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ORIGINAL ARTICLE
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Rivaroxaban Treatment for Patients With Unprovoked or Provoked Venous Thromboembolism

— Subanalysis of the J'xactly Study —

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Background: The efficacy and safety of direct oral anticoagulants (DOACs) in patients with unprovoked venous thromboembolism (VTE) remain unclear.

Methods and Results: In this subanalysis of the J'xactly study, a multicenter prospective observational study, we evaluated the safety and effectiveness of rivaroxaban in patients with acute VTE according to unprovoked (n=388) or provoked (n=557) VTE status. Median follow-up was 21.2 months. Compared with patients in the provoked group, patients in the unprovoked group were younger, less likely to be female, and had higher body weight. The incidence of symptomatic VTE recurrence was significantly higher in the unprovoked than provoked VTE group (3.54% vs. 1.77% per patient-year; P=0.032). There was no significant difference in the incidence of major bleeding events between rivaroxaban-treated patients with unprovoked and provoked VTE (2.31% vs. 3.75% per patient-year; P=0.289). Although the proportion of patients with a body mass index (BMI) ≥25 kg/m^2 who were non-users of antiplatelet agents was higher in the unprovoked VTE group, there was no interaction effect (BMI: 4.58% vs. 1.55% per patient-year [P=0.040; P for interaction=0.361]; concomitant antiplatelet agent non-users: 3.65% vs. 1.72% per patient-year [P=0.028; P for interaction=0.627]).

Conclusions: This subanalysis suggests the safety and effectiveness of rivaroxaban in patients with unprovoked VTE. In such patients, DOAC discontinuation should be considered carefully, particularly in those not using antiplatelet agents and those with a high BMI.

Key Words: Direct oral anticoagulant; Real-world data; Rivaroxaban; Unprovoked; Venous thromboembolism

Venous thromboembolism (VTE), which comprises deep vein thrombosis (DVT) and pulmonary embolism (PE), is a leading cause of morbidity and mortality worldwide,[1,2] with a long-term risk of recurrence resulting, in part, from provoked and unprovoked risk factors at the time of the initial VTE event.[3] Although the risk factors for provoked VTE may be transient (e.g., major surgery or trauma) or persistent (e.g., in the case of active cancer), up to 50% of patients with VTE have no identifiable risks (unprovoked VTE) and are at a greater risk of VTE recurrence than those with transient provoking risk factors.[4]

Anticoagulation is the cornerstone of treatment for patients with acute VTE;[5,6] however, the risk factors at the

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The J'xactly Study has been registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000025072).

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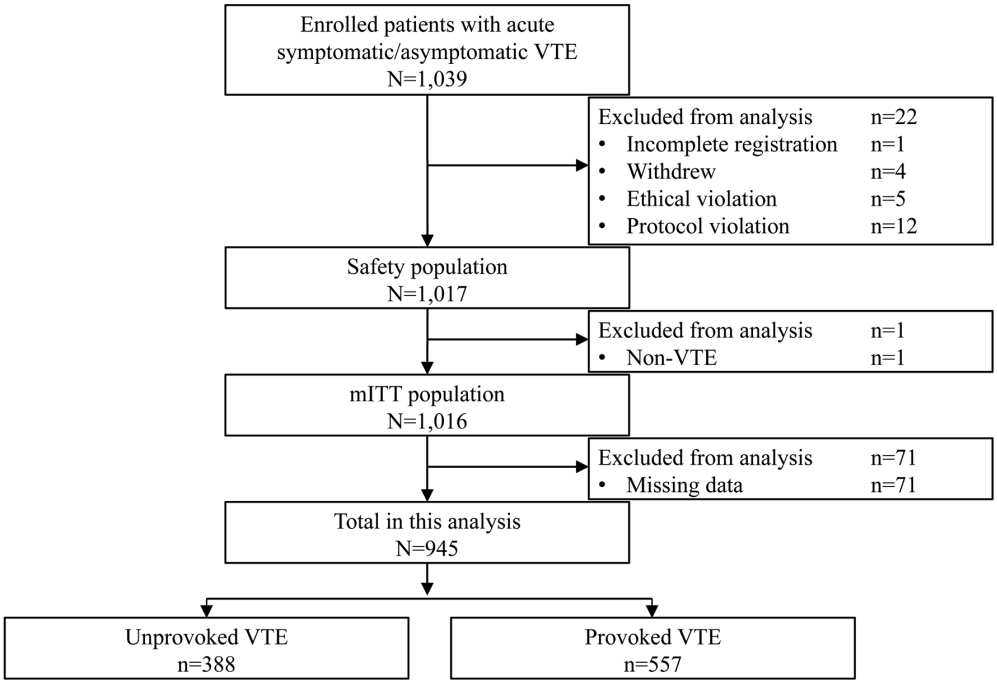

Figure 1. Flow diagram of patient disposition. Venous thromboembolism (VTE) includes deep vein thrombosis, pulmonary embolism, or both. mITT, modified intention to treat.

time of the event affect treatment duration. Following a provoked VTE event, standard anticoagulation may be discontinued after 3–6 months.[5,6] In contrast, the optimal management of a first unprovoked VTE event is less clear because the long-term risk of recurrence outweighs the long-term risk of bleeding in such patients, and anticoagulation therapy may be required indefinitely.[7] Hence, patients with unprovoked VTE require closer attention during discontinuation of anticoagulant therapy than patients with provoked VTE.

Direct oral anticoagulants (DOACs), associated with a lower risk of bleeding than vitamin K antagonists, are the first-line treatment choice for most patients with acute VTE.[5,6] An increasing body of evidence has demonstrated the efficacy and safety of DOACs in clinical settings in Japan since they became available to treat VTE.[8–12] A 2-year analysis of the Japanese registry of rivaroXAban effectiveness and safety for the prevention of reCurrence in patients with deep vein Thrombosis and puLmonarY embolism (J'xactly study) demonstrated the effectiveness and safety of rivaroxaban in a broad range of Japanese patients with VTE in a real-world setting.[9] The 1-year Edoxaban Treatment in routiNe clinical prActice in patients with Venous ThromboEmbolism – Japan (ETNA-VTE-Japan) study of real-world data in Japanese patients with VTE, including those with a high risk of bleeding who lacked clinical trial safety information, showed no major concerns regarding the safety and effectiveness of edoxaban.[10,11] In addition, a large post-marketing surveillance study showed the safety and effectiveness of apixaban for the prevention or treatment of recurrent VTE in Japanese patients in real-world clinical practice.[12] However, the efficacy and safety of DOACs in patients with unprovoked VTE have not been established.[7]

The present subanalysis of the J'xactly study evaluated the effectiveness and safety of the DOAC rivaroxaban in patients with unprovoked VTE, and compared the effectiveness and safety in patients with unprovoked VTE by VTE risk.

Methods

Study Design, Patients, and Treatment

Details of the study design, data collection process, and baseline characteristics of the full J'xactly study population have been reported previously.[8,9] Briefly, the J'xactly study was a multicenter prospective observational study of patients with acute symptomatic and/or asymptomatic DVT, PE, or both who were prescribed oral rivaroxaban for the treatment of acute VTE and the prevention of recurrent VTE at centers in Japan. Patients were enrolled from December 2016 to April 2018 and were followed up for at least 18 months and up to 3 years after enrollment.

The J'xactly study was conducted in compliance with the principles of the Declaration of Helsinki and with all applicable legal and regulatory requirements in Japan. All study protocols and related documentation were reviewed and approved by the Institutional Review Board of Nihon University Itabashi Hospital (RK-160913-4), and all participating institutions provided ethics approval. In addition, an independent data and safety monitoring committee reviewed the study data. The study was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000025072).

For each patient, the dose and duration of rivaroxaban treatment were at the discretion of the treating physician.

The standard regimen for rivaroxaban treatment in patients following a diagnosis of VTE at the time of the study was 15 mg twice daily for 3 weeks and 15 mg once daily thereafter. During the follow-up period, at the investigator's discretion, rivaroxaban treatment could be suspended, discontinued, terminated, or switched to other treatments, and data on the treatment status during the follow-up period were collected.

Only patients with available information regarding VTE-inducible factors and other risk factors (body mass index [BMI], age, sex, and concomitant antiplatelet or corticosteroid use) were included in this subgroup analysis.

Patients were stratified into 2 groups (provoked or unprovoked VTE). Specifically, patients with ≥1 of 5 factors,[13] namely comorbid malignancy or transient risk factors (physical inactivity, injury, surgery, or concomitant use of estrogen preparations), were allocated to the provoked VTE group.[14,15] All other patients were allocated to the unprovoked VTE group, including patients with previous VTE and without malignancy.

A subgroup analysis was conducted to evaluate the duration of rivaroxaban treatment in the unprovoked VTE group according to the following factors: BMI, age, sex, and concomitant antiplatelet and corticosteroid use. In terms of age, the cut-off was determined as 65 years based on the study by Cosmi et al.[16]

Outcomes and Other Analyses

The outcomes assessed in this subanalysis of the J'xactly study[9] were the incidence of symptomatic VTE recurrence, death from any cause, recurrence or aggravation of symptomatic PE, and recurrence of symptomatic DVT in the unprovoked group (without active cancer or transient risk factors) vs. the provoked VTE group (with active cancer or a transient risk factor for VTE [physical inactivity, injury, surgery, or the use of estrogen preparations]).

The following subgroup analyses were conducted: baseline characteristics in unprovoked and provoked VTE groups; clinical outcomes in patients with unprovoked VTE; clinical outcomes in patients with unprovoked VTE according to baseline characteristics; and safety outcomes in patients with unprovoked VTE. The duration of DOAC treatment and rivaroxaban discontinuation were also assessed.

Table 1. Baseline Characteristics Overall and in Patients With Unprovoked or Provoked VTE Separately

	Overall (n=945)	VTE risk		P value
		Unprovoked (n=388)	Provoked (n=557)	
Age (years)	68.1±14.6	66.8±14.2	68.9±14.8	0.002
Female sex	552 (58.4)	195 (50.3)	357 (64.1)	<0.001
Body weight (kg)	60.3±14.1	62.7±15.1	58.7±13.1	<0.001
BMI (kg/m²)	23.8±4.2	24.1±4.3	23.6±4.2	0.249
CrCl (mL/min)	78.1±36.3	79.6±37.7	77.0±35.3	0.321
<30	9 (1.0)	2 (0.5)	7 (1.3)	0.401
≥30–<50	202 (21.4)	76 (19.6)	126 (22.6)	
≥50–<80	353 (37.4)	152 (39.2)	201 (36.1)	
≥80	377 (39.9)	157 (40.5)	220 (39.5)	
D-dimer (μg/mL)	8.0 [3.8–15.2]	7.4 [3.4–13.8]	8.8 [3.9–17.5]	0.014
Medical history				
Hypertension	360 (38.1)	145 (37.4)	215 (38.6)	0.734
Diabetes	114 (12.1)	46 (11.9)	68 (12.2)	0.919
Heart failure	33 (3.5)	12 (3.1)	21 (3.8)	0.719
Atrial fibrillation	29 (3.1)	11 (2.8)	18 (3.2)	0.849
Coronary artery disease	42 (4.4)	20 (5.2)	22 (3.9)	0.423
Chronic heart and lung disease	46 (4.9)	16 (4.1)	30 (5.4)	0.443
Previous stroke	67 (7.1)	23 (5.9)	44 (7.9)	0.303
Risk factor				
Inactivity	351 (37.1)	16 (4.1)	335 (60.1)	<0.001
Injury	89 (9.4)	2 (0.5)	87 (15.6)	<0.001
Surgery	252 (26.7)	11 (2.8)	241 (43.3)	<0.001
Active cancer	191 (20.2)	0 (0.0)	191 (34.3)	<0.001
Thrombophilia	35 (3.7)	26 (6.7)	9 (1.6)	<0.001
Previous VTE	81 (8.6)	66 (17.0)	15 (2.7)	<0.001
Concomitant medications				
Antiplatelet agent	96 (10.2)	41 (10.6)	55 (9.9)	0.744
Estrogen preparation	20 (2.1)	1 (0.3)	19 (3.4)	<0.001
Anticancer agent	88 (9.3)	0 (0.0)	88 (15.8)	<0.001
Corticosteroid	85 (9.0)	35 (9.0)	50 (9.0)	1
NSAID	191 (20.2)	47 (12.1)	144 (25.9)	<0.001

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

	Overall (n=945)	VTE risk		P value
		Unprovoked (n=388)	Provoked (n=557)	
Presentation				
DVT	848 (89.7)	349 (89.9)	499 (89.6)	
Proximal	513 (54.3)	239 (61.5)	274 (49.2)	<0.001
Distal	335 (35.4)	110 (28.4)	225 (40.4)	
Symptoms of DVT	537 (56.8)	266 (68.6)	271 (48.7)	<0.001
PE	405 (42.9)	183 (47.2)	222 (39.9)	
Cardiac arrest or collapse	7 (0.7)	3 (0.8)	4 (0.7)	
Massive	16 (1.7)	10 (2.6)	6 (1.1)	0.494
Sub-massive	119 (12.6)	58 (14.9)	61 (11.0)	
Non-massive	240 (25.4)	103 (26.5)	137 (24.6)	
Unknown	23 (2.4)	9 (2.3)	14 (2.5)	
Symptoms of PE	216 (22.9)	114 (29.4)	102 (18.3)	0.001
Prior treatment	312 (33.0)	150 (38.7)	162 (29.1)	0.003
Anticoagulation therapy	250 (26.5)	122 (31.4)	128 (23.0)	
Inferior vena cava filter	84 (8.9)	40 (10.3)	44 (7.9)	
Thrombolytic therapy	46 (4.9)	32 (8.2)	14 (2.5)	
Catheterization	12 (1.3)	9 (2.3)	3 (0.5)	
Pulmonary thrombus removal	1 (0.1)	1 (0.3)	0 (0.0)	
PCPS	3 (0.3)	1 (0.3)	2 (0.4)	
Other	20 (2.1)	7 (1.8)	13 (2.3)	
Initial rivaroxaban treatment				
Dose (mg/day)				
30	625 (66.1)	266 (68.6)	359 (64.5)	0.244
20	19 (2.0)	4 (1.0)	15 (2.7)	
15	262 (27.7)	103 (26.5)	159 (28.5)	
10	39 (4.1)	15 (3.9)	24 (4.3)	
Treatment duration (days)	357.3±268.4	414.0±269.0	317.8±261.1	<0.001

Unless stated otherwise, data are presented as the mean±SD, median [interquartile range], or n (%). BMI, body mass index; CrCl, creatinine clearance; DVT, deep vein thrombosis; NSAID, non-steroidal anti-inflammatory drug; PCPS, percutaneous cardiopulmonary support; PE, pulmonary embolism; VTE, venous thromboembolism.

Statistical Analysis

The modified intention-to-treat population was used for effectiveness calculations; this included all enrolled patients except those excluded from study participation (**Figure 1**). Safety was assessed in the on-treatment population, which included all patients who received at least one dose of rivaroxaban and included all principal safety outcome occurrences from the time of the first rivaroxaban treatment to 2 days after the last rivaroxaban treatment.

This analysis was conducted to compare the following items between the unprovoked and provoked VTE groups: patient characteristics, VTE and major bleeding (using Kaplan-Meier analysis), and event rates and hazard ratios (HRs) of secondary endpoints.

Continuous variables are reported as the mean±SD, and categorical variables are reported as numbers and percentages. Standard- and under-dose groups were compared using the t-tests for continuous variables and the Chi-squared test for categorical variables.

Cumulative event incidences and 95% confidence intervals (CIs) were determined using the Kaplan-Meier method. Cox proportional hazards model results for between-group differences in clinical outcomes are expressed as HRs and 95% CIs.

All statistical analyses were performed using SAS version 9.4 for Windows (SAS Institute, Cary, NC, USA).

Results

Patient Baseline Characteristics in the Unprovoked and Provoked VTE Groups

Of the 1,039 patients with acute DVT, PE, or both enrolled across 152 centers in Japan, 945 and 946 patients were eligible for inclusion in the effectiveness and safety analyses, respectively, in the present study (**Figure 1**). The median follow-up period was 21.2 months (interquartile range 18.1–24.1 months). In this study, 388 and 557 patients with unprovoked and provoked VTE, respectively, were included in the effectiveness analyses, whereas 389 and 557 patients, respectively, were included in the safety analyses.

Patient characteristics, overall and for the unprovoked and provoked VTE subgroups separately, are presented in **Table 1**. Several significant (P<0.05) between-group differences in patient characteristics were identified (**Table 1**). Patients in the unprovoked VTE group were younger, less likely to be female, and had a higher body weight and lower median D-dimer concentration than those in the provoked VTE group. In addition, there was a higher percentage of patients with proximal DVT, symptomatic DVT, or PE in the unprovoked than provoked group. There were no significant between-group differences in the rate of use of concomitant antiplatelet agents and corticosteroids, but the rate of use of non-steroidal anti-inflammatory drugs

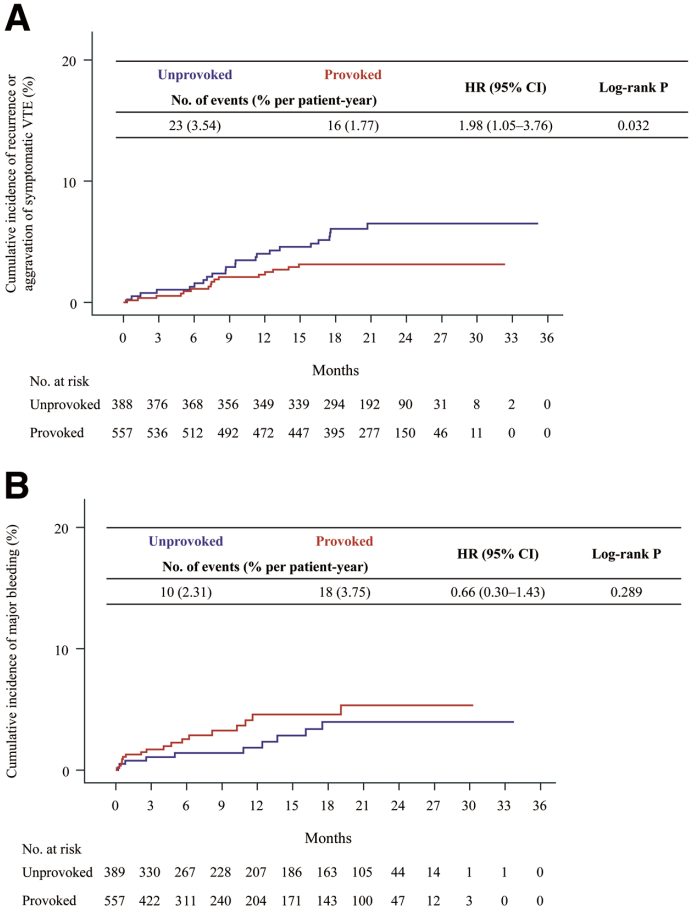

Figure 2. Cumulative incidence, as determined by the Kaplan-Meier method, of the (**A**) recurrence or aggravation of symptomatic venous thromboembolism (VTE) and (**B**) major bleeding according to the International Society on Thrombosis and Haemostasis criteria in patients with unprovoked or provoked VTE. CI, confidence interval; HR, hazard ratio.

was higher in the provoked than unprovoked group (**Table 1**).

When the unprovoked group was stratified according to concomitant corticosteroid use (use vs. non-use), the D-dimer concentration was significantly higher in the group with concomitant corticosteroids (P=0.006; **Supplementary Table 1**). There were no differences between the 2 groups in terms of age, sex, BMI, and prior treatment (**Supplementary Table 1**).

Clinical Outcomes in the Unprovoked and Provoked VTE Groups

According to the Kaplan-Meier analysis, the incidence of symptomatic VTE recurrence was significantly higher in patients in the unprovoked than provoked VTE group (**Figure 2A**). The breakdown of symptomatic VTE by type showed a significant between-group difference for symptomatic PE recurrence, but no significant between-group difference for symptomatic DVT recurrence (**Supplementary Table 2**). In addition, the incidence of death from any cause was significantly lower in the unprovoked than provoked VTE group (P<0.001; **Supplementary Table 2**). Although the proportion of patients with a BMI ≥25 kg/m^2 and no concomitant antiplatelet agent use was higher in the unprovoked VTE group, there was no interaction effect (**Table 2**).

In the safety comparisons, Kaplan-Meier analyses showed no significant difference between the unprovoked and provoked VTE groups in the incidence of major bleeding events (**Figure 2B**). There were also no major differences in major bleeding events between the unprovoked and provoked VTE groups when stratified according to baseline characteristics (**Table 2**).

Subgroup Analysis of Clinical Outcomes in Patients With Unprovoked VTE

In the subgroup analysis of the incidence of VTE recurrence in patients with unprovoked VTE, there were no significant differences according to age (≥65 vs. <65 years), sex, or BMI (≥25 vs. <25 kg/m^2; **Table 2**).

Among the subgroup of patients with unprovoked VTE, there was no significant difference in the incidence of VTE recurrence between those with and without concomitant corticosteroids (**Table 2**), whereas the incidence of acute coronary syndrome, ischemic stroke, death from any cause, VTE-related death, and cardiovascular disease-related death was significantly higher among those with concomitant corticosteroids (**Supplementary Table 3**). Similarly, there were no significant differences in clinical outcomes between patients with and without concomitant antiplatelet agent use (**Table 2**).

Subgroup Analysis of Safety Outcomes in Patients With Unprovoked VTE

A subgroup analysis of major bleeding events in patients with unprovoked VTE according to baseline characteris-

Table 2. Recurrence or Aggravation of Symptomatic VTE and Major Bleeding in Patients With Unprovoked or Provoked VTE Risks[A]

	No. events/total no. (% per patient-year)		HR (95% CI)	P value	P for interaction
	Unprovoked	Provoked			
Recurrence or aggravation of symptomatic VTE					
Overall	23/388 (3.54)	16/557 (1.77)	1.98 (1.05–3.76)	0.032	
Sex					0.500
Male	10/193 (3.06)	3/200 (0.99)	2.94 (0.81–10.70)	0.086	
Female	13/195 (4.02)	13/357 (2.16)	1.84 (0.85–3.96)	0.115	
Age (years)					0.833
<65	10/133 (4.49)	6/174 (2.10)	2.13 (0.77–5.86)	0.134	
≥65	13/255 (3.05)	10/383 (1.62)	1.86 (0.81–4.23)	0.135	
BMI (kg/m^2)					0.361
<25	13/264 (3.01)	11/366 (1.89)	1.58 (0.71–3.53)	0.259	
≥25	10/124 (4.58)	5/191 (1.55)	2.93 (1.00–8.57)	0.040	
Concomitant antiplatelet agent use					0.627
No	21/347 (3.65)	14/502 (1.72)	2.10 (1.07–4.12)	0.028	
Yes	2/41 (2.69)	2/55 (2.18)	1.20 (0.17–8.52)	0.856	
Concomitant corticosteroid use					0.479
No	20/353 (3.37)	15/507 (1.82)	1.83 (0.94–3.58)	0.072	
Yes	3/35 (5.32)	1/50 (1.23)	4.26 (0.44–40.96)	0.172	
Major bleeding					
Overall	10/389 (2.31)	18/557 (3.75)	0.66 (0.30–1.43)	0.289	
Sex					0.386
Male	3/193 (1.32)	6/200 (3.29)	0.42 (0.11–1.70)	0.212	
Female	7/196 (3.39)	12/357 (4.04)	0.91 (0.36–2.31)	0.840	
Age (years)					0.181
<65	5/133 (3.52)	4/174 (2.73)	1.36 (0.36–5.09)	0.645	
≥65	5/256 (1.72)	14/383 (4.20)	0.44 (0.16–1.22)	0.106	
BMI (kg/m^2)					0.445
<25	6/264 (2.10)	13/366 (4.20)	0.55 (0.21–1.45)	0.222	
≥25	4/125 (2.70)	5/191 (2.94)	0.94 (0.25–3.51)	0.923	
Concomitant antiplatelet agent use					0.546
No	9/348 (2.37)	15/502 (3.48)	0.72 (0.31–1.64)	0.429	
Yes	1/41 (1.87)	3/55 (6.23)	0.38 (0.04–3.70)	0.389	
Concomitant corticosteroid use					0.809
No	9/349 (2.38)	17/513 (3.94)	0.64 (0.29–1.44)	0.279	
Yes	1/40 (1.80)	1/44 (2.09)	1.10 (0.07–17.60)	0.946	

[A]The modified intention-to-treat population was used for the effectiveness calculations. The on-treatment population was used for safety assessments; this included all patients who received at least one dose of rivaroxaban and all principal safety outcome occurrences from the time of first rivaroxaban treatment to 2 days after the last rivaroxaban treatment. BMI, body mass index; CI, confidence interval; HR, hazard ratio; VTE, venous thromboembolism.

tics showed no significant differences according to age, sex, or BMI (**Table 2**). However, the higher incidence of major bleeding events was among those with than without concomitant corticosteroids (**Table 2**). There were no significant differences in any outcomes between groups with and without concomitant antiplatelet agents (**Table 2**).

Duration of DOAC Use in the Unprovoked and Provoked VTE Groups

Overall, the duration of rivaroxaban treatment was longer in the unprovoked than provoked VTE group (mean 414.0 vs. 317.8 days, respectively; P<0.001; **Table 1**). The incidence of rivaroxaban discontinuation was significantly lower in patients in the unprovoked than provoked VTE group (48.07% vs. 80.36% per patient-year; **Figure 3A**). In a subgroup analysis of rivaroxaban discontinuation in the unprovoked group, there were no significant differences according to age, sex, BMI, concomitant corticosteroid use, or concomitant antiplatelet agent use at baseline (**Figure 3B–F**).

Discussion

In the present subanalysis of the observational J'xactly study of patients with VTE in a real-world clinical setting in Japan, the incidence of VTE recurrence was significantly higher in patients with unprovoked VTE than in those with provoked VTE, despite the duration of rivaroxaban treatment being longer in the unprovoked than provoked group. Notably, there was no significant difference in the incidence of major bleeding events between rivaroxaban-treated patients with unprovoked and provoked VTE.

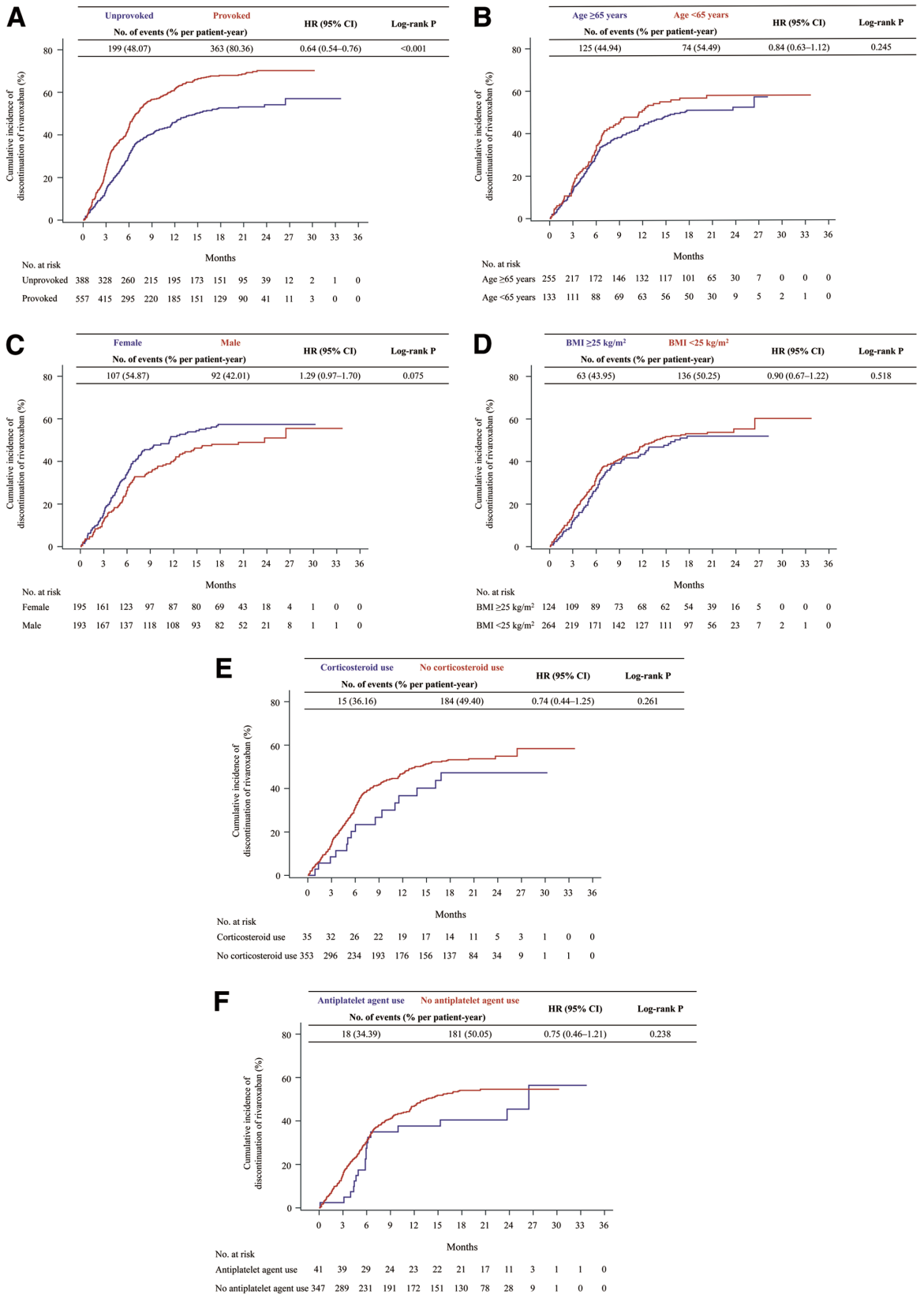

Figure 3. Incidence of rivaroxaban discontinuation (**A**) in patients with unprovoked or provoked venous thromboembolism (VTE) and (**B**–**F**) in patients with unprovoked VTE according to age (**B**), sex (**C**), body mass index (BMI; **D**), and the concomitant use of corticosteroids (**E**) or antiplatelet agents (**F**) at baseline. CI, confidence interval; HR, hazard ratio.

However, a subanalysis of the data showed that among those in the unprovoked VTE group, major bleeding occurred significantly more frequently in those with than without concomitant corticosteroids. Importantly, corticosteroid use is an established risk factor for peptic ulcer complications;[17–20] hence, the major bleeding events reported in this analysis may have been caused by peptic ulcer perforations.

DOACs may be discontinued in patients with identifiable VTE risk factors, whereas discontinuation of DOAC therapy in patients with unprovoked VTE requires closer attention, especially in patients with a high BMI, women, and those on concomitant corticosteroids; thus, deciding the timing of DOAC discontinuation requires careful consideration.[21]

Regarding factors that contribute to VTE recurrence, in our analysis there was no significant difference in the incidence of VTE recurrence between the unprovoked and provoked groups among patients with a BMI of <25 kg/m^2. However, within the unprovoked group, VTE recurrence was more frequent among patients with a BMI of ≥25 kg/m^2 than in those with a BMI of <25 kg/m^2. At baseline, patients' body weight was higher in the unprovoked than provoked group, suggesting that higher body weight may be a risk factor for unprovoked VTE. This is consistent with Virchow's triad[22] and other literature[23–26] supporting obesity as a risk factor for VTE. Indeed, DOAC discontinuation requires close attention among patients with unprovoked VTE with a high BMI.[27]

The association between sex and VTE recurrence is not clear. The COntemporary ManageMent AND outcomes in patients with Venous ThromboEmbolism (COMMAND VTE) registry of real-world VTE patients in Japan showed no considerable sex-related difference in the risk of VTE recurrence or major bleeding.[28] VTE recurrence rate is reported to be 1.5- to 1.8-times higher in men than in women, according to the results of multiple studies various studies.[29–31] However, one study has reported the opposite evidence.[32] Thus, a DOAC treatment extension may not be applicable depending on sex. Nevertheless, the COMMAND VTE and JCS guidance were released before the availability of DOACs, whereas the present analysis is a report using real-world data in the DOAC era; hence, further investigation is needed.

Notably, in the present analysis women tended to have a higher incidence of VTE recurrence than men, and VTE recurrence was higher among female patients with unprovoked VTE than among female patients with provoked VTE. Moreover, the duration of rivaroxaban treatment in female patients tended to be shorter. Regardless, it appears that antiplatelet therapy with DOACs for an extended period may be required for female patients with VTE without identifiable risk factors, with dose adjustment and close monitoring needed depending on bleeding risk.

In the large (n=10,207) global (across 28 countries) prospective observational Global Anticoagulant Registry in the FIELD (GARFIELD)-VTE study in patients with objectively diagnosed VTE at 1 year, almost 40% of patients with transient risk factors and just over half of patients with unprovoked VTE were undergoing anticoagulant therapy, and the event rates were comparable between groups.[33]

Study Limitations

The present analysis of the J'xactly study has several limitations, including potential confounders. The data for this analysis were obtained from a prospective observational study; hence, the results are not confirmatory. In this study, dividing patients into groups depended on the attending physician's judgment because there were no objective criteria for VTE risk assessment, including active cancer, inactivity, injury, and surgery, among others. It is possible that the statistical power of the study was limited because of an insufficient number of patients overall, and the number of patients in each group (unprovoked and provoked VTE) differed, limiting the between-group comparisons. In addition, this analysis did not include a detailed assessment regarding the reasons for rivaroxaban discontinuation. Nevertheless, the results provide insights into the real-world clinical setting for patients with unprovoked and provoked VTE.

Conclusions

This analysis is the largest real-world observational study of VTE treatment and recurrence prevention in Japanese patients with acute symptomatic and/or asymptomatic DVT, PE, or both. It provides important insights into the clinical outcomes of rivaroxaban treatment in patients with unprovoked VTE. DOACs may be discontinued after 3–6 months in patients with identifiable provoking risk factors for VTE following acute treatment. In contrast, patients with unprovoked VTE require careful consideration of the timing of DOAC discontinuation, particularly those with a high BMI and concomitant corticosteroid use. The findings of this analysis of the J'xactly study add to evidence to inform treatment decisions for VTE.

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IRB Information

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Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
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