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ORIGINAL ARTICLE

Clinical characteristics and outcomes of incidental venous thromboembolism in cancer patients: Insights from the Caravaggio study

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Abstract

Background: Clinical guidelines advise similar anticoagulant treatment for symptomatic and incidental cancer-associated venous thromboembolism (VTE). We investigated clinical features and outcomes of cancer patients with incidental or symptomatic VTE randomized in the Caravaggio study.

Objectives: We performed a predefined sub-analysis of the Caravaggio study in order to investigate the clinical features and outcomes of incidental and symptomatic VTE in patients with cancer. The relative efficacy and safety of apixaban and dalteparin in patients with incidental and symptomatic VTE was also assessed.

Methods: The Caravaggio study compared apixaban to dalteparin for the 6-month treatment of cancer-associated VTE. The primary efficacy and safety outcomes were recurrent VTE and major bleeding.

Results: Two hundred thirty patients (20%) had incidental and 925 (80%) symptomatic VTE. Pulmonary embolism with or without deep vein thrombosis as index event,

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colorectal cancer, Eastern Cooperative Oncology Group (ECOG) score of 0, and locally advanced or metastatic cancer were more frequent in patients with incidental VTE. Deep vein thrombosis as index event, hematological cancer, and ECOG score of 2 were more frequent in patients with symptomatic VTE. Ten patients (4.3%) with incidental and 68 (7.4%) with symptomatic VTE had recurrent VTE (hazard ratio [HR] 0.57, 95% confidence interval [CI] 0.29–1.10). Major bleeding occurred in 12 (5.2%) patients with incidental VTE and in 33 (3.6%) patients with symptomatic VTE (HR 1.43, 95% CI 0.74–2.77). When comparing apixaban to dalteparin in patients with symptomatic and incidental VTE, the HR for recurrence was 0.73 (95% CI 0.45–1.19) and 0.41 (95% CI 0.11–1.56), respectively, and the HR for major bleeding 0.93 (95% CI 0.47–1.83) and 0.96 (95% CI 0.31–2.96), respectively.

Conclusions: Compared to cancer patients with symptomatic VTE, those with incidental VTE have different clinical features at presentation, with a numerically lower incidence of recurrent VTE and a numerically higher incidence of major bleeding.

KEYWORDS
apixaban, cancer, incidental venous thromboembolism, symptomatic venous thromboembolism, venous thromboembolism

1 | BACKGROUND

Venous thromboembolism (VTE) occurs in approximately 20% of patients with cancer and is associated with an increased rate of hospital admission, reduced quality of life, and reduced overall survival.[1,2] In some patients, VTE may be unsuspected and detected incidentally on imaging studies performed for reasons other than confirming the clinical suspicion of VTE.[3] Incidental VTE could be asymptomatic or have related symptoms attributed to the underlying disease or other clinical conditions. Incidental VTE is particularly common in patients with cancer, as they undergo frequent imaging tests for cancer diagnosis, staging, and follow-up. A recent meta-analysis of 28,626 cancer patients reported an overall frequency of incidental pulmonary embolism of 3.36%.[4]

Knowledge about the clinical course and optimal management of incidental VTE in patients with cancer is limited. For these patients, international guidelines recommend the same management as for those with symptomatic VTE.[3,5,6] These guidelines are mostly based on retrospective studies, which suggest a similar risk of recurrence in patients with incidental or symptomatic VTE.[7,8]

Recently, a prospective multicenter cohort study of 695 cancer patients with incidental pulmonary embolism, mostly treated with low molecular weight heparin (LMWH), reported a 12-month rate of recurrent VTE of 6.0% and of major bleeding of 5.7%.[9] In addition, a post hoc analysis of the Hokusai VTE cancer study, including 331 patients with incidental VTE and 679 patients with symptomatic VTE treated with edoxaban or LMWH, showed a similar 6- and 12-month risk of recurrent VTE and major bleeding in patients with incidental or symptomatic VTE.[10]

The Caravaggio study compared the efficacy and safety of apixaban and dalteparin for the treatment of VTE in patients with cancer.[11] This study included both symptomatic and incidental VTE patients.

Essentials

- Knowledge about the optimal management of incidental venous thromboembolism (VTE) in patients with cancer is limited.
- Cancer patients with incidental or symptomatic VTE of the Caravaggio study were compared.
- Cancer patients with incidental VTE showed a considerable risk of recurrent VTE.
- They also showed a numerically lower risk of recurrence and higher risk of major bleeding.

We performed a predefined subanalysis of the Caravaggio study to investigate the clinical features and outcomes of incidental and symptomatic VTE in patients with cancer. The relative efficacy and safety of apixaban and dalteparin in patients with incidental and symptomatic VTE was also assessed.

2 | STUDY DESIGN AND METHODS

2.1 | Patients

The Caravaggio study was a multinational, randomized, investigator-initiated, open-label with blind outcome assessment, non-inferiority trial (ClinicalTrials.gov NCT03045406). Study protocol, inclusion and exclusion criteria, treatment allocation, and study outcome assessment

has been previously reported.[11] In brief, consecutive patients with cancer with symptomatic or incidental acute proximal deep vein thrombosis (DVT) or pulmonary embolism (PE) were randomized in a 1:1 ratio to receive 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, followed by 150 IU per kilogram once daily). The study treatment duration was 6 months. Incidental DVT or PE were events detected on imaging tests performed for reasons other than clinical suspicion of VTE. Incidental PE was defined as involving a segmental or more proximal pulmonary artery.[11] Of note, according to the study protocol the maximum proportion of patients with incidental VTE was set at 20% of the overall trial population and, consequently, the randomization of these patients in the study was terminated after the inclusion of 230 patients. Randomization was centrally performed through an interactive web-based randomization system and stratified by symptomatic versus incidental VTE and active cancer versus history of cancer.

2.2 | Outcomes

The primary efficacy outcome of Caravaggio was recurrent VTE occurring during the 6-month study period. The primary safety outcome was major bleeding, occurring during the study treatment and through 72 h after its last administration.

Secondary outcomes were: the composite of recurrent VTE and major bleeding, clinically relevant non-major bleeding, the composite of major bleeding and clinically relevant non-major bleeding, all-cause death.

Recurrent VTE was defined as the composite of objectively confirmed symptomatic, incidental, or fatal PE, symptomatic or incidental proximal DVT of the lower limbs, and symptomatic DVT of the upper limbs.[11]

Major bleeding was defined as clinically overt bleeding associated with one or more of the following: 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 such as intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal; bleeding resulting in surgical intervention; or fatal bleeding.[11]

Clinically relevant non-major bleeding was any acute clinically overt bleeding that does not meet the criteria for major bleeding but required medical attention.

All the study outcomes were centrally and blindly adjudicated.

2.3 | Statistical analysis

We compared the baseline patient characteristics of patients with incidental or symptomatic VTE by using the $\chi 2$ test for categorical variables or the Mann-Whitney *U* test for continuous variables. The categorization of patients as "incidental" or "symptomatic" VTE was based on the randomization strata. For categorical data, patients' characteristics are presented as frequencies (%) and standard deviation (SD); for continuous data, patients' characteristics are presented as mean and SD, if normally distributed median, or as interquartile range (Q1--Q3), if not normally distributed. Percentages are calculated on total number of patients in each group.

The incidental-to-symptomatic hazard ratio (HR) adjusted for the competing risk of death unrelated to event was computed for the all clinical outcomes other than death for any cause by resorting to the Fine & Gray regression model using symptomatic versus incidental VTE and active cancer versus history of cancer as covariates.[12] In a second model, adjustment was made for age, sex, index event (PE vs. DVT), anticoagulant treatment (apixaban vs. dalteparin), Eastern Cooperative Oncology Group (ECOG) performance status (2 vs. 0 or 1), cancer type (hematological, lung, breast, gastrointestinal, urogenital, gynecological, or other), previous VTE, and cancer stage (locally advanced or metastatic vs. no locally advanced or metastatic).

All comparisons are presented as HR and corresponding 95% confidence intervals (CIs). Study outcome events are presented as the numbers of first occurring events. The following subgroup analyses of risk of recurrent VTE and major bleeding in patients with incidental and symptomatic VTE were performed according to: (1) qualifying diagnosis of VTE, (2) history of VTE, (3) age, (4) site of cancer, (5) active cancer at randomization, (6) anticoagulant treatment. All data were analyzed with the use of SAS software, version 9.4 (SAS Institute).

3 | RESULTS

A total of 1155 cancer patients were included in the analysis. Of these, 230 (20%) patients had incidental VTE and 925 symptomatic VTE (80%). The main clinical characteristics of patients with incidental and symptomatic VTE are shown in Table 1. The index VTE event was PE with or without DVT in 176 patients (76.5%) with incidental VTE and in 462 patients (49.9%) with symptomatic VTE ($P < .001$) while DVT was the index VTE event in 54 (23.5%) and in 463 (50.1%) patients with incidental and symptomatic VTE, respectively ($P < .001$). A higher proportion of patients with incidental VTE had colorectal cancer than those with symptomatic VTE (27.8% vs. 18.4%, $P = .001$) while hematological cancer (3.9% vs. 8.6%, $P = .025$) and an ECOG score of 2 were more frequent in patients with symptomatic VTE (13.5% vs. 22.7%, $P = .002$). Patients with incidental VTE had a lower body weight (72.4±14.2 vs. 76.7±16.8, $P = .0005$), and more often an ECOG score of 0 (41.3% vs. 28.2%, $P = .001$) and an increased proportion of locally advanced or metastatic cancer (74.8% vs. 66.3%, $P = .013$) compared to patients with symptomatic VTE.

3.1 | Study outcomes

The rate of recurrent VTE during the study period was 4.3% in patients with incidental VTE and 7.4% in those with symptomatic VTE (HR 0.57, 95% CI 0.29–1.10, adjusted-HR 0.60, 95% CI

TABLE 1 Clinical characteristics of patients with incidental or symptomatic VTE

	Incidental VTE *N* = 230	Symptomatic VTE *N* = 925	*P*-value
Age, years, mean (SD)	67.3 (11.0)	68.0 (11.2)	.492
Male sex, *n* (%)	115 (50.0)	453 (49.0)	.780
Weight, kg, mean (SD)	72.4 (14.2)	76.7 (16.8)	.0005
Platelet count <100 000/μl, *n* (%)	9 (3.9)	34 (3.7)	.862
Creatinine clearance≤50 ml/min, *n* (%)	20 (8.7)	92 (9.9)	.563
Qualifying diagnosis of VTE, *n* (%)			
DVT only	54 (23.5)	463 (50.1)	<.001
PE with/without DVT	176 (76.5)	462 (49.9)	<.001
History of VTE, *n* (%)	20 (8.7)	86 (9.3)	.777
Active cancer, *n* (%)	224 (97.4)	900 (97.3)	.749
Recurrent locally advanced/ metastatic cancer	172 (74.8)	613 (66.3)	.013
Anti-cancer treatment, *n* (%)			
At enrollment	137 (59.6)	580 (62.8)	.380
Within previous 6 months	64 (27.8)	208 (22.5)	.087
During trial period	131 (57.0)	559 (60.4)	.336
Site of cancer			
Colorectal	64 (27.8)	170 (18.4)	.001
Lung	44 (19.1)	156 (16.9)	.416
Genitourinary	20 (8.7)	119 (12.9)	.082
Breast	24 (10.4)	131 (14.2)	.137
Pancreatic or hepato-biliary	19 (8.3)	68 (7.4)	.640
Gynecological	24 (10.4)	95 (10.3)	.941
Upper gastrointestinal	13 (5.7)	41 (4.4)	.432
Head and neck	4 (1.7)	18 (2.0)	.837
Bone/Soft tissue	3 (1.3)	15 (1.6)	.728
Skin- Melanoma	1 (0.4)	10 (1.1)	.366
Hematological malignancy	9 (3.9)	76 (8.6)	.025
Other	5 (2.2)	24 (2.6)	.715
ECOG, *n* (%)			
0	95 (41.3)	261 (28.2)	.001
1	104 (45.2)	454 (49.1)	.351
2	31 (13.5)	210 (22.7)	.002
Apixaban treatment, *n* (%)	116 (50.4)	460 (49.7)	.848
Dalteparin treatment, *n* (%)	114 (49.6)	465 (50.3)	.848

Abbreviations: DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.

0.30–1.19; Table 2). During the 6-month study period, 10 patients with incidental VTE experienced a recurrent VTE, three (1.3%) as DVT and seven (3.0%) as PE. Of these seven with recurrent PE, four were symptomatic, two incidental, and one undefined. Recurrent VTE occurred in 68 patients with symptomatic VTE, of whom 44 (4.8%) had PE (Table 2). Of these recurrences as PE, 20 were symptomatic, 16 incidental, and 8 undefined. Recurrent fatal PE occurred in 1 patient (0.4%) with incidental VTE and in 6 patients (0.6%) with symptomatic VTE (HR 0.65, 95% CI 0.08–5.38, adjusted HR 0.51, 95% CI 0.06–4.56). The time-course of VTE recurrence in patients with incidental and symptomatic VTE is shown in Figure 1, panel A.

Major bleeding occurred in 12 patients (5.2%) with incidental VTE and in 33 patients (3.6%) with symptomatic VTE (HR 1.43, 95% CI 0.74–2.77, adjusted HR 1.31, 95% CI 0.65–2.61). No fatal bleeding occurred in patients with incidental VTE while two fatal bleeds (0.2%) occurred in patients with symptomatic VTE. The time-course of major bleeding in patients with incidental and symptomatic VTE is shown in Figure 1, panel B.

TABLE 2 Study outcomes in patients with incidental and symptomatic VTE

	Incidental VTE N = 230	Symptomatic VTE N = 925	HR[b] (95% CI)	Adjusted HR[c] (95% CI)
Primary efficacy outcome				
Recurrent VTE[a], *n* (%)	10 (4.3)	68 (7.4)	0.57 (0.29, 1.10)	0.60 (0.30, 1.19)
Recurrent DVT, *n* (%)	3 (1.3)	25 (2.7)	0.47 (0.14, 1.54)	0.47 (0.14, 1.60)
Incidental, *n* (%)	0 (0.0)	4 (0.4)	NA	NA
Symptomatic, *n* (%)	3 (1.3)	20 (2.2)	0.59 (0.17, 1.96)	0.59 (0.17, 2.05)
Undetermined, *n* (%)	0 (0.0)	1 (0.1)	NA	NA
Recurrent PE, *n* (%)	7 (3.0)	44 (4.8)	0.62 (0.28, 1.36)	0.66 (0.29, 1.49)
Incidental, *n* (%)	2 (0.9)	16 (1.7)	0.49 (0.11, 2.11)	0.74 (0.16, 3.33)
Symptomatic, *n* (%)	4 (1.7)	20 (2.2)	0.78 (0.27, 2.28)	0.75 (0.25, 2.28)
Undetermined, *n* (%)	1 (0.4)	8 (0.9)	0.49 (0.06, 3.88)	0.38 (0.05, 3.20)
Fatal PE, *n* (%)	1 (0.4)	6 (0.6)	0.65 (0.08, 5.38)	0.51 (0.06, 4.56)
Primary safety outcome				
Major bleedings, *n* (%)	12 (5.2)	33 (3.6)	1.43 (0.74, 2.77)	1.31 (0.65, 2.61)
Major GI bleedings, *n* (%)	6 (2.6)	15 (1.6)	1.58 (0.61, 4.10)	1.29 (0.47, 3.51)
Major non-GI bleedings, *n* (%)	6 (2.6)	18 (1.9)	1.30 (0.52, 3.27)	1.39 (0.53, 3.65)
Fatal bleeding, *n* (%)	0 (0.0)	2 (0.2)	NA	NA
Secondary outcomes				
Recurrent VTE or major bleeding, *n* (%)	20 (8.7)	97 (10.5)	0.80 (0.50, 1.29)	0.79 (0.48, 1.29)
CRNMB[a], *n* (%)	11 (4.8)	76 (8.2)	0.56 (0.30, 1.05)	0.54 (0.28, 1.03)
Major and/or CRNMB, *n* (%)	22 (9.6)	104 (11.2)	0.82 (0.52, 1.29)	0.77 (0.48, 1.24)
Death for any cause, *n* (%)	61 (26.5)	227 (24.5)	1.05 (0.79–1.39)	0.97 (0.72–1.30)

Abbreviations: CRNMB, clinically relevant non-major bleeding; DVT, deep vein thrombosis; GI, gastrointestinal; HR, hazard ratio; NA, not available; PE, pulmonary embolism; VTE, venous thromboembolism.

[a]In patients who had more than one event, only the first event was counted.

[b]The incidental-to-symptomatic HR adjusted for the competing risk of death unrelated to event was computed for the all clinical outcomes other than death for any cause by resorting to the Fine & Gray regression model.

[c]Adjusted for age, sex, index event (PE vs. DVT), anticoagulant treatment (apixaban vs. dalteparin), Eastern Cooperative Oncology Group (ECOG) performance status (2 vs. 0 or 1), cancer type (hematological, lung, breast, gastrointestinal, urogenital, gynecological, or other), previous VTE, and cancer stage (locally advanced or metastatic vs. no locally advanced or metastatic).

The rate of clinically relevant non-major bleeding was 4.8% in patients with incidental VTE and 8.2% in those with symptomatic VTE (HR 0.56, 95% CI 0.30–1.05, adjusted HR 0.54, 95% CI 0.28–1.03).

Rate of all-cause mortality was 26.5% and 24.5% in patients with incidental and symptomatic VTE, respectively (HR 1.05, 95% CI 0.79–1.39; Table 2).

3.2 | Subgroup analyses

In the subgroup analyses performed, there were no significant differences between patients with incidental and symptomatic VTE in terms of risk of recurrent VTE and major bleeding. These results are shown in Table 3.

When comparing apixaban to dalteparin, the HR for recurrence in patients with symptomatic and incidental VTE was 0.73 (95% CI 0.45–1.19) and 0.41 (95% CI 0.11–1.56; *P* for interaction .42), and the HR for major bleeding in patients with symptomatic and incidental VTE was 0.93 (95% CI 0.47–1.83) and 0.96 (95% CI 0.31–2.96; *P* for interaction .96), respectively.

4 | DISCUSSION

In this study, the following main observations were made: (1) PE with or without DVT as index event, colorectal cancer, ECOG score of 0, and locally advanced or metastatic cancer were more frequent in patients with incidental VTE while DVT, hematological cancer, and ECOG score of 2 were more frequent in patients with symptomatic VTE; (2) despite anticoagulation, cancer patients with incidental VTE have a considerable rate of recurrent VTE; the 6-month risk of recurrent VTE is numerically lower compared to patients with symptomatic VTE; (3) the 6-month risk of major bleeding is numerically higher in patients with incidental VTE compared to those with symptomatic VTE, although not statistically significantly different; (4) the

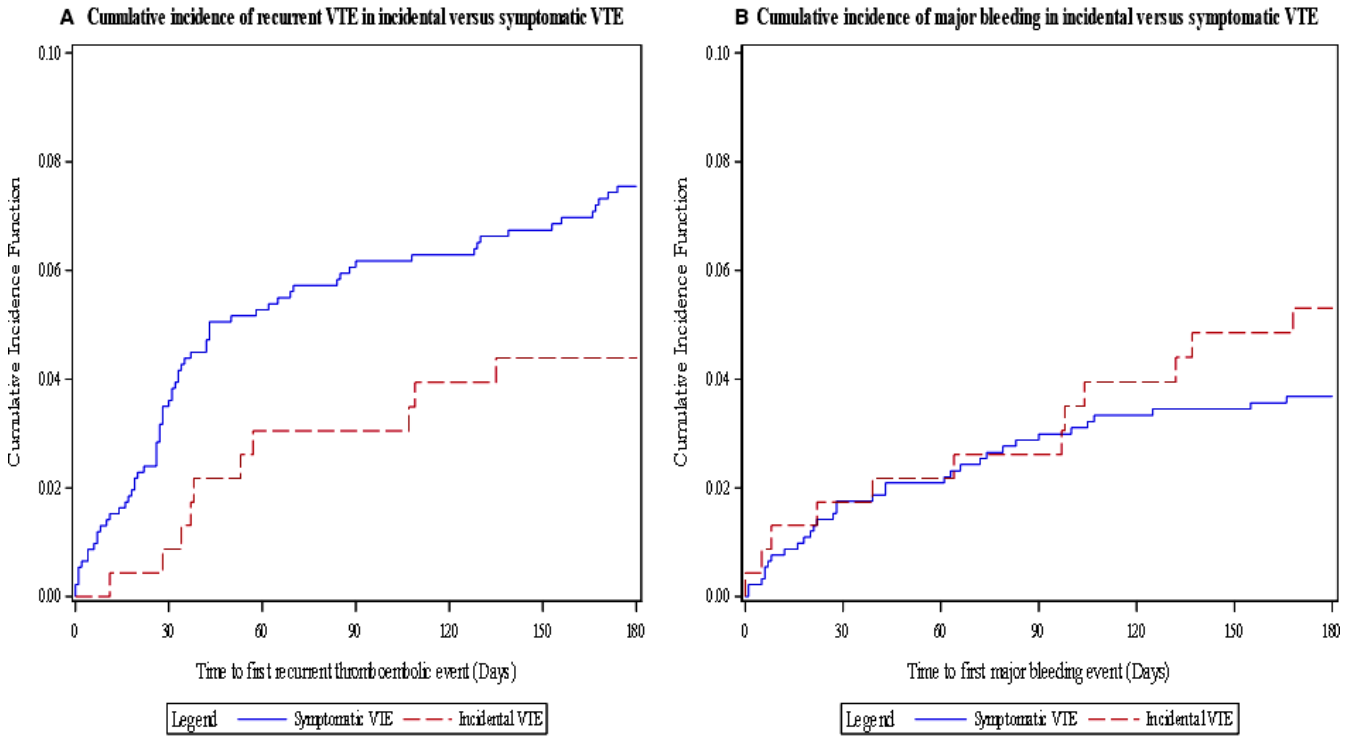

FIGURE 1 Cumulative incidence of (A) recurrent venous thromboembolism (VTE) and (B) major bleeding in incidental versus symptomatic VTE [Color figure can be viewed at wileyonlinelibrary.com]

rates for recurrence and major bleeding associated with apixaban and dalteparin were consistent in patients with symptomatic and incidental cancer-associated VTE.

The management of cancer patients with incidental VTE remains controversial. Recent guidelines advise anticoagulation treatment rather than observation in these patients, with low level of evidence.[13] Our findings of a 6-month rate of 4.3% of recurrence despite anticoagulation in cancer patients with incidental VTE support this recommendation. Our results could be related to the baseline characteristics of cancer patients with incidental VTE included in the Caravaggio study. Patients with incidental VTE had more often recurrent locally advanced or metastatic cancer, which is a well-known risk factor for recurrence. These patients were also affected by a higher proportion of colorectal cancer (41.7% vs. 30.2%) and PE as the index event. These findings are similar to those observed in the Hokusai VTE cancer study,[10] and are noteworthy as locally advanced or metastatic cancers and gastrointestinal cancers have been shown in the Caravaggio study to be associated with an increased risk of both recurrence and bleeding.

In our study, patients with incidental VTE had a numeric not statistically significant lower risk of recurrence than patients with symptomatic VTE. Similar results were observed in the post hoc analysis of the Hokusai VTE cancer study.[10] These results may be partially related to differences between cancer patients with symptomatic and incidental VTE and suggest that patients with symptomatic VTE may have an intrinsically higher risk of recurrence. Indeed, a recent meta-analysis showed a point estimation of the relative risk rate for recurrence of 0.77 (confidence limit 0.52–1.11) in cancer patients with incidental versus symptomatic VTE.[14] Individual patient meta-analyses with adequate adjustment for the intrinsic risk factors for VTE recurrence should definitively clarify this controversial issue.

Both in patients with incidental and symptomatic VTE, most of the recurrences occurred as symptomatic events and as PE. These findings reinforce the recommendations of optimal anticoagulant treatment in cancer patients with incidental VTE.

In our study, the rate of major bleeding was numerically higher in patients with incidental VTE (5.2%) than patients with symptomatic VTE (3.7%). This observation was also made in previous studies despite differences in study inclusion criteria, definition of major bleeding, and type of anticoagulation.[7,9,11,15] The increased risk of bleeding in patients with incidental VTE seen in our study and in the Hokusai cancer study[10] may be due to the high proportion of patients with colorectal cancer as it is well known that patients with cancer at this site have an increased risk of bleeding while on anticoagulation.[3,16] However, the risk of clinically relevant non-major bleeding was lower in patients with incidental VTE compared to patients with symptomatic VTE. Whether this argues against a real difference in bleeding risk between patients with symptomatic or incidental VTE is to be defined.

The estimated relative risk reduction for recurrent VTE in patients treated with apixaban or dalteparin was 39% in the overall Caravaggio population; this reduction was 59% and 27% for patients with incidental or symptomatic VTE, respectively. The rates of major bleeding were similar in patients with symptomatic and incidental VTE treated with apixaban or dalteparin. Based on these data,

TABLE 3 Subgroup analysis for recurrent VTE and for major bleeding

	Incidental VTE	Symptomatic VTE	HR (95% CI)	*P*-value*
Recurrent VTE				
Qualifying diagnosis of VTE, *n*/*N* (%)				
DVT only	2/54 (3.7)	44/463 (9.5)	0.37 (0.09, 1.53)	.3226
PE with/without DVT	8/176 (4.5)	24/462 (5.2)	0.84 (0.38, 1.87)	
History of VTE, *n*/*N* (%)				
Yes	1/20 (0.5)	8/86 (9.3)	0.52 (0.07, 1.87)	.9261
No	9/210 (4.2)	60/839 (7.2)	0.57 (0.29, 1.15)	
Age, years, *n*/*N* (%)				
<65 years	5/81 (6.2)	29/328 (8.8)	0.67 (0.26, 1.73)	.8078
≥65 and <75 years	4/84 (4.8)	26/314 (8.3)	0.55 (0.19, 1.56)	
≥75 years	1/65 (1.5)	13/283 (4.6)	0.32 (0.04, 2.44)	
Site of cancer, *n*/*N* (%)				
Solid tumor	10/221 (4.5)	64/849 (7.5)	0.57 (0.30, 1.11)	NA
Hematological cancer	0/9 (0.0)	4/76 (5.3)	NA	
Active cancer at randomization, *n*/*N* (%)				
Active	10/224 (4.4)	67/900 (7.4)	0.58 (0.30, 1.11)	NA
Past	0/6 (0.0)	1/25 (0.4)	NA	
Anticoagulant treatment, *n*/*N* (%)				
Apixaban	3/116 (2.5)	29/460 (6.3)	0.39 (0.12, 1.29)	.4291
Dalteparin	7/114 (6.1)	39/465 (8.4)	0.70 (0.32, 1.56)	
Major bleeding				
Qualifying diagnosis of VTE, *n*/*N* (%)				
DVT only	1/54 (1.9)	14/463 (3.0)	0.60 (0.08, 4.46)	.4043
PE with/without DVT	11/176 (6.2)	19/462 (4.1)	1.48 (0.71, 3.12)	
History of VTE, *n*/*N* (%)				
Yes	0/20 (0.0)	2/86 (2.3)	NA	NA
No	12/210 (5.7)	31/839 (3.7)	1.52 (0.78, 2.94)	
Age, years, *n*/*N* (%)				
<65 years	4/81 (4.9)	13/328 (4.0)	1.23 (0.40, 3.76)	.1853
≥65 and <75 years	3/84 (3.6)	14/314 (4.5)	0.77 (0.22, 2.67)	
≥75 years	5/65 (7.7)	6/283 (2.1)	3.62 (1.11, 11.84)	
Site of cancer, *n*/*N* (%)				
Solid tumor	12/221 (5.4)	33/849 (3.9)	1.37 (0.78, 2.41)	NA
Hematological cancer	0/9 (0.0)	0/76 (0.0)	NA	
Active cancer at randomization, *n*/*N* (%)				
Active	12/224 (5.4)	32/900 (3.6)	1.48 (0.76, 2.87)	NA
Past	0/6 (0.0)	1/25 (0.4)	NA	
Anticoagulant treatment, *n*/*N* (%)				
Apixaban	6/116 (5.2)	16/460 (3.5)	1.46 (0.57, 3.70)	.9636
Dalteparin	6/114 (5.3)	17/465 (3.7)	1.41 (0.56, 3.57)	

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; NA, not available; PE, pulmonary embolism; VTE, venous thromboembolism.

**P*-values for interaction.

apixaban appears to be a valid alternative to dalteparin for the treatment of incidental VTE in cancer patients.

The risk of all-cause mortality was similar between patients with symptomatic and incidental VTE. This finding is consistent with previous studies and indicates that there is not a difference in term of prognosis between these two groups of patients.[7,8]

Our study has several limitations. First, a limited number of patients with incidental VTE were randomized in the Caravaggio study as the proportion of these patients was set by the study protocol at a maximum of 20% of the study population. Second, symptoms in patients with incidental VTE were not adequately collected. Therefore, it was not possible to make a distinction between patients with truly asymptomatic clinically unsuspected pulmonary embolism and those with clinically unsuspected pulmonary embolism with symptoms attributed to the underlying disease or other clinical conditions. Third, the location of symptomatic and incidental PE was not made available, so that the clinical relevance of proximal or segmental PE in patients with incidental or symptomatic VTE was not assessed.

Our study also has strengths including the large sample size, the uniform treatment of patients with incidental and symptomatic VTE, the complete follow-up of almost all randomized patients, and the adjudication of the study outcome by an independent committee unaware of the treatment allocation.

In conclusion, in the Caravaggio trial baseline features were different in cancer patients with incidental and symptomatic VTE. Particular attention for incidental VTE should be paid in patients with colorectal cancer, and locally advanced or metastatic cancer. Cancer patients with incidental VTE showed a considerable risk of recurrent VTE. These results support the current guidelines that recommend anticoagulant treatment rather than observation in patients with incidental VTE. They also showed a numerically lower risk of recurrence and higher risk of major bleeding. The favorable relative profile of apixaban versus dalteparin was confirmed in patients with incidental VTE.

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CONFLICT OF INTERESTS

Michela Giustozzi, Ana Belen Ruperez Blanco, Sebastian Szmit, Nicolas Falvo have nothing to disclose. Jean M Connors has received honoraria/consulting fees from Abbott, Bristol-Myers Squibb, Pfizer, Takeda, and research funding to the institution from CSL Behring. Menno Huisman has received grants from ZonMw Dutch Healthcare Fund, Dutch Heart foundation, Boehringer-Ingelheim, Pfizer-BMS, Leo Pharma, Bayer Health Care. Rupert Bauersachs has received funding from Bayer, BMS, Boehringer Ingelheim, Daiichi-Sankyo and Pfizer. Alexander T Cohen has received honoraria/consulting fees from a number of companies including AbbVie, Alexion, Bristol-Myers Squibb, Pfizer, Bayer, Daiichi, and Sanofi, research funding from Boston Scientific, Bristol-Myers Squibb, Pfizer, Bayer, and Daiichi. Francesco Dentali has received honoraria/consulting fee from Bayer, BMS, Boehringer Ingelheim, Daiichi-Sankyo and Pfizer. Cecilia Becattini reports personal fees from Bristol Myers Squibb, Pfizer, Bayer Healthcare, and Daichi Sankyo outside the submitted work. Giancarlo Agnelli reports personal fees from Bristol Myers Squibb, Pfizer, Bayer Healthcare, and Daichi Sankyo outside the submitted work.

AUTHOR CONTRIBUTIONS

M.G., J.M.C, A.T.C., M.H., R.B., C.B., and G.A. contributed substantially to the study design, data analysis and interpretation, and writing of the manuscript. A.B.R.S., S.S, N.F, and F.D. contributed substantially to data interpretation and writing the manuscript. All the authors reviewed and approved the final manuscript.

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REFERENCES

1. Cohen AT, Katholing A, Rietbrock S, Bamber L, Martinez C. Epidemiology of first and recurrent venous thromboembolism in patients with active cancer. A population-based cohort study. *Thromb Haemost*. 2017;117(1):57-65.
2. Lloyd AJ, Dewilde S, Noble S, Reimer E, Lee AYY. What impact does venous thromboembolism and bleeding have on cancer patients' quality of life? *Value Health*. 2018;21(4):449-455.
3. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J*. 2020;41(4):543-603.
4. Meyer HJ, Wienke A, Surov A. Incidental pulmonary embolism in oncologic patients-a systematic review and meta-analysis. *Support Care Cancer*. 2021;29(3):1293-1302.
5. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of chest physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 Suppl):e419S-e496.
6. Lyman GH, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of clinical oncology clinical practice guideline update. *J Clin Oncol*. 2013;31(17):2189-2204.
7. den Exter PL, Hooijer J, Dekkers OM, Huisman MV. Risk of recurrent venous thromboembolism and mortality in patients with cancer incidentally diagnosed with pulmonary embolism: a comparison with symptomatic patients. *J Clin Oncol*. 2011;29(17):2405-2409.
8. Dentali F, Ageno W, Becattini C, et al. Prevalence and clinical history of incidental, asymptomatic pulmonary embolism: a meta-analysis. *Thromb Res*. 2010;125(6):518-522.
9. Kraaijpoel N, Bleker SM, Meyer G, et al. Treatment and long-term clinical outcomes of incidental pulmonary embolism in patients with cancer: an international prospective cohort study. *J Clin Oncol*. 2019;37(20):1713-1720.
10. Mulder FI, Di Nisio M, Ay C, et al. Clinical implications of incidental venous thromboembolism in cancer patients. *Eur Respir J*. 2020;55(2):1901697.
11. Agnelli G, Becattini C, Meyer G, et al. Apixaban for the treatment of venous thromboembolism associated with cancer. *N Engl J Med*. 2020;382(17):1599-1607.

12. Fine JPGR. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496-509.
13. Lyman GH, Carrier M, Ay C, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. *Blood Adv*. 2021;5(4):927-974.
14. Moik F, Posch F, Zielinski C, Pabinger I, Ay C. Direct oral anticoagulants compared to low-molecular-weight heparin for the treatment of cancer-associated thrombosis: updated systematic review and meta-analysis of randomized controlled trials. *Res Pract Thromb Haemost*. 2020;4(4):550-561.
15. van der Hulle T, den Exter PL, Planquette B, et al. Risk of recurrent venous thromboembolism and major hemorrhage in cancer-associated incidental pulmonary embolism among treated and untreated patients: a pooled analysis of 926 patients. *J Thromb Haemost*. 2016;14(1):105-113.
16. Mulder FI, van Es N, Kraaijpoel N, et al. Edoxaban for treatment of venous thromboembolism in patient groups with different types of cancer: results from the Hokusai VTE cancer study. *Thromb Res*. 2020;185:13-19.

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