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Cancer-Associated Venous Thromboembolism in the Real World

— From the COMMAND VTE Registry —

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on behalf of the COMMAND VTE Registry Investigators

Background: There is a paucity of data on the management and prognosis of cancer-associated venous thromboembolism (VTE), leading to uncertainty about optimal management strategies.

Methods and Results: The COMMAND VTE Registry is a multicenter registry enrolling 3,027 consecutive acute symptomatic VTE patients in Japan between 2010 and 2014. We divided the entire cohort into 3 groups: active cancer (n=695, 23%), history of cancer (n=243, 8%), and no history of cancer (n=2089, 69%). The rate of anticoagulation discontinuation was higher in patients with active cancer (43.5%, 27.0%, and 27.0%, respectively, at 1 year, P<0.001). The cumulative 5-year incidences of recurrent VTE, major bleeding, and all-cause death were higher in patients with active cancer (recurrent VTE: 17.7%, 10.2%, and 8.6%, P<0.001; major bleeding: 26.6%, 8.8%, and 9.3%, P<0.001; all-cause death: 73.1%, 28.6%, 14.6%, P<0.001). Among the 4 groups classified according to active cancer status, the cumulative 1-year incidence of recurrent VTE was higher in the metastasis group (terminal stage group: 6.4%, metastasis group: 22.1%, under chemotherapy group: 10.8%, and other group: 5.8%, P<0.001).

Conclusions: In a current real-world VTE registry, patients with active cancer had higher risk for VTE recurrence, bleeding, and death, with variations according to cancer status, than patients without active cancer. Anticoagulation therapy was frequently discontinued prematurely in patients with active cancer in discordance with current guideline recommendations.

Key Words: Bleeding; Cancer; Mortality; Recurrence; Venous thromboembolism

Cancer is a progressive disease with a high mortality rate despite intensive treatment, but many cancer patients are surviving longer because of progress in early diagnosis and treatment.[1,2] Thus, complications during the treatment course of cancer are becoming more clinically relevant. Cancer is a strong risk factor for the development of venous thromboembolism (VTE), and patients with cancer are reported to have a 7-fold higher incidence compared with patients without cancer.[3] VTE is reported to be the second most frequent cause of death in patients with cancer undergoing chemotherapy.[4] Furthermore, VTE in patients with cancer could develop through not only hypercoagulability with cancer, but also treatment-related factors including new molecular target therapeutic agents, which have further increased the risk for development of VTE in the current era.[5] A recent study reported

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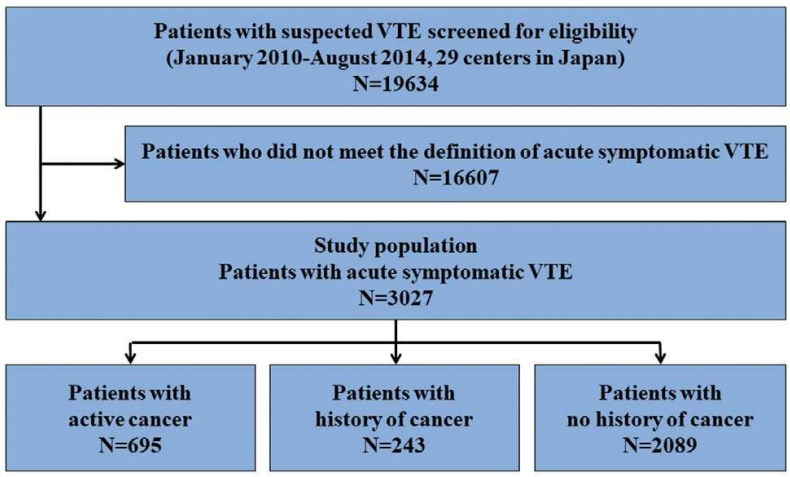

Figure 1. Study flow chart. Venous thromboembolism (VTE) included pulmonary embolism (PE) and/or deep vein thrombosis (DVT).

that the incidence of VTE in patients with cancer has been increasing over time, but not in patients without cancer.[6]

Optimal management strategies of VTE patients with cancer have become a major concern that challenges clinicians in daily clinical practice. VTE patients with active cancer are reported to have a markedly higher risk of recurrence as well as bleeding, compared with those without active cancer, creating difficulty in achieving a good risk-benefit balance with anticoagulation therapy.[7] Despite several guideline recommendations about treatment strategies including anticoagulation therapy for patients with cancer-associated VTE, there is still a lack of data on these patients, leading to uncertainty about optimal management strategies.[8] Data on current real-world management strategies and clinical outcomes in cancer-associated VTE patients are important for understanding the current issues and unmet needs. Therefore, we sought to evaluate the clinical characteristics, management strategies, and outcomes of patients with cancer-associated VTE in the real world using a large Japanese observational database of VTE.

Methods

Study Population

The COMMAND VTE (COntemporary ManageMent AND outcomes in patients with Venous ThromboEmbolism) Registry is a physician-initiated, retrospective, multicenter cohort study enrolling consecutive patients with acute symptomatic VTE objectively confirmed by imaging examinations or autopsy in 29 centers in Japan between January 2010 and August 2014 before the introduction of direct oral anticoagulants (DOAC) for VTE in Japan. The design of the registry has been reported in detail.[9,10] The relevant review board or ethics committee in all 29 participating centers (**Supplementary Appendix 1**) approved the research protocol.

A total of 3,027 consecutive patients with acute symptomatic VTE were enrolled in the registry after screening of 19,634 consecutive patients with suspected VTE for eligibility through chart review by physicians at each institution. In the current study, we divided the entire cohort into 3 groups according to cancer status: active cancer, history of cancer, and no history of cancer (**Figure 1**).

Definitions of Patients' Characteristics

Patients with active cancer were defined as those on treatment for cancer such as chemotherapy or radiotherapy, those scheduled to undergo surgery for cancer, those with metastasis to other organs, and/or those with terminal cancer (expected life expectancy ≤6 months) at the time of diagnosis of VTE. Patients with active cancer were further subdivided into 4 groups according to the most advanced cancer status: terminal stage group, metastasis group, under chemotherapy group, and other group. Patients with a history of cancer were defined as those who were previously diagnosed as having cancer, but did not meet the criteria for active cancer.

The initial parenteral anticoagulation therapy was defined as parenteral anticoagulation therapy in the acute phase (heparin or fondaparinux) for ≤10 days after the diagnosis, whereas anticoagulation therapy beyond the acute phase

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was defined as anticoagulation therapy (warfarin, DOACs, or heparin) that was continued beyond 10 days after the diagnosis. The definitions of other characteristics are described in **Supplementary Appendix 2**.

Clinical Follow-up and Endpoints

Collection of follow-up information was mainly through review of hospital charts, and additional follow-up information was collected through contact with patients, relatives, and/or referring physicians by phone and/or mail with questions regarding vital status, recurrent VTE, bleeding, invasive procedures, and status of anticoagulation therapy. In this retrospective cohort study, data collection for follow-up events was performed between July 2016 and March 2017.

The outcome measure was recurrent VTE, major bleeding, and all-cause death. Recurrent VTE was defined as pulmonary embolism (PE) and/or deep vein thrombosis (DVT) with symptoms accompanied by confirmation of new thrombus or exacerbation of the thrombus by objective imaging examinations or autopsy.[11] Major bleeding was defined as International Society of Thrombosis and Hemostasis (ISTH) major bleeding, which consisted of a reduction in the hemoglobin level by at least 2 g/dL, a transfusion of ≥2 units of blood, or symptomatic bleeding in a critical area or organ.[12] Stroke event was also evaluated, which was defined as ischemic or hemorrhagic stroke either requiring or prolonging hospitalization with symptoms lasting >24 h.

The independent clinical event committee (**Supplementary Appendix 3**), unaware of the patient characteristics, reviewed all study outcomes, and classified the cause of deaths as PE, cardiac event, cancer, bleeding event, other non-cardiac event, or unknown cause.[13] Death was judged to be caused by PE (fatal PE) if it was confirmed by autopsy or if death followed a clinically severe PE, either initially or after recurrent PE events. Death from endstage cancer without a specific cause of death was regarded as cancer origin. Death was judged to be bleeding-related if it followed an intracranial hemorrhage or a bleeding episode leading to hemodynamic deterioration. Death was judged to be from cardiac events if it followed acute myocardial infarction, heart failure, or ventricular arrhythmia. Final classification of the cause of death was made by full consensus of the independent clinical event committee.

Anticoagulation therapy cessation was classified as

Table 1. Patients' Characteristics

	Active cancer (n=695)	History of cancer (n=243)	No history of cancer (n=2,089)	P value
Baseline characteristics				
Age (years)*,†,‡	66.5±12.2	72.2±11.4	66.8±16.5	<0.001
Women*,†,‡	414 (60%)	133 (55%)	1,311 (63%)	0.03
Body weight (kg)	55.3±12.3	55.3±12.0	59.1±14.3	<0.001
Body mass index (kg/m^2)	22.1±4.0	22.5±3.8	23.7±4.6	<0.001
≥30 kg/m^2*	26 (3.7%)	8 (3.3%)	135 (6.5%)	0.007
Comorbidities				
Hypertension‡	202 (29%)	101 (42%)	858 (41%)	<0.001
Diabetes mellitus‡	88 (13%)	38 (16%)	260 (12%)	0.37
Dyslipidemia	97 (14%)	51 (21%)	460 (22%)	<0.001
Chronic kidney disease†,‡	117 (17%)	58 (24%)	397 (19%)	0.053
Dialysis	5 (0.7%)	2 (0.8%)	14 (0.7%)	0.96
History of chronic lung disease	56 (8.1%)	33 (13.6%)	182 (8.7%)	0.03
History of heart failure	10 (1.4%)	13 (5.4%)	78 (3.7%)	0.003
History of myocardial infarction	6 (0.9%)	6 (2.5%)	41 (2.0%)	0.11
History of stroke‡	36 (5.2%)	33 (13.6%)	201 (9.6%)	<0.001
Atrial fibrillation	24 (3.5%)	15 (6.2%)	90 (4.3%)	0.19
Liver cirrhosis†,‡	8 (1.2%)	5 (2.1%)	13 (0.6%)	0.046
Connective tissue disease‡	21 (3.0%)	18 (7.4%)	205 (9.8%)	<0.001
Varicose vein*,‡	13 (1.9%)	14 (5.8%)	112 (5.4%)	<0.001
History of VTE*,‡	40 (5.8%)	18 (7.4%)	120 (5.7%)	0.57
History of major bleeding†,‡	72 (10.4%)	20 (8.2%)	139 (6.7%)	0.006
Transient risk factors for VTE*,†,‡	196 (28%)	86 (35%)	804 (38%)	<0.001
Presentation				
PE with or without DVT*,†,‡	393 (57%)	130 (54%)	1,192 (57%)	0.57
Hypoxemia	161/393 (41%)	61/130 (47%)	628/1,192 (53%)	<0.001
Shock	25/393 (6.4%)	15/130 (11.5%)	139/1,192 (11.7%)	0.01
Cardiac arrest/collapse	7/393 (1.8%)	8/130 (6.2%)	65/1,192 (5.5%)	0.008
DVT only*,†,‡	302 (43%)	113 (46%)	897 (43%)	0.57
Proximal DVT*,†,‡	217/302 (72%)	79/113 (70%)	625/897 (70%)	0.77
Out-of-hospital onset	458 (66%)	185 (76%)	1,665 (80%)	<0.001

(**Table 1** continued the next page.)

	Active cancer (n=695)	History of cancer (n=243)	No history of cancer (n=2,089)	P value
Laboratory tests at diagnosis				
Anemia†,‡	529 (76%)	139 (57%)	959 (46%)	<0.001
Thrombocytopenia (platelet count <100×10⁹/L)†,‡	55 (7.9%)	20 (8.2%)	92 (4.4%)	<0.001
D-dimer (μg/mL) (n=2,852)	13.3 (6.2–25.5)	9.9 (4.5–19.5)	9.7 (5.0–19.7)	<0.001
Thrombophilia*,‡	19 (2.7%)	11 (4.5%)	117 (5.6%)	0.009
Treatment in the acute phase				
Initial parenteral anticoagulation therapy	577 (83%)	207 (85%)	1,750 (84%)	0.73
Thrombolysis	53 (7.6%)	28 (11.5%)	349 (16.7%)	<0.001
Inferior vena cava filter use	191 (27%)	51 (21%)	478 (23%)	0.03
Ventilator support	10 (1.4%)	11 (4.5%)	71 (3.4%)	0.01
Percutaneous cardiopulmonary support	1 (0.1%)	4 (1.7%)	34 (1.6%)	0.01
Concomitant medications at discharge				
Corticosteroids	109 (16%)	25 (10%)	213 (10%)	<0.001
Non-steroidal anti-inflammatory drugs	111 (16.0%)	17 (7.0%)	169 (8.1%)	<0.001
Proton pump inhibitors/H2-blockers	313 (45%)	104 (43%)	919 (44%)	0.81
Statins	54 (7.8%)	34 (14.0%)	349 (16.7%)	<0.001
Antiplatelet agents	43 (6.2%)	29 (11.9%)	235 (11.3%)	<0.001
Anticoagulation therapy beyond the acute phase	614 (88%)	221 (91%)	1,968 (94%)	<0.001
Warfarin	576 (83%)	211 (87%)	1,889 (90%)	
Direct oral anticoagulant	20 (2.9%)	6 (2.5%)	52 (2.5%)	<0.001
Heparin	18 (2.6%)	4 (1.7%)	27 (1.3%)	
TTR for INR 1.5–2.5 (%) (n=2,509)	60.7 (36.8–81.3)	67.2 (43.8–90.1)	75.8 (50.5–93.8)	<0.001
TTR for INR 2.0–3.0 (%) (n=2,509)	30.9 (11.6–50.6)	31.9 (8.1–56.7)	30.6 (7.4–57.7)	0.94
Maximum INR value during warfarin administration (n=2,620)	3.4±1.8	3.0±1.4	2.7±1.1	<0.001
Discontinuation of anticoagulation during follow-up	266/614	92/221	731/1968	0.02
Reason for discontinuation				
Physician's judgment	81/266 (30%)	54/92 (59%)	513/731 (70%)	<0.001
Bleeding event	86/266 (32%)	21/92 (23%)	94/731 (13%)	
Other	99/266 (37%)	17/92 (18%)	124/731 (17%)	
Interruption of anticoagulation during follow-up period	107/614 (17%)	25/221 (11%)	215/1,968 (11%)	0.001

Categorical variables are presented as numbers and percentages, and continuous variables are presented as the mean and standard deviation or the median and interquartile range based on their distributions. Categorical variables were compared using the chi-squared test when appropriate; otherwise, Fisher's exact test was used. Continuous variables were compared using one-way analysis of variance or Kruskal-Wallis test based on their distributions. Chronic kidney disease was diagnosed if there was persistent proteinuria or if estimated glomerular filtration rate (eGFR) was <60 mL/min/1.73 m² for more than 3 months. The eGFR was calculated based on the equation reported by Japan Association of Chronic Kidney Disease Initiative [male: $194*Scr^{-1.094}*age^{-0.287}$, female: $194*Scr^{-1.094}*age^{-0.287}*0.739$]. Thrombophilia included protein C deficiency, protein S deficiency, antithrombin deficiency, and antiphospholipid syndrome. *Risk-adjusting variables for the multivariable Cox regression model to estimate the risk for recurrent VTE. †Risk-adjusting variables for the multivariable Cox regression model to estimate the risk for major bleeding. ‡Risk-adjusting variables for the multivariable Cox regression model to estimate the risk for all-cause death. DVT, deep vein thrombosis; INR, international normalized ratio; PE, pulmonary embolism; TTR, time in therapeutic range; VTE, venous thromboembolism.

discontinuation or interruption according to prespecified definitions. Discontinuation of anticoagulation was defined as withdrawal of anticoagulation therapy lasting >14 days for any reason such as bleeding event, drug side effect, physicians' judgment in the absence of adverse events, and non-adherence of the patient. Interruption of anticoagulation was defined as temporary cessation of anticoagulation therapy with reinstitution within 14 days for any reason including invasive procedure and bleeding events, etc. Scheduled switch from one anticoagulation therapy to another was not regarded as interruption of anticoagulation. Data for the international normalized ratio (INR) during follow-up in patients receiving warfarin were collected from the hospital charts of the centers where the index VTE was diagnosed. Time in therapeutic range (TTR) was calculated by the Rosendaal method,[14] according to a therapeutic INR range of 1.5–2.5, which is recommended in the Japanese guidelines,[8] as well as a therapeutic INR range of 2.0–3.0, which is recommended in the Western guidelines.[15–17]

Statistical Analysis

Categorical variables are presented as numbers and percentages. Continuous variables are presented as the mean and standard deviation or the median and interquartile range based on their distributions. Categorical variables were compared with the chi-square test when appropriate; otherwise, Fisher's exact test was used. Continuous variables were compared using one-way analysis of variance or Kruskal-Wallis test based on their distributions. We used the Kaplan-Meier method to estimate the cumulative incidence and assessed the differences with the log-rank test. To adjust for clinically relevant confounders, we used the multivariable Cox proportional hazard to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the risk of patients with active cancer and patients with a

Table 2. Cancer Characteristics

	Overall (n=938)	Active cancer (n=695)	History of cancer (n=243)
Cancer site			
Lung	127 (13.5)	114 (16.4)	13 (5.4)
Colon	127 (13.5)	88 (12.7)	39 (16.1)
Stomach	90 (9.6)	51 (7.3)	39 (16.1)
Uterus	78 (8.3)	61 (8.8)	17 (7.0)
Blood	75 (8.0)	62 (8.9)	13 (5.4)
Ovary	64 (6.8)	59 (8.5)	5 (2.1)
Prostate	57 (6.1)	36 (5.2)	21 (8.6)
Breast	53 (5.7)	26 (3.7)	27 (11.1)
Pancreas	44 (4.7)	41 (5.9)	3 (1.2)
Bladder	25 (2.7)	14 (2.0)	11 (4.5)
Brain	23 (2.5)	18 (2.6)	5 (2.1)
Kidney/ureter	16 (1.7)	10 (1.4)	6 (2.5)
Esophagus	15 (1.6)	10 (1.4)	5 (2.1)
Gall bladder/bile duct	14 (1.5)	13 (1.9)	1 (0.4)
Skin	13 (1.4)	8 (1.2)	5 (2.1)
Thyroid gland	12 (1.3)	4 (0.6)	8 (3.3)
Liver	11 (1.2)	11 (1.6)	0 (0.0)
Oral cavity/pharynx	9 (1.0)	7 (1.0)	2 (0.8)
Small intestine	3 (0.3)	2 (0.3)	1 (0.4)
Others	24 (2.6)	20 (2.9)	4 (1.7)
Multiple	58 (6.2)	40 (5.8)	18 (7.4)
Cancer status			
Scheduled to be operated		72 (10)	
Under chemotherapy	–	381 (55)	–
Distant metastasis	–	223 (32)	–
Terminal stage	–	120 (17)	–

Variables are presented as numbers and proportions (%).

history of cancer relative to patients with no history of cancer for the clinical outcomes. Based on the previous reports[15–17] and consideration of clinical relevance, we selected 8 risk-adjusting variables for recurrent VTE, 9 risk-adjusting variables for major bleeding, and 16 risk-adjusting variables for all-cause death (**Table 1**). Furthermore, we compared the clinical outcomes among the 4 groups classified according to active cancer status. All statistical analyses were conducted using JMP version 10.0.2 (SAS Institute Inc., Cary, NC, USA). All reported P-values are 2-tailed, and P<0.05 was considered statistically significant.

Results

Patients' Characteristics

The groups with active cancer, a history of cancer, and no history of cancer comprised 695 (23%), 243 (8%), and 2,089 (69%) patients, respectively. Baseline characteristics were different across the 3 groups in several aspects (**Table 1**). Patients with active cancer were younger, and more often had a history of major bleeding and anemia. As for cancer site in patients with active cancer, lung cancer was the most common (16.4%), followed by colorectal cancer (12.7%), hematological malignancy (8.9%), uterine (8.8%), and ovarian cancer (8.5%) (**Table 2**). Among the patients with active cancer, more than half were under chemotherapy, and approximately one-third had distant metastasis.

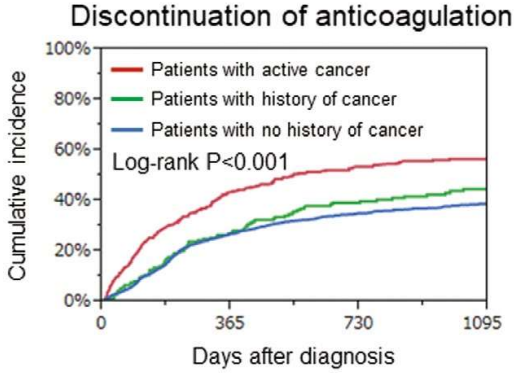
Management Strategies

The prevalence of initial parenteral anticoagulation therapy was not significantly different among the 3 groups (patients with active cancer: 83%, patients with history of cancer: 85%, and patients with no history of cancer: 84%, P=0.73) (**Table 1**). Thrombolysis was implemented least frequently in patients with active cancer (7.6%, 11.5%, and 16.7%, respectively; P<0.001), and inferior vena cava filters were placed most frequently in patients with active cancer (27%, 21%, and 23%, P=0.03).

Anticoagulation therapy beyond the acute phase was implemented least frequently in patients with active cancer (88%, 91%, and 94%, P<0.001). Most of the anticoagulation therapy beyond the acute phase was warfarin in all groups, and the prevalence of heparin usage was low even in patients with active cancer (2.6%). Median TTR for warfarin users according to Japanese guideline recommendations was lowest in patients with active cancer (**Table 1**). The rate of anticoagulation discontinuation was highest in patients with active cancer (43.5% vs. 27.0% vs. 27.0% at 1 year, P<0.001) (**Figure 2**). Discontinuation because of a bleeding event was most frequent in patients with active cancer, and interruption of anticoagulation during the entire follow-up period was also most frequent in patients with active cancer (**Table 1**).

Clinical Outcomes

The median follow-up period was 1,218 (IQR: 847–1,764)



	0-day	90-day	180-day	1-year	3-year
Patients with active cancer					
N of patients with event		103	159	215	256
N of patients at risk	614	429	316	213	77
Cumulative incidence		18.0%	29.5%	43.5%	56.7%
Patient with history of cancer					
N of patients with event		16	34	54	84
N of patients at risk	221	189	165	137	67
Cumulative incidence		7.6%	16.6%	27.0%	44.7%
Patients with no history of cancer					
N of patients with event		127	278	495	682
N of patients at risk	1968	1734	1548	1278	700
Cumulative incidence		6.7%	14.9%	27.0%	39.0%

Figure 2. Kaplan-Meier curves for discontinuation of anticoagulation therapy in the 3 groups of patients with active cancer, history of cancer and no history of cancer. The discontinuation of anticoagulation was estimated in patients who received anticoagulation therapy beyond the acute phase, and defined as withdrawal of anticoagulation therapy lasting >14 days for any reason.

days for surviving patients (95.1% follow-up rate at 1 year). The cumulative 5-year incidences of recurrent VTE and major bleeding were much higher in patients with active cancer (recurrent VTE: 17.7%, 10.2%, and 8.6%, P<0.001; major bleeding: 26.6%, 8.8%, and 9.3%, P<0.001, respectively) (**Figure 3A**,**B**). After adjusting for confounders, the excess risks of patients with active cancer relative to patients with no history of cancer for recurrent VTE and major bleeding remained highly significant (recurrent VTE: adjusted HR 2.94, 95% CI 2.20–3.92, P<0.001; major bleeding: adjusted HR 2.48, 95% CI 1.90–3.23, P<0.001, respectively), whereas the risks of patients with history of cancer relative to patients with no history of cancer for recurrent VTE and major bleeding were not significant (adjusted HR 1.47, 95% CI 0.87–2.36, P=0.15 and adjusted HR 1.01, 95% CI 0.60–1.59, P=0.97, respectively) (**Table 3**).

The cumulative 5-year incidence of all-cause death was markedly higher in patients with active cancer (73.1%, 28.6%, and 14.6%, P<0.001) (**Figure 3C**). After adjusting for confounders, the excess risks of patients with active cancer and patients with history of cancer relative to patients with no history of cancer for all-cause death were significant (patients with active cancer: adjusted HR 8.55, 95% CI 7.22–10.15, P<0.001; patients with history of cancer: adjusted HR 1.94, 95% CI 1.44–2.57, P<0.001, respectively) (**Table 3**). The cause of death was cancer in the majority of patients with active cancer (81.7%) (**Table 4**).

The cumulative 5-year incidence of stroke was higher in patients with active cancer (9.3%, 4.5%, and 4.5%, P=0.002) (**Supplementary Table**). The proportion of hemorrhagic stroke was numerically higher than that of ischemic stroke in all groups. The cumulative 5-year incidence of ischemic stroke was also higher in patients with active cancer (4.4%, 1.0%, and 1.8%, P=0.003), whereas the cumulative 5-year incidence of hemorrhagic stroke was not significantly different among the groups (5.2%, 3.6%, and 2.7%, P=0.11). There was 1 patient with active cancer who died of an ischemic stroke (**Table 4**).

Clinical Outcomes According to Active Cancer Status

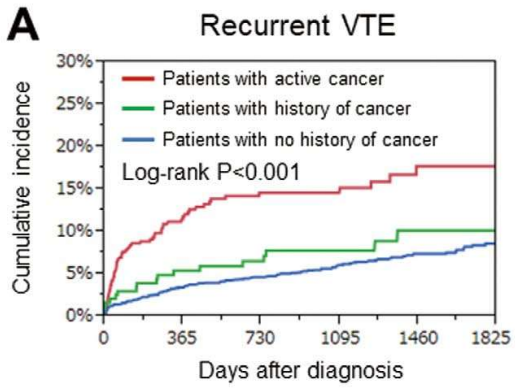
The cumulative 1-year incidence of recurrent VTE was much higher in the metastasis group than in the other cancer status groups (terminal stage group: 6.4%, metastasis group: 22.1%, under chemotherapy group: 10.8%, and other group: 5.8%, P<0.001), whereas the cumulative 1-year incidences of major bleeding and all-cause death were much higher in the terminal stage group than in the other cancer status groups (major bleeding: 32.1%, 17.8%, 11.7%, and 13.4%, P<0.001, and all-cause death: 90.1%, 61.7%, 40.7%, and 21.8%, P<0.001) (**Figure 4**). The rate of anticoagulation discontinuation was highest in the terminal stage group (57.7%, 43.2%, 38.5%, and 45.7%, at 1-year, P=0.004) (**Supplementary Figure**).

Discussion

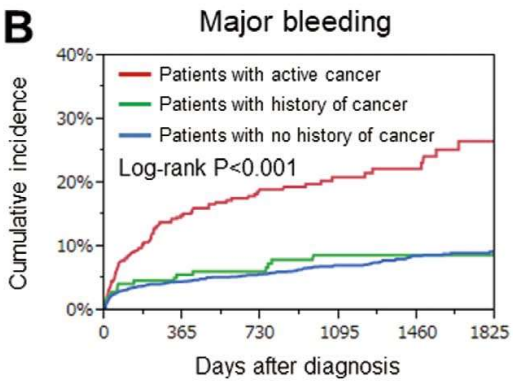
The major findings of the current study were: (1) VTE patients with active cancer had a dismal prognosis, with higher rates of recurrent VTE, major bleeding and all-cause death than those without active cancer, while patients with a history of cancer had comparable risks for recurrent VTE and major bleeding as patients with no history of cancer; (2) VTE patient with active cancer had frequent discontinuation of anticoagulation therapy during the follow-up period, and the quality of warfarin control was poor; and (3) the risks for clinical events varied widely according to cancer status in VTE patient with active cancer.

A previous study reported that VTE patients with cancer had higher risks of recurrence and bleeding than those without cancer.[3] Consistent with that report, the current study showed higher risks of VTE recurrence and bleeding in patients with active cancer than in those without active cancer. However, there are few reports evaluating clinical outcomes in patients not in the active condition of cancer (i.e., patients with history of cancer).[18,19] The present study demonstrated comparable risks of VTE recurrence and bleeding in patients with a history of cancer relative to those with no history of cancer, suggesting that the adverse effects of cancer for VTE recurrence and bleeding are significant if cancer is non-active.

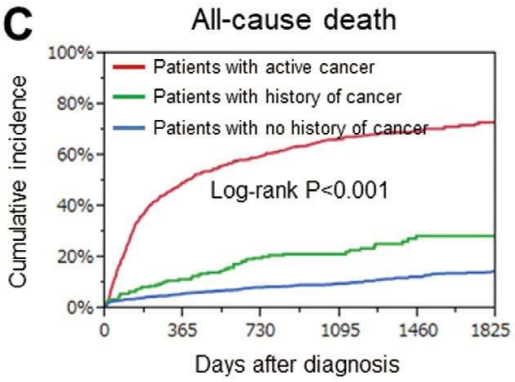
Because active cancer is a strong risk factor for recurrence of VTE, VTE patients with active cancer are considered candidates for indefinite anticoagulation therapy. Actually, several current guidelines recommend prolonged anticoagulation therapy as long as the disease is considered active.[8,15–17] Furthermore, a previous study reported the importance of cancer-associated hypercoagulability as a possible stroke etiology in patients with cancer.[20] Consistent with that report, the current study showed that VTE patients with active cancer had a higher risk for subsequent



	0-day	90-day	1-year	3-year	5-year
Patients with active cancer					
N of patients with event		48	65	75	78
N of patients at risk	695	496	311	144	42
Cumulative incidence		7.7%	11.8%	15.2%	17.7%
Patient with history of cancer					
N of patients with event		7	12	16	18
N of patients at risk	243	215	190	107	37
Cumulative incidence		3.0%	5.4%	7.8%	10.2%
Patients with no history of cancer					
N of patients with event		33	67	107	126
N of patients at risk	2089	1919	1769	1076	402
Cumulative incidence		1.6%	3.4%	6.1%	8.6%



	0-day	90-day	1-year	3-year	5-year
Patients with active cancer					
N of patients with event		50	82	98	104
N of patients at risk	695	500	312	141	40
Cumulative incidence		7.9%	15.3%	21.0%	26.6%
Patient with history of cancer					
N of patients with event		10	13	18	18
N of patients at risk	243	214	193	108	37
Cumulative incidence		4.3%	5.7%	8.8%	8.8%
Patients with no history of cancer					
N of patients with event		66	92	131	148
N of patients at risk	2089	1888	1753	1077	410
Cumulative incidence		3.3%	4.6%	7.2%	9.3%



	0-day	90-day	1-year	3-year	5-year
Patients with active cancer					
N of patients with event		153	338	442	462
N of patients at risk	695	530	341	153	43
Cumulative incidence		22.3%	49.6%	66.6%	73.1%
Patient with history of cancer					
N of patients with event		14	27	48	56
N of patients at risk	243	221	201	115	40
Cumulative incidence		5.9%	11.5%	21.5%	28.6%
Patients with no history of cancer					
N of patients with event		76	122	189	232
N of patients at risk	2089	1955	1850	1146	437
Cumulative incidence		3.7%	6.0%	9.9%	14.6%

Figure 3. Kaplan-Meier event curves for (**A**) recurrent VTE, (**B**) major bleeding and (**C**) all-cause death in the 3 groups of patients with active cancer, history of cancer and no history of cancer. VTE included PE and/or DVT. DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Table 3. Crude and Adjusted Clinical Outcomes

	No history of cancer (Reference) (n=2,089)	History of cancer (n=243)					Active cancer (n=695)				
	N of patients with event*	N of patients with event*	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value	N of patients with event*	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Recurrent VTE	130 (8.6%)	18 (10.2%)	1.31 (0.77–2.08)	0.30	1.47 (0.87–2.36)	0.15	78 (17.7%)	2.81 (2.11–3.73)	<0.001	2.94 (2.20–3.92)	<0.001
Major bleeding	151 (9.3%)	19 (8.8%)	1.16 (0.70–1.83)	0.54	1.01 (0.60–1.59)	0.97	105 (26.6%)	3.08 (2.39–3.96)	<0.001	2.48 (1.90–3.23)	<0.001
All-cause death	241 (14.6%)	59 (26.6%)	2.31 (1.72–3.04)	<0.001	1.94 (1.44–2.57)	<0.001	464 (73.1%)	9.21 (7.87–10.79)	<0.001	8.55 (7.22–10.15)	<0.001
Death from cancer	18 (1.3%)	12 (8.2%)	6.24 (2.93–12.84)	<0.001	–	–	379 (63.9%)	100.21 (64.37–166.96)	<0.001	–	–
Fatal PE	56 (2.7%)	9 (3.8%)	1.40 (0.65–2.69)	0.37	–	–	20 (3.2%)	1.12 (0.66–1.84)	0.66	–	–
Fatal bleeding	15 (1.3%)	2 (1.1%)	1.29 (0.20–4.56)	0.75	–	–	18 (6.1%)	6.17 (3.07–12.57)	<0.001	–	–

*Cumulative 5-year incidence. N of patients with event was counted throughout the entire follow-up period. Cumulative 5-year incidence was estimated using the Kaplan-Meier method. Crude and adjusted HRs and 95% CIs were estimated using the Cox proportional hazard models. HRs for the active cancer group and history of cancer group were estimated relative to the no history of cancer group. Recurrent VTE, major bleeding and all-cause death were adjusted by the respective risk-adjusting covariates listed in Table 1. CI, confidence interval; HR, hazard ratio; PE, pulmonary embolism; VTE, venous thromboembolism.

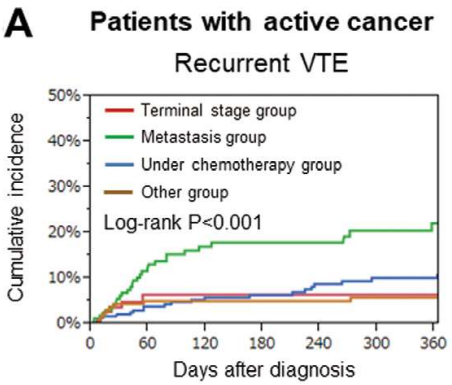
Table 4. Causes of Death During the Entire Follow-up Period

	Active cancer (n=464)	History of cancer (n=59)	No history of cancer (n=241)
Cancer	379 (81.7)	12 (20.3)	18 (7.5)
Fatal pulmonary embolism	20 (4.3)	9 (15.3)	56 (23.2)
Bleeding events	18 (3.9)	2 (3.4)	15 (6.2)
Cardiac events	4 (0.9)	6 (10.2)	27 (11.2)
Other non-cardiac events	24 (5.2)	21 (35.6)	92 (38.2)
Ischemic stroke	1 (0.2)	0 (0.0)	2 (0.8)
Unknown	19 (4.1)	9 (15.3)	33 (13.7)

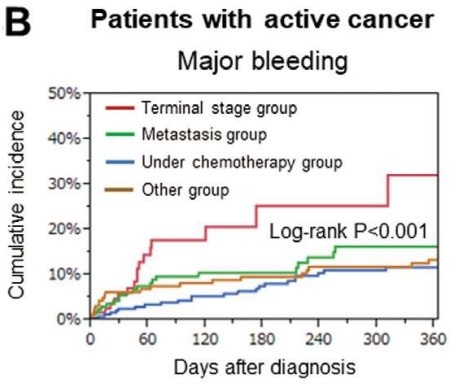
Variables are presented as numbers and proportions (%). Death was judged as cardiac if it followed acute myocardial infarction, heart failure, or ventricular arrhythmia.

ischemic stroke. In addition, it should be noted that the proportion of hemorrhagic stroke was numerically greater than that of ischemic stroke. The current study also showed that discontinuation of anticoagulation therapy during follow-up was most frequent in patients with active cancer. This might be partly because patients with active cancer generally have a higher risk for bleeding and they often have difficulty in continuing anticoagulation therapy, because of cancer progression. Patients with active cancer frequently receive various drugs that interact with warfarin, including chemotherapy, and often have unstable dietary intake, leading to difficulty in maintaining good control of warfarin.[21,22] In fact, the current study showed poor-quality warfarin control in patients with active cancer. In this context, DOACs have been reported to have comparable efficacy and safety compared with low-molecular-weight heparin in patients with cancer-associated VTE.[23,24] Considering the lower likelihood of food and drug interactions of DOACs, they could be good alternative to warfarin for cancer-associated VTE.

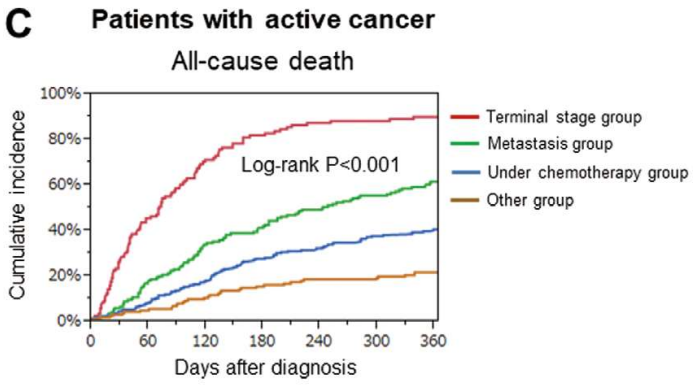
The risks for recurrence and bleeding can be higher in more advanced cancer.[25–27] Consistent with previous reports, the current study also showed that the risks for recurrence and bleeding, as well as death, tended to be higher in parallel with the progression of cancer status. Furthermore, patients in the terminal stage of cancer had the highest risk for major bleeding with a dismal mortality risk. Actually, the current study also showed that anticoagulation therapy was discontinued most frequently in patients in the terminal stage of cancer, partly because of a bleeding event. We should be cautious about considering the need and duration of anticoagulation therapy for patients in the terminal stage of cancer. A recent study reported that approximately one-third of patients with



	0-day	90-day	180-day	1-year
Terminal stage group				
N of patients with event		6	6	6
N of patients at risk	120	46	20	12
Cumulative incidence		6.4%	6.4%	6.4%
Metastasis group				
N of patients with event		23	26	29
N of patients at risk	168	110	81	50
Cumulative incidence		15.3%	17.9%	22.1%
Under chemotherapy group				
N of patients with event		11	14	21
N of patients at risk	244	199	164	131
Cumulative incidence		4.8%	6.4%	10.8%
Other group				
N of patients with event		8	8	9
N of patients at risk	163	144	131	122
Cumulative incidence		5.1%	5.1%	5.8%



	0-day	90-day	180-day	1-year
Terminal stage group				
N of patients with event		14	16	17
N of patients at risk	120	40	17	11
Cumulative incidence		17.7%	25.3%	32.1%
Metastasis group				
N of patients with event		15	16	22
N of patients at risk	168	119	91	57
Cumulative incidence		9.7%	10.5%	17.8%
Under chemotherapy group				
N of patients with event		9	16	23
N of patients at risk	244	204	164	134
Cumulative incidence		3.9%	7.5%	11.7%
Other group				
N of patients with event		12	15	20
N of patients at risk	163	140	126	113
Cumulative incidence		7.5%	9.6%	13.4%



	0-day	90-day	180-day	1-year
Terminal stage group				
N of patients with event		69	95	104
N of patients at risk	120	48	21	12
Cumulative incidence		58.6%	82.0%	90.1%
Metastasis group				
N of patients with event		38	69	101
N of patients at risk	168	127	96	63
Cumulative incidence		23.0%	42.0%	61.7%
Under chemotherapy group				
N of patients with event		33	67	98
N of patients at risk	244	209	175	143
Cumulative incidence		13.6%	27.7%	40.7%
Other group				
N of patients with event		13	25	35
N of patients at risk	163	149	136	127
Cumulative incidence		8.1%	15.6%	21.8%

Figure 4. Kaplan-Meier event curves for (**A**) recurrent VTE, (**B**) major bleeding and (**C**) all-cause death in the 4 groups classified according to active cancer status: terminal stage group, metastasis group, under chemotherapy group, and other group. VTE included PE and/or DVT. DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

advanced cancer admitted to palliative care units had a DVT, although thromboprophylaxis for these patients seemed to be of little benefit.[28] For the decision-making on anticoagulation therapy in cancer patients in the terminal stage, it might be important to consider not only the prognosis, but also quality of life based on the individual patient. In addition to the progression of cancer status, cancer sites could also have some influence on the recurrence and bleeding risk, which should be take into consideration. Further studies are warranted for optimal treatment strategies according to cancer sites.

Study Limitations

First, this was an observational cohort study with the limitations inherent to the study design. The decisions regarding management strategies were left to the discretion of the attending physicians. Second, demographics, practice patterns as well as clinical outcomes in patients with VTE in Japan may be different from those outside Japan. Third, low-molecular-weight heparin for VTE was not covered by Japanese national insurance. Therefore, warfarin was mostly used as the anticoagulation therapy beyond the acute phase for patients with active cancer, although low-molecular-weight heparin is recommended over warfarin in the Western guideline. Fourth, cancer treatments, including platinum-based chemotherapy and molecular targeted therapy, were not evaluated. Fifth, the time period of cancer relapse-free survival in the patients with history of cancer was also not evaluated. Finally, cancer status was not evaluated after the index VTE event, and we could not assess the influence of the course of cancer during follow-up on clinical outcomes.

Conclusions

In a current real-world Japanese VTE registry, patients with active cancer had higher risk for VTE recurrence, bleeding, and death than patients without active cancer. Anticoagulation therapy was frequently discontinued prematurely in VTE patients with active cancer in discordance with current guideline recommendations.

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Conflicts of Interest

Dr. Yamashita received lecture fees from Daiichi-Sankyo, Bristol-Myers Squibb, and Bayer Healthcare. Dr. Morimoto received lecture fees from Mitsubishi Tanabe Pharma and Pfizer Japan, and consultant fees from Asahi Kasei, Bristol-Myers Squibb, and Boston Scientific. Dr. Akao received lecture fees from Pfizer, Bristol-Myers Squibb, Boehringer Ingelheim, Bayer Healthcare, and Daiichi-Sankyo. Dr. Kimura received a research grant from Daiichi-Sankyo. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Supplementary Files

Please find supplementary file(s);
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Circ J 2019; **83:** 2271–2281
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Supplementary File

Cancer-Associated Venous Thromboembolism in the Real World

— From the COMMAND VTE Registry —

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on behalf of the COMMAND VTE Registry Investigators

Supplementary File

Supplementary Appendix 1

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Supplementary Appendix 2

Definitions of Patients' Characteristics

Transient risk factors for VTE included recent surgery (within 2 months prior to VTE), recent immobilization (defined as non-surgical bed-ridden patients with bathroom privileges for >4 days within 2 months prior to VTE), long-distance travel (travel lasting >=6 hours in the previous 3 weeks), central venous catheter use, pregnancy or puerperium, recent leg trauma, fracture or burn (any events requiring immobilization in the past 2 months), severe infection, and estrogen use[1]. Hypertension was diagnosed if peripheral blood pressure was >140/90 mmHg or if the patient was taking medication for hypertension. The presence of diabetes was diagnosed using hemoglobin A1c (HbA1c) [National Glycohemoglobin Standardization Program (NGSP), 6.5%] as the standard or was assumed if the patient was taking medication for the treatment of diabetes. Dyslipidemia was diagnosed if total cholesterol was >240 mg/dL, if high-density lipoprotein cholesterol was <40 mg/dL, or if the patient was taking statins. Chronic kidney disease was diagnosed if there was persistent proteinuria or if estimated glomerular filtration rate (eGFR) was <60 mL/min/1.73 m^2 for more than 3 months. The values of eGFR were calculated based on the equation reported by Japan Association of Chronic Kidney Disease Initiative [male: $194*Scr^{-1.094}*age^{-0.287}$, female: $194*Scr^{-1.094}*age^{-0.287}*0.739$]. Dialysis was defined as hemodialysis or peritoneal dialysis. Chronic lung disease was defined as persistent lung disorders such as asthma, chronic obstructive pulmonary disease, and restrictive lung diseases. History of heart failure was diagnosed if the patient had a history of hospitalization for heart failure, if the patient had symptoms due to heart failure [New York Heart Association (NYHA) functional class ≥2], or if the left ventricular ejection fraction was <40%. Anemia was diagnosed if the value of hemoglobin was <13 g/dL for man and <12 g/dL for woman. Thrombophilia included protein C deficiency, protein S deficiency, antithrombin deficiency, and antiphospholipid syndrome. History of major bleeding was diagnosed if the patient had a history of International Society of Thrombosis and Hemostasis (ISTH) major bleeding, which consisted of a reduction in the hemoglobin level by at least 2 g/dL, transfusion of at least 2 units of blood or symptomatic bleeding in a critical area or organ[2]. Antiplatelets included aspirin, clopidogrel, ticlopidine, cilostazol, and prasugrel.

Supplementary Appendix 3

Independent Clinical Event Committee

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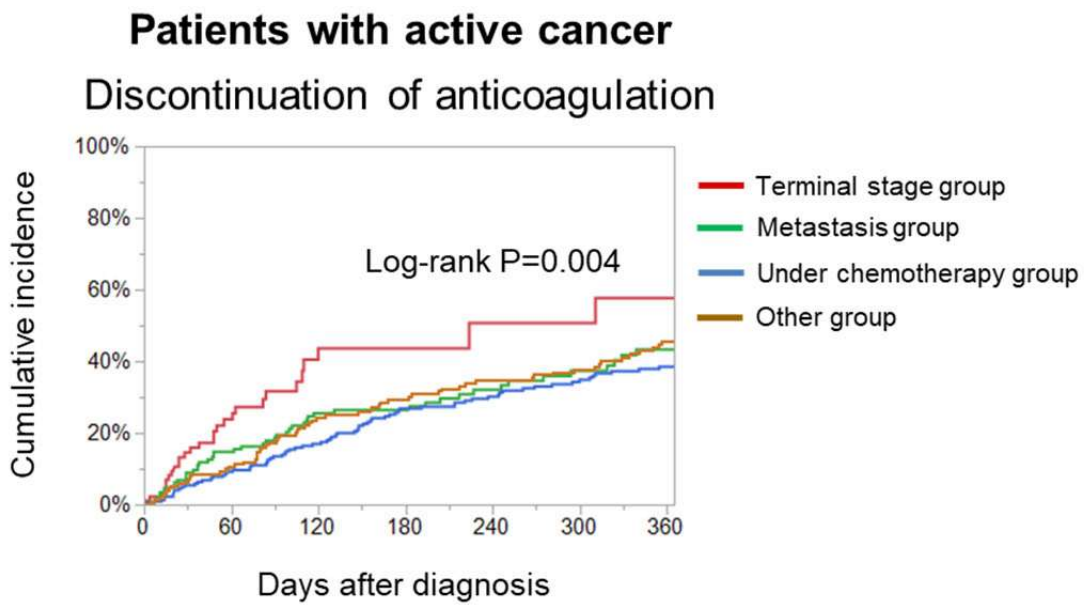
Supplementary Table. Stroke Events

	Active cancer (N=695)	**History of cancer (N=243)**	**No history of cancer (N=2089)**	**Log-rank P value**
	N of patients with event (Cumulative 5-year incidence)	N of patients with event (Cumulative 5-year incidence)	N of patients with event (Cumulative 5-year incidence)	
Stroke	29 (9.3%)	9 (4.5%)	63 (4.5%)	0.002
Ischemic	13 (4.4%)	2 (1.0%)	23 (1.8%)	0.003
Hemorrhagic	16 (5.2%)	7 (3.6%)	40 (2.7%)	0.11

N of patients with event was counted throughout the entire follow-up period. Cumulative 5-year incidence was estimated using the Kaplan-Meier method. We assessed the differences with the log-rank test.

Supplementary Figure



	0-day	90-day	180-day	1-year
Terminal stage group				
N of patients with event		22	26	28
N of patients at risk	90	29	12	6
Cumulative incidence		31.6%	43.6%	57.7%
Metastasis group				
N of patients with event		26	35	48
N of patients at risk	147	101	73	36
Cumulative incidence		18.7%	26.4%	43.2%
Under chemotherapy group				
N of patients with event		29	55	75
N of patients at risk	225	179	137	100
Cumulative incidence		13.5%	26.8%	38.5%
Other group				
N of patients with event		26	43	64
N of patients at risk	152	122	97	69
Cumulative incidence		17.5%	29.5%	45.7%

Kaplan-Meier curves for discontinuation of anticoagulation therapy comparing the 4 groups classified according to the active cancer status; the terminal stage group, metastasis group, under chemotherapy group, and other group.

The discontinuation of anticoagulation was estimated in patients who received anticoagulation therapy beyond the acute phase, and defined as withdrawal of anticoagulation therapy lasting >14 days for any reasons.

Supplementary References

1. Laporte S, Mismetti P, Decousus H, et al. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry. *Circulation* 2008; **117:** 1711–1716.

2. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; 3: 692–694.