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Original article

Risk factors for recurrence and major bleeding in patients with cancer-associated venous thromboembolism

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ABSTRACT

Risks of recurrence and treatment-emergent bleeding are high in patients with cancer-associated venous thromboembolism (VTE) but factors associated with these risks remain substantially undefined.

The aim of this analysis in patients with cancer-associated VTE included in the Caravaggio study was to identify risk factors for recurrent VTE and major bleeding. Variables potentially predictive for recurrent VTE or major bleeding were evaluated in a Cox proportional hazard multivariable analysis with backward variable selection.

Recurrent VTE occurred in 78 patients (6.8%) and major bleeding in 45 (3.9%). Independent risk factors for recurrent VTE were deep vein thrombosis (DVT) as index event (Hazard ratio (HR) 1.84, 95% CI 1.17–2.88), ECOG status of 1 or more (HR 1.95, 95% CI 1.11–3.43), pancreatic or hepatobiliary cancer site (HR 2.20, 95% CI 1.19–4.06), concomitant anti-cancer treatment (HR 1.98, 95% CI 1.03–3.81) and creatinine clearance (HR 1.10, 95% CI 1.00–1.20 for every 10 ml/min absolute increase). Independent risk factors for major bleeding were ECOG status of 2 (HR 2.31, 95% CI 1.24–4.29), genitourinary cancer site (HR 2.72, 95% CI 1.28–5.77), upper gastrointestinal cancer site (HR 3.17, 95% CI 1.22–8.23), and non-resected luminal gastrointestinal cancer (HR 2.77, 95% CI 1.38–5.56).

This analysis of the Caravaggio study in patients with cancer-associated VTE who were on standardized anticoagulant treatment identified five independent predictors for recurrent VTE and four independent predictors of treatment-emergent major bleeding. Considering these risks could help clinicians to optimize the anticoagulant treatment in patients with cancer-associated VTE.

1. Introduction

Cancer and venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), are linked by a two-way association [1]. On one hand, 15–20% of patients who are diagnosed with acute VTE are concomitantly affected by cancer [2] and, on the other hand, about 15% of patients with cancer experience VTE during the course of their disease [3].

Abbreviations: CI, Confidence Interval; DVT, Deep Vein Thrombosis; ECOG, Eastern Cooperative Oncology Group; HR, Hazard Ratio; PE, Pulmonary Embolism; VTE, Venous Thromboembolism.

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Anticoagulant treatment in patients with cancer-associated VTE is particularly challenging as these patients, despite well-conducted anticoagulation, are exposed to high risks of both VTE recurrence and anticoagulant treatment-emergent bleeding [4,5]. Both VTE recurrence and major bleeding have a deleterious impact on cancer management as they may interfere with anticancer treatment or delay scheduled surgery. The high risk for recurrence observed in cancer patients has been associated with patient-related factors (among others, site of cancer and advanced stage of the disease), intervenient conditions (among others, hospitalization, surgery, central venous lines) and the prothrombotic state promoted by cancer cells, which is only partially controlled by the conventional anticoagulant treatment, and the administration of anti-cancer agents [6]. Several factors have been associated to the high risk of anticoagulant treatment-emergent bleeding including the cancer status (resected vs non-resected, locally invasive, intraluminal, ulcerated, friable), anticancer treatment-induced thrombocytopenia, mucositis and invasive procedures [7]. The large majority of these risk factors were derived from observational studies or registries and their value might be at least partially limited by the absence of the standardization of the study populations and event adjudication as well as of the anticoagulant treatment.

The aim of this study in patients with cancer-associated VTE included in the Caravaggio study was to identify the risk factors for recurrent VTE or major bleeding in patients with definite inclusion and exclusion criteria, blinded outcomes adjudication and treated with standardized anticoagulant treatment.

2. Methods

Caravaggio was a multinational, randomized, open-label, non-inferiority study with blind assessment of the study outcomes. The rationale, design and results of the Caravaggio study were reported previously [8,9]. Briefly, consecutive adult patients with cancer and symptomatic or incidental acute proximal DVT or PE were randomized to receive, in a 1:1 fashion, oral apixaban (at a dose of 10 mg twice daily for the first 7 days, followed by 5 mg twice daily) or subcutaneous dalteparin (at a dose of 200 IU per kilogram of body weight once daily for the first month, maximum dose of 18,000 IU, followed by 150 IU per kilogram once daily). Study treatments were intended to be given for six months. Any type of cancer (other than basal-cell or squamous-cell carcinoma of the skin, primary brain tumor or known intracerebral metastases and acute leukemia) that met at least one of the following criteria were included in the study: i) active cancer defined as diagnosis of cancer within six months before the study randomization, or treated with anti-cancer treatment at the time of randomization or in 6 months prior to randomization; ii) recurrent locally advanced or metastatic cancer; iii) cancer diagnosed within 2 years before the study inclusion (history of cancer).

Main exclusion criteria were: i) Eastern Cooperative Oncology Group (ECOG) Performance Status III or IV or life expectancy of less than 6 months [10]; ii) administration before randomization of therapeutic doses of low molecular weight heparin, fondaparinux, or unfractionated heparin for more than 72 h or of 3 or more doses of vitamin K antagonists; iii) active bleeding or high risk of bleeding contraindicating anticoagulant treatment; iv) concomitant thienopyridine therapy (clopidogrel, prasugrel, or ticagrelor) or aspirin over 165 mg daily or dual antiplatelet therapy; v) hemoglobin level lower than 8 g/dL or platelet count $< 75\times10^9$/L; vi) history of heparin-induced thrombocytopenia; vii) creatinine clearance $<$ 30 ml /min based on the Cockcroft Gault equation or liver failure.

Randomization was centrally performed through an interactive online system and stratified according to the type of VTE (symptomatic or incidental) and timing of the cancer diagnosis (active cancer or history of cancer).

The aim of the Caravaggio trial was to assess whether oral apixaban would have been noninferior to subcutaneous dalteparin for the prevention of recurrent VTE in patients with cancer. Anticoagulant-emergent bleeding was carefully assessed.

The primary outcome was objectively confirmed recurrent VTE, which included proximal DVT of the lower limbs (symptomatic or incidental), symptomatic DVT of the upper limbs, and PE (symptomatic, incidental, or fatal) occurring during the 6-month study period.

The principal safety outcome was major bleeding defined as acute clinically overt bleeding associated with one or more of the following criteria: a decrease in the hemoglobin level of at least 2 g per deciliter, a transfusion of 2 or more units of red cells, bleeding occurring at a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), bleeding requiring surgical intervention, or fatal bleeding.

The aim of this sub-analysis was to identify the risk factors for recurrent VTE and for major bleeding in patients with cancer-associated VTE included in the Caravaggio study and treated with apixaban or dalteparin.

Data from the main analysis and from the other sub-analysis of the Caravaggio population indicated potential predictors for the risk of recurrent VTE and for the risk of major bleedings [9,11–15]. Based on these data, we identified the following potential risk factors: patient characteristics (age, gender, weight, ECOG performance status; laboratory findings (anemia, thrombocytopenia, creatinine clearance calculated with the Cockcroft-Gault formula); concomitant antiplatelet therapy; history of VTE; index DVT or index PE or both DVT and PE as index event; symptomatic PE or DVT at admission; previous bleeding; adenocarcinoma histology; different cancer sites (lung, genitourinary, gynecological, colorectal, upper gastrointestinal, pancreatic or hepatobiliary, luminal gastrointestinal, breast, head and neck, bone/soft tissue, skin-melanoma, hematological); metastatic disease; locally advanced cancer; surgery within 2 weeks prior randomization; anti-cancer treatment during the study period; active cancer at randomization; apixaban treatment; presence of bleeding risk factor (one among: surgery within the 2 weeks prior randomization; use of concomitant anti-platelet therapy; regionally advanced or metastatic cancer; diagnosis of gastrointestinal cancer within 6 months prior randomization; use of bevacizumab within 6 weeks prior randomization).

2.1. Statistical analysis

All analyses were performed in the modified-ITT population of the Caravaggio study [8], which included all randomized patients who received at least one dose of the study drug.

The univariate analysis determined the strength of association between: i) each potential predictor and recurrent VTE and ii) each potential predictor and major bleeding. Hazard ratios (HRs) and relative 90% confidence intervals (CIs) were reported. Variables potentially predictive for recurrent VTE or major bleeding (univariate p-value $\leq$ 0.1) were evaluated in a Cox proportional hazard multivariable analysis with backward variable selection (recurrent VTE or major bleeding as the dependent variable): non-significant variables at the level of at least 0.05 were progressively eliminated. The deleted variables in the subsequent steps of the model were not reintegrated in the model itself. The following prespecified variables deemed of clinical interest were included in the final model: metastatic cancer and adenocarcinoma for recurrent VTE, and metastatic cancer for major bleeding. Variables closely related the one to the other, as non-resected luminal gatrointestinal cancer and upper gastrointestinal cancer, were not included in the same multivariable model but in two separate models (1 and 2, respectively).

All associations at multivariable analysis were presented as HR, corresponding 95% confidence intervals and p-value. A p-value of $<$ 0.05 was considered statistically significant. Due to the expected high mortality in study patients, risk-adjusted models for recurrent VTE and major bleeding were also assessed with death unrelated to the study

outcome as competing event [16]. Data were reported as sub-distribution hazard ratios (sHR), corresponding 95% confidence interval and p-value.

In order not to miss any potential predictors, a wider confidence interval (90%, significant p-value ≤ 0.10) was chosen for the univariable analysis, than for the multivariable analyses, where the 95% confidence interval (significant p-value < 0.05) was chosen.

All data were analyzed with the use of SAS software, version 9.4 (SAS Institute).

3. Results

Overall, 1155 patients with cancer-associated VTE were included in the analysis. Recurrent VTE occurred in 78 patients (6.8%) and major bleeding in 45 (3.9%). Death occurred in 288 patients (24.9%); fatal PE or fatal bleeding occurred in 7 and 2 patients, respectively.

3.1. Predictors for recurrent VTE

At univariate analysis, predictors of VTE recurrence were DVT as index event (HR 1.77, CI 1.21–2.58), symptomatic VTE as index event (HR 1.75, CI 1.01–3.05), metastatic disease (HR 1.84, CI 1.26–2.68), ECOG status of 1 or more (HR 2.06, CI 1.29–3.30), adenocarcinoma histology (HR 1.74, CI 1.14–2.67), gynecological cancer (HR 1.81, CI 1.10–2.98), pancreatic or hepatobiliary cancer (HR 2.62, CI 1.57–4.36), anti-cancer treatment during the study period (HR 2.49, 1.42–4.34), creatinine clearance for every increase of 10 ml/min (HR 1.10, CI 1.00–1.20) and presence of one or more bleeding risk factors (HR 3.55, CI 1.86–6.79) (Table 1). Similar results were observed when a competing-risk analysis was performed (Table 1).

Predictor variables at univariate analysis were evaluated in a multivariable analysis. Independent predictors for recurrence were DVT as index event (1.84, CI 1.17–2.88), an ECOG status of 1 or more (HR 1.95, CI 1.11–3.43), cancer at pancreatic or hepatobiliary site (HR 2.20, CI 1.19–4.06), treatment with anti-cancer agents during the study period (HR 1.98, CI 1.03–3.81) and creatinine clearance for every increase of 10 ml/min (HR 1.10, CI 1.00–1.20) (Table 2). Similar results were observed when a competing-risk analysis was performed (Table 2).

3.2. Predictors for major bleedings

At univariate analysis, predictors for major bleeding were metastatic cancer (HR 1.95, CI 1.19–3.22), ECOG status of 2 (HR 2.27, CI 1.34–3.82), cancer at genitourinary site (HR 2.03, CI 1.13–3.65), upper gastrointestinal cancer (HR 3.00, CI 1.38- 6.53), non-resected luminal gastrointestinal cancer (HR 2.32, CI 1.38–3.90), at least one bleeding risk factor (HR 2.26 CI 1.10–4.64) (Table 3). Similar results were observed when a competing-risk analysis was performed (Table 3).

At multivariable analysis, independent predictors for major bleeding were ECOG status of 2, (HR 2.31, CI 1.24–4.29), cancer at genitourinary site (HR 2.72, CI 1.28–5.77), non-resected luminal gastrointestinal cancer (HR 2.77, CI 1.38–5.56, model 1) and upper gastrointestinal cancer (HR 3.17, CI 1.22–8.23, model 2) (Table 4). Similar results were observed when a competing-risk analysis was performed (Table 4).

4. Discussion

This analysis of the results of the Caravaggio study in patients with cancer-associated VTE who were on standardized anticoagulant treatment identified five independent predictors for recurrent VTE and four independent predictors of treatment-emergent major bleeding. At multivariable analysis, DVT as index event, ECOG status of 1 or more, cancer at pancreatic or hepatobiliary site as well as concomitant anticancer treatment were associated with a nearly 2 times higher risk for recurrent VTE. High creatinine clearance was also significantly associated with recurrent VTE. At multivariable analysis, genitourinary or upper gastrointestinal sites or a non-resected luminal gastrointestinal site were associated with a 2 to 3 times higher risk of major bleeding. An ECOG status of 2 was associated with a nearly 2 times higher risk of major bleeding.

The risk factors associated with VTE recurrence revealed by our analysis appear clinically sound and linked to plausible pathophysiology knowledge. The risk of major bleeding seems to be mainly, although not exclusively, related to the site of cancer and its anatomical status (as resected vs. unresected).

Different sites of cancer have been found to be associated with different risks of VTE recurrence during anticoagulant treatment [14]. Our univariate analysis showed a high risk of recurrence in patients with gynecological and pancreatic or hepatobiliary cancer. The high risk for recurrence in patients with cancer at pancreatic or hepatobiliary site was confirmed by multivariable analysis. The increased risk of recurrence associated with cancer at pancreatic or hepatobiliary sites observed in our analysis is consistent with the markedly high activation of blood coagulation reported in patients with cancer at these sites [17].

The risk of recurrence of VTE related to concomitant anticancer treatment observed in our analysis confirmed the thrombogenicity of these treatments. However, the large spectrum of anticancer agents and their variable administration in the individual patients during the disease course does not allow the correlation of the risk of recurrence with a specific agent or class of agents.

The increased risk of recurrence associated with DVT as index event could be partially explained by the higher rate of symptomatic events found in patients with DVT as index event as compared with patients with pulmonary embolism as index events [11]. Indeed, in the Caravaggio study among the 230 patients with incidental VTE, 23.5% had a DVT and 76.5% a pulmonary embolism. Overall and regardless of the study treatment, the rate of recurrence was 4.3% and 7.4% in patients with asymptomatic and symptomatic VTE, respectively.

A high creatinine clearance was found to be independently associated with recurrent VTE. It should be noted that the average creatinine clearance was 99.2 ml/min in patients with VTE recurrence and 87.3 ml/min in patients that did not experience a VTE recurrence. The high risk of VTE recurrence in patients with a creatinine clearance above 90 mL/min has been already observed in a recently published sub-analysis of the Caravaggio study [15]. The association of the ECOG performance status of 1 or more with a significantly higher rate for recurrent VTE is clinically plausible and could mirror a more advanced cancer disease.

In our analysis, we found that genitourinary sites were associated with high rates of major bleeding. In two different models, we observed that both non-resected luminal gastrointestinal cancer and upper gastrointestinal cancer were associated with a high rate of bleeding events. Finally, an ECOG score of 2, a mirror of fragile patients, was also correlated with major bleedings.

As anticipated, the results of our analysis indicate that the risk of major bleeding seems to be related to the site of cancer more than patient clinical conditions and laboratory findings. However, it is worth noting that the Caravaggio study did not include patients with a creatinine clearance lower than 30 ml/min and platelet counts lower than 75,000. Patients with a recent history of severe bleeding were excluded as well.

A main issue when dealing with antithrombotic treatment in patients with VTE is the balance between the risks of recurrence and bleeding. This balance is particularly challenging in patients with cancer-associated VTE as in these patients, despite anticoagulant treatment, the risk of VTE recurrence is three times higher compared to patients without cancer [3]. As well, bleeding complications associated with anticoagulant treatment are two to three times more frequent in patients with cancer-associated VTE than in non-cancer patients [18]. A further complication factor is that some predictors for recurrent VTE are also associated with bleeding [19,20]. Interestingly, the results of our analysis showed a limited overlapping between the risk of VTE recurrence and bleeding. Indeed, the ECOG status only was a risk factor for both

Table 1
Predictors for recurrent VTE at univariate analysis.

Variable	Recurrent VTE 78	No recurrent VTE 1077	HR (90% CI)	p-value	sHR (90% CI)	p-value
Age, mean ± SD	**65.5 ± 10.2**	**68.0 ± 11.2**	**0.983 (0.970,0.997)**	**0.0420**	**0.982 (0.969,0.996)**	**0.0294**
Age ≥ 70, n (%)	**28 (35.9%)**	**525 (48.7%)**	**0.605 (0.411,0.892)**	**0.0384**	**0.600 (0.407,0.884)**	**0.0302**
Age ≥ 75, n (%)	**14 (17.9%)**	**334 (31.0%)**	**0.499 (0.308,0.811)**	**0.0184**	**0.492 (0.303,0.798)**	**0.0160**
Male gender, n%	40 (51.3%)	528 (49.0%)	1.096 (0.755,1.591)	0.6842	1.099 (0.757,1.594)	0.6772
Weight (kg), n, mean ± SD	76.0 ± 17.8	75.9 ± 16.3	0.999 (0.986,1.011)	0.8796	1.000 (0.988,1.013)	0.9553
Concomitant antiplatelet therapy, n (%)	7 (8.9%)	136 (12.6%)	0.688 (0.359,1.316)	0.3426	0.686 (0.359,1.314)	0.3404
Platelet count (mmc), n, mean ± SD	213.5 ± 89.1	236.2 ± 103.1	0.998 (0.996,1.000)	0.0816	0.998 (0.995,1.000)	0.0708
Platelet count <100,000/mmc, n (%)	3 (3.8%)	34 (3.2%)	1.221 (0.464,3.212)	0.7341	1.210 (0.460,3.184)	0.7461
Hemoglobin (g/dl), mean ± SD	**10.6 ± 1.8**	**11.1 ± 2.2**	**0.908 (0.852,0.969)**	**0.0139**	**0.910 (0.853,0.971)**	**0.0168**
Hemoglobin (g/dl) <10 g/dl, n (%)	24 (30.8%)	290 (26.9%)	1.220 (0.816,1.826)	0.4159	1.195 (0.799,1.789)	0.4669
Creatinine clearance (ml/min), n, mean ± SD	**99.2 ± 41.9°**	**87.3 ± 32.0^**	**1.090 (1.040,1.150)**	**0.0055**	**1.090 (1.040,1.150)**	**0.0039**
Creatinine clearance≤ 50 ml/min, n (%)	5 (10.4%)	107 (9.9%)	0.661 (0.309,1.410)	0.3685	0.614 (0.287,1.311)	0.2899
Diagnosis of index DVT, n (%)	**46 (58.9%)**	**471 (43.7%)**	**1.768 (1.211,2.582)**	**0.0132**	**1.806 (1.238,2.635)**	**0.0101**
Diagnosis of index PE, n (%)	**25 (32.1%)**	**613 (56.9%)**	**0.441 (0.293,0.664)**	**0.0010**	**0.554 (0.379,0.808)**	**0.0101**
Diagnosis of index PE and DVT, n (%)	7 (8.9%)	86 (7.9%)	1.158 (0.609,2.202)	0.7080	1.105 (0.580,2.103)	0.7990
History of VTE, n (%)	9 (11.5%)	97 (9.0%)	1.273 (0.710,2.284)	0.4967	1.288 (0.718,2.311)	0.4757
Symptomatic PE or DVT, n (%)	**68 (87.2%)**	**857 (79.6%)**	1.752 (1.007,3.048)	0.0958	1.763 (1.013,3.066)	0.0923
Previous bleeding, n (%)	2 (2.6%)	13 (1.2%)	1.915 (0.618,5.938)	0.3447	1.952 (0.628,6.064)	0.3319
Locally advanced cancer, n (%)	22 (28.2%)	263 (24.4%)	1.185 (0.782,1.796)	0.5028	1.206 (0.796,1.826)	0.4589
Metastatic cancer, n (%)	**44 (56.4%)**	**462 (42.9%)**	**1.835 (1.257,2.679)**	**0.0083**	**1.695 (1.164,2.467)**	**0.0209**
ECOG status ≥1, n (%)	**63 (80.8%)**	**736 (68.3%)**	**2.062 (1.288,3.302)**	**0.0114**	**1.919 (1.199,3.073)**	**0.0228**
ECOG status 1, n (%)	**50 (64.1%)**	**508 (47.2%)**	**1.889 (1.282,2.783)**	**0.0069**	**1.940 (1.317,2.859)**	**0.0049**
ECOG status = 2, n (%)	13 (16.7%)	228 (21.2%)	0.881 (0.535,1.452)	0.6768	0.766 (0.464,1.262)	0.3798
Adenocarcinoma histotype, n (%)	**58 (74.4%)**	**670 (62.2%)**	**1.742 (1.138,2.667)**	**0.0320**	**1.722 (1.125,2.637)**	**0.0357**
Lung cancer, n (%)	11 (14.1%)	189 (17.5%)	0.834 (0.489,1.421)	0.5751	0.795 (0.467,1.354)	0.4788
Genitourinary cancer, n (%)	9 (11.5%)	130 (12.1%)	0.911 (0.580,1.632)	0.7927	0.940 (0.525,1.683)	0.8607
Gynecological cancer, n (%)	**13 (16.7%)**	**106 (9.8%)**	**1.810 (1.101,2.976)**	**0.0495**	**1.781 (1.083,2.928)**	**0.0562**
Colorectal cancer, n (%)	16 (20.5%)	218 (20.2%)	0.956 (0.602,1.519)	0.8741	0.995 (0.627,1.579)	0.9852
Upper gastrointestinal cancer, n (%)	5 (6.4%)	49 (4.5%)	1.658 (0.762,3.608)	0.2846	1.491 (0.684,3.250)	0.3994
Pancreatic or hepatobiliary cancer, n (%)	**12 (15.4%)**	**75 (7.0%)**	**2.618 (1.572,4.361)**	**0.0019**	**2.327 (1.398,3.874)**	**0.0064**
Luminal gastrointestinal (esophageal, stomach, colorectal) cancer, n (%)	17 (21.8%)	255 (23.7%)	0.883 (0.561,1.391)	0.6534	0.893 (0.567,1.405)	0.6811
Resected luminal gastrointestinal cancer, n (%)	4 (5.1%)	63 (5.8%)	0.829 (0.349,1.968)	0.7211	0.881 (0.372,2.086)	0.8095
Non resected luminal gastrointestinal cancer, n (%)	13 (16.7%)	192 (17.8%)	0.920 (0.557,1.518)	0.7838	0.911 (0.552,1.502)	0.7582
Breast cancer, n (%)	6 (7.7%)	149 (13.8%)	0.506 (0.250,1.025)	0.1125	0.527 (0.260,1.065)	0.1341
Head and neck cancer, n (%)	1 (1.3%)	21 (1.9%)	0.600 (0.116,3.112)	0.6096	0.641 (0.124,3.318)	0.6563
Bone/Soft tissue cancer, n (%)	0	18 (1.7%)	NA	NA	NA	NA
Skin- Melanoma cancer, n (%)	0	11 (1.0%)	NA	NA	NA	NA
Hematological malignancy, n (%)	4 (5.1%)	81 (7.5%)	0.629 (0.274,1.445)	0.3595	0.661 (0.287,1.520)	0.4136
Surgery within 2 weeks prior randomization, n (%)	0	20 (1.9%)	NA	NA	NA	NA
Cancer treatment during trial period, n (%)	**68 (87.2%)**	**763 (70.8%)**	**2.486 (1.423,4.343)**	**0.0072**	**2.591 (1.484,4.524)**	**0.0050**
Active cancer at randomization, n (%)	77 (98.7%)	1047 (97.2%)	2.302 (0.437,12.138)	0.4095	2.185 (0.415,11.510)	0.4390
Apixaban, n (%)	**32 (41.0%)**	**544 (50.5%)**	**0.680 (0.465,0.992)**	**0.0934**	**0.690 (0.473,1.008)**	**0.1070**
Bleeding risk factors, n (%) *						
≥1	**71 (91.0%)**	**804 (74.7%)**	**3.553 (1.859,6.789)**	**0.0013**	**3.340 (1.748,6.384)**	**0.0022**
≥2	13 (16.7%)	171 (15.9%)	1.090 (0.659,1.802)	0.7782	1.062 (0.642,1.756)	0.8453
≥3	1 (1.3%)	14 (1.3%)	1.011 (0.193,5.294)	0.9910	0.968 (0.185,5.079)	0.9744

°data available on 77 patients; ^data available on 1042 patients.
Percentages are calculated on total number of modified intention-to-treat (mITT) patients in each stratum.
HR = hazard ratio. sHR = sub-distribution hazard ratio.
Death unrelated to the outcome is considered as competing risk in sHR calculation.
The significance level used in the univariate model is 0.1.
HR and sHR with relative 90% CIs and p-value derived from Cox proportional hazard univariate model using only the predictor as covariate of the model.
Stratum reported in the first column is the reference for HR and sHR calculation.
For continuous variables, HR and sHR was calculated relative to an increase of 1 unit of the variable value, except for creatinine clearance were an increase of 10 unit of the variable value was considered.

* The following bleeding risk factors were considered:
- Surgery within the 2 weeks prior randomization
- Use of concomitant anti-platelet therapy.
- Regionally advanced or metastatic cancer.
- Diagnosis of GI cancer within 6 months prior randomization.
- Use of Bevacizumab within 6 weeks prior randomization.

Table 2
Predictive variables for recurrent VTE at multivariable analyses.

	Multivariable model			*Competing-risk multivariable model*		
Predictive variables for recurrent VTE	Wald χ^2	HR (95% CI)	p-value	Wald χ^2	sHR (95% CI)	p-value
Creatinine clearance (ml/min)	7.9664	1.090 (1.030,1.160)	0.0048	8.7559	1.100 (1.030,1.160)	0.0031
Diagnosis of index DVT	6.9918	1.835 (1.170,2.877)	0.0082	7.6919	1.887 (1.205,2.955)	0.0055
ECOG status ≥ 1	5.3146	1.946 (1.105,3.427)	0.0211	4.4029	1.837 (1.041,3.241)	0.0359
Pancreatic or hepatobiliary cancer	6.2982	2.196 (1.188,4.061)	0.0121	5.1119	2.034 (1.099,3.765)	0.0238
Cancer treatment during trial period	4.1557	1.979 (1.027,3.814)	0.0415	5.1318	2.134 (1.108,4.110)	0.0235
Metastatic cancer	2.3055	1.427 (0.902,2.259)	0.1289	1.5534	1.337 (0.847,2.109)	0.2126
Adenocarcinoma histotype	1.6135	1.417 (0.828,2.427)	0.2040	1.5577	1.408 (0.823,2.409)	0.2120

HR and sHR with relative 95% CIs and p-value derived from Cox proportional hazard multivariate model.
Stratum reported in the first column is the reference for HR and sHR calculation.
HR = hazard ratio. sHR = sub-distribution hazard ratio.
Death unrelated to the outcome is considered as competing risk in sHR calculation.
For continuous variables, HR and sHR was calculated relative to an increase of 1 unit of the variable value, except for creatinine clearance were an increase of 10 unit of the variable value was considered.

recurrence and bleeding. Interestingly, only an ECOG status of 2, an index of more advanced disease, was a risk factor for bleeding while an ECOG status of 1 or greater was a risk for recurrence.

The risk factors for VTE recurrence and bleeding have been used to build risk scores. The Ottawa and the modified Ottawa scores were developed to identify cancer patients at risk for VTE recurrence [21]. In the recent prospective PREDICARE cohort which included 178 patients with cancer-associated VTE, the predictive value of the Ottawa score was relatively low (c-statistics 0.6, 95% CI 0.55–0.65) [22]. The RIETE-VTE score also showed controversial results [22–25]. Recently, the 'CAT-BLEED' model was developed based on the results of the Hokusai-VTE study [26]. Unfortunately, this score also showed a modest performance in predicting clinically relevant bleeding (c-statistic 0.61, 95% CI 0.56–0.66). Overall, the available scores specifically proposed for patients with cancer-associated VTE do not seem to provide satisfactory results. It may be argued that some of the existing risk scores for VTE recurrence and bleeding may perform insufficiently as they were not developed by using data specifically derived in studies including exclusively cancer patients. Furthermore, the risks for both VTE recurrence and bleeding are dynamic (not stable), cancer-dependent and can change significantly during the course of the cancer disease. They probably need to be assessed periodically in order to improve their accuracy. The absence of overlap between risk factors for recurrence and bleeding observed in our analysis could facilitate the development of improved risk scores for recurrence or bleeding and for overall risk benefit of anticoagulant treatment.

The optimal duration of anticoagulant treatment in patients with cancer-associated VTE remains an unsolved issue even after the most recent clinical trials with direct oral anticoagulants in which study treatment was planned to be given for six months. This issue is made more relevant by the improvement in patients survival associated with newer anticancer treatments. Indeed, the six-month mortality in the Caravaggio study was 22.0% leaving most of the patents with question of continuing anticoagulant treatment beyond 6 months. It has been argued that in patients with cancer-associated VTE, the risks for recurrence and anticoagulant-emergent bleeding are persistent and unchanged over time so that indefinite anticoagulation is required in all patients. Alternatively, it could be claimed that a careful initial evaluation and a subsequent periodic re-evaluation of the risks for recurrence and bleeding could help clinicians in tailoring the treatment duration with the potential advantage of minimizing the risk of recurrence without exposing patients to an unnecessary risk of bleeding.

Despite backward selection still has some limits, this procedure seems to be the best among those currently in use. The open label design may be considered a limitation of this study; however, the adjudication of all study events was made by a blind independent committee, which mitigates possible bias related to the open-label design. Patients with primary or metastatic brain cancer and acute leukemia were excluded and, thus, the obtained results cannot be applied to these patients. Patients were not equally distributed in the study across different cancer sites. This is a common finding in the "all comers trials" where consecutive patients with cancer and VTE are included. This approach favors the inclusion of patients with cancer at sites where cancer is most common and with cancers that more commonly associated with VTE. Indeed, in this study baseline characteristics and distribution of the sites of cancer were similar to those of the most recent registry in consecutive cancer patients [27]. Although Caravaggio is one of the largest studies on the treatment of VTE in cancer patients, its sample size could have been insufficient to identify some underrepresented risk factors. Larger individual patient meta-analysis of the existing studies could potentially improve and refine the results of this analysis.

Strengths of this analysis include the standardized anticoagulant treatment, and the inclusion of patients with a large spectrum of cancer sites. A high proportion of the analyzed patients were affected by advanced cancer, who are the most challenging patients due to the particularly high rate of both recurrence and bleeding.

In conclusion, different cancer sites (pancreatic or hepatobiliary, genitourinary, upper gastrointestinal or non-resected luminal gastrointestinal), index DVT event, ECOG performance status, creatinine clearance and anticancer treatment are useful to identify patients at high risk for recurrent VTE or major bleeding. The results of the present analysis provide data for a potential improvement of the stratification of cancer patients according to the risks for recurrent VTE and major bleeding. These findings may help clinicians tailor the optimal anticoagulant management for individual patient with cancer-associated VTE.

5. Authorship contributions

MCV, MG, CB and GA designed the research, analyzed and interpreted data, wrote the manuscript

AM, LB, ATC, FK, JC, RB, BB and MC designed the research, analyzed and interpreted data, manuscript review and editing

Table 3
Predictors of major bleedings at univariate analysis.

Variable	Major bleeding 45	No major bleeding 1110	HR (90% CI)	p-value	sHR (90% CI)	p-value
Age, n, mean ± SD	68.3 ± 8.5	67.8 ± 11.2	1.005 (0.988,1.023)	0.6229	1.004 (0.987,1.021)	0.7233
Age ≥ 70, n (%)	19 (42.2%)	534 (48.1%)	0.798 (0.486,1.310)	0.4533	0.787 (0.479,1.291)	0.4257
Age ≥ 75, n (%)	11 (24.4%)	337 (30.4%)	0.750 (0.424,1.325)	0.4052	0.734 (0.416,1.297)	0.3723
Male gender, n (%)	25 (55.6%)	543 (48.9%)	1.298 (0.792,2.125)	0.3849	1.301 (0.795,2.130)	0.3799
Weight (kg), n, mean ± SD	73.0 ± 13.7	76.0 ± 16.5	0.987 (0.973,1.001)	0.1160	0.989 (0.975,1.002)	0.1754
Concomitant antiplatelet therapy, n (%)	5 (11.1%)	138 (12.4%)	0.877 (0.401,1.919)	0.7827	0.877 (0.401,1.919)	0.7828
Platelet count (mmc), n, mean ± SD	239.4 ± 102.1	234.4 ± 102.4°	1.001 (0.998,1.003)	0.6280	1.001 (0.998,1.003)	0.6691
Platelet count <100,000/mmc, n (%)	1 (2.2%)	36 (3.3%)	0.699 (0.131,3.720)	0.7247	0.692 (0.130,3.682)	0.7173
Hemoglobin (g/dl), n, mean ± SD	10.8 ± 2.5	11.1 ± 2.2°	0.944 (0.838,1.064)	0.4310	0.948 (0.840,1.070)	0.4655
Hemoglobin (g/dl) <10 g/dl, n (%)	11 (24.4%)	303 (27.3%)	0.878 (0.497,1.552)	0.7069	0.854 (0.483,1.508)	0.6478
Creatinine clearance (ml/min), n, mean ±SD	83.6 ± 25.6ˆ	88.3 ± 33.2§	0.952 (0.891,1.020)	0.2539	0.961 (0.892,1.020)	0.2827
Creatinine clearance ≤ 50 ml/min, n (%)	6 (13.3%)	106 (9.5%)	1.552 (0.754,3.195)	0.3162	1.426 (0.692,2.941)	0.4196
Diagnosis of index DVT, n (%)	15 (33.3%)	502 (45.1%)	0.598 (0.356,1.006)	0.1041	0.608 (0.362,1.022)	0.1154
Diagnosis of index PE, n (%)	28 (62.2%)	610 (54.9%)	1.560 (0.922,2.639)	0.1645	1.645 (0.978,2.766)	0.1154
Diagnosis of index PE + DVT, n (%)	2 (4.4%)	91 (8.2%)	0.548 (0.165,1.817)	0.4092	0.523 (0.158,1.737)	0.3745
History of VTE, n (%)	2 (4.4%)	104 (9.4%)	0.449 (0.136,1.481)	0.2699	0.450 (0.136,1.484)	0.2709
Symptomatic PE or DVT, n (%)	33 (73.3%)	892 (80.4%)	0.691 (0.397,1.200)	0.2708	0.697 (0.401,1.212)	0.2831
Previous bleeding, n (%)	1 (2.2%)	14 (1.3%)	1.639 (0.327,8.207)	0.6140	1.652 (0.330,8.272)	0.6085
Locally advanced cancer, n (%)	10 (22.2%)	275 (24.8%)	0.847 (0.469,1.530)	0.6449	0.866 (0.480,1.563)	0.6892
Metastatic cancer, n (%)	**26 (57.8%)**	**480 (43.2%)**	**1.953 (1.185,3.219)**	**0.0276**	**1.788 (1.088,2.937)**	**0.0543**
ECOG status ≥ 1, n (%)	35 (77.8%)	764 (68.8%)	1.709 (0.946,3.086)	0.1360	1.577 (0.875,2.842)	0.2037
ECOG status 1, n (%)	20 (44.4%)	538 (48.5%)	0.831 (0.507,1.359)	0.5353	0.852 (0.521,1.395)	0.5936
ECOG status 2, n (%)	**15 (33.3%)**	**226 (20.4%)**	**2.263 (1.342,3.816)**	**0.0101**	**1.938 (1.152,3.258)**	**0.0363**
Adenocarcinoma histotype, n (%)	30 (66.7%)	698 (62.9%)	1.188 (0.706,1.998)	0.5860	1.175 (0.699,1.976)	0.6099
Lung cancer, n (%)	7 (15.6%)	193 (17.4%)	0.937 (0.477,1.843)	0.8747	0.901 (0.458,1.772)	0.8002
Genitourinary cancer, n (%)	**10 (22.2%)**	**129 (11.6%)**	**2.029 (1.129,3.646)**	**0.0472**	**2.099 (1.167,3.775)**	**0.0378**
Gynecological cancer, n (%)	4 (8.8%)	115 (11.6%)	0.867 (0.365,2.059)	0.7861	0.846 (0.356,2.011)	0.7510
Colorectal cancer, n (%)	11 (24.4%)	223 (20.1%)	1.0193 (0.676,2.103)	0.6093	1.252 (0.709,2.211)	0.5154
Upper gastrointestinal cancer, n (%)	**5 (11.1%)**	**49 (4.4%)**	**3.003 (1.381,6.533)**	**0.0199**	**2.665 (1.222,5.814)**	**0.0387**
Pancreatic or hepatobiliary cancer, n (%)	2 (4.4%)	85 (7.7%)	0.672 (0.204,2.215)	0.5836	0.575 (0.175,1.887)	0.4438
Luminal gastrointestinal (esophageal, stomach, colorectal) cancer, n (%)	15 (33.3%)	257 (7.7%)	1.583 (0.943,2.657)	0.1448	1.608 (0.957,2.702)	0.1318
Resected Luminal gastrointestinal cancer, n (%)	0	67 (6.0%)	NA	NA	NA	NA
Non resected luminal gastrointestinal **cancer, n** (%)	**15 (33.3%)**	**190 (17.1%)**	**2.324 (1.384,3.902)**	**0.0074**	**2.326 (1.385,3.906)**	**0.0074**
Breast cancer, n (%)	4 (8.8%)	151 (17.1%)	0.591 (0.249,1.404)	0.3176	0.620 (0.261,1.470)	0.3625
Head and neck cancer, n (%)	2 (4.4%)	20 (1.8%)	2.190 (0.666,7.199)	0.2785	2.386 (0.729,7.807)	0.2277
Bone/Soft tissue cancer, n (%)	0	18 (1.6%)	NA	NA	NA	NA
Skin- Melanoma cancer, n (%)	0	11 (0.9%)	NA	NA	NA	NA
Hematological malignancy, n (%)	0	85 (7.7%)	NA	NA	NA	NA
Surgery within 2 weeks prior randomization, n (%)	0	20 (1.8%)	NA	NA	NA	NA
Cancer treatment during trial period, n (%)	38 (84.4%)	793 (71.4%)	1.957 (0.996,3.847)	0.1022	2.045 (0.999,4.021)	0.1004
Active cancer at randomization, n (%)	44 (3.9%)	1080 (96.1%)	1.313 (0.251,6.874)	0.7868	1.242 (0.237,6.505)	0.8293
Apixaban, n (%)	22 (97.8%)	554 (97.3%)	0.940 (0.576,1.533)	0.8341	0.954 (0.584,1.556)	0.8737
Bleeding risk factors, n (%)*						
≥1	**39 (86.7%)**	**836 (75.3%)**	**2.262 (1.103,4.640)**	**0.0617**	**2.113 (1.029,4.338)**	**0.0871**
≥2	7 (15.6%)	177 (15.9%)	0.986 (0.501,1.942)	0.9734	0.965 (0.490,1.900)	0.9317
≥3	1 (2.2%)	14 (1.3%)	1.790 (0.361,8.866)	0.5496	1.654 (0.330,8.285)	0.6074

°data available on 1101 patients; ˆdata available on 44 patients; §data available on 1075 patients.
Percentages are calculated on total number of modified intention-to-treat (mITT) patients in each stratum.
HR = hazard ratio. sHR = subdistribuction hazard ratio.
Death unrelated to the outcome is considered as competing risk in sHR calculation.
The significance level used in the univariate model is 0.1.
HR and sHR with relative 90% CIs and p-value derived from Cox proportional hazard univariate model using only the predictor as covariate of the model.
Stratum reported in the first column is the reference for HR and sHR calculation.
For continuous variables, HR and sHR was calculated relative to an increase of 1 unit of the variable value, except for creatinine clearance were an increase of 10 unit of the variable value was considered.
* The following bleeding risk factors were considered:
- Surgery within the 2 weeks prior randomization
- Use of concomitant anti-platelet therapy.
- Regionally advanced or metastatic cancer.
- Diagnosis of GI cancer within 6 months prior randomization.
- Use of Bevacizumab within 6 weeks prior randomization.

Table 4
Predictors of major bleeding at multivariable analyses.

	Multivariable model			*Competing-risk multivariable model*		
Predictive variables for major bleeding (model 1)	Wald χ^2	HR (95% CI)	p-value	Wald χ^2	sHR (95% CI)	p-value
ECOG status = 2	6.9898	2.306 (1.241,4.285)	0.0082	4.5661	1.965 (1.058,3.653)	0.0326
Genitourinary cancer	6.8241	2.722 (1.284,5.770)	0.0090	7.6500	2.885 (1.362,6.113)	0.0057
Non resected luminal gastrointestinal cancer	8.2125	2.770 (1.380,5.561)	0.0042	8.5489	2.825 (1.408,5.668)	0.0035
Metastatic cancer	1.8743	1.549 (0.828,2.900)	0.1710	1.1652	1.411 (0.755,2.637)	0.2804
Predictive variables for major bleeding (model 2)	**Wald χ^2**	**HR (95% CI)**	**p-value**	**Wald χ^2**	**sHR (95% CI)**	**p-value**
ECOG status = 2	6.3146	2.225 (1.192,4.151)	0.0120	4.0076	1.887 (1.013,3.515)	0.0453
Genitourinary cancer	4.6055	2.173 (1.070,4.416)	0.0319	5.2093	2.283 (1.124,4.637)	0.0225
Upper gastrointestinal cancer	5.6205	3.170 (1.221,8.228)	0.0178	4.4285	2.821 (1.074,7.411)	0.0353
Metastatic cancer	3.2070	1.737 (0.949,3.179)	0.0733	2.1455	1.573 (0.858,2.884)	0.1430

HR and sHR with relative 95% CIs and p-value derived from Cox proportional hazard multivariate model.
Stratum reported in the first column is the reference for HR and sHR calculation.
HR = hazard ratio. sHR = sub-distribution hazard ratio.
Death unrelated to the outcome is considered as competing risk in sHR calculation.
For continuous variables, HR and sHR was calculated relative to an increase of 1 unit of the variable value, except for creatinine clearance were an increase of 10 unit of the variable value was considered.

Declaration of Competing Interest

MCV and MG have non conflict of interest to declare

AM reports honoraria for consulting or advisory role from Celgene, Sanofi, BMS/Pfizer, Leo Pharma, Daichii Sankyo, Incyte, Astra Zeneca, MSD, Lilly, Roche, Servier; for being part of Speakers' Bureau by Rovi, Bayer, Menarini, STADA, Amgen, Merck Serono; Research Funding by Sanofi, Leo Pharma, Rovi, Celgene. He also reports honoraria for Patents, Royalties, and other Intellectual Property (Risk assessment model in venous thromboembolism in cancer patients) and Travel, Accommodations, Expenses: by Celgene, Merck Serono, Amgen, Servier, Pfizer, Roche.

LB reports grants from Bayer, grants and personal fees from MSD, personal fees and non-financial support from BMS/Pfizer, personal fees and non-financial support from Léo-Pharma.

ATC declares receiving fees for serving on an adjudication committee from AbbVie and Boehringer Ingelheim, consulting fees and fees for serving on a committee from Bayer, grant support and fees for serving on a committee from Bristol-Myers Squibb and Daiichi Sankyo Europe, grant support, consulting fees, and fees for serving on a committee from Pfizer, consulting fees from Janssen and Ono Pharmaceutical, consulting fees and fees for serving on a steering committee from Portola Pharmaceuticals, and fees for serving on a steering committee from Exom Group.

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JC declares receiving fees for serving on an independent review committee from Bristol-Myers Squibb–Pfizer, grant support, paid to her institution, from CSL Behring, consulting fees from Abbott, and advisory board fees from Portola.

RB declares receiving consultation and speaker's honoraria from Bayer, Bristol Myers Squibb, LEO, Pfizer and VIATRIS.

BB declares receiving honoraria for lectures and advisory board contributions from Sanofi, ROVI Laboratories, Johnson & Johnson and HORIBA Medical.

MC has non conflict of interest to declare

CB declares receiving lecture fees and consulting fees from Bayer Healthcare, Bristol-Myers Squibb, and Daiichi Sankyo.

GA has received honoraria for lecture and advisory board contribution from BMS, Pfizer, Daiichi Sankyo and Anthos Therapeutics.

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