

# 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)

C. Michael Gibson, MS, MD,<sup>a</sup> Roxana Mehran, MD,<sup>b</sup> Christoph Bode, MD,<sup>c</sup> Johnathan Halperin, MD,<sup>b</sup> Freek Verheugt, MD,<sup>d</sup> Peter Wildgoose, PhD,<sup>e</sup> Martin van Eickels, MD,<sup>f</sup> Gregory Y. H. Lip, MD,<sup>g</sup> Marc Cohen, MD,<sup>h</sup> Steen Husted, MD,<sup>i</sup> Eric Peterson, MD,<sup>j</sup> and Keith Fox, MD<sup>k</sup> *Boston, MA; New York, NY; Freiburg, Germany; Nijmegen, the Netherlands; Titusville, Newark, NJ; Berkeley, CA; Birmingham, Edinburgh, United Kingdom; Herning, Denmark; and Durham, NC*

**Background** Guidelines recommendations regarding anticoagulant therapy after percutaneous coronary intervention (PCI) among patients with atrial fibrillation (AF) rely on retrospective, nonrandomized observational data. Currently, patients are treated with triple-therapy (dual antiplatelet therapy [DAPT] + oral anticoagulation therapy), but neither the duration of DAPT nor the level of anticoagulation has been studied in a randomized fashion. Recent studies also suggest dual pathway therapy with clopidogrel plus oral anticoagulation therapy may be superior, and other studies suggest that novel oral anticoagulants such as rivaroxaban may further improve patient outcomes.

**Design** PIONEER AF-PCI ([ClinicalTrials.gov](http://ClinicalTrials.gov) NCT01830543) is an exploratory, open-label, randomized, multicenter clinical study assessing the safety of 2 rivaroxaban treatment strategies and 1 vitamin K antagonist (VKA) treatment strategy in subjects who have paroxysmal, persistent, or permanent nonvalvular AF and have undergone PCI with stent placement. Approximately 2,100 subjects will be randomized in a 1:1:1 ratio to receive either rivaroxaban 15 mg once daily plus clopidogrel 75 mg daily for 12 months (a WOEST trial-like strategy), or rivaroxaban 2.5 mg twice daily (with stratification to a prespecified duration of DAPT 1, 6, or 12 months, an ATLAS trial-like strategy), or dose-adjusted VKA once daily (with stratification to a prespecified duration of DAPT 1, 6, or 12 months, traditional triple therapy). All patients will be followed up for 12 months for the primary composite end point of Thrombolysis in Myocardial Infarction major bleeding, bleeding requiring medical attention, and minor bleeding (collectively, clinically significant bleeding).

**Conclusion** The PIONEER AF-PCI study is the first randomized comparison of VKA vs novel oral anticoagulant therapy in patients with NVAf receiving antiplatelet therapy after PCI to assess the relative risks of bleeding complications. (Am Heart J 2015;169:472-478.e5.)

From the <sup>a</sup>Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, <sup>b</sup>Department of Cardiology, Mount Sinai Medical Center, Mount Sinai Medical School, New York, NY, <sup>c</sup>Heart Center, Department for Cardiology and Angiology I, University of Freiburg, Freiburg, Germany, <sup>d</sup>Radboud University Medical Center, Nijmegen, the Netherlands, <sup>e</sup>Janssen Pharmaceuticals, Inc, Titusville, NJ, <sup>f</sup>Bayer Pharmaceuticals, Inc, Berlin, Germany, <sup>g</sup>University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom, <sup>h</sup>Division of Cardiology, Newark Beth Israel Medical Center, Newark, NJ, <sup>i</sup>Aarhus University Hospital, Medical Department, Hospital Unit West, Herning, Denmark, <sup>j</sup>Duke Clinical Research Institute, Durham, NC, and <sup>k</sup>Centre for Cardiovascular Science, University of Edinburgh and Royal Infirmary of Edinburgh, Edinburgh, United Kingdom. Stuart J. Connolly, MD, served as guest editor for this article. RCT No. NCT01830543.

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Reprint requests: C. Michael Gibson, MS, MD, Cardiovascular Division, Beth Israel Deaconess Medical Center, 185 Pilgrim Rd, Farr 319, Boston, MA 02215.

E-mail: [mgibson@perfuse.org](mailto:mgibson@perfuse.org)  
0002-8703

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## Background

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia of clinical significance,<sup>1</sup> with a prevalence ranging from less than 1% among people younger than 60 years to approximately 10% among those older than 80 years.<sup>2</sup> More than 6 million patients in Europe and approximately 2.3 million patients in the United States have been diagnosed as having AF, and this number continues to grow rapidly due to the aging of the population.<sup>2</sup> Atrial fibrillation is an independent risk factor for stroke,<sup>3</sup> and the morbidity and mortality associated with AF-related stroke are more severe than that of other underlying causes.<sup>4</sup>

The 2012 focused update of the European Society of Cardiology guidelines and 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines, cite antithrombotic therapy as a cornerstone in the management of AF to prevent thromboembolism. Antithrombotic therapy should be carefully chosen, however, to minimize both the risk of ischemic stroke and the risk of bleeding. Although anticoagulation with a vitamin K antagonist (VKA) is recommended for moderate- and high-risk patients, acetylsalicylic acid (ASA) is recommended for AF patients at low risk for subsequent stroke.<sup>5</sup> Although warfarin is commonly used in the management of AF,<sup>6</sup> its use is limited by an increased risk of intracranial hemorrhage and gastrointestinal bleeding,<sup>7</sup> its interaction with food and other medications, and<sup>8</sup> its need for frequent monitoring. These limitations have prompted the development of novel anticoagulants that can provide similar efficacy with an improved safety profile.

Among acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI), approximately 5% to 21% of patients have concomitant AF.<sup>9</sup> Despite overlap in the occurrence of these syndromes, the pharmacotherapies used to manage AF and ACS differ. The management of AF patients who undergo stent placement for an ACS is challenging in so far as the risks of AF-related ischemic stroke and bleeding associated with the antithrombotic therapy and stent thrombosis must all be balanced. Although oral anticoagulation therapy (OAC) is more effective than dual antiplatelet therapy (DAPT) in preventing ischemic and embolic events associated with AF,<sup>10</sup> OAC with warfarin was inferior to DAPT in reducing the risk of stent thrombosis among ACS patients requiring first-generation stent implantation.<sup>11</sup>

In the past, DAPT and OAC were combined in a treatment strategy labeled “triple therapy.” Meta-analyses of studies involving patients with AF and coronary stents found the risk of major bleeding on triple therapy to be 2.2% within the first month and 4% to 12% within the first year on treatment.<sup>12</sup> The safety and effectiveness of triple therapy, however, has recently been challenged in the What is the Optimal antiplatelet & Anticoagulant Therapy in Subjects With Oral Anticoagulation and Coronary Stenting (WOEST) trial, which demonstrated that the use of a single antiplatelet treatment (clopidogrel) in combination with an oral anticoagulant therapy was associated with significantly less bleeding and mortality than triple therapy,<sup>13</sup> despite no increase in stent thrombosis or ischemic stroke.

Current European guidelines regarding anticoagulant therapy after PCI for ACS in patients with AF rely on limited retrospective data. Triple therapy consisting of a VKA, aspirin, and clopidogrel is recommended for 6 months in patients with low or intermediate hemorrhagic risk and 4 weeks among those with higher bleeding risks irrespective of the type of stent. This triple-therapy

regimen is followed by a combination of VKA and one antiplatelet therapy up to 12 months, after which lifelong treatment with VKA should be continued.<sup>14</sup> In North America, The American College of Chest Physician provided recommendations based on (1) the risk of bleeding, (2) the syndrome (ACS or stable angina), and (3) the type of stent deployed (drug-eluting stents vs bare-metal stent).<sup>15</sup>

Rivaroxaban is an oral factor Xa inhibitor that is approved to reduce the risk of stroke and systemic embolism among patients with nonvalvular AF by both the European Medicines Agency and the US Food and Drug Administration. Rivaroxaban is also approved by the European Medicines Agency to reduce the risk of cardiovascular death, myocardial infarction (MI) and stroke after an ACS among patients with elevated biomarkers. The optimal dose of rivaroxaban may differ in the management of AF and ACS. The administration of 15 and 20 mg of rivaroxaban once daily to patients with nonvalvular AF was noninferior to dose-adjusted warfarin in reducing stroke and systemic embolism and decreasing the risk of fatal and intracranial bleeding in the ROCKET-AF trial (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation).<sup>16</sup> A reduced dose of 15 mg daily in patients with moderate impairment of renal function (creatinine clearance 30–49 mL/min) displayed efficacy and safety profiles similar to the overall trial results. However, both 15 and 20 mg of rivaroxaban may significantly increase bleeding if administered concomitantly with DAPT. Indeed, the addition of rivaroxaban to DAPT among ACS patients at daily doses  $\geq 10$  mg was associated with excess bleeding including an excess risk of fatal bleeding relative to a total daily dose of 5 mg.<sup>17,18</sup> Thus, ACS patients on DAPT may not be able to safely tolerate the rivaroxaban doses administered in AF. Among ACS patients treated with background therapy with DAPT, a lower dose of rivaroxaban, 2.5 mg twice daily, however, was associated with a reduction in cardiovascular death, MI, and stroke (ATLAS ACS 2-TIMI 51) compared with DAPT alone.<sup>18</sup> Although safe and effective in ACS patients, this lower 2.5 mg BID dose of rivaroxaban administered with DAPT has not been evaluated in patients with AF for the prevention of stroke or systemic embolism.

This article describes the design of the PIONEER AF-PCI trial ([ClinicalTrials.gov](http://ClinicalTrials.gov) NCT01830543), an open-label, randomized, multicenter trial assessing the safety of an “ATLAS 2-like” low-dose rivaroxaban plus DAPT strategy vs a “WOEST-like” rivaroxaban plus single thienopyridine strategy vs a traditional “triple-therapy strategy” (OAC plus DAPT) after PCI with stent placement in patients with paroxysmal, persistent, or permanent nonvalvular AF. Based on the exploratory study design and a relatively small sample size, the study proceeds with the null hypothesis that bleeding rates will be similar

across these 3 strategies. In order to be considered clinically meaningful, any observed between-group differences will have to be sufficiently large.

## Study operations

The trial is funded by Johnson and Johnson and Bayer. The authors, members of the Executive Steering Committee, are responsible for the design and conduct of the study, the drafting and editing of this manuscript, as well as the analysis and reporting of the final results. The executive committee consists of members of the academic leadership of the trial and members from each sponsoring company. The executive committee appointed an independent Data Monitoring Committee (DMC) Chair, identified the DMC members, created the DMC charter, and receives recommendations from the DMC regarding the safety of participants, the scientific integrity of the study, possible additional analysis, or modifications to the trial.

## Study objectives

The primary objective of the PIONEER AF-PCI study is to assess the safety of 2 rivaroxaban treatment strategies as compared with the current standard of care (a dose-adjusted VKA treatment strategy) in subjects with paroxysmal, persistent, or permanent nonvalvular AF undergoing PCI with stent placement, based on the composite of Thrombolysis in Myocardial Infarction (TIMI) major bleeding, minor bleeding, and bleeding requiring medical attention events (known collectively as clinically significant bleeding) during 12 months of therapy.

## Study population and patient selection

Approximately 2,100 men and women at least 18 years of age who have electrocardiographically documented paroxysmal, persistent, or permanent nonvalvular AF (defined as AF not considered to be caused by a primary valve stenosis) and have undergone a PCI procedure (with stent placement) are being enrolled.

The principal inclusion and exclusion criteria are provided in the online [Appendix Supplementary Table 1](#) and include conditions that contraindicate OAC or confer an unacceptable risk of bleeding, a history of stroke or transient ischemic attack or hemodynamic or cardiac electrical instability. The international normalized ratio (INR) must be  $\leq 2.5$  at the time of randomization. Eligible subjects must provide written informed consent prior to randomization in the study as well as informed consent to collect their vital status at the end of scheduled follow-up, 12 months after entry in order to minimize missing data.

## Randomization and treatment protocol

Randomization in equal proportion to 1 of 3 treatment strategies is stratified by the intended duration of DAPT

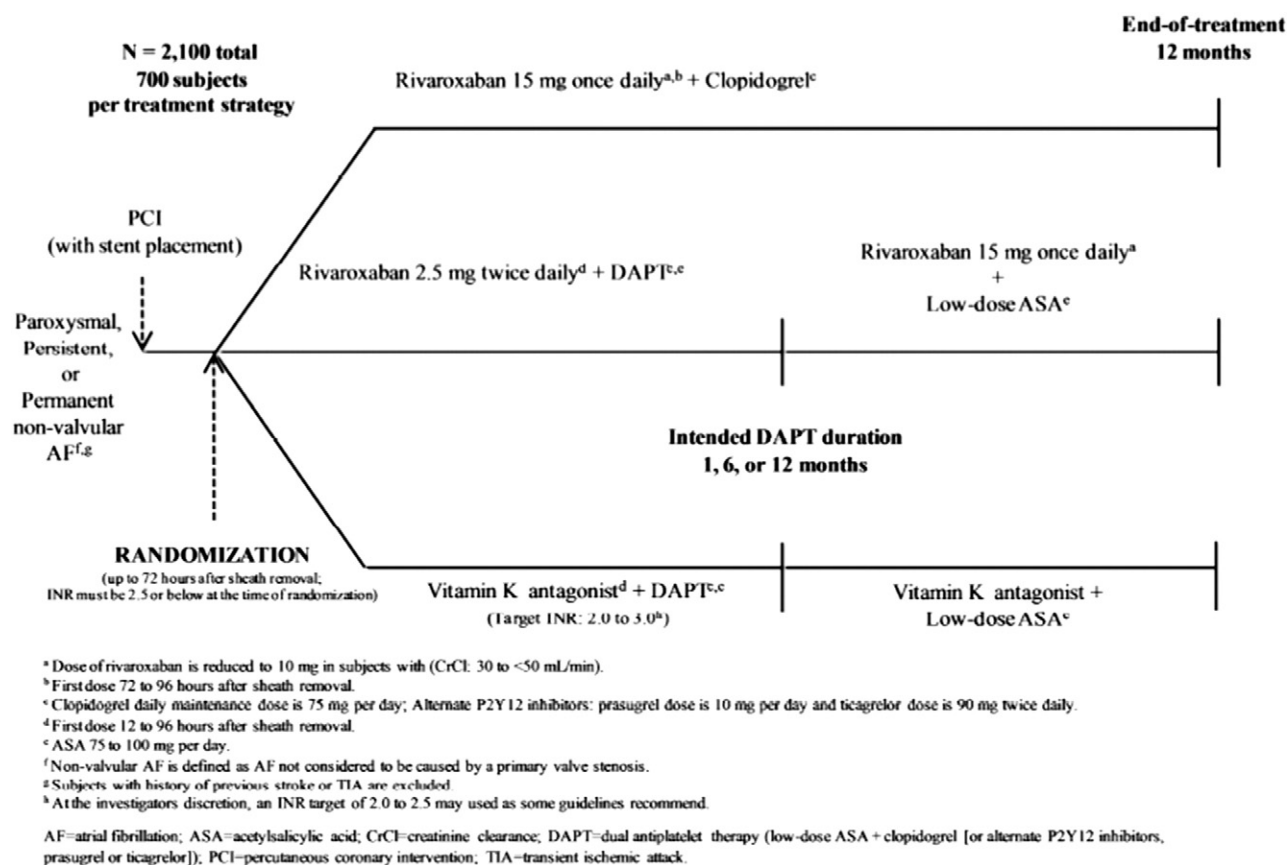
(1, 6, or 12 months) and balanced by randomly permuted blocks ([Figure](#)):

- “Arm 1” rivaroxaban 15-mg once-daily treatment strategy (12 months) (WOEST-like strategy): rivaroxaban 15 mg (or 10 mg for subjects with moderate renal impairment [creatinine clearance: 30-50 mL/min]) once daily plus background single antiplatelet therapy with clopidogrel 75 mg (or alternate P2Y<sub>12</sub> inhibitor) daily for 12 months. Therapy with low-dose ASA should be withheld following randomization; however, at the discretion of the investigator, ASA may be continued for up to 24 hours before the first dose of study drug.
- “Arm 2” rivaroxaban 2.5 mg twice-daily treatment strategy (prespecified duration of DAPT 1, 6, or 12 months; ATLAS 2-like strategy): rivaroxaban 2.5 mg twice daily plus background DAPT with low-dose ASA (75-100 mg/d) plus clopidogrel 75 mg (or alternate P2Y<sub>12</sub> inhibitor) daily for prespecified duration of 1, 6, or 12 months followed by rivaroxaban 15 mg (or 10 mg for subjects with moderate renal impairment) once daily plus background single antiplatelet therapy with low-dose (75-100 mg) of ASA.
- “Arm 3” VKA treatment strategy (prespecified duration of DAPT of 1, 6, or 12 months; triple-therapy strategy): dose-adjusted VKA once daily (target INR 2.0-3.0), or as directed by the investigator, plus background DAPT for the length of intended DAPT. At the end of the intended duration of 1 or 6 months, subjects will remain on a dose-adjusted VKA once daily (target INR 2.0-3.0) plus background single antiplatelet therapy with low-dose (75-100 mg) ASA.

Subjects are randomly assigned a treatment strategy by an interactive voice/Web response system on day 1. The investigator must prespecify the intended duration of DAPT (1, 6, or 12 months) and the intended use of an alternate P2Y<sub>12</sub> inhibitor (prasugrel or ticagrelor) instead of clopidogrel before randomization. Randomization must occur after the INR is 2.5 or below within 72 hours after sheath removal and may be performed while the subject is in the hospital or at the study site if after hospital discharge.

Subjects will be administered the first dose of study drug (rivaroxaban or VKA) according to the timing specified for each of the treatment strategy groups and no sooner than 2 hours after the final dose of bivalirudin; 4 hours after the final dose of intravenous unfractionated heparin, eptifibatide, or tirofiban; 12 hours after the final dose of other intravenous or subcutaneous anticoagulants, dabigatran or apixaban; or 24 hours after the final dose of abciximab, fondaparinux, or nonstudy rivaroxaban. If at any time during DAPT, the investigator determines that clopidogrel (or alternate P2Y<sub>12</sub> inhibitor) should be permanently discontinued earlier than the

**Figure**



Study design of PIONEER AF-PCI.

intended DAPT duration (1, 6, or 12 months; as prespecified before randomization) due to the subject's clinical status, the subject will be transitioned to the single antiplatelet therapy phase with low-dose aspirin (75-100 mg) while maintaining the randomized OAC treatment strategy (ie, rivaroxaban, 15 mg daily for those in arm 2, or VKA for those in arm 3). For those subjects in arm 1 for whom antiplatelet therapy must be discontinued, they will continue with rivaroxaban 15 mg daily alone for the remainder of the study. All study drugs are administered orally.

For patients randomized to the triple-therapy strategy (arm 3), careful attention is given to maintaining anticoagulation intensity in the targeted INR of 2.0 to 3.0. Compliance with all other assigned therapies will be assessed by pill counts.

The study consists of a screening phase, a 12-month open-label treatment phase, and an end of treatment/early withdrawal visit. The total duration of participation in the study for each subject is approximately 12 months. Subjects will return to the study center for multiple scheduled visits. Additional unscheduled telephone calls

and visits by the subject to the site are permissible for management of therapy, to enhance treatment compliance or for evaluation of adverse events. Subjects must permanently discontinue study drug if they have an MI, ischemic stroke, intracranial bleeding, or bleeding into a critical organ, including intraocular bleeding. If a subject permanently discontinues study drug or withdraws before the end of the open-label treatment phase, he or she will have an early withdrawal/end-of-treatment visit assessment no more than 7 days after the last dose of study drug. During the early withdrawal visit or the end-of-treatment visit at 12 months, investigators must ensure that all subjects initiate therapeutic anticoagulation based upon protocol-specified instructions during transitions between rivaroxaban and VKA or another anticoagulant according to standard practice.

## Primary and secondary safety end points

The primary safety end point is the percentage of subjects experiencing either TIMI major bleeding, minor bleeding, or bleeding requiring medical attention events



**Table I.** Summary of primary end point analysis methods

End point	Analysis period	Analysis set	Method
Primary safety end point	Treatment-emergent period (primary)	Safety analysis set	2-sample proportion
	Postrandomization period (supportive)		Cox model (hazard ratio, 95% CI) Kaplan-Meier

(known collectively as clinically significant bleeding) by the end of 12 months of randomized therapy, assessed according to intention-to-treat (ITT) for all patients receiving at least one dose of the randomized study medications. Secondary safety end points include the incidence of each component of the TIMI clinically significant bleeding composite (TIMI major bleeding, minor bleeding, and bleeding requiring medical attention), the composite of adverse cardiovascular events (cardiovascular death, MI, and stroke), as well as cardiovascular death, MI, stroke, and stent thrombosis.

### Safety outcomes and definitions

Safety evaluations performed throughout the study include monitoring of clinical events (cardiovascular death, MI, stroke, bleeding events, and stent thrombosis), adverse events, and performing clinical laboratory tests. Investigators will be required only to classify bleeding events by the TIMI scale. An independent Clinical Endpoints Committee assesses bleeding events according to the TIMI scale and alternative scales, including clinically insignificant bleeding events to the extent these are documented. The TIMI scale effectively accounts for large or catastrophic bleeding events, but places less emphasis on declining hemoglobin levels or transfusions of small volumes of blood products that occur commonly in patients undergoing PCI. The Clinical Endpoints Committee will therefore also assess bleeding using the International Society on Thrombosis and Hemostasis (ISTH) classification, which designates major bleeding events, clinically relevant nonmajor bleeding, and minimal bleeding events. A third bleeding assessment schema, the Bleeding Academic Research Consortium scale, defines 5 degrees of bleeding, including none, bleeding that is not actionable and does not require additional evaluation, hospitalization or treatment by a health care professional, any overt, actionable hemorrhage, clinical, laboratory, and/or imaging evidence of bleeding with specific health care provider responses, bleeding related to myocardial revascularization surgery, and fatal bleeding events. Finally, the GUSTO scale categorizes bleeding as severe, moderate, or mild.

In order to account for transfusion, hemoglobin measurements will be adjusted for any packed red blood cells or whole blood transfused between the prebleeding and postbleeding hemoglobin measurements. The number of units of packed red blood cells

and whole blood combined will be added to the change in hemoglobin. If only a hematocrit value is known, the corresponding hemoglobin value will be assumed to be one third of the hematocrit value (in g/dL).

Other adverse events of special interest include any bleeding event that does not meet serious adverse event criteria and any event occurring within 30 days before a permanent discontinuation.

### Exploratory secondary analyses

Blood samples for pharmacokinetic and pharmacodynamic analyses will be collected from 120 subjects at selected participating sites.

### Statistical considerations

This is an open-label, randomized controlled multicenter study; the study team will remain blinded to treatment information until database lock. All reported bleeding events will be adjudicated, and analyses of the primary safety end point and other bleeding end points will be based on adjudicated events. The primary safety end point is the percent of subjects developing the composite of TIMI major bleeding, minor bleeding, and bleeding requiring medical attention (clinically significant bleeding) over the course of the 12-month randomized treatment period.

PIONEER is an exploratory trial designed to generate hypotheses of interest with a sample size that is calculated based on showing the minimum number of subjects needed to detect a difference of >6% in the incidence between 2 groups at 80% statistical power with a 2-sided  $\alpha$  of .05. Assuming a 16% incidence of clinically significant bleeding with the VKA treatment strategy, a sample size of 700 subjects per treatment strategy group (total study sample size of 2,100 across 3 treatment strategy groups) will have about 80% power to detect a >6% difference in incidence rates between any 1 of the 2 rivaroxaban treatment strategy groups against the VKA treatment strategy group.

### Analysis data sets

Two analysis sets are to be used: the ITT analysis set and the safety analysis set. All primary analyses in the trial will be based on the safety analysis set, which consists of all randomized subjects who receive at least 1 dose of study drug. The ITT analysis set includes all randomized

**Table II.** Summary of secondary end point analysis methods

End point	Analysis period	Analysis set	Method
Components of primary safety end point (TIMI major, TIMI minor, bleeding requiring medical attention)	Treatment-emergent period	Safety analysis set	2-sample proportion When appropriate, Cox model (hazard ratio, 95% CI) Kaplan-Meier
Composite of adverse cardiovascular events	Treatment-emergent period	Safety analysis set	2-sample proportion When appropriate, Cox model (hazard ratio, 95% CI) Kaplan-Meier
Components of adverse cardiovascular events (MI, stroke, cardiovascular death) + stent thrombosis	Treatment-emergent period	Safety analysis set	2-sample proportion When appropriate, Cox model (hazard ratio, 95% CI) Kaplan-Meier

subjects. Subjects will be analyzed in the treatment groups on an “as randomized” basis. The safety analysis set includes all ITT subjects who received at least one dose of study medication.

## Methods of analysis

The primary safety analysis will describe percentages of cumulative treatment-emergent end point events observed from the time of the first study drug administration up to 2 days after discontinuation of the study drug. The primary analysis will be based on pooled data across all strata within each randomized treatment strategy group. The time from administration of the first dose of study drug to the first occurrence of the primary safety end point event, major bleeding, will be analyzed using a Cox proportional hazard model with treatment strategy group as a covariate, stratified by intended DAPT period, to provide a point estimate and 2-sided 95% CI for the treatment effect of relative risk reduction (RRR) ( $RRR = 100 \times [1 - \text{hazard ratio}]$ ). Cumulative event rates over time will be summarized using the Kaplan-Meier method. Sensitivity analyses to assess the robustness of the time to event analysis described above will include an unstratified log-rank test and an analysis that includes all postrandomization events (including those that occur after 2 days of discontinuation of the last study drug). [Tables I and II](#) summarize the analysis methods for the primary and secondary safety end point respectively.

## Interim analysis

Two formal interim reviews of the safety data will be performed by the DMC when approximately 10% and 50% of subjects have completed at least 1 month of the allocated treatment. The data review will include adverse events (specifically, clinically significant bleeding, adverse cardiovascular events, stent thrombosis), dosing information, completion/withdrawal information, demographic and baseline characteristics, laboratories, and treatment assignment information. The following sum-

maries will be provided for the interim analyses: summaries of the frequency of observed INR measurements after randomization and time in therapeutic range, which is the percentage of INR values in target ranges from 2 to 3 and from 1.8 to 3.2, based on imputed INR values. A closer examination may be warranted for the subjects taking rivaroxaban 10 mg, as they may have renal impairment. There is no formal stopping rule for either success or futility prespecified for these interim safety data analyses because this study is exploratory in nature. The interim analyses are designed to help the DSMB with adequate level of safety data monitoring support and are not meant for testing any interim hypotheses. Besides, the trial sample size is not adequate for testing any safety end points at the interim basis. The primary focus in this trial remains on collecting evidence on key safety end points at the end of proposed 12-month follow up.

## Conclusion

The PIONEER AF-PCI exploratory trial evaluates the safety of 3 treatment strategies among a broad group of patients with paroxysmal, persistent, or permanent nonvalvular AF after PCI with stenting. The trial provides an assessment of the safety of rivaroxaban when added to current guidelines-based medical therapy for AF.

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## Disclosures

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## Appendix

**Supplementary Table I.** Definition of patient's eligibility

### Inclusion criteria:

Patients must undergo performance of PCI plus:

1. The minimum source documentation requirements for inclusion and exclusion criteria that specify a need for "documented medical history" are as follows:
  - Electrocardiogram, Holter monitor, pacemaker/defibrillator, or any device that provides a rhythm strip documenting paroxysmal, persistent, or permanent nonvalvular AF within 1 y before screening.

OR

- Electrocardiogram, Holter monitor, pacemaker/defibrillator, or any device that provides a rhythm strip documenting paroxysmal, persistent, or permanent nonvalvular AF that was performed more than 1 y before screening if the subject has been receiving oral anticoagulation therapy (VKA or a novel oral anticoagulant) for the AF for 3 mo immediately before the index PCI.
2. Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, laboratory assessment) and documented in the source documents.

### Exclusion criteria:

Major exclusion criteria include any condition that contraindicates anticoagulant therapy or would confer an unacceptable risk of bleeding, such as, but not limited to:

1. Active internal bleeding
2. Clinically significant bleeding
3. Bleeding at a noncompressible site
4. Bleeding diathesis within 30 d before randomization
5. A platelet count <90,000/ $\mu$ L at screening or prerandomization
6. A history of intracranial hemorrhage
7. Clinically significant gastrointestinal bleeding within 12 mo before randomization
8. A PT or INR test result that is higher than the upper limit of normal at the time of screening or pre-randomization that suggests an underlying coagulation disorder (except for subjects taking VKA), or an INR that does not drop to 2.5 or below by 72 h after sheath removal following the index PCI procedure.
9. A history of stroke or transient ischemic attack
10. Cardiogenic shock at the time of randomization
11. Ventricular arrhythmias refractory to treatment
12. Biopsy of a parenchymal organ
13. Serious trauma within 30 d prior to randomization
14. Calculated creatinine clearance <30 mL/min at screening or prerandomization
15. Anemia of unknown cause with a hemoglobin level <10 g/dL (<6.21 mmol/L) at screening or pre-randomization
16. Abciximab bolus or infusion within the preceding 8 h, or an eptifibatide or tirofiban bolus or infusion within the past 2 h preceding randomization  
Any other condition known to increase the risk of bleeding
17. Known significant liver disease (eg, acute hepatitis, chronic active hepatitis, cirrhosis), or liver function test abnormalities at screening (confirmed with repeat testing): alanine transaminase (ALT) >5 times the upper limit of normal or ALT >3 times the upper limit of normal plus total bilirubin >2 times the upper limit of normal,
18. Known clinical history of human immunodeficiency virus infection
19. Current substance abuse (drug or alcohol) problem or a history within the previous 6 mo or any severe condition that would limit life expectancy to less than 12 mo
20. Suspected or documented stent thrombosis during the index procedure OR has a PCI with stent placement for a previously stented lesion (stent within a stent) during the index procedure or within the previous 12 mo
21. Incomplete staged PCI procedure (once the completion of the staged procedure has occurred, the final PCI may become the index event and is allowed)
22. Planned CABG
23. Contraindications to the use of VKAs, ASA, or P2Y12 platelet inhibitors (clopidogrel, prasugrel, or ticagrelor), per prescribing information.



**Supplementary Table II.** Safety outcomes, definitions, and details of statistical testing

The primary safety end point is the proportion of subjects with the composite of TIMI major bleeding, minor bleeding, and bleeding requiring medical attention events (known collectively as clinically significant bleeding) at the end of month 12.

The primary safety end point will be summarized for each randomized treatment strategy group and for both investigator-determined and adjudicated responses. The primary safety analysis will describe percentages of cumulative treatment-emergent end point events observed from the time of the first study drug administration up to 2 d after discontinuation of the study drug. The primary analysis will be based on pooled data across all strata within each randomized treatment strategy group. Additional summaries of primary bleeding outcome will also be provided separately by:

- Dose of study medication at the time of the event (Riva 2.5 mg, Riva 10 mg, Riva 15 mg, VKA) within a randomized treatment group;
- Intended DAPT (1, 6, 12 mo) within a treatment group
- Type of stent used within a treatment group (eg, bare-metal stents, drug-eluting stents)
- Type of antiplatelet therapy within a treatment group

A closer examination may be warranted for the subjects taking Riva 10 mg, as they may have renal impairment.

The time from administration of the first dose of study drug to the first occurrence of the primary safety end point event, major bleeding, will be analyzed using a Cox proportional hazard model with treatment strategy group as a covariate, stratified by intended DAPT period, to provide a point estimate and 2-sided 95% CI for the treatment effect of RRR ( $RRR = 100 \times [1 - \text{hazard ratio}\%]$ ). Cumulative event rates over time will be summarized using the Kaplan-Meier method.

Sensitivity analyses to assess the robustness of the time to event analysis described above will include an unstratified log-rank test and an analysis that includes all post-randomization events (including those that occur after 2 d of discontinuation of the last study drug). The secondary end points for this study are the proportions of subjects at the end of DAPT and at month 12 with the following events:

- Each component of the TIMI clinically significant bleeding composite (TIMI major bleeding, minor bleeding, and bleeding requiring medical attention); summarized by treatment and by pooling over strata
- The composite of adverse cardiovascular events (cardiovascular death, MI, and stroke)
  - (1) Cardiovascular death
  - (2) MI
  - (3) Stroke
  - (4) Stent thrombosis

The secondary end points will be summarized for both the investigator-determined and adjudicated responses.

All cardiovascular and bleeding outcomes will be listed. Secondary end points will be summarized for each treatment strategy group using descriptive statistics. If appropriate, the time from administration of the first dose of study drug to the first occurrence of end point will be analyzed using a Cox proportional hazard model with treatment strategy group as a covariate, stratified by intended DAPT period, to provide a point estimate and 2-sided 95% CI for the treatment effect of RRR ( $RRR = 100 \times [1 - \text{hazard ratio}\%]$ ). When appropriate, cumulative event rates over time will be summarized using the Kaplan-Meier method.

### Supplementary Table III. Detailed bleeding definitions

#### TIMI Bleeding Event Classification Scale

##### TIMI Major Bleeding Event

A TIMI major bleeding event is defined as:

- Any symptomatic intracranial hemorrhage, or
- Clinically overt signs of hemorrhage (including imaging) associated with a drop in hemoglobin of  $\geq 5$  g/dL (or when the hemoglobin concentration is not available, an absolute drop in hematocrit of  $\geq 15\%$ ).

##### TIMI Minor Bleeding Event

A TIMI minor bleeding event is defined as any clinically overt sign of hemorrhage (including imaging) that is associated with a fall in hemoglobin concentration of 3 to  $<5$  g/dL (or when hemoglobin concentration is not available, a fall in hematocrit of 9% to  $<15\%$ ).

##### Bleeding Events Requiring Medical Attention

A bleeding event requiring medical attention is defined as any bleeding event that requires medical treatment, surgical treatment, or laboratory evaluation, and does not meet criteria for a major or minor bleeding event, as defined above.

##### Insignificant Bleeding Events

An insignificant bleeding event is defined as a reported blood loss or bleeding event episode not meeting any of the above criteria.

##### Clinically Significant Bleeding Events

The composite end point of TIMI major bleeding event, TIMI minor bleeding event, or bleeding event requiring medical attention is considered clinically significant for the TIMI scale.

#### ISTH Bleeding Event Classification Scale

##### Major Bleeding Events

A major bleeding event is defined using ISTH criteria as clinically overt bleeding that is associated with:

- A fall in hemoglobin of 2 g/dL or more, or
- A transfusion of 2 or more units of packed red blood cells or whole blood, or
- A critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or
- A fatal outcome.

##### Clinically Relevant Nonmajor Bleeding Events

A clinically relevant nonmajor bleeding event is defined as an overt bleeding event not meeting the criteria for a major bleeding event, but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study drug treatment, or associated with discomfort for the subject such as pain or impairment of activities of daily life.

Examples of nonmajor clinically relevant bleeding events are:

- Epistaxis if it lasts for more than 5 min, if it is repetitive (ie, 2 or more episodes of true bleeding, ie, no spots on a handkerchief, within 24 h), or leads to an intervention (packing, electrocautery, etc)
- Gingival bleeding if it occurs spontaneously (ie, unrelated to tooth brushing or eating), or if it lasts for more than 5 min
- Hematuria if it is macroscopic, and either spontaneous or lasts for more than 24 h after instrumentation (eg, catheter placement or surgery) of the urogenital tract

- Macroscopic gastrointestinal hemorrhage: at least 1 episode of melena or hematemesis, if clinically apparent
- Rectal blood loss, if more than a few spots
- Hemoptysis, if more than a few speckles in the sputum, or
- Intramuscular hematoma
- Subcutaneous hematoma if the size is larger than 25 cm<sup>2</sup> or larger than 100 cm<sup>2</sup> if provoked
- Multiple source bleeding events

##### Minimal Bleeding Events

All other overt bleeding events not meeting the criteria for major or clinically relevant nonmajor bleeding events will be classified as minimal bleeding events.

#### Bleeding Academic Research Consortium Definition for Bleeding

Type 0: no bleeding

Type 1: bleeding that is not actionable and does not cause the subject to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional; may include episodes leading to self-discontinuation of medical therapy by the subject without consulting a health care professional.

Type 2: any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a health care professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation.

Type 3: clinical, laboratory, and/or imaging evidence of bleeding with specific health care provider responses, as listed below:

Type 3a

- Overt bleeding plus hemoglobin drop of 3 to  $<5$  g/dL (provided hemoglobin drop is related to bleed)
- Any transfusion with overt bleeding

Type 3b

- Overt bleeding plus hemoglobin drop  $\geq 5$  g/dL<sup>a</sup> (provided hemoglobin drop is related to bleed)
- Cardiac tamponade
- Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
- Bleeding requiring intravenous vasoactive agents

Type 3c

- Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
- Subcategories confirmed by autopsy or imaging or lumbar puncture
- Intraocular bleed compromising vision

Type 4: CABG-related bleeding

- Perioperative intracranial bleeding within 48 h

(continued on next page)

- Reoperation after closure of sternotomy for the purpose of controlling bleeding
- Transfusion of  $\geq 5$  units whole blood or packed red blood cells within a 48-h period; cell saver products are not counted.
- Chest tube output  $\geq 2$  L within a 24-h period

If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (ie, within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

Type 5: Fatal Bleeding

Type 5a

- Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b

- Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes.

GUSTO Scale

Mild: Mild bleeding is defined as bleeding that does not meet criteria for either severe or moderate bleeding.

Moderate: Moderate bleeding is defined as bleeding that requires blood transfusion but does not result in hemodynamic compromise.

Severe or Life Threatening: Severe or life-threatening bleeding is defined as either an intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention.

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**Supplementary Table IV.** Criteria for the definition of ACS

ST-segment elevation MI:

Elevation of ST-segment more than 0.1 mV in 2 or more continuous electrocardiogram leads, or new left bundle-branch block, or ST-segment depression 0.1 mV or greater in 2 of the precordial leads V<sub>1</sub> to V<sub>4</sub> with evidence suggestive of true posterior infarction, all with elevated biomarkers of myocardial necrosis (CK-MB or troponin)

Non-ST-segment elevation MI:

Elevated biomarkers of myocardial necrosis (CK-MB or troponin) plus 1 of the following:

- Transient ST-segment elevation, or ST-segment depression, or T-wave changes consistent with myocardial ischemia  
or
  - Identification of a culprit lesion at coronary angiography demonstrating recent, active intracoronary atherothrombosis (eg, thrombus or an ulcerated plaque)
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