




BMJ Open Randomised controlled trial to investigate optimal antithrombotic therapy in patients with non-valvular atrial fibrillation undergoing percutaneous coronary intervention: a study protocol of the OPTIMA-AF trial

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ABSTRACT

Introduction The optimal antithrombotic strategy for patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) is uncertain. For patients with non-AF, many trials are now evaluating short 1-month dual antiplatelet therapy. In patients with AF undergoing PCI, in contrast, short dual therapy (P2Y₁₂ inhibitor +direct oral anticoagulant (DOAC)) has not yet been evaluated.

Methods and analysis The OPTIMA-AF trial (*OPTIMA* antiplatelet therapy in combination with direct oral anticoagulants in patients with non-valvular Atrial Fibrillation undergoing percutaneous coronary intervention with everolimus-eluting stent) is an investigator-initiated, open-label, nationwide, multicentre, prospective, randomised controlled trial. The primary objective is to compare the efficacy and safety of short dual therapy (1-month DOAC +P2Y₁₂ inhibitor followed by DOAC monotherapy) against long dual therapy (12-month DOAC +P2Y₁₂ inhibitor followed by DOAC monotherapy) in the treatment of AF subjects undergoing PCI. The primary efficacy endpoint is a composite of death or thromboembolic events (myocardial infarction, definite stent thrombosis, stroke or systemic embolism) at 365 days; and the primary safety endpoint is bleeding (International Society on Thrombosis and Haemostasis major or clinically relevant non-major bleeding) at 365 days. This trial is intended to show the non-inferiority of short dual therapy versus long dual therapy in terms of the primary efficacy endpoint and show superiority in terms of the primary safety endpoint. A total of 1090 subjects will be randomised in a 1:1 ratio at approximately 60 sites.

Ethics and dissemination This study received approval from the Certified Review Board of Osaka University (a certified research ethics committee by the Japanese Clinical Research Act). The findings will be disseminated through peer-reviewed publications and conference presentations.

Strengths and limitations of this study

- OPTIMA-AF (*OPTIMA* antiplatelet therapy in combination with direct oral anticoagulants in patients with non-valvular Atrial Fibrillation undergoing percutaneous coronary intervention with everolimus-eluting stent) is the first trial in patient with non-valvular atrial fibrillation undergoing percutaneous coronary intervention (PCI) for coronary artery disease to compare short versus long dual therapy followed by direct oral anticoagulant monotherapy.
- This trial will provide essential evidence to guide the selection of an optimal antithrombotic strategy for this challenging group of patients.
- Racial difference and geographical variety in PCI strategy will impair the external validity of the findings of the present study.

Trial registration number Japan Registry of Clinical Trials: jRCTs051190053; Pre-results.

INTRODUCTION

The number of patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) with metallic stent implantation is increasing worldwide because of the overlapping risk factors of coronary artery disease and AF. AF accounts for approximately 5%–8% of all patients who undergo PCI. In these patients, ‘triple therapy’, defined as the concurrent use of an oral anticoagulant (vitamin K antagonist or direct oral anticoagulant (DOAC)) and dual antiplatelet therapy (DAPT) (aspirin and P2Y₁₂ inhibitor), was the standard strategy. A recent consensus has recommended ‘dual therapy’, defined as a

P2Y₁₂ inhibitor (clopidogrel) in combination with DOAC, to prevent stent thrombosis up to 1 year after the index procedure.^{1–3} This is based on the results of recent trials (WOEST (What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting), RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention), PIONEER AF PCI (Open-Label, Randomized, Controlled, Multi-center Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention), AUGUSTUS (Open-Label, 2×2 Factorial, Randomized, Controlled Clinical Trial to Evaluate the Safety of Apixaban vs Vitamin K Antagonist and Aspirin versus Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention), ENTRUST AF PCI (Edoxaban-based versus Vitamin K Antagonist-based Antithrombotic Regimen after Successful Coronary Stenting in Patients with Atrial Fibrillation)), which demonstrated not only the superiority of DOAC over vitamin K antagonist but also the safety and efficacy of dual therapy of DOAC and P2Y₁₂ inhibitor in the acute phase.^{4–7} However, the combination of oral anticoagulants and antiplatelet therapy is still associated with a high annual risk of fatal and non-fatal bleeding episodes.^{8–10} A shortened duration of the dual therapy (DOAC +antiplatelet agent) would be preferable, provided it does not compromise antithromboembolic efficacy.

For patients with non-AF, a number of randomised trials are now evaluating a short DAPT duration (1 month).^{411–13} Some trials have already demonstrated the safety and efficacy of this strategy as compared with long DAPT (12 months).^{412 13} The best-in-class drug-eluting stent, Xience cobalt chromium everolimus-eluting stent (Abbott Vascular, Santa Clara, California), which is characterised by thin struts and an antithrombogenic fluoropolymer coating, could lead to lower thrombogenicity than earlier generation drug-eluting stents, and presumably provide better safety and efficacy. This has been recently confirmed by the STOPDAPT-2 trial,¹³ which suggested that 1 month of DAPT followed by clopidogrel monotherapy provided benefit compared with 12 months of DAPT in patients undergoing PCI with the Xience stent. In patients with AF undergoing PCI, in contrast, short dual therapy (P2Y₁₂ inhibitor +DOAC) has not yet been evaluated. Given the recent data, we hypothesised that shortened dual therapy for patients with AF undergoing PCI could be justified if contemporary PCI with newer generation drug-eluting stents can be performed.^{4–7 14 15} Standard imaging-guided PCI, which enables optimal stent implantation, will further support this hypothesis.¹⁶ Moreover, especially for East Asian patients who have a higher bleeding risk than white patients,¹⁷ attention should be focused on bleeding rather than thrombosis.

The purpose of the present study is to evaluate the safety and efficacy of short dual therapy in patients with AF undergoing PCI with the Xience in order to investigate the optimal regimen for this population.

METHODS AND ANALYSIS

Trial design and objective

The OPTIMA-AF trial (*OPTIMAL* antiplatelet therapy in combination with DOACs in patients with non-valvular AF undergoing PCI with everolimus-eluting stent) is an investigator-initiated, open-label, nationwide, multi-centre, prospective, randomised controlled trial (RCT). The primary objective of the OPTIMA-AF RCT is to compare the efficacy and safety of short dual therapy (1-month DOAC +P2Y₁₂ inhibitor followed by DOAC monotherapy) against long dual therapy (12-month DOAC +P2Y₁₂ inhibitor followed by DOAC monotherapy) in the treatment of AF subjects with ischaemic heart disease undergoing PCI. A total of 1090 subjects (545 in the 1-month dual therapy group and 545 in the 12-month dual therapy group) will be randomised at approximately 60 sites in Japan. All subjects will be screened according to the inclusion and exclusion criteria prior to enrolment. This RCT is intended to show the non-inferiority of short dual therapy versus long dual therapy in terms of the primary endpoint—the cumulative incidence of a composite of death or thromboembolic events at 12 months—and show superiority in terms of bleeding at 12 months.

Study population

Eligibility criteria are summarised in [box 1](#). Briefly, any PCI indication for native coronary lesions in non-valvular patients with AF with CHADS₂ score ≥1 will be evaluated for eligibility. Patients presenting with ST elevation myocardial infarction and non-ST elevation myocardial infarction will be excluded.

RANDOMISATION AND TREATMENT

Randomisation

The trial schema is shown in [figure 1](#). Eligible patients will be informed about the trial and required to sign the informed consent form prior to PCI. After eligibility criteria have been checked and written informed consent has been obtained prior to PCI, patients who have been successfully implanted with a Xience stent will be randomised. Randomisation will be concealed using web-based central randomisation and stratified according to centre. Subjects will be randomised in a 1:1 fashion to either the experimental arm or control arm.

PCI procedure

Patients with stable/unstable angina or silent myocardial ischaemia for target lesions in the native coronary artery are eligible for participation in this study. Target lesions fulfil at least one of the following criteria: (1) visually

Box 1 Eligibility criteria

Inclusion criteria

Subjects must meet all the inclusion criteria to be considered for the clinical evaluation.

General inclusion criteria

Any PCI indication for native coronary lesions in non-valvular atrial fibrillation patients with a CHADS₂ score ≥ 1 , who satisfy the following criteria:

1. Adjunctive oral anticoagulation treatment with a direct oral anticoagulant (DOAC) planned to continue after percutaneous coronary intervention (PCI).
2. PCI indication for stable angina, unstable angina and silent ischaemia.
3. Subject is appropriate for treatment by PCI as determined in accordance with local practice (operator's judgement or heart team decision).
4. Patient age at least 20 years.
5. Signed informed consent.
6. The patient understands and accepts clinical follow-up.

Angiographic criteria

1. Angiographically significant stenosis in de novo, native, previously unstenosed lesions, which is in the operator's opinion appropriate for treatment by PCI.
2. Significant stenosis, defined as 90% or greater stenosis of a major epicardial vessel, or proof of functional ischaemic test.³¹
3. Angiographically significant stenosis, which is in operator's opinion related to symptoms of angina.

Exclusion criteria

General exclusion criteria

1. No expectation of compliance with 1-month clopidogrel or prasugrel and DOAC.
2. Requirement for a planned-staged PCI procedure more than 2 weeks (+14 days as occasion demands) after the index procedure.
3. Presentation with ST elevation myocardial infarction and non-ST elevation myocardial infarction.
4. Active bleeding at the time of inclusion.
5. Reference vessel diameter < 2.25 mm to > 5.75 mm
6. PCI for bypass graft vessel.
7. Cardiogenic shock.
8. Compliance with long-term single antiplatelet therapy with DOAC unlikely.
9. Known hypersensitivity or contraindication to aspirin, clopidogrel, prasugrel, DOAC, cobalt chromium, everolimus or sensitivity to contrast media, which cannot be adequately avoided by premedication.
10. PCI during the previous 6 months for a lesion other than the target lesion of the index procedure.
11. Participation in another clinical trial (up to 12 months after the index procedure).
12. Life expectancy of < 1 year.
13. Known severe renal insufficiency (eg, creatinine clearance < 15 mL/min or receipt of dialysis).
14. Pregnant or breastfeeding.
15. Those judged inappropriate for study participation in the opinion of the investigators.

Angiographic exclusion criteria

Patients inappropriate for study participation in the opinion of the investigators.

estimated % diameter stenosis $\geq 90\%$, (2) fractional flow reserve (FFR) ≤ 0.80 or (3) presence of myocardial ischaemia as assessed by a non-invasive test such as scintigraphy, stress echocardiography and stress electrocardiography. Physicians are encouraged to confirm the significance of stenosis by a FFR test (≤ 0.80) or non-invasive test. PCI will be performed with the Xience Expedition Everolimus

Eluting Stent (EES), Xience Alpine EES, Xience Sierra EES or Xience Skypoint EES (all Abbott Vascular, Santa Clara, California, USA).

Treatment strategies including predilatation, atherectomy, postdilatation, etc will be left to the operators' discretion. Operators should follow the instructions for use in terms of predilatation, device sizing and postdilatation. An atherectomy device can be used at the operators' discretion. Treatment of multiple target vessels (within the same procedure) and a staged procedure within 14 days (+14 days as occasion demands) of the initial implant procedure are permitted. Any subsequent treatment of a lesion within 14 days (+14 days as occasion demands) of the index procedure or already present at the time of the index procedure will be considered as a staged procedure, instead of a repeat PCI. For patients undergoing a staged procedure, the follow-up schedule will be calculated from the date of the index procedure. The antiplatelet and anticoagulation schedule will be calculated from the date of the staged procedure, if applicable. All subjects require preprocedure and postprocedure imaging evaluation. Preprocedure optical coherence tomography (OCT) or intravascular ultrasound (IVUS) needs to be done before predilatation of each target lesion. If not technically feasible (ie, the OCT/IVUS catheter does not cross the lesion) predilatation with a small balloon dilatation catheter is allowed for OCT/IVUS catheter access, subsequently followed by OCT/IVUS and then full predilatation. The intravascular imaging system used for OCT must be Dragonfly OPTIS Imaging Catheter with ILUMIEN OPTISTM PCI Optimization Systems throughout the study. The intravascular imaging system used for IVUS must be capable of operation at 40–60 MHz throughout the study (60 MHz is recommended).

Medication strategy

The experimental arm will receive DOAC plus 75 mg of clopidogrel per day or 3.75 mg of prasugrel daily for up to 1 month and DOAC monotherapy thereafter permanently. The conventional treatment arm will receive DOAC plus 75 mg of clopidogrel per day or 3.75 mg of prasugrel per day for up to 12 months and DOAC monotherapy thereafter permanently.

Antiplatelet medication

Subjects must receive DAPT (aspirin plus P2Y₁₂ inhibitor) during the PCI procedure. Dual antiplatelet medication will include a P2Y₁₂ inhibitor (clopidogrel or prasugrel) and aspirin. As to the pre-PCI medication, physicians basically follow the instruction for use (IFU) of each drug. Subjects will receive a loading dose of antiplatelet medication according to the IFU, unless the subject has already taken a loading dose and is continuing antiplatelet medication (75 mg clopidogrel per day or 3.75 mg prasugrel per day or 100 mg aspirin per day). If loading is performed, the following periprocedural loading doses are required: clopidogrel, 300 mg; prasugrel, 20 mg and aspirin, 200 mg. This pre-PCI antiplatelet medication can

Short versus long dual therapy followed by DOAC monotherapy in patients with AF and CAD: the OPTIMA-AF trial

An investigator-initiated, open-label, nationwide, multicenter, prospective, randomized controlled trial

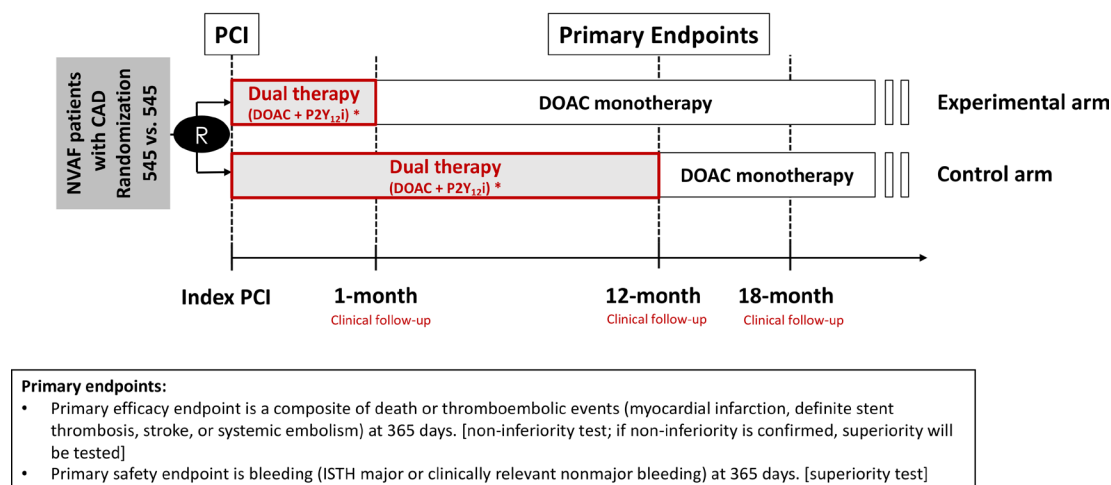


Figure 1 Trial schema. CAD, coronary artery disease; DOAC, direct oral anticoagulant; NVAf, non-valvular atrial fibrillation; PCI, percutaneous coronary intervention. *Add-on aspirin is permitted for up to 1 month in cases where an attending physician considers it more appropriate (e.g. CYP2C19 polymorphism, etc.).

be modified at a physician's discretion if needed. Aspirin will be stopped immediately after the procedure in both arms. Add-on aspirin is permitted for up to 1 month in cases where an attending physician considers it more appropriate (eg, CYP2C19 polymorphism, etc). The antiplatelet medication can be halted for clinical indications if required but must be resumed as soon as possible per physician discretion.

Anticoagulation medication

All subjects will receive DOAC throughout the duration of the clinical investigation. DOACs (dabigatran, rivaroxaban, apixaban or edoxaban) should be prescribed according to the standard hospital practice in terms of dose and timing. During the index procedure, subjects will receive appropriate anticoagulation according to standard hospital practice. For all subjects taking chronic anticoagulation therapy in whom the physician has deemed it appropriate to temporarily halt this therapy, therapy can be stopped per local hospital standard procedures. Vitamin K antagonist (warfarin) should be switched to DOAC according to the standard switch protocol at least 1 week in advance of the index procedure.

Other medication

Subjects will be recommended to adhere to the Japan Circulation Society Guidelines for prevention of cardiovascular disease.¹⁸ The drug prescription data will be collected at baseline and at 1, 12 and 18 months of follow-up.

Study endpoints

The present trial has the following primary efficacy and safety endpoints: (1) primary efficacy endpoint is a composite of death or thromboembolic events

(myocardial infarction,¹⁹ definite stent thrombosis,²⁰ stroke²¹ or systemic embolism) at 365 days and (2) primary safety endpoint is bleeding (International Society on Thrombosis and Haemostasis (ISTH) major or clinically relevant non-major bleeding) at 365 days.²² All primary and secondary endpoints are summarised in [box 2](#).

Clinical follow-up

Subjects will be followed at 1 (-7 days to +14 days), 12 (±28 days) and 18 months (±28 days).

Clinical events committee

Adverse events will be classified by an independent trained committee (clinical event committee: CEC) according to the study protocol. The committee consists of three experienced interventional cardiologists. Two matching votes are needed to finalise the classification. The adjudicating members of the CEC will remain blinded to all treatment assignments throughout the adjudication process and the duration of the trial.

SAMPLE SIZE CALCULATION AND STATISTICAL ANALYSIS

Statistical overview

The OPTIMA-AF RCT is a prospective, randomised, multi-centre clinical investigation. A total of approximately 1090 subjects (545 in the short dual therapy group and 545 in the long dual therapy group) will be randomised at up to approximately 60 sites in Japan. The study is powered based on the non-inferiority test of the primary efficacy endpoint (a composite of death or thromboembolic events) at 1 year.

The following three hypotheses will be tested in the following order: (1) non-inferiority of the primary

Box 2 Study endpoints

Primary endpoint

The present trial has primary efficacy and safety endpoints as follows:

- ▶ Primary efficacy endpoint is a composite of death or thromboembolic events (myocardial infarction,¹⁹ definite stent thrombosis,²⁰ stroke²¹ or systemic embolism) at 365 days.
- ▶ Primary safety endpoint is bleeding (ISTH major or clinically relevant non-major bleeding) at 365 days.²²

Secondary endpoints

In this study, the following secondary endpoints will be evaluated at 1, 12 and 18 months.

Net adverse clinical and cerebrovascular event (a composite of death, thromboembolic events (myocardial infarction, definite stent thrombosis, stroke or systemic embolism) or bleeding (ISTH major or clinically relevant non-major bleeding)).

Bleeding per Bleeding Academic Research Consortium (BARC) criteria³²

- ▶ BARC 2–5.
- ▶ BARC 3–5.
- ▶ All BARC.

Bleeding per Thrombolysis in Myocardial Infarction (TIMI) criteria³³

- ▶ Major.
- ▶ Minor.
- ▶ Minimal.

All individual components of primary endpoints including following clinical endpoints:

Death²⁰

- ▶ All-cause death.
- ▶ Cardiac death.
- ▶ Non-cardiac death.

Myocardial infarction according to the Third Universal Definition¹⁹

- ▶ Q wave myocardial infarction.
- ▶ Non-Q wave myocardial infarction.
- ▶ All myocardial infarction.
- ▶ Target vessel myocardial infarction.
- ▶ Non-target vessel myocardial infarction.

Stent thrombosis per Academic Research Consortium (ARC) definition²⁰

- ▶ Definite, probable and possible.
- ▶ Acute, subacute, late, very late.

Stroke²¹

- ▶ Haemorrhagic stroke.
- ▶ Ischaemic stroke.

Systemic embolisation

Target lesion revascularisation (TLR)²⁰

- ▶ All TLR.
- ▶ Clinically driven TLR.
- ▶ Not clinically driven TLR.

Target vessel revascularisation (TVR)²⁰

- ▶ All TVR.
- ▶ Clinically driven TVR.
- ▶ Not clinically driven TVR.

Non-target vessel revascularisation (NTVR)²⁰

- ▶ All NTVR.
- ▶ Clinically driven NTVR.
- ▶ Not clinically driven NTVR.

All coronary revascularisation²⁰

Definitions of the endpoints are described elsewhere.^{19–22 32 33}

efficacy endpoint. The multiplicity of the three hypotheses testing will be controlled by the fixed sequence procedure: if a statistical test does not reject the null hypothesis, the subsequent tests will not be performed.

Main analysis will be done with the full analysis set according to the principle of intention-to-treat, while sensitivity analyses will be performed with the per-protocol set and safety analysis set.

The sample size is also powered for the primary safety endpoint of bleeding (ISTH major or clinically relevant non-major bleeding) as explained in the sample size calculation below. All statistical analyses will be performed by an independent statistician.

Sample size calculations and assumptions

Approximately 1090 subjects will be randomised in this clinical trial at approximately 60 sites in Japan. Data are to be pooled across all clinical trial/investigation sites for all analyses.

The sample size calculation was driven by the non-inferiority test for the rate of a composite of death or thromboembolic events based on the following.

Assumption:

- ▶ $\alpha=0.05$ (one sided).
- ▶ Power=85%.
- ▶ 1 (short dual therapy): 1 (long dual therapy) randomisation.
- ▶ Incidence of the primary efficacy endpoint (death or thromboembolic event) within 1 year was assumed to be 10% in the control arm (long dual therapy arm).⁴
- ▶ Non-inferiority margin=5%.
- ▶ Attrition rate=5%.

If there is truly no difference between the standard and experimental treatment, then 1036 patients are required to ensure with a power of 85% that the upper limit of a one-sided 95% CI (or equivalently a 90% two-sided CI) of the risk difference for the primary efficacy endpoint will exclude a difference in favour of the standard group of more than 5%. Considering the attrition rate of 5%, a total of 1090 patients will be required.

In terms of the statistical power of the test for the second hypothesis, conducted by the Fisher's exact test, the sample size of 1036 patients in total has a statistical power of 99.2% with a two-sided alpha of 0.10 based on the following event rate assumptions^{4 23}: (1) incidence of the primary safety endpoint in the control arm is assumed to be 25% and (2) incidence of the primary safety endpoint in the experimental arm is assumed to be 15%.

Survival analyses

The efficacy and safety endpoints will be assessed from the last procedure. Events in patients with staged procedure will be assessed from the staged procedure. In addition to the evaluation of probabilities at 1, 12 and 18 months since randomisation, time to incidence of each endpoint will be evaluated. Survival analysis techniques will be used to analyse the time-to-event variables (primary endpoints and all individual components of the primary

efficacy endpoint (composite of death or thromboembolic events), (2) superiority of the primary safety endpoint (bleeding) and (3) superiority of the primary

and secondary endpoints). Subjects without events will be censored at their last known event-free time point. Cumulative event curves will be constructed using Kaplan-Meier estimates. Event rates (Kaplan-Meier estimates), HRs (using Cox proportional hazards regression), CI for the HR and p value (Log-rank test) will be presented. Landmark analysis at 1 month and 1 year will be performed.

Predefined subgroup analysis

Comparisons will be made between treatment arms within each of the following subgroups: imaging analysis (OCT and IVUS), type of DOAC (dabigatran, rivaroxaban, apixaban or edoxaban), dose of DOAC, use of proton pump inhibitor, type of AF, renal dysfunction (estimated glomerular filtration rate <60 mL/min/1.73 m²), diabetes mellitus, gender (female), small vessel (<2.5 mm), elderly patients (≥ 75 years), DAPT score/PRECISE-DAPT score (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy), HAS-BLED score (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly)/ORBIT score (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) and complex PCI.²⁴

Monitoring

To secure adequate study performance, monitoring of study progress or observance of the study protocol shall be performed. Central monitoring shall be continuously performed with the database on the internet with regards to the progress of the study. Additionally, if needed, on-site monitoring, including checking of consent forms and direct inspection of clinical records or original sources, shall be performed for selected participating facilities. Monitoring personnel shall prepare a report per monitoring and submit it to the principal investigator.

Data on monitoring will be appropriately retained by the research office of this study.

Research discontinuation and completion

In principle, this research will continue until the target patient sample size is fully enrolled and evaluation of all patients is finished. The estimated date of patient enrolment completion is the end of 2023. If, however, any serious research-related adverse event occurs, the independent Certified Review Board will discuss the continuation or discontinuation of the research.

Patient and public involvement

We will not involve patients or the public in the development, design, conduct or reporting of the study.

Ethics and dissemination

The study is registered at the Japan Registry of Clinical Trials. The study is being conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies issued by the Ministry of Health, Labour and Welfare, Japan. This study received approval from the

Certified Review Board of Osaka University (a certified research ethics committee by the Japanese Clinical Research Act). All participants will provide written informed consent and may withdraw their consent at any time.

We will present analysed data at domestic and international medical conferences and will publish them as scientific papers in peer-reviewed journals.

DISCUSSION

Over the past four decades, antiplatelet therapy after PCI has become an essential medication. Prevention of stent thrombosis is one of the ultimate goals of interventional cardiologists. In order to overcome this adverse event, stent technology, stent implantation techniques and antiplatelet drugs have been evolving rapidly.²⁵ Nevertheless, patients with AF undergoing PCI were one of the excluded cohorts from previous RCTs.

The STARS trial showed that the DAPT provides superior suppression of stent thrombosis compared with anticoagulation therapy in patients with coronary artery disease undergoing PCI.²⁶ In contrast, the ACTIVE W trial (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events W) demonstrated that oral anticoagulant therapy rather than DAPT (clopidogrel and aspirin) is a better approach to preventing stroke in patients with AF.²⁷ Based on these findings, the standard regimen for patients with AF undergoing PCI has long been ‘triple therapy’ (addition of dual antiplatelet agents to vitamin K antagonists). Nevertheless, patients continued to suffer from bleeding events for more than a decade. The triple therapy was called into question by the WOEST trial, the first trial in which patients undergoing PCI on oral anticoagulation with vitamin K antagonists were randomised to either clopidogrel plus aspirin or clopidogrel without aspirin.²⁸ The study caused a substantial paradigm shift, namely, that aspirin can be eliminated from the regimen. At the time of initial planning of the present study, only the RE-DUAL PCI (dabigatran) and PIONEER AF PCI (rivaroxaban) studies were available, which were then followed by the AUGUSTUS (apixaban) and ENTRUST-AF PCI (edoxaban) studies.⁴⁻⁷ These trials and their meta-analysis confirmed the safety and efficacy of dual therapy (P2Y₁₂ inhibitor and all four types of DOAC) for patients with AF undergoing PCI.²⁹ The event rates (death or thromboembolic events) ranged from 6.5% to 14.3% among the four studies, although slightly different definitions of the endpoints. We estimated the adverse event rate based on the data from the RE-DUAL PCI (approximately 10%) for the sample size calculation. This assumption is the middle of the range and seems reasonable.

The current guidelines recommend the maintenance of dual therapy for 12 months after PCI.^{1-3 24 30} However, the combination of antiplatelets and DOAC may increase the frequency of bleeding events. In a real-world Asian study, the event rate of ISTH major bleeding and clinically relevant non-major bleeding was 1.42-fold higher in patients with dual

or triple therapy of DOAC plus antiplatelets than in those with DOAC monotherapy.¹⁰ Short dual therapy would be, therefore, preferable if its safety and efficacy are confirmed. The STOPDAPT-2 trial confirmed the safety and efficacy of a 1-month DAPT strategy in non-AF Japanese patients undergoing imaging-guided PCI with the Xience stent.^{13 16} The AFIRE trial demonstrated the superiority of rivaroxaban monotherapy over dual therapy in the late phase.¹⁵ These results—both from Japanese cohorts—provide a green light justification to conduct a short dual therapy trial. Racial difference and geographical variety in PCI strategy, especially the substantially high rate of imaging-guided PCI in Japan compared with those in the United States and Europe, will impair the external validity of the findings of the present study. The relatively large non-inferiority margin would also be of concern. The risk for the so-called ‘bio-creep’ with this margin may be considerable. This study might not be perfect as a confirmatory trial but has an exploratory aspect as a first trial to evaluate the ultrashort dual therapy in patients with AF undergoing PCI. The trial will show actual incidence rates of the events with CIs under this specific condition, which will also be the basis for future studies. The OPTIMA-AF trial will provide essential evidence to guide the selection of an optimal antithrombotic strategy for this challenging group of patients.

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Contributors All authors made substantial contributions to the conception or design of the work. YSo, KKo, KKa, YH and YSa drafted the work and revised it critically for important intellectual content. KA, YM, JA, KT, TM, GN and SH revised it critically for important intellectual content. All authors approved the final version of the manuscript to be published. All authors made agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interests YSo reports an institutional grant from Takeda and personal fees from Abbott Medical Japan LLC. KKo reports personal fees from Abbott Medical Japan LLC, Boehringer Ingelheim, Bayer, Daiichi-Sankyo, and Sanofi. YMo reports personal fees from Abbott Medical Japan LLC, Boehringer Ingelheim, Bayer,

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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