International Journal of Cardiology 292 (2019) 198–204

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

# The association of recurrence and bleeding events with mortality after venous thromboembolism: From the COMMAND VTE Registry

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## ARTICLE INFO

*Article history:*
Received 4 January 2019
Received in revised form 10 May 2019
Accepted 12 June 2019
Available online 13 June 2019

*Keywords:*
Venous thromboembolism
Recurrence
Bleeding
Mortality

## ABSTRACT

*Background:* The duration of anticoagulation therapy after venous thromboembolism (VTE) should be based on the balance between risks of recurrent VTE and bleeding. However, there is uncertainty about the impact of these events on subsequent mortality.

*Methods:* We evaluated the association of recurrent VTE and major bleeding events with mortality among 3026 patients in the COMMAND VTE Registry. We estimated the risks of the recurrent VTE events and the major bleeding events for subsequent mortality by the time-updated multivariable Cox proportional hazard model.

*Results:* During the median follow-up period of 1218 days, 225 patients developed recurrent VTE events, 274 patients developed major bleeding events, and 763 patients died. The multivariable Cox proportional hazard model revealed that both the recurrent VTE and major bleeding events were strongly associated with subsequent mortality risk (recurrent VTE: HR 3.24, 95%CI 2.57–4.08, $P < 0.001$; major bleeding: HR 3.53, 95%CI 2.88–4.31, $P < 0.001$). Both the recurrent pulmonary embolism (PE) and recurrent deep vein thrombosis (DVT) events were associated with subsequent mortality risk (recurrent PE events: HR 4.42, 95%CI 3.28–5.95, $P < 0.001$; recurrent DVT events: HR 2.42, 95%CI 1.75–3.36, $P < 0.001$).

*Conclusions:* In the real-world patients with VTE, both the recurrent VTE events and the major bleeding events were strongly associated with subsequent mortality risk with the comparable effect size. The

*Abbreviations:* CI, confidence interval; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; HR, hazard ratio; IQR, interquartile range; PE, pulmonary embolism; TTR, time in therapeutic range; VTE, venous thromboembolism.

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https://doi.org/10.1016/j.ijcard.2019.06.032
0167-5273/

recurrent PE and recurrent DVT events were also associated with increased risks for mortality, although the magnitude of the effect on mortality was numerically greater with the recurrent PE events than with the recurrent DVT events.



## 1. Introduction

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), has a long-term risk for recurrence, which can be prevented by anticoagulation therapy [1]. The current guidelines recommend specific durations of anticoagulation therapy for the prevention of recurrent VTE depending on the risks for recurrence [2–5]. However, there is a concern on an increased risk for bleeding associated with anticoagulation therapy, and the optimal duration of anticoagulation therapy after VTE remains a matter of active debate.

Recently, extended anticoagulation therapy with direct oral anticoagulants (DOAC) after the specific durations of anticoagulation therapy has been reported to reduce the risk of recurrent VTE with only a slight increase in bleeding events compared with no anticoagulation therapy [6–8]. Based on these randomized clinical trials, prolonged anticoagulation therapy might be recommended in patients with high-risk for recurrent VTE. However, many physicians currently stop anticoagulation therapy within 3 to 12 months after VTE, suggesting the presence of the physicians' concern about the risk for bleeding events [9]. This is partly because there is still uncertainty about the benefit-risk trade-off of reduced recurrent VTE events versus increased important bleeding events in the real-world clinical practice. The impact of recurrent VTE events and bleeding events on subsequent mortality after VTE has not been thoroughly evaluated yet, which is important for appropriate decision making on the duration of anticoagulation therapy. Therefore, we sought to evaluate the impact of recurrent VTE events and bleeding events on subsequent mortality in patients with VTE in a large retrospective observational database in Japan.

## 2. Methods

### 2.1. Study population

The COMMAND VTE (COntemporary ManageMent AND outcomes in patients with Venous ThromboEmbolism) Registry is a physician-initiated, multicenter, retrospective cohort study enrolling consecutive patients with acute symptomatic VTE objectively confirmed by imaging examinations (ultrasound, contrast-enhanced computed tomography, ventilation-perfusion lung scintigraphy, pulmonary angiography, or contrast venography) or by autopsy among 29 centers in Japan between January 2010 and August 2014 [10,11]. The study conforms to the Declaration of Helsinki and the relevant review boards or ethics committees in all 29 participating centers (Online Appendix 1) approved the research protocol. Written informed consent from each patient was waived, because we used clinical information obtained in routine clinical practices, and no patients refused to participate in the study when contacted for follow-up. This method is concordant with the guidelines for epidemiological studies issued by the Ministry of Health, Labor, and Welfare in Japan.

We searched the hospital databases for clinical diagnosis and imaging examinations, and enrolled consecutive patients who met the definition of acute symptomatic VTE diagnosed within 31 days from symptom onset during the study period [12]. The symptoms of VTE were defined as follows; sudden onset dyspnea, pleuritic chest pain, substernal chest pain, cough, fever, hemoptysis, and syncope for PE, and erythema, warmth, pain, swelling, tenderness, and pain upon dorsiflexion of the foot for DVT [13,14]. Additionally, sudden onset abnormalities in vital signs such as a decrease in arterial oxygen saturation and hypotension were also regarded as symptoms of PE. The presence or absence of symptoms was evaluated at the time of the imaging studies.

We enrolled 3027 consecutive patients with acute symptomatic VTE after screening of the consecutive 19,634 patients with suspected VTE for eligibility through chart review by the physicians at each institution. We excluded 1 patients, who developed the first recurrent VTE and major bleeding events on the same day during the follow-up period. The current study population consisted of 3026 patients who were categorized into 3 groups based on the types of the events during the follow-up period (recurrent VTE or major bleeding): recurrent VTE group (patients with recurrent VTE events without or ahead of major bleeding), major bleeding group (patients with major bleeding events without or ahead of recurrent VTE), and no-event group (patients without recurrent VTE or major bleeding events) (Fig. 1). Thus, 39 patients who developed both recurrent VTE and major bleeding events during the follow-up period were classified according to the first events of either recurrent VTE or major bleeding events; 23 patients had bleeding events after the recurrent VTE event, while 16 patients had recurrent VTE events after the bleeding event. We compared the clinical characteristics, management strategies and long-term outcomes among the 3 groups.

### 2.2. Data collection and definitions for patient characteristics

Data for the baseline characteristics were collected from the hospital charts or hospital databases according to the pre-specified definitions. The physicians at each institution were responsible for data entry into an electronic case report form in a web-based database system. Data were automatically checked for missing or contradictory input and values out of the expected range. Additional monitoring for the quality of data was performed at the general office of the registry. The detailed definitions of other patient characteristics are described in Online Appendix 3.

### 2.3. Clinical follow-up and endpoints

Collection of follow-up information was mainly conducted 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 procedure, acute myocardial infarction, stroke and status of anticoagulation therapy.

The outcome measure in the current study was all-cause death, recurrent VTE and major bleeding. Recurrent VTE was defined as symptomatic PE and/or DVT accompanied by confirmation of new thrombus or exacerbation of the thrombus by objective imaging examinations or autopsy [15]. 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, transfusion of at least 2 units of blood or symptomatic bleeding in a critical area or organ [16]. The independent clinical event committee (Online Appendix 2) unaware of the patient characteristics reviewed all the death events, and classified the causes of deaths as due to PE, due to bleeding events, due to cancers, due to other non-cardiac causes, due to cardiac causes, or due to unknown causes [17]. Death was judged to be due to PE (fatal PE) if it was confirmed by autopsy or if death followed a clinically severe PE, either initially or after recurrent pulmonary embolic events. Death was judged to be bleeding related (fatal bleeding) if it followed an intracranial hemorrhage or a bleeding episode leading to hemodynamic deterioration. Death in patients with the end-stage cancer without

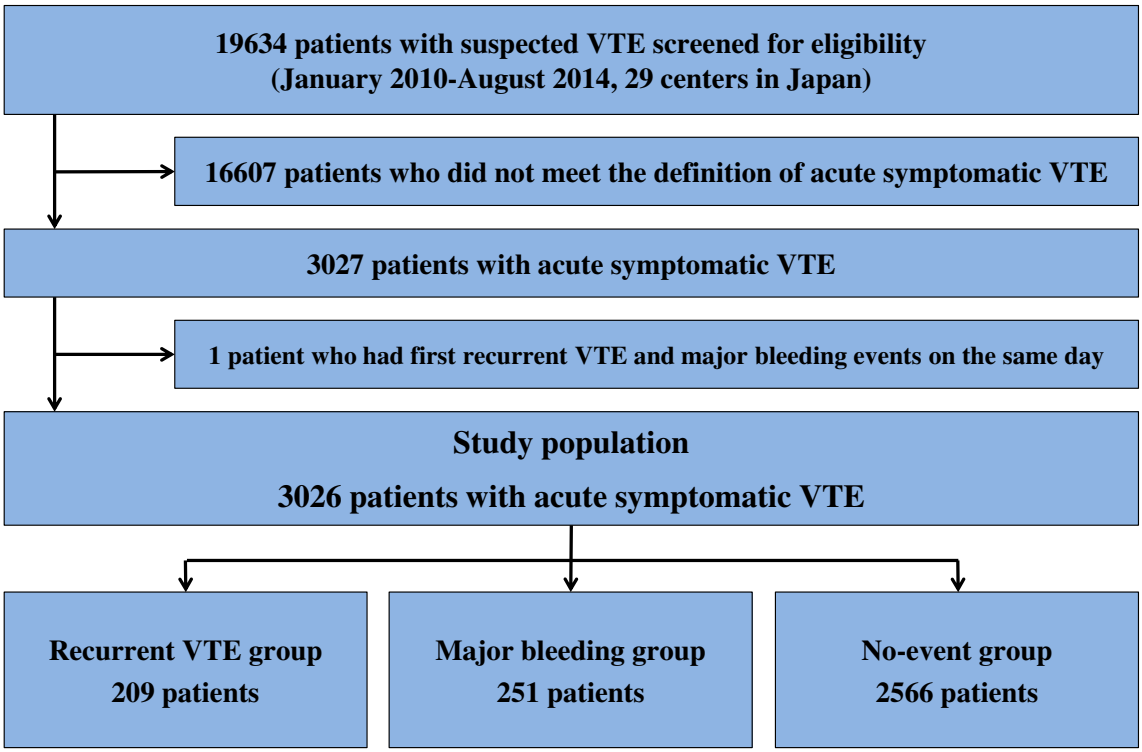



**Fig. 1.** Study flow chart. VTE included PE and/or DVT. PE, pulmonary embolism; DVT, deep vein thrombosis; VTE, venous thromboembolism.

a specific cause of death was regarded as cancer in origin. Final classifications for causes of deaths were made on the basis of the full consensus of the independent clinical event committee. The definitions of other clinical events are described in Online Appendix 4.

### 2.4. Statistical analysis

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 (IQR) 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 among 3 groups using one-way analysis of variance or Kruskal-Wallis test based on their distributions. We used the Kaplan-Meier method to estimate the cumulative incidences of all-cause death and assessed the differences with the log-rank test. We estimated the risks of recurrent VTE events and major bleeding events for subsequent all-cause death with the multivariable Cox proportional hazard model. We incorporated the recurrent VTE events and major bleeding events during follow-up into the multivariable Cox model as time-updated covariates together with the clinically-relevant 16 risk-adjusting factors listed in the Table 1. We expressed the adjusted risks of each covariate as hazard ratios (HR) and their 95%confidence intervals (CI). Furthermore, to assess the risks of recurrent PE and recurrent DVT events for subsequent all-cause death respectively, we divided recurrent VTE events into recurrent PE (PE with or without DVT) and recurrent DVT (DVT only), and incorporated these events as well as major bleeding events into the multivariable Cox model as time-updated covariates. As a sensitivity analysis, to clarify the influence of active cancer, we conducted additional stratified analysis with the same multivariable Cox proportional hazard model as the main analysis according to presence or absence of active cancer. The statistical analyses were conducted by the 2 physicians (Y. Yamashita and Y. Yoshikawa) and the statistician (T. Morimoto). The multivariable Cox proportional hazard model with time-updated covariates was performed with SPSS version 25 (IBM Corp.). All the other analyses were performed with JMP version 10.0.2 (SAS Institute Inc., Cary, NC, USA). The reported *P* values were 2-sided and P values <0.05 were considered statistically significant.

## 3. Results

### 3.1. Patient characteristics and clinical events

In the current study population, the mean age was 67 years, 61% were women, and mean body weight and body mass index were 57.9 kg and 23.2 kg/m$^2$, respectively. During the follow-up period, 763 patients died, 225 patients developed recurrent VTE events, and 274 patients developed major bleeding events. The cumulative 5-year incidences of recurrent VTE and major bleeding events were 10.5% and 12.1%, respectively (Online Figs. 1 and 2). Recurrent VTE, major bleeding, and no-event group accounted for 209 patients (6.9%), 251 patients (8.3%), and 2566 patients (84.8%), respectively. The baseline patient characteristics were different in several aspects across the 3 groups (Table 1). Major bleeding group was older, and more often had lower body weight, and co-morbidities such as history of major bleeding, anemia, and thrombocytopenia, although the proportions of PE at presentation were not significantly different among the 3 groups.

### 3.2. Anticoagulation therapy during the follow-up period

The median follow-up period was 1218 (IQR: 847–1764) days for surviving patients (95.1% follow-up rate at 1 year). The prevalence of anticoagulation therapy beyond the acute phase was not significantly different among the 3 groups, whereas median time in therapeutic range (TTR) according to the Japanese guidelines recommendations among warfarin users beyond the acute phase was higher in the no-event group (Table 1). Among patients who received anticoagulation therapy beyond the acute phase, any discontinuation of anticoagulation therapy during the follow-up period was more frequent in the recurrent VTE group and in the major bleeding group than in the no-event group.

**Table 1**
Patient characteristics.

| | Recurrent VTE group ($N = 209$) | Major bleeding group ($N = 251$) | No-event group ($N = 2566$) | *P*-value |
|---|---|---|---|---|
| Baseline characteristics | | | | |
| Age (years)[a] | 63.6 ± 15.8 | 69.1 ± 15.4 | 67.3 ± 15.3 | <0.001 |
| Men[a] | 76 (36%) | 106 (42%) | 987 (38%) | 0.40 |
| Body weight (kg) | 59.0 ± 13.3 | 54.7 ± 12.2 | 58.1 ± 13.9 | <0.001 |
| Body mass index (kg/m$^2$) | 23.0 ± 3.9 | 22.2 ± 4.0 | 23.3 ± 4.5 | 0.001 |
| Body mass index ≥30 kg/m$^2$ | 12 (5.7%) | 11 (4.4%) | 146 (5.7%) | 0.69 |
| Comorbidities | | | | |
| Hypertension[a] | 70 (33%) | 97 (39%) | 994 (39%) | 0.32 |
| Diabetes mellitus[a] | 22 (11%) | 36 (14%) | 328 (13%) | 0.47 |
| Dyslipidemia | 26 (12%) | 47 (19%) | 535 (21%) | 0.01 |
| Chronic kidney disease[a] | 56 (27%) | 65 (26%) | 451 (18%) | <0.001 |
| Dialysis | 3 (1.4%) | 4 (1.6%) | 14 (0.6%) | 0.07 |
| History of cancer | 85 (41%) | 108 (43%) | 744 (29%) | <0.001 |
| Active cancer at diagnosis[a] | 70 (33%) | 91 (36%) | 533 (21%) | <0.001 |
| Chronic lung disease | 18 (8.6%) | 29 (11.6%) | 224 (8.7%) | 0.32 |
| Heart failure | 1 (0.5%) | 16 (6.4%) | 84 (3.3%) | 0.002 |
| History of myocardial infarction | 1 (0.5%) | 7 (2.8%) | 45 (1.8%) | 0.17 |
| History of stroke[a] | 19 (9.1%) | 35 (13.9%) | 216 (8.4%) | 0.01 |
| Atrial fibrillation | 8 (3.8%) | 14 (5.6%) | 107 (4.2%) | 0.54 |
| Liver cirrhosis[a] | 0 (0.0%) | 3 (1.2%) | 23 (0.9%) | 0.34 |
| Connective tissue disease[a] | 21 (10.1%) | 30 (12.0%) | 193 (7.5%) | 0.03 |
| Varicose vein[a] | 15 (7.2%) | 6 (2.4%) | 118 (4.6%) | 0.051 |
| History of VTE[a] | 16 (7.7%) | 13 (5.2%) | 149 (5.8%) | 0.49 |
| History of major bleeding[a] | 16 (7.7%) | 45 (17.9%) | 170 (6.6%) | <0.001 |
| Transient risk factors for VTE[a] | 60 (29%) | 83 (33%) | 943 (37%) | 0.04 |
| Presentation | | | | |
| PE with or without DVT[a] | 125 (60%) | 144 (57%) | 1445 (56%) | 0.60 |
| Hypoxemia | 56/125 (45%) | 64/144 (44%) | 730/1445 (51%) | 0.20 |
| Shock | 5/125 (4.0%) | 22/144 (15.3%) | 152/1445 (10.5%) | 0.01 |
| Cardiac arrest/collapse | 1/125 (0.8%) | 12/144 (8.3%) | 67/1445 (4.6%) | 0.01 |
| DVT only[a] | 84 (40%) | 107 (43%) | 1121 (44%) | 0.60 |
| Proximal DVT[a] | 56/84 (67%) | 77/107 (72%) | 788/1121 (70%) | 0.72 |
| Laboratory tests at diagnosis | | | | |
| Anemia[a] | 109 (52%) | 172 (69%) | 1345 (52%) | <0.001 |
| Thrombocytopenia (platelet count <100 × 10$^9$/L)[a] | 11 (5.3%) | 29 (11.6%) | 127 (5.0%) | <0.001 |
| D-dimer (μg/mL) ($N = 2851$) | 11.5 (5.3–22.7) | 13.8 (5.6–27.9) | 10.0 (5.0–20.0) | 0.002 |
| Thrombophilia[a] | 17 (8.1%) | 14 (5.6%) | 116 (4.5%) | 0.056 |
| Treatment in the acute phase | | | | |
| Initial anticoagulation therapy | 165 (79%) | 221 (88%) | 2147 (84%) | 0.03 |
| Thrombolysis | 39 (19%) | 34 (14%) | 357 (14%) | 0.16 |
| Inferior vena cava filter use | 51 (24%) | 90 (36%) | 579 (23%) | <0.001 |
| Ventilator support | 4 (1.9%) | 13 (5.2%) | 75 (2.9%) | 0.09 |
| Percutaneous cardiopulmonary support | 4 (1.9%) | 7 (2.8%) | 28 (1.1%) | 0.053 |
| Concomitant medications at discharge | | | | |
| Corticosteroids | 28 (13%) | 38 (15%) | 280 (11%) | 0.09 |
| Non-steroidal anti-inflammatory drugs | 25 (12.0%) | 28 (11.2%) | 243 (9.5%) | 0.38 |
| Proton pump inhibitors/H2-blockers | 85 (41%) | 122 (49%) | 1128 (44%) | 0.21 |
| Statins | 16 (7.7%) | 34 (13.6%) | 387 (15.1%) | 0.01 |
| Antiplatelet agents | 19 (9.1%) | 28 (11.2%) | 260 (10.1%) | 0.76 |
| Anticoagulation therapy beyond the acute phase | 185 (89%) | 231 (92%) | 2386 (93%) | 0.056 |
| Warfarin | 172 (82%) | 213 (85%) | 2290 (89%) | <0.001 |
| Direct oral anticoagulant | 7 (3.4%) | 5 (2.0%) | 66 (2.6%) | |
| Heparin | 6 (2.9%) | 13 (5.2%) | 30 (1.2%) | |
| TTR for INR 1.5–2.5 (%) ($N = 2508$) | 61.9 (41.9–83.1) | 63.2 (38.1–84.1) | 74.0 (47.4–92.5) | <0.001 |
| TTR for INR 2.0–3.0 (%) ($N = 2508$) | 30.6 (13.2–51.1) | 30.3 (12.2–56.0) | 30.8 (7.2–56.4) | 0.81 |
| Discontinuation of anticoagulation during follow-up | 112/185 (61%) | 156/231 (68%) | 821/2386 (34%) | <0.001 |
| Reason for discontinuation | | | | |
| Bleeding event | 21/112 (19%) | 129/156 (83%) | 51/821 (6.2%) | <0.001 |
| Physician's judgment in the absence of adverse event | 66/112 (59%) | 16/156 (10%) | 566/821 (69%) | |
| Others | 25/112 (22%) | 11/156 (7.1%) | 204/821 (25%) | |
| Interruption of anticoagulation during follow-up period | 42/185 (23%) | 55/231 (24%) | 245/2386 (10%) | <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 m$^2$ for >3 months. The values of eGFR were calculated based on the equation reported by Japan Association of Chronic Kidney Disease Initiative [man: $194^{*}Scr^{-1.094}{}^{*}age^{-0.287}$, woman: $194^{*}Scr^{-1.094}{}^{*}age^{-0.287}{}^{*}0.739$]. 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.

VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; INR, international normalized ratio; TTR, time in therapeutic range.

[a] Potential variables for the multivariable Cox regression model to estimate the risk for all-cause death.

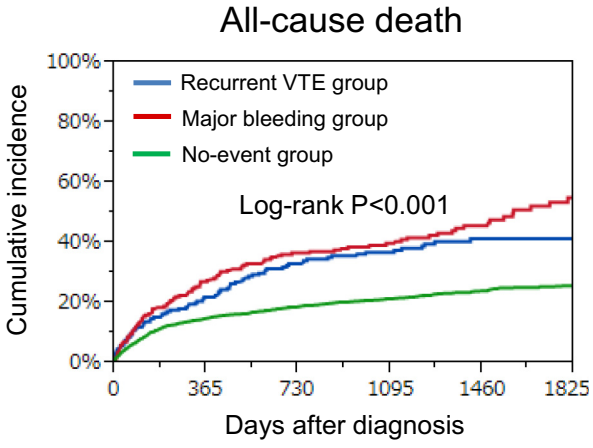
The reasons for discontinuation of anticoagulation were different across the 3 groups, and the bleeding event was the dominant reason for discontinuation of anticoagulation in the major bleeding group (Table 1). The prevalence of interruption of anticoagulation therapy during the follow-up period was also higher in the recurrent VTE group and in the major bleeding group than in the no-event group.

### 3.3. Mortality during the follow-up period

Among 763 patients who died during follow-up, more than half of the causes of deaths were due to cancers (Online Table 1). The cumulative 5-year incidence of all-cause death was significantly higher in the recurrent VTE group and in the major bleeding group than in the no-event group (recurrent VTE group: 41.5%, major bleeding group: 55.0%, and no-event group: 25.7%, $P < 0.001$) (Fig. 2). The predominant cause of deaths was cancer in all groups, whereas the proportion of deaths due to PE was markedly higher in the recurrent VTE group, and the proportion of deaths due to bleeding events was markedly higher in the major bleeding group (Online Table 1). As for subsequent mortality after the events, the cumulative 1-year incidences of subsequent all-cause death after the events were 33.0% in the recurrent VTE group and 43.7% in the major bleeding groups, respectively (Online Fig. 3). The cumulative 1-year incidences of subsequent all-cause death after the event were 40.4% in the recurrent PE group and 25.9% in the recurrent DVT group, respectively (Online Fig. 4).

The time-updated multivariable Cox proportional hazard model revealed that both the recurrent VTE events and the major bleeding events were strongly associated with subsequent mortality risk (recurrent VTE events: HR 3.24, 95%CI 2.57–4.08, $P < 0.001$; major bleeding events: HR 3.53, 95%CI 2.88–4.31, $P < 0.001$) (Table 2). Both the recurrent PE events and the recurrent DVT events were associated with subsequent mortality risk with the numerically greater magnitude of effect with the recurrent PE events than with the recurrent DVT events (recurrent PE events: HR 4.42, 95%CI 3.28–5.95, $P < 0.001$; recurrent DVT events: HR 2.42, 95%CI 1.75–3.36, $P < 0.001$).

The baseline patient characteristics according to presence or absence of active cancer were shown in Online Tables 2 and 3. Stratified analysis with the time-updated multivariable Cox proportional hazard model revealed consistent results irrespective of active cancer, although the HRs were numerically lower in active cancer patients than in no active cancer patients (Active cancer patients; recurrent VTE events: HR 2.56, 95% CI 1.94–3.40, $P < 0.001$; major bleeding events: HR 3.12, 95%CI 2.42–4.02, $P < 0.001$, and No active cancer patients; recurrent VTE events: HR 4.13, 95%CI 2.74–6.22, $P < 0.001$; major bleeding events: HR 3.58, 95%CI 2.56–5.01, $P < 0.001$) (Online Tables 4 and 5). The predominant cause of death was cancer in active cancer patients (Online Table 6), whereas among no active cancer patients, the predominant cause of death was PE events in the recurrent VTE group, and that was bleeding event in the major bleeding group (Online Table 7).




| | 0-day | 90-day | 1-year | 3-year | 5-year |
|---|---|---|---|---|---|
| Recurrent VTE group | | | | | |
| N of patients with event | | 25 | 46 | 75 | 81 |
| N of patients at risk | 209 | 185 | 163 | 100 | 37 |
| Cumulative incidence | | 12.0% | 22.0% | 36.9% | 41.5% |
| Major bleeding group | | | | | |
| N of patients with event | | 32 | 67 | 95 | 111 |
| N of patients at risk | 251 | 218 | 178 | 99 | 30 |
| Cumulative incidence | | 12.8% | 27.1% | 39.9% | 55.0% |
| No-event group | | | | | |
| N of patients with event | | 186 | 373 | 508 | 557 |
| N of patients at risk | 2566 | 2302 | 2052 | 1215 | 454 |
| Cumulative incidence | | 7.4% | 15.0% | 21.4% | 25.7% |

**Fig. 2.** Kaplan-Meier event curves for all-cause death among the 3 groups; recurrent VTE group, major bleeding group, and no-event group. VTE, venous thromboembolism.

## 4. Discussion

The main findings of the current study were as follows; 1) both the recurrent VTE events and the major bleeding events were strongly associated with subsequent mortality risk with the comparable effect size; and 2) The recurrent PE events and the recurrent DVT events were also associated with increased risks for mortality, although the magnitude of the effect on mortality was numerically greater with the recurrent PE events than with the recurrent DVT events.

The duration of anticoagulation therapy after VTE should be based on the balance between the risk of recurrence and bleeding events, as well as the clinical importance of each event. Recently, the randomized clinical trial evaluating the efficacy and safety of edoxaban for cancer-associated VTE (HOKUSAI-VTE-Cancer) has been reported [18]. In the trial, the primary outcome was defined as a composite of recurrent VTE or major bleeding, which might be based on the assumption that recurrent VTE and major bleeding are equivalent in terms of clinical importance. The trial revealed that oral edoxaban was noninferior to dalteparin with respect to the composite outcome; the rate of recurrent VTE was lower, while the rate of major bleeding was higher with edoxaban than with dalteparin. Considering the uncertainty about the benefit-risk trade-off of reduced recurrent VTE events versus increased major bleeding events, the results should be interpreted with caution. The current study showed that recurrent VTE events and major bleeding events after VTE were associated with increased risks for mortality with the comparable effect size, suggesting the similar importance of recurrent VTE events and major bleeding events in terms of subsequent mortality. The current study confirmed the previous studies suggesting that survival is significantly worse for patients with active cancer who have both recurrent VTE (especially PE) and anticoagulant bleeding [19,20].

The current guideline states that the outcomes important to patients with VTE are recurrent VTE, major bleeding, and all-cause death [21]. Actually, most of previous reports, including large clinical trials,

**Table 2**
Effects of the recurrent VTE events and major bleeding events on subsequent mortality.

| Time-updated covariate | Adjusted HR (95%CI) | P-value |
|---|---|---|
| Recurrent VTE events | 3.24 (2.57–4.08) | <0.001 |
| Recurrent PE events | 4.42 (3.28–5.95) | <0.001 |
| Recurrent DVT events | 2.42 (1.75–3.36) | <0.001 |
| Major bleeding events | 3.53 (2.88–4.31) | <0.001 |

Adjusted HRs and 95%CIs for all-cause death were estimated by the multivariable Cox proportional hazard model. We incorporated the recurrent VTE events and major bleeding events during follow-up into the multivariable Cox model as time-updated covariates together with the clinically-relevant 16 risk-adjusting factors listed in the Table 1.
HR, hazard ratio; CI, confidence interval; VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis.

evaluated symptomatic recurrent VTE as recurrence events [7,15,22–24]. However, PE is the most serious clinical presentation of VTE, and the clinical importance might be different between recurrent PE events and recurrent DVT events. A study reported that patients presented with PE had a significantly higher 3-month incidence of mortality than those with only DVT [25]. The current study showed that not only the recurrent PE events but also the recurrent DVT events were associated with increased risks for mortality, suggesting the importance of both the recurrent PE events and the recurrent DVT events. However, the magnitude of the effect was numerically greater with the recurrent PE events than with the recurrent DVT events, suggesting that recurrent PE events were more important in terms of mortality, which was not surprising given the cardio-respiratory consequences of PE. We should take the difference of mortality impact between the recurrent PE events and the recurrent DVT events into consideration for the decision-making on the duration of anticoagulation therapy.

Active cancer was reported to be the major predictor of recurrent VTE and bleeding [26]. Thus, the association of mortality with recurrent VTE and major bleeding in the current study could be heavily biased by active cancer. However, stratified analysis according to presence or absence of active cancer revealed consistent results irrespective of active cancer. Considering the higher proportions of deaths due to PE and bleeding events after each event, respectively, the increased risk for mortality could be due to the recurrence and bleeding events themselves.

## 5. Study limitations

The current study has several limitations. The current study showed the association of recurrence and bleeding events with mortality. However, it is still uncertain whether these clinical events were the direct causes for increased mortality, or poor outcome was due to the comorbidities and greater frailty in these patients, even if we conducted extensive adjustment for known confounders. Considering that more than half of mortality was due to cancer, these clinical events could partly reflect poor condition of patients with active cancer. Second, the therapeutic decision-making for the duration on anticoagulation was variable according to the attending physicians. Third, patient demographics, practice patterns, and medical therapy, as well as clinical outcomes in patients with VTE in Japan may be different from those outside Japan [27]. Fourth, the results could be influenced by the high rate of competing mortality. Finally, the current study was conducted before introduction of DOACs for VTE in Japan. Thus, it should be interpreted with caution whether the present results could be extrapolated to patients treated with DOAC.

## 6. Conclusions

In the real-world patients with VTE, both the recurrent VTE events and the major bleeding events were strongly associated with subsequent mortality risk with the comparable effect size. The recurrent PE and recurrent DVT events were also associated with increased risks for mortality, although the magnitude of the effect on mortality was numerically greater with the recurrent PE events than with the recurrent DVT events.

## Declaration of Competing Interest

Dr. Yamashita received lecture fees from Daiichi-Sankyo, Bristol-Myers Squibb, Pfizer, 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 serves as an advisory board member for Abbott Vascular and Terumo Company. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

## Acknowledgements

We appreciate the support and collaboration of the co-investigators participating in the COMMAND VTE Registry. The COMMAND VTE Registry is supported by the independent clinical research organization (Research Institute for Production Development, Kyoto, Japan) and research funding from Mitsubishi Tanabe Pharma Corporation. The research funding had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.06.032.

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