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Original Research

Recurrent venous thromboembolism and major bleeding in patients with localised, locally advanced or metastatic cancer: an analysis of the Caravaggio study

Melina Verso [a], Giancarlo Agnelli [a,*], Andrés Munoz [b], Jean M. Connors [c], Olivier Sanchez [d,e], Menno Huisman [f], Benjamin Brenner [g], Gualberto Gussoni [h], Alexander T. Cohen [i], Cecilia Becattini [a]

[a] *Internal, Vascular and Emergency Medicine – Stroke Unit, University of Perugia, Perugia, Italy*
[b] *Medical Oncology Service, Hospital General Universitario Gregorio Marañón, Universidad Complutense, Madrid, Spain*
[c] *Brigham and Women's Hospital, Hematology Division, Harvard Medical School, Boston, United States*
[d] *Université de Paris, Service de Pneumologie et Soins Intensifs, AP-HP, Hôpital Européen Georges Pompidou, INSERM UMR-S 1140 Innovative Therapies in Haemostasis, F-75006, Paris, France*
[e] *F-CRIN INNOVTE, F-42000, St-Etienne, France*
[f] *Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands*
[g] *Institute of Hematology and BMT Rambam Health Care Campus Technion, Israel Institute of Technology Haifa, Israel*
[h] *Federazione delle Associazioni dei Dirigenti Ospedalieri Internisti (FADOI) Research Center, Milan, Italy*
[i] *Guy's and St. Thomas' NHS Foundation Trust Hospital, King's College London, London, United Kingdom*

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Abstract ***Background:*** Patients with cancer-associated venous thromboembolism (VTE) have a high risk of VTE recurrence and anticoagulant treatment–related bleeding, but the correlation of these risks with the cancer stage is unclear.
Methods: We evaluated the risks of VTE recurrence and treatment-related major bleeding according to the cancer stage in patients with VTE and solid cancer randomised to apixaban or dalteparin in the Caravaggio study. Cancer stage was categorised by expert cancer physicians according to pre-specified criteria, and study outcomes were adjudicated by an independent committee unaware of cancer stage and treatment allocation.
Results: Of the 1034 patients included in this analysis, 217 (21.0%) had localised cancer, 279 (27.0%) locally advanced cancer and 503 (48.7%) metastatic cancer. Cancer stage was undetermined in 35 patients (3.4%). VTE recurrence and major bleeding rates were 2.8% and 3.2% in patients with localised cancer, respectively. In comparison to patients with localised cancer,

* *Corresponding author*: Internal Vascular and Emergency Medicine- Stroke Unit, University of Perugia, 06123, Perugia, Italy.
E-mail address: giancarlo.agnelli@unipg.it (G. Agnelli).

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the VTE recurrence rate was higher in patients with locally advanced cancer (7.5%, hazard ratio [HR] = 2.8, 95% confidence interval [CI] = 1.1–6.9) and metastatic cancer (8.7%, HR = 3.3, CI = 1.4–7.7, CI). Patients with metastatic cancer had numerically increased major bleedings compared to those with localised cancer (5.2%, HR = 1.65, CI = 0.7–3.8). The efficacy and safety of apixaban and dalteparin across patients with different cancer stages were consistent with the findings observed in the overall patients with cancer randomised in the study.

Conclusions: Patients with locally advanced and metastatic cancer have a higher rate of VTE recurrence than patients with localised cancer with no statistically significant difference in treatment-related major bleeding.

1. Introduction

Several studies showed that patients with cancer and venous thromboembolism (VTE) have a higher risk of VTE recurrence and anticoagulant treatment–related bleeding than patients without cancer [1,2]. This observation has been confirmed in recently published studies [3,4].

Predictors of VTE recurrence in patients with cancer include age [5–7], cancer site [8–11], advanced stage [2,12–14], disease progression [8], cancer histology [5,8,13] and biomarkers [15,16]. Recurrent VTE was also reported to be high in patients who had a diagnosis of cancer made in the three months prior to the presentation with VTE [5] and in those treated with chemotherapy [17,18].

Risk factors associated with an increased risk of anticoagulant treatment–related bleeding include age older than 75 years [5,19,20], history of major bleeding (MB) [5], anaemia [19,20], thrombocytopenia [9,19,20], chronic kidney disease [5,21], site of cancer [9,12,19,21,22,23] and concomitant anticancer therapies [19]. The risk of bleeding was also shown to be higher in patients with extensive than in those with limited cancer disease [2,4,6,19,21].

Most of the observations on the risk factors for VTE recurrence and bleeding in patients with cancer-associated VTE were made many years ago in patients treated with low-molecular-weight heparin followed by vitamin K antagonists. Contemporary data for the use of Direct Oral AntiCoagulant (DOAC) in combination with the new cancer treatments are needed. In addition, categorisation of the cancer stage in most of the previous studies was based on the clinical report forms provided by the local investigators without central adjudication.

The Caravaggio study evaluated the efficacy and safety of apixaban and dalteparin in the treatment of VTE in patients who received contemporary anticancer treatment. The aim of this analysis of the Caravaggio study was to evaluate the rates of recurrent VTE and MB in patients with solid cancer categorised according to localised, locally advanced or metastatic disease. For the purpose of this analysis, to provide a careful and consistent categorisation of the cancer stage, the clinical report forms were reviewed by an independent panel of expert cancer physicians according to pre-specified criteria. The efficacy and safety of apixaban in comparison to those of dalteparin in patients with different stage of cancer were also evaluated.

2. Material and methods

2.1. Study design and study population

Caravaggio was a multinational, randomised, open-label, non-inferiority study with blind assessment of all study outcomes [24]. A detailed description of the study design was previously published [25], and the study protocol is available at ClinicalTrials.gov (NCT05406304).

The Caravaggio study included patients with active cancer or cancer diagnosed within 2 years before randomisation who presented with symptomatic or incidental proximal lower limb deep vein thrombosis or symptomatic or incidental pulmonary embolism. Incidental deep vein thrombosis and/or pulmonary embolism were events detected on imaging tests performed for reasons other than confirming the clinical suspicion of VTE. To be included in the study, patients with incidental pulmonary embolism were required to have the involvement of a segmental or more proximal pulmonary artery. Patients with basal-cell or squamous-cell carcinoma of the skin, primary brain tumour or known intra-cerebral metastases and patients with acute leukaemia were excluded from the study. Other main exclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status III or IV; life expectancy of less than 6 months; active or high risk of bleeding contraindicating anticoagulant treatment; concomitant use of thienopyridines or aspirin over 165 mg or dual antiplatelet therapy;

haemoglobin levels lower than 8 g/dL or platelet count lower than 75×10^9/L; severe renal or liver insufficiency.

2.2. Eligibility criteria

Only patients with solid active cancer were included in this analysis. Patients with active cancer were those with cancer diagnosed within the past 6 months, cancer for which anticancer treatment was being given at the time of enrollment or during 6 months after randomisation, or locally advanced or metastatic cancer. Patients with a history of cancer (those in whom a diagnosis had been made within 2 years before enrollment not fulfilling the criteria for active cancer) and those with haematological malignancy were excluded from this analysis.

Patients with active solid cancers were categorised as follows:

1. *Patients with localisedcancer:* patients with cancer that is limited to the primary site, without evidence of spread to different areas
2. *Patients with locally advanced cancer*: patients with cancer that has spread to nearby lymph nodes, tissues or organs
3. *Patients with metastatic cancer*: patients with cancer that has spread from the original site to distant areas of the body
4. *Patients with unknown stage of cancer*: patients without sufficient information to ascertain the stage of cancer.

For the purpose of this analysis, the clinical records of the patients were analysed by two expert cancer physicians unaware of study treatment allocation. Patients were determined to have localised, locally advanced, metastatic cancer or unknown stage of cancer according to pre-specified criteria. As a result of central adjudication and classification of the cancer stage, the number of patients in stage categories can differ from those previously reported that were based on data provided by the study investigators and dichotomised as localised or locally advanced and metastatic cancer.

2.3. Anticoagulant treatment

Patients with cancer in the apixaban group received apixaban at a dose of 10 mg twice daily for the first 7 days and 5 mg twice daily thereafter. Patients with cancer in the dalteparin group received 200 IU/kg during the first month, followed by 150 IU/kg for the remainder of the treatment period. The study treatment duration was 6 months.

2.4. Anticancer treatment

Patients with cancer were categorised as 'treated with anticancer agents' and 'not treated with anticancer agents'. Patients were categorised as treated with anticancer agents if they were receiving these agents, as monotherapy or in combination regimen, at study inclusion or started during the study period. Anticancer agents were classified, according to the mechanism of action, as antimetabolites, platinum-based chemotherapy, monoclonal antibodies, taxanes, hormonal agents for the breast cancer, hormonal agents for prostate cancer, topoisomerase inhibitors, alkylating agents, anthracyclines, vinca alkaloids, kinase inhibitors, immunomodulating agents, proteasome inhibitors and antitumour antibiotics. Patients were categorised as not treated with anticancer agents if they neither were receiving these agents at study inclusion nor started them during the study period.

2.5. Outcome measures

Primary analysis outcomes were recurrent VTE and MB. Recurrent VTE was defined as objectively confirmed recurrent proximal deep vein thrombosis of the lower limbs (symptomatic or incidental), symptomatic deep vein thrombosis of the upper limbs and pulmonary embolism (symptomatic, incidental or fatal) occurring during the 6-month study period.

MB events were classified using the European Medicine Agency (EMA) criteria which include the four International Society of Haemostasis and Thrombosis (ISTH) items with the addition of bleeding requiring surgical intervention [26].

We also evaluated the rates of clinically relevant non-major bleeding (CRNMB), the composite of MB and CRNMB, all-cause death and event-free survival as secondary study outcomes. CRNMB events were defined as acute clinically overt bleeding that did not meet the criteria for MB but required non-surgical, medical intervention by a healthcare professional, hospitalisation or increased level of care or prompting evaluation [26]. Event-free survival was defined as the absence of recurrent VTE, MB and death.

An independent adjudication committee, unaware of treatment allocation, adjudicated all suspected recurrent VTE and bleeding outcomes and classified causes of deaths.

2.6. Statistical analysis

The baseline characteristics of patients with localised, locally advanced and metastatic cancer were analysed by using the χ^2 test for categorical variables or the Mann–Whitney U test for continuous variables. 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 the total number of patients in each group. Cumulative incidences are presented as proportion with 95% confidence interval (CI). Time-to-event curves were calculated using the

Kaplan–Meier method. Time-to-outcome event was analysed using a Cox proportional hazard model.

The event hazard ratio (HR) for recurrent VTE and bleeding (major and CRNMB individually) in patients with different stage categories adjusted for the competing risk of death unrelated to event was computed by resorting to the Fine & Gray regression model. For all-cause death and event-free survival (absence of recurrence, bleeding and death), the same Fine & Gray regression model was used to calculate the HR without adjustment for the competing risk.

In a second model, adjustment was made for age, sex, index event (pulmonary embolism versus deep vein thrombosis), incidental versus symptomatic VTE, anticoagulant treatment (apixaban versus dalteparin), ECOG performance status (2 versus 0 or 1), cancer site and adenocarcinoma versus other histologies.

The efficacy and safety of apixaban in comparison to those of dalteparin in patients in different categories were also analysed.

All data were analysed using SAS software, version 9.4 (SAS Institute).

3. Results

3.1. Patients

Of the 1034 patients included in this analysis (90.0% of randomised patients), 217 (21.0%) had localised cancer, 279 (27.0%) locally advanced cancer and 503 (48.7%) metastatic cancer (Table 1). Cancer stage was undefined in 35 (3.4%). Thirty-one patients with a history of cancer were excluded from this analysis as well as 90 patients with haematological cancer. The distribution of patients according to the cancer stage in the general study population and according to the antithrombotic treatment is shown in Table 1. The demographic and clinical characteristics of patients with localised, locally advanced and metastatic cancer are shown in Table 2. Patients with locally advanced or metastatic cancer more often had a reduced platelet count and gynaecological cancer and less often had breast and genitourinary cancer than patients with localised cancer. Adenocarcinoma and anticancer treatment were more common in patients with metastatic cancer than in patients with localised cancer.

Table 1
Distribution of patients according to the cancer stage in the overall study population and according to antithrombotic treatment.

Variables	Overall population (N = 1034)	Apixaban (N = 525)	Dalteparin (N = 509)	P value
Localised cancer, n (%)	217 (21.0)	116 (22.1)	101 (19.8)	0.4010
Locally advanced cancer, n (%)	279 (27.0)	146 (27.8)	133 (26.1)	0.5752
Metastatic cancer, n (%)	503 (48.7)	242 (46.1)	261 (51.3)	0.1056
Unknown cancer extension, n (%)	35 (3.4)	21 (4.0)	14 (2.8)	0.3042

Notes:
Patients with haematological malignancy and a history of cancer were not included in this analysis.
Percentages were calculated for the total number of patients overall and for each treatment group.
The comparison between cancer stages in the two treatment groups were tested by using the Fisher exact test.

The demographic and clinical characteristics of patients with localised, locally advanced and metastatic cancer according to the anticoagulant study treatment are shown in Tables S1 and S2 in the Supplementary Appendix. The different classes of pharmacological anticancer therapies in patients with localised, locally advanced or metastatic cancer are reported in Table 3.

3.2. Study outcomes

The rate of VTE recurrence was 2.8% in patients with localised cancer (Table 4). Compared to patients with localised cancer, the VTE recurrence rate was higher in patients with locally advanced cancer (7.5%, HR = 2.80, 95% CI = 1.14–6.92%) and metastatic cancer (8.7%, HR = 3.30, 95% CI = 1.40–7.73) (Table 4).

The rate of MB was 3.2% in patients with localised cancer. The rate of MB was 3.2% in patients with locally advanced cancer (HR = 1.01, 95% CI = 0.38–2.71%, compared with patients with localised cancer) and 5.2% in patients with metastatic cancer (HR = 1.65, 95% CI = 0.71–3.79, compared with patients with localised cancer) (Table 4). Recurrent VTE and MB in patients with localised, locally advanced and metastatic stages in different cancer sites are reported in Table S3 in the supplementary appendix.

The rate of CRNMB was 6.0% in patients with localised cancer, 9.7% in patients with locally advanced cancer (HR = 1.66, 95% CI = 0.86–3.21, compared with patients with localised cancer) and 7.6% in patients with metastatic cancer (HR = 1.29, 95% CI = 0.69–2.42, compared with patients with localised cancer) (Table 4).

The rates of clinically relevant bleeding, the composite of MB and CRNMB, was 9.2% in patients with localised cancer, 12.3% and 11.9% in patients with locally advanced cancer and metastatic cancer, respectively, with no statistically significant difference between the rates in the two more advanced stages in comparison to localised cancer (Table 4).

Death of any cause was higher and event-free survival lower in patients with locally advanced and metastatic cancer than in patients with localised cancer (Table 4).

The comparative efficacy (VTE recurrence) and safety (MB) of apixaban and dalteparin were similar across patients of different cancer stages (Table S4 and Table S5 in the Supplementary Appendix). Main

Table 2
Demographic and clinical characteristics of patients with localised, locally advanced and metastatic cancer.

Variables	Patients with localised cancer (N = 217)	Patients with locally advanced cancer (N = 279)		Patients with metastatic cancer (N = 503)		Patients with unknown extension of cancer (N = 35)	
	n (%)	n (%)	p value[a]	n (%)	p value[a]	n (%)	p value[a]
Age (yr. ± SD)	68.5 ± 12.1	67.7 ± 10.9	0.280	67.1 ± 11.0	0.721	68.7 ± 9.5	0.676
Male	108 (49.8%)	125 (44.8%)	0.272	250 (49.7%)	0.987	22 (62.9%)	0.150
Platelet count<100.000 per mm3	2 (0.9%)	11 (3.9%)	0.046	22 (4.4%)	0.021	1 (2.9%)	0.355
Creatinine clearance ≤50 ml per min	20 (9.2%)	25 (9.0%)	0.958	50 (9.9%)	0.748	3 (8.6%)	0.910
Pulmonary embolism ± DVT	119 (54.8%)	145 (52.0%)	0.526	294 (58.4%)	0.369	21 (60.0%)	0.568
DVT only	98 (45.2%)	134 (48.0%)		209 (41.6%)		14 (40.0%)	
Symptomatic VTE	178 (82.0%)	220 (78.9%)	0.378	395 (78.5%)	0.285	26 (74.3%)	0.279
Incidental VTE	39 (18.0%)	59 (21.1%)		108 (21.5%)		9 (25.7%)	
Colorectal	40 (18.4%)	66 (23.7%)	0.159	118 (23.5%)	0.135	5 (14.3%)	0.552
Lung	35 (16.1%)	55 (19.7%)	0.304	96 (19.1%)	0.345	9 (25.7%)	0.166
Breast	46 (21.2%)	34 (12.2%)	0.007	62 (12.3%)	0.002	7 (20.0%)	0.872
Genitourinary	44 (20.3%)	20 (7.2%)	<0.0001	67 (13.3%)	0.018	3 (8.6%)	0.099
Gynaecological	14 (6.5%)	52 (18.6%)	<0.0001	47 (9.3%)	0.201	1 (2.9%)	0.404
Pancreatic or hepatobiliary	13 (6.0%)	22 (7.9%)	0.414	46 (9.1%)	0.157	5 (14.3%)	0.077
Upper gastrointestinal	7 (3.2%)	11 (3.9%)	0.810	35 (7.0%)	0.056	1 (2.9%)	1.000
Head and neck	6 (2.8%)	8 (2.9%)	1.000	5 (1.0%)	0.097	1 (2.9%)	1.000
Bone/soft tissue	4 (1.8%)	3 (1.1%)	0.705	6 (1.2%)	0.499	0 (0.0%)	1.000
Skin melanoma	1 (0.5%)	3 (1.1%)	0.635	5 (1.0%)	0.674	1 (2.9%)	0.259
Other cancer site	7 (3.2%)	5 (1.8%)	0.381	16 (3.2%)	1.000	2 (5.7%)	0.362
Adenocarcinoma	132 (60.8%)	190 (68.1%)	0.092	366 (72.8%)	0.001	20 (57.1%)	0.679
Other histologies	85 (39.2%)	89 (31.9%)		137 (27.2%)		15 (42.9%)	
Cancer treatment:							
- within 6 months[b]	74 (34.1%)	71 (25.4%)		99 (19.7%)		8 (22.9%)	
- ongoing at inclusion	117 (53.9%)	174 (62.4%)	0.099	343 (68.2%)	0.0001	22 (62.9%)	0.419
- started after inclusion	48 (22.1%)	79 (28.3%)	0.117	152 (30.2%)	0.026	6 (17.1%)	0.506
ECOG PS[c] = 0	79 (36.4%)	85 (30.5%)	0.074	126 (25.0%)	0.0004	15 (42.9%)	0.524
ECOG PS = 1	109 (50.2%)	136 (48.7%)		255 (50.7%)		14 (40.0%)	
ECOG PS = 2	29 (13.4%)	58 (20.8%)		122 (24.3%)		6 (17.1%)	

DVT = deep vein thrombosis; SD = standard deviation; VTE = venous thromboembolism.
Notes:
Patients with haematological malignancy and a history of cancer were not considered in this analysis.
Percentages were calculated for the total number of patients in each cancer stage.
[a] in comparison with localised cancer.
[b] cancer treatment started in the previous 6 months and discontinued at randomisation.
[c] ECOG PS: Eastern Cooperative Oncology Group (ECOG) performance status.

outcomes among patients with not resected locally advanced cancer according to the antithrombotic treatment are reported in the Table S6 in the Supplementary Appendix.

The time course of VTE recurrence and MB in the localised, locally advanced or metastatic cancer are shown in Figs. 1 and 2, respectively. The time course of CRNMB and death are shown in Figs. S1 and S2 in the Supplementary Appendix.

4. Discussion

This analysis shows that patients with locally advanced or metastatic cancer treated with contemporary anticoagulant and anticancer agents have a higher rate of VTE recurrence than patients with localised cancer. Although no significant difference was observed in anticoagulant treatment–related bleeding complications across the different cancer stage categories, a numerical increase in MB was observed in patients with metastatic cancer.

Several mechanisms have been proposed to explain the thrombus generation and progression in patients with metastatic cancer [27–32]. These include the elevated activity of microparticle-associated tissue factor [27,28], the impairment of the activated protein C resistance induced by the host immune response [29,30], the expression of C-type lectin-like receptor 2 (CLEC-2), the activation of platelet receptor by tumour cells [31] and the generation of neutrophil extracellular traps (NETs) [32].

In the Caravaggio study, the proportion of patients with metastatic cancer was about 50%. This result is in line with the rate of metastatic cancer reported in

Table 3
Different classes of pharmacological anticancer therapies in patients with localised, locally advanced and metastatic cancer.

Variables	Patients with localised cancer (N = 217)	Patients with locally advanced cancer (N = 279)		Patients with metastatic cancer (N = 503)		Patients with unknown cancer stage (N = 35)	
	n (%)	n (%)	p value vs localised cancer	n (%)	p value vs localised cancer	n (%)	p value vs localised cancer
Antimetabolites	41 (18.9%)	72 (25.8%)	0.069	134 (26.6%)	0.026	11 (31.4%)	0.089
Platinum-based chemotherapy	35 (16.1%)	66 (23.7%)	0.039	105 (20.9%)	0.140	7 (20.0%)	0.568
Monoclonal antibodies	21 (9.7%)	34 (12.2%)	0.377	74 (14.7%)	0.067	1 (2.9%)	0.185
- Antiangiogenic monoclonal antibodies	4 (1.8%)	14 (5.0%)	0.088	29 (5.8%)	0.020	0 (0.0%)	1.000
- Immune checkpoint inhibitors	5 (2.3%)	12 (4.3%)	0.320	25 (5.0%)	0.108	0 (0.0%)	1.000
- Non-antiangiogenic monoclonal antibodies	12 (5.5%)	10 (3.6%)	0.380	22 (4.4%)	0.566	1 (2.9%)	1.000
Taxanes	18 (8.3%)	32 (11.5%)	0.244	69 (13.7%)	0.040	2 (5.7%)	0.600
Hormonal therapy (breast)	23 (10.6%)	12 (4.3%)	0.008	23 (4.6%)	0.004	5 (14.3%)	0.560
Hormonal therapy (prostate)	8 (3.7%)	9 (3.2%)	0.807	32 (6.4%)	0.213	0 (0.0%)	0.604
Topoisomerase inhibitors	6 (2.8%)	9 (3.2%)	0.799	39 (7.8%)	0.011	6 (17.1%)	0.002
Alkylating agents	10 (4.6%)	11 (3.9%)	0.823	9 (1.8%)	0.041	1 (2.9%)	1.000
Anthracyclines	6 (2.8%)	13 (4.7%)	0.348	8 (1.6%)	0.377	0 (0.0%)	1.000
Vinca alkaloids	3 (1.4%)	5 (1.8%)	1.000	12 (2.4%)	0.571	0 (0.0%)	1.000
Kinase inhibitors	3 (1.4%)	10 (3.6%)	0.162	52 (10.3%)	<0.0001	2 (5.7%)	0.143
Other immunomodulating agents	0 (0.0%)	0 (0.0%)		0 (0.0%)		0 (0.0%)	
Proteasome inhibitors	0 (0.0%)	0 (0.0%)		0 (0.0%)		0 (0.0%)	
Antitumour antibiotics	0 (0.0%)	2 (0.7%)	0.507	0 (0.0%)		0 (0.0%)	
None of the above agents	6 (2.8%)	10 (3.6%)	0.798	16 (3.2%)	1.000	3 (8.6%)	0.114

previous trials evaluating anticoagulant treatment in cancer-associated thrombosis [33–37].

Several studies showed that the metastatic stage is a risk factor for the first VTE event in patients with cancer [38–43]. However, data on the role of advanced stages of cancer as a predictor of VTE recurrence are less consistent [5,8,12,13,33,44]. Most of the previous studies indicated that patients with cancer with metastatic disease have a 2- to 4-fold increased risk of VTE recurrence in comparison with less extensive stages; however, the risk of VTE recurrence in patients with locally advanced disease is unknown.

In our analysis, a different distribution of cancer sites was observed in patients with advanced or metastatic cancer in comparison to those with localised cancer. Patients with locally advanced or metastatic cancer more often had gynaecological cancer and less often breast and genitourinary cancer than patients with localised cancer. In addition, in line with a previous study [14], adenocarcinoma was the most common histological type in patients with metastatic cancer.

A numerical non-statistically significant increase in the risk for MB was observed in metastatic cancer in comparison to other cancer stages, confirming the results of a post hoc analysis of the CATCH study [45]. In our analysis, no significant difference was observed in clinically relevant bleeding, the composite of MB and CRNMB, across the different cancer stages.

The observation of an increased rate of VTE recurrence in patients with cancer with locally advanced or metastatic disease has some potential clinical implications. These patients deserve a particularly careful management and may require a prolonged duration of the anticoagulant treatment.

In our analysis, the comparative efficacy of apixaban and dalteparin was similar across patients in different cancer stage categories and consistent with that seen in the general study population (overall risk reduction = 37%). In particular, apixaban in comparison with dalteparin was associated with a non-significant 26% risk reduction in VTE recurrence in patients with metastatic cancer (46% in patients with locally advanced cancer). No increased risk of MB was observed in patients with locally advanced and metastatic cancer treated with apixaban in comparison to dalteparin. These findings reinforce the use of apixaban as a valid and more patient-friendly choice than dalteparin for the treatment of a large spectrum of patients with cancer-associated VTE including patients with locally advanced and metastatic cancer. This is particularly relevant when considering the extended treatment of VTE-associated thrombosis. Indeed, owing to the high rate of VTE recurrence, patients with locally advanced and metastatic cancer are candidates for extended anticoagulant treatment beyond six months. Of note, in the Caravaggio study, about 80% of patients with locally advanced cancer and more than 60% of patients with metastatic cancer were alive at 6 months after study randomisation.

Table 4
Study outcomes in patients with localised, locally advanced and metastatic cancer.

Variables	Localised cancer (N = 217)	Locally advanced cancer (N = 279)		Metastatic cancer (N = 503)		Unknown extension of cancer (N = 35)	
	n (%)	n (%)	HR[a]	n (%)	HR[a]	n (%)	HR[a]
Recurrent VTE	6 (2.8)	21 (7.5)	2.80 (1.14–6.92)	44 (8.7)	3.30 (1.40–7.73)	2 (5.7)	–
MB	7 (3.2)	9 (3.2)	1.01 (0.38–2.71)	26 (5.2)	1.65 (0.71–3.79)	2 (5.7)	–
CRNMB	13 (6.0)	27 (9.7)	1.66 (0.86–3.21)	38 (7.6)	1.29 (0.69–2.42)	3 (8.6)	1.49 (0.43–5.16)
MB + CRNMB	20 (9.2)	34 (12.2)	1.35 (0.78–2.34)	60 (11.9)	1.34 (0.81–2.21)	5 (14.3)	1.64 (0.62–4.31)
Death from any cause	23 (10.6)	57 (20.4)	2.08 (1.28–3.37)	187 (37.2)	4.29 (2.78–6.62)	7 (20)	2.05 (0.90–4.68)
Event-free survival	187 (86.2)	207 (74.2)	2.01 (1.32–3.08)	295 (58.6)	3.62 (2.46–5.32)	26 (74.3)	2.06 (1.00–4.27)

CRNMB = clinically relevant non-major bleeding; HR = hazard ratio; MB = major bleeding; VTE = venous thromboembolism.
Notes:
Patients with haematological malignancy and a history of cancer were not considered in this analysis.
Percentages are calculated on the total number of patients in each cancer extension group.
A cut-off of 210 days is considered for the clinical outcome death from any cause. A cut-off of 180 days is considered for the other clinical outcomes.
MB and CRNMB within 180 days from randomisation and within 3 days from the last study drug administration are considered in this table.
Event-free survival is defined as the absence of recurrent VTE, MB or death from any cause.
The hazard ratio adjusted for the competing risk of death unrelated to event was computed for all the clinical outcomes (except for death from any cause and event-free survival) by resorting to the Fine & Gray regression model using cancer extension as fixed effect.
For the clinical outcomes all-cause death and event-free survival, the same Fine & Gray regression model was used to calculate the HR without adjustment for the competing risk.
[a] in comparison with localised cancer.

Our analysis has some limitations. Patients with brain metastases were not included in the Caravaggio study. Ninety patients included in Caravaggio were excluded from this analysis owing to the haematological malignancy. Furthermore, the sample size of patients in the different stage categories was related to a post hoc adjudication and was not stratified a priori.

Our analysis has some strengths that include the large sample size and the proportion of patients with advanced cancer or metastatic. In addition, a complete follow-up was achieved in nearly all randomised patients, there was a high adherence to study treatments, adjudication of cancer stages was performed by a panel of expert cancer physicians and all study outcome events were assessed by an independent committee unaware of treatment allocation.

In conclusion, patients with locally advanced and metastatic cancer have a higher rate of VTE recurrence than patients with localised cancer with no significant difference in anticoagulant treatment–related bleeding complications. Efficacy and safety of apixaban and dalteparin in patients with different cancer stages were consistent with those in the general cancer population. The high VTE recurrence rate in patients with locally advanced and metastatic cancer is an indication for

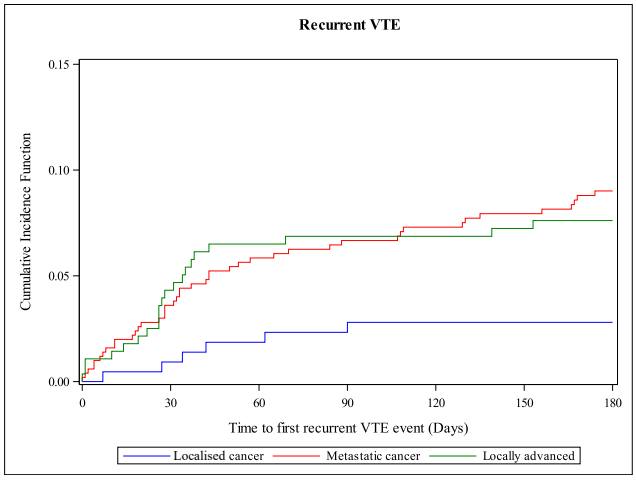

Fig. 1. VTE recurrence in patients with localised cancer, locally advanced cancer and metastatic cancer. VTE = venous thromboembolism.

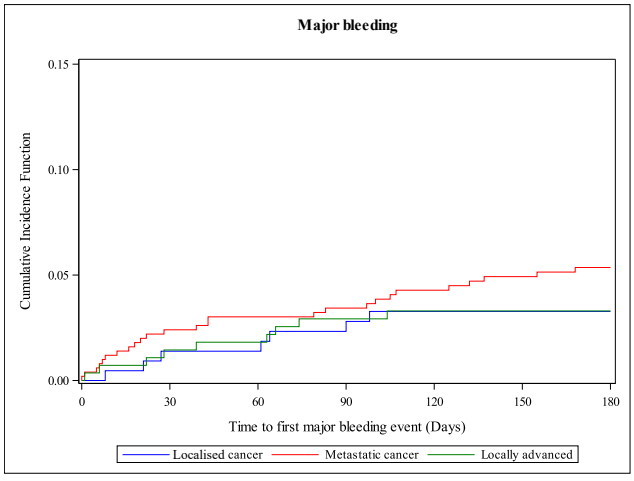

Fig. 2. Major bleeding in patients with localised cancer, locally advanced cancer and metastatic cancer.

optimal anticoagulation and extended anticoagulant treatment in these patients.

Authors' contributions

Conception and design: M Verso, G Agnelli.
Collection and assembly of data: All authors.
Data analysis and interpretation: All authors.
Manuscript writing: All authors.
Final approval of manuscript: All authors.

Conflict of interest statement

M. Verso reports personal fees from Pfizer, Bristol Meyer Squibb and Bayer Healthcare, outside the submitted work; G. Agnelli reports personal fees from Bristol Myers Squibb, Pfizer and Daiichi Sankyo, outside the submitted work; A. Munoz reports personal fees from Celgene, Sanofi, Pfizer, BMS, Leo Pharma, Daiichi-Sankyo, Bayer Healthcare, Halozyme, AstraZeneca, Rovi, Menarini, Stada, Merck Sharp & Dohme, Roche, Eli Lilly, Servier, Merck Serono, Incyte and Amgen, outside the submitted work; J. Connors reports grants and personal fees from CSL Behring, Abbott, Alnylam, Anthos, Bristol Myers Squibb, Roche, Sanofi and Takeda outside the submitted work.; O. Sanchez reports grants and personal fees from Sanofi, Pfizer, Bristol-Myers Squibb, Leo Pharma, Daiichi-Sankyo, Bayer Healthcare, Merck Sharp & Dohme, Boehringer Ingelheim and Chiesi, outside the submitted work; M.V. Huisman reports receiving grant support from Dutch Heart Foundation, ZonMw Dutch Healthcare Fund, Boehringer Ingelheim, Pfizer-BMS, Bayer Healthcare and Leo Pharma, outside the submitted work; B. Brenner reports advisory board fees from Leo Pharma, Sanofi, ROVI Laboratories and Bayer Pharmaceuticals; G. Gussoni reports no grant and personal fees; A.T. Cohen reports grants and personal fees from Abbott, AbbVie, Alexion Pharmaceuticals, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Janssen, Johnson & Johnson, Leo Pharma, Pfizer, Portola Pharmaceuticals and Sanofi, outside the submitted work; C Becattini reports personal fees from Bristol Myers Squibb, Bayer HealthCare, Daiichi Sankyo and Pfizer, outside the submitted work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.01.023.

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