

# Evaluation of the safety and efficacy of an edoxaban-based antithrombotic regimen in patients with atrial fibrillation following successful percutaneous coronary intervention (PCI) with stent placement: Rationale and design of the ENTRUST-AF PCI trial



Pascal Vanruxx<sup>a</sup> Thorsten Lewalter<sup>b</sup> Marco Valgimigli<sup>c</sup> Jan G. Tijssen<sup>d</sup> Paul-Egbert Reimitz<sup>e</sup> Lars Eckardt<sup>f</sup> Hans-Joachim Lanz<sup>e</sup> Wolfgang Zierhut<sup>e</sup> Rüdiger Smolnik<sup>e</sup> and Andreas Goette<sup>g</sup> Hasselt, Belgium; Munich, Muenster, Magdeburg, Germany; Bern, Switzerland and Amsterdam, the Netherlands

**Background** The optimal antithrombotic treatment after percutaneous coronary intervention (PCI) with stenting in patients with atrial fibrillation (AF) is unknown. In the ENGAGE AF-TIMI 48 trial, edoxaban was noninferior to a vitamin K antagonist (VKA) with respect to the prevention of stroke or systemic embolism and was associated with significantly lower rates of bleeding and cardiovascular death in patients with nonvalvular AF. The effects of edoxaban in combination with single- or dual-antiplatelet therapy in the setting of PCI are unexplored.

**Design** The ENTRUST-AF PCI trial is a multinational, multicenter, randomized, open-label phase 3b trial with blinded end point evaluation involving 1,500 patients on oral anticoagulation for AF. Patients are randomized between 4 hours and 5 days after successful PCI to either an edoxaban-based strategy (experimental arm; 60 mg [or 30 mg according to dose reduction criteria] once daily plus a P2Y<sub>12</sub> antagonist [default clopidogrel, 75 mg once daily] for 12 months) or a VKA-based strategy (control arm; VKA plus a P2Y<sub>12</sub> antagonist [as above] plus acetylsalicylic acid [100 mg once daily] for 30 days to 12 months). The primary safety end point is the incidence of International Society on Thrombosis and Haemostasis–defined major or clinically relevant nonmajor bleeding. The main efficacy end point is the composite of cardiovascular death, stroke, systemic embolic events, spontaneous myocardial infarction, and definite stent thrombosis.

**Summary** The ENTRUST-AF PCI trial tests the hypothesis that an edoxaban-based antithrombotic strategy reduces the risk of bleeding complications after PCI compared with VKA plus conventional dual-antiplatelet therapy in patients with AF in need of oral anticoagulation. The relative risk of ischemic events between groups will be compared. (Am Heart J 2018;196:105-12.)

From the <sup>a</sup>Department of Cardiology and Critical Care Medicine, Hartcentrum Hasselt, Jessa Ziekenhuis, Stadsomvaart 11, 3500 Hasselt, Belgium and Faculty of Medicine and Life Sciences Hasselt University, Hasselt, Belgium, <sup>b</sup>Department of Medicine-Cardiology and Intensive Care, Hospital Munich-Thalkirchen, Peter Osypka Heart Center Munich, Am Isarkanal 36, Munich, Germany, <sup>c</sup>Swiss Cardiovascular Center Bern, Bern University Hospital, Freiburgstrasse 8, Bern, Switzerland, <sup>d</sup>Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands, <sup>e</sup>Daiichi Sankyo Europe GmbH, Zielstattstr. 48, Munich, Germany, <sup>f</sup>Division of Electrophysiology, Department of Cardiology and Angiology, University of Muenster, Muenster, Germany, and <sup>g</sup>St. Vincenz-Hospital, Paderborn, Am Busdorf 2, Paderborn, Nordrhein-Westfalen, 33098, Germany and Working Group: Molecular Electrophysiology, University Hospital Magdeburg, Magdeburg, Germany.

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Reprint requests: Andreas Goette, MD, Chief of Cardiology and Intensive Care Medicine, St. Vincenz-Hospital, Paderborn, Am Busdorf 2, Paderborn, Nordrhein-Westfalen, Germany 33098.

E-mail: [Andreas.Goette@vincenz.de](mailto:Andreas.Goette@vincenz.de)  
0002-8703

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## Background

Up to one-third of patients with atrial fibrillation (AF) have concomitant coronary artery disease (CAD) and may require stent placement to treat symptomatic stable CAD or acute coronary syndromes (ACS).<sup>1</sup> Dual-antiplatelet therapy with aspirin and P2Y<sub>12</sub> antagonist is currently recommended after percutaneous coronary intervention (PCI) with stent placement,<sup>2,3</sup> and further oral anticoagulation is required in 5% to 7% of these patients for AF.<sup>4</sup>

The optimal antithrombotic treatment for patients with AF following coronary stenting has not been well established and is determined empirically rather than by evidence from randomized controlled trials. Therapy with an oral anticoagulant (OAC), aspirin, and clopidogrel

(P2Y<sub>12</sub> inhibitor) is generally considered the standard of care for patients with AF following coronary stent placement.<sup>1-3,5</sup> Consensus recommendations<sup>1,6-8</sup> have endorsed the use of such therapy with the duration of treatment for the individual drugs being guided by the clinical presentation, the bleeding risk, and thrombotic risk (ie, stable coronary disease or ACS) of the patient.<sup>1,6-10</sup> However, triple therapy with OAC, aspirin, and clopidogrel is associated with 3- to 4-fold increased risk of bleeding complications.<sup>11</sup>

The 2016 European Society of Cardiology/European Heart Rhythm Association AF guidelines<sup>12</sup> and the current practical guide for non-vitamin k oral anticoagulant (NOAC) therapy<sup>5</sup> state that “a short period of triple therapy (OAC, aspirin, clopidogrel) is recommended, followed by a period of dual therapy” (OAC plus aspirin 75–100 mg daily or clopidogrel 75 mg daily). The AF guideline recommendation is class IIaB such that it “should be considered” and has “favor of usefulness/efficacy.” The “level of evidence B” was based on the What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary Stenting (WOEST) trial<sup>13</sup> in which 573 anticoagulated patients undergoing PCI (70% with AF) were randomized either to dual therapy with OAC and clopidogrel (75 mg once daily) or to triple therapy with OAC, clopidogrel, and aspirin. Bleeding was lower in the dual- versus triple-therapy arm, driven by fewer events fulfilling the minor but not the major categories. The rates of myocardial infarction (MI), stroke, target vessel revascularization, and stent thrombosis did not differ (albeit with low event numbers). Nevertheless, all-cause mortality was lower in the dual-therapy group at 1 year (2.5% vs triple therapy 6.4%). Although the trial was too small to conclusively evaluate the trade-off for ischemic outcomes, dual therapy with oral anticoagulation and clopidogrel has emerged as an alternative to triple therapy in patients with AF undergoing coronary intervention. Similar to WOEST, larger patient registries including >11,000 patients have also shown that triple therapy increases the risk for bleeding with no benefit on the number of ischemic events.<sup>14</sup>

Risk factors summarized in the CHA<sub>2</sub>DS<sub>2</sub>-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74 years, female sex) score induce persistent thrombogenic alterations of the atrial endocardium.<sup>15</sup> Therefore, chronic oral anticoagulation is recommended in patients with AF at moderate or high risk of thromboembolism.<sup>10,16</sup> Non-vitamin K antagonist oral anticoagulants are an alternative to VKAs to prevent stroke in patients with nonvalvular AF.<sup>5</sup> The recently published 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) trial<sup>17</sup> was the first to study the use of a NOAC as an alternative to VKA for patients with nonvalvular AF who required stent implantation. A 15-mg rivaroxaban dose once daily (plus P2Y<sub>12</sub> inhibitor) and 2.5-mg rivaroxaban dose twice daily (plus P2Y<sub>12</sub> inhibitor and aspirin 75 mg or 100 mg once daily) were associated with a lower risk of clinically significant bleeding than standard triple therapy (16.8%, 18.0%, and 26.7%; hazard ratio [HR] 0.59, 95% CI 0.47-0.76, *P* < .001 and HR 0.63, 95% CI 0.50-0.80, *P* < .001, respectively). However, the trial was grossly underpowered for the protective effect of the 2 rivaroxaban regimens on the risks of stroke or recurrent cardiovascular ischemic events compared with the warfarin-based triple therapy. Although the rates of death from cardiovascular causes, MI, and stroke were similar across study groups, CIs entailed a large degree of uncertainty around the point estimates. Rivaroxaban 15 mg once daily and 2.5 mg twice daily are not approved for stroke prevention in AF (the standard dose is 20 mg once daily).<sup>17</sup> Thus, in PIONEER-AF PCI, the favorable bleeding results under rivaroxaban could be due to the lower doses used.

The Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (RE-DUAL) PCI trial compared the use of regimens of dual-antithrombotic therapy that included dabigatran at 2 different (110 mg twice daily or 150 mg twice daily) but fixed doses with the use of triple-antithrombotic therapy that included warfarin among patients with AF who had undergone PCI.<sup>18</sup> The majority of patients received clopidogrel; only 12% received ticagrelor. In the triple-therapy group, aspirin was discontinued after 1 month in patients in whom a bare-metal stent was implanted and after 3 months in patients in whom a drug-eluting stent was implanted. The incidence of International Society of Thrombosis and Haemostasis ISTH major or clinically relevant nonmajor bleeding was 15.4% in the 110-mg dual-therapy group as compared with 26.9% in the triple-therapy group (HR 0.52, 95% CI 0.42-0.63, *P* < .001 for noninferiority, *P* < .001 for superiority) and 20.2% in the 150-mg dual-therapy group as compared with 25.7% in the corresponding triple-therapy group, which did not include elderly patients outside the United States (HR 0.72, 95% CI 0.58-0.88, *P* < .001 for noninferiority). RE-DUAL PCI failed to show superiority of dabigatran 150 mg dual therapy to warfarin triple therapy for the primary bleeding end point. The rates of death, MI, stroke, or unplanned revascularization were similar for the 3 groups (110 mg twice daily, 150 mg twice daily, triple therapy with warfarin) (Kaplan-Meier estimates 15.2%, 11.8%, and

13.4%, respectively; *P* values for all comparisons were not significant), although the observed broad CIs diminish the surety of any conclusions regarding efficacy. The incidence of thrombotic events or death in the dabigatran 110-mg group (11.0%) as compared with the triple-therapy group with warfarin (8.5%) raises concerns (HR 1.30, 95% CI 0.98-1.73, *P* < .07).<sup>18</sup>

The oral factor Xa inhibitor edoxaban has been proven a safer and at least similarly efficacious alternative to warfarin and enoxaparin-warfarin in recent prospective randomized trials.<sup>19,20</sup> In the phase 3 ENGAGE AF-TIMI 48 trial, edoxaban (60 mg or dose-adjusted 30 mg once daily) was noninferior to warfarin with respect to the prevention of stroke or systemic embolism and was associated with significantly lower rates of bleeding and death from cardiovascular causes in patients with nonvalvular AF.

Moreover, the combination of edoxaban with a P2Y<sub>12</sub> inhibitor represents an emerging area of clinical interest, as it has the potential to reduce the risk of bleeding while preserving protection from ischemic events. Bleeding is a central safety outcome in cardiovascular clinical trials, especially for antithrombotic strategies and invasive procedures.<sup>21,22</sup>

Hereafter, we describe the design of the Edoxaban Treatment versus US VKA in patients with AF undergoing PCI (ENTRUST-AF PCI) trial (NCT02866175). The ENTRUST-AF PCI trial is designed to evaluate the safety and accrue exploratory information on the efficacy of an edoxaban-based antithrombotic regimen compared with a VKA-based antithrombotic regimen in patients with AF following successful PCI with stent implantation.

## Methods

### Primary study objective

The primary objective of the ENTRUST-AF PCI trial is to compare the incidence of major or clinically relevant nonmajor ISTH-defined bleeding<sup>22</sup> (MCRB) over a 12-month period of an edoxaban-based antithrombotic regimen including a P2Y<sub>12</sub> antagonist against a VKA-based regimen consisting of a P2Y<sub>12</sub> antagonist and acetylsalicylic acid (ASA) for 1 month or more in AF PCI patients. For both study groups, the default P2Y<sub>12</sub> antagonist choice is clopidogrel, whereas prasugrel or ticagrelor are allowed if justified clinically.

Two hypotheses are tested in a hierarchical manner, noninferiority followed by superiority to control the type I error rate, with adequate power for each of the 2 hypotheses.

### Study design

The ENTRUST-AF PCI trial is a multinational, multicenter, randomized, open-label, phase-3b study with blinded evaluation of end points by an independent Clinical Event

Committee (PROBE design). An independent Data and Safety Monitoring Board (DSMB) is responsible for monitoring safety during the study.

The study is divided into a screening period, a planned treatment period, and an observational posttreatment follow-up period (Figure). The screening period begins after a successful PCI procedure with stent placement.

### Study population

It is planned to enroll 1,500 patients (750 per antithrombotic regimen) in approximately 150 study sites in Europe and Asia.

The inclusion criteria for ENTRUST-AF PCI listed in Table I should allow enrollment of a representative sample of post-PCI patients with indication for chronic OAC for nonvalvular AF for a period of at least 12 months following successful PCI with stenting. Nonvalvular AF could be paroxysmal, persistent, or permanent but not secondary to a reversible disorder (eg, MI, pulmonary embolism, recent surgery, pericarditis, or thyrotoxicosis). Patients with mechanical heart valves, moderate to severe mitral stenosis, end-stage renal disease (creatinine clearance [CrCl] <15 mL/min), and other major comorbidities are excluded. For a full list of the exclusion criteria, please see Supplementary Table I.

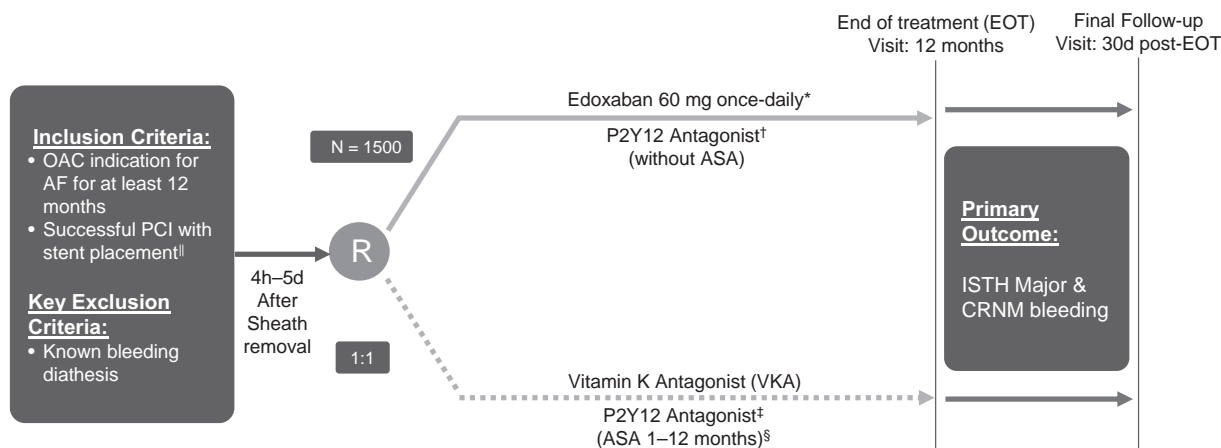
The study is being conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation guidelines on Good Clinical Practice (ICH E6), and applicable regulatory requirements. The final study protocol and informed consent form have been reviewed and approved by the ethics boards/institutional review boards and corresponding health authorities for all participating study sites.

### Randomization and treatment

Once written informed consent is obtained, randomization takes place within 4 hours and 5 days post-PCI and before hospital discharge. If a staged PCI is planned, consenting and randomization take place after successful completion of the last stage. Patients are randomly assigned, in a 1:1 ratio, to receive either VKA (control group) or edoxaban 60 mg (or 30 mg dose adjusted) once daily (experimental group) according to the licensed edoxaban dose for patients with nonvalvular AF. Randomization is performed with the use of a central, 24-hour, interactive Web response system and stratified according to geographic region (Asia, Eastern Europe, Western Europe), clinical presentation (ACS or stable coronary disease), and presence of edoxaban dose reduction criteria.

The edoxaban-based regimen consists of edoxaban 60 mg (or 30 mg dose adjusted) once daily and clopidogrel bisulfate 75 mg once daily (or, in the presence of a documented clinical need, prasugrel [5 or 10 mg once daily] or ticagrelor [90 mg twice daily]) for 12 months. As

## Figure



Study design of the ENTRUST-AF PCI trial. \*Edoxaban dose adjustment to 30 mg once daily if CrCl  $\leq 50$  mL/min, body weight  $\leq 60$  kg, or concomitant therapy with certain P-glycoprotein inhibitors. †Clopidogrel 75 mg once daily (or in the presence of a documented clinical need, prasugrel [5 or 10 mg once daily]/ticagrelor [90 mg twice daily] may be used.) ‡VKA of choice with dosing for target INR of 2.0–3.0 inclusive. §ASA (100 mg once daily) for 1–12 months guided by the clinical presentation (ACS or stable coronary disease) and the CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED score. ||Goal of at least 25% ACS.CRNM, clinically relevant nonmajor.

**Table I.** Inclusion criteria

OAC indication for AF for a period of at least 12 m following successful PCI with stenting.

Successful PCI is defined by 2 interrelated components: angiographic findings and procedural/clinical outcomes, as detailed below:

(a) Angiographic success (minimum stenosis diameter of  $<20\%$  residual blockage or stenosis of the artery's diameter; sufficient enlargement of the lumen at the target site to improve coronary artery blood flow with final Thrombolysis in Myocardial Infarction flow grade 3 without occlusion of a significant side branch, flow-limiting dissection, distal embolization, or angiographic thrombus).

(b) Procedural success (no major in-hospital clinical complications [eg, ongoing ISTH major or clinical relevant nonmajor procedural bleeding at the time of randomization, stroke, emergency CABG]).

per current label, edoxaban 30 mg instead of 60 mg once daily is to be used if any of the following characteristics apply: moderate or severe renal impairment (calculated CrCl 15–50 mL/min), low body weight of  $\leq 60$  kg (132 lb), or concurrent use of certain potent P-glycoprotein inhibitors (such as cyclosporine, dronedarone, erythromycin, or ketoconazole but not quinidine, verapamil, or amiodarone).

The VKA-based regimen, dose-adjusted to achieve an international normalized ratio (INR) between 2.0 and 3.0 inclusive, consists of a VKA in combination with clopidogrel bisulfate 75 mg once daily (or in the presence of a documented clinical need, prasugrel [5 or 10 mg once daily] or ticagrelor [90 mg twice daily]) for 12 months and ASA (100 mg once daily) for a minimum of 1 month and up to 12 months' duration at the investigators' discretion. In the control group, INR management is according to the standard of care and may be performed by the investigator, the patient's primary care physician, or other private physicians at a specialized anticoagulation clinic or patient self-monitoring. The duration of the

ASA treatment in the VKA-based regimen is predeclared by the investigator prior to randomization and should be guided by the clinical presentation (ACS or stable coronary disease) as well as the risk of bleeding (eg, HAS-BLED [hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol] score). The investigators are encouraged to follow the applicable regional clinical guidelines.<sup>1,12</sup>

The transition to edoxaban in the experimental group and to VKA in the control group is detailed in Table II.

The assigned regimen is implemented after randomization without any undue delay, and the randomized regimens (edoxaban based or VKA based) and clopidogrel (or another P2Y<sub>12</sub> antagonist if clinically justified) are continued for 12 months until the scheduled end of treatment (EOT) is reached. The use of gastric protection drugs that do not interact with cytochrome P450 2C19 (such as pantoprazole) is strongly recommended.

At the end of the trial, patients in the edoxaban group can transition to VKA and will receive both edoxaban 30

**Table II.** Transitioning to edoxaban at randomization

Switching to edoxaban		
From	To	Recommendation
VKA	Edoxaban	Discontinue the VKA and start edoxaban when INR is $\leq 2.5$
Other non-VKA OAC drugs	Edoxaban	Discontinue the OAC and start edoxaban at the time of the next OAC dose
<ul style="list-style-type: none"> <li>• Dabigatran</li> <li>• Rivaroxaban</li> <li>• Apixaban</li> </ul>		
Parenteral anticoagulants	Edoxaban	These agents should not be administered simultaneously. Subcutaneous anticoagulant (ie, LMWH, fondaparinux): Discontinue subcutaneous anticoagulant and start edoxaban at the time of the next scheduled subcutaneous anticoagulant dose. Intravenous unfractionated heparin: Discontinue the infusion and start edoxaban 4 h later.

LMWH, low-molecular weight heparin.

**Table III.** Secondary and exploratory study end points

1. *Main efficacy end point*, defined as the composite of CVD, stroke, SEE, spontaneous MI, and definite stent thrombosis (as per ARC consensus definitions)
2. *Net clinical benefit*, defined as the composite of CVD, stroke, SEE, spontaneous MI, definite stent thrombosis, and ISTH-defined major bleeding
3. *Main thromboembolic event*, defined as composite of cardiac or thromboembolic death, ischemic stroke, SEE, spontaneous MI, and definite stent thrombosis.
4. Composite of all-cause death, stroke, SEE, spontaneous MI, and definite stent thrombosis
5. Composite of CVD, spontaneous MI, and definite stent thrombosis
6. The single components of the composite primary and secondary end points mentioned above are explored, as well as specific subcategories (eg, hemorrhagic, ischemic, and undetermined stroke)
7. Composite of CV death and fatal bleedings
8. ISTH-defined major bleeding
9. ISTH- defined clinically relevant nonmajor bleeding
10. Any bleeding defined as the composite of major, clinically relevant nonmajor, and minor bleeding (ISTH definition)
11. Symptomatic intracranial hemorrhage
12. Composite of stroke and SEE
13. Transient ischemic attack
14. Systemic embolism
15. Pulmonary embolism
16. Safety parameters such as (serious) adverse events, laboratory parameters, ECG, and vital signs.

SEE, systemic embolic event; ARC, Academic Research Consortium; ECG, electrocardiogram.

mg once daily (15 mg for patients qualifying for dose adjustment at randomization) and a VKA until an INR of 2.0 is reached. This transition scheme has been previously described in detail.<sup>20</sup>

All randomized patients are followed until 12 months after randomization irrespective of possible deviations from the assigned treatment, and every effort is made to complete the clinical follow-up. For this purpose, on-site visits can be replaced by telephone contacts at the patient's request, and clinical follow-up information is collected from hospital records and national death registries unless explicitly forbidden by patient. Per protocol, on-site visits are planned at 1, 3, 6, 9, and 12 months after randomization. Telephone assessments are planned at 2, 4, 5, 7, 8, 10, and 11 months after randomization. All randomized patients have a contact planned 1 month after the EOT visit; therefore, the overall

duration of patient participation is approximately 13 months.

### Study end points

The primary end point is the composite of MCRB defined according to the ISTH-defined bleeding scale. The secondary and exploratory end points are listed in Table III. All primary and secondary end points are analyzed as time to first occurrence of the end point or—in case of a composite end point—as time to first occurrence of any of its components. Bleeding events are also classified according to Bleeding Academic Research Consortium<sup>21</sup> and Thrombolysis In Myocardial Infarction<sup>23,24</sup> classifications for descriptive purposes only.

All suspected end points are blindly adjudicated by an independent Clinical Events Committee. End point

definitions for the efficacy and safety metrics are described in Supplementary Table II.

## Study statistics

### Analysis sets and data scopes

Patients are categorized according to the group to which they were assigned by the randomization process. The *intention-to-treat (ITT) analysis* set consists of all randomized patients irrespective of whether they received a single dose of the randomized study regimen or not. The *safety analysis set* (modified intention-to-treat [mITT]) consists of all randomized patients who receive at least 1 dose of study edoxaban or study VKA. The per-protocol set consists of all randomized patients who receive at least 1 dose of the study regimen and do not have any major protocol violation (eg, violation of inclusion/exclusion criteria deemed to have a significant potential impact on study results, no successful PCI with stent placement, any intake of study medication other than what the subject was randomized to). All analyses will be performed on observed data only. No missing data will be imputed. Data on patients who do not reach a specific end point will be censored in the corresponding statistical analyses.

For the analysis of adjudicated end points, the following analysis time periods are defined: (1) *Overall study period* is defined as the time from the reference date (date and time of randomization or date and time of first study edoxaban or study VKA intake) to date of EOT/month 12 visit. (2) *Overall study period + 30 days* is defined as the time from the reference date (date and time of randomization or date and time of first study edoxaban or study VKA intake) to date of EOT/month 12 visit + 30 days. (3) *Initial dose to final dose + 30 days* is defined as the time period between the date and time of initial dose of study edoxaban or study VKA and the date and time of final dose of study edoxaban or study VKA plus 30 days, including study regimen interruptions.

### Analysis of the primary end point

The confirmatory analysis of the primary end point (MCRB) is based on the “overall study period” using the ITT analysis set. There are 2 primary hypotheses for bleeding to be tested in this study: (1) the edoxaban-based antithrombotic regimen is noninferior to the VKA-based antithrombotic regimen with regards to MCRB, and (2) the edoxaban-based antithrombotic regimen is superior to the VKA-based antithrombotic regimen with regard to MCRB. The time from date of randomization to the first (adjudicated) event of major or clinically relevant nonmajor bleeding will be analyzed using a Cox proportional hazard model including treatment regimen and the 3 stratification factors as covariates. The HR (edoxaban regimen vs VKA regimen),

*P* values, and the corresponding 95% CI will be estimated from the model. The test for superiority is hierarchically preceded by a test for noninferiority to control the type I error rate, with adequate power for each of the 2 hypotheses. Noninferiority will be concluded if the upper boundary of the 95% CI falls below 1.20, whereas superiority will be concluded when the upper boundary of the 95% CI falls below 1.00. To evaluate the robustness of the primary analysis, the analysis will be repeated using the mITT and per-protocol analysis set. In addition, the statistical results based on the following analysis periods, “initial dose to final dose plus 30 days” and “overall study period plus 30 days,” will be presented using descriptive statistics. Results for other combinations of analysis sets and analysis periods may be presented if considered necessary.

### Analysis of the secondary end points

The main analysis for all secondary end points will be based on first occurrence of an (adjudicated) end point during the “overall study period” for all subjects belonging to the ITT analysis set and applying the aforementioned statistical method. There will be no formal statistical testing for secondary end points. HRs, CI, and *P* values will be provided but should be interpreted in a purely descriptive manner. To be considered clinically meaningful, any observed between-group differences need to be sufficiently large.

### Determination of sample size

The sample size determination for the study was driven by requirements for testing superiority of the edoxaban-based regimen over the VKA-based regimen as described above.

The expected 1-year event rate of the primary end point (MCRB; ie, ISTH major or clinically relevant nonmajor bleeding) under the VKA-based antithrombotic regimen is 24%.<sup>11,16</sup> The edoxaban-based antithrombotic regimen is anticipated to reduce the 1-year incidence to 18% (a relative risk of 0.75). Under the assumption of an exponential distribution, the HR equals 0.7231. The accrual of 2 × 712 evaluable patients is anticipated to provide an 80% power to demonstrate superiority of the edoxaban-based antithrombotic regimen over the VKA-based antithrombotic regimen at a 2-sided  $\alpha = .05$ . To compensate for dropouts within 12 months, the final sample size is set at 2 × 750 patients. With this sample size, the study has at least a nominal 82% power to show noninferiority with a noninferiority margin of 1.20 at a 1-sided significance level of 2.5%. The noninferiority margin of 1.20 was selected based on clinical appropriateness. The power calculation is based on a test using the Cox proportional hazards model and was performed with PASS version 14.0.4, with the module for 2 survival curves using Cox proportional hazards model, under the ITT principle with a fixed follow-up time of 12 months.

## Subgroup analyses

Subgroup analyses for the primary end point are based on the same analysis sets and analysis time periods as in the main analyses of the study outcome variables. The subgroup analyses are presented descriptively without formal superiority hypothesis testing. The prespecified subgroup analyses include, for example, gender, age, weight, body mass index, renal function, hypertension, diabetes mellitus, prior stroke, prior MI, CHA<sub>2</sub>DS<sub>2</sub>-VASC, and HAS-BLED.

## Dosing rationale

The ENTRUST-AF PCI trial will be the first study investigating edoxaban with regard to bleeding events in patients who underwent a successful PCI with stent placement. Based on the results of the ENGAGE AF-TIMI 48<sup>20</sup> and Hokusai-VTE<sup>25</sup> studies, edoxaban dose in this trial (ie, 60 mg once daily [30 mg dose reduced in selected patients]) is consistent with the licensed dose for patients with non-valvular AF or venous thromboembolism.

## Additional scientific investigations

To address broadly the pathophysiologic impact of the 2 treatment regimens, pharmacokinetic, biomarkers, and health economics and outcomes research substudies are planned. Additional potential exploratory scientific investigations are listed in Supplement Table III.

## Study organization

The ENTRUST-AF PCI trial operations group is a partnership composed of members of the Academic Research Organizations, European Cardiovascular Research Institute (ECRI, [www.ECRI-trials.com](http://www.ECRI-trials.com)), and Atrial Fibrillation Network (AFNET e.V., [www.atrial-fibrillation-network.eu](http://www.atrial-fibrillation-network.eu)) and the Contract Research Organizations (CROs), Cardialysis and Chiltern, and the Sponsor Daiichi Sankyo Europe GmbH. The authors are solely responsible for the design of this study, all study analyses, and the drafting and editing of the final manuscript and its contents. The study conduct is overseen by an Executive Committee which consists of members of the academic leadership of the trial, CRO, and sponsor. The Executive Committee provides oversight of trial conduct and independent data analysis, oversees publication of the trial results, appoints members of the steering committee, appoints the independent DSMB chair, and identifies the DSMB members. To protect the safety of the subjects participating in the study, an independent DSMB of acknowledged experts in related fields, not otherwise associated with the trial, reviews pertinent study data to ensure prompt identification of safety issues. If the data at hand would precipitate a substantial safety concern about the edoxaban-based regimen, the DSMB will carefully balance the observed risk profile against possible signs of improved efficacy. The DSMB is entitled to recommend early

termination of the trial when the edoxaban-based regimen would show an unfavorable benefit/risk balance with respect to the rate of MCRB, the main efficacy endpoint, or mortality.

An independent, blinded Clinical Events Committee applies the protocol definitions as detailed in the charter and adjudicates all suspected study events.

## Present status

The first patient in The ENTRUST-AF PCI trial was enrolled in Hospital La Paz, Madrid, Spain, on February 24, 2017. End of enrollment is projected for March 2018.

## Conclusion

Subjects requiring dual-antiplatelet therapy and concomitant oral anticoagulant therapy, such as those with AF, represent a challenging and so far not adequately investigated patient population. Warfarin and clopidogrel remain the most widely used oral anticoagulant and P2Y<sub>12</sub> receptor inhibitor, respectively. Over the past years, several NOACs, including edoxaban, have been studied in the setting of AF showing at least similar efficacy but also safer profiles as compared with warfarin. Moreover, the role of edoxaban as part of a dual-antithrombotic treatment strategy, including a P2Y<sub>12</sub> inhibitor but no aspirin, represents another important area of clinical interest. The ENTRUST-AF PCI trial will largely broaden our understanding in this challenging patient population.

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## Appendix. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ahj.2017.10.009>.

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