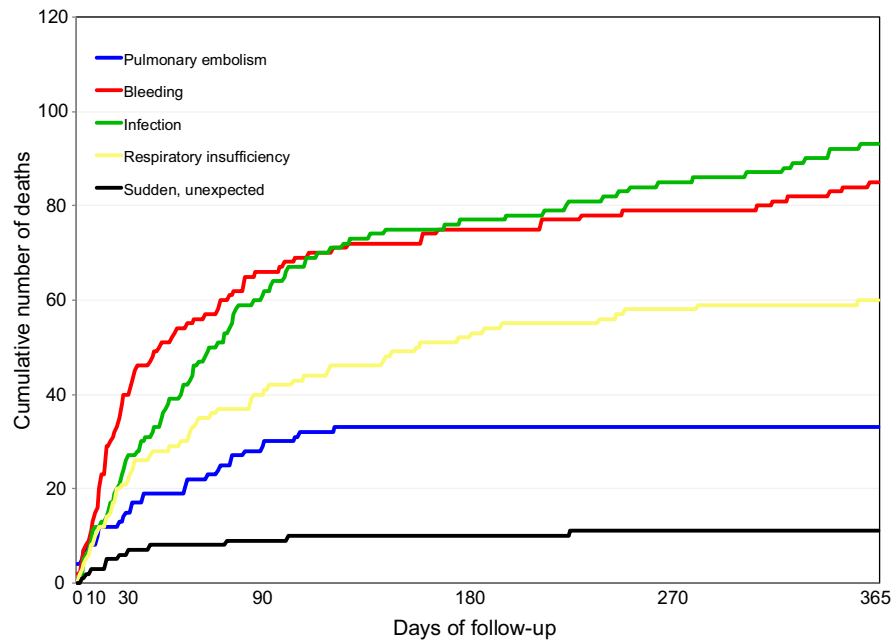
**Fig. 2.** Most frequent causes of death in patients initially presenting with DVT alone: time-to-event data for the 12 months after initial DVT (curve for patients dying from disseminated cancer not include).

Despite clinical guidelines and recommendations on anticoagulant treatment of cancer patients with acute symptomatic VTE, cancer patients with VTE are at greater risk than non-cancer patients with VTE of recurrent VTE and major bleeding during anticoagulant treatment [23, 26, 27]. The guidelines are based on low quality evidence [25], because clinical trial trials of anticoagulation in cancer patients with VTE are not sufficiently powered for determining the respective risk of VTE recurrence and of bleeding [9, 10].

Published cohort studies have attempted to quantify the prevalence of VTE recurrence and of bleeding in cancer patients treated with anticoagulants but we found no study with a 12-month follow-up and aiming to determine how the initial presentation of VTE may affect outcome. Our study is currently the largest analysis of RIETE registry-derived data on cancer patients with VTE — it is derived from a 40% larger cohort of patients than that used in the most recently published report [28]. Similar to previous analyses, 18% of the patients in the registry had active cancer (Table 1). The incidence of fatal PEs was greater than the incidence of fatal bleedings (238 [2.17%] vs 170 [1.51%]). After disseminating cancer, fatal PE was the second most common cause of death in our cohort and ahead of common cancer-related morbidities (respiratory insufficiency and infection) and bleeding was fourth most frequent. Thus, fatal PE was the most common cause of preventable death, accounting for 5·4% of deaths (238 of 4406), with some deaths even after 3–6 months of anticoagulant treatment.
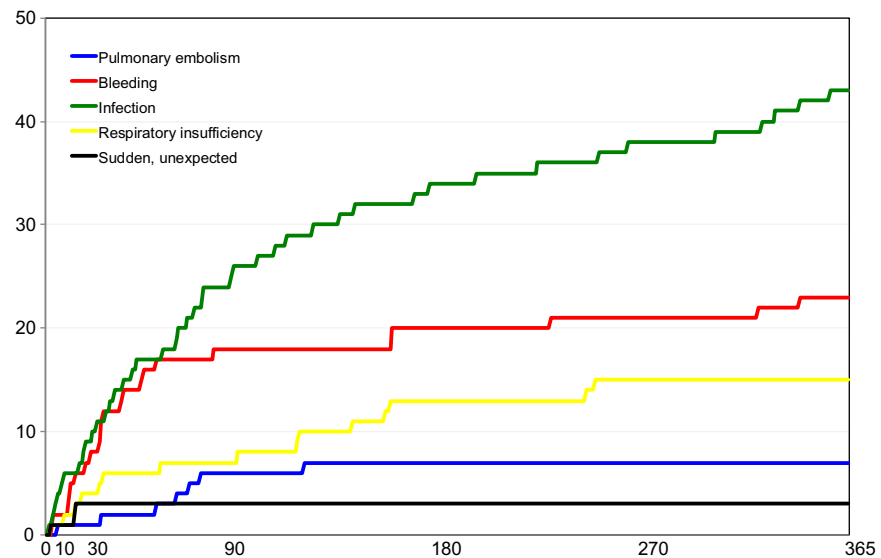
**Fig. 3.** Most frequent causes of death in patients (A: with metastases; B: without metastases) initially presenting with PE: time-to-event data for the 12 months after initial PE (curves for patients dying from disseminated cancer not include).

Most cases of fatal PE and fatal bleeding occurred while on anticoagulant treatment but a higher proportion (1/11) of fatal bleedings than fatal PE (1/25) occurred after anticoagulation (Table 1). As previously reported for a smaller cohort of RIETE patients, most cases of fatal PE and fatal bleeding occurred within the first three months of anticoagulation therapy (Fig. 1 and Fig. 2) [28]. Our data (Table 3) indicate that fatal bleedings occurred, on average, after a much longer period of treatment than did fatal PE, with 50% of fatal bleedings occurring after about four weeks compared to 50% of fatal PEs occurring within 6 days of the start

**A:**
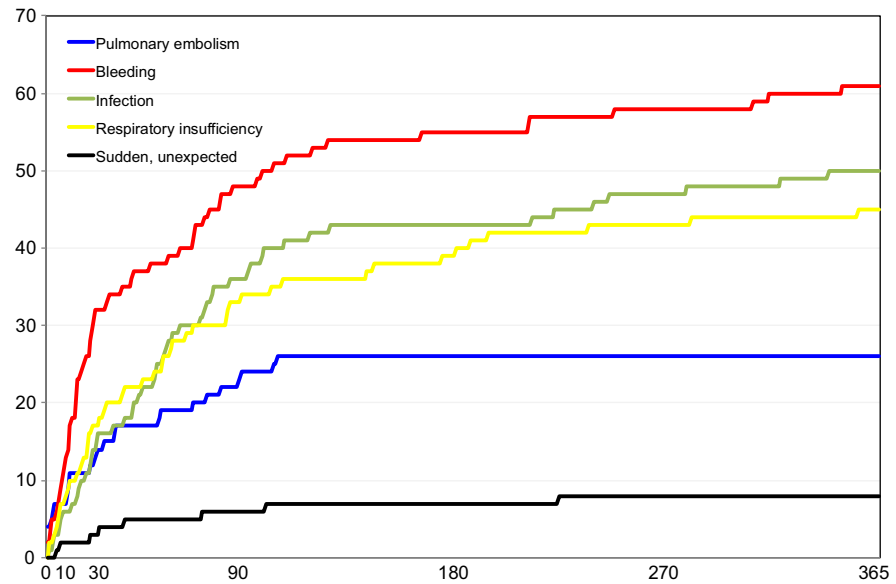


**B:**



**Fig. 4.** Most frequent causes of death in patients (A: with metastases; B: without metastases) initially presenting with DVT: time-to-event data for the 12 months after initial DVT (curves for patients dying from disseminated cancer not include).

of treatment. This is also clear from the Kaplan Meier analyses fatalities (Fig. 1 and Fig. 2). Most cases of fatal PE occurred in the first month of anticoagulation and very few cases after three months. In contrast, fatal bleeding cases occurred throughout the 12 months, with >50% after the first month of treatment. For cancer patients with PE at the start of anticoagulant treatment, subsequent PE is, after disseminated cancer, the most prominent cause of death and 3-times more common

than bleeding (Fig. 1), while in patients with DVT alone at baseline, bleeding is as common as infection as a cause of death and 3-fold more common than PE (Fig. 2). These data suggest that the initial presentation of VTE may be a key factor in determining changes in the intensity and duration of anticoagulation aimed at reducing the respective risks of PE and major bleeding.

An earlier analysis of cancer patient data from the RIETE register identified being older than 65 years and having VTE within three months of cancer diagnosis as independent risk factors for VTE recurrence, while PE was more likely in patients with a previous PE than in patients with previous DVT [19]. Independent risk factors for bleeding in cancer patients were identified as immobility, metastases, recent bleeding, and impaired creatinine clearance [19]. Our data for fatal PE and fatal bleeding are consistent with these earlier findings but we identify additional baseline characteristics that may influence the management of cancer patients requiring anticoagulation.

A significant number of cases of fatal PE (10%) and of fatal bleeding (8.1%) were aged below 50 years (Table 1) and a significant number did not have metastasic cancer (24% and 29%, respectively) (Table 2). Thus, fatal PE and fatal bleeding are not always associated with terminal phases of malignancy [27, 29]. It is particularly critical that fatalities in cancer patients of relatively good prognosis are avoided. Fatal PEs and fatal bleedings were similarly frequent in patients who had had their first acute symptomatic VTE within three months of cancer diagnosis. Several studies indicate that the risk of VTE is highest in the initial period after cancer diagnosis [30]. It is unclear how much this relates to the underlying cancer or to cancer treatment; different modes of cancer treatment, including support treatment, are independently associated with increased risk of VTE [30]. Our cancer patient cohort is heterogeneous in regard to site of cancer and type of cancer treatment. Notably, women with breast cancer had fewer cases of fatal bleeding than cases of fatal PE, which contrast to similar rates in patients with gastrointestinal cancer (Table 2).

These data may provide important hints at factors relating to type of cancer and cancer treatment that may critically determine the intensity and duration of anticoagulation treatment. For example, the lower proportion of cases with fatal PE or fatal bleeding in women with breast cancer and the correlating lower values for hormonal treatment and estrogen use, might reflect the lower prevalence of the use of chemotherapy in this indication [31].

Our study is limited by the fact that many of the fatal cases in our cohort were recorded with "disseminating cancer", "sudden death" or "unknown", as cause of death, when the cause of death may not have been so objectively assessed. Thus, some of these cases may have been fatal PE and, therefore, the prevalence of fatal PE in our study may be an under-estimate. Pulmonary embolism is difficult to

diagnose and is often overlooked, especially in the presence of other symptoms [33]. The RIETE registry documents "fatal PE" only with objective diagnosis (CT-scan, ventilation-perfusion lung scan or documented DVT plus echocardiogram with signs of right ventricle or atrium enlarged). Fatal PE was confirmed at necropsy in 21 cases. Given that fatal PE in the absence of autopsy was defined as any death appearing within the first 10 days after PE diagnosis (either initial episode or recurrent PE), there may be a systematic bias favouring death from PE in the PE group based on how PE fatality was defined. It is also possible that some of our fatal cases died of cerebral bleeding and that we have underestimated the prevalence of fatal bleeding. Furthermore, clinically unsuspected pulmonary embolism is being increasingly diagnosed in cancer patients undergoing computed tomography for other diagnostic purposes [32] and there is little data on survival of such cases and their risk of recurrent VTE [34]. Of note, in a 3-month follow-up of a cohort of cancer patients on anticoagulation for recurrent VTE (n = 212), Schulman and colleagues reported 27% fatalities with 76% of the survivors having residual thrombosis symptoms [25].

Our findings provide important insight in to what factors may be used to guide the physician in adapting recommended anticoagulant regimens to the individual patient. In particular, cancer patients presenting with PE may benefit from more intense anticoagulant treatment early on in treatment, while those presenting with DVT alone may benefit from curtailing treatment intensity as anticoagulant treatment progresses. However, other factors will also need to be considered, for example how soon after cancer diagnosis did VTE occur, the intensity of chemotherapy and the site of cancer. Current guidelines for anticoagulant treatment do not so far suggest any form of differentiated approach to cancer patients with VTE. We conclude from our data that the new treatment strategies for cancer patients with VTE should involve adjusting the current general approach so as to tailor the treatment to the patient, as oncologists are increasingly doing with cancer treatments. Our data provide important pointers for further investigations, which are urgently needed in order to more clearly identify which cancer patients with VTE are likely to benefit from adjustments in the current practice of anticoagulant treatment.

## Declarations

## Author contribution statement

Javier Trujillo-Santos: Conceived and designed the experiments; performed the experiments; analyzed and interpreted the data.

Francisco Martín Martos, Carme Font, Dominique Farge-Bancel, Vladimir Rosa, Alicia Lorenzo, Manuel Barrón, Manuel Alejandro Lorente, José María Pedrajas: Performed the experiments; analyzed and interpreted the data.

Manuel Monreal: Conceived and designed the experiments; performed the experiments; analyzed and interpreted the data; wrote the paper.

## Competing interest statement

The authors declare no conflict of interest.

## Funding statement

## Additional information

Data associated with this study is available at www.riete.org for registered physicians.

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