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Original Article

Prognostication of Patients with Pulmonary Thromboembolism with and without Residual Deep Vein Thrombosis: A Subanalysis of the J'xactly Study

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Objectives: It is unclear whether patients with acute pulmonary thromboembolism (PE) with and without residual deep vein thrombosis (DVT) have different prognoses, and there is debate over whether inferior vena cava filters (IVCFs) should be used in conjunction with oral anticoagulants in patients with venous thromboembolism (VTE).

Materials and Methods: The J'xactly involved 1,016 patients and was a multicenter, prospective, observational research. In this subanalysis, 419 patients with PE with or without residual DVT who received rivaroxaban with or without IVCFs between February 2016 and April 2018 in Japan were examined.

Results: Of 419 patients with PE, 320 had residual DVT. There was no difference between the groups with and without DVT in terms of the percentage of patients who experienced symptomatic PE recurrence (2.8% [9/320] vs. 3.0% [3/99]) or who died from VTE-related complications (0.9% [3/320] vs. 1.0% [1/99]). The percentages of patients with symptomatic PE recurrence were 0% and 3.2%, and the percentages of patients who died from VTE-related causes were 0% and 1.1%, respectively, in the groups with (n=39) and without (n=281) IVCF, albeit not being statistically different.

Conclusion: Patients with PE with and without residual DVT did not have a different incidence of symptomatic PE recurrence. These results require additional study to be confirmed.

Keywords: venous thromboembolism, direct oral anticoagulant, rivaroxaban, prognosis, inferior vena cava filter

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Introduction

A significant contributor to morbidity and mortality globally is venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary thromboembolism (PE).[1,2] VTE has a long-term risk of recurrence resulting, in part, from provoked and unprovoked risk factors at the time of the initial VTE event.[3]

Earlier studies have shown contradictory results regard-

ing the relationship between prognosis and the existence of residual DVT at the time of PE diagnosis. Specifically, in 1 study, residual DVT was an independent risk factor for mortality due to acute PE and was associated with a 4.25-fold increase in mortality,[4] whereas other studies have shown no influence or even a survival benefit.[5,6] Consequently, this is a matter that needs to be clarified.

Anticoagulant therapy is the cornerstone of treatment for patients with acute VTE.[7,8] In the American College of Chest Physicians guidelines,[9] inferior vena cava filters (IVCFs) are not advised in addition to anticoagulant medication for patients with VTE. However, guidelines from the Society of Interventional Radiology/American College of Radiology[10] and the American Heart Association[11] do support the insertion of an IVCF with concomitant anticoagulation. Thus, the use of IVCFs remains controversial, and clinical practice variations exist.

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 prospectively enrolled 1,016 patients and investigated the effectiveness and safety of rivaroxaban in patients with VTE, including isolated distal DVT, in the real-world clinical setting. In the J'xactly study, 419 patients (41.2%) had PE, of whom 320 also had DVT.[12,13] In this subanalysis of the J'xactly study, we used the data of these 419 patients to examine the differences in prognosis between patients with PE with and without residual DVT, as well as to determine the usefulness of rivaroxaban therapy in patients with PE with and without IVCF implantation.

Materials and Methods

Study design

The study design, data collection methodology, and baseline characteristics of the J'xactly study population have been described previously.[12,13] In summary, the J'xactly study was a multicenter, prospective, observational study involving patients with acute symptomatic/asymptomatic DVT, PE, or both. Patients were given oral rivaroxaban for acute VTE and recurrence prevention in Japan. Patients were enrolled from December 2016 to April 2018, and data were collected for at least 18 months and up to 3 years after enrollment (up to November 2019).

The J'xactly study was conducted in accordance with the principles of the Declaration of Helsinki and with all relevant legal and regulatory requirements in Japan. The study protocol 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. Additionally, an independent data and safety monitoring group examined the study data. The study was registered in the University hospital Medical Information Network Clinical Trials Registry as UMIN000025072. Each patient gave their written consent for participating in the study.

Patients

The J'xactly study included patients with acute symptomatic/asymptomatic DVT, PE, or both, who were prescribed rivaroxaban for VTE treatment and prevention. The main exclusion criteria were 1) active bleeding; 2) presence of chronic thromboembolic pulmonary hypertension (CTEPH), except for CTEPH plus acute PE or DVT; and 3) contraindications to rivaroxaban. Eligible patients were consecutively enrolled within 3 weeks of initiating rivaroxaban treatment. Data were gathered until the end of the follow-up period (November 2019), regardless of whether rivaroxaban was continued, discontinued, or ended according to each local doctor's clinical judgment. In total, 1,039 patients were enrolled from December 2016 to April 2018 across 152 sites in Japan. A total of 23 patients were removed from the analysis sample (**Fig. 1**), leaving 1,016 patients in the modified intention-to-treat group. For the purpose of the present subanalysis, 597 patients without PE were excluded, and 419 patients with PE with or without residual DVT were included. PE and DVT were diagnosed by physicians at the participating institutions in accordance with Japanese criteria.[14] Patients were selected to undergo IVCF implantation according to the local physician's clinical decision. The severity of PE and whether PE was of the massive, submassive, or nonmassive type were identified according to Japanese regulations.[14] DVT was classified by localization of the thrombus and was defined as proximal if the thrombus was located on the central side (including in the popliteal vein) and distal if the thrombus was located below the popliteal vein.

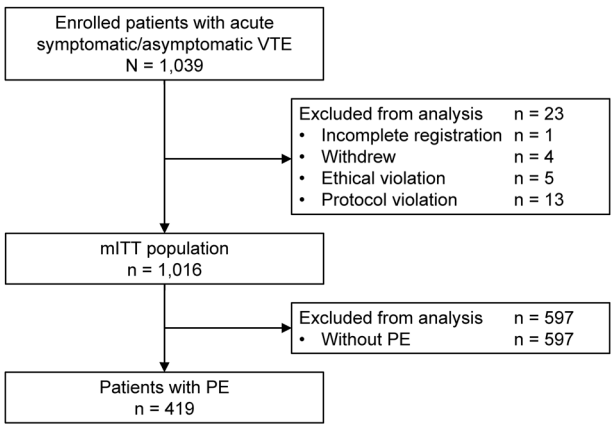

Fig. 1 Flowchart of patient selection.
mITT: modified intention-to-treat; PE: pulmonary thromboembolism; VTE: venous thromboembolism

Outcomes

The main outcome was symptomatic VTE recurrence/aggravation during the follow-up period.[12] VTE was defined according to established diagnostic criteria.[15,16] The main safety outcome was major bleeding (according to the International Society on Thrombosis and Haemostasis criteria[17]) during the treatment period and up to 2 days after rivaroxaban discontinuation.

The secondary endpoints were recurrence/aggravation of symptomatic DVT or PE, death from any cause, death related to VTE and cardiovascular disease, a vascular event (acute coronary syndrome or ischemic stroke), and nonmajor bleeding. An independent, blinded clinical events committee determined the results.

Statistical analysis

Continuous variables are reported as mean ± standard deviation and were compared using the Student's t-test. Categorical variables are presented as number (percentage) and were compared using the chi-square test. The incidences of cumulative events and their 95% confidence intervals (CIs) were determined using the Kaplan–Meier method. Cox proportional hazards regression modeling was used to determine between-group variations in clinical outcomes, and the results are presented as hazard ratios (HRs) and 95%CIs. All statistical analyses were performed using SAS software (version 9.4) for Windows (SAS Institute, Cary, NC, USA). A P value of <0.05 was considered statistically significant.

Results

The baseline characteristics of the patients are displayed in **Table 1**. For this subanalysis of the J'xactly study, the data of 419 patients, 320 (76.4%) of whom had PE with residual DVT and 99 (23.6%) of whom had PE without residual DVT, were analyzed. The average age of patients in the entire group was 65.7 ± 14.6 years.

In terms of the severity of PE, in the overall cohort, the majority of cases of PE were nonmassive-type PE (59.2%), followed by submassive-type PE (29.4%) and massive-type PE (3.8%). There was no discernable change between the two groups in the clinical severity classification of PE. In the PE with residual DVT group, DVT was classed as proximal DVT in 74.4% of cases and as distal DVT in 25.6% of cases (**Table 1**). Information of the symptoms of PE and DVT and the thrombus localization of DVT are provided in **Supplemental Table 1**.

VTE risk factors, including physical inactivity, active cancer, and previous VTE, were not significantly different between the PE with residual DVT and the PE without residual DVT groups (**Table 1**). Similarly, the rates of recurrence or aggravation of symptomatic VTE and VTE-related death were not significantly different between PE with and without residual DVT.

Male sex and asymptomatic PE were significantly more common in the PE with residual DVT group than in the PE without residual DVT group. Additionally, the proportion of patients with thrombophilia was considerably greater in the PE with residual DVT group compared to the PE without residual DVT. The initial standard dose of rivaroxaban (30 mg/day) was significantly more frequently prescribed in the PE with residual DVT group than in the PE without residual DVT group. D-dimer concentration was noticeably greater in the PE with residual DVT group than in the PE without residual DVT group. Conversely, the rates of surgery and active cancer were significantly higher in the PE without residual DVT group (**Table 1**).

There were also no discernable differences between the PE with residual DVT group and the PE without residual DVT group regarding clinical outcomes (**Table 2**). Recurrence or aggravation of symptomatic VTE was observed in 14/320 patients (4.4%) in the PE with residual DVT group and in 3/99 patients (3.0%) in the PE without residual DVT group (2.7% vs. 1.9% per patient-year; HR, 1.35; 95%CI, 0.39–4.70; log-rank P = 0.634) (**Fig. 2A**). In patients with PE with symptoms (156/320 [48.8%] in the PE with residual DVT group and 66/99 [66.7%] in the PE without residual DVT group [**Table 1**]), there was no discernable difference in the symptomatic PE recurrence rate between patients with (6/156 [3.8%]) and without (3/66 [4.5%]) residual DVT (2.4% vs. 2.8% per patient-year; HR, 1.16; 95%CI, 0.29–4.66; log-rank P = 0.830) (**Supplemental Fig. 1**). Major bleeding was observed in 9/320 patients (2.8%) in the PE with residual DVT group and in 2/99 patients (2.0%) in the PE without residual DVT group (2.8% vs. 2.0% per patient-year; HR, 1.27; 95%CI, 0.27–5.87; log-rank P = 0.761) (**Fig. 2B**).

Of the 320 patients with PE with residual DVT, 39 patients (12.2%) had implanted IVCFs, whereas 281 (87.8%) did not. There were statistically significant differences between patients with and without implanted IVCFs in the numbers of patients with DVT symptoms (79.5% vs. 61.9%, respectively; P = 0.032) and with distal thrombus localization (10.3% vs. 27.8%, respectively; P = 0.043) (**Supplemental Table 2**). There were no cases of PE recurrence, fatal PE, ischemic stroke, or death from cardiovascular disease in the group with IVCFs; however, nine patients (3.2%) without IVCFs presented with PE recurrence, three patients (1.1%) died from VTE-related causes, seven patients (2.5%) experienced ischemic stroke, and four patients (1.4%) experienced death related to cardiovascular disease (**Table 3**).

Table 1 Baseline characteristics of the overall PE cohort and of patients with and without residual DVT

		Overall n=419	PE with residual DVT n=320	PE without residual DVT n=99	P value
Sex	Male	199 (47.5)	161 (50.3)	38 (38.4)	0.039
Age, years	Mean±SD	65.7±14.6	65.9±14.2	65.0±15.8	0.709
	≥75	137 (32.7)	105 (32.8)	32 (32.3)	0.952
PE	With symptoms	222 (53.0)	156 (48.8)	66 (66.7)	0.002
	Clinical severity classification				0.167
	Cardiac arrest/collapse	7 (1.7)	3 (0.9)	4 (4.0)	
	Massive	16 (3.8)	12 (3.8)	4 (4.0)	
	Submassive	123 (29.4)	92 (28.8)	31 (31.3)	
	Nonmassive	248 (59.2)	191 (59.7)	57 (57.6)	
	Unknown	25 (6.0)	22 (6.9)	3 (3.0)	
DVT	With symptoms	205 (48.9)	205 (64.1)	NA	—
	Distal	82 (19.6)	82 (25.6)	NA	—
	Proximal	238 (56.8)	238 (74.4)	NA	
Body weight, kg	Mean±SD	63.0±14.9	63.1±14.3	62.5±16.8	0.299
	<50	80 (19.1)	58 (18.1)	22 (22.2)	0.513
CrCl, mL/min	Mean±SD	82.1±37.6	81.4±34.7	84.2±45.7	0.904
	Distribution, n (%)				0.631
	<30	5/417 (1.2)	3/318 (0.9)	2/99 (2.0)	
	≥30, <50	66/417 (15.8)	48/318 (15.1)	18/99 (18.2)	
	≥50, <80	164/417 (39.3)	129/318 (40.6)	35/99 (35.4)	
	≥80	182/417 (43.6)	138/318 (43.4)	44/99 (44.4)	
D-dimer, μg/mL	Median [IQR]	10.0 [5.5, 19.0]	10.7 [6.3, 19.9]	7.0 [4.2, 13.6]	0.002
VTE risk factors	Physical inactivity	130 (31.0)	100 (31.3)	30 (30.3)	0.902
	Injury	31 (7.4)	26 (8.1)	5 (5.1)	0.384
	Surgery	78 (18.6)	49 (15.3)	29 (29.3)	0.003
	Active cancer	88 (21.0)	58 (18.1)	30 (30.3)	0.011
	Thrombophilia	21 (5.0)	21 (6.6)	0 (0.0)	0.006
	Previous VTE	28 (6.7)	25 (7.8)	3 (3.0)	0.110
Medical history	Previous stroke	28 (6.7)	21 (6.6)	7 (7.1)	0.821
	Cardiovascular disease	19 (4.5)	13 (4.1)	6 (6.1)	0.411
	Hypertension	169 (40.3)	128 (40.0)	41 (41.4)	0.816
	Diabetes mellitus	54 (12.9)	41 (12.8)	13 (13.1)	1
	Heart failure	18 (4.3)	14 (4.4)	4 (4.0)	1
	Atrial fibrillation	16 (3.8)	13 (4.1)	3 (3.0)	0.772
	Chronic heart and lung disease	27 (6.4)	23 (7.2)	4 (4.0)	0.351
Concomitant use	Antiplatelet agent	38 (9.1)	30 (9.4)	8 (8.1)	0.842
	NSAID	61 (14.6)	45 (14.1)	16 (16.2)	0.626
	Estrogen preparation	7 (1.7)	5 (1.6)	2 (2.0)	0.671
	Anticancer agents	43 (10.3)	32 (10.0)	11 (11.1)	0.709
Initial dose of rivaroxaban					0.003
	30 mg/day	341 (81.4)	271 (84.7)	70 (70.7)	
	20 mg/day	6 (1.4)	5 (1.6)	1 (1.0)	
	15 mg/day	64 (15.3)	41 (12.8)	23 (23.2)	
	10 mg/day	8 (1.9)	3 (0.9)	5 (5.1)	

A P value of <0.05 was considered statistically significant. Values are n (%) unless stated otherwise.
CrCl: creatinine clearance; DVT: deep vein thrombosis; IQR: interquartile range; NA: not applicable; NSAID: nonsteroidal anti-inflammatory drug; PE: pulmonary thromboembolism; SD: standard deviation; VTE: venous thromboembolism

Table 2 Clinical outcomes of patients with PE with and without residual DVT

	PE with DVT (n=320)		PE only (n=99)		HR (95%CI)	P value
	n (%)	% per patient-year (95%CI)	n (%)	% per patient-year (95%CI)		
Recurrence or aggravation of symptomatic VTE	14 (4.4)	2.7 (1.3–4.0)	3 (3.0)	1.9 (0.0–4.1)	1.35 (0.39–4.70)	0.634
Recurrence or aggravation of symptomatic PE	9 (2.8)	1.7 (0.6–2.8)	3 (3.0)	1.9 (0.0–4.1)	0.88 (0.24–3.27)	0.854
Recurrence or aggravation of symptomatic DVT	6 (1.9)	1.1 (0.2–2.0)	1 (1.0)	0.6 (0.0–1.9)	1.75 (0.21–14.50)	0.601
Acute coronary syndrome	1 (0.3)	0.2 (0.0–0.6)	—	—	—	0.591
Ischemic stroke	7 (2.2)	1.3 (0.3–2.3)	1 (1.0)	0.6 (0.0–1.9)	2.15 (0.26–17.45)	0.464
Death from any cause	25 (7.8)	4.6 (2.8–6.5)	9 (9.1)	5.6 (2.0–9.3)	0.82 (0.38–1.76)	0.614
Death related to VTE	3 (0.9)	0.6 (0.0–1.2)	1 (1.0)	0.6 (0.0–1.9)	0.92 (0.10–8.84)	0.941
Death related to CVD	4 (1.3)	0.7 (0.0–1.5)	1 (1.0)	0.6 (0.0–1.9)	1.21 (0.13–10.82)	0.866
Major bleeding	9 (2.8)	2.5 (0.9–4.1)	2 (2.0)	2.0 (0.0–4.7)	1.27 (0.27–5.87)	0.761
Minor bleeding	28 (8.8)	8.1 (5.1–11.1)	3 (3.0)	3.0 (0.0–6.4)	4.09 (0.97–17.19)	0.037

A P value of <0.05 was considered statistically significant.
CI: confidence interval; CVD: cardiovascular disease; DVT: deep vein thrombosis; HR: hazard ratio; PE: pulmonary thromboembolism; VTE: venous thromboembolism

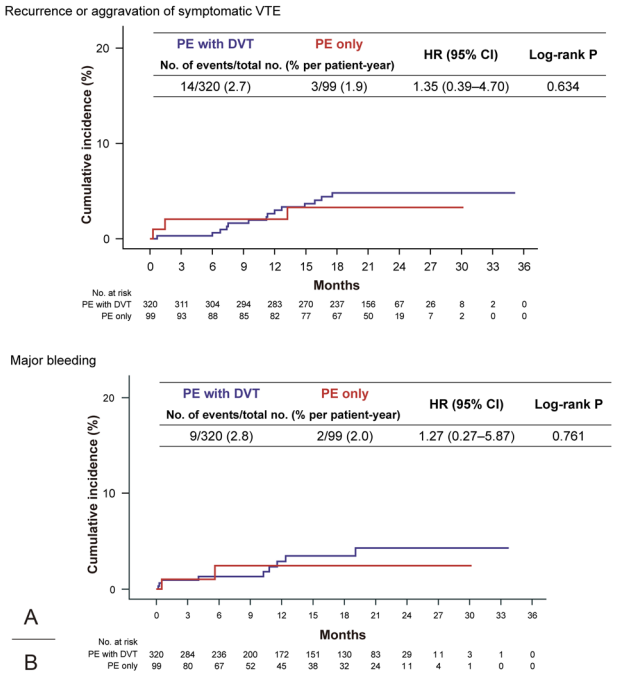

Fig. 2 Cumulative incidence of (**A**) recurrence or aggravation of symptomatic VTE and (**B**) major bleeding in the PE with residual DVT and PE without residual DVT groups.
CI: confidence interval; DVT: deep vein thrombosis; HR: hazard ratio; PE: pulmonary thromboembolism; VTE: venous thromboembolism

Discussion

In this J'xactly study subanalysis, we showed comparable rates of PE recurrence and mortality between patients with PE with and without residual DVT, and there were no discernable differences between these patients in any of the clinical outcomes examined. Although not statistically significant, we did, however, show that the proportion of patients with symptomatic PE recurrence, VTE-related death, ischemic stroke, and cardiovascular disease-related death was lower in patients treated with rivaroxaban with implanted IVCFs than in those without implanted IVCFs.

In a recent meta-analysis, residual DVT in patients with PE was significantly associated with an increased risk of death within the first 30 days following the symptomatic PE incident.[18] Our findings may contradict the findings of this meta-analysis because many previous studies included only patients with symptomatic PE, whereas only 53% (222/419) of patients in this J'xactly study subanalysis were symptomatic. For instance, in the study by Jiménez et al.,[4] 12% of participants experienced syncope, 8% had a systolic blood pressure of <100 mmHg, and 37% had an arterial partial pressure of oxygen of <60 mmHg; thus, high-risk patients with PE were included. In comparison, the severity of PE may have been milder in this J'xactly study subanalysis.

In the present study, the initial standard dose of rivaroxaban (30 mg/day) was significantly more frequently prescribed in the PE with residual DVT group than in the PE without residual DVT group. This may be related to worries about postsurgical bleeding in the PE without residual DVT group, who had considerably higher rates of surgery and active malignancy. A previous subanalysis of the J'xactly study showed that there were no differences in the incidence of symptomatic VTE recurrence or major bleeding between the underdose (20, 15, or 10 mg/day) and standard-dose (30 mg/day) groups,[19] suggesting that the clinical outcomes are comparable irrespective of the dose of rivaroxaban used.

The American College of Chest Physicians guidelines advise against the use of IVCFs in addition to anticoagulant therapy.[9] Conversely, other guidelines from the Society of Interventional Radiology/American College of

Table 3 Clinical outcomes of patients with DVT according to the use of IVCFs

	PE with DVT				HR (95%CI)	P value
	With IVCF (n=39)		Without IVCF (n=281)			
	n (%)	% per patient-year (95%CI)	n (%)	% per patient-year (95%CI)		
Recurrence or aggravation of symptomatic VTE	1 (2.6)	1.6 (0.0–4.7)	13 (4.6)	2.8 (1.3–4.3)	0.58 (0.08–4.47)	0.601
Recurrence or aggravation of symptomatic PE	0	0	9 (3.2)	1.9 (0.7–3.2)	0	0.275
Recurrence or aggravation of symptomatic DVT	1 (2.6)	1.6 (0.0–4.7)	5 (1.8)	1.1 (0.1–2.0)	1.56 (0.18–13.40)	0.680
Acute coronary syndrome	0	0	1 (0.4)	0.2 (0.0–0.6)	0	0.716
Ischemic stroke	0	0	7 (2.5)	1.5 (0.4–2.6)	0	0.327
Death from any cause	4 (10.3)	6.3 (0.1–12.4)	21 (7.5)	4.4 (2.5–6.3)	1.42 (0.49–4.13)	0.522
Death related to VTE	0	0	3 (1.1)	0.6 (0.0–1.3)	0	0.531
Death related to CVD	0	0	4 (1.4)	0.8 (0.0–1.7)	0	0.473
Major bleeding	1 (2.6)	2.0 (0.0–6.0)	8 (2.8)	2.5 (0.8–4.3)	0.81 (0.10–6.49)	0.843
Minor bleeding	5 (12.8)	11.0 (1.4–20.6)	23 (8.2)	7.6 (4.5–10.8)	1.47 (0.56–3.88)	0.431

A P value of <0.05 was considered statistically significant.

CI: confidence interval; CVD: cardiovascular disease; DVT: deep vein thrombosis; HR: hazard ratio; IVCF: inferior vena cava filter; PE: pulmonary thromboembolism; VTE: venous thromboembolism

Radiology[10] and the American Heart Association[11] support the use of IVCFs alongside direct oral anticoagulants, leading to substantial variability in clinical practice. In the current investigation, there were statistically significant differences in DVT variables (both in the presence of symptoms and localization of the thrombus) between patients with implanted IVCFs and patients without IVCFs, indicating that these factors might have influenced the choice of IVCF usage. Although not statistically significant, our findings of lower rates of PE recurrence and VTE-related death in patients treated with rivaroxaban plus IVCFs than in those without IVCFs support the notion that some PE patients with residual DVT may benefit from IVCF implantation. Our findings corroborate those of the PREPIC study, which showed that the incidence of PE recurrence was considerably greater in the group without IVCFs than in the group with IVCFs. Moreover, no cases of fatal PE occurred in the IVCF group, whereas four cases of fatal PE occurred in the group without IVCFs within 12 days.[20]

Limitations

This J'xactly study subanalysis has certain limitations. First, one of the adaptations for rivaroxaban use was that the patients should be hemodynamically stable. As such, this study may not be applicable for very-high-risk patients, such as those with PE who are hemodynamically unstable. This might have had a considerable influence on the results of this study. Second, the J'xactly trial did not gather data about the form of residual DVT, such as free-floating type or obstructive type. In addition, the present study is a noninterventional, observational study, and the method of examination was therefore left to the judgment of the physician in charge. Consequently, it is probable that some individuals underwent echocardiography and some by computed tomography. Third, the dosage and maintenance period of rivaroxaban were selected at the discretion of the attending physicians; thus, patient eligibility bias could emerge because patients were chosen for anticoagulation. Moreover, symptomatic PE and DVT were defined by the attending physicians according to Japanese guidelines[14]; however, no central examination was performed to verify consistency between physicians. Fourth, direct comparisons with other therapies were not possible because this was a single-arm observational study that included patients administered with rivaroxaban only. Fifth, the finding that four deaths due to cardiovascular disease occurred in the without IVCF group, but none occurred in the with IVCF group, is difficult to explain, but we hypothesize that this difference is caused by the sample size discrepancy between the with and without IVCF groups. Finally, the DVT and PE diagnosis methods and testing frequencies differed among the attending physicians and study centers; consequently, biases may have affected the outcome results.

Conclusion

The results of this J'xactly study subanalysis suggest that the incidence of recurrent PE and fatal PE is comparable between patients with PE with and without residual DVT. Further research is required to confirm these findings.

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Disclosure Statement

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Author Contributions

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Analysis: NY, Ts Y
Investigation: YO, AH
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Critical review and revision: all authors
Final approval of the article: all authors
Accountability for all aspects of the work: all authors

Supplementary Information

Supplementary materials are available at the online article sites on J-STAGE and PMC.

Availability of Data and Materials

The deidentified participant data will not be shared.

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