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)

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ABSTRACT

Background: Guidelines recommendations regarding anticoagulant therapy following percutaneous coronary intervention (PCI) among patients with atrial fibrillation (AF) rely on retrospective, non-randomized observational data. Currently patients are treated with triple therapy (dual antiplatelet therapy [DAPT] + oral anticoagulation therapy [OAC]) 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 OAC may be superior, and other studies suggest that novel oral anticoagulants (NOACs) such as rivaroxaban may further improve patient outcomes. **Design:** PIONEER AF-PCI (ClinicalTrials.gov NCT01830543) is an exploratory, open-label, randomized, multicenter clinical study assessing the safety of two rivaroxaban treatment strategies and one vitamin K antagonist (VKA) treatment strategy in subjects who have paroxysmal, persistent, or permanent non-valvular 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 pre-specified duration of DAPT 1, 6, or 12 months, an ATLAS trial like strategy) or dose adjusted vitamin K antagonist once daily (with stratification to a pre-specified duration of DAPT 1, 6, or 12 months, traditional triple therapy). All patients will be followed for 12 months for the primary composite endpoint of TIMI 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. NOAC therapy in patients with NVAF receiving antiplatelet therapy following PCI to assess the relative risks of bleeding complications.

Key words: atrial fibrillation, rivaroxaban, percutaneous coronary intevention

Background

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

The 2012 focused update of the ESC guidelines and 2014 AHA/ACC/HRS 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. While 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[5]. Although warfarin is commonly used in the management of atrial fibrillation[6], its use is limited by an increased risk of intracranial hemorrhage and gastrointestinal bleeding [7], its interaction with food and other medications and [8], as well as 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 [9]. 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. While OAC is more effective than dual antiplatelet therapy (DAPT) in preventing ischemic and embolic events associated with AF [10], OAC with warfarin was inferior to DAPT in reducing the risk of stent thrombosis among ACS patients requiring first generation stent implantation [11].

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 4–12 % within the first year on treatment [12]. The safety and effectiveness of triple therapy, however, has recently been challenged in the WOEST trial (What is the Optimal antiplatElet & Anticoagulant Therapy in Subjects With Oral Anticoagulation and Coronary StenTing) 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[13] despite no increase in stent thrombosis or ischemic stroke.

Current European guidelines regarding anticoagulant therapy following percutaneous coronary intervention (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 [14]. In North America, The American College of Chest Physician (ACCP) provided recommendations based upon 1) the risk of bleeding, 2) the

syndrome (ACS or stable angina) and 3) the type of stent deployed (DES vs bare metal stent (BMS)) [15].

Rivaroxaban is an oral factor Xa inhibitor which is approved to reduce the risk of stroke and systemic embolism among patients with non-valvular atrial fibrillation (AF) by both the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA). Rivaroxaban is also approved by the EMA to reduce the risk of cardiovascular death, myocardial infarction (MI) and stroke following an acute coronary syndrome among patients with elevated biomarkers. The optimal dose of rivaroxaban may differ in the management of AF and ACS. The administration of 15 mg and 20 mg of Rivaroxaban once daily to patients with non-valvular atrial fibrillation was non-inferior 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) [16]. 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 [17] [18]. 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, myocardial infarction (MI), and stroke (ATLAS ACS 2-TIMI 51) compared to DAPT alone [18]. While 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 manuscript describes the design of the PIONEER AF-PCI Trial (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) (ClinicalTrials.gov NCT01830543), an open-label, randomized, multicenter trial assessing the safety of an "ATLAS 2 like" low dose rivaroxaban plus DAPT strategy versus a "WOEST like" rivaroxaban plus single thienopyridiene strategy versus a traditional "triple therapy strategy" (OAC plus DAPT) following PCI with stent placement in patients with paroxysmal, persistent, or permanent non-valvular 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 three 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 paper, 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 two rivaroxaban treatment strategies as compared to the current standard of care (a dose-adjusted VKA treatment strategy) in subjects with paroxysmal, persistent, or permanent non-valvular 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 non-valvular 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 a provided in the on line supplement Table I, and include conditions that contraindicate OAC or confer an unacceptable risk of bleeding, a history of stroke or transient ischemic attack (TIA) or hemodynamic or cardiac electrical instability. The 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 1):

- **"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 (CrCl): 30 to 50 ml/min]) once daily plus background single antiplatelet therapy with clopidogrel 75 mg (or alternate P2Y12 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 (pre-specified 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 mg to 100 mg per day) plus clopidogrel 75 mg (or alternate P2Y12 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 (pre-specified duration of DAPT of 1, 6, or 12 months) (Triple Therapy Strategy):** Dose-adjusted VKA once daily (target INR 2.0 to 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 to 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 pre-specify the intended duration of DAPT (1, 6, or 12

months) and the intended use of an alternate P2Y12 inhibitor (prasurgrel or ticagrelor) instead of clopidogrel before randomization. Randomization must occur after the INR is 2.5 or below within 72 hours following 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, fondapariunx, or non-study rivaroxaban. If at any time during DAPT the investigator determines that clopidogrel (or alternate P2Y12 inhibitor) should be permanently discontinued earlier than the intended DAPT duration (1, 6, or 12 months; as pre-specified 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 (i.e., 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 15mg daily alone for the remained of the study. All study drugs are administered orally.

For patients randomized to the triple therapy (TT) strategy (Arm 3), careful attention is given to maintaining anticoagulation intensity in the targeted INR (international normalized ratio) 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 Month, 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 endpoints

The primary safety endpoint is the percentage of subjects experiencing either TIMI major bleeding, minor bleeding, or bleeding requiring medical attention events (known collectively as clinically significant bleeding) by the end of 12 months of randomized therapy, assessed according to intention-to-treat for all patients receiving at least one dose of the randomized study medications. Secondary safety endpoints 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 (CEC) 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 CEAC will therefore also assess bleeding using the International Society on Thrombosis and Hemostasis (ISTH) classification, which designates major bleeding events, clinically relevant non-major bleeding, and minimal bleeding events. A third bleeding assessment schema, the BARC (Bleeding Academic Research Consortium) scale, defines 5 degrees of bleeding, including none, bleeding that is not actionable and does require additional evaluation, hospitalization or treatment by a healthcare professional, any overt, actionable hemorrhage, clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare 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 pre-bleeding and post-bleeding 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 endpoint and other bleeding endpoints will be based on adjudicated events. The primary safety endpoint 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 12month 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 two groups at 80% statistical power with a 2-sided alpha of 0.05. 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 intent-to-treat (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 intent-to-treat (ITT) analysis set includes all randomized 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 endpoint events observed from the time of the first study drug administration up to 2 days following 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 endpoint 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 x [1 – 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 days of discontinuation of the last study drug). Table 1 and 2 summarize the analysis methods for the primary and secondary safety endpoint 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 one 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, labs, and treatment assignment information. The following summaries will be provided for the interim analyses: summaries of the frequency of observed INR measurements after randomization and time in therapeutic range (TTR) 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 Riva 10 mg, as they may have renal impairment. There is no formal stopping rule for either success or futility pre-specified for these interim safety data analyses since 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 endpoints at the interim basis. The primary focus in this trial remains on collecting evidence on key safety endpoints at the end of proposed 12 month follow up.

Conclusion

The PIONEER AF-PCI exploratory trial evaluates the safety of three treatment strategies among a broad group of patients with paroxysmal, persistent, or permanent non-valvular AF following 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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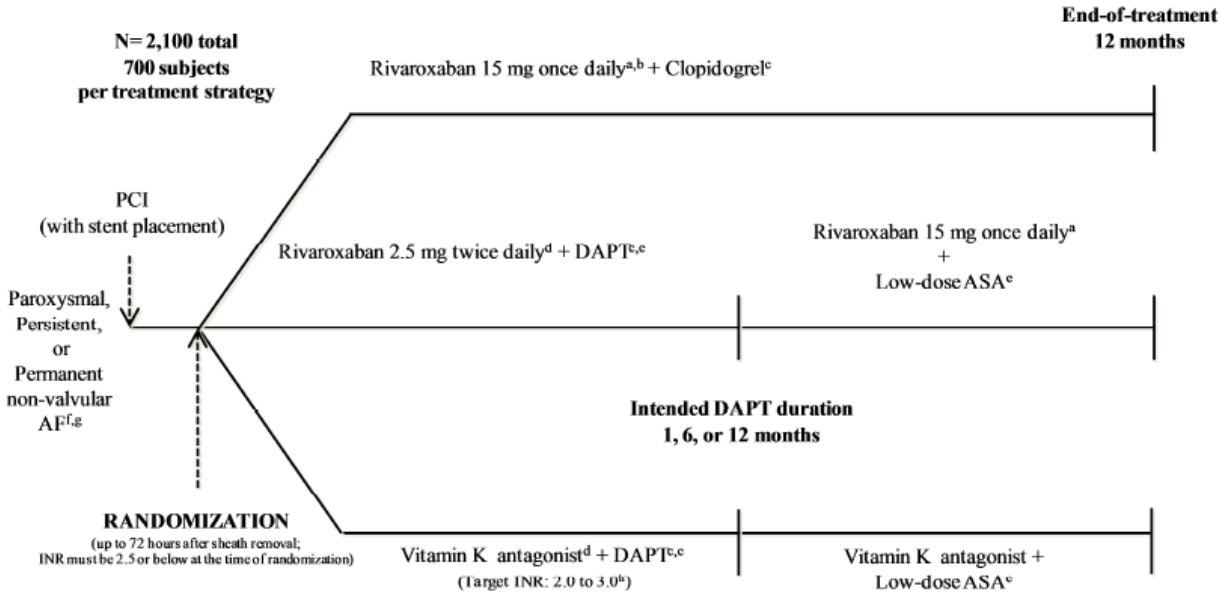
Figure 1: Study design of PIONEER AF-PCI



[a] Dose of rivaroxaban is reduced to 10 mg in subjects with (CrCl: 30 to <50 mL/min).
[b] First dose 72 to 96 hours after sheath removal.
[c] Clopidogrel daily maintenance dose is 75 mg per day; Alternate P2Y12 inhibitors: prasugrel dose is 10 mg per day and ticagrelor dose is 90 mg twice daily.
[d] First dose 12 to 96 hours after sheath removal.
[e] ASA 75 to 100 mg per day.
[f] Non-valvular AF is defined as AF not considered to be caused by a primary valve stenosis.
[g] Subjects with history of previous stroke or TIA are excluded.
[h] At the investigators discretion, an INR target of 2.0 to 2.5 may used as some guidelines recommend.

AF=atrial fibrillation; ASA=acetylsalicylic acid; CrCl=creatinine clearance; DAPT=dual antiplatelet therapy (low-dose ASA + clopidogrel [or alternate P2Y12 inhibitors, prasugrel or ticagrelor]); PCI=percutaneous coronary intervention; TIA=transient ischemic attack.

Table 1: Summary of Primary Endpoint Analysis Methods

Endpoint	Analysis Period	Analysis Set	Method
Primary Safety Endpoint	Treatment-emergent period (primary) Post-randomization period (supportive)	Safety Analysis Set	Two-sample proportion Cox-model (HR, 95% CI) Kaplan-Meier

Table 2: Summary of Secondary Endpoint Analysis Methods

Endpoint	Analysis Period	Analysis Set	Method
Components of primary safety endpoint (TIMI Major, TIMI Minor, Bleeding Requiring Medical Attention	Treatment-emergent period	Safety Analysis Set	2-sample proportion When appropriate, Cox-Model (HR, 95% CI) Kaplan-Meier
Composite of adverse cardiovascular events	Treatment-emergent period	Safety Analysis Set	2-sample proportion When appropriate, Cox-Model (HR, 95% CI) Kaplan-Meier
Components of adverse cardiovascular events (MI, Stroke, CV Death)+ Stent thrombosis	Treatment-emergent period	Safety Analysis Set	2-sample proportion When appropriate, Cox-Model (HR, 95% CI) Kaplan-Meier

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