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Anticoagulation strategies and clinical outcomes after bleeding events during anticoagulation therapy for venous thromboembolism in the practice-based Japanese registry

Yugo Yamashita[1] · Takeshi Morimoto[2] · Frederikus A. Klok[3,4] · Stefano Barco[4,5] · Yuji Nishimoto[6] · Takao Kato[1] · Koh Ono[1] · Takeshi Kimura[1] on behalf of the COMMAND VTE Registry Investigators

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Abstract

There is a paucity of data on anticoagulation strategies and clinical outcomes after bleeding events for venous thromboembolism (VTE). In a multicenter Japanese registry enrolling 3027 patients with acute symptomatic VTE, after excluding 430 patients with thrombolysis and 207 patients without anticoagulation therapy, the current study population consisted of 2390 patients, who were divided into patients with major bleeding, clinically relevant non-major (CRNM) bleeding and no bleeding during anticoagulation therapy. All-cause death at 90 days after the bleeding events was evaluated as the primary outcome. There were 189 patients with major bleeding, 147 patients with CRNM bleeding, and 2054 patients without bleeding. Among 189 patients with major bleeding, 142 patients (75%) discontinued anticoagulants, of whom patients with temporary discontinuation and those with permanent discontinuation accounted for 63 patients (44%) and 79 patients (56%), and 58 patients (30.7%) died within 90 days after the bleeding events. The multivariable logistic regression model among patients with bleeding events revealed that active cancer and bleeding events within 90 days after VTE diagnosis were independently associated with 90-day mortality after the bleeding events (active cancer: OR 5.05, 95%CI 2.82–9.05; bleeding events within 90 days after VTE diagnosis: OR 2.23, 95%CI 1.25–3.96). In this practice-based large registry, anticoagulants were frequently discontinued in patients who experienced major bleeding events during anticoagulation therapy and nearly half of them restarted anticoagulants with mortality rate of approximately 30% within 90 days after the bleeding events, and active cancer was the most prevalent cause of death.

Clinical trial registration COMMAND VTE Registry: http://www.umin.ac.jp/ctr/index.htm. Unique identifier: UMIN000021132.

Keywords Venous thromboembolism · Anticoagulant · Bleeding · Mortality

✉ Yugo Yamashita
yyamashi@kuhp.kyoto-u.ac.jp

Takeshi Kimura
taketaka@kuhp.kyoto-u.ac.jp

[1] Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan

[2] Department of Clinical Epidemiology, Hyogo College of Medicine, Nishinomiya, Japan

[3] Department of Medicine, Thrombosis and Haemostasis, Leiden University Medical Center, Leiden, The Netherlands

[4] Center for Thrombosis and Hemostasis, University Medical Center, Mainz, Germany

[5] Clinic of Angiology, University Hospital Zurich, Zurich, Switzerland

[6] Department of Cardiology, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan

Highlights

- There is limited data after bleeding during anticoagulation for venous thromboembolism.
- We investigated anticoagulation strategies and clinical outcomes after bleeding in the real world.
- Anticoagulants were frequently discontinued and nearly half of them restarted it.
- The current results could help guiding strategies in the absence of randomized clinical trials.
- Further studies are warranted to investigate the optimal management strategies after bleeding events.

Introduction

The main goal of treating venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), is to prevent recurrent VTE and its complications, which can be achieved by anticoagulation therapy [1, 2]. However, anticoagulation therapy is associated with an increased risk of bleeding events [3, 4]. Previous studies reported that bleeding events during anticoagulation therapy had a considerable impact on mortality in patients with VTE [5–7], which should be taken into account when deciding on the optimal duration of anticoagulant therapy for VTE. When a bleeding event occurs during anticoagulation therapy, a decision should be made on whether the anticoagulation therapy should be permanently discontinued, or alternatively, after how long it can be restarted.

Evidence on the optimal anticoagulation strategies after bleeding complications in VTE patients is scarce, and randomized clinical trials focusing on the optimal strategies are currently unavailable. Current VTE guidelines do hardly provide any specific recommendations for the management of anticoagulation therapy after bleeding events in patients with VTE [8–11], which likely leads to widely varying anticoagulation strategies in daily clinical practice. The aim of the current study therefore was to investigate the anticoagulation strategies and clinical outcomes of anticoagulation-associated bleeding events in VTE patients, using a large practice-based large observational Japanese database.

Methods

Study population

The COMMAND VTE (COntemporary ManageMent AND outcomes in patients with Venous ThromboEmbolism) Registry is a physician-initiated, retrospective, multicenter cohort study in which consecutive patients with acute objectivated symptomatic VTE among 29 centers in Japan were included between January 2010 and August 2014. The design of the registry was previously reported in detail [12, 13]. We searched the hospital databases for clinical diagnosis and imaging examinations, and retrospectively enrolled consecutive patients who met the definition of acute symptomatic VTE diagnosed within 31 days from symptom onset during the study period [14]. 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 practice and none of the 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 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. After excluding 430 patients who received systemic or local thrombolysis at the index VTE events and 207 patients who did not receive any anticoagulation therapy, the current study population consisted of 2390 patients with acute symptomatic VTE (Fig. 1). In the current study, we evaluated all bleeding events during anticoagulation therapy. According to the occurrence of bleeding events during anticoagulation therapy, the current study population was divided into the following three groups: (1) Major bleeding during anticoagulation therapy; (2) Clinically relevant non-major (CRNM) bleeding during anticoagulation therapy; and (3) No bleeding during anticoagulation therapy. We defined the bleeding event during anticoagulation therapy as the first bleeding event from the index VTE diagnosis to 3 days after first discontinuation of anticoagulants during the follow-up period. Patients who experienced both major and CRNM bleeding were classified according to the first bleeding event. 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, symptomatic bleeding in a critical area or organ, or fatal bleeding [15]. CRNM bleeding was defined as overt bleeding that did not meet the criteria for major bleeding, but was associated with medical intervention, unscheduled contact with a physician, or cessation of anticoagulation therapy, based on the previous report [16]. The management strategies of bleeding events were at the discretion of the physicians in charge including temporary/permanent discontinuation of anticoagulation, restarting anticoagulation and use of reversal agents for warfarin.

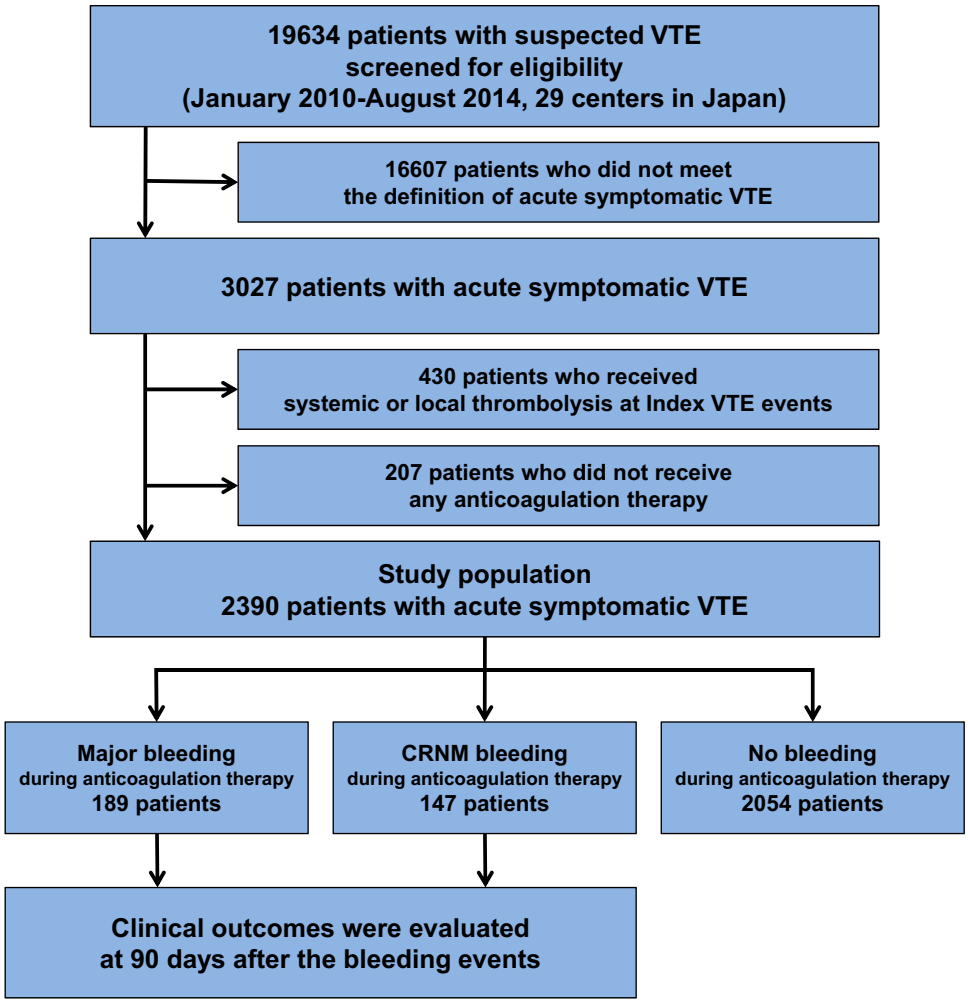

Fig. 1 Study flowchart. VTE included PE and/or DVT. *CRNM* clinically relevant non-major; *DVT* deep vein thrombosis; *PE* pulmonary embolism; *VTE* venous thromboembolism

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.

Patients with active cancer were defined as those on treatment for cancer such as chemotherapy or radiotherapy, those scheduled to undergo cancer-surgery, those with metastasis to other organs, and/or those with terminal cancer (expected life expectancy of 6 months or less) at the time of the diagnosis. Anemia was defined as hemoglobin level < 13 g/dL for men and < 12 g/dL for women. Thrombocytopenia was defined as platelet count $< 100 \times 10^9$/L. The detailed definitions of patient characteristics are described in Online Appendix 2.

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, stroke, acute myocardial infarction, invasive procedures, and status of anticoagulation therapy. The independent clinical event committee (Online Appendix 3) unaware of the patient characteristics reviewed all the clinical events with the clinical course in Japanese, and checked the accurateness and validity of data entry. Data for 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 [17] according to a therapeutic INR range of 1.5–2.5, which is recommended in the Japanese guidelines [18], as well as according to a therapeutic INR range of 2.0–3.0, which is recommended in the Western guidelines [8–10]. In the current study, we

evaluated the clinical outcomes at 90 days after the bleeding events among patients with bleeding events, and all the clinical outcomes were evaluated irrespective of the status of anticoagulation therapy after the bleeding events.

The primary outcome measure in the current study was all-cause death at 90 days after the bleeding events. The independent clinical event committee (Online Appendix 3) unaware of the patient characteristics reviewed all the death events, and classified the causes of deaths as due to bleeding events, due to cancers, due to PE, due to other non-cardiac causes, due to cardiac causes, or due to unknown causes [19]. Death was judged to be bleeding related if it followed an intracranial hemorrhage or a bleeding episode leading to hemodynamic deterioration. Death in patients with the end-stage cancer without a specific cause of death was regarded as cancer in origin. 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. Final classifications for the causes of deaths were made on the basis of the full consensus of the independent clinical event committee.

The secondary outcome measure in the current study were recurrent VTE, bleeding, acute myocardial infarction, and ischemic stroke at 90 days after the bleeding events. Recurrent VTE was defined as PE and/or DVT with symptoms accompanied by confirmation of new thrombus or exacerbation of the thrombus by objective imaging examinations or autopsy [20, 21]. Acute myocardial infarction was defined in accordance with the universal myocardial infarction guidelines [22]. Ischemic stroke was defined stroke either requiring or prolonging hospitalization with symptoms lasting more than 24 h accompanied by confirmation by objective imaging examinations.

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 using one-way analysis of variance or Kruskal–Wallis test based on their distributions. The 90-day clinical outcomes after the bleeding events are presented as numbers of events and percentages with 95% confidence intervals (CI). Furthermore, to explore the potential risk factors for 90-day all-cause death after the all bleeding events, we constructed a multivariable logistic regression models to estimate the odds ratio (OR) and the 95% CI of the potential risk factors. Based on the previous reports [8–10, 23] and consideration of clinical relevance, we selected those potential risk factors such as age, sex, location of thrombus at diagnosis, chronic kidney disease, active cancer, anemia, thrombocytopenia, bleeding type (major bleeding or CRNM bleeding), and timing of bleeding events after diagnosis of the index VTE (bleeding events within 90 days after VTE diagnosis or beyond 90 days). All statistical analyses were conducted using JMP version 14.0.0 (SAS Institute Inc., Cary, NC, USA). All reported P-values were 2-tailed, and P-values < 0.05 were considered statistically significant.

Results

Patient characteristics

The mean age of the study population was 68 years, 38% were men, and mean body weight and body mass index were 57.4 kg and 23.1 kg/m^2, respectively, and 2273 patients (95%) received warfarin as anticoagulation therapy. According to the first bleeding event, there were 189 patients (7.9%) with major bleeding, 147 patients (6.2%) with CRNM bleeding, and 2054 patients (86%) without bleeding during anticoagulation therapy (Fig. 1). The patient characteristics were different in several aspects across the three groups (Table 1). Patients in the two groups with bleeding during anticoagulation therapy had a lower mean body weight and body mass index, and more often had chronic kidney disease, active cancer, anemia, and thrombocytopenia than those without bleeding. Patients with major bleeding showed the highest-bleeding risk profile based on VTE BLEED score (Table 1). The median TTR for warfarin users according to a therapeutic INR range of 1.5–2.5 in the Japanese guidelines were 61.3 in patients with major bleeding, 57.1 in those with CRNM bleeding and 72.6 in those without bleeding events ($P < 0.001$) (Table 1).

Bleeding events and management strategies of anticoagulants

The detailed timing of bleeding events after VTE diagnosis is described in Supplementary Fig. 1, and 59% (111 patients) of major bleeding and 42% (62 patients) of CRNM bleeding during anticoagulation therapy occurred within 90 days after the VTE diagnosis (Table 1). The median INR values at bleeding events were 2.6 in major bleeding and 2.1 in CRNM bleeding. Among 189 patients with major bleeding during anticoagulation therapy, 142 patients (75%) discontinued anticoagulants, of whom 63 patients (44%) restarted anticoagulants with a median interval of 14 days from bleeding to restart. Among 147 patients with CRNM bleeding during anticoagulation therapy, 95 patients (65%) discontinued anticoagulants, of whom 43 patients (45%) restarted anticoagulants with a median interval of 3 days from bleeding to restart.

Table 1 Patient characteristics

	Major bleeding during anticoagulation therapy (N = 189)	CRNM bleeding during anticoagulation therapy (N = 147)	No bleeding during anticoagulation therapy (N = 2054)	P value
Baseline characteristics				
Age (years)	68.1 ± 15.8	70.1 ± 13.2	67.4 ± 15.5	0.12
Age ≥ 75 years	82 (43%)	61 (42%)	770 (37%)	0.19
Men	77 (41%)	55 (37%)	779 (38%)	0.74
Body weight (kg)	54.3 ± 11.4	56.0 ± 12.7	57.8 ± 13.7	0.001
Body mass index (kg/m^2)	22.2 ± 3.9	22.5 ± 3.7	23.3 ± 4.4	0.002
Body mass index ≥ 30 kg/m^2	8 (4.2%)	2 (1.4%)	119 (5.8%)	0.054
Comorbidities				
Hypertension	70 (37%)	60 (41%)	783 (38%)	0.76
Diabetes mellitus	25 (13%)	20 (14%)	270 (13%)	0.99
Chronic kidney disease	44 (23%)	45 (31%)	339 (17%)	< 0.001
History of cancer	93 (49%)	82 (56%)	586 (29%)	< 0.001
Active cancer at diagnosis	79 (42%)	59 (40%)	428 (21%)	< 0.001
Chronic lung disease	21 (11%)	20 (14%)	172 (8.4%)	0.054
Heart failure	12 (6.4%)	9 (6.1%)	68 (3.3%)	0.03
History of myocardial infarction	6 (3.2%)	1 (0.7%)	32 (1.6%)	0.16
History of stroke	22 (12%)	17 (12%)	174 (8.5%)	0.17
Atrial fibrillation	8 (4.2%)	8 (5.4%)	91 (4.4%)	0.84
Liver cirrhosis	0 (0%)	4 (2.7%)	13 (0.6%)	0.007
Connective tissue disease	25 (13%)	17 (12%)	164 (8.0%)	0.02
History of VTE	11 (5.8%)	9 (6.1%)	113 (5.5%)	0.94
History of major bleeding	30 (16%)	14 (9.5%)	127 (6.2%)	< 0.001
Transient risk factors for VTE	59 (31%)	34 (23%)	777 (38%)	< 0.001
Recent surgery	19 (10%)	12 (8.2%)	308 (15%)	0.02
Unprovoked VTE	66 (35%)	67 (46%)	976 (48%)	0.004
VTE BLEED score* (N = 2093)	4.5 (3–5)	4.5 (2.5–5)	3 (1.5–4.5)	< 0.001
High-bleeding risk patients based on VTE BLEED score more than 2 (N = 2093)	146/168 (87%)	107/135 (79%)	1258/1790 (70%)	< 0.001
Presentation				
PE with or without DVT	110 (58%)	79 (54%)	1074 (52%)	0.29
Laboratory tests at diagnosis				
Anemia	134 (71%)	85 (58%)	1108 (54%)	< 0.001
Thrombocytopenia	18 (9.5%)	11 (7.5%)	85 (4.1%)	0.001
Treatment in the acute phase				
Inferior vena cava filter use	63 (33%)	46 (31%)	393 (19%)	< 0.001
Concomitant medications				
Corticosteroids	33 (17%)	33 (22%)	235 (11%)	< 0.001
Non-steroidal anti-inflammatory drugs	27 (14%)	17 (12%)	208 (10%)	0.19
Proton pump inhibitors/H2-blockers	92 (49%)	68 (46%)	887(43%)	0.29
Statins	28 (15%)	30 (20%)	291 (14%)	0.12
Antiplatelet agents	25 (13%)	20 (14%)	194 (9.4%)	0.08
Anticoagulation therapy beyond the acute phase				
Warfarin	175 (93%)	140 (95%)	1958 (95%)	< 0.001
Direct oral anticoagulant	2 (1.1%)	5 (3.4%)	64 (3.1%)	
Heparin	12 (6.4%)	2 (1.4%)	32 (1.6%)	
TTR for INR 1.5–2.5 for warfarin users (%) (N = 2118)	61.3 (37.2–82.3)	57.1 (36.7–77.3)	72.6 (45.8–91.7)	< 0.001

Table 1 (continued)

	Major bleeding during anticoagulation therapy (N = 189)	CRNM bleeding during anticoagulation therapy (N = 147)	No bleeding during anticoagulation therapy (N = 2054)	P value
TTR for INR 2.0–3.0 for warfarin users (%) (N = 2118)	28.6 (12.2–54.9)	30.4 (8.9–49.9)	30.1 (6.6–55.8)	0.83
Timing of bleeding events				
Within 90 days after VTE diagnosis	111 (59%)	62 (42%)	–	–
Anticoagulants at bleeding events				
Warfarin	175 (93%)	140(95%)	–	–
INR at bleeding events (N = 210)	2.6 (1.8–3.9)	2.1 (1.6–3.6)	–	–
DOAC	2 (1.1%)	5 (3.4%)	–	–
Heparin	12 (6.4%)	2 (1.4%)	–	–
Site of bleeding				
Gastrointestinal	64 (34%)	43 (29%)	–	–
Intracranial	40 (21%)	0 (0%)	–	–
Genitourinary tract	16 (8.5%)	23 (16%)	–	–
Intrathoracic/intra-abdominal	15 (7.9%)	0 (0%)	–	–
Respiratory	5 (2.6%)	23 (16%)	–	–
Surgery-related/iatrogenic	14 (7.4%)	10 (6.8%)	–	–
Subcutaneous/intramuscular/intra-articular	10 (5.3%)	35 (24%)	–	–
Others	25 (13%)	13 (8.8%)	–	–
Anticoagulation strategies after bleeding events				
Discontinuation of anticoagulants	142 (75%)	95 (65%)	–	–
Restart of anticoagulants after transient discontinuation	63/142 (44%)	43/95 (45%)	–	–
Days from bleeding events to restart of anticoagulants	14 (4–39)	3 (1–30)	–	–
Restart with different anticoagulants	24/63 (38%)	22/43 (51%)	–	–
From warfarin to DOAC	19/24	17/22	–	–
From warfarin to heparin	3/24	3/22	–	–
From DOAC to warfarin	0/24	2/22	–	–
From DOAC to heparin	0/24	0/22	–	–
From heparin to warfarin	1/24	0/22	–	–
From heparin to DOAC	1/24	0/22	–	–
All-cause death within 48 h after bleeding events	16 (8.5%)	7 (4.8%)	–	–

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 was < 60 mL/min/1.73 m^2 for more than 3 months. Patients with active cancer were defined as those on treatment for cancer such as chemotherapy or radiotherapy, those scheduled to undergo cancer-surgery, those with metastasis to other organs, and/or those with terminal cancer (expected life expectancy of 6 months or less) at the time of the diagnosis. Recent surgery was defined as surgery within 2 months prior to VTE. Unprovoked VTE was defined as VTE without activecancer nor transient risk factors for VTE. Anemia was defined as hemoglobin level < 13 g/dL for men and < 12 g/dL for women. Thrombocytopenia was defined as platelet count $< 100 \times 10^9$/L. Antiplatelets included aspirin, clopidogrel, ticlopidine, cilostazol, and prasugrel

CRNM clinically relevant non-major; *VTE* venous thromboembolism; *DVT* deep vein thrombosis; *PE* pulmonary embolism; *INR* international normalized ratio; *TTR* time in therapeutic range; *DOAC* direct oral anticoagulant

*Based on the original report (Klok FA, et al. Eur Respir J. 2016;48:1369–1376), we calculated the VTE-BLEED score of each patient by the following six variables: active cancer (2 points), men with uncontrolled arterial hypertension (1 point), anemia (1 point), a history of major bleeding (1.5 points), ≥ 60 years of age (1.5 points), and renal dysfunction (1.5 points)

Clinical outcomes after bleeding events

Among the patients with bleeding during anticoagulation therapy, 58 patients (30.7%) in the major bleeding group, and 30 patients (20.4%) in the CRNM bleeding group died within 90 days after the bleeding events (Table 2). Of the 58 deaths after major bleeding, deaths due to bleeding events accounted for 22 (38%), and deaths due to cancer accounted for 23 (40%). The incidence of bleeding-related death after major bleeding was 11.6%. Among 22 bleeding-related death, 10 deaths (45%) and 8 deaths (36%) were due to intracranial bleeding and gastrointestinal bleeding, and the median day from bleeding to death was 1 day. Among the 30 deaths in patients with CRNM bleeding during anticoagulation therapy, no patients died due to bleeding events, and deaths due to cancer accounted for 18 (60%).

Patients with major bleeding during anticoagulation therapy experienced recurrent VTE in 8 patients (4.2%), recurrent bleeding in 9 patients (4.8%) and ischemic stroke in 2 patients (1.1%), and no patient experienced acute myocardial infarction at 90 days after the bleeding events (Table 2). Patients with CRNM bleeding during anticoagulation therapy experienced recurrent VTE in 8 patients (5.4%), recurrent bleeding in 6 patients (4.1%) and ischemic stroke in 2 patients (1.4%), and no patient experienced acute myocardial infarction at 90 days after the bleeding events.

Among 142 patients who discontinued anticoagulants, patients with temporary discontinuation accounted for 63 patients (44%) and those with permanent discontinuation accounted for 79 patients (56%). Among 95 patients who discontinued anticoagulants, patients with temporary discontinuation accounted for 43 patients (45%) and those with permanent discontinuation accounted for 52 patients (55%). Patient characteristics according to the status of anticoagulation therapy after the bleeding events are shown in Online Table 1. Patients who discontinued anticoagulation therapy permanently showed a higher prevalence of bleeding within 90 days after VTE diagnosis compared with patients who continued anticoagulation therapy and patients who restarted anticoagulation therapy. As for clinical outcomes according to the status of anticoagulation therapy, recurrent VTE and recurrent bleeding occurred in 2 patients (2.0%) and in 1 patients (1.0%) who continued anticoagulation therapy, in 8 patients (7.5%) and in 8 patients (7.5%) who restarted anticoagulation therapy (temporary discontinuation) and in 6 patients (4.6%) and in 6 patients (4.6%) who discontinued anticoagulation therapy permanently (permanent discontinuation) (Online Table 2).

Table 2 Clinical outcomes at 90-day after bleeding events

	Major bleeding during anticoagulation therapy (N = 189)	CRNM bleeding during anticoagulation therapy (N = 147)
All-cause death	58 (30.7 [24.2–37.2]%)	30 (20.4 [13.9–26.9]%)
Causes of death		
Bleeding events	22/58 (38%)	0/30 (0%)
Cancer	23/58 (40%)	18/30 (60%)
Fatal PE	4/58 (6.9%)	6/30 (20%)
Other non-cardiac events	5/58 (8.6%)	5/30 (17%)
Cardiac events	3/58 (5.2%)	0/30 (0%)
Unknown	1/58 (1.7%)	1/30 (3.3%)
Recurrent VTE	8 (4.2 [1.1–7.4]%)	8 (5.4 [1.5–9.4]%)
Recurrent PE with or without DVT	4 (2.1 [0.6–5.5]%)	3 (2.0 [0.4–6.1]%)
Recurrent DVT	4 (2.1 [0.6–5.5]%)	5 (3.4 [1.2–7.9]%)
Recurrent bleeding	9 (4.8 [2.4–8.9]%)	6 (4.1 [1.7–8.8]%)
Major bleeding	8 (4.2 [1.1–7.4]%)	2 (1.4 [0.0–3.9]%)
CRNM bleeding	1 (0.5 [0.0–2.3]%)	4 (2.7 [0.0–5.8]%)
Acute myocardial infarction	0 (0 [0.0–1.4]%)	0 (0 [0.0–1.8]%)
Ischemic stroke	2 (1.1 [0.0–3.1]%)	2 (1.4 [0.0–3.9]%)

Categorical variables are presented as numbers and percentages with their 95% confidence intervals. 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 PE events. Death from end-stage cancer without a specific cause of death was regarded as of 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 due to cardiac events, if it followed acute myocardial infarction, heart failure, or ventricular arrhythmia

CRNM clinically relevant non-major; *VTE* venous thromboembolism; *DVT* deep vein thrombosis; *PE* pulmonary embolism

Independent risk factors for all-cause death within 90 days after the all bleeding events

The multivariable logistic regression model revealed that active cancer and bleeding events within 90 days after VTE diagnosis were independently associated with all-cause death within 90 days after the all bleeding events (active cancer: OR 5.05, 95% CI 2.82–9.05; bleeding events within 90 days after VTE diagnosis: OR 2.23, 95% CI 1.25–3.96) (Online Table 3). The absolute 90-day incidence rate of all-cause death after bleeding events in patients with active cancer and that in those without were 46.4% (64/138) and 12.1% (24/198). Major bleeding was associated with a trend toward higher risk for all-cause death within 90 days after the bleeding events as compared with CRNM bleeding, although it was not statistically significant (OR 1.59, 95% CI 0.90–2.82).

Discussion

The main findings of the current study were as follows: (1) Anticoagulants were discontinued in 65–75% of patients who experienced bleeding events during anticoagulation therapy, and restarted in 44–45% of patients among those who had discontinued anticoagulants after a median interval of 14 days from major bleeding to restart and 3 days from CRNM bleeding to restart; (2) Approximately 30% of patients died within 90 days after the major bleeding, and 38% of deaths were due to bleeding events; (3) Active cancer and bleeding events within 90 days after VTE diagnosis were independent risk factors for all-cause death within 90 days after the bleeding events.

When patients with VTE experience clinically relevant bleeding events during anticoagulation therapy, anticoagulant therapy usually is discontinued or even reversed, aiming at achieving hemostasis. The important question for clinicians is whether anticoagulants should be restarted or discontinued permanently. A previous study reported that restart of anticoagulants after intracranial hemorrhage in patients with atrial fibrillation was associated with a lower rate of thromboembolic events and a higher rate of recurrent intracranial hemorrhage, compared with persistent discontinuation of anticoagulants [24]. Another study reported that restart of anticoagulants after upper gastrointestinal bleeding in patients with anticoagulants was associated with a reduced risk of thromboembolism and all-cause death, but with an increased risk of recurrent gastrointestinal bleeding [25]. However, there has been limited data in patients with VTE. The current VTE guidelines state only a few nonspecific recommendations for this issue [8–10]. The American Society of Hematology 2018 guidelines weakly recommends restart of anticoagulants within 90 days rather than persistent discontinuation for patients with VTE who survive an episode of major bleeding based on very low certainty in the evidence [11]. The current study showed more than half of patients with bleeding events during anticoagulation therapy discontinued anticoagulants at least temporally after a diagnosis of bleeding events, suggesting that control of bleeding and avoidance of recurrent bleeding are often the priority of clinicians in the real world practice. The current study showed that patients diagnosed with major or CRNM bleeding faced a high incidence of relevant complications. Because the incidence rates of recurrent VTE and recurrent bleeding were numerically higher in patients who restarted anticoagulant therapy than in those patients who discontinued anticoagulant therapy permanently, it may be assumed that the assumed risk of recurrent VTE plays a major role in anticoagulation management decisions after bleeding complications. Interestingly, the incidence rate of recurrent bleeding in patients who discontinued anticoagulant therapy permanently was non-neglectable and in the same order of magnitude than the incidence rate of recurrent VTE.

Previous studies performed mostly in patients with atrial fibrillation reported that mortality rates after major bleeding during anticoagulation therapy ranged from 10 to 20% and up to more than 30% for intracranial hemorrhage [5, 26, 27]. Consistent with previous reports, the current study showed a relatively high mortality rate within 90 days after major bleeding (30.7%), which could be explained by the large proportion of patients with active cancer. Notably, deaths due to bleeding events accounted for more than one third of all mortalities, and bleeding-related deaths occurred soon after bleeding events, which suggested the clinical importance of anticoagulation-related bleeding events. The previous studies reported the case-fatality rate of long-term major bleeding events was 8–10% [5, 6], which was line with the current study (bleeding-related death rate of 11.6%). Even so, the most common cause of death was due to cancer, which should be taken into consideration when evaluating the clinical impact of major bleeding on mortality in patients with VTE. Patients with advanced cancer could be at a high risk of bleeding [28] as well as at a high risk of mortality after bleeding events. In daily clinical practice, patient preference of anticoagulation therapy also could have a certain influence on management strategies of anticoagulation therapy.

The risk factors for mortality after bleeding events found in the current study inform VTE caretakers on the prognosis of patients with bleeding complications and may help determining the decision to continue or discontinue anticoagulation therapy. From the current study, we cannot conclude that either restarting or permanently discontinuing anticoagulation therapy is the optimal strategy for all patients. If anything, the current study confirms the major impact of a bleeding complication on the prognosis of a VTE patient, and shows that management decisions are mostly based on

the specific risk profile of the patients. Considering the low incidence of fatal VTE and fatal bleeding in patients with a first-anticoagulant associated VTE, the chosen anticoagulation strategy may not be the most important determinant of survival.

Study limitations

The current study has several limitations. First, the current study was an observational study, which can be subject to various biases inherent to observational study design. The therapeutic decision-making was left to the discretion of the attending physicians, which could have influences on clinical outcomes. In addition, the current study was conducted based on the search through hospital databases for clinical diagnosis and imaging examinations, and collection of follow-up information was mainly conducted through review of hospital charts. Second, detailed management strategies of medical intervention for hemostasis such as surgical treatment, plasma transfusion, use of prothrombin complex concentrate were not evaluated in the current study, which should be interpreted with caution. Third, demographics, practice patterns as well as clinical outcomes in patients with VTE in Japan may be different from those outside Japan. Fourth, the current study evaluated long-term bleeding events, and clinical features of bleeding events could be changed during the follow-up period. Fifth, the clinical outcomes according to the status of anticoagulation therapy after the bleeding events could be influenced by immortal time bias. Finally and most importantly, the current study was conducted before introduction of direct oral anticoagulants for VTE in Japan. Thus, it should be interpreted with caution whether the present results could be extrapolated to patients treated with direct oral anticoagulants.

Conclusions

In this practice-based large registry, anticoagulants were frequently discontinued in patients who experienced major bleeding events during anticoagulation therapy and nearly half of them restarted anticoagulants with mortality rate of approximately 30% within 90 days after the bleeding events, and active cancer was the most prevalent cause of death, which could help guiding anticoagulation strategies in the absence of randomized clinical trials.

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Author contributions YY, FK, SB contributed to the design of the study, the analysis and interpretation of data, and drafted the manuscript. TM and TK contributed to the analysis and interpretation of data, and drafted the manuscript. All other authors contributed to acquisition and interpretation of data, and reviewed the manuscript.

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Declarations

Conflict of interest Dr. Yamashita received lecture fees from Daiichi-Sankyo, Bristol-Myers Squibb, Pfizer, and Bayer Healthcare. Dr Morimoto reports lecturer's fees from Bristol-Myers Squibb, Daiichi Sankyo, Japan Lifeline, Kowa, Kyocera, Novartis, and Toray; manuscript fees from Bristol-Myers Squibb and Kowa; advisory board for Sanofi. Dr. Klok reports research grants from Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, MSD, Daiichi-Sankyo, Actelion, the Dutch thrombosis association, The Netherlands Organization for Health Research and Development and the Dutch Heart foundation, all outside the current work. Dr. Nishimoto received lecture fees from Daiichi-Sankyo, Bristol-Myers Squibb, Pfizer, and Bayer Healthcare. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For the COMMAND VTE Registry of retrospective study formal consent is not required.

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