

# BMJ Open 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

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## ABSTRACT

**Introduction** Rivaroxaban, a factor Xa inhibitor used as a direct oral anticoagulant, is beneficial over warfarin in terms of food–drug interactions and the need for therapeutic monitoring in patients with acute venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism. Because there is little data regarding VTE treatment in Japan, a real-world survey of Japanese patients being treated with rivaroxaban for VTE is needed.

**Methods and analysis** The Japanese Registry of Rivaroxaban Effectiveness & Safety for the Prevention of Recurrence in Patients with Deep Vein Thrombosis and Pulmonary Embolism has been established to investigate the clinical outcomes of rivaroxaban for the initial treatment and prevention of symptomatic recurrent VTE in Japanese patients with acute symptomatic/asymptomatic VTE. 150 institutions in Japan will enrol patients in the study; the target enrolment is 1000. All patients will be followed up two times a year for at least 18 months and up to 3 years after their enrolment. The primary outcome is symptomatic recurrent VTE occurring during the study period. The principal safety outcome is clinically relevant bleeding (ie, major bleeding or clinically relevant non-major bleeding) occurring during treatment. A clinical events committee will adjudicate all outcomes.

**Ethics and dissemination** The study protocol has been approved by the Nihon University Itabashi Hospital, Clinical Research Ethics Committee and all local institutional ethics committees of the participating hospitals. Findings of the study will be presented in scientific sessions and will be published in peer-reviewed journals.

**Trial registration number** NCT03091621, UMIN000025072; Pre-results.

## INTRODUCTION

### Background and rationale

Venous thromboembolism (VTE), the term used to describe formation of a blood clot

## Strengths and limitations of this study

- This is the largest ongoing prospective observational research study with a great statistical power to investigate the clinical outcomes of one of the direct oral anticoagulants (rivaroxaban) for clinical use in Japanese patients with venous thromboembolism (VTE).
- This study will provide important information on the use of rivaroxaban in Japanese patients with VTE, including symptomatic/asymptomatic VTE, isolated distal deep vein thrombosis or cancer-associated VTE.
- Japan approved a specific continuous therapy dose of rivaroxaban (15 mg once daily) for VTE prevention, which is lower than that (20 mg once daily) in other Asian or Western countries. The dose difference should be considered when interpreting our results.
- Because of no interference with the clinical decision-making process by physicians and patients, the duration or dose of the rivaroxaban use or the VTE subjects enrolled in this study will vary.
- As this study included only patients treated with rivaroxaban and no concurrent control arm for a comparison, we will be unable to elucidate the effectiveness of rivaroxaban as compared with the current treatment in Japan such as with the use of unfractionated heparin or fondaparinux transitioning to warfarin.

or clots in a vein, covers deep vein thrombosis (DVT) and pulmonary embolism (PE). The standard therapy for patients with acute VTE has been administration of unfractionated heparin (UFH) for the first 5–10 days after the VTE event, followed by administration of warfarin for 3 months or

longer.<sup>1 2</sup> Anticoagulation with warfarin (a vitamin K antagonist (VKA)) provides effective VTE prophylaxis, but the use of warfarin can be troublesome for patients because of food–drug interactions, the narrow therapeutic range, the need for frequent monitoring of the international normalised ratio (INR) and/or warfarin's slow onset of action. Rivaroxaban, a factor Xa inhibitor, has been used as a direct oral anticoagulant (DOAC) to overcome limitations of the VKAs, and it has been approved in many countries for the initial treatment of acute VTE and prevention of recurrent VTE in at-risk adults. Rivaroxaban's onset and offset of action are both fast, the drug has been shown to have a low propensity for drug–drug interactions, and there is no need for laboratory monitoring.<sup>3–6</sup> Randomised clinical trials have shown use of rivaroxaban to be non-inferior to standard therapy for the initial treatment and long-term prevention of VTE in patients with DVT or PE, and it has a potentially improved benefit–risk profile.<sup>3–6</sup> A particular therapy for Japanese patients with VTE has not been established, mainly because, with the incidence of VTE being lower in Japan than in Western countries, adequate data have not been collected. Several specific situations exist for the initial treatment and long-term prevention of VTE in Japan. Low-molecular-weight heparin is not approved in Japan, so the current initial treatment of acute VTE is UFH or fondaparinux transitioning to warfarin. As compared with Western countries, a lower continuous therapy dose of 15 mg once daily for the prevention of recurrent VTE has been chosen and approved in Japan because it is based on rivaroxaban pharmacokinetics in Japanese subjects.<sup>7</sup> The 15 mg two times per day dose for a total of 3 weeks and then, a continuous therapy dose of 15 mg, were tested in Japanese patients in the J-EINSTEIN study. This study showed a similar efficacy and safety profile as the rivaroxaban and warfarin control treatment, which was consistent with that evidenced by the global EINSTEIN DVT/PE studies,<sup>3–5</sup> but the J-EINSTEIN study included only 100 patients.<sup>6</sup> A pooled analysis of the EINSTEIN-DVT and PE randomised studies included only 42 patients of a body weight of <50 kg in the rivaroxaban groups.<sup>5</sup> As the Western and Asian countries have approved a 20 mg once daily dose as a continuous therapy dose for the prevention of recurrent VTE, it remains unclear whether that dose regimen is suitable for low body weight patients such as Japanese people in other countries. Such a situation requires real-world evidence on the benefit of a specific rivaroxaban dose in Japanese patients with VTE. Further, the regimen of the use of rivaroxaban in Japan does not restrict the inclusion to just symptomatic DVT/PE, and thus, rivaroxaban may be clinically used in specific patients such as those that are asymptomatic, have isolated distal DVT or have cancer that have not been validated in the phase III trials of the EINSTEIN-DVT/PE study<sup>3–5</sup> and J-EINSTEIN study.<sup>6</sup>

We, therefore, established a multicentre registry, which we refer to as the J'xactly study (Japanese Registry of Rivaroxaban Effectiveness & Safety for the Prevention of

Recurrence in Patients with Deep Vein Thrombosis and Pulmonary Embolism), to support prospective observational research aimed at clarifying the effectiveness and safety of rivaroxaban for clinical use in Japanese patients with VTE (UMIN000025072, NCT03091621) including symptomatic/asymptomatic VTE, isolated distal DVT and cancer-associated VTE. The rationale for and design of the first J'xactly study are described herein.

### Study objectives

The aim of the J'xactly study is to investigate the clinical outcomes of the use of rivaroxaban for the initial treatment of acute VTE and prevention of recurrent VTE in Japanese patients with acute VTE.

## METHODS AND ANALYSIS

### Study design

The J'xactly study is designed as a prospective, multi-centre, observational cohort investigation into clinical outcomes in Japanese patients with acute DVT or PE or both who are treated with rivaroxaban in real-world clinical practice and followed up for at least 18 months and up to 3 years after their enrolment in the study.

The study will be conducted according to the principles of the Declaration of Helsinki, Ethical Guidelines for Clinical Studies from the Japanese Ministry of Health, Labour and Welfare, and all applicable laws and regulations in Japan. Written informed consent for enrolment in the study, including use of patients' data (anonymised) for study purposes, is required of all registrants.

The study is being coordinated by a steering committee. A clinical events committee (CEC) has been set up to adjudicate the presenting index diagnoses, all reported recurrences/exacerbations of symptomatic VTE (DVT and/or PE, in particular), bleeding, acute coronary syndrome, cerebral infarction and any death. An independent data monitoring committee has been set up to monitor patient safety and outcomes at set intervals during the study and to make recommendations to the steering committee.

### Participating institutions, registry enrolment and patient follow-up

The J'xactly study represents a collaboration of 150 enrolling institutions in Japan. Patient recruitment was begun in December 2016 and will cease in May 2018, and the patient follow-up information will be collected until November 2019.

### Population

The study enrolls consecutive patients eligible if acute symptomatic/asymptomatic DVT or PE or both have been diagnosed and rivaroxaban has been started for the initial treatment of acute VTE and prevention of recurrent VTE. Patients not eligible for enrolment are those with a condition that contraindicates the use of rivaroxaban (significant hepatic disease, including moderate to severe hepatic impairment, that is, Child-Pugh B and C, a systolic blood

pressure of more than 180 mm Hg or a diastolic blood pressure of more than 110 mm Hg; childbearing potential without proper contraceptive measures, pregnancy or breast feeding, undergoing dialysis or patients with severe renal impairment with a creatinine clearance (CrCl) of <30 mL/min, concomitantly treated with strong inhibitors of both CYP 3A4 and P-glycoprotein, such as HIV protease inhibitors (eg, ritonavir) or systemically administered azole antimycotics (eg, ketoconazole)), those with chronic thromboembolic pulmonary hypertension (CTEPH) (but those with CTEPH plus acute PE or DVT are eligible), and those with active bleeding. Patients who fail to provide written informed consent and those who are deemed non-compliant will not be enrolled. To minimise the selection bias, all patients treated with rivaroxaban meeting the inclusion criteria, but not the exclusion criteria will be enrolled. Therefore, the eligible patients include those who have clinical events prior to the enrolment from the start of rivaroxaban, those with an isolated distal DVT or cancer-associated VTE or those treated with non-standard regimens or off-label doses of rivaroxaban (eg, 10 mg two times per day for an acute therapy dose or 10 mg once daily for a continuous therapy dose).

### Treatment

The study is intended to analyse real-world data, and therefore, the decision of the type, dose and duration of anticoagulant drug therapy given to each patient is left to the discretion of each patient's physician. This is a standard regimen. After a diagnosis of DVT or PE or both, patients will be given 15 mg of oral rivaroxaban two times per day for 3 weeks and then 15 mg once daily thereafter (a continuous dose of 10 mg once daily should be considered only if the patients are concomitantly treated with fluconazole, posaconazole, clarithromycin or erythromycin). Rivaroxaban-treated patients will be classified into four groups: (1) rivaroxaban is received according to the standard regimen, (2) UFH or fondaparinux is administered first for a maximum of 48 hours before enrolment, and then rivaroxaban two times per day and once daily thereafter (EINSTEIN protocol), (3) UFH or fondaparinux is administered first for at least 2–14 days, and then warfarin (or rivaroxaban two times per day or other DOACs), and then rivaroxaban once daily thereafter and (4) only rivaroxaban once daily is administered or switched from warfarin (or other DOACs) without any parenteral therapy, or acute treatment of rivaroxaban two times per day.

### Data collection

The following baseline information will be obtained from each patient record at the time of enrolment: presence or absence of symptoms of DVT/PE and, if present, the exact symptoms; date when rivaroxaban was started and the dosage; patient characteristics, including age and sex, body weight and height, systolic/diastolic blood pressure, heart rate, blood oxygen saturation, type of VTE (DVT and/or PE), regional distribution of thromboses for

DVTs (proximal DVT located in the popliteal, femoral or iliac veins or distal DVT below the popliteal vein), classification of the PE (massive, submassive or low-risk PE/non-massive), medication(s) currently used (any antiplatelet agents, nonsteroidal anti-inflammatory drugs, oestrogen compound, steroid, drugs including VKA and/or anticancer drug), comorbidities (hypertension, diabetes, stroke, coronary artery disease, congestive heart failure and/or atrial fibrillation) and both perceived and established risk factors for VTE, limitations in daily activity, previous trauma, previous surgery, previous malignancy, congenital or acquired thrombophilia, history of DVT and any intervention for DVT/PE. Each patient's laboratory data, including the haemoglobin level, platelet count, total bilirubin level, liver releasing enzyme levels, serum creatinine (Cr) level, blood urea nitrogen, N-terminal pro-brain natriuretic peptide or brain natriuretic peptide level and troponin T level will also be obtained. The prothrombin time (PT), PT-INR, activated partial thromboplastin time and D-dimer level will be determined and recorded at the time of enrolment. The CrCl will be calculated according to the Cockcroft-Gault formula:  $((140 - \text{age in years}) \times (\text{weight in kg})) \div (72 \times \text{serum Cr})$  for men and  $((140 - \text{age in years}) \times (-\text{weight in kg})) \div (72 \times \text{serum Cr}) (\times 0.85)$  for women.<sup>8</sup> In patients with PE, the left ventricular and right ventricular end-diastolic diameters measured on an echocardiogram or CT image will be recorded, and the ratio of the right-to-left ventricular end-diastolic diameter ratio will be calculated automatically when the data are entered online.

### Management of the patient information and follow-up data

A website was created for the J'xactly study, and it is used to store all patient data, which are to be collected through a web-based registration system. All participating investigators have been trained in how to use the study website, and for security purposes, each received his or her own ID and password for access to the website. Patients are registered within 3 weeks after rivaroxaban is started. Each patient's baseline clinical information and follow-up data are entered into online forms and saved to the website. The data entry is checked by data managers at the central Registry office. One month before each patient's required follow-up assessment, the investigator involved in the patient's care is reminded, via email, of the upcoming assessment and to enter the follow-up data.

Information pertaining to each patient enrolled in the study is checked, through a central Registry office, two times a year for up to 3 years and updated if necessary. For all enrollees, those in whom an event has occurred and those in whom an event has not occurred, the continuation or termination of rivaroxaban, body weight, specific laboratory test results and medications used are obtained routinely and recorded. If a patient is transferred to another hospital, discontinues the rivaroxaban treatment or completes the rivaroxaban treatment during the follow-up period, the information will be collected as long as possible until the follow-up period ends.

## Outcome assessments

The primary outcome variable in this study is symptomatic recurrent VTE, defined as recurrent DVT, new non-fatal symptomatic PE and/or fatal PE occurring during the follow-up period, as adjudicated by the CEC according to established diagnostic criteria.<sup>9–11</sup> The principal safety outcome variable is clinically relevant bleeding (ie, major bleeding and/or clinically relevant non-major bleeding) occurring during treatment. Major bleeding is defined as a reduction in the haemoglobin level of at least 2 g/dL, transfusion of at least 2 units of blood or symptomatic bleeding in a critical area or organ or fatal bleeding. Clinically relevant non-major bleeding is defined as overt bleeding that does not meet the criteria for major bleeding but is associated with medical intervention, unscheduled contact with a physician, interruption or discontinuation of a study drug, or discomfort or impairment of activities of daily life.<sup>6</sup> Any other bleeding is recorded as minor bleeding. The secondary outcome variables include death from any cause, a vascular event (acute coronary syndrome or cerebral infarction), and the D-dimer level on recurrence.

## Statistical methods

The primary and secondary outcome analyses will be carried out in an intention-to-treat population, defined as all participants who receive at least one dose of rivaroxaban, and will include all primary and secondary events occurring from the time of patient enrolment to the end of the survey period. The principal safety outcome analysis will be carried out in an on-treatment population. The cumulative incidence of primary and secondary outcomes and its 95% CI will be determined by the Kaplan-Meier method. Numerical data will be summarised as mean±SD. Categorical data will be reported as the number and percentage of patients. Subanalyses of the incidence of clinical events will be performed according to age, renal function, VTE risk factors, prior VTE therapy, classification of the PE (massive, submassive or low-risk PE) and the use of rivaroxaban and its dosage. All statistical analyses will be performed with the use of JMP V.11.0.2 (SAS Institute) or SPSS V.24 (SPSS).

## Sample size

According to the EINSTEIN DVT/PE study, the annual incidences of symptomatic recurrent VTE and major bleeding are 2.1% and 1.0%, respectively.<sup>3–5</sup> In Japan, the recommended dose of rivaroxaban for continuous therapy is now 15 mg (reduced from 20 mg and based on rivaroxaban pharmacokinetics). A study of a small number of Japanese patients (n=78), the J-EINSTEIN study, conducted according to this specific regimen, revealed reduced annual incidences of symptomatic recurrent VTE and major bleeding (1.8% and 0.0%, respectively).<sup>6</sup> Considering the possibility of inappropriate dose reduction and of patient non-adherence to the treatment regimen, we estimated annual incidences of 2% and 1.0%, respectively. If the desired margin of error

is ±1% and the desired CI is 95%, the sample size required to determine the incidence of symptomatic recurrent VTEs would be 753, and that required to determine the incidence of major bleeding would be 381. Therefore, at least 753 patients are needed for us to reach our target event rates. We expect 10% of all participants to be lost to follow-up or to drop out of the study before the end of the survey period. Thus, we are aiming for a sample size of 1000 patients.

## Public and patient involvement

There were no particular challenges in managing the patient and public involvement for the J'xactly study.

## DISCUSSION

The J'xactly study will be one of the most important real-world observational studies for the initial treatment and prevention of VTE in Japanese with acute symptomatic/asymptomatic DVT/PE. The study will also provide important insight into the effectiveness and safety of DOAC rivaroxaban for treatment of VTE and into the prognosis of VTE.

Little data regarding the epidemiology, treatment and prognosis of VTE among patients in Japan have been reported. A questionnaire-based epidemiological study conducted in 2006 documented dramatic increases in the incidences of DVT and PE, with the number of new patients reaching 14674 and 7864, respectively.<sup>12</sup> The estimated annual incidences of DVT and PE are 12/100 thousand persons (0.012%) and 62/1 million persons (0.0062%), respectively, one-fourth and one-eighth lower than those in the USA.<sup>13</sup> A more recent epidemiological study in Japan showed the annual incidence of VTE to be 4/10 thousand persons (0.04%).<sup>14</sup> In a multicentre retrospective cohort study involving 1076 Japanese with acute VTE, the overall annual incidence of recurrent VTE was 3.9%, but it increased to 8.1% if anticoagulant therapy was terminated.<sup>15</sup> The annual incidences of major bleeding and VTE-related death were 3.2% and 1.7%, respectively. These data suggest that the VTE recurrence rate is as high as the latest rates obtained from Western registries. These data increase the urgency for establishing treatment protocols for VTE in Japanese patients. The patient population to be included in the J'xactly study is of sufficient size that the exact incidence of recurrent VTE and bleeding events in Japanese patients treated with DOAC rivaroxaban can be documented and a rivaroxaban-based VTE treatment protocol appropriate for routine clinical practice can be established.

One of the most notable changes to the latest consensus guidelines of the American College of Chest Physicians<sup>16</sup> is the type of anticoagulant recommended for patients with acute DVT or PE without cancer. DOACs, including dabigatran, rivaroxaban, capixaban and edoxaban, are recommended over warfarin. Although this is a weak recommendation based on moderate-quality evidence (grade 2B), this is the first time that warfarin has not

been considered a first-line therapeutic agent. DOACs, including edoxaban, rivaroxaban and apixaban, have been approved in Japan, and the use of DOACs has been increasing in clinical practice. The J-EINSTEIN study showed a similar efficacy and safety profile with rivaroxaban and control treatment receiving intravenous UFH followed by warfarin, but included only 100 patients.<sup>6</sup> In addition, data are lacking in the world for the prevention of VTE by the use of rivaroxaban in patients with a low body weight.<sup>5</sup> More data on the effectiveness and safety of the Japan-specific dose will also provide clinical insight into understanding the VTE treatment and prevention for Japanese patients, and for some Western and Asian patients who have a similar body type to Japanese people.

The phase III trials in the EINSTEIN-DVT/PE-targeted patients with acute symptomatic VTE.<sup>3-5</sup> A pooled subgroup analysis of those trials revealed a similar efficacy and safety compared with treatment with enoxaparin and a VKA in patients with active cancer and VTE, but the number of subjects was small.<sup>17</sup> Because rivaroxaban use was not restricted to patients with symptomatic acute VTE in Japan, rivaroxaban will be widely used in patients with acute symptomatic VTE and in patients such as those with asymptomatic VTE or isolated distal DVT incidentally detected by lower-extremity venous ultrasonography or cancer-associated VTE in clinical practice. This study will provide the important information for the initial treatment of acute VTE and prevention of recurrent VTE in these specific patients.

Most guidelines recommend that treatment be maintained for at least 3 months for patients with proximal DVT or PE.<sup>13-16</sup> Extending anticoagulant treatment may be of benefit, but the optimal treatment period remains uncertain.<sup>13,18</sup> Prolonging warfarin therapy prevents recurrence of VTE, but the benefit is offset by the increased risk of a bleeding event.<sup>18</sup> The clinical trials of rivaroxaban for the prevention of DVT/PE have shown the primary efficacy at a fixed duration of 12 months after treatment is initiated.<sup>3-5</sup> The J'xactly survey data will be obtained for at least 1 year and 6 months, and up to 3 years, and thus, will clarify the effectiveness of a prolonged rivaroxaban treatment. Recently, the EINSTEIN CHOICE study showed an equivalent efficacy between a 20 mg dose and 10 mg dose of rivaroxaban, which are superior to aspirin without an increase in major bleeding in patients who completed the 6–12 months' VTE treatment.<sup>19</sup> This raises a question of whether patients with unprovoked VTE or VTE associated with weak risk factors should receive 10 mg once daily in the chronic phase. The real-world data obtained on the use of DOACs in Japanese patients with atrial fibrillation revealed that physicians tended to reduce the DOAC dose down to 10 mg as a precaution against future bleeding events.<sup>20-21</sup> This is also expected to happen in the VTE treatment in Japan. Therefore, the dose of rivaroxaban in clinical practice will allow us to determine the optimum evidence-based dose of rivaroxaban therapy in a diverse population of Japanese patients with DVT/PE.

In conclusion, the J'xactly study will be an important real-world observational study of VTE treatment and prognosis in Japanese patients with acute symptomatic/asymptomatic DVT/PE. This study will provide the data we need to establish a guideline for rivaroxaban treatment in such patients.

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**Contributors** AH contributed to conception and design. YO reviewed the literature, contributed to the design and wrote the draft of the manuscript. IF, MN, NY, MT, HM, TY, TI and MM served on the steering committee for the study. TY contributed to data analysis. All authors contributed to refinement of the study protocol and approved the final manuscript.

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**Patient consent** Obtained.

**Ethics approval** Analysis of the study data has been approved by our Institutional Review Board (IRB) of Nihon University Itabashi Hospital, Clinical Research Ethics Committee and the IRBs of the participating hospitals.

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