Clinical Outcome After Discontinuation of Anticoagulation Therapy in Japanese Patients With Venous Thromboembolism — Insights From the J’xactly Study —

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Background: Rivaroxaban, a direct oral anticoagulant, is used as first-line treatment to prevent venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE). However, the frequency of rivaroxaban discontinuation and the subsequent clinical outcomes remain unclear.

Methods and Results: The study was a subanalysis of the prospective, multicenter, observational J’xactly study, conducted in Japan, and included patients who underwent anticoagulant discontinuation without major bleeding and recurrent VTE. The modified intention-to-treat population (n=1,016) included 579 patients (57%) who underwent anticoagulant discontinuation during a mean follow-up period of 20.2 months (mean [±SD] anticoagulation period 6.9±6.2 months). Patients were divided into 3 groups: those with active cancer, those without active cancer and a transient risk factor for VTE, and those without active cancer or a transient risk factor and/or with previous VTE (unprovoked group). After discontinuation, VTE recurrence occurred in 4.1% of patients, with an annual incidence of 4.6%/year and an increased tendency in the unprovoked group; major bleeding occurred in 8 patients (1.4%; annual incidence 1.1%/year), of whom half were in the cancer group.

Conclusions: This analysis of a real-world observational study provides data on VTE recurrence after rivaroxaban discontinuation, which will facilitate anticoagulant discontinuation according to individual risk-benefit considerations.

Key Words: Anticoagulation discontinuation; Deep vein thrombosis; Pulmonary embolism; Rivaroxaban
tion therapy persists. Primary treatment usually requires 3–6 months of anticoagulation, which is followed by decision making about stopping or continuing anticoagulation for secondary prevention, because recurrent VTE may occur not only within the first few weeks, but also several months or years after discontinuation. The risk of recurrence varies according to patient characteristics and risk factors, and individualizing the process requires consideration of the balance between the risks of recurrence and the potential for adverse events as a result of anticoagulation. The American Society of Hematology 2020 guidelines for the management of VTE recommend indefinite antithrombotic therapy over discontinuation for patients with chronic persistent risk factors and unprovoked-type VTE, although this recommendation does not apply to patients who have a high risk for bleeding complications. However, the real-world status of discontinuation of anticoagulation and clinical outcomes after discontinuation are worth investigating in the DOAC era. Therefore, the aims of the present study were to describe the discontinuation of anticoagulation among VTE patients after the introduction of DOAC and subsequent clinical outcomes using the observational cohort of the Japanese Registry of Rivaroxaban Effectiveness & Safety for the Prevention of Recurrence in Patients With Deep Vein Thrombosis and Pulmonary Embolism (J’xactly) study.

Methods

Full details of the study design, data collection processes, and baseline characteristics of the study population have been reported previously. J’xactly was a multicenter prospective observational cohort study that enrolled patients diagnosed with acute symptomatic or asymptomatic DVT, PE, or both who were prescribed rivaroxaban for the treatment and prevention of VTE from December 2016 to April 2018. Key exclusion criteria were contraindications to rivaroxaban, the presence of chronic thromboembolic pulmonary hypertension (CTEPH), with the exception of CTEPH plus acute PE or DVT, and active bleeding. All patients provided written informed consent to take part in the study. J’xactly was conducted in accordance with the principles of the Declaration of Helsinki and all applicable legal and regulatory requirements in Japan. The protocol and related documentation were reviewed and approved by the Institutional Review Board of Nihon University Itabashi Hospital; all participating institutions also provided ethics approval. In addition, an independent data and safety monitoring committee reviewed all study data. The study was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (ID UMIN000025072).

All eligible patients were enrolled in the study within 3 weeks of starting a rivaroxaban prescription, and data were collected until the end of the follow-up period (November 2019) whenever possible, regardless of whether rivaroxaban was continued, discontinued, or terminated according to patient preference or physician discretion.

The primary effectiveness outcome was the recurrence or aggravation of symptomatic VTE after discontinuation of rivaroxaban during the follow-up period. VTE was defined according to established diagnostic criteria. The primary effectiveness outcome was the recurrence or aggravation of symptomatic VTE after discontinuation of rivaroxaban during the follow-up period. VTE was defined according to established diagnostic criteria. The primary effectiveness outcome was the recurrence or aggravation of symptomatic VTE after discontinuation of rivaroxaban during the follow-up period. VTE was defined according to established diagnostic criteria.

Figure 1. Kaplan-Meier curves for discontinuation of rivaroxaban in the unprovoked (red), transient risk factor (blue), and cancer (green) groups after the initiation of rivaroxaban. There were significant differences between the transient risk group and the unprovoked and cancer groups.
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Secondary outcomes included recurrence or aggravation of symptomatic DVT and PE, death from any cause, death related to VTE and cardiovascular disease, vascular events (acute coronary syndrome or ischemic stroke), and non-major bleeding after discontinuation of rivaroxaban during the follow-up period. An independent, blinded clinical events committee adjudicated outcomes.

Among the modified intention-to-treat (mITT) population, we analyzed patients who had VTE or major bleeding under rivaroxaban treatment. Discontinuation of rivaroxaban was defined as withdrawal of rivaroxaban lasting >14 days for any reason, including based on a physician’s judgment. Patients in the present study were divided into 3 groups according to the risk factors for VTE, as in COMMAND VTE (COntemporary ManageMent AND outcomes in patients with Venous ThromboEmbolism) Registry,14 as follows: (1) a cancer group with active cancer; (2) a transient risk group without active cancer and with a transient risk factor for VTE (e.g., inactivity, injury, surgery, or using estrogen preparations); and (3) an unprovoked group without active cancer or a transient risk factor and/or with previous VTE.

Continuous variables are reported as the mean±SD or median with interquartile range; categorical variables are reported as numbers and percentages. Cumulative event incidences and their 95% confidence intervals (CIs) were determined using Kaplan-Meier analysis. The results of Cox proportional hazards modeling for between-group differences in clinical outcomes are expressed as hazard ratios (HRs) and 95% CIs. All statistical analyses were performed using SAS version 9.4 for Windows (SAS Institute, Cary, NC, USA).

Results

Among the mITT population in the J'actly study (n=1,016), the present study analyzed data for the 579 patients (57%)

Table. Baseline Characteristics

| Overall | Transient risk | Cancer | Unprovoked | Risk factor group for VTE^a |
|---------|----------------|--------|------------|-----------------------------|
| No. patients discontinuing/initiating rivaroxaban | 579/1,016 | 278/390 | 88/193 | 213/433 | P value |
| % Patients discontinuing rivaroxaban during follow-up | 57 | 71 | 46 | 49 | 0.416 |
| Age (years) | 67.6±15.1 | 67.7±16.7 | 69.4±10.4 | 66.8±14.4 | <0.001 |
| <60 | 147 (25.4) | 70 (25.2) | 14 (15.9) | 63 (29.6) | 0.014 |
| ≥60, <75 | 221 (38.2) | 104 (37.4) | 47 (53.4) | 70 (32.9) | 0.014 |
| ≥75 | 211 (36.4) | 104 (37.4) | 27 (30.7) | 80 (37.6) | 0.014 |
| Female sex | 361 (62.3) | 205 (73.7) | 43 (48.9) | 113 (53.1) | 0.014 |
| Outpatient | 238 (41.1) | 67 (24.1) | 36 (40.9) | 136 (63.4) | 0.014 |
| DVT | 531 (91.7) | 260 (93.5) | 74 (84.1) | 197 (92.5) | 0.014 |
| Distal | 266 (45.9) | 146 (52.5) | 33 (37.5) | 87 (40.8) | 0.014 |
| Proximal | 265 (45.7) | 114 (41.0) | 41 (46.6) | 110 (51.6) | 0.014 |
| Symptomatic DVT | 312 (53.9) | 123 (44.2) | 34 (38.6) | 156 (72.8) | 0.014 |
| PE | 203 (35.1) | 92 (33.1) | 34 (38.6) | 77 (36.2) | 0.014 |
| Cardiac arrest or collapse | 4 (0.7) | 1 (0.4) | 1 (1.1) | 2 (0.9) | 0.014 |
| Massive | 8 (1.4) | 4 (1.4) | 0 (0.0) | 4 (1.9) | 0.014 |
| Submassive | 60 (10.4) | 32 (11.5) | 7 (8.0) | 21 (9.9) | 0.014 |
| Non-massive | 115 (19.9) | 47 (16.9) | 23 (26.1) | 45 (21.1) | 0.014 |
| Unknown | 16 (2.8) | 8 (2.9) | 3 (3.4) | 5 (2.3) | 0.014 |
| Symptomatic PE | 103 (17.8) | 44 (15.8) | 12 (13.6) | 47 (22.1) | 0.014 |
| Risk factor | Inactivity | 256 (44.2) | 222 (79.9) | 26 (29.5) | 8 (3.8) | <0.001 |
| Injury | 73 (12.6) | 73 (26.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | <0.001 |
| Surgery | 186 (32.1) | 145 (52.2) | 36 (40.9) | 5 (2.3) | 0.001 |
| Active cancer | 88 (15.2) | 88 (100.0) | 0 (0.0) | 0 (0.0) | 0.001 |
| Thrombophilia | 15 (2.6) | 1 (1.1) | 10 (4.7) | 0.051 |
| Previous VTE | 41 (7.1) | 9 (10.2) | 32 (15.0) | <0.001 |
| CrCl (mL/min) | 79.0±36.8 | 79.0±34.7 | 76.0±34.2 | 80.4±40.8 | 0.641 |
| <30 | 4 (0.7) | 3 (1.1) | 0 (0.0) | 1 (0.5) | 0.620 |
| ≥30 to <50 | 115 (19.9) | 58 (20.9) | 21 (23.9) | 36 (16.9) | 0.001 |
| ≥50 to <80 | 203 (35.1) | 94 (33.8) | 36 (40.9) | 73 (34.3) | 0.001 |
| ≥80 | 230 (39.7) | 118 (42.4) | 30 (34.1) | 82 (38.5) | 0.001 |

(Table continued the next page.)
who discontinued anticoagulation therapy without VTE or major bleeding under rivaroxaban treatment during a mean follow-up period of 20.2 months. Anticoagulant treatment was discontinued in 71%, 46%, and 49% of patients in the transient risk factor, cancer, and unprovoked groups, respectively. At 3 months from the start of treatment, 29%, 14%, and 14% of patients in the transient risk factor, cancer, and unprovoked groups, respectively, discontinued treatment (Figure 1). Approximately one-third of patients stopped anticoagulation within 6 months after starting anticoagulants following primary treatment for VTE. The mean duration of anticoagulation was 6.9±±6.2 months.

Patient characteristics are summarized in the Table. The mean age of patients was 67.6±±15.1 years, and 62.3% were female. PE and DVT were observed in 203 (35.1%) and 531 (91.7%) patients, respectively. The median D-dimer concentration was 7.0µg/mL and mean creatinine clearance was 79.0±±36.8mL/min. There were significant differences in some baseline characteristics among the 3 groups, specifically in the proportion of females, outpatients, symptomatic patients, and risk factors, as well as body weight and D-dimer concentrations. The duration of anticoagulation treatment also differed, with patients in the transient risk factor group having a shorter duration of anticoagulation treatment than those in the other 2 groups.

After discontinuation of rivaroxaban, 24 patients (4.1%) experienced recurrence or aggravation of symptomatic VTE at a mean annual incidence of 3.3%. Recurrence occurred gradually after discontinuation (Figure 2), and, numerically, tended to occur more frequently in the unprovoked than transient risk factor group (annual incidence 4.6% vs. 2.9%/year, respectively; log-rank, P=0.333), although the difference did not reach statistical significance. In the transient risk factor group, rivaroxaban was discontinued within 3 months after initiation in 4 of 11 patients with VTE recurrence. The cancer group showed the least recurrence (1.2%/year), although the number of patients and events was too small to allow for statistical analysis. As expected, a small number of major bleeding events (8 patients; 1.4%) was observed after discontinuation (Figure 3), half of which occurred in the cancer group. The rate of major bleeding events was higher in the cancer group than in the transient risk factor group (annual incidence 4.8% vs. 0.3%/year, respectively; log-rank, P<0.001). The incidence of major bleeding in the unprovoked group (1.1%/year) was similar to that in the transient risk factor group.

The overall cohort of the J’xactly study included 1,016 patients, with 43 reported instances of recurrence or aggravation of symptomatic VTE and 29 major bleeding events during the follow-up period.* Of these, 24 VTE and 8 major bleeding events occurred after discontinuation of rivaroxaban in 57% of patients who stopped anticoagulation. Thus, the present study provides a comprehensive picture of discontinuation of anticoagulation for VTE and its subsequent outcomes; approximately half the VTE

| Medical history | Overall | Transient risk | Cancer | Unprovoked | P value |
|-----------------|---------|---------------|-------|-----------|---------|
| Previous stroke | 42 (7.3) | 23 (8.3) | 5 (5.7) | 14 (6.6) | 0.638   |
| Coronary artery disease | 20 (3.5) | 11 (4.0) | 0 (0.0) | 9 (4.2) | 0.154   |
| Hypertension | 194 (33.5) | 98 (35.3) | 31 (35.2) | 65 (30.5) | 0.509   |
| Diabetes | 72 (12.4) | 33 (11.9) | 14 (15.9) | 25 (11.7) | 0.562   |
| Heart failure | 12 (2.1) | 8 (2.9) | 1 (1.1) | 3 (1.4) | 0.421   |
| Atrial fibrillation | 13 (2.2) | 9 (3.2) | 2 (2.3) | 2 (0.9) | 0.234   |
| Chronic heart and lung disease | 19 (3.3) | 9 (3.2) | 4 (4.5) | 6 (2.8) | 0.745   |

Concomitant medications

| Antiplatelet agents | Overall | Transient risk | Cancer | Unprovoked | P value |
|---------------------|---------|---------------|-------|-----------|---------|
| Acetylsalicylic acid | 56 (9.7) | 30 (10.8) | 7 (8.0) | 19 (8.9) | 0.659   |
| Dipyridamole | 130 (22.5) | 91 (32.7) | 15 (17.0) | 24 (11.3) | <0.001   |
| Aspirin | 18 (3.1) | 15 (5.4) | 2 (2.3) | 1 (0.5) | 0.007   |
| Antiplatelet inhibitors | 35 (6.0) | 0 (0.0) | 35 (39.8) | 0 (0.0) | <0.001   |

Initial dose of rivaroxaban (mg/day)

| Overall | Transient risk | Cancer | Unprovoked | P value |
|---------|---------------|-------|-----------|---------|
| Mean±SD | 209.8±187.6 | 186.1±171.5 | 244.8±211.1 | 226.3±194.2 | 0.009   |
| Median [IQR] | 158 [81–277] | 133.5 [73–230] | 178.5 [92–343] | 170 [89–314] |         |

Unless indicated otherwise, data are given as the mean±±SD, median [IQR] or n (%). Patients were divided into 3 groups: those with active cancer (cancer), those without active cancer and a transient risk factor for VTE (transient risk), and those without active cancer or a transient risk factor and/or with previous VTE (unprovoked). CrCl, creatinine clearance; DVT, deep vein thrombosis; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; PE, pulmonary embolism; VTE, venous thromboembolism.
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Figure 2. Kaplan-Meier curves for the recurrence or aggravation of symptomatic venous thromboembolism (VTE) after rivaroxaban discontinuation in the unprovoked (red), transient risk factor (blue), and cancer (green) groups.

Figure 3. Kaplan-Meier curves for major bleeding after rivaroxaban discontinuation in the unprovoked (red), transient risk factor (blue), and cancer (green) groups.
recurrences occurred after discontinuation, and approximately three-quarters of major bleeding events occurred during anticoagulation.

**Discussion**

The major findings of the present study are as follows: (1) 57% of patients treated with rivaroxaban for VTE stopped anticoagulation without VTE or major bleeding under anticoagulation during the follow-up period, with the mean duration of anticoagulation being 6.9±±2.6 months; (2) VTE recurrence was observed in 4.1% of patients, at an annual incidence of 3.3%/year, with a tendency for increased VTE recurrence in the unprovoked group; and (3) the rate of major bleeding was very low, at 1.1%/year, with a significantly greater occurrence in the cancer group. These data may facilitate decision making regarding the continuation of anticoagulation after primary treatment of VTE.

In the warfarin era, the COMMAND VTE Registry reported discontinuation of anticoagulation in 51.0%, 56.7%, and 33.5% of patients in the transient risk, cancer, and unprovoked groups, respectively, over a maximum follow-up period of 5 years. Most of the discontinuation events were observed within 6 months, and the most frequent reason was the treating physician’s judgment. In the present study, which was conducted in the DOAC era, discontinuation of anticoagulation was reported in 71%, 46%, and 49% of patients in the transient risk factor, cancer, and unprovoked groups, respectively. The mean duration of anticoagulation was 6.9 months. Although there may have been some differences in the proportion of discontinuations in each group, other aspects of anticoagulation discontinuation seem to be unchanged in the DOAC compared with warfarin era.

The COMMAND VTE Registry identified VTE recurrence after warfarin discontinuation in 6.1%, 13.2%, and 15.3% of patients in the transient risk factor, cancer, and unprovoked groups over a 3-year follow-up period. The recurrence rates in the transient and unprovoked groups in the present study, performed in the DOAC era, were almost the same. Strangely, the rate of VTE recurrence seemed to be equivalent in the early phase after discontinuation in the transient risk and unprovoked groups; this may be due to too-early discontinuation of rivaroxaban in the transient risk group. In fact, in 4 of 11 patients with VTE recurrence, rivaroxaban was discontinued within 3 months after initiation, when the transient risk for VTE could be maintained. The cancer group had a lower recurrence rate, but the number of the events and patients was too small for us to assess in the present study. Moreover, VTE recurrence in this group depends on the occurrence of cancer remission. Thus, the VTE recurrence rate in the cancer group requires further evaluation.

A recent Japanese study retrospectively enrolled 893 patients with acute VTE between 2011 and 2019, and reported rates of VTE and VTE-associated deaths at 3 years in the transient risk factor, unprovoked, continued cancer treatment, and cancer remission groups of 12.4%, 28.9%, 39.0%, and 1.6%, respectively. That study differed from the present study in its retrospective design and in including patients who discontinued anticoagulation because of major bleeding. The VTE recurrence rate in that study seemed to be higher in the transient risk factor, unprovoked, and cancer remission groups than rates found in the present study, but these differences could be explained by the presence of patients who discontinued anticoagulation because of major bleeding in the previous study, as these patients are more likely to experience VTE recurrence.

Previous global meta-analyses have reported that the VTE recurrence rate after discontinuation of anticoagulation was 3.1%/year in the transient risk factor group and 10.3%/year in the first year in the unprovoked group. These figures seem to be relatively higher than those reported in the present study and the COMMAND VTE Registry, although there are differences in patient backgrounds among the studies. Therefore, decisions regarding anticoagulation discontinuation after primary treatment of VTE should be made on the basis of prospective data in these registry and/or trials in the Japanese population. This study has several limitations. The decisions regarding the doses and duration of anticoagulation therapy during the follow-up period were at the discretion of the attending physicians. There was also selection bias in terms of participant recruitment, because all patients enrolled in the study were administered rivaroxaban. In the present study there were no objective criteria for VTE risk assessment, including active cancer, inactivity, injury, and surgery, and so dividing patients into groups was dependent on the judgment of the attending physicians. Moreover, because the number of patients and events was too small, the study was underpowered and the results should be considered descriptive. Despite these limitations, we believe that the results of this study provide useful information that can be used to support discussions between physicians and patients.

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IRB Information

This study was approved by Nihon University Itabashi Hospital, Clinical Research Judging Committee (RK-160913-4).

Data Availability

The deidentified participant data will not be shared.

References

1. Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol 2015; 12: 464–474.
2. Essien EO, Rali P, Mathai SC. Pulmonary embolism. Med Clin North Am 2019; 103: 549 – 564.
3. Wendelboe AM, Raskob GE. Global burden of thrombosis: Epidemiologic aspects. Circ Res 2016; 118: 1340–1347.
4. van Es N, Coppens M, Schulman S, Middeldorp S, Böller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: Evidence from Phase 3 trials. Blood 2014; 124: 1968 – 1975.
5. Beyer-Westendorf J. What have we learned from real-world NOAC studies in venous thromboembolism treatment? Thromb Res 2018; 163: 83–91.
6. Ageno W, Dentali F, Donadini MP, Squizzato A. Optimal treatment duration of venous thrombosis. J Thromb Haemost 2013; 11(Suppl 1): 151–160.
7. Duffett L, Castellucci LA, Forgie MA. Pulmonary embolism: Update on management and controversies. BMJ 2020; 370: m2177.
8. Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: Treatment of deep vein thrombosis and pulmonary embolism. Blood Adv 2020; 4: 4693–4738.
9. Okumura Y, Fukuda I, Nakamura M, Yamada N, Takayama M, Maeda H, et al. A multicenter prospective observational cohort study to investigate the effectiveness and safety of rivaroxaban in Japanese venous thromboembolism patients (the J’xactly study). Circ J 2020; 84: 1912–1921.
10. Okumura Y, Fukuda I, Nakamura M, Yamada N, Takayama M, Maeda H, et al. Design and rationale for the Japanese Registry of Rivaroxaban Effectiveness & Safety for the Prevention of Recurrence in Patients With Deep Vein Thrombosis and Pulmonary Embolism (J’xactly) study. BMJ Open 2018; 8: e020286.
11. Buller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. N Engl J Med 2003; 349: 1695–1702.
12. van Gogh Investigators, Buller HR, Cohen AT, Davidson B, Decousus H, Gallus AS, Gent M, et al. Idraparinux versus standard therapy for venous thromboembolic disease. N Engl J Med 2007; 357: 1094–1104.
13. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005; 3: 692–694.
14. Yamashita Y, Morimoto T, Amano H, Takase T, Hiramori S, Kim K, et al. Anticoagulation therapy for venous thromboembolism in the real world-from the COMMAND VTE Registry. Circ J 2018; 82: 1262–1270.
15. Sakamoto J, Yamashita Y, Morimoto T, Amano H, Takase T, Hiramori S, et al. Cancer-associated venous thromboembolism in the real world-from the COMMAND VTE Registry. Circ J 2019; 83: 2271–2281.
16. Hara N, Lee T, Nozato T, Terui Matsuyama M, Okata S, Nagase M, et al. Effectiveness and safety of direct oral anticoagulants vs. warfarin and recurrence after discontinuation in patients with acute venous thromboembolism in the real world. Circ J 2022; 86: 923–933.
17. Iorio A, Kearon C, Filippucci E, Marcucci M, Macura A, Peng V, et al. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: A systematic review. Arch Intern Med 2010; 170: 1710–1716.
18. Khan F, Rahman A, Carrier M, Kearon C, Weitz JI, Schulman S, 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: h363.