OPEN ACCESS Freely available online

Journal of Clinical Trials

Research Article

Design and Rational for a Prospective Randomized Study of Safety Outcomes Treated with Edoxaban in Patients with Stable Coronary Artery Disease and Atrial Fibrillation (PRAEDO AF Study)

Daisuke Fukamachi[1], Yasuo Okumura[1]*, Naoya Matsumoto[1], Eizo Tachibana[2], Koji Oiwa[3], Makoto Ichikawa[4], Kazumiki Nomoto[5], Hironori Haruta[6], Ken Arima[7], Atsushi Hirayama[8]

[1]Department of Cardiology, Nihon University Hospital, Tokyo, Japan; [2]Department of Cardiology, Kawaguchi Municipal Medical Center, Saitama, Japan; [3]Department of Cardiology, Yokohama Chuo Hospital, Kanagawa, Japan; [4]Department of Cardiology, Sekishindo Hospital, Saitama, Japan; [5]Department of Cardiology, TMG Asaka Hospital, Saitama, Japan; [6]Department of Cardiology, Tokyo Rinkai Hospital, Tokyo, Japan; [7]Department of Cardiology, Kasukabe Municipal Hospital, Saitama, Japan; [8]Department of Cardiology, Osaka Police Hospital, Japan

ABSTRACT

Background: In non-valvular atrial fibrillation (NVAF) patients with coronary artery disease (CAD), using antiplatelet drugs in addition to anticoagulants for stroke prevention may further increase the bleeding risk. Several guidelines have recommended an oral anticoagulant (OAC) monotherapy in patients with stable CAD one year after percutaneous coronary intervention (PCI). When considering early neointima healing of current 3rd generation drug-eluting stents (DESs), the duration of the de-escalation from a single antiplatelet drug plus an OAC to an OAC alone therapy can be shortened by less than one year after PCI. The data on the clinical acceptability of short durations for de-escalation to an edoxaban monotherapy in those patients are still lacking.

Methods: A multicenter, prospective, randomized, open-label, parallel group study has been established to investigate the safety outcomes of an edoxaban monotherapy in NVAF patients with stable CAD for over at least 6 months after PCI (PRAEDO AF study). From 7 institutions in Japan, approximately 200 participants will be randomized to receive either edoxaban monotherapy or edoxaban plus clopidogrel. All patients will be followed-up at least 1 year after enrollment. The primary endpoint is the percentage of serious bleeding complications and clinically significant bleeding combined events according to the ISTH criteria for edoxaban alone and edoxaban plus an antiplatelet agent.

Conclusion: This will be the first study to assess the safety of edoxaban monotherapy in NVAF patients with stable CAD over 6 months after the 3rd generation DES and over 12 months after 1st or 2nd DES implantations.

Keywords: Atrial fibrillation; Anticoagulants; Edoxaban; Trial protocol

INTRODUCTION

Dual antiplatelet therapy (DAPT) has been conventionally prescribed in the acute phase after implanting a drug eluting stent (DES) in patients with coronary artery disease (CAD) to prevent recurrence of stent thromboses and cardiovascular events. In nonvaluvular atrial fibrillation (NVAF) patients with CAD, it is problematic because the use of DAPT in addition to anticoagulants (eg. triple therapy) for stroke prevention may further increase the risk of bleeding [1] In the WOEST trial (the What is the Optimal antiplatElet anBanticoagulant therapy in patients with oral anticoagulation anB coronary StenTing study) [2,3] the bleeding complications after percutaneous coronary intervention (PCI) in a triple therapy with a vitamin K antagonist (VKA) were significantly higher than in a dual

Correspondence to: Yasuo Okumura, Department of Cardiology, Nihon University Itabashi Hospital, Tokyo, Japan, E-mail: okumura.yasuo@nihon-u.ac.jp

Received date: March 10, 2020; **Accepted date:** March 24, 2020; **Published date:** March 31, 2020

Citation: Fukamachi D, Okumura Y, Matsumoto N, Tachibana E, Oiwa k, Ichikawa M, et al. (2020) Design and Rational for a Prospective Randomized Study of Safety Outcomes Treated with Edoxaban in Patients with Stable Coronary Artery Disease and Atrial Fibrillation (PRAEDO AF Study). J Clin Trials 10:405. doi: 10.35248/2167-0870.20.10.405

therapy with a VKA and single antiplatelet drug (SAPT), and importantly, cardiovascular events were also more prevalent than in the dual therapy. Recently, [4] randomized control trials (RCTs) that compared the efficacy and safety of a dual therapy with any of the [4] DOACs (including dabigatran, rivaroxaban, apixaban, and edoxaban) and SAPT with a triple therapy with a VKA in patients with NVAF and CAD immediately after the PCI were sequentially conducted. The PIONEER PCI, [3] RE-DUAL PCI, [4] AUGUSTUS, [5] and ENTRUST trials [6] all showed consistent bleeding risk reduction results during ≤ 1 year and an equivalent ischemic risk with a dual therapy as that with a triple therapy. Growing that clinical evidence in this era has led to a significant trend in the recent European, American, and Japanese guidelines for PCI patients with AF [7-10]. In brief, those guidelines typically recommended that a triple therapy should de-escalated to a dual therapy at less within 1 month after stenting, [7-10] but in cases with a high thromboembolic risk, the duration of the triple therapy is considered to be prolonged from 3 months to 6 months [7-10]. Regarding the use of OACs for a combination therapy, the DOACs were preferable to warfarin or VKAs [8-10].

Regarding the antithrombic therapy in AF with stable CAD patients, a Danish registered observational study showed no significant differences in the risk of an infarction between a VKA monotherapy and a dual therapy with a VKA and SAPT.10 In contrast, the combination of a VKA and aspirin increased the bleeding complications by 1.50-fold, and a combination of a VKA and thienopyridine, increased the bleeding complications by 1.84-fold as compared to a VKA alone.10 Based on these results from the observational study, the recent European, American, and Japanese guidelines for PCI patients with AF generally recommend an OAC monotherapy in NVAF patients with stable CAD 1 year after the PCI [7-11]. Those guidelines are recently supported by the results of two RCTs from Japan. The OAC ALONE trial [12] was the first prospective, multicenter, open-label, noninferiority trial comparing an OAC alone (most of OACs were warfarin) to a combined OAC and SAPT among patients with AF beyond 1 year after stenting in a 1:1 randomization fashion. Although the patient enrollment was prematurely terminated and the study was underpowered, this randomized trial found the noninferiority of an OAC alone to a combined OAC and SAPT in terms of a primary composite of all-cause death, myocardial infarction, strokes, or systemic embolisms. The Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease (AFIRE) study [13] showed that a rivaroxaban monotherapy was noninferior to a dual therapy for the efficacy and superior safety in patients with NVAF and stable CAD. A sub-analysis of Engage AF TIMI-48 showed a lower MI incidence rate in edoxaban than in warfarin, [14] which implicates that edoxaban may be useful in patients with NVAF and stable CAD. Edoxaban has been widely used in Japanese NVAF patients, however, there are no data regarding the efficacy and safety of an edoxaban monotherapy in patients with NVAF and stable CAD.

On the other hand, the stent technology has also advanced rapidly in recent years. Persistent polymer stents have been designed to solve the long-term safety (very late stent thromboses) and efficacy issues of the 1st-generation and 2nd-generation drug-eluting stents (DESs). A 3rd generation DES has been developed to promote early and rapid healing of the neointima, which was supported by the fact that the polymer has been absorbed within four months [15]. This indicates that, theoretically, a shorter duration of de-escalation from a dual therapy to an OAC monotherapy may become a better option to reduce the bleeding risk while preventing stent thromboses. To clarity any unresolved issues, we established an RCT, which we refer to as the PRAEDO study (Prospective RAndomized study of safety outcomes treated with EDOxaban in patients with stable coronary artery disease and atrial fibrillation) to examine the efficacy and safety of an edoxaban monotherapy in NVAF patients with stable CAD over 6 months after the 3rd generation DES and one year after the 1st or 2nd generation DES implantations.

METHODS

Study design and setting

The PRAEDO AF study is a multicenter, prospective, randomized, open-label, parallel group study being conducted within Japan from 30 March 2018 to 30 June 2021. Seven hospitals will be participated in this study. The enrollment period is from 30 March 2018 to 30 June 2020, and all patients will be followed-up at least 1 year (Final follow-up ended at 30 June 2021).

Eligibility criteria

This study will enroll eligible patients if, 1) they are patients with NVAF and stable CAD, 2) they have a CHADS2 score ≥ 1 (Heart failure, hypertension, 75 years old or older, diabetes, 1 point each: cerebral infarction / TIA, 2 points), 3) they are 20 years or older, and 4) written consent obtained. Stable CAD is defined as follows: 1) it has been stable for more than 6 months after a PCI including Plain OlB Balloon Angioplasty (POBA), but a 3rd generation DES may be acceptable if the patient has participated from 6 to 12 months after the PCI, 2) coronary CT or coronary angiography (CAG) that does not require a PCI with a stenotic lesion (stenotic lesion of more than 50%), and 3) are stable 6 months after a coronary artery bypass graft (CABG). Patients not eligible for enrollment are 1) patients who are contraindicated for edoxaban administration, 2) those who have a contraindication to clopidogrel, 3) those scheduled for revascularization, 4) those planning to undergo open surgery (excluding gastrointestinal endoscopy and biopsy), 5) those with an active tumor and uncontrolled hypertension (clinic systolic pressure 160 mmHg or more), and 6) those who are judged inappropriate by the research director or research coordinator as subjects of this study.

Interventions

We will explain the contents of the study to patients and obtain written consent to participate in the study and make sure that the case meets the registration criteria and does not violate the exclusion criteria, and then register the case (assign a study subject identification code). After the case registration, the patients will be randomly assigned to edoxaban alone or

edoxaban / antiplatelet alone in a 1: 1 ratio according to the allocation table. The antiplatelet drug in the edoxaban / antiplatelet drug combination group will be the thienopyridine antiplatelet drug (Plavix). Sixty mg of edoxaban will be administered orally once a day. The dose may be reduced to 30mg once a day in patients with a CrCl of 15–50 mL/min or body weight of <60 kg.

Data collection

The following baseline information will be obtained from each patient record at the time of enrollment: the date when edoxaban was started and the dosage; type of stent (1st DES [Cypher® and TAXUS®], 2nd DES [PROMUS®, XIENCE®, and Endeavor®], or 3rd DES [SYNERGY®, Orsiro® and Ultimaster®]); the site of the stent implantation; patient characteristics, including the age and sex, body weight and height, systolic/diastolic blood pressure, heart rate, CHADS score, type of AF (paroxysmal AF, persistent AF, or long-lasting AF); medication(s) currently used (any antiplatelet agents, nonsteroidal anti-inflammatory drugs, anti-arrhythmia agents, anti-ulcer agents antihypertensive agents, and/or steroids); comorbidities (hypertension, diabetes, stroke, other vascular disease, congestive heart failure, and peripheral artery disease); current habits including tabaco and alcohol, and a previous history including a previous coronary intervention or CABG, previous surgery, previous malignancy, or any other interventions. Blood samples will be taken at the time of enrollment, six months later, and at the end of the follow-up. The blood sample items will include the blood count, liver function, renal function, and BNP or NT-proBNP levels.

Management of the patient information and follow-up data

A website was created for the PRAEDO study, and it will be 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 after randomization 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 antithrombic drugs, body weight, specific laboratory test results, and medications used are obtained routinely and recorded. If a patient is transferred to another hospital and discontinues or completes the antithrombic drugs during the follow-up period, the information will be collected as long as possible until the follow-up period ends.

Outcomes

The primary endpoint is the percentage of major bleeding and clinically significant bleeding combined events according to the ISTH (International Society on Thrombosis and Haemostasis) criteria for edoxaban alone and edoxaban plus an antiplatelet agent. Major bleeding is clinically apparent bleeding that meets at least one of the following: 1) fatal bleeding, 2) symptomatic bleeding in the retroperitoneum, intracranial, intraocular, intrathecal, intraarticular, pericardial, or intramuscular with compartment syndrome, and 3) a decreased hemoglobin by 2.0 g / dL or more, and clinically obvious bleeding requiring a blood transfusion (bleeding associated with surgical procedures is defined as bleeding that exceeds the amount of bleeding observed during normal surgeries and procedures and if there is no hemoglobin data, a hematocrit level that has decreased by 6.0% or more and a blood transfusion is required). Clinically significant bleeding is a clinically significant bleed that requires treatment, for example, the following tests and treatments: hospitalization or extension of the hospitalization period, laboratory tests, image inspection, endoscopy, colonoscopy, cystoscopy, bronchoscopy, nasal packing, compression bleeding, coil embolization, inotropic therapy, surgery, interruption or discontinuation of anticoagulant administration as instructed by a doctor, change in a concomitant treatment according to the doctor's instructions.

The secondary endpoint is the following incidence rates, which are shown for the edoxaban monotherapy group and edoxaban / antiplatelet drug combination group. 1) Complex myocardial infarctions, stent thromboses, unstable angina pectoris requiring revascularization, 2) a composite endpoint of a stroke, systemic embolism, and cardiovascular death, 3) myocardial infarctions, 4) stent thromboses, 5) unstable angina requiring revascularization, 6) strokes / systemic embolisms, 7) small bleed or major bleed or that not meeting the criteria for a clinically significant bleed, 8) cardiovascular death, and 9) other death.

Sample size and calculation data

This study compared the major treatments with edoxaban alone and conventional treatment with edoxaban and antiplatelets as major endpoints for major bleeding and clinically significant combined bleeding events that do not match major bleeding. In the J-ROCKET study [16] with the rivaroxaban DOAC, bleeding and clinically significant bleeding were 14% (major bleeding 2.5%) with rivaroxaban alone and 20.6% (major bleeding 6.6%) with antiplatelet drugs. A sub-analysis of the ENGAGE-TIMI48 [14] trial reported a total bleeding event rate of 9.72% for an edoxaban monotherapy and 14.93% for edoxaban plus antiplatelet drugs. In addition, previous reports have reported that the risk of an annual major hemorrhagic event associated with warfarin / clopidogrel in combination with a warfarin monotherapy was 1.11 to 3.06 times the hazard ratio [11]. NVAF patients with CAD are considered to have a similar or greater risk of bleeding events, and the estimated major bleeding and clinically significant combined bleeding events are 13% for the edoxaban monotherapy group versus 30% for the edoxaban plus clopidogrel group, respectively. With a power of 80%, the

number of each sample is 90. Considering a 10% deviation, a total of 200 subjects were set for the total study patients (100 per each group).

Randomization

The Principal Investigator or Assigned Researcher attaches the study subject identification code and registers for this study. The researcher fills in and stores the study subject identification code and the treatment group in the study subject identification code list together with the date of consent acquisition according to a random "assignment table" created in advance. If withdrawal, cancellation, or withdrawal of consent occurs, the report shall be immediately reported to the research director through the anonymization director.

Ethics and study oversight

The study is registered at the Japan Registry of Clinical Trials (JRCT). 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 specified clinical trials. All participants will provide written informed consent and may withdraw their consent at any time.

DISCUSSION

This study will be one of the most important studies to clarify the safety of an edoxaban monotherapy compared to edoxaban plus clopidogrel in patients with NVAF and stable CAD. Little data regarding the efficacy and safety of a DOAC monotherapy in patients with NVAF and stable CAD have been reported, although the European, American, and Japanese guidelines have recommended an OAC alone in patients with NVAF and stable CAD [7-10]. Only two RCTs from Japan were conducted, but the OAC ALONE trial [12] was inconclusive because of being under-powered. The AFIRE study [13] showed that rivaroxaban monotherapy was noninferior to a combination therapy for the efficacy and a superior safety in patients with AF and stable CAD as an antithrombotic therapy. Although our trial is smaller, the PRAEDO trial will provide not only important information for the safety, but also clinical insight into the efficacy of an edoxaban monotherapy in those patients. In another aspect, with the rapid advance of the stent technology over the past decade, 3rd generation DESs have been developed and are widely used in Japan. In a large clinical trial, the target lesion revascularization six months after a 3rd DES stenting was comparable to the conventional 2nd generation DES treatment, with no in-stent thromboses, myocardial infarctions, or cardiac death [17]. Third-generation DES stents have enabled a complete endothelialization within 28 days of the implantation in porcine coronary arteries [15]. When considering the process of the 3rd DES stent intima coating, it is possible to de-escalated from a dual therapy to a DOAC monotherapy in a shorter period of time. This study will also give us some answers about the usefulness of an early de-escalation to a DOAC monotherapy.

Study limitations

In this study, only the 3rd generation DESs will be allowed entry in six months. However, the STOPDAPT2 trial [18] was published after this study had been planned, and it is possible to shorten the DAPT period for the XIENCE® by 1 month. Even with the XIENCE®, the possibility of entry in six months after the PCI is also considered, as with the 3rd generation DESs, but it is not permitted. In this study, we used only clopidogrel as an antiplatelet agent. The results of ticagrelor and prasugrel are unclear.

CONCLUSION

This study will provide the evidence for the safety of an edoxaban monotherapy in NVAF patients with stable CAD in whom a 3rd DES was implanted for over 6 months, or a 1st or 2nd DES was implanted for over 12 months after the PCI.

FUNDING SOURCE

This study is funded by Daiichi-Sankyo.

DECLARATION OF INTEREST

The following authors have potential conflicts of interest: Y.O. has received research funding from Bayer Healthcare, Daiichi-Sankyo, Bristol-Meyers Squibb, Nippon Boehringer Ingelheim, Pfizer Japan, TORAY, and Boston Scientific Japan and has accepted remuneration from Bayer Healthcare, Daiichi-Sankyo, and Bristol-Meyers Squibb. A.H has received research funding from Bayer Healthcare, Daiichi-Sankyo, Otsuka Pharmaceutical, Astellas Pharma, Eisai, Sumitomo Dainippon Pharma, MSD, Nihon Medi-Physics, Bristol-Meyers Squibb, Boehringer Ingelheim, Pfizer, Boston Scientific Corporation, Hokushin Medical, and has accepted remuneration from Bayer Healthcare, Daiichi-Sankyo, Eisai, Bristol-Meyers Squibb, Astellas Pharma, Sanofi, and Takeda Pharmaceutical. N.M. has received research funding from Daiichi-Sankyo. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

ACKNOWLEDGMENTS

We thank Mr. John Martin for their encouragement and assistance with the reporting of our findings in English.

REFERENCES

1. Toyoda K, Yasaka M, Iwade K, Nagata K, Koretsune Y. Bleeding with Antithrombotic Therapy (BAT) Study Group. Dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease: A prospective, multicenter, observational study. Stroke. 2008;39:1740–1745.
2. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ. WOEST study investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: An open-label, randomised, controlled trial. Lancet. 2013;381:1107–1015.
3. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt F. An open-label, randomized, controlled, multicenter 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 (PIONEER AF-PCI). Am Heart J. 2015;169:472–478.

4. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG. RE-DUAL PCI Steering Committee and Investigators. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. N Engl J Med. 2017;377:1513–1524.
5. Lopes RD, Aronson R, Vora AN, Massaro T, Mehran R, et al; AUGUSTUS Investigators. Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. N Engl J Med. 2019;380:1509–1524.
6. Vranckx P, Valgimigli M, Eckardt L, Tijssen J, Lewalter T. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): A randomised, open-label, phase 3b trial. Lancet. 2019;394:1335–1343.
7. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F. 2017 esc focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with eacts: The task force for dual antiplatelet therapy in coronary artery disease of the european society of cardiology (esc) and of the european association for cardio – thoracic surgery (eacts). Eur Heart J. 2018;39:213–260.
8. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M. ESC Scientific Document Group. The 2018 european heart rhythm association practical guide on the use of non–vitamin k antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018;39:1330–1393.
9. Angiolillo DJ, Goodman SG, Bhatt DL, Eikelboom JW, Price MJ. Antithrombotic Therapy in Patients With Atrial Fibrillation Treated With Oral Anticoagulation Undergoing Percutaneous Coronary Intervention. A North American Perspective – 2018 Update. Circulation. 2018;138:527–536.
10. JCS 2018 Guideline on Revascularization of Stable Coronary Artery Disease.
11. Lamberts M, Gislason GH, Lip GY, Lassen JF, Olesen JB. Antiplatelet therapy for stable coronary artery disease in atrial fibrillation patients taking an oral anticoagulant: A nationwide cohort study. Circulation. 2014;129:1577–1585.
12. Matsumura-Nakano Y, Shizuta S, Komasa A, Morimoto T, Masuda H. OAC-ALONE Study Investigators Open-Label Randomized Trial Comparing Oral Anticoagulation with and without Single Antiplatelet Therapy in Patients with Atrial Fibrillation and Stable Coronary Artery Disease Beyond 1 Year After Coronary Stent Implantation. Circulation. 2019;139:604–616.
13. Yasuda S, Kaikita K, Akao M, Ako J, Matoba T. AFIRE Investigators. Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease. N Engl J Med. 2019; 381:1103-1113.
14. Xu H, Ruff CT, Giugliano RP, Murphy SA, Nordio F. Concomitant use of single antiplatelet therapy with edoxaban or warfarin in patients with Atrial Fibrillation: Analysis From the ENGAGE AF-TIMI48 Trial. J Am Heart Assoc. 2016;5(2).
15. Wilson GJ, Huibregtse BA, Pennington DE, Dawkins KD. Comparison of the SYNERGY with the PROMUS (XIENCE V) and bare metal and polymer-only Element control stents in porcine coronary arteries. EuroIntervention. 2012;8:250–257.
16. Hori M, Matsumoto M, Tanahashi N, Momomura SI, Uchiyama S. J-ROCKET AF Study Investigators. Predictive factors for bleeding during treatment with rivaroxaban and warfarin in Japanese patients with atrial fibrillation-Subgroup analysis of J-ROCKET AF. J Cardiol. 2016;68:523–528.
17. Kereiakes DJ, Windecker S, Jobe RL, Mehta SR, Sarembock IJ. Clinical Outcomes Following Implantation of Thin-Strut, Bioabsorbable Polymer-Coated, Everolimus-Eluting SYNERGY Stents. Circ Cardiovasc Interv. 2019;12:8152.
18. Watanabe H, Domei T, Morimoto T, Natsuaki M, Shiomi H. STOPDAPT-2 Investigators. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet theray on cardiovascular and bleeding events in patients receiving PCI: The STOPDAPT-2 Randomized Clinical Trial. JAMA. 2019;321:2414–2427.