European Journal of Internal Medicine 118 (2023) 59–72

Contents lists available at ScienceDirect

European Journal of Internal Medicine

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

Original article

Anticoagulation strategies and long-term recurrence in patients with venous thromboembolism in the era of direct oral anticoagulants

Kazuhisa Kaneda [a], Yugo Yamashita [a,*], Takeshi Morimoto [b], Ryuki Chatani [c], Yuji Nishimoto [d], Nobutaka Ikeda [e], Yohei Kobayashi [f], Satoshi Ikeda [g], Kitae Kim [h], Moriaki Inoko [i], Toru Takase [j], Shuhei Tsuji [k], Maki Oi [l], Takuma Takada [m], Kazunori Otsui [n], Takeshi Kimura [o], COMMAND VTE Registry-2 Investigators

[a] Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[b] Department of Clinical Epidemiology, Hyogo College of Medicine, Nishinomiya, Japan
[c] Department of Cardiovascular Medicine, Kurashiki Central Hospital, Kurashiki, Japan
[d] Department of Cardiology, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan
[e] Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, Tokyo, Japan
[f] Department of Cardiovascular Center, Osaka Red Cross Hospital, Osaka, Japan
[g] Department of Cardiovascular Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
[h] Department of Cardiovascular Medicine, Kobe City Medical Center General Hospital, Kobe, Japan
[i] Cardiovascular Center, The Tazuke Kofukai Medical Research Institute, Kitano Hospital, Osaka, Japan
[j] Department of Cardiology, Kinki University Hospital, Osaka, Japan
[k] Department of Cardiology, Japanese Red Cross Wakayama Medical Center, Wakayama, Japan
[l] Department of Cardiology, Japanese Red Cross Otsu Hospital, Otsu, Japan
[m] Department of Cardiology, Tokyo Women's Medical University, Tokyo, Japan
[n] Department of General Internal Medicine, Kobe University Hospital, Kobe, Japan
[o] Department of Cardiology, Hirakata Kohsai Hospital, Hirakata, Japan

ARTICLE INFO

Keywords:
Venous thromboembolism
Anticoagulants
Recurrence
Bleeding
Mortality

ABSTRACT

Background: There has been limited data on anticoagulation strategies and long-term recurrence in patients with venous thromboembolism (VTE) in the era of direct oral anticoagulant (DOAC).

Methods: The COMMAND VTE Registry-2 is a multicenter retrospective cohort study enrolling 5197 consecutive patients with acute symptomatic VTE between January 2015 and August 2020 among 31 centers in Japan. In this primary report, the entire cohort was divided into 5 groups; major transient risk factors ($N = 475$, 9.1%), minor transient risk factors ($N = 788$, 15%), unprovoked ($N = 1913$, 37%), non-malignant persistent risk factors ($N = 514$, 9.9%), and active cancer ($N = 1507$, 29%) groups.

Results: DOACs were administered in 79% of patients who received oral anticoagulants. Discontinuation of anticoagulant at 1 year was most frequent in the major transient risk factors group (57.2%, 46.3%, 29.1%, 32.0%, and 45.6%). The cumulative 5-year incidence of recurrent VTE was lowest in the major transient risk factors group (2.6%, 6.4%, 11.0%, 12.1%, and 10.1%, $P < 0.001$). The cumulative 5-year incidence of major bleeding was highest in the active cancer group (9.8%, 11.4%, 11.0%, 15.5%, and 20.4%, $P < 0.001$). After discontinuation of anticoagulation therapy, the cumulative 5-year incidence of recurrent VTE was highest in the unprovoked group (3.3%, 11.0%, 24.9%, 17.5%, and 11.8%, $P < 0.001$).

Conclusions: In this large real-world VTE registry, anticoagulation strategies and long-term recurrence widely differed depending on the baseline characteristics. Detailed risk stratifications of recurrent VTE could be useful for decision-making of anticoagulation strategies, whereas the bleeding-risk assessment might be especially important in the era of DOAC.

Clinical Trial Registration: URL: http://www.umin.ac.jp/ctr/index.htm Unique identifier: UMIN000044816.

Abbreviations: DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ESC, European society of cardiology; ISTH, international society on thrombosis and haemostasis; IQR, interquartile range; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.

* Corresponding author.
E-mail address: yyamashi@kuhp.kyoto-u.ac.jp (Y. Yamashita).

https://doi.org/10.1016/j.ejim.2023.08.007
Received 20 June 2023; Received in revised form 1 August 2023; Accepted 7 August 2023
Available online 11 August 2023

1. Introduction

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), is a major health problem all over the world [1]. VTE has a long-term risk of recurrence, and the prevention of recurrent VTE by anticoagulation therapy is essential for the long-term management of patients with VTE [2]. International Society on Thrombosis and Haemostasis (ISTH) recommends classifications of risk of recurrent VTE based on whether an episode of VTE is unprovoked or provoked by an environmental risk factor and, if it is provoked, whether the provoking risk factor is transient or persistent [3]. The latest 2019 European Society of Cardiology (ESC) guidelines for PE also recommend the classification based on the ISTH classification such as major transient risk factors, minor transient risk factors, unprovoked, non-malignant persistent risk factors, and active cancer [4].

The current guidelines recommend specific durations of anticoagulation therapy depending on the risks of recurrent VTE [4–7], although there could be still uncertainty about the risk estimation and optimal duration of anticoagulation therapy. Actually, recommendations for the durations of anticoagulation therapy have been somewhat conflicting according to each guideline [4,5]. Furthermore, direct oral anticoagulants (DOAC) have become available for VTE [8–12]. Some of DOACs were reported to be safer than vitamin K antagonist (VKA) in terms of bleeding risk except for certain patients with active cancer, leading to a favor of longer duration of anticoagulation therapy [13]. However, there is still limited data on anticoagulation strategies and long-term risk of recurrence in patients with VTE in the era of DOAC, which could be clinically relevant for understanding the current issues and unmet needs. Therefore, we sought to evaluate anticoagulation strategies and long-term risk of recurrence according to the risk-stratification groups defined in the current guidelines in a large-scale observational study of VTE in the era of DOAC.

2. Methods

2.1. Study population

The COMMAND VTE (Contemporary management and outcomes in patients with venous thromboembolism) Registry-2 is a physician-initiated, multicenter, retrospective cohort study enrolling consecutive patients with acute symptomatic VTE objectively confirmed by imaging examination (ultrasound, contrast-enhanced computed tomography, ventilation–perfusion lung scintigraphy, pulmonary angiography or contrast venography) or by autopsy among 31 centers in Japan between January 2015 and August 2020 after the introduction of DOAC for VTE in Japan.

We searched the hospital databases for clinical diagnosis and/or imaging examinations, and enrolled consecutive patients who met the definitions of acute symptomatic VTE diagnosed within 31 days from symptom onset during the study period [14]. 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 [15,16]. 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. The relevant review board or ethics committee in all 31 participating centers (Supplementary Appendix 1) approved the research protocol. Written informed consent from each patient was waived, because we used clinical information obtained in routine clinical practice. We presented the information of the study in all 31 participating centers using the opt-out method, 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.

After screening of 51,313 patients with suspected VTE for eligibility through chart review by the physicians at each institution, a total of 5197 patients with acute symptomatic VTE were enrolled in the registry. In this primary report from the COMMAND VTE Registry-2, we divided

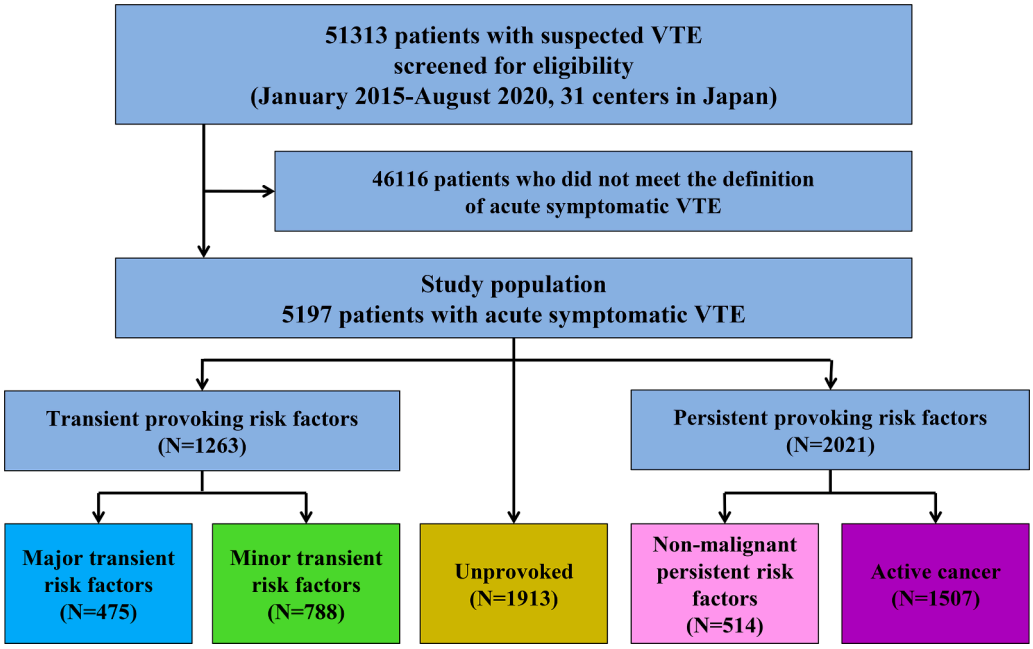


Fig. 1. Study flowchart.
VTE included PE and/or DVT.
VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism.

the entire cohort into 5 groups based on the classification of risk of recurrence recommended by ISTH [3]; major transient risk factors, minor transient risk factors, unprovoked, non-malignant persistent risk factors, and active cancer groups (Fig. 1).

For the current classifications of 5 groups, we categorize each patient according to the patient characteristics at the time of diagnosis for VTE. First, patients associated with active cancer were classified into the cancer group. Second, patients associated with non-malignant persistent provoking risk factors were classified into the non-malignant persistent risk factors group. Third, patients associated with major transient provoking risk factors were classified into the major transient risk factors group. Fourth, patients associated with minor transient provoking risk factors were classified into the minor transient risk factors group. Finally, patients without environmental provoking risk factor for VTE (transient or persistent) were classified into the unprovoked group. We compared clinical characteristics, management strategies and long-term outcomes among the 5 groups with a median follow-up period of 1002 (interquartile range [IQR]: 515–1594) days for surviving patients (86.0% follow up rate at 1 year).

2.2. Data collection and definitions for patient characteristics

Data for patient characteristics were collected from hospital charts or hospital databases according to the prespecified definitions, using an electronic case report form in a web-based database system. The expert physicians for VTE at each institution, who are investigators participating in the current study with training for data collection before the start of the enrollment, were responsible for data entry, and data were automatically checked for missing or contradictory input and values out of the expected range. Additional manual editing checks for all the data were performed at the general office of the registry, and if there was argument for the correctness of data, we checked the data through reconfirming original hospital charts or hospital databases at each institution.

Major transient provoking risk factors included major surgery with general anesthesia for greater than 30 min and within 2 months prior to VTE, confinement to bed in hospital with only bathroom privileges for at least 4 days with an acute illness within 2 months prior to VTE, and cesarean section within 2 months prior to VTE [3]. We also classified patients with major trauma or fracture based on the definition above, and patients who need major surgery or confinement to bed in hospital were defined as major transient provoking risk factors group. Minor transient provoking risk factors included minor surgery with general anesthesia for less than 30 min and within 2 months prior to VTE, admission to hospital without confinement to bed due to acute illness within 2 months prior to VTE, estrogen therapy within 2 months prior to VTE, pregnancy or puerperium within 2 months prior to VTE, confinement to bed out of hospital for at least 4 days within 2 months prior to VTE, leg injury associated with reduced mobility for at least 4 days within 2 months prior to VTE, long-distance travel lasting more than 6 h in the previous 3 weeks, and central venous catheter use, and infection of coronavirus disease 2019 within 3 months prior to VTE [3].

Non-malignant persistent provoking risk factors included on-going non-malignant condition associated with at least a 2-fold risk of recurrent VTE after stopping anticoagulation therapy such as autoimmune disorders including inflammatory bowel disease and antiphospholipid syndrome [3,5]. 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 [17].

Initial parenteral anticoagulation therapy included heparin (single or continuous injection) and fondaparinux within 10 days after the diagnosis [18]. Oral anticoagulation therapy included VKA (warfarin) and DOACs. DOACs included dabigatran, rivaroxaban, apixaban, and edoxaban. Prolonged anticoagulation therapy was defined as oral or parenteral anticoagulation therapy (warfarin, DOAC, or heparin) that was continued beyond the acute phase of 10 days after the diagnosis [18]. The detailed definitions of other patient characteristics are described in Supplementary Appendix 2.

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, clinical events, invasive procedure, and status of anticoagulation therapy. In this cohort study, final data collection for follow-up events was performed between September 2021 and April 2022.

The primary outcome measure was recurrent VTE, which 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 [12]. The secondary outcome measures were major bleeding and all-cause death. Major bleeding consisted of fatal bleeding, symptomatic bleeding in a critical area or organ, and bleeding causing a reduction in the hemoglobin level by at least 2 g/dL or leading to transfusion of at least 2 units of whole blood or red cells according to ISTH definitions [19].

Anticoagulation therapy cessation was classified as discontinuation or interruption according to the prespecified definitions [18]. Discontinuation of anticoagulation was defined as withdrawal of anticoagulation therapy lasting more than 14 days for any reason, such as physician's judgment in the absence of adverse events, bleeding event, drug side effect, 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 cessation of anticoagulation.

The independent clinical event committee (Supplementary Appendix 3) unaware of the patient characteristics reviewed all the detailed clinical course, and adjudicated the clinical events. If there was inconsistency, final adjudication for clinical events was made on the basis of the full consensus of the independent clinical event committee. The adjudication procedure was conducted between June 2022 and August 2022. The definitions of other clinical events are described in Supplementary Appendix 4.

2.4. Statistical analysis

Categorical variables are presented as number and percentages. Continuous variables are presented as the mean and standard deviation or the median and IQR based on their distributions. Categorical variables were compared with the chi-square test. 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 a log-rank test. We also compared the incidence for recurrent VTE after discontinuation of anticoagulation therapy among the 5 groups. Eligible patients for this analysis were those who received prolonged anticoagulation therapy, and were free from recurrent VTE before discontinuation. Furthermore, to examine the effect of anticoagulation therapy beyond 180 days on recurrent VTE, we conducted a landmark analysis based on the status of anticoagulation at 180 days. We compared the cumulative incidences for recurrent VTE beyond 180 days between the 2 groups of patients on and off anticoagulation at the 180-day landmark point. Eligible patients for this analysis were those who received prolonged anticoagulation therapy, and were free from recurrent VTE within 180 days. The specific landmark point of 180 days was selected by the minimum duration of 3 to 6 months of prolonged anticoagulation therapy, which is recommended for all patients with VTE in the current

Table 1
. Patient characteristics.

	Total ($N = 5197$)	Major transient risk factors ($N = 475$)	Minor transient risk factors ($N = 788$)	Unprovoked ($N = 1913$)	Non-malignant persistent risk factors ($N = 514$)	Active cancer ($N = 1507$)	*P*-value
Baseline characteristics							
Age (years)	67.7 ± 15.7	69.0 ± 14.8	64.0 ± 19.3	68.9 ± 15.5	66.6 ± 17.6	68.1 ± 12.8	<0.001
Women	3063 (59%)	321 (68%)	510 (65%)	1021 (53%)	367 (71%)	844 (56%)	<0.001
Body weight (kg)	58.9 ± 14.3	60.0 ± 13.8	59.1 ± 14.6	61.3 ± 15.4	56.3 ± 13.7	56.6 ± 12.5	<0.001
Body mass index (kg/m^2) ($N = 4816$)	23.3 ± 4.5	24.2 ± 4.4	23.5 ± 4.6	23.9 ± 4.6	22.8 ± 4.5	22.4 ± 4.2	<0.001
Comorbidities							
Hypertension	2229 (43%)	238 (50%)	297 (38%)	903 (47%)	216 (42%)	575 (38%)	<0.001
Diabetes mellitus	823 (16%)	76 (16%)	107 (14%)	303 (16%)	100 (19%)	237 (16%)	0.09
Dyslipidemia	1285 (25%)	131 (28%)	164 (21%)	540 (28%)	149 (29%)	301 (20%)	<0.001
Chronic kidney disease	991 (19%)	73 (15%)	129 (16%)	385 (20%)	128 (25%)	276 (18%)	<0.001
Dialysis	46 (0.9%)	7 (1.5%)	12 (1.5%)	16 (0.8%)	8 (1.6%)	3 (0.2%)	0.003
Chronic heart disease	494 (9.5%)	38 (8.0%)	95 (12%)	196 (10%)	53 (10%)	112 (7.4%)	0.003
Heart failure	213 (4.1%)	16 (3.4%)	36 (4.6%)	99 (5.2%)	30 (5.8%)	32 (2.1%)	<0.001
History of myocardial infarction	113 (2.2%)	7 (1.5%)	19 (2.4%)	45 (2.4%)	15 (2.9%)	27 (1.8%)	0.41
Atrial fibrillation	237 (4.6%)	24 (5.1%)	51 (6.5%)	79 (4.1%)	19 (3.7%)	64 (4.3%)	0.06
Chronic lung disease	527 (10%)	23 (4.8%)	75 (9.5%)	196 (10%)	112 (22%)	121 (8.0%)	<0.001
History of stroke	466 (9.0%)	54 (11%)	104 (13%)	166 (8.7%)	53 (10%)	89 (5.9%)	<0.001
Liver cirrhosis	46 (0.9%)	2 (0.4%)	4 (0.5%)	18 (0.9%)	4 (0.8%)	18 (1.2%)	0.38
Varicose vein	227 (4.4%)	22 (4.6%)	26 (3.3%)	119 (6.2%)	17 (3.3%)	43 (2.9%)	<0.001
History of VTE	362 (7.0%)	14 (3.0%)	36 (4.6%)	181 (9.5%)	49 (9.5%)	82 (5.4%)	<0.001
History of major bleeding	353 (6.8%)	45 (9.5%)	77 (9.8%)	96 (5.0%)	35 (6.8%)	100 (6.6%)	<0.001
Presentation							
PE with or without DVT	2787 (54%)	218 (46%)	423 (54%)	1140 (60%)	235 (46%)	771 (51%)	<0.001
Hypoxemia	1238/2787 (44%)	129/218 (59%)	206/423 (49%)	501/1140 (44%)	91/235 (39%)	311/771 (40%)	<0.001
Shock	291/2787 (10%)	33/218 (15%)	64/423 (15%)	120/1140 (11%)	20/235 (8.5%)	54/771 (7.0%)	<0.001
Cardiac arrest/collapse	136/2787 (4.9%)	18/218 (8.3%)	27/423 (6.4%)	69/1140 (6.1%)	5/235 (2.1%)	17/771 (2.2%)	<0.001
DVT only	2410 (46%)	257 (54%)	365 (46%)	773 (40%)	279 (54%)	736 (49%)	<0.001
Proximal DVT in lower extremities	1405/2410 (58%)	117/257 (46%)	238/365 (65%)	473/773 (61%)	163/279 (58%)	414/736 (56%)	<0.001
Out-of-hospital onset	3794/5197 (73%)	98/475 (21%)	526/788 (67%)	1829/1913 (96%)	366/514 (71%)	975/1507 (65%)	<0.001
Home treatment	1175/3794 (31%)	31/98 (32%)	106/526 (20%)	579/1829 (32%)	124/366 (34%)	335/975 (34%)	<0.001
Home treatment for PE	293/2140 (14%)	6/44 (14%)	23/298 (7.7%)	154/1106 (14%)	20/180 (11%)	90/512 (18%)	0.002
Laboratory tests at diagnosis							
Anemia	2882 (55%)	347 (73%)	418 (53%)	657 (34%)	297 (58%)	1163 (77%)	<0.001
Thrombocytopenia ($N = 5194$)	272 (5.2%)	14 (3.0%)	29 (3.7%)	60 (3.1%)	41 (8.0%)	128 (8.5%)	<0.001
D-dimer (μg/mL) ($N = 4930$)	9.3 (4.4–18.8)	12.4 (6.0–23.2)	9.6 (4.1–20.3)	8.1 (4.0–15.2)	8.1 (3.3–17.3)	10.3 (4.9–22.6)	<0.001
Hereditary thrombophilia	182 (3.5%)	8 (1.7%)	35 (4.4%)	92 (4.8%)	21 (4.1%)	26 (1.7%)	<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. Continuous variables were compared using one-way analysis of variance or Kruskal–Wallis test based on their distributions.
Chronic lung disease was defined as persistent lung disorders such as asthma, chronic obstructive pulmonary disease, and restrictive lung diseases. History of major bleeding was diagnosed if the patient had a history of International Society of Thrombosis and Hemostasis (ISTH) major bleeding. Hypoxemia was defined as arterial oxygen partial pressure of <60 mmHg or percentage saturation of hemoglobin with oxygen of <90%. Shock was defined as systolic blood pressure <90 mmHg for at least 15 min, a pressure drop of ≥40 mmHg for at least 15 min, or requiring inotropic support. Proximal DVT in lower extremities was defined as venous thrombosis which was located in popliteal, femoral, or iliac veins. 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. Hereditary thrombophilia included protein C deficiency, protein S deficiency, and antithrombin III deficiency.
VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis.

guidelines [4–6]. All statistical analyses were conducted by physicians (K. Kaneda and Y. Yamashita) and a statistician (T. Morimoto) with the use of JMP version 15.2.0 (SAS Institute Inc., Cary, NC, USA). All reported *P*-values were 2-tailed, and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

In the entire study population, the mean age was 67.7 ± 15.7 years, 59% was women, and mean body weight and body mass index were 58.9 ± 14.3 kg and 23.3 ± 4.5 kg/m^2, respectively. There were 475 patients (9.1%) in the major transient risk factors group, 788 patients (15%) in the minor transient risk factors group, 1913 patients (37%) in the unprovoked group, 514 patients (9.9%) in the non-malignant persistent

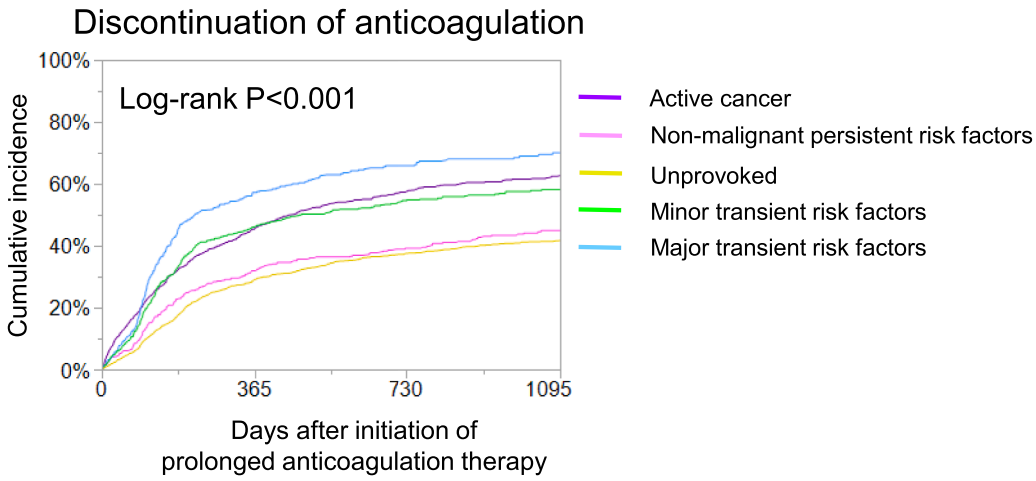
Table 2
Treatment strategies.

	Total (*N* = 5197)	Major transient risk factors (*N* = 475)	Minor transient risk factors (*N* = 788)	Unprovoked (*N* = 1913)	Non-malignant persistent risk factors (*N* = 514)	Active cancer (*N* = 1507)	*P*-value
Treatment in the acute phase							
Initial parenteral anticoagulation therapy	2671 (51%)	216 (45%)	492 (62%)	1002 (52%)	242 (47%)	719 (48%)	<0.001
Heparin	2623 (50%)	213 (45%)	485 (62%)	989 (52%)	232 (45%)	704 (47%)	<0.001
Single injection at diagnosis	159/2623 (6.1%)	10/213 (4.7%)	23/485 (4.7%)	78/989 (7.9%)	14/232 (6.0%)	34/704 (4.8%)	0.04
Continuous injection	2464/2623 (94%)	203/213 (95%)	462/485 (95%)	911/989 (92%)	218/232 (94%)	670/704 (95%)	
Fondaparinux	67 (1.3%)	3 (0.6%)	8 (1.0%)	18 (0.9%)	15 (2.9%)	23 (1.5%)	0.004
Oral anticoagulation therapy	4790 (92%)	453 (95%)	697 (88%)	1799 (94%)	478 (93%)	1363 (90%)	<0.001
Vitamin K antagonist (warfarin)	662 (13%)	55 (12%)	119 (15%)	250 (13%)	74 (14%)	164 (11%)	<0.001
DOAC	4128 (79%)	398 (84%)	578 (73%)	1549 (81%)	404 (79%)	1199 (80%)	<0.001
Dabigatran	6/4128 (0.2%)	0/398 (0%)	3/578 (0.5%)	1/1549 (0.1%)	0/404 (0%)	2/1199 (0.2%)	<0.001
Rivaroxaban	1206/4128 (29%)	90/398 (23%)	172/578 (30%)	544/1549 (35%)	103/404 (26%)	297/1199 (25%)	<0.001
Initial intensive treatment: 30 mg/day	911/1206 (76%)	56/90 (62%)	132/172 (77%)	432/544 (79%)	81/103 (79%)	210/297 (71%)	0.002
Maintenance dose: 15 mg/day	1068/1206 (89%)	81/90 (90%)	157/172 (91%)	490/544 (91%)	91/103 (88%)	249/297 (84%)	0.16
Maintenance dose: 10 mg/day	59/1206 (4.9%)	3/90 (3.3%)	4/172 (2.3%)	24/544 (4.4%)	7/103 (6.8%)	21/297 (7.1%)	
Apixaban	912/4128 (22%)	84/398 (21%)	112/578 (19%)	352/1549 (23%)	107/404 (26%)	257/1199 (21%)	<0.001
Initial intensive treatment: 20 mg/day	551/912 (60%)	54/84 (64%)	74/112 (66%)	235/352 (67%)	54/107 (50%)	134/257 (52%)	<0.001
Maintenance dose: 10 mg/day	770/912 (84%)	70/84 (83%)	95/112 (85%)	300/352 (85%)	82/107 (77%)	223/257 (87%)	0.52
Maintenance dose: 5 mg/day	113/912 (12%)	12/84 (14%)	15/112 (13%)	42/352 (12%)	20/107 (19%)	24/257 (9.3%)	
Edoxaban	2004/4128 (49%)	224/398 (56%)	291/578 (50%)	652/1549 (42%)	194/404 (48%)	643/1199 (54%)	<0.001
60 mg/day	664/2004 (33%)	76/224 (34%)	108/291 (37%)	255/652 (39%)	42/194 (22%)	183/643 (28%)	<0.001
30 mg/day	1309/2004 (65%)	142/224 (63%)	177/291 (61%)	388/652 (60%)	149/194 (77%)	453/643 (70%)	
15 mg/day	31/2004 (1.6%)	6/224 (2.7%)	6/291 (2.1%)	9/652 (1.4%)	3/194 (1.6%)	7/643 (1.1%)	
Oral anticoagulation therapy alone	2301 (44%)	245 (52%)	257 (33%)	833 (44%)	253 (49%)	713 (47%)	<0.001
Thrombolysis with tPA	128 (2.5%)	7 (1.5%)	25 (3.2%)	69 (3.6%)	12 (2.3%)	15 (1.0%)	<0.001
Inferior vena cava filter use	476 (9.2%)	46 (9.7%)	79 (10%)	180 (9.4%)	34 (6.6%)	137 (9.1%)	0.29
Ventilator support	141 (2.7%)	17 (3.6%)	29 (3.7%)	68 (3.6%)	8 (1.6%)	19 (1.3%)	<0.001
Percutaneous cardiopulmonary support	76 (1.5%)	10 (2.1%)	15 (1.9%)	43 (2.3%)	2 (0.4%)	6 (0.4%)	<0.001
Prolonged anticoagulation therapy	4856 (93%)	454 (96%)	733 (93%)	1802 (94%)	484 (94%)	1383 (92%)	0.01
Discontinuation of anticoagulation during follow-up	2142/4856 (42%)	280/454 (62%)	345/733 (47%)	670/1802 (37%)	201/484 (42%)	646/1383 (47%)	<0.001
Reason for discontinuation							
Physician's judgment	1704/2142 (80%)	244/280 (87%)	296/345 (86%)	575/670 (86%)	157/201 (78%)	432/646 (67%)	<0.001
Bleeding event	347/2142 (16%)	26/280 (9%)	35/345 (10%)	81/670 (12%)	39/201 (19%)	166/646 (26%)	
Other	91/2142 (4%)	4/280 (4%)	14/345 (4%)	14/670 (2%)	5/201 (3%)	48/646 (7%)	
Concomitant medications at discharge							
Corticosteroids	693 (13%)	18 (3.8%)	41 (5.2%)	113 (5.9%)	311 (61%)	210 (14%)	<0.001
Non-steroidal anti-inflammatory drugs	454 (8.7%)	92 (19%)	39 (5.0%)	77 (4.0%)	56 (11%)	190 (13%)	<0.001
Proton pump inhibitors/H2-blockers	2627 (51%)	236 (50%)	369 (47%)	901 (47%)	358 (70%)	763 (51%)	<0.001
Statins	865 (17%)	84 (18%)	114 (14%)	363 (19%)	114 (22%)	190 (13%)	<0.001
Antiplatelet agents	423 (8.1%)	45 (9.5%)	75 (9.5%)	162 (8.5%)	56 (11%)	85 (5.6%)	<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. Continuous variables were compared using one-way analysis of variance or Kruskal–Wallis test based on their distributions.

Initial parenteral anticoagulation therapy included heparin (single or continuous injection) and fondaparinux within 10 days after the diagnosis. Oral anticoagulation therapy included vitamin K antagonist (warfarin) and DOACs. Prolonged anticoagulation therapy was defined as oral or parenteral anticoagulation therapy (warfarin, DOAC, or heparin) that was continued beyond the acute phase of 10 days after the diagnosis. Antiplatelet drugs included aspirin, ticlopidine, clopidogrel, prasugrel, ticagrelor, and cilostazol.

DOAC, direct oral anticoagulant; tPA, tissue plasminogen activator.



	0 day	90 days	180 days	1 year	3 years
Active cancer					
N of patients with discontinuation		242	380	504	623
N of patients at risk	1383	906	676	464	154
Cumulative incidence		19.0%	32.1%	45.6%	62.7%
Non-malignant persistent risk factors					
N of patients with discontinuation		47	104	143	188
N of patients at risk	484	412	342	283	139
Cumulative incidence		10.1%	22.8%	32.0%	44.9%
Unprovoked					
N of patients with discontinuation		126	287	467	621
N of patients at risk	1802	1538	1303	1035	465
Cumulative incidence		7.4%	17.3%	29.1%	41.8%
Minor transient risk factors					
N of patients with discontinuation		97	206	281	334
N of patients at risk	733	532	387	289	127
Cumulative incidence		14.7%	32.9%	46.3%	58.2%
Major transient risk factors					
N of patients with discontinuation		76	181	229	268
N of patients at risk	454	341	216	153	56
Cumulative incidence		18.0%	44.4%	57.2%	70.0%

Fig. 2. Kaplan–Meier curves for discontinuation of anticoagulation in patients with prolonged anticoagulation therapy among the 5 groups.
Prolonged anticoagulation therapy was defined as oral or parenteral anticoagulation therapy that was continued beyond the acute phase of 10 days after the diagnosis.

risk factors group, and 1507 patients (29%) in the active cancer group (Fig. 1).

Patient characteristics were different in several aspects across the 5 groups (Table 1). The unprovoked and non-malignant persistent risk factors groups more often had a history of VTE (major transient risk factors: 3.0%, minor transient risk factors: 4.6%, unprovoked: 9.5%, non-malignant persistent risk factors: 9.5%, and active cancer: 5.4%, $P < 0.001$). Patients presented with PE were most prevalent in the unprovoked group (46%, 54%, 60%, 46%, and 51%, $P < 0.001$), while the non-malignant persistent risk factors and active cancer groups presented with less severe status of PE as indicated by lower prevalence of shock and cardiac arrest/collapse (shock: 15%, 15%, 11%, 8.5%, and 7.0%, $P < 0.001$; cardiac arrest/collapse: 8.3%, 6.4%, 6.1%, 2.1%, and 2.2%, $P < 0.001$).

3.2. Treatment strategies

Treatment strategies were different in several aspects across the 5 groups (Table 2). In the entire study population, initial parenteral anticoagulation therapy was administered in 2671 patients (51%), and oral anticoagulation therapy was administered in 4790 patients (92%), 79% of which were DOACs. Among DOAC users, 6 patients (0.2%) used dabigatran, 1206 patients (29%) rivaroxaban, 912 patients (22%) apixaban, and 2004 patients (49%) edoxaban.

In patients with prolonged anticoagulation therapy, the cumulative incidence of discontinuation of anticoagulation was significantly different among the 5 groups (Fig. 2). Discontinuation of anticoagulant at 90 days was most frequent in the active cancer group (major transient risk factors: 18.0%, minor transient risk factors: 14.7%, unprovoked: 7.4%, non-malignant persistent risk factors: 10.1%, and active cancer: 19.0%), whereas discontinuation of anticoagulant at 1 year was most

frequent in the major transient risk factors group (57.2%, 46.3%, 29.1%, 32.0%, and 45.6%). As for the reason of discontinuation of anticoagulation during follow-up, bleeding event was the most frequent reason in the active cancer group (Table 2).

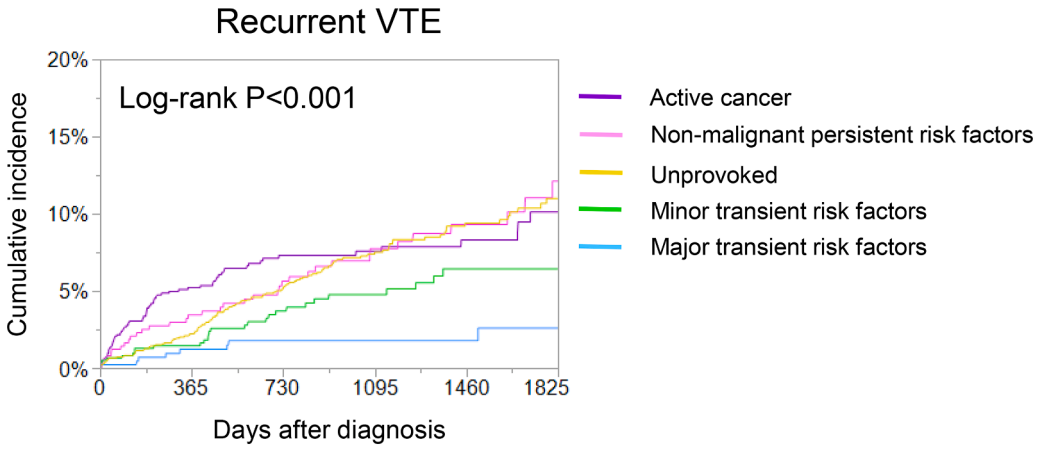
3.3. Clinical outcomes

The cumulative 5-year incidence of recurrent VTE was lowest in the major transient risk factors group (major transient risk factors: 2.6%, minor transient risk factors: 6.4%, unprovoked: 11.0%, non-malignant persistent risk factors: 12.1%, and active cancer: 10.1%, $P < 0.001$) (Fig. 3A). The cumulative 5-year incidence of major bleeding was highest in the active cancer group (9.8%, 11.4%, 11.0%, 15.5%, and 20.4%, $P < 0.001$) (Fig. 3B). The cumulative 5-year incidence of all-cause death was markedly high in the active cancer group (13.9%, 19.5%, 15.9%, 24.6%, and 64.8%, $P < 0.001$) (Fig. 3C). Among 1323 all-cause death, death due to PE accounted for 89 (6.7%), due to bleeding 38 (2.9%), due to cancer 812 (61%), due to other non-cardiac death 297 (22%), due to cardiac death 58 (4.4%), and due to unknown causes 29 (2.2%).

After discontinuation of anticoagulation therapy, the cumulative 5-year incidence of recurrent VTE was lowest in the major transient risk factors group, while it was highest in the unprovoked group (3.3%, 11.0%, 24.9%, 17.5%, and 11.8%, $P < 0.001$) (Fig. 4).

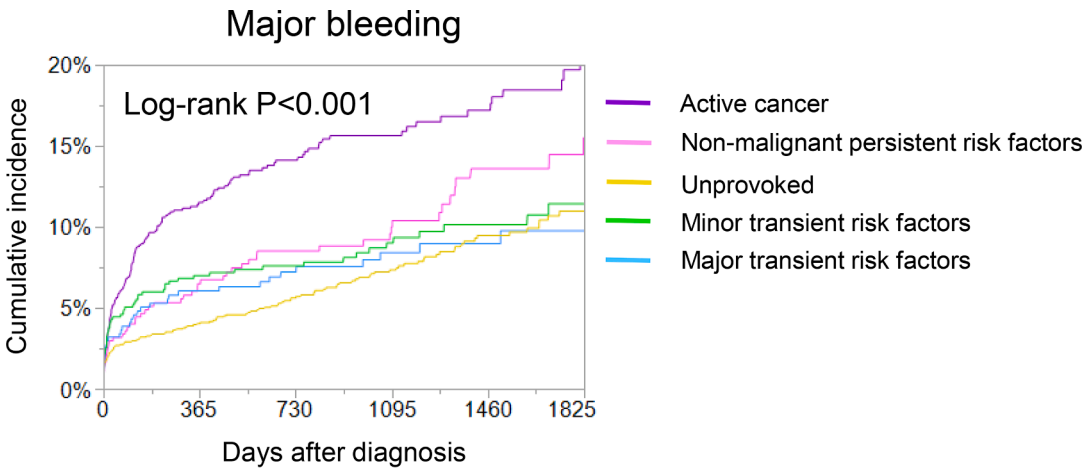
3.4. Effect of status of anticoagulation therapy at 180 days on recurrent VTE

In the landmark analysis at 180 days, the cumulative 3-year incidence of recurrent VTE beyond 180 days was significantly lower in patients on anticoagulation than in patients off anticoagulation in the entire study population (on: 4.2% versus off: 6.9%, $P = 0.002$) (Fig. 5A).



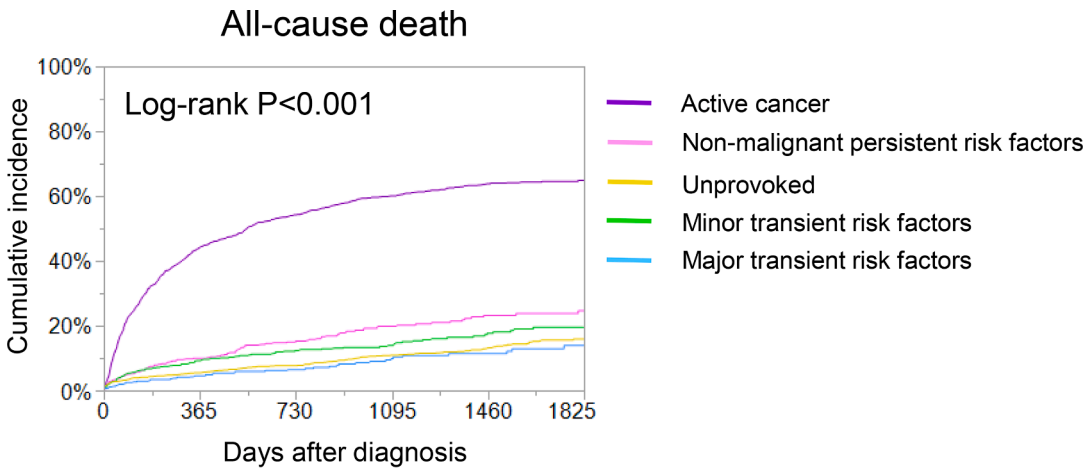
	0 day	90 days	1 year	3 years	5 years
Active cancer					
N of patients with event		32	59	74	79
N of patients at risk	1507	1096	740	325	107
Cumulative incidence		2.4%	5.2%	7.6%	10.1%
Non-malignant persistent risk factors					
N of patients with event		7	16	30	36
N of patients at risk	514	463	405	225	82
Cumulative incidence		1.4%	3.5%	7.8%	12.1%
Unprovoked					
N of patients with event		13	37	100	118
N of patients at risk	1913	1706	1457	726	254
Cumulative incidence		0.7%	2.2%	7.5%	11.0%
Minor transient risk factors					
N of patients with event		6	10	25	29
N of patients at risk	788	663	548	278	117
Cumulative incidence		0.8%	1.5%	4.8%	6.4%
Major transient risk factors					
N of patients with event		1	5	7	8
N of patients at risk	475	435	376	198	78
Cumulative incidence		0.2%	1.2%	1.8%	2.6%

Fig. 3. Kaplan–Meier curves for recurrent VTE (A), major bleeding (B), and all-cause death (C) among the 5 groups.
Patients with and without anticoagulation therapy were included.
VTE included PE and/or DVT.
VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism.



	0 day	90 days	1 year	3 years	5 years
Active cancer					
N of patients with event		95	143	170	181
N of patients at risk	1507	1065	724	318	108
Cumulative incidence		6.8%	11.5%	15.6%	20.4%
Non-malignant persistent risk factors					
N of patients with event		18	31	43	52
N of patients at risk	514	457	397	226	82
Cumulative incidence		3.6%	6.5%	10.0%	15.5%
Unprovoked					
N of patients with event		54	72	110	130
N of patients at risk	1913	1681	1448	740	267
Cumulative incidence		2.9%	4.0%	7.3%	11.0%
Minor transient risk factors					
N of patients with event		38	50	58	63
N of patients at risk	788	638	524	275	114
Cumulative incidence		5.0%	7.0%	9.0%	11.4%
Major transient risk factors					
N of patients with event		18	27	34	36
N of patients at risk	475	422	364	188	74
Cumulative incidence		3.9%	6.0%	8.4%	9.8%

Fig. 3. (*continued*).



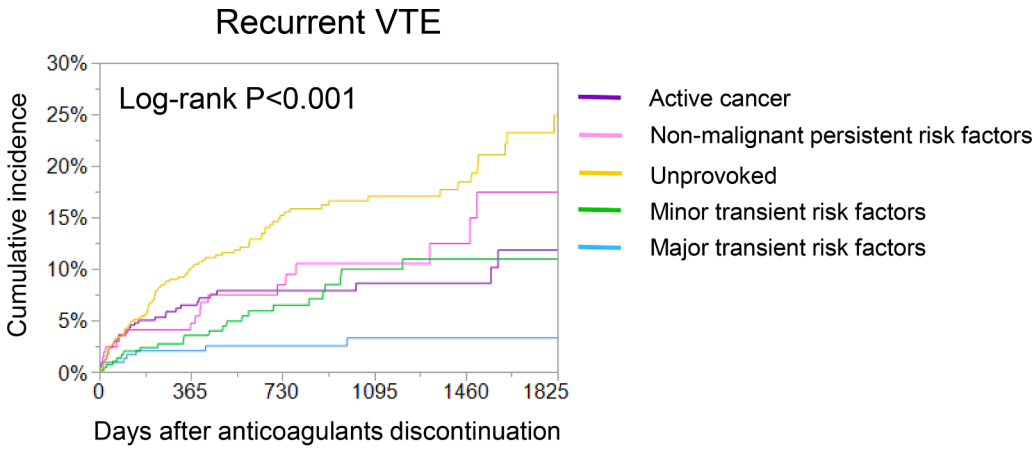
	0 day	90 days	1 year	3 years	5 years
Active cancer					
N of patients with event		329	637	825	858
N of patients at risk	1507	1119	765	344	120
Cumulative incidence		22.3%	44.3%	60.0%	64.8%
Non-malignant persistent risk factors					
N of patients with event		26	49	88	98
N of patients at risk	514	469	417	241	93
Cumulative incidence		5.2%	10.0%	19.8%	24.6%
Unprovoked					
N of patients with event		63	99	165	194
N of patients at risk	1913	1717	1489	779	280
Cumulative incidence		3.4%	5.5%	10.9%	15.9%
Minor transient risk factors					
N of patients with event		39	65	88	103
N of patients at risk	788	667	555	295	124
Cumulative incidence		5.2%	9.3%	13.9%	19.5%
Major transient risk factors					
N of patients with event		11	20	36	42
N of patients at risk	475	436	381	199	79
Cumulative incidence		2.4%	4.6%	9.9%	13.9%

Fig. 3. (*continued*).

The cumulative 3-year incidence of recurrent VTE beyond 180 days was significantly lower in patients on anticoagulation than in patients off anticoagulation in the minor transient risk factors, unprovoked and active cancer groups (minor transient risk factors: on: 2.3% versus off: 6.3%, $P = 0.04$; unprovoked: 5.3% versus 11.8%, $P < 0.001$; active cancer: 3.8% versus 7.1%, $P = 0.04$), whereas the cumulative 3-year incidence of recurrent VTE beyond 180 days was not significantly different between patients on and off anticoagulation in the major transient risk factors and non-malignant persistent risk factors groups (major transient risk factors: 1.0% versus 1.3%, $P = 0.75$; non-malignant persistent risk factors: 5.0% versus 5.5%, $P = 0.96$) (Fig. 5B–F). The landmark analysis for major bleeding and all-cause death according to anticoagulation status at 180 days are shown in the Supplementary Figs. 1 and 2.

4. Discussion

The main findings of the current study were as follows; (1) Among patients with transient provoking risk factors, those with major transient provoking risk factors were at the lowest risk of recurrence, whereas those with minor transient provoking risk factors were at a relatively high risk of recurrence and might have a potential benefit of extended anticoagulation therapy beyond 6 months. (2) Patients with unprovoked VTE showed persistently higher risk of recurrence in the long term after discontinuation of anticoagulation therapy, who might get a potential more benefit of extended anticoagulation therapy in terms of recurrence. (3) Among patients with persistent provoking risk factors, those with active cancer were at a high risk of recurrence as well as at the highest risk of major bleeding, which lead to a high discontinuation rate of anticoagulation therapy in discordance with the current guideline recommendations.



	0 day	1 year	3 years	5 years
Active cancer				
N of patients at risk	1343	285	114	23
Cumulative incidence		6.5%	8.6%	11.8%
Non-malignant persistent risk factors				
N of patients at risk	469	144	60	16
Cumulative incidence		4.7%	10.5%	17.5%
Unprovoked				
N of patients at risk	1766	429	175	46
Cumulative incidence		10.0%	17.1%	24.9%
Minor transient risk factors				
N of patients at risk	722	230	104	39
Cumulative incidence		3.6%	10.0%	11.0%
Major transient risk factors				
N of patients at risk	450	226	106	33
Cumulative incidence		2.1%	3.3%	3.3%

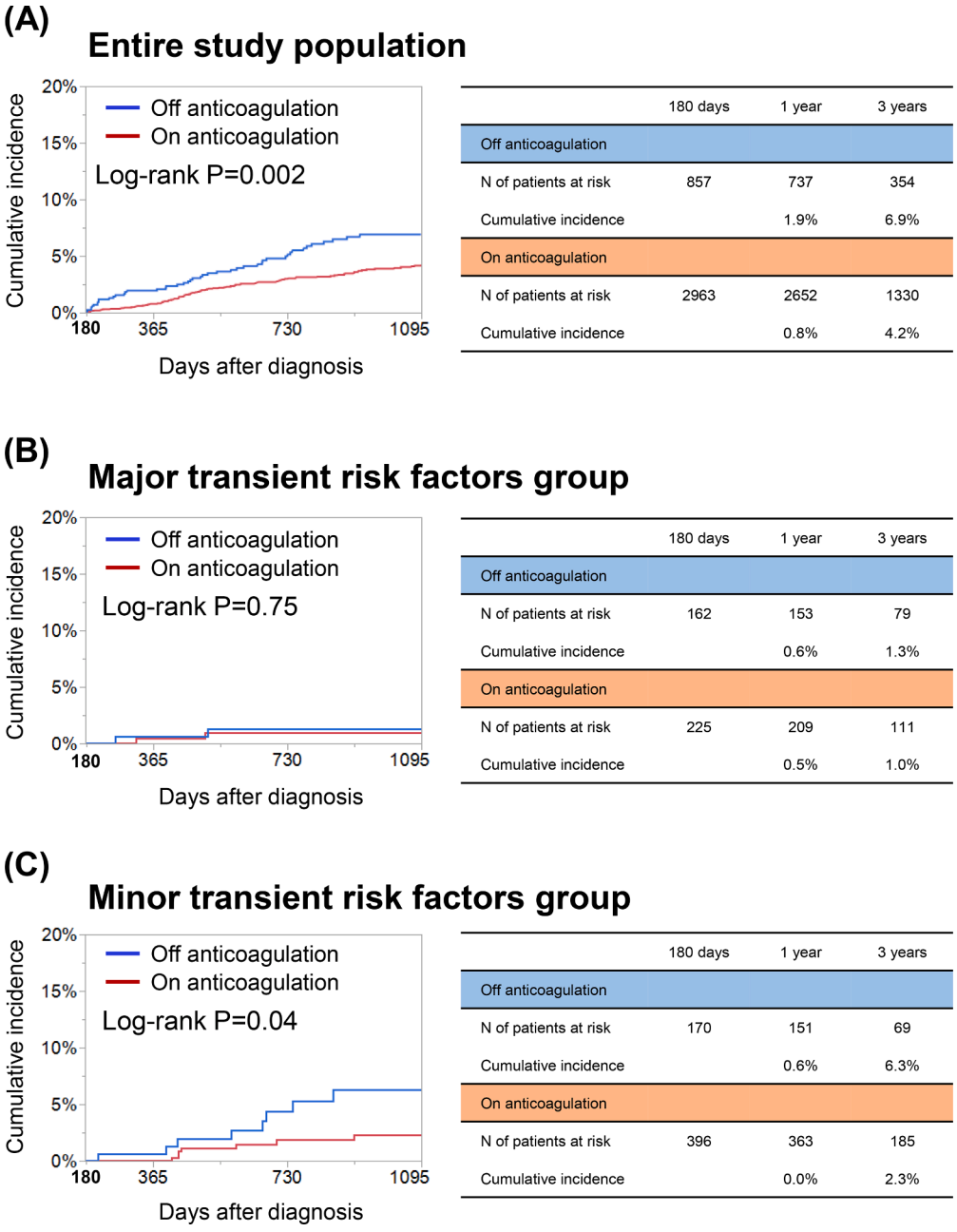
Fig. 4. Kaplan–Meier curves for recurrent VTE after discontinuation of anticoagulation therapy among the 5 groups.
VTE included PE and/or DVT. Eligible patients for this analysis were those who received prolonged anticoagulation therapy, and were free from recurrent VTE before discontinuation. Prolonged anticoagulation therapy was defined as oral or parenteral anticoagulation therapy that was continued beyond the acute phase of 10 days after the diagnosis.
VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism.

The current guidelines recommend specific durations of anticoagulation therapy preferably with DOAC depending on the risks of recurrence in individual patients [4–7], although most of these recommendations have been based on the data in the pre-DOAC era. The current study could have a strength of analysis in the current era of DOAC based on the detailed risk-classifications recommended by ISTH with long-term follow-up data, which might provide several clinically relevant insights for the current issues and unmet needs. Generally, the incidence rates of recurrent VTE and major bleeding in the current DOAC era seemed to be comparable with those in the previous warfarin era [18]. On the other hand, the incidence rate of recurrent VTE among patients with active cancer could be lower in the current DOAC era than that in the previous warfarin era, which might suggest the potential benefit of DOAC over warfarin.

Historically, patients with transient provoking risk factors were thought to be at a low risk of recurrence and were recommended to receive a limited duration of anticoagulation therapy [20]. Recently, ISTH has recommended to further classify these patients into those with major and minor transient provoking risk factors [3]. However, there have been still only a few reports about the risk estimation and optimal duration of anticoagulation therapy for these patients. The latest 2019 ESC guidelines for PE weakly recommends extended oral anticoagulation of indefinite duration for patients with a minor transient risk factor with a low evidence level [4]. On the other hand, the latest 2021 CHEST guidelines for VTE recommends against offering extended-phase anticoagulation for patients a minor transient risk factor [5]. A previous study from GARFIELD-VTE reported that patients with minor and major transient provoking factors had a similar risk of recurrent VTE, although the study evaluated the clinical outcomes in the relatively short-term of 1 year [21]. The current study evaluating long-term risk of recurrence showed that patients with minor transient provoking risk factors were at a relatively high risk of recurrence beyond 1 year and could have a higher risk of recurrence after discontinuation of anticoagulation therapy compared with those with major transient provoking risk factors. These findings might suggest the potential benefit of different anticoagulation strategies according to the sub-types of transient provoking risk factors, which might support the recommendations by the latest 2019 ESC guideline. Notably, the current study also showed that the 1-year discontinuation rate of anticoagulation therapy was relatively low even in major transient risk factor group (57.2%), and a certain number of patients with major transient risk factors continued anticoagulation therapy beyond a minimum duration of 3 months, which was discordant with the current guideline recommendations. In line with the current results, a previous study from RIETE also reported the relatively longer duration of anticoagulation therapy in patients with transient risk factors who were considered as those at a low risk of recurrence (the proportion of patients treated beyond 1 year was 41.9%) [22]. These results might reflect that anticoagulation management could not always follow guidelines in daily clinical practice. In addition, the decision-making of continuation and discontinuation of anticoagulation therapy could be associated with potential different risks of major bleeding and mortality.

A previous study reported that incidence rates of recurrent VTE after discontinuation of anticoagulation therapy in patients with a first episode of unprovoked VTE were 10% at 1 year, 25% at 5 years and 36% at 10 years [23]. Consistent with the previous study, the current study revealed that patients with unprovoked VTE showed persistently elevated risk of recurrence in the long term after discontinuation of anticoagulation therapy (10.0% at 1 year and 24.9% at 5 years). Based on the high risk of recurrence, the current guidelines recommend extended or indefinite duration of anticoagulation therapy for patients with unprovoked VTE [4,5]. In the era of DOAC, patients with unprovoked VTE might get a potential more benefit of indefinite anticoagulation therapy in terms of recurrence, and thus, identification of high-risk patients for bleeding during anticoagulation therapy could become more clinically relevant in determining the optimal duration of anticoagulation therapy in individual patients. In addition, the risk assessment of mortality could be important. Although a previous study reported that currently available bleeding risk scores for DOAC patients had modest predictive ability [24], generalizability of these scores and optimal risk scores should be further investigated in the future.

A recent study reported that the incidence of VTE in patients with cancer has been increasing over time, but not in patients without cancer [25]. In line with the previous study, the current study showed a high

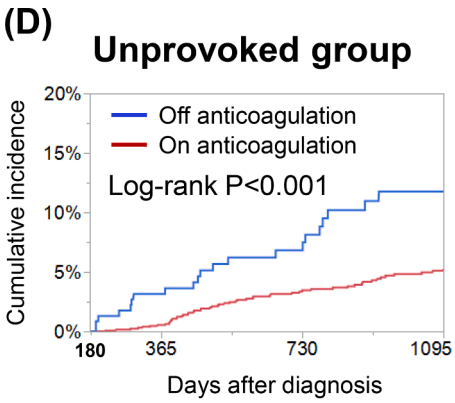


	180 days	1 year	3 years
Off anticoagulation			
N of patients at risk	857	737	354
Cumulative incidence		1.9%	6.9%
On anticoagulation			
N of patients at risk	2963	2652	1330
Cumulative incidence		0.8%	4.2%

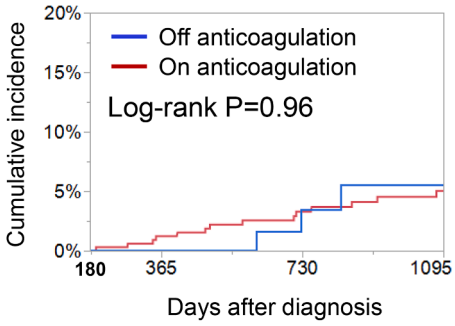
	180 days	1 year	3 years
Off anticoagulation			
N of patients at risk	162	153	79
Cumulative incidence		0.6%	1.3%
On anticoagulation			
N of patients at risk	225	209	111
Cumulative incidence		0.5%	1.0%

	180 days	1 year	3 years
Off anticoagulation			
N of patients at risk	170	151	69
Cumulative incidence		0.6%	6.3%
On anticoagulation			
N of patients at risk	396	363	185
Cumulative incidence		0.0%	2.3%

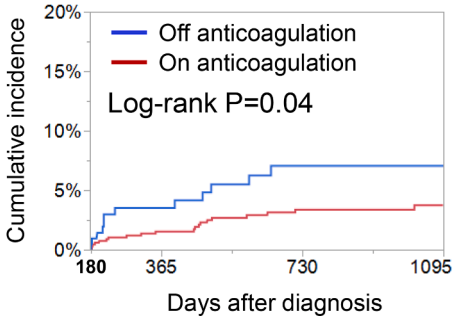
Fig. 5. Kaplan–Meier curves for the landmark analysis on recurrent VTE beyond 180 days between the 2 groups of patients on and off anticoagulation at the 180-day landmark point in the entire study population (A), major transient risk factors group (B), minor transient risk factors group (C), unprovoked group (D), non-malignant persistent risk factors group (E), and active cancer group (F).
VTE included PE and/or DVT. Eligible patients for this analysis were those who received prolonged anticoagulation therapy, and were free from recurrent VTE within 180 days. Prolonged anticoagulation therapy was defined as oral or parenteral anticoagulation therapy that was continued beyond the acute phase of 10 days after the diagnosis.
VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism.



	180 days	1 year	3 years
Off anticoagulation			
N of patients at risk	231	204	97
Cumulative incidence		3.2%	11.8%
On anticoagulation			
N of patients at risk	1313	1205	609
Cumulative incidence		0.6%	5.3%



	180 days	1 year	3 years
Off anticoagulation			
N of patients at risk	84	77	38
Cumulative incidence		0.0%	5.5%
On anticoagulation			
N of patients at risk	341	318	183
Cumulative incidence		1.2%	5.0%



	180 days	1 year	3 years
Off anticoagulation			
N of patients at risk	210	156	71
Cumulative incidence		3.5%	7.1%
On anticoagulation			
N of patients at risk	688	561	242
Cumulative incidence		1.5%	3.8%

Fig. 5. (*continued*).

prevalence of active cancer (29%), which suggested the importance of active cancer among patients with VTE in the current era. The previous study reported that VTE patients with active cancer had a markedly higher risk of recurrence as well as bleeding, compared with those without active cancer, posing difficulty in achieving a good risk benefit balance with anticoagulation therapy [26]. In the pre-DOAC era, low-molecular-weight heparin (LMWH) was preferable anticoagulation therapy for cancer-associated VTE. Recently, several clinical trials have reported the efficacy and safety of DOACs for cancer-associated VTE compared with LMWH [27–30], which revealed that DOACs seemed to be reasonable alternatives to LMWH for cancer-associated VTE. The current study showed a high prevalence of DOACs as oral anticoagulation therapy for patients with active cancer, and DOACs seemed to be the first choice of anticoagulation therapy for cancer-associated VTE in the current daily clinical practice. However, the current study also showed patients with active cancer were at the highest risk of major bleeding and the proportion of discontinuation of anticoagulation due to bleeding events was highest in patients with active cancer, which might lead to a relatively high discontinuation rate of anticoagulation therapy in discordance with the current guideline recommendations. Optimal management strategies of VTE patients with cancer might still be a major concern even in the era of DOAC, which might be overcome by the potential alternatives to DOAC in the future [31,32].

The current study has several limitations. First, the current study was an observational retrospective study with the limitation inherent to the study design. Because the decisions including anticoagulation strategies were left to the discretion of the attending physician, the analysis for the optimal duration of anticoagulation therapy was exploratory. Second, demographics, practice patterns as well as clinical outcomes in patients with VTE in Japan may be different from those outside Japan [33]. However, standard management strategies proposed by Japanese Circulation Society guidelines for VTE have been based on recommendations by ESC guidelines and CHEST guidelines, and thus, the main findings of the current study could be anticipated to apply to Western

population. In particular, the difference in the prevalence of hereditary thrombophilia could have a certain influence on clinical outcomes. There are few patients with homozygous factor V Leiden or homozygous prothrombin G20210A among Asians, but both conditions are more common in Caucasians [34]. Furthermore, mean body mass index of patients in the current study was 23.3 kg/m^2, which were lower compared with those in should be less compared with other Western countries. Previous studies reported that lean patients with VTE including low body mass index (<18.5 kg/m^2) and low body weight (<60 kg) showed higher risk of bleeding but comparable risk of recurrence [35,36]. Thus, it should be interpreted with caution whether the results of the current study can be generalized to more obese patients especially in terms of a bleeding risk. In addition, a relatively lower rate of antiplatelet therapy in the current study compared with that in Western countries [33] could have a certain influence on clinical outcomes including bleeding events [37,38]. Third, the current study aimed to investigate the current status of VTE in the DOAC era as a descriptive analysis. Thus, we did not conduct the adjusted analysis including multivariable analysis or competing risk analysis. Forth, because the current study aimed to investigate the current real-world status of VTE in the DOAC era, we included all kinds of anticoagulation therapy. Different kinds of anticoagulation therapy could have different influence on clinical outcomes. Fifth, in current study, we just analyzed the cause of death on PE and major bleeding. Future detailed investigation was warranted as sub-analysis. Finally, we evaluated long-term clinical outcomes based on patient characteristics at the time of VTE diagnosis. However, the patient characteristics including the status of persistent provoking risk factors could change over time.

5. Conclusion

In this large real-world VTE registry, anticoagulation strategies and long-term recurrence widely differed depending on the baseline characteristics. Detailed risk stratifications of recurrent VTE could be useful for decision-making of anticoagulation strategies, whereas the bleeding-risk assessment might be especially important in the era of DOAC.

Funding

The COMMAND VTE Registry-2 is partly supported by JSPS KAKENHI Grant Number JP 21K16022. 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.

CRediT authorship contribution statement

Kazuhisa Kaneda: Formal analysis, Data curation, Writing – original draft. **Yugo Yamashita:** Formal analysis, Data curation, Writing – original draft. **Takeshi Morimoto:** Data curation, Writing – original draft, Formal analysis. **Ryuki Chatani:** Funding acquisition, Formal analysis, Writing – review & editing. **Yuji Nishimoto:** Funding acquisition, Formal analysis, Writing – review & editing. **Nobutaka Ikeda:** Funding acquisition, Formal analysis, Writing – review & editing. **Yohei Kobayashi:** Funding acquisition, Formal analysis, Writing – review & editing. **Satoshi Ikeda:** Funding acquisition, Formal analysis, Writing – review & editing. **Kitae Kim:** Funding acquisition, Formal analysis, Writing – review & editing. **Moriaki Inoko:** Funding acquisition, Formal analysis, Writing – review & editing. **Toru Takase:** Funding acquisition, Formal analysis, Writing – review & editing. **Shuhei Tsuji:** Funding acquisition, Formal analysis, Writing – review & editing. **Maki Oi:** Funding acquisition, Formal analysis, Writing – review & editing. **Takuma Takada:** Funding acquisition, Formal analysis, Writing – review & editing. **Kazunori Otsui:** Funding acquisition, Formal analysis, Writing – review & editing. **Takeshi Kimura:** Data curation, Writing – review & editing, Formal analysis.

Declaration of Competing Interest

Dr. Kaneda received lecture fees from Bristol-Myers Squibb, Pfizer, and Daiichi-Sankyo. Dr. Yamashita received lecture fees from Bayer Healthcare, Bristol-Myers Squibb, Pfizer, and Daiichi-Sankyo, and grant support from Bayer Healthcare and Daiichi-Sankyo. 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. Nishimoto received lecture fees from Bayer Healthcare, Bristol-Myers Squibb, Pfizer, and Daiichi-Sankyo. Dr. Ikeda N. received lecture fees from Bayer Healthcare, Bristol-Myers Squibb, and Daiichi-Sankyo. Dr. Ikeda S. received lecture fees from Bayer Healthcare, Bristol-Myers Squibb and Daiichi-Sankyo. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Acknowledgments

We appreciate the support and collaboration of the co-investigators participating in the COMMAND VTE Registry-2.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2023.08.007.

References

[1] Di NM, van EN, Büller HR. Deep vein thrombosis and pulmonary embolism. Lancet N Am Ed 2016;388:3060–73.
[2] Kyrle PA, Rosendaal FR, Eichinger S. Risk assessment for recurrent venous thrombosis. Lancet N Am Ed 2010;376:2032–9.
[3] Kearon C, Ageno W, Cannegieter SC, et al. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. J Thromb Haemost 2016;14:1480–3.
[4] Konstantinides SV, Meyer G, Bueno H, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European respiratory society (ERS). Eur Heart J 2020;41:543–603.
[5] Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. Chest 2021;160:e545–608.
[6] Witt DM, Nieuwlaat R, Clark NP, et al. American society of hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv 2018;2:3257–91.
[7] Kakkos SK, Gohel M, Baekgaard N, et al. Editor's choice – European society for vascular surgery (ESVS) 2021 clinical practice guidelines on the management of venous thrombosis. Eur J Vasc Endovasc Surg 2021;61:9–82.
[8] Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009;361:2342–52.
[9] Scott D, Brenner B, Buller HR, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499–510.
[10] Bailey AL. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366:1287–97.
[11] Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013;10:25–6.
[12] Hokusai VTE Investigators, Büller HR, Décousus H, Grosso MA, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013;369:1406–15.
[13] Gómez-Outes A, Terleira-Fernández AI, Lecumberri R, et al. Direct oral anticoagulants in the treatment of acute venous thromboembolism: a systematic review and meta-analysis. Thromb Res 2014;134:774–82.
[14] Goldhaber SZ, Visani L, De RM. Acute pulmonary embolism: clinical outcomes in the international cooperative pulmonary embolism registry (ICOPER). Lancet 1999;353:1386–9.
[15] Pollack CV, Schreiber D, Goldhaber SZ, et al. Clinical characteristics, management, and outcomes of patients diagnosed with acute pulmonary embolism in the emergency department: initial report of EMPEROR (multicenter emergency medicine pulmonary embolism in the real world registry). J Am Coll Cardiol 2011; 57:700–6.
[16] Meissner MH, Moneta G, Burnand K, et al. The hemodynamics and diagnosis of venous disease. J Vasc Surg 2007;46:4–24.
[17] Sakamoto J, Yamashita Y, Morimoto T, et al. Cancer-associated venous thromboembolism in the real world – from the command VTE registry. Circ J 2019; 83:2271–81.
[18] Yamashita Y, Morimoto T, Amano H, et al. Anticoagulation therapy for venous thromboembolism in the real world: from the command VTE registry. Circ J 2018; 82:1262–70.

[19] Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692–4.
[20] Kearon C, Iorio A, Palareti G. Risk of recurrent venous thromboembolism after stopping treatment in cohort studies: recommendation for acceptable rates and standardized reporting. J Thromb Haemost 2010;8:2313–5.
[21] Ageno W, Farjat A, Haas S, et al. Provoked versus unprovoked venous thromboembolism: findings from GARFIELD-VTE. Res Pract Thromb Haemost 2021;5:326–41.
[22] Ageno W, Samperiz A, Caballero R, et al. Duration of anticoagulation after venous thromboembolism in real world clinical practice. Thromb Res 2015;135:666–72.
[23] Khan F, Rahman A, Carrier M, et al. Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: systematic review and meta-analysis. BMJ 2019;366:I4363.
[24] Vedovati MC, Mancuso A, Pierpaoli L, et al. Prediction of major bleeding in patients receiving DOACs for venous thromboembolism: a prospective cohort study. Int J Cardiol 2020;301:167–72.
[25] Walker AJ, Card TR, West J, et al. Incidence of venous thromboembolism in patients with cancer-A cohort study using linked United Kingdom databases. Eur J Cancer 2013;49:1404–13.
[26] Prandoni P, Lensing AWA, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 2002;100:3484–8.
[27] Raskob GE, van EN, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 2018;378:615–24.
[28] Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). J Clin Oncol 2018;36:2017–23.
[29] McBane RD, Wysokinski WE, Le-Rademacher JG, et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: the ADAM VTE trial. J Thromb Haemost 2020;18:411–21.
[30] Agnelli G, Becattini C, Meyer G, et al. Apixaban for the treatment of venous thromboembolism associated with cancer. N Engl J Med 2020;382:1599–607.
[31] Weitz JI, Strony J, Ageno W, et al. Milvexian for the prevention of venous thromboembolism. N Engl J Med 2021;385:2161–72.
[32] Piccini JP, Caso V, Connolly SJ, et al. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. Lancet N Am Ed 2022;399:1383–90.
[33] Yamashita Y, Bikdeli B, Monreal M, et al. Difference between Japanese and White patients with acute pulmonary embolism. Thromb Res 2021;204:52–6.
[34] Ridker PM, Miletich JP, Hennekens CH, et al. Ethnic distribution of factor V Leiden in 4047 men and women: implications for venous thromboembolism screening. JAMA 1997;277:1305–7.
[35] Weitz JI, Farjat AE, Ageno W, et al. Influence of body mass index on clinical outcomes in venous thromboembolism: insights from GARFIELD-VTE. J Thromb Haemost 2021;19:3031–43.
[36] Kaneda K, Yamashita Y, Morimoto T, et al. Influence of low body weight on long-term clinical outcomes in patients with venous thromboembolism: from the COMMAND VTE registry. Thromb Res 2021;198:26–33.
[37] Davidson BL, Verheijen S, Lensing AWA, et al. Bleeding risk of patients with acute venous thromboembolism taking nonsteroidal anti-inflammatory drugs or aspirin. JAMA Intern Med 2014;174:947–53.
[38] Tzoran I, Brenner B, Sakharov G, et al. Clinical outcome in patients with venous thromboembolism receiving concomitant anticoagulant and antiplatelet therapy. Eur J Intern Med 2014;25:821–5.