Bleeding and venous thromboembolic events in patients with active cancer hospitalized for an acute medical illness

Running head: Bleeding in cancer inpatients

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Abstract

Background: Cancer patients hospitalized for an acute medical illness are considered to be at high risk of venous thromboembolism (VTE). Information on bleeding and symptomatic VTE in these patients remains scant. The objectives of this study were to evaluate the incidence of bleeding and VTE during hospitalization and after discharge in a prospective cohort of hospitalized medically-ill cancer patients.

Methods: Consecutive patients with active cancer admitted for an acute medical illness. The primary outcome was the incidence of clinically relevant bleeding. Secondary outcomes included symptomatic and incidentally detected VTE. Outcomes were recorded during hospitalization up to three months after discharge.

Results: The study population consisted of 330 patients with a mean age of 73.2 (± 12.1) years. During a median hospitalization of eight days, six patients (1.8%) developed a clinically relevant bleeding. Pharmacological thromboprophylaxis was administered to four of these six patients (66.6%), and 108 of 324 (33.3%) patients without bleeding. Twelve (3.6%) were diagnosed with VTE, of whom two had received thromboprophylaxis. In ten patients, VTE was detected incidentally. After discharge, 11 patients experienced major bleeding and two developed symptomatic VTE during a median follow-up of 92 days (range 19 - 110). Two thirds of all major bleeding events were gastrointestinal, and 87% occurred in patients with gastrointestinal or genitourinary cancer.

Conclusions: In patients with active cancer admitted for an acute medical illness, the risk of bleeding and symptomatic VTE appeared to be low during hospitalization. After discharge, the risk of bleeding was higher and significantly outweighed that of VTE.

Keywords: Hemorrhage, venous thromboembolism, neoplasm, hospitalization, prospective studies

47 **Highlights**

- In patients with active cancer admitted for an acute medical illness, the incidence of clinically relevant bleeding and symptomatic venous thromboembolism was low during hospitalization
- After discharge, the rate of bleeding was higher and significantly outweighed that of venous thromboembolism
- Prophylaxis for venous thromboembolism in these patients is underused relative to guideline recommendations

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67 **Abbreviations**

68 CI = Confidence Intervals

69 OR = Odds Ratio

70 RCT = Randomized Clinical Trials

71 VTE = Venous Thromboembolism

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Introduction

Patients with cancer who are hospitalized for an acute medical illness are considered to be at increased risk of venous thromboembolism (VTE) [1-4]. Prospective data on the incidence of bleeding complications and symptomatic VTE in this high-risk population are lacking and recommendations on the use of pharmacological thromboprophylaxis in these patients are largely based on indirect evidence [1-8]. In addition, a pooled analysis of 307 hospitalized medically-ill cancer patients from three placebo-controlled randomized clinical trials (RCTs) found that thromboprophylaxis was not associated with a significant reduction of the incidence of VTE [9]. It is of note that nearly one third of hospitalized patients with cancer may have relative contraindications to pharmacological prophylaxis, and among those without apparent contraindications, still one third does not receive any prophylaxis [10]. The low frequency of use of recommended VTE prophylaxis in these patients could be due to many factors, including physicians' awareness as well as lack of solid efficacy data and direct evidence on safety. In addition, the risk of VTE in some hospitalized cancer patients may be perceived as insufficiently high to justify the risks and burden of daily parenteral prophylaxis.

Cancer patients may remain at risk of VTE after hospital discharge and could take advantage of extended pharmacological prophylaxis [11-12]. However, the increased bleeding tendency and risk of major bleeding complications in these patients could offset the benefits of thromboprophylaxis [11-12]. It is therefore of outmost importance to clarify the trade-off between bleeding and VTE both during hospitalization and after discharge to inform the decision on the use of thromboprophylaxis.

The aim of this study was to evaluate the incidence of clinically relevant bleeding and VTE in a prospective cohort of cancer patients admitted for an acute medical illness.

106 **Materials and Methods**

107 *Study population*

108 We conducted a prospective, observational, non-interventional cohort study including a consecutive
109 series of patients with active cancer hospitalized for an acute medical illness in our Internal
110 Medicine Unit in Chieti, Italy from April 2015 to August 2017. Active cancer was defined by any
111 of the following: a) cancer diagnosis within the past six months, b) recurrent, regionally advanced,
112 or metastatic disease, c) ongoing cancer treatment or any treatment for cancer during six months
113 prior to hospitalization, or d) hematologic malignancy not in complete remission. Patients were
114 excluded if they were on anticoagulant treatment for other indications or refused to sign informed
115 consent forms. In addition, we excluded patients if active bleeding or VTE were the cause of
116 hospitalization or developed within 24 hours of admission. The study was approved by the local
117 institutional review board and all patients provided informed consent. The study is registered in
118 clinicaltrials.gov with accession number NCT02407717.

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120 *Study outcomes*

121 The primary outcome of the study was the incidence of clinically relevant bleeding during
122 hospitalization, which was defined as the composite of major and clinically relevant non-major
123 bleeding. Major bleeding was defined according to the definition of the International Society on
124 Thrombosis and Haemostasis as overt bleeding that was fatal, occurred in a critical area or organ
125 (e.g. intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or
126 intramuscular with compartment syndrome), resulted in a drop in hemoglobin level of 2 g/dL or
127 more (i.e. 1.24 mmol/L), or lead to the transfusion of two or more units of whole blood or packed
128 red blood cells [13]. A clinically relevant non-major bleeding was defined as bleeding that did not
129 fit the criteria for major bleeding, but required a medical intervention by a healthcare professional

and/or required an increased level of care. Following discharge, a bleeding event was also considered as clinically relevant non-major when it led to hospitalization and/or prompted a face-to-face evaluation.

Secondary outcomes included symptomatic and incidental VTE during hospitalization; bleeding events (major and clinically relevant non-major bleeding), symptomatic and incidental VTE, and all-cause mortality up to three months after discharge. VTE, which included deep vein thrombosis of the lower extremities and pulmonary embolism, had to be objectively confirmed by standard diagnostic methods which included compression ultrasonography for deep vein thrombosis and computed tomography pulmonary angiography or lung scan for pulmonary embolism [14]. Deep venous thrombosis at other sites (e.g. splanchnic vein thrombosis) was also recorded. Incidental VTE was defined as VTE detected during imaging tests performed for other reasons than VTE suspicion, such as the diagnostic work-up of the medical illness causing hospitalization or its complications.

Study procedures

We collected information on demographics (age, gender, body mass index), cancer characteristics (metastatic disease, recent cancer treatment), co-morbidities (e.g. renal insufficiency, thrombocytopenia, cardiovascular disease), VTE risk factors (e.g. history of VTE), reasons for hospitalization, and concomitant treatment (e.g. antiplatelet agents). The decision on the use and duration of thromboprophylaxis was not dictated by study protocol and was left to the treating physician who was asked to report the reasons for withholding thromboprophylaxis at admission. A phone or visit contact was planned at three months after discharge in all patients to verify the development of thrombotic or bleeding events.

154 *Statistical considerations*

155 Continuous variables were reported as mean ($\pm$ standard deviations) or median (range) depending
 156 on distribution, categorical variables as number (percentages). The incidence with 95% Wilson
 157 confidence intervals (CIs) of bleeding and VTE events were calculated during hospitalization and
 158 up to three months after discharge. The association between use of pharmacological
 159 thromboprophylaxis and patient characteristics was evaluated reporting odds ratio (OR) and the
 160 relative 95% CIs [12]. Exploratory analyses were conducted to evaluate the discriminative
 161 performance of the score derived in the International Medical Prevention Registry on Venous
 162 Thromboembolism (IMPROVE) study for bleeding events, and of the Khorana and Padua
 163 prediction models for VTE [12, 15-16]. Patients with seven points or higher on the IMPROVE
 164 score were considered at high risk, those with six points or less at low risk [11-12]. The Khorana
 165 score was assessed at the conventional threshold of three points as well as at the exploratory two
 166 and four cut points. In the absence of adequate information from previous studies on the incidence
 167 of the primary outcome in patients with active cancer hospitalized for a medical illness [9], a formal
 168 sample size calculation was not performed. We aimed to enroll a cohort of at least 300 consecutive
 169 patients.

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171 **Results**

172 A total of 535 patients were evaluated for inclusion and 205 excluded, mainly because of an
 173 ongoing use of anticoagulant therapy (n = 96) or active bleeding on admission (n = 52; Figure). The
 174 final population consisted of 330 hospitalized patients with a mean age of 73.2 (SD 12.1) years. The
 175 most frequent cancer types were gastrointestinal (n = 73, 22.1%), lung (n = 52, 15.8%), and prostate
 176 (n = 40, 12.1%). Baseline characteristics of the study population and reasons for hospitalization are
 177 reported in Table 1.

One hundred and thirty-nine patients out of 330 (42%) did not receive pharmacological thromboprophylaxis due to the presence of concomitant bleeding risk factors. Treating physicians reported the following reasons for withholding thromboprophylaxis: history of major bleeding (n = 5, 1.5%), active gastroduodenal ulcer (n = 2, 0.6%), thrombocytopenia (n = 4, 1.2%), moderate to severe renal insufficiency (n = 27, 8.2%), moderate to severe anemia (n = 93, 28.2%), liver dysfunction (n = 7, 2.1%), and patient refusal (n = 1, 0.3%).

Among 191 patients without reported contraindications for anticoagulation, 112 (58.6%) received pharmacological prophylaxis during hospitalization, while in the remaining 79 patients the risk of VTE was not perceived high enough to use thromboprophylaxis. Prophylaxis was administered for a median of seven days (range 1 to 35) and consisted of low-molecular-weight heparin (n = 91) or fondaparinux (n = 21). Patients more likely to receive pharmacological thromboprophylaxis were 75 years or older (OR 2.6;95%CI, 1.46 to 4.61), had metastatic disease (OR 1.79;95% CI, 1.13 to 2.85), or worse ECOG performance status (OR 1.70;95%CI, 1.26 to 2.30). After discharge, thromboprophylaxis with heparin or fondaparinux was administered to 48 out of 289 alive patients (17%) for a median of 15 days (range 2 to 90). No patient received oral anticoagulants or mechanical prophylaxis with elastic compression stockings or intermittent pneumatic compression devices during any phase of the study.

Clinically relevant bleeding

During a median hospitalization of eight days (range 1 to 96), six patients (1.82%; 95% CI 0.84 to 3.91) had clinically relevant bleeding, which included four major bleeding (1.21%; 95% CI 0.47 to 3.07) of the gastrointestinal (n = 2) or genitourinary (n = 2) tracts, and two clinically relevant non-major bleeding (0.61%; 95% CI 0.17 to 2.18; Tables 2 and 3). Pharmacological thromboprophylaxis was administered to four of these six patients (66.6%) and 108 of 324 (33.3%) patients without

bleeding. The risk of clinically relevant bleeding was fivefold higher in patients classified as at high risk by the IMPROVE score (n = 56) compared to those at low risk (n = 274, 5.3% versus 0.8%, OR 5.1; 95% CI, 1.0 to 26.0, p = 0.049).

After discharge, there were eleven major bleeding and one clinically relevant non-major bleeding (4.15%; 95% CI 2.16 to 7.14) out of 289 patients during a median follow-up of 92 days (range 19 to 110). Only one of these twelve patients was on pharmacological thromboprophylaxis. One patient had an intracranial hemorrhage and nine patients had a major bleeding, mostly gastrointestinal, which required the transfusion of two or more units of packed red blood cells (Table 3). A 79 years old man with metastatic cancer of the bladder developed a fatal retroperitoneal bleeding from the rupture of an aneurysm of the abdominal aorta. One patient was admitted to the Emergency for rectal bleeding, which did not require blood transfusion and was classified as clinically relevant non-major bleeding.

Venous thromboembolism

Overall, 12 out of 330 patients (3.64%; 95% CI 1.89% to 6.27%) were diagnosed with VTE during hospitalization (Tables 2 and 4). Ten VTEs (83%) including seven pulmonary embolism and three deep vein thrombosis were detected incidentally by computed tomography scanning performed as part of the diagnostic work-up of the disease leading to hospitalization (Table 4). The most proximal pulmonary artery was segmental in six patients, whereas the main or lobar artery were involved in one patient each. Pulmonary embolism was bilateral in one case. An 82-year old man with prostate cancer complained of pain and edema of the lower limb on the fourth day of hospitalization. Compression ultrasonography confirmed deep vein thrombosis of the popliteal and posterior tibial veins. Another 80-year old man with metastatic lung cancer who was hospitalized due to heart failure with pulmonary congestion, complained of worsening dyspnea on day twelve.

Computed tomography pulmonary angiography detected multiple segmental and subsegmental pulmonary embolism. A patient with liver cancer was diagnosed with incidental splanchnic vein thrombosis.

During hospitalization, two out of 112 patients (1.79%; 95% CI 0.22% to 6.30%) on pharmacological thromboprophylaxis developed VTE versus ten out of 218 (4.59%; 95% CI 2.22% to 8.27%) without thromboprophylaxis. Five out of 49 patients (10.2%) with a Khorana score ≥ 3 developed VTE compared to 7 of 281 patients (2.5%) with a score below 2 points (OR 4.4; 95% CI, 1.3 to 14.6). A Khorana score ≥ 4 was associated with a sevenfold higher risk of in-hospital VTE (20% versus 3.1%, respectively, OR 7.7; 95% CI, 1.4 to 41.3), whereas the threshold of 2 cut-points and the Padua prediction model did not discriminate between patients at high versus low risk of VTE (OR for the Khorana ≥ 2 , 1.5; 95% CI, 0.5 to 4.8, and OR for the Padua model, 0.68; 95% CI, 0.18 to 2.6).

After discharge, two symptomatic VTEs occurred in 289 patients (0.69%; 95% CI 0.08% to 2.48%). A 56-year old woman with lung cancer was diagnosed with symptomatic pulmonary embolism ten weeks after discharge and a man with metastatic cancer of the testicle who had restarted chemotherapy one week after hospitalization developed symptomatic bilateral femoral deep vein thrombosis 34 days after discharge. Both these patients had received prophylactic low-molecular-weight heparin during their hospital stay until the post-discharge VTE.

Other events

Forty-one patients died in-hospital (12.42%; 95% CI 9.07% to 16.48%) and 134 during follow-up (46.37%; 95% CI 40.51% to 52.30%). An autopsy was not performed in these patients and the ultimate cause of death was not ascertained. In those who died at home, the most likely cause of death according to the treating physician was the progression of cancer or worsening of the medical

illness. Fifty-six patients were re-hospitalized during follow-up and two died during re-hospitalization due to cancer progression and septic shock with multiorgan failure, respectively. There were no cardiovascular or cerebrovascular complications during hospitalization or follow-up.

Discussion

The incidence of clinically relevant bleeding and symptomatic VTE was low during hospitalization. After discharge, the background risk of bleeding in absence of thromboprophylaxis was higher and significantly outweighed the one of VTE. The current study showed underuse of recommended VTE prophylaxis in cancer patients hospitalized for an acute medical illness.

The overall incidence of clinically relevant bleeding during hospitalization was 1.8%, consistent with prior studies [17,18]. A lower rate was reported in a post-hoc analysis of the CERToparIn For thromboprophylaxis in medical patients (CERTIFY) study, which could hinge on differences in outcome definitions, length of observation, or study populations as suggested by the fourfold higher in-hospital mortality in our cohort compared to that study [19].

The incidence of VTE during hospitalization was 3.6%, consistent with the rate of 3.8% observed in a recent retrospective cohort of 2780 cancer inpatients [20]. In agreement with prior studies, the large majority of these VTEs were detected incidentally [17,19,21]. Although incidental VTE is still an area of investigation and debate, available data suggest that incidental VTE, in particular incidental pulmonary embolism, has important implications for overall and cancer-specific prognosis [22]. Treatment and prevention of incidental VTE are currently regarded as important as for symptomatic VTE [23]. The onset of incidental VTE in this patient population remains unclear and we cannot rule out that part of these events developed prior to hospitalization.

Prospective data on the incidence of bleeding and VTE in cancer patients after hospitalization for an acute medical illness are lacking [24-25]. In a relatively sick population with a

high mortality rate, we observed a high incidence of clinically relevant bleeding, most off-thromboprophylaxis, which significantly outweighed the incidence of VTE. Thus, the trade-off between bleeding and thrombotic events was different compared to the in-hospital phase when the risk of bleeding or symptomatic VTE was low. Of note, two thirds of all major bleeding events during study were gastrointestinal, and 87% occurred in patients with gastrointestinal or genitourinary cancer, suggesting a higher bleeding tendency in these tumor types.

Bleeding and thrombotic risk stratification are strongly advocated by most clinical practice guidelines to guide the use of thromboprophylaxis in hospitalized patients, but validated risk assessment tools for patients with cancer are not yet available [1,4]. The Padua Prediction Score was empirically derived for estimating the overall risk of thrombosis in hospitalized medically-ill patients [16]. The usefulness of this model has been questioned, and preliminary observations suggested that the score had limited influence, if any, on the decision about the use of thromboprophylaxis in hospitalized cancer patients [10, 26-27]. In the current study population, the Padua score appeared not to discriminate patient risk of VTE, whereas the Khorana score, originally developed to predict VTE in cancer outpatients, seemed to hold discriminative value, in agreement with recent observations [20]. While the IMPROVE score seemed able to identify a subgroup at high bleeding risk, the relatively low number of patients with some of the characteristics included in this model represent a limitation.

Strengths of the current study are the prospective design, the a-priori definition of active cancer status, and the follow-up for VTE and bleeding complications after discharge. The study did not include patients admitted for minor procedures or short chemotherapy infusion, thus our findings may not extend to these patients. As the focus was on patients with active cancer, the results may not apply to those with a history of cancer. The lack of randomization and statistical power precluded a formal evaluation of the efficacy and safety of VTE thromboprophylaxis. Of note, about 40% of the patients in our study were perceived as having a relative contraindication to

anticoagulation or a risk of VTE not sufficiently high to justify the use of pharmacological thromboprophylaxis. Similar findings were reported in a large cross-sectional study by Zwicker and colleagues where prophylaxis was withheld in nearly one third of patients [10].

In summary, patients with cancer admitted for an acute medical illness presented a low risk of symptomatic VTE despite the relative underuse of prophylaxis and had infrequent bleeding complications during hospitalization. After discharge, however, the background risk of bleeding in absence of thromboprophylaxis is high and outweighs that of VTE. Large randomized controlled trials specifically focusing on cancer patients or even specific tumor subgroups are warranted to clarify the safety and efficacy of VTE thromboprophylaxis in this challenging group of patients.

320 **Addendum**

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322 content, and final approval of the version to be published: MDN, MC, AWSR, VG, MT, EP.

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330 **Declarations of interest**

331 None of the authors have potential conflicts of interest to declare in relation to the current work.

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Table 1. Baseline characteristics of study participants

	Patients n = 330
Age in years, mean (SD)	73.2 (12.1)
Female sex	134 (40.6 %)
Body mass index in kg/m ² , mean (SD)	24.0 (3.4)
Smoking	
Current	14 (4.2 %)
Former	36 (10.9 %)
Cancer type	
Lung	52 (15.8 %)
Colorectal	57 (17.3 %)
Gastric	16 (4.8 %)
Breast	33 (10.0 %)
Liver	12 (3.6 %)
Pancreas	19 (5.8 %)
Gynecological	15 (4.5 %)
Prostate	40 (12.1 %)
Unknown primary	3 (0.9 %)
Leukemia/Lymphoma	15 (4.5 %)
Primary brain	9 (2.7 %)
Other	59 (17.9 %)
Metastasis	172 (52.1 %)
Medical Illness causing hospitalization	
Acute heart failure	22 (6.7 %)
Acute respiratory insufficiency	28 (8.5 %)
Acute infection	38 (11.5 %)
Acute inflammatory or rheumatological disease	16 (4.8 %)
Nausea-vomiting	32 (9.7 %)
Malnutrition-dehydration	21 (6.4 %)
Dysphagia	9 (2.7 %)
Diarrhea	8 (2.4 %)
Obstructive jaundice	8 (2.4 %)
Intestinal (sub-)occlusion	13 (3.9 %)
Refractory pain	29 (8.8 %)
Cancer Progression/chemotherapy toxicity	42 (12.7 %)
Acute stroke/Transient ischemic attack	9 (2.7 %)
Arrhythmia	3 (0.9 %)
Cancer cachexia	27 (8.2 %)
Pleural effusion	19 (5.8 %)
Worsening ascites	19 (5.8 %)
Syncope	4 (1.2 %)
Seizures	2 (0.6 %)
Other	11 (3.3 %)
History of stroke or transient ischemic attack	18 (5.4 %)
Chronic renal insufficiency	34 (10.3 %)
Central venous catheter	2 (0.6 %)
Previous venous thromboembolism	9 (2.7 %)
Cancer treatment ≤ 3 months	
Chemotherapy	62 (18.8 %)
Radiotherapy	13 (3.9 %)
Chemo-radiotherapy	15 (4.5 %)
Hormonal treatment	23 (7.0 %)
Trauma or surgery ≤ 3 months	23 (7.0 %)

Table 1. "Continued"

Antiplatelet agents	68 (20.6 %)
Non Steroidal Anti-Inflammatory drugs	16 (4.8 %)
Previous gastroduodenal ulcer	6 (1.8 %)
ECOG	
0	5 (1.5 %)
1	42 (12.7 %)
2	120 (36.4 %)
3	147 (44.5 %)
4	16 (4.8 %)
Padua score, median (range)	5 (1 -11)
Khorana score, median (range)	1 (0 - 5)
0	93 (28.2 %)
1	105 (31.8 %)
2	83 (25.2 %)
3	39 (11.8 %)
4	9 (2.7 %)
5	1 (0.3 %)
Khorana ≥ 3	49 (14.8 %)
IMPROVE score, median (range)	4.5 (1 - 14.5)
IMPROVE ≥ 7	56 (16.9 %)

Data are reported as number of patients (%), unless otherwise indicated

Table 2. Number of bleeding and thrombotic events during hospitalization and after discharge

	During hospitalization n = 330	After discharge n = 289 *
Bleeding	9	25
Major bleeding	4	11
Clinically relevant non-major bleeding	2	1
Minor bleeding	3	13
Venous thromboembolism	12	2
Deep vein thrombosis	4	1
Symptomatic	1	1
Incidental	3	0
Pulmonary embolism	8	1
Symptomatic	1	1
Incidental	7	0
Death	41	134
Cardiovascular event		
Acute coronary syndrome	0	0
Ictus	0	0
Re-hospitalization	-	56

* 41 participants died during hospitalization

Table 3. Characteristics of patients with clinically relevant bleeding during hospitalization and after discharge

Patient ID	Cancer type	Metastasis	Bleeding site	Units transfused	Days since hospitalization
Bleeding events during hospitalization					
On-thromboprophylaxis					
<i>Major bleeding</i>					
45	Bladder	Yes	Upper gastrointestinal	6	4
292	Bladder	No	Vaginal	12	8
<i>Clinically relevant non-major bleeding</i>					
181	Colorectal	Yes	Lower gastrointestinal	-	2
244	Prostate	No	Hematuria	-	5
Off-thromboprophylaxis					
<i>Major bleeding</i>					
192	Pancreas	Yes	Upper gastrointestinal	2	8
268	Prostate	No	Urinary tract	2	5
Bleeding events after discharge					Days since discharge
On-thromboprophylaxis					
<i>Major bleeding</i>					
124	Colorectal	No	Lower gastrointestinal	3	63
Off-thromboprophylaxis					
<i>Major bleeding</i>					
94	Colorectal	Yes	Lower gastrointestinal	3	40
103	Breast	No	Intracranial		88
133	Prostate	Yes	Lower gastrointestinal	23	30
192	Pancreas	Yes	Lower gastrointestinal	2	15
217	Stomach	Yes	Upper gastrointestinal	4	28
220	Lung	Yes	Lower gastrointestinal	10	50
227	Stomach	No	Lower gastrointestinal	3	80
262	Biliary	Yes	Upper gastrointestinal	3	7
292	Bladder	No	Vaginal	3	11
294	Bladder	Yes	Fatal retroperitoneal bleeding	-	36
<i>Clinically relevant non-major bleeding</i>					
63	Lung	Yes	Lower gastrointestinal	0	50

Table 4. Patients with venous thromboembolic events during hospitalization

Patient ID	Cancer type	Metastasis	VTE	Incidental	Reason for hospitalization	Days since admission
On-thromboprophylaxis						
78*	Prostate	No	Proximal DVT	No	Heart failure	4
228†	Lung	Yes	Segmental and subsegmental PE	No	Heart failure	12
Off-thromboprophylaxis						
18	Pancreas	No	Lobar PE	Yes	Jaundice	2
20	Colorectal	Yes	Segmental PE	Yes	Asthenia, weight loss, physical decay	9
27	Gynecological	Yes	Segmental PE	Yes	Worsening ascitis	15
65	Head-neck	No	Bilateral proximal DVT	Yes	Asthenia, weight loss, physical decay	2
71	Gynecological	Yes	Lobar PE	Yes	Ascitis	10
174	Colorectal	Yes	Segmental PE	Yes	Abdominal pain	5
185	Stomach	No	Segmental PE	Yes	Nausea, abdominal pain	11
201	Stomach	Yes	Segmental PE	Yes	Jaundice, abdominal pain	2
231	Stomach	No	External iliac DVT	Yes	Refractory pain, anemia	7
324	Lung	Yes	Distal DVT	Yes	Pleural effusion	6

DVT = deep vein thrombosis; PE = pulmonary embolism; * the participant received 2 days of Enoxaparin 4000 IU prior to the event; † the participant received 6 days of Enoxaparin 6000 IU prior to the event.