Rationale and Design of Rivaroxaban Estimation With Warfarin in Atrial Fibrillation Patients With Coronary Stent Implantation (REWRAPS)

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Background: Recent major randomized trials revealed the superiority of non-vitamin K antagonist oral anticoagulants (NOACs) over vitamin K antagonists (VKAs) from 6 months to 2 years after percutaneous coronary intervention (PCI). However, whether NOAC monotherapy superiority over warfarin continues in real-world patients with a history of atrial fibrillation (AF), coronary stenting, and underlying chronic kidney disease (CKD) >1 year after PCI (e.g., at 5 years) has not been established.

Methods and Results: In the Rivaroxaban Estimation with Warfarin in Atrial Fibrillation Patients with Coronary Stent Implantation (REWRAPS) study (NCT02024230), a multicenter, prospective, non-randomized, open-label, physician-initiated efficacy and safety study in Japan, 493 patients received either rivaroxaban or warfarin. The primary efficacy endpoint was major adverse cardiac and cerebrovascular events (MACCE), consisting of cardiac and stroke death, non-fatal myocardial infarction, non-fatal stroke, systemic embolism, and coronary revascularization. The primary safety endpoint was major bleeding (Bleeding Academic Research Consortium 3 and 5). The primary composite endpoint was net adverse clinical events (NACE), defined as a combination of all-cause death and major bleeding.

Conclusions: Completion of REWRAPS will provide, for the first time, evidence as to whether rivaroxaban is superior or non-inferior to warfarin with regard to the primary efficacy (MACCE), safety (major bleeding), or combined (all-cause death, major bleeding) endpoints in real-world patients with AF, coronary stenting, and underlying CKD an average of 5 years after PCI.

Key Words: Atrial fibrillation; Chronic kidney disease; Coronary stent; Rivaroxaban; Warfarin
study was not to compare non-VKA oral anticoagulants (NOACs) and VKA. Based on the findings described above, recent guidelines from the European Society of Cardiology (ESC) recommend triple therapy (an oral anticoagulant plus aspirin and a P2Y12 inhibitor) from a minimum of 1 week to 6 months in patients with AF and acute coronary syndrome, with such therapy followed by combination therapy with an oral anticoagulant plus single antiplatelet therapy from 6 to 12 months, followed by monotherapy with either a VKA or NOAC after 1 year.

Although the ESC guidelines recommend oral anticoagulant monotherapy with either a VKA or NOAC after 1 year following PCI, this evidence was derived from a Danish cohort study based on data from 2002 to 2011 that indicated the use of antiplatelet agents in combination with anticoagulation in patients >1 year after the onset of acute myocardial infarction or PCI resulted in an increased risk of bleeding events over a mean follow-up period of 3.3 years. However, since a cohort study was not a prospective study of long-term duration, it has not yet been demonstrated which oral anticoagulant (either VKA or NOAC) is superior in real-world patients over a long-term follow-up.

To resolve this clinical question, we designed a multicenter, prospective, non-randomized, open-label, physician-initiated efficacy and safety study to test whether rivaroxaban therapy over a mean follow-up period of 5 years could be non-inferior or superior to warfarin therapy in terms of the incidence of primary major adverse cardiac and cerebrovascular events (MACCE) endpoint in patients with AF, coronary stenting, and underlying chronic kidney disease (CKD).

Methods

Study Design and Hypothesis

The Rivaroxaban Estimation with Warfarin in Atrial Fibrillation Patients with Coronary Stent Implantation (REWRAPS) study (NCT02024230) is a prospective, multicenter, non-randomized, open-label, physician-initiated, all-comer registry study. In this study, patients with a history of AF, coronary stenting, and underlying CKD or non-CKD were treated with either rivaroxaban or VKA therapy for 5 years. All patients are scheduled to be followed up for a minimum of 3 years and a maximum of 7 years (i.e., an average of 5 years).

We hypothesize that 5 years of rivaroxaban therapy will be non-inferior or may be superior to VKA in the primary efficacy endpoint of MACCE, the primary safety endpoint of major bleeding (Bleeding Academic Research Consortium [BARC] 3 or 5), and the primary composite endpoint of all-cause death and major bleeding in real-world patients with AF, coronary stenting and CKD.

Inclusion and Exclusion Criteria

Men and women aged ≥20 years with a history of AF and coronary stenting >1 year ago, and who had been treated with anticoagulant drugs (regardless of the type of stent and AF), were eligible for inclusion in the REWRAPS study, regardless of the presence or absence of CKD.

Those with a contraindication to anticoagulant drugs, any planned coronary intervention or catheter ablation, a history of stent thrombosis, past or planned prosthetic valve replacement for valvular disease, and judged ineligible for the study by the attending physician were excluded.

Ethics approval was obtained from the Fujita Health University Ethics Review Committee (HM13-191) and the relevant ethics committees at all participating sites. All patients provided written informed consent. The study was conducted in accordance with ethical principles outlined in the Declaration of Helsinki.

Study Endpoints

Three ranked primary outcomes are assessed in the study. The primary efficacy endpoint is a composite of cardiac death, stroke death, non-fatal myocardial infarction, non-fatal stroke, systemic embolism, and coronary revascularization (MACCE). The primary safety endpoint was major bleeding, defined as BARC 3 and 5. The primary composite endpoint was net adverse clinical events (NACE), defined as a combination of all-cause mortality and major bleeding. The original primary endpoints included conventional MACCE and major bleeding (BARC 3 and 5), but the composite endpoint of all-cause mortality and major bleeding (NACE) was added in October 2018, because the importance of this composite endpoint has been recently recognized in the field of cardiology.

Secondary endpoints were the individual components of the primary endpoints. Blinded adjudication of the endpoints was conducted by an independent clinical events committee.

Clinical Risk Evaluation in AF

The risk of stroke was evaluated using the CHA2DS2-VASc scale, which has been associated with improved stratification among low-risk patients. Patients are evaluated based on the 5 criteria of the CHADS2 scale plus an additional 3 criteria: the presence of vascular disease, age 64–74 years, and sex. The CHA2DS2-VASc score ranges from 0 to 9, with 2 points for age ≥75 years or older: higher scores indicate a greater risk. We also evaluated the risk of major bleeding using the HAS-BLED scale, which ranges from 0 to 9, with higher scores indicating a greater risk of bleeding.

Anticoagulant Therapy

All patients were treated over an average of 5 years with either rivaroxaban (10mg once daily for patients with a creatinine clearance of 15–49mL/min or 15 mg once daily for patients with a creatinine clearance ≥50mL/min) or warfarin (once daily dosing, with dose adjustment to achieve a target international normalized ratio [INR] of 2.0–3.0 or, in patients aged >70 years and with a high bleeding risk, a target INR of 1.6–2.6).22

Statistical Design and Sample Size

Since REWRAPS is non-randomized study, we plan to compare rivaroxaban and warfarin based on the intention-to-treat (ITT) population using a propensity score-matched (PSM) cohort. To minimize differences in baseline characteristics between the 2 groups, propensity score matching analysis will also be performed with a greedy matching algorithm using a multivariate logistic regression model including all baseline variables, because of the non-randomized nature of this study.

Differences will be considered statistically significant at P<0.05. All tests are 2-sided, except for the non-inferiority test being 1-sided. All statistical analyses will be performed using SPSS V21.0 (SPSS Inc., Chicago, IL, USA), except the non-inferiority test, which will be performed using R version 3.4.1 (https://www.r-project.org). While we referred
to post hoc analysis of PIONEER AF-PCI study, we envisaged that the annual event rate could be 23.92% in rivaroxaban group and 31.51% in warfarin group based on the late breaking presentation by Gibson et al at the American Heart Association (AHA) conference in 2016.1 Assuming a significance level of 0.05, a detection ability of 0.90, a non-inferiority margin of 1.35, and a follow-up period of 5 years, the number of patients needed in the PSM population is 248. Assuming that the PSM cohort could be at least 55% of the entire population and allowing for a drop-out rate of 5%, the minimum number of patients needed is 474. Thus, we thought that 474 patients would be the minimum number needed to address our hypothesis.

**Study Operations**

The executive steering committee consists of members of the academic leadership of the trial, with the REWRAPS study being designed and led by the executive steering committee. An independent data and safety monitoring board (DSMB) was selected by the executive steering committee. The independent DSMB will periodically evaluate safety and efficacy data and make recommendations regarding continuation of the study. An event adjudication committee will review all potential primary and secondary endpoint events to adjudicate the endpoint designation. Members of the event adjudication committee are independent of the study investigators in the trial. Under the guidance of the investigators, NEUES Co. Ltd (Tokyo, Japan), a contracted research organization, helped with the selection, supervision, and monitoring of participating centers, as well as with the collection and management of trial data. Statistical analyses of the trial data were performed by a statistician. Members of the executive steering committee are responsible for data analysis, interpretation of the trial results, and writing manuscripts. Details of committee members, investigators involved in the trial and their institutions, and supporting research organizations are provided in the Appendix. Funding for the study was provided by the Fujita Health University Research Foundation under a contract with Bayer Yakuhin. The company had no role in trial design, data analysis nor interpretation.

**Results**

**Baseline Data**

Baseline data for the REWRAPS study population are presented in the Table. The REWRAPS population comprised 493 patients from 39 institutions. Allocation to either rivaroxaban or warfarin was performed between January 2014 and December 2018. A total of 538 patients aged ≥20 years with a history of AF, coronary stenting, and underlying CKD or non-CKD were considered for inclusion. All patients received coronary stenting at least 1 year prior to the study. Of the 538 candidate patients, 493 who agreed to take part in the study were allocated to receive either rivaroxaban or warfarin in a non-randomized fashion.

**Discussion**

Although ESC guidelines recommend oral anticoagulant monotherapy with either a VKA or NOAC after 1 year following PCI, it has not yet been definitively demonstrated which oral anticoagulant (either VKA or NOAC) is superior in real-world patients with AF, coronary stenting, and especially underlying CKD over a long-term follow-up, such as 5 years.6

Previous major trials, such as PIONEER AF-PCI and RE-DUAL PCI, indicated that the combination of NOAC (either rivaroxaban or dabigatran) and a P2Y12 inhibitor, reduced the risk of clinically significant bleeding compared with triple therapy consisting of a VKA, P2Y12 inhibitor, and aspirin within 12 months (PIONEER AF-PCI) and 14 months (RE-DUAL PCI).12 The AUGUSTUS study also revealed that an antithrombotic regimen using apixaban resulted in less bleeding and fewer hospitalizations without significant differences in ischemic events within 6 months compared with regimens included a VKA.7 Furthermore, ENTRUST-AF PCI revealed that the edoxaban-based regimen was non-inferior for bleeding compared with the VKA-based regimen in patients with AF up to 1 year after PCI.13 However, the follow-up period of these major studies was limited within 2 years.

Although the recent AFIRE study demonstrated that rivaroxaban monotherapy was superior to combination therapy with rivaroxaban and aspirin for major bleeding in patients with AF and stable coronary artery disease over a median follow-up of 24.1 months, this study did not compare NOAC with VKA.
Study Limitations

The REWRAPS study has several limitations. First, since this study is not randomized study but a registry study, there is selection bias regarding the choice of rivaroxaban or warfarin. Second, only rivaroxaban is used; therefore, we do not know whether our findings can be applied to other NOACs. Finally, we will first compare 2 groups in an ITT analysis; therefore, we still have to wait for the effect of modifications in medications during follow-up.

Implications of the REWRAPS Study

Although previous guidelines recommend oral anticoagulant monotherapy after 1 year following PCI, this recommendation was derived from a Danish cohort study with a mean follow-up period of 3.3 years; however, the Danish cohort study did not examine outcomes prospectively and did not compare NOAC and VKA over a long-term follow-up of 5 years. To determine which oral anticoagulant (VKA or NOAC) is superior in real-world patients over a long-term follow-up, we designed a multicenter, prospective, non-randomized, open-label, physician-initiated efficacy and safety study to test whether 5 years of rivaroxaban therapy can reduce the incidence of the three ranked primary endpoints compared with warfarin in patients with AF, coronary stenting, and underlying CKD. After the 5-year follow-up in REWRAPS is completed, we will, for the first time, have evidence as to whether NOAC is superior or non-inferior to VKA with regard to the primary efficacy endpoint of MACCE, the primary safety endpoint of major bleeding, or the primary composite endpoint of all-cause of mortality and major bleeding (i.e., NACE) in real-world patients with AF, coronary stenting, and underlying CKD over the longer term.

Disclosures

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IRB Information

This study was approved by the Fujita Health University Review Board (HM13-191).

Data Availability

The deidentified participant data will not be shared.

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Appendix

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Appendix Information

This study was approved by the Ethics Committee of the University of Tokyo Hospital (15141).

Appendix Data Availability

The deidentified participant data will not be shared.
