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The clinical course of venous thromboembolism may differ according to cancer site

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Abstract

Background We hypothesized that the clinical course of venous thromboembolism in patients with active cancer may differ according to the specificities of primary tumor site.

Aim and Methods We used data from RIETE (international registry of patients with venous thromboembolism) to compare the clinical venous thromboembolism-related outcomes during the course of anticoagulation in patients with with one of the 4 more frequent cancer (breast, prostate, colorectal or lung cancer).

Results As of September 2014, 3947 cancer patients were recruited, of whom 938 had breast, 629 prostate, 1189 colorectal and 1191 lung cancer. Overall, 55% had metastatic disease (42%, 36%, 53%, and 72%, respectively). During the course of anticoagulant therapy (mean duration, 139 days), the rate of thromboembolic recurrences was similar to the rate of major bleeding in patients with breast (5.6 [95%CI: 3.8-8.1] vs. 4.1 [95%CI: 2.7-5.9] events per 100 patient-years) or colorectal cancer (10 [95%CI: 7.6-13] vs. 12 [95%CI: 9.4-15] per 100 patient-years). In contrast, in patients with prostate cancer, the rate of venous thromboembolic recurrences was half the rate of major bleeding (6.9 [95%CI: 4.4-10] vs. 13 [95%CI: 9.2-17] events per 100 patient-years) whereas in those with lung cancer, the rate of thromboembolic recurrences was two-fold higher than the rate of major bleeding (27 [95%CI: 22-23] vs. 11 [95%CI: 8.6-15] per 100 patient-years).

Conclusions Significant differences in the clinical profile of venous thromboembolic related outcomes were observed according to the site of

cancer. These findings suggest the development of cancer-specific anticoagulant strategies as an area for further research.

Introduction

Progress in the screening and treatment of cancer has resulted in a growing survival of cancer patients and an increasing number of alive patients in recent years.[1] In parallel, the incidence of venous thromboembolism has been reported to progressively increase in cancer patients, in contrast to stable figures in venous thromboembolism incidence in the general population without cancer.[2] In this context, optimal venous thromboembolism management as a common and potentially life-threatening complication in patients with cancer has become an issue of major concern that challenges clinicians and has a great impact on safety, quality of life and cost of care.[3]

Current guidelines of antithrombotic therapy, based on the results of randomized clinical trials, recommend that cancer patients with acute venous thromboembolism be treated initially with low-molecular-weight heparin (LMWH), fondaparinux or unfractionated heparin (UFH), followed by long-term treatment with LMWH rather than with vitamin K antagonists (VKA).[4-6] These recommendations apply to all cancer patients, irrespectively of the initial venous thromboembolic presentation, spread and specific therapies according to primary tumor type. Nonetheless, numerous studies reported the highly different risk of venous thromboembolism per site of cancer, with relative low risk of venous thromboembolism for breast and prostate cancer as compared with lung and pancreas cancer.[7] It appears that the more the cancer are biologically active (reflected by a high 1-year mortality and early metastatic spread) the highest is the risk of developing venous thromboembolism.[1,2,7-9] On the other hand, less data are available with regard to the venous thromboembolism

clinical course once the thrombotic event has been established. A number of studies revealed that a number of cancer variables (i.e., advanced stage at venous thromboembolism diagnosis,[1,7-9] concomitant therapies and comorbidities) may influence on outcomes.[1,9] However, there is uncertainty about the influence of the site of cancer on the risk of venous thromboembolism-related outcomes including venous thromboembolic recurrences or major bleeding events during the course of anticoagulant therapy. It is likely that the biological and clinical heterogeneity among different types of malignancies might influence the balance between the rate of venous thromboembolic recurrences and major bleeding during follow-up. If this hypothesis is confirmed, it would support that cancer patients might likely benefit from different anticoagulant strategies according to primary tumor site. Overall, a cancer per cancer approach allows to take into account the variety of natural history, anticancer treatment, concomitant medications. In a first approach, in order to reliably assess the thromboembolic risk according to the cancer site, we have to consider cancer associated with a high number of thromboembolic events and with a life expectancy more than 6 months.[9] The most common malignancies associated with venous thromboembolism reported in the literature are those of the lung, breast, colon or prostate, reflecting the prevalence of these malignancies in the general population.[10-13]

The RIETE (Registro Informatizado de Enfermedad TromboEmbólica) Registry is an ongoing, multicenter, international (Spain, Argentina, Belgium, Canada, Czech Republic, Ecuador, France, Greece, Israel, Italy, Latvia, Portugal, Republic of Macedonia, Switzerland and Venezuela), observational registry of clinical data of consecutive patients with objectively confirmed venous

thromboembolism including deep vein thrombosis and pulmonary embolism and their outcomes regarding major bleeding complications, recurrent venous thromboembolic events and date and cause of death. Patients are managed according to treating physicians criteria in the real world. The RIETE Registry started in Spain in 2001, and 6 years later the database was translated into English with the aim to expand the Registry to other countries. Data from this registry have been used to evaluate short-term and long-term outcomes after acute venous thromboembolism, such as the frequency of recurrent venous thromboembolism, bleeding and mortality, and risk factors for these outcomes.[14-18] As of September 2014 9,646 patients out of 48,481 included in the RIETE registry had cancer. The aim of the present study was to assess the differences on epidemiology, clinical presentation and outcome of patients with breast, prostate, colorectal or lung cancer during the course of anticoagulant therapy for venous thromboembolism.

Patients and Methods

Consecutive patients with symptomatic, acute deep vein thrombosis or pulmonary embolism, confirmed by objective tests (compression ultrasonography [CUS] or contrast venography for deep vein thrombosis; helical CT-scan or high probability ventilation-perfusion lung scintigraphy for pulmonary embolism), were enrolled in RIETE. We considered as having pulmonary embolism all those patients with symptomatic pulmonary embolism, either with or without concomitant deep vein thrombosis. Patients were excluded if they were currently participating in a clinical trial with a blinded therapy. All patients

(or their relatives) provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements.

For the present analysis, only patients with active cancer defined as newly diagnosed cancer or cancer that is being treated [i.e. surgery, chemotherapy, radiotherapy, hormonal, support therapy, or combined treatments]), either localized or metastatic tumors of the breast, prostate, colon or lung origin were included. These patients were receiving anticancer therapy [i.e. surgery, chemotherapy, radiotherapy, hormonal, or combined treatments]) and/or supportive or palliative care.

We certify that RIETE received Institutional Review Board (IRB)'s approval, always in accordance with the internal requirements of each of the centers participating. This analysis was approved by the IRB of Hospital Universitari Germans Trias i Pujol (Badalona, Spain) and the NorthShore University HealthSystem (Evanston, Illinois, USA). As to the need for written consent, RIETE started in 2001 and then oral consent was enough. For France we got the approval of the INSERM Ethical committee for oral consent solely, as it is only an epidemiological study. However, as more and more centers have been joining us, most of them have obtained approval only if consent was written. We have the copies of these approvals.

Physicians participating in the RIETE registry ensured that eligible patients were consecutively enrolled. Data were recorded on to a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. The study coordinating center assigned patients with a unique identification number to maintain patient confidentiality

and was responsible for all data management. Data quality was regularly monitored electronically, including checks to detect inconsistencies or errors, which were resolved by contacting the local coordinators. Data quality was also monitored by periodic visits to participating hospitals by contract research organizations that compared medical records with the submitted data.

Outcomes

The major venous thromboembolism-related outcome measures included: (1) the rate of symptomatic, objectively confirmed, venous thromboembolic recurrences; and (2) the rate of major bleeding events occurring during the course of anticoagulant therapy. 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. We also studied the cumulative overall mortality rate during anticoagulation as a secondary outcome. All the outcome measures were performed according to primary tumor site and compared between them.

Baseline variables

The following parameters were recorded when the qualifying episode of venous thromboembolism was diagnosed: patient's gender, age, and body weight and height; presence of coexisting conditions; concomitant therapies; additional risk factors for venous thromboembolism including prior venous thromboembolism; laboratory data, and use of anticoagulant therapy (drug, dose, date of start and date of discontinuation for each drug).

Treatment and Follow-up

Patients were managed according to the clinical practice of each participating hospital (i.e., there was no standardization of treatment). Patients were followed-up for at least 3 months in the outpatient clinic. During each visit, any signs or symptoms suggesting venous thromboembolic recurrences or bleeding complications were noted. Each episode of clinically suspected recurrent venous thromboembolism was investigated by repeat CUS (compression ultrasound), lung scanning, helical-CT scan or pulmonary angiography as appropriate. Most outcomes were classified as reported by the clinical centers. However, if staff at the coordinating center were uncertain how to classify a reported outcome, that event was reviewed by a central adjudicating committee (less than 10% of events).

Statistical analysis

We compared baseline characteristics of patients according to cancer location using chi-square tests for categorical variables (or Fisher exact test where appropriate) and ANOVA test for continuous variables. Tables are expressed as incidence rates (events per 100 patient-years of anticoagulant therapy) and comparisons were made for each two locations of cancer. The hazard rates are expressed in figures as (1 - cumulative survival) and Kaplan-Meier curves were calculated to compare the event rate dynamic (deep venous thrombosis recurrences, pulmonary embolism recurrences and major bleeding). All analyses were performed using a commercial software package (SPSS 15, SPSS Inc., Chicago, IL, USA).

In order to measure predictors of outcome, a multivariate analysis was carried out using a Cox proportional hazard regression analysis; candidate variables

were selected from clinical variables based on published literature and on expert opinion and those with a p<0.20 on bivariate analysis. All patients without an adverse event were considered as censored. A backward stepwise regression was done.

The multivariate analysis didn't include the type of anticoagulant treatment for several reasons: (1) the lack of systematic control in data collection of transient interruptions or variations on anticoagulant doses due to surgery, low platelet count or other intercurrent circumstances common in cancer patients that are likely to be underreported (compared to controlled trials); (2) the demonstration in previous analyses that clinicians frequently prescribe suboptimal anticoagulant doses in cancer patients perceived to be at risk for bleeding; and (3) because LMWH is more frequently used over AVK in patients who bled during initial anticoagulant therapy.[19]

Results

Patient characteristics

Up to September 2014, 48481 patients were recruited in RIETE, of whom 3947 had 'active' cancer and were eligible for the present study including 938 (24%) cases of breast, 629 (16%) prostate, 1189 (30%) colorectal and 1191 (30%) lung cancer respectively. The baseline characteristics of patients are summarized in Table 1. Besides gender and age, significant differences regarding the rate of metastatic disease (42%, 36%, 53% and 72% respectively), the proportion of patients for whom cancer was recently diagnosed (<3 months) prior to venous thromboembolism (11%, 21%, 30% and 43% respectively) according the tumor site. Around 50% of patients in each subgroup were receiving chemotherapy at venous thromboembolism diagnosis

(and less for patients with prostate cancer), and around 15% were receiving radiotherapy. As to the initial venous thromboembolism presentation 54%, 52%, 50% and 64% respectively, presented with pulmonary embolism. Patients with prostatic cancer were significantly older and were more likely to have chronic lung disease, recent major bleeding or anemia than those with breast cancer, but presented less likely with upper-extremity deep venous thrombosis (Table I). Patients with colorectal cancer were more likely to have recent bleeding, anemia or abnormal platelet count, but most likely had recent surgery and proximal deep venous thrombosis than those with breast cancer. Finally, patients with lung cancer more likely had chronic lung disease, anemia, abnormal platelet count or immobility but less likely had recent surgery than those with breast cancer.

Management and outcomes

Mean duration of anticoagulant therapy was similar in patients with breast, prostate or colorectal cancer (Table II). The duration was shorter in those with lung cancer, most likely because of their higher mortality. Most patients in all subgroups (90%, 90%, 92% and 91%, respectively) received initial therapy with LMWH, at similar daily doses (Table II). Then, 20%, 30%, 16% and 11%, respectively, switched to VKA drugs. The proportion of patients receiving long-term therapy with fondaparinux or rivaroxaban was small in all subgroups.

As shown in Table III, during the course of anticoagulant therapy (mean duration: 139 days), the rate of venous thromboembolic recurrences was similar to incidence of major bleeding in patients with breast (5.6 [95%CI: 3.8-8.1] vs.

4.1 [95%CI: 2.7-5.9] events per 100 patient-years) or colorectal cancer (10 [95%CI: 7.6-13] vs. 12 [95%CI: 9.4-15] events per 100 patient-years), higher than bleeding in patients with lung cancer (27 [95%CI: 22-33] vs 11 [95%CI: 8.6-15] events per 100 patient-years) and lower in patients with prostate cancer (6.9 [95%CI: 4.4-10] vs 13 [95%CI: 9.2-17] events per 100 patient-years. Of note, the rate of venous thromboembolic recurrences and major bleeding was highest during the first month following the index event whatever the site of cancer (Figure 1-4). Interestingly, the rate of venous thromboembolic recurrences during the first 30 days of therapy was half the rate of major bleeding in patients with either breast (10 vs. 21 events, Figure 1), prostate (9 vs. 23 events, Figure 2) or colorectal cancer (19 vs. 43 events, Figure 3). However, in patients with lung cancer the rate of venous thromboembolic recurrences was two-fold higher than the rate of major bleeding (40 vs. 22 events, Figure 4). Moreover, the rate of deep venous thrombosis and pulmonary embolism recurrences was similar in patients with breast, colorectal or lung cancer, but the rate of deep venous thrombosis recurrences was two-fold higher than the rate of pulmonary embolism recurrences in patients with prostate cancer (Table III and Figure 3). In term of mortality, it was highly increased in patients with lung cancer as compared with patients with colorectal, breast and prostate cancer (respectively 150, 44, 33, 31 events, Table III and Figure 5).

Of note 8 of 11 patients with cerebral bleeding had metastatic cancer although unfortunately information on whether or not the metastases were in the brain

In order to adjust the risk of outcomes, a multivariate analysis including the most important confounders was performed (Table IV). The site of cancer was found to have a clear independent influence on the risk of venous

thromboembolic-related outcome : with breast cancer as a reference lung cancer wais associated with the highest risk for venous thromboembolism recurrence (HR 3.8) and death (HR 3.1), being also associated to an increased risk of bleeding (HR 1.8). On the other hand, prostate and colo-rectal cancer were associated with a similar higher risk of major bleeding (HR 2.1) than the risk of venous thromboembolic recurrences (HR 1.7). Additional variables associated to increased risk of bleeding were abnormal platelet count (HR 2), recent major bleeding (HR 5) and cancer diagnosis within 3 months (HR 1.6). Notably, metastasis (HR 3.3) and lung cancer (HR 3.1) were found to be the variables associated to the highest increased risk of death whereas chemotherapy (HR 0.8) and postoperative venous thromboembolism (HR 0.7) were identified as protective variables of mortality.

Discussion

Current guidelines of antithrombotic therapy recommend that all cancer patients with venous thromboembolism receive long-term therapy with LMWH (at similar doses) for at least 3 months.[4-6] Beyond the third month, there is scarce information on the factors influencing outcome. Our findings, obtained from a large series of consecutive patients with active cancer and venous thromboembolism, reveal important differences in the rate of venous thromboembolic recurrences and major bleeding according to the site of cancer. In our series, the rates of venous thromboembolic recurrences and major bleeding during the course of anticoagulant therapy were similar in patients with breast (26 vs. 25 events, respectively) or colorectal cancer (55 vs. 67 events), higher than bleeding in patients with lung cancer (105 vs. 47 events) and lower in patients with prostate cancer. (21 vs. 39 events). These findings may be

explained by differences in the characteristics of the different tumors and/or their therapies. Our data also confirm the hypothesis that different clinical profiles with regard to venous thromboembolic related outcomes are observed according to the primary tumor origin. Thus, these data further support the development of specific research addressed to evaluate cancer-specific anticoagulant strategies, either with regard to intensity and duration, according to the cancer site that would help tailoring venous thromboembolism management by clinicians.

Similar figures in the rates of venous thromboembolic recurrences and major bleeding during the course of anticoagulant therapy for cancer-related venous thromboembolism were reported in a recent single-arm study (DALTECAN) designed to evaluate the safety of LMWH within 12-months.[20] In agreement with our series, we found the highest rates of venous thromboembolic recurrences and major bleeds during the first month of therapy considering the whole cohort of patients. Unfortunately, data about the development of major bleeding events taking into account the different cancer sites were not reported, maybe because of the small size of the sample.

Of note, most of thromboembolic events and major bleeding occur in the first weeks of treatment whatever the site of cancer; we observe an excess of major bleeding as compared to thromboembolic events in patients with breast, colorectal and prostate cancer while the risk of venous thromboembolic recurrence was highest in patients with lung cancer. Moreover, we also found differences in the time-course of venous thromboembolic -related complications according to site of cancer. Patients with breast, prostate or colorectal cancer suffered half the rate of venous thromboembolic recurrences than major bleeds

during the first month of therapy. On the contrary, patients with lung cancer suffered a two-fold higher rate of venous thromboembolic recurrences than major bleeds, both during and beyond the first 30 days of therapy. Thus, our findings support that cancer site would be a relevant variable to be considered in the design of interventional studies addressed to evaluate optimal secondary venous thromboembolism prophylaxis in this setting. All phase-III clinical trials supporting the recommendation for long-term therapy with LMWH in cancer patients with venous thromboembolism were performed pooling patients with cancer from various sites[20-24]. Certainly, including patients with a large variety of cancers may induce a large heterogeneity making the results in term of venous thromboembolic recurrences and bleedings difficult to interpret.

The RIETE Registry was designed to gather and analyze data on treatment patterns and outcomes in patients with acute venous thromboembolism. In contrast to randomized controlled trials, there is no imposed experimental intervention: management is determined solely by physicians. Thus, it provides data on patients with venous thromboembolism in a real-world situation with an unselected patient population who accepted to take part to the registry. Data from RIETE are hypothesis-generating and provide feedback from real-world clinical situations.

The study has some limitations. First, specific anticancer therapies and/or additional venous thromboembolic risk factors during follow-up were no recorded. Second, included patients had symptomatic, objectively proven pulmonary embolism confirmed by objective tests including CT scanning. We acknowledge that the sample of patients with symptomatic, objectively proven pulmonary embolism may have been overestimated[25] but our study reflects

situations encountered everywhere in usual care, in real life and therefore in other cohort studies and randomized trials. Moreover, concerns are growing about false negative CT scan (up to 10% of CT scan specifically asked for pulmonary embolism evaluation); especially in patients with cancer, who may undergo their CT scan for cancer evaluation.[26] In addition, not all outcomes are systematically adjudicated by independent reviewers. Finally, one could consider that including all patients in the analysis even when receiving different anticoagulant may confuse the findings and limit the relevance of our findings: again, it reflects the usual practice and all of those patients are of interest and seen in practice, they do receive either LMWH or VKA as anticoagulant treatment and have to be taken into consideration. If guidelines are not followed and LMWH not prescribed, there are most often patient and physician-related reasons which may contribute to explain it. However the type of anticoagulation was therefore not included in the multivariate analysis.[27]

But strengths of the current analysis include that a large number of consecutive unselected patients were enrolled, and that fatal pulmonary embolism is by far the most important outcome during the treatment of acute PE. But unfortunately, data about histological differentiation and grade, TNM classification, molecular testing and surgical oncologic history was not recorded in our registry and thus we couldn't assess the effect of these parameters on clinical outcomes.

In conclusion, our results reveal that the rate of venous thromboembolic recurrences and major bleeding during the course of anticoagulant therapy

largely varies according to the location of cancer in patients with cancer. These findings suggest the development of cancer-specific anticoagulant strategies as an area for further research.

Authorship section

Isabelle MAHE : designed research, performed research, contributed analytical tools, analyzed data, and wrote the paper

Jean CHIDIAC : performed research, and wrote the paper

Laurent BERTOLETTI : designed research, performed research, contributed analytical tools, analyzed data, and wrote the paper

Carme FONT : contributed analytical tools, analyzed data, and wrote the paper

Javier TRUJILLO-SANTOS : designed research, contributed vital analytical tools, analyzed data

Marisa PERIS : analyzed data, and wrote the paper

Cristina PÉREZ DUCTOR : analyzed data, and wrote the paper

Santiago NIETO : analyzed data, and wrote the paper

Elvira GRANDONE : analyzed data, and wrote the paper

Manuel MONREAL : designed research, performed research, contributed analytical tools, analyzed data, and wrote the paper

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Table I. Clinical characteristics of the patients, according to site of cancer.

	Breast	Prostate	Colorectal	Lung
Patients, N	***938***	***629***	***1,189***	***1,191***
Clinical characteristics,				
Gender (male)	21 (2.2%)	629 (100%)‡	682 (57%)‡	881 (74%)‡
Age (years±SD)	68±13	75±9.3‡	70±11‡	64±12‡
Body weight (kg±SD)	70±14	76±13‡	71±14	71±13
Cancer characteristics,				
Metastases	392 (42%)	223 (36%)*	625 (53%)‡	853 (72%)‡
Diagnosis <3 months	107 (11%)	134 (21%)‡	359 (30%)‡	516 (43%)‡
Chemotherapy	524 (56%)	217 (35%)*	623 (52%)‡	655 (55%)†
Radiotherapy	131 (14%)	62 (9.9%)‡	99 (8.3%)	222 (19%)
Underlying conditions,				
Chronic lung disease	74 (7.9%)	86 (14%)‡	90 (7.6%)	264 (22%)‡
Chronic heart failure	52 (5.5%)	46 (7.3%)	61 (5.1%)	50 (4.2%)
CrCl levels (mL/min)	69±37	63±26†	68±30	77±33‡
Recent major bleeding	16 (1.7%)	21 (3.3%)*	43 (3.6%)†	19 (1.6%)
Anemia	490 (52%)	376 (60%)†	802 (68%)‡	723 (61%)‡
Abnormal platelet count	51 (5.4%)	48 (7.6%)	118 (9.9%)‡	199 (17%)‡
VTE risk factors,				
Postoperative	100 (11%)	78 (12%)	238 (20%)‡	78 (6.5%)†
Immobility ≥4 days	151 (16%)	126 (20%)*	222 (19%)	229 (19%)*
Estrogen use	111 (12%)	52 (8.6%)*	10 (0.9%)‡	12 (1.0%)‡
Pregnancy/puerperium	0	0	1 (0.1%)	3 (0.3%)
Recent travel	11 (1.2%)	6 (1.0%)	5 (0.4%)*	10 (0.8%)
Prior VTE	132 (14%)	94 (15%)	150 (13%)	134 (11%)‡
Initial VTE presentation,				
Pulmonary embolism	505 (54%)	324 (52%)	590 (50%)	756 (64%)‡
For patients with PE,				
SBP levels <100 mm Hg	52 (10%)	26 (8.0%)	63 (11%)	74 (9.8%)
Heart rate >100 bpm	163 (32%)	83 (26%)*	161 (27%)	269 (36%)
Sat O2 <90%	102 (20%)	55 (17%)	84 (14%)†	154 (20%)
For patients with DVT alone,				
Proximal DVT	258 (60%)	242 (79%)‡	443 (74%)‡	248 (57%)
Bilateral DVT	16 (3.7%)	13 (4.3%)	37 (6.2%)	45 (10%)‡
Upper-extremity DVT	110 (25%)	16 (5.2%)‡	83 (14%)‡	119 (27%)
Other : distal DVT, unspecified	49 (5.2%)	34 (5.4%)	36 (3%)	23 (1.9%)

Comparisons between patients with breast cancer vs. other sites: *p <0.05; †p <0.01; ‡p <0.001.

Abbreviations: SD, standard deviation; CrCl, creatinine clearance; VTE, venous thromboembolism; PE, pulmonary embolism; SBP, systolic blood pressure; bpm, beats per minute; DVT, deep vein thrombosis.

Table II. Treatment strategies according to site of cancer.

	Breast	Prostate	Colorectal	Lung
Patients, N	***938***	***629***	***1,189***	***1,191***
Duration of therapy (mean days±SD)	228±292	241±364	200±214	135±215‡
Duration of therapy (median days, IQR)	153 (160)	151 (157)	144 (139)	96 (142)‡
Initial therapy,				
Unfractionated heparin	62 (6.6%)	37 (5.9%)	58 (4.9%)	80 (6.7%)
LMWH	845 (90%)	565 (90%)	1097 (92%)	1078 (91%)
Mean LMWH dose (IU/kg/day)	175±45	171±41	174±45	175±43
Fondaparinux	13 (1.4%)	10 (1.6%)	17 (1.4%)	15 (1.3%)
Rivaroxaban	6 (0.6%)	4 (0.6%)	0†	0†
Thrombolytics	6 (0.6%)	4 (0.6%)	6 (0.5%)	10 (0.8%)
Inferior vena cava filter	8 (0.9%)	5 (0.8%)	27 (2.3%)	15 (1.3%)
Long-term treatment,				
LMWH	605 (67%)	331 (55%)‡	820 (73%)†	833 (78%)‡
Mean LMWH dose (IU/kg/day)	150±45	149±44	151±47	152±43
Vitamin K antagonists	175 (20%)	182 (30%)‡	178 (16%)*	119 (11%)‡
Rivaroxaban	10 (1.1%)	6 (1.0%)	2 (0.2%)†	1 (0.1%)†
Fondaparinux	14 (1.6%)	7 (1.2%)	16 (1.4%)*	17 (1.6%)

Comparisons between patients with breast cancer vs. other sites: *p <0.05; †p <0.01; ‡p <0.001

Abbreviations: SD, standard deviation; IQR, interquartile range; LMWH, low-molecular-weight heparin; IU, international units.

Table III. Outcome during the course of anticoagulant therapy, according to site of cancer.

	Breast		Prostate		Colorectal		Lung	
Patients, N	***938***		***629***		***1,189***		***1,191***	
	N	**Events per 100 patient-years**	**N**	**Events per 100 patient-years**	**N**	**Events per 100 patient-years**	**N**	**Events per 100 patient-years**
Recurrent PE	13	2.8 (1.6-4.7)	6	1.9 (0.8-4.0)	28	5.0 (3.4-7.2)	55	14 (11-18)‡
Recurrent DVT	13	2.8 (1.6-4.7)	15	4.9 (2.8-7.9)	27	4.9 (3.3-7.0)	50	13 (9.5-16)‡
Recurrent VTE	26	5.6 (3.8-8.1)	21	6.9 (4.4-10)	55	10 (7.6-13)*	105	27 (22-33)‡
Major bleeding	25	4.1 (2.7-5.9)	39	13 (9.2-17)‡	67	12 (9.4-15)‡	47	11 (8.6-15)‡
Site of bleeding,								
Gastrointestinal	8	1.7 (0.8-3.3)	16	5.2 (3.1-8.3)	42	7.6 (5.5-10)‡	18	4.4 (2.7-6.8)
Cerebral	4	0.9 (0.3-2.1)	4	1.3 (0.4-3.1)	4	0.7 (0.2-1.7)	11	2.7 (1.4-4.7)
Death	144	31 (26-36)	103	33 (27-40)	308	44 (40-49)†	612	150 (138-162)‡

Comparisons between patients with breast cancer vs. other sites: *p <0.05; †p <0.01; ‡p <0.001.

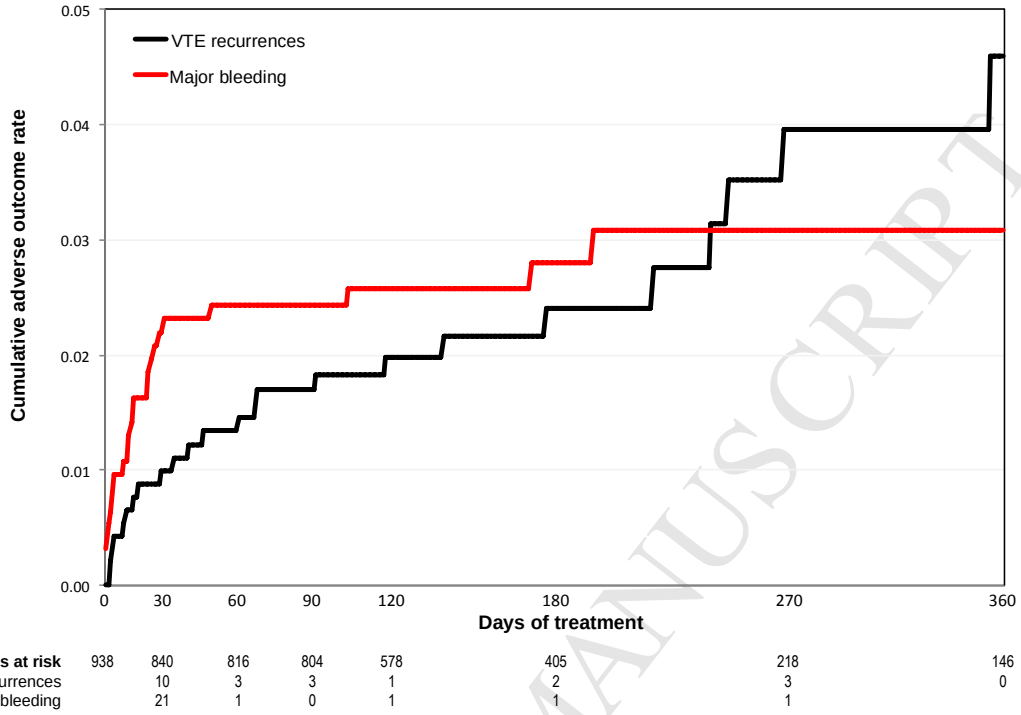
Abbreviations: PE, pulmonary embolism; DVT, deep vein thrombosis; VTE, venous thromboembolism.

Table IV : Multivariate analysis (4 cancers) : variables at baseline independently correlated to recurrent thromboembolic events, bleedings, deaths.

	VTE recurrence		Major bleeding		Overall death	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Age	0.97 (0.96-0.98)	<0.001	-		-	
Site of cancer						
Breast	1 (ref.)	<0.001	1 (ref.)	0.008	1 (ref.)	<0.001
Prostate	1.7 (1.1-2.9)	0.03	2.1 (1.3-3.5)	0.003	1 (0.8-1.3)	0.91
Colorectal	1.7 (1.1-2.7)	0.01	2.1 (1.3-3.4)	0.001	1.6 (1.3-1.9)	<0.001
Lung	3.8 (2.6-5.6)	<0.001	1.8 (1.1-3.0)	0.02	3.1 (2.6-3.8)	<0.001
Metastases	-	-	-	-	3.3 (2.9-3.8)	<0.001
Chemotherapy	-	-	-	-	0.8 (0.7-0.9)	<0.001
Postoperative	0.5 (0.3-0.8)	0.008	-	-	0.7 (0.6-0.9)	0.003
PE vs. DVT	-	-	-	-	1.2 (1.0-1.3)	0.01
Creatinine clearance Cockcroft formula, ml/min	0.99 (0.99-0.999)	0.03	0.99 (0.98-0.99)	<0.001	0.99 (0.99-1.0)	<0.001
Platelet count<100,000/mm3t	-	-	2.0 (1.4-3.0)	<0.001	1.4 (1.2-1.6)	<0.001
Recent major bleeding	-	-	5.0 (3.1-7.9)	<0.001	-	-
Anaemia	-	-	-	-	1.2 (1.05-1.3)	0.007
Diagnosis <3 months	-	-	1.6 (1.1-2.3)	0.008	-	-

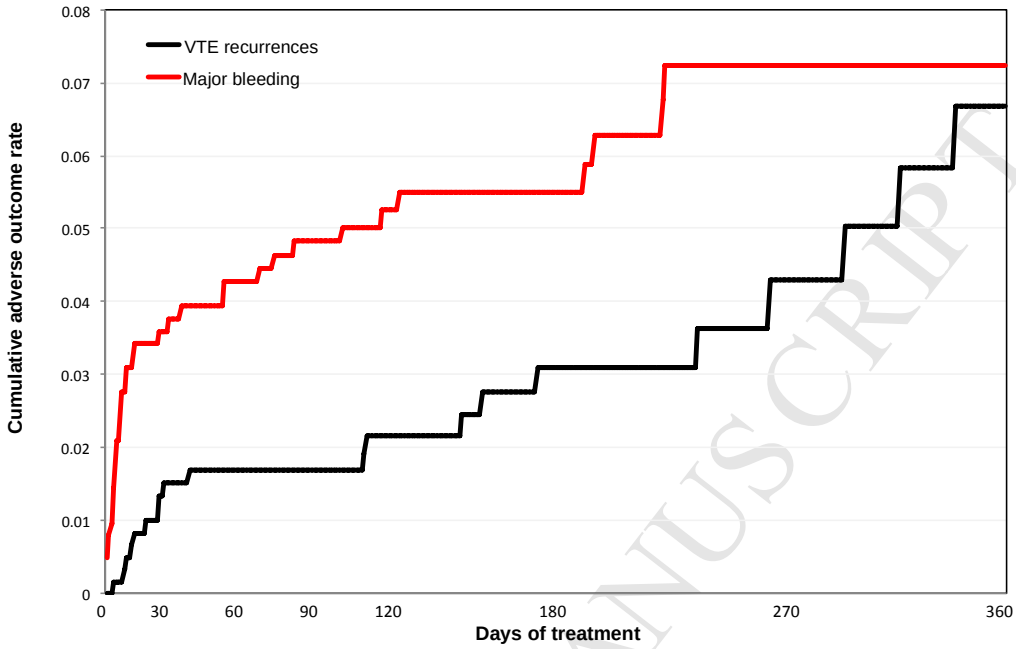
Abbreviations: PE, pulmonary embolism; DVT, deep vein thrombosis; VTE, venous thromboembolism.

Figure 1. Cumulative rate of VTE recurrences and major bleeding during the first 12 months of anticoagulant therapy in patients with breast cancer.



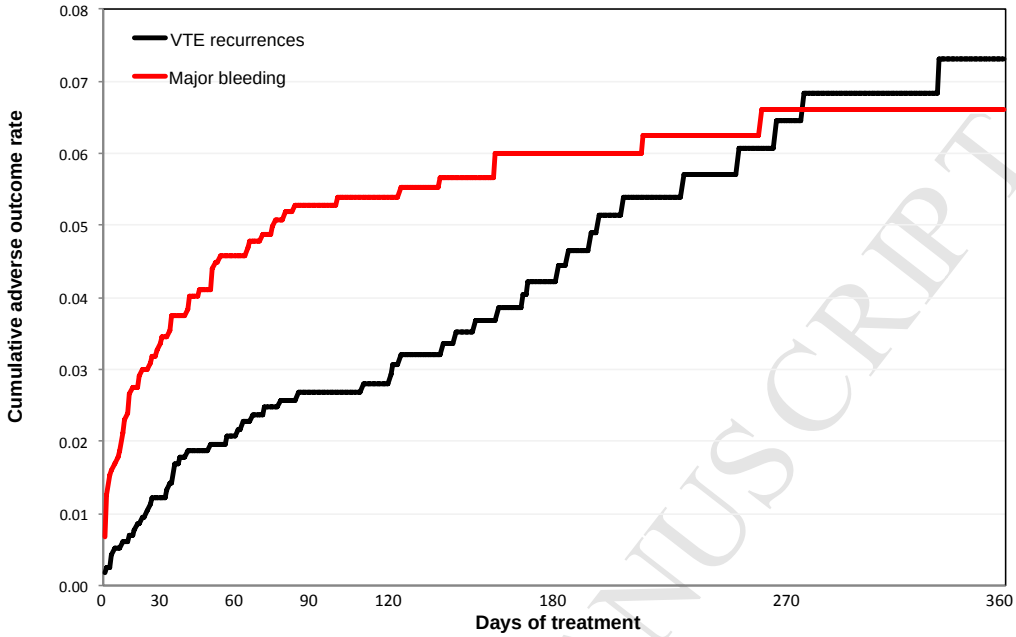
Patients at risk	938	840	816	804	578	405	218	146
VTE recurrences		10	3	3	1	2	3	0
Major bleeding		21	1	0	1	1	1	

Figure 2. Cumulative rate of VTE recurrences and major bleeding during the first 12 months of anticoagulant therapy in patients with prostate cancer.



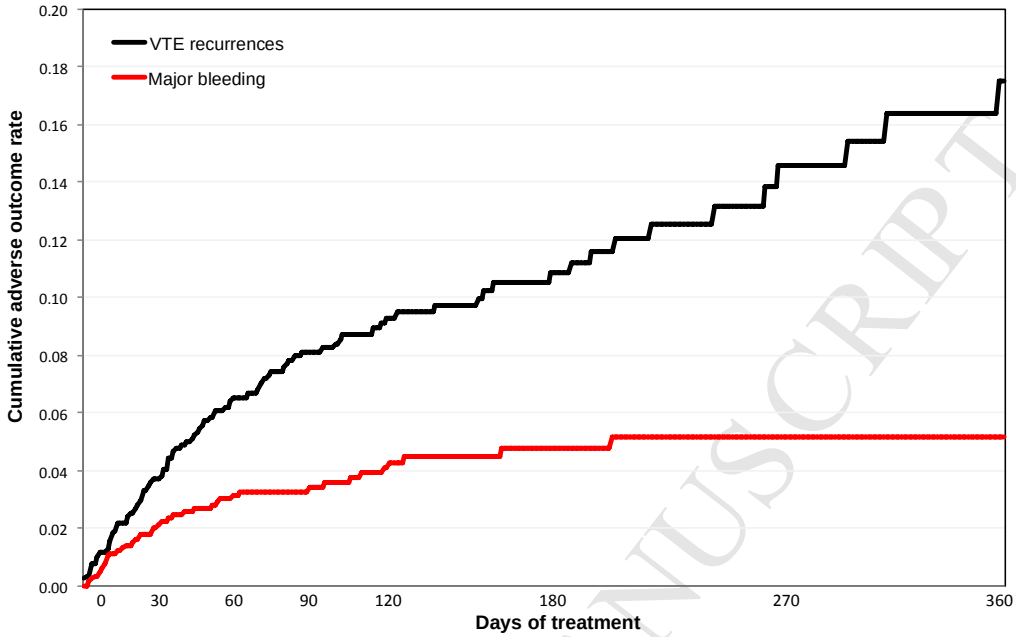
Patients at risk	629	553	534	520	370	279	142	103
VTE recurrences		10	1	0	2	3	2	2
Major bleeding		23	3	3	3	0	4	0

Figure 3. Cumulative rate of VTE recurrences and major bleeding during the first 12 months of anticoagulant therapy in patients with colorectal cancer.



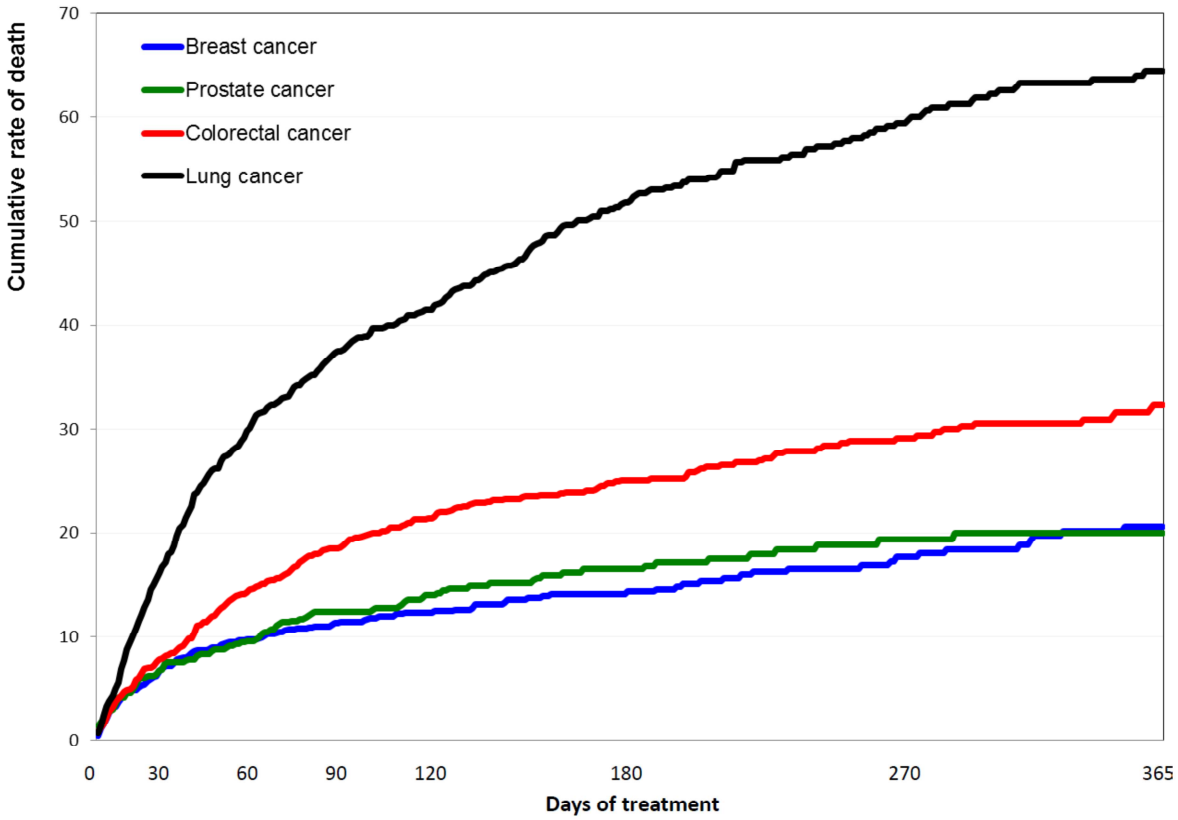
Patients at risk	1,189	1,036	956	906	681	470	247	170
VTE recurrences		19	6	4	4	6	8	2
Major bleeding		43	11	5	2	3	2	0

Figure 4. Cumulative rate of VTE recurrences and major bleeding during the first 12 months of anticoagulant therapy in patients with lung cancer.



Patients at risk	1,191	906	752	675	472	280	120	74
VTE recurrences		40	25	12	7	5	7	4
Major bleeding		22	10	2	4	3	1	0

Figure 5. Cumulative rate of death during the first 12 months of anticoagulant therapy in patients with lung, colorectal, breast and prostate cancer.



Significance : The clinical course of venous thromboembolism may differ according to cancer site

In a separate document, include a maximum of 3-4 bullet points that succinctly and specifically explain the clinical significance of your manuscript. Bullets should provide readers with your manuscript's "take home" messages for practicing internists. Do not restate information that would be considered common knowledge. Do not call for additional research in this area. (Maximum 70 words)

- Low molecular weight heparins are considered as first line treatment for cancer associated thrombosis. There are very few data for long-term treatment in those patients while life expectancy is increasing.
- The risk of thromboembolic recurrence, major bleeding and mortality while on anticoagulant treatment is different according to the site of cancer.
- Our results may help individualize the type and the dose of long-term anticoagulant treatment.