Clinical relevance of ticagrelor monotherapy following 1-month dual antiplatelet therapy after bifurcation percutaneous coronary intervention: Insight from GLOBAL LEADERS trial

Peer-reviewed author version

Kogame, Norihiro; Chichareon, Ply; De Wilder, Kenneth; Takahashi, Kuniaki; Modolo, Rodrigo; Chang, Chun Chin; Tomaniak, Mariusz; Komiyama, Hidenori; Chieffo, Alaide; Colombo, Antonio; Garg, Scot; Louvard, Yves; Juni, Peter; Steg, Philippe G.; Hamm, Christian; VRANCKX, Pascal; Valgimigli, Marco; Windecker, Stephan; Stoll, Hans-Peter; Onuma, Yoshinobu; Janssens, Luc & Serruys, Patrick W. (2020) Clinical relevance of ticagrelor monotherapy following 1-month dual antiplatelet therapy after bifurcation percutaneous coronary intervention: Insight from GLOBAL LEADERS trial. In: CATHETERIZATION AND CARDIOVASCULAR INTERVENTIONS, 96 (1), p. 100-111.

DOI: 10.1002/ccd.28428
Handle: http://hdl.handle.net/1942/29117

The impact of ticagrelor monotherapy following one-month dual antiplatelet therapy after bifurcation percutaneous coronary intervention in a largest all-comers trial: insight from GLOBAL LEADERS trial.

Short running title: Ticagrelor monotherapy after bifurcation PCI in the GLOBAL LEADERS trial

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Author/funding disclosures:
Dr. Spitzer reports institutional grants from European Cardiovascular Research Institute, during the conduct of the study.
Dr. Hamm reports personal fees from AstraZeneca.
Dr. Vranckx reports personal fees from AstraZeneca and the Medicines Company during the conduct of the study and personal fees from Bayer Health Care, Terumo, and Daiichi-Sankyo outside the submitted work.
Dr. Valgimigli reports grants and personal fees from Abbott, personal fees from Chiesi, personal fees from Bayer, personal fees from Daiichi Sankyo, personal fees from Amgen, grants and personal fees from Terumo, personal fees from Alvimedica, grants from Medicure, grants and personal fees from Astrazeneca, personal fees from Biosensors, outside the submitted work.
Dr. Windecker's institution has research contracts with Abbott, Amgen, Bayer, Biotronik, Boston Scientific, Edwards Lifesciences, Medtronic, St Jude Medical, Symetis SA, and Terumo, outside the submitted work.
Dr. Serruys reports personal fees from Abbott Laboratories, personal fees from Biosensors, personal fees from Cardialysis, personal fees from Medtronic, personal fees from Micel Technologies, personal fees from Sinomedical Sciences Technology, personal fees from St. Jude Medical, personal fees from Stentys, personal fees from Svelte Medical Systems, personal fees from Philips/Volcano, personal fees from Xeltis, personal fees from StentIt and personal fees from HeartFlow, outside the submitted work.
All other authors declare no competing interests.

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Total word count: 4,944 words

Number of figures: 4, Number of tables: 3
Number of supplementary figures: 1, Number of supplementary tables: 4

Sources of funding: The Global Leaders trial was supported by the resource from AstraZeneca, Biosensors, and The Medicines Company.

Abstract

OBJECTIVES:

The aim of this study was to investigate the impact of ticagrelor monotherapy following one-month dual antiplatelet therapy (DAPT) after bifurcation percutaneous coronary intervention (PCI).

BACKGROUND:

The evidence regarding optimal antiplatelet strategy after bifurcation PCI is scarce.

METHODS:

GLOBAL LEADERS was a randomized, superiority, all-comers trial comparing one-month DAPT with ticagrelor and aspirin followed by 23-month ticagrelor monotherapy (experimental treatment) with standard 12-month DAPT followed by 12-month aspirin monotherapy (reference treatment) in patients treated with a biolimus A9-eluting stent. Bifurcation PCI was identified using a dedicated e-CRF based on the MADS classification. The primary endpoint at 2 years was a composite of all-cause death or new Q-wave myocardial infarction (MI).

Results:

A total of 15,845 patients were included in this subgroup analysis. There were 2,498 patients (15.8%) who underwent at least one bifurcation PCI, of whom 489 patients (19.6%) were treated with 2-stent technique. The incidence of primary endpoint at 2 years was similar between bifurcation and non-bifurcation group (4.7% vs 4.0%, p=0.083). Two-stent technique for bifurcation PCI was associated with higher incidences of primary endpoint and compared with One-stent technique (primary endpoint: 7.0% vs 4.2%, p=0.008). The experimental treatment showed a significant benefit in 2-year definite or probable stent thrombosis in patients with bifurcation PCI (HR: 0.46; 95% CI: 0.22-0.97) compared with those without bifurcation PCI (HR: 1.20; 95% CI: 0.85-1.69; p for interaction = 0.022).

CONCLUSIONS:

PCI for bifurcation lesion with a biolimus A9-eluting stent was associated with worse clinical outcomes than non-bifurcation lesion. When compared with aspirin monotherapy following 12-month standard DAPT, ticagrelor monotherapy for 23 month following one-month DAPT after bifurcation PCI showed a significant benefit on definite or probable stent thrombosis but not on the primary endpoint at 2 years.

Keywords: Percutaneous coronary intervention, drug-eluting stents, bifurcation lesion, antiplatelet treatment

Condensed abstract

The aim of this analysis was to investigate the impact of ticagrelor monotherapy following one-month dual antiplatelet therapy (DAPT) after bifurcation percutaneous coronary intervention. A total of 15,968 all-comer patients were randomly assigned either one-month DAPT with ticagrelor and aspirin followed by 23-month ticagrelor monotherapy as experimental treatment or standard 12-month DAPT followed by 12-month aspirin monotherapy. The difference in a composite of all-cause death and new Q-wave myocardial infarction at 2 years did not reach statistical significance between bifurcation and non-bifurcation group (4.7% vs 4.0%, p=0.083). A benefit of experimental treatment was statistically demonstrated in 2-year definite or probable stent thrombosis in patients with bifurcation versus non-bifurcation (p for interaction = 0.022).

Abbreviations

ARC = Academic Research Consortium

DES = drug-eluting stent

e-CRF = electronic case record form

MI = myocardial infarction

TVR = target vessel revascularization

PCI = percutaneous coronary intervention

POCE = patient oriented composite endpoint

ST = stent thrombosis

Introduction

Bifurcation lesions are associated with a lower rate of procedural success and a higher risk of complications compared to non-bifurcation lesions in patients treated with percutaneous coronary intervention (PCI) (1,2). A number of randomized controlled trials have investigated the optimal intervention strategy in patients with bifurcation lesions and showed no benefit in terms of clinical outcomes for the systematic two-stent approach versus main branch-only stenting with provisional stenting of the side branch (2). Therefore, the provisional side branch stenting strategy is recommended for treatment of bifurcation lesions as class IA recommendation by the current guideline (3), whereas in 5 to 25% of cases, a second stent for the side branch may be needed (4-6). When two-stent strategy is necessary, which two-stent technique should be preferred is still debated (3).

The complexity and the numerous subtypes of two-stent techniques render their comparison difficult. For that reason, the European bifurcation club (EBC) introduced the MADS classification to standardize reports, to allow comparison between studies, and to facilitate interpretation of published results in the evolving literature (7,8). The MADS classification classifies different stenting techniques according to which segment is initially stented; main proximal first (M), main across side first (A), distal first (D), and side branch first (S), and how many stents are used. In the GLOBAL LEADERS trial, the dedicated electronic case record form (e-CRF) based MADS classification was achieved in all site-reported bifurcation lesions, which represents a unique opportunity to analyze complete case study stratified for presence of bifurcation within the large contemporary PCI trial (9).

In terms of antiplatelet therapy after bifurcation PCI, while high PCI complexity including 2-stent technique for bifurcation lesions represent a driver for favoring a prolonged dual antiplatelet therapy (DAPT) over a shorten DAPT, the evidence regarding optimal DAPT duration based on complexity of intervention is limited, especially due to the low

prevalence of bifurcation PCI in the previous clinical trials (10,11). Furthermore, the role of potent P2Y12 inhibitor after bifurcation PCI is uncertain.

In this prespecified subgroup analysis of the GLOBAL LEADERS trial (12), we sought to investigate the impact of ticagrelor monotherapy following one-month DAPT after bifurcation PCI.

Methods

The GLOBAL LEADERS trial

The design and main results of the GLOBAL LEADERS trial have been published previously (13). Briefly, it was a prospective, multicenter, randomized, open-label, superiority trial comparing two antiplatelet regimens in 15,991 all-comers patients who were exclusively treated with a biolimus A9-eluting stent for stable coronary artery disease or acute coronary syndromes.

Patients were randomly assigned in a 1:1 fashion to one-month DAPT with aspirin and ticagrelor followed by 23 months of ticagrelor monotherapy, or standard DAPT with aspirin plus either clopidogrel (for patients with stable coronary artery disease) or ticagrelor (for patients with acute coronary syndromes) for 12 months, followed by aspirin monotherapy for 12 months.

In terms of bifurcation PCI, the choice of bifurcation treatment technique was left to the discretion of the operators.

The trial was approved by the institutional review board at each investigating center. The study followed the ethical principles of the Declaration of Helsinki. All the participants provided written informed consent at the time of participation in the trial.

Study population and data collection

According to the all-comers concept, only a limited number of in- and exclusion criteria were applied in the GLOBAL LEADERS trial (Supplementary methods). There were no restrictions as to the number, severity, or location of lesions to be treated, or number of stents used. Patients in need of chronic anticoagulation were deemed not eligible.

In this prespecified subgroup analysis, patients undergoing bifurcation PCI were identified from the dedicated e-CRF based MADS classification reported by investigators. Bifurcation lesions were defined by investigators in accordance with the practical definition of the European Bifurcation Club (7), as "a coronary artery narrowing occurring adjacent to, and/or involving the origin of a significant side branch." All bifurcation PCI were classified whether treated with 1-stent or 2-stent technique using the results of MADS classification. Three-stent techniques such as "extended V" and "trouser legs and seat" were included in the 2-stent technique. The stenting technique for trifurcation lesion is not covered by the MADS classification, therefore trifurcation (7 lesions in 7 patients) was identified according to the definition of SYNTAX Score (14).

Total stent length per patient was calculated according to the cumulative nominal length of the stent used in each individual case without consideration for overlapping of stents.

As many as seven on-site monitoring visits were done at individual sites, with 20% of reported events checked against source documents. Additionally, the trial was monitored for event under-reporting and event definition consistency. However, no overall central independent adjudication of clinical events was implemented.

Endpoint definitions

The primary endpoint was the composite of all-cause death or new Q-wave myocardial infarction (MI) up to two years after randomization. Deaths from any cause were

ascertained without adjudication(15), due to the fact that the survival data were derived from thorough site reports and search for vital status obtained from public domains. Q-wave MI was centrally adjudicated and defined in compliance with the Minnesota classification (new major Q-QS wave abnormalities) or by the appearance of a new left bundle branch block in conjunction with abnormal biomarkers.

The key secondary endpoint was bleeding defined according to the Bleeding Academic Research Consortium (BARC) criteria (type 3 or 5) up to two years (16). Other secondary endpoints included individual components of the primary endpoint (all-cause death and new Q-wave MI); any stroke; any MI; any revascularization; target vessel revascularization (TVR); definite stent thrombosis (ST) and definite or probable ST (17).

In addition, the risk of patient-oriented composite endpoint (POCE) according to the Academic Research Consortium (ARC)-2 was assessed up to two years(17). POCE was defined as the composite of all-cause death, any stroke (ischemic and hemorrhagic), any MI (periprocedural or spontaneous with STEMI or non-ST segment elevation MI (NSTEMI), and any revascularization (repeat PCI or coronary artery bypass graft [CABG] surgery in target or non-target vessel) (17). The third universal definition of MI was the recommended criteria to report MI (18). Composite endpoints were analysed hierarchically. Individual components were reported non-hierarchically (19).

Statistical Analysis

Clinical outcomes were compared between the following groups:

1. Patients treated for at least one bifurcation lesions versus patients not treated for any bifurcation lesion (Bifurcation vs. non-bifurcation);
2. Patients treated for at least one bifurcation lesions with 1-stent technique versus 2-stent technique (1-stent vs. 2-stent);

Due to the absence of classification for trifurcation PCI according to the MADS classification, patients with trifurcation PCI (7 lesions in 7 patients) were described separately in supplementary table 3 and were excluded from the analysis comparing 1-stent vs. 2-stent.

The effect of experimental versus reference antiplatelet therapy according to presence/absence of bifurcation PCI was estimated with a Cox regression model. In addition, the treatment effect of experimental versus reference treatment according to one or two-stent strategy was estimated with a Cox regression model as exploratory analysis due to too much sub-calcification and small numbers of patients.

Categorical variables were compared with the $\chi 2$ test or Fisher's exact test. Continuous variables were compared with Student's t test or Mann-Whitney U test for non-normally distributed data. Composite endpoints were calculated using time-to-first of any of the composite event(s) per patient. Patients started being at risk on the day of index percutaneous coronary intervention, if no procedure was performed, on the day of randomization. Survival curves were constructed using Kaplan-Meier estimates and the log-rank test was used to compare between-group differences. Landmark analyses were performed with prespecified cut-offs at 30 days (at the time of the planned date of discontinuation of aspirin in the experimental treatment) and one year (at the time of the planned dates of discontinuation of a P2Y12 inhibitor in the reference treatment). In total, there were six outpatient protocol visits at 30 days, 3, 6, 12, 18, and 24 months. A two-sided P value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were done in SPSS (version 25.0.0, IBM, New York). The trial is registered with ClinicalTrials.gov, number NCT01813435.

Results

The GLOBAL LEADERS trial recruited a total of 15,991 patients(20), of whom 146 patients were excluded from this analysis (85 patients were randomised but not treated with PCI; in 38 patients, PCI was attempted but detailed data on PCI procedure were not available; and 23 patients withdrew consent and formally requested the complete deletion of their data from the database), leaving 15,845 patients in this analysis. From the 15,845 patients included in the GLOBAL LEADERS trial, 2,498 patients (15.7%) underwent at least one bifurcation PCI and 7 patients (0.04%) underwent at least one trifurcation PCI. From those 2,498 patients with at least one bifurcation PCI, 2002 (80.1%) were treated with 1-stent technique, and 489 (19.6%) with 2-stent technique (Figure 1).

Baseline characteristics

Baseline and procedural characteristics of each comparison are shown in Table 1 and Supplementary table 1.

There were some differences between non-bifurcation group and bifurcation group. Patients in the non-bifurcation group had a higher body-mass index and higher prevalence of diabetes mellitus or previous history of PCI and CABG, whereas patients in the bifurcation group presented more often with acute coronary syndrome. In terms of procedural characteristics, patients in the bifurcation group as expected had more lesions, stents, and longer total stent length per patients.

Among patients with at least one bifurcation PCI, there were no differences in baseline characteristics between 1-stent group and 2-stent group. In terms of procedural characteristics, patients in 2-stent group were more frequently treated with femoral approach, and had more lesions and stents, and longer total stent length per patients. Bifurcation lesions involving left main stem were more frequently observed in 2-stent group (7.3% vs. 12.2%, $p<0.001$), and also kissing balloon inflation was more frequently performed in 2-stent group

(34.3% vs. 73.6%, p<0.001). Proximal optimization technique captured in the eCRF was equally performed in both groups (30.6% vs. 34.8%, p=0.074).

Reflecting proper randomization, allocation of antiplatelet treatment was balanced amongst various subgroups.

Clinical outcomes

Clinical outcomes at 30 days, 1 and 2 years, and landmark analysis at 30 days and 1 year are shown for each comparison (Table 2, Figure 2, and supplementary table 2).

In terms of primary endpoint (a composite of all-cause death or new Q-wave MI) at 2 years, there was a trend toward higher incidence in the bifurcation group compared with the non-bifurcation group (4.72% in bifurcation group vs. 3.98% in non-bifurcation group, hazard ratio (HR) 1.19 [95% confidential internal (95%CI): 0.98-1.46], p=0.083). This difference was driven by higher incidence of new Q-wave MI in bifurcation group compared with non-bifurcation group (1.84% vs 1.04%, HR 1.78 [95%CI: 1.27-2.48], p=0.001). The incidences of 2-year POCE in bifurcation group was higher compared with no bifurcation group (15.05% vs. 13.27%, HR 1.16 [95%CI: 1.03-1.29], p=0.011). This difference was driven by higher incidence of any revascularization in bifurcation group compared with non-bifurcation group (11.21% vs 9.19%, HR 1.24 [95%CI: 1.09-1.41], p=0.001). In addition, the incidences of 2-year TVR in bifurcation group was higher compared with no bifurcation group (6.69% vs. 4.83%, HR 1.40 [95%CI: 1.18-1.66], p<0.001). The differences in TVR were also observed at 30-day and 1-year follow-up, whereas no differences were observed in landmark analysis at 1 year. Bifurcation PCI was not associated with an increased risk of BARC 3 or 5 bleeding at 2 years (2.48% vs. 2.02%, HR 1.23, [95%CI: 0.94-1.63], p=0.134).

Two-stent group had higher incidences of primary endpoint, all-cause death, POCE, any MI, any revascularization, TVR, and definite or probable stent thrombosis compared with

1-stent group at 2-year follow-up. At 30-day follow-up, there was trend toward higher incidences of all-cause death, POCE, and definite or probable stent thrombosis in 2-stent group compared with 1-stent group, whereas a landmark analysis at 30days demonstrated the same trend as 2-year follow-up. At 1-year follow-up, the trend was similar to 2-year follow-up except for all-cause death, whereas a landmark analysis at 1 year demonstrated that there were no significant differences on all endpoints between groups. In terms of BARC 3 or 5 bleeding, there were no differences between 2-stent group and 1-stent group in all periods.

In terms of trifurcation PCI, the clinical outcomes at 2 years in 7 patients are shown in supplementary table 3.

Treatment effect of antiplatelet therapy

Results for experimental versus reference antiplatelet treatment in the bifurcation and non-bifurcation groups are reported in Figure 3 and Table 3. In terms of hard endpoint such as a composite of all-cause death and new-Q wave MI at 2 years, the experimental strategy did not show any benefit in patient undergoing bifurcation PCI against the reference strategy (bifurcation: HR: 0.74; 95% CI: 0.51-1.07, non-bifurcation: HR: 0.90; 95% CI: 0.76-1.07; p for interaction = 0.343). The experimental antiplatelet treatment showed a significant benefit on 2-year definite or probable stent thrombosis in patients with bifurcation PCI (HR: 0.46; 95% CI: 0.22-0.97) compared with those without bifurcation PCI (HR: 1.20; 95% CI: 0.85-1.69; p for interaction = 0.022) (Figure 4A). The same trend was observed on 1-year definite or probable stent thrombosis (bifurcation: HR: 0.51; 95% CI: 0.22-1.18, non-bifurcation: HR: 1.46; 95% CI: 0.98-2.18; p for interaction = 0.026), whereas this significant benefit of ticagrelor monotherapy against aspirin monotherapy was subsided beyond 1 year (bifurcation: HR: 0.33; 95% CI: 0.07-1.66, non-bifurcation: HR: 0.63; 95% CI: 0.31-1.30; p for interaction = 0.478) (Figure 4B). In addition, the landmark analysis at 30 days did not

demonstrate any significant benefit of the experimental antiplatelet treatment against the reference antiplatelet treatment on clinical outcomes (Table 3). In terms of 2-year incidence of stroke, the experimental strategy showed negative effect in patient undergoing bifurcation PCI against the reference strategy (bifurcation: HR: 2.72; 95% CI: 1.06-6.94, non-bifurcation: HR: 0.82; 95% CI: 0.58-1.14; p for interaction = 0.018). This negative effect was observed at 1 year follow-up (bifurcation: HR: 4.07; 95% CI: 1.15-14.43, non-bifurcation: HR: 0.85; 95% CI: 0.55-1.30; p for interaction = 0.021), whereas it was subsided beyond 1 year (bifurcation: HR: 1.36; 95% CI: 0.30-6.08, non-bifurcation: HR: 0.77; 95% CI: 0.45-1.32; p for interaction = 0.479).

Results for experimental versus reference antiplatelet treatment in 2-stent and 1-stent groups are reported in supplementary figure 1 and supplementary table 4. In terms of 2-year clinical outcomes, there were no effect of experimental antiplatelet treatment against reference antiplatelet treatment. However, the experimental antiplatelet treatment showed a trend toward lower incidence of 1-year primary endpoint in 2-stent group (HR: 0.33; 95% CI: 0.12-0.89) compared with 1-stent group (HR: 0.92; 95% CI: 0.51-1.63; p for interaction = 0.081). In addition, the experimental antiplatelet treatment showed possibly a trend toward lower incidence of 1-year all-cause death in 2-stent group (HR: 0.21; 95% CI: 0.05-0.96) compared with 1-stent group (HR: 0.87; 95% CI: 0.41-1.82; p for interaction = 0.100), whereas this trend was subsided beyond 1 year. In addition, the experimental antiplatelet treatment showed a trend toward lower incidence of 1 and 2-year definite of probable stent thrombosis in 2-stent group (HR: 0.26; 95% CI: 0.06-1.23, p = 0.089 at 1 year, HR: 0.23; 95% CI: 0.05-1.07, p = 0.061 at 2 years).

Discussion

The main findings of the study are following:

1. PCI for bifurcation lesion with a biolimus A9-eluting stent was associated with worse clinical outcomes compared with non-bifurcation lesion, in terms of POCE, new Q-wave MI, any revascularization and TVR at 2 years, whereas no significant difference was observed on primary endpoint (all-cause death or new Q-wave MI) between groups.
2. The use of 2-stent technique for bifurcation PCI was associated with higher incidences of primary endpoint, all-cause death, POCE, any MI, any revascularization, TVR, and definite or probable stent thrombosis at 2-years compared with the use of 1-stent technique.
3. One-month DAPT with aspirin and ticagrelor followed by 23-month ticagrelor monotherapy (experimental treatment) was associated with a significant benefit in the risk of definite or probable stent thrombosis but had no impact on primary endpoint compared with 12-month standard DAPT followed by 12-month aspirin monotherapy (reference treatment) in patients who underwent bifurcation PCI.
4. The experimental treatment strategy was not associated with an increased risk of BARC 3 or 5 major bleeding in patients who underwent PCI, irrespective of bifurcation and the stenting techniques.

Bifurcation vs. non-bifurcation group

The difference in POCE rate between patients with at least one bifurcation lesion versus patients without any bifurcation lesion was observed up to 1year and were mainly driven by a difference in any revascularization (bifurcation 8.7% vs. non-bifurcation 6.2%, HR 1.41 [95%CI: 1.22-1.64], <0.001), whereas the 2-year all-cause death rate was similar (bifurcation 3.0% vs. non-bifurcation 3.0%, p=0.964). The Kaplan-Meier curve showed an early divergency of any revascularization, whereas beyond 1 year patients undergoing bifurcation PCI were no longer at high risk of any revascularization (bifurcation 2.9% vs. non-bifurcation

3.3%, p=0.318). The similar trend was also observed on the incidence of TVR. However, the higher incidence of new Q-wave MI in bifurcation group over non-bifurcation group was consistently observed at 1 year and 2 years and landmark analysis at 1 year, whereas the incidence of any MI was similar between groups. This finding may suggest that bifurcation PCI can be associated with the occurrence of more severer MI when compared with non-bifurcation PCI.

2-stent vs. 1-stent technique for bifurcation PCI

In the present study, a substantial predominance of 1-stent technique against 2-stent technique was observed for the bifurcation PCI. This finding is in line with the increasing amount of evidence in favor of main branch-only stenting with provisional stenting of the side branch strategy for most of the bifurcation lesions (2). These data reflect the findings of a recently reported pooled analysis of 2 randomized controlled trials comparing simple versus complex stenting for bifurcation lesions (21). However, in absence of the information whether 2-stent technique is provisional or up front these data should be interpreted with caution and considered as hypothesis generating.

Optimal antiplatelet strategy for patients undergoing bifurcation PCI

The evidence of optimal antiplatelet strategy after bifurcation PCI is scarce, especially for potent antiplatelet drugs such as ticagrelor and prasugrel. Recent pooled patients-level analysis demonstrated that short DAPT of 3 or 6 months is associated with higher incidence of 1-year major adverse cardiac events mainly driven by MI compared with prolonged DAPT of more than 1 year in patients undergoing PCI for complex lesions including bifurcation treated with 2-stent technique (10). In addition, the multicenter observational study reported that the risks of a composite of all-cause death or MI, MI, and definite or probable ST at 4

years were significantly lower in the prolonged DAPT group (≥12 months) than shorter DAPT group (<12 months) after bifurcation PCI with DES (22). From these results, it seems that patients undergoing bifurcation PCI need at least 12-month DAPT. Previously coronary bifurcation lesions were reported as independent risk factor of for stent thrombosis (23-25). Several reasons could explain increased risk of stent thrombosis. Firstly, bifurcation stenting modifies the local hemodynamics and creates low endothelial shear stress and stagnation areas that could result in local thrombogenicity (26). Secondly, pathology study demonstrated that the flow divider zone was associated with a high percentage of uncovered struts and fibrin deposition several months after DES implantation, that could represent a substrate for stent thrombosis (27). Thirdly, two-stent strategies have been suspected of inducing overlapping device segments that could result in local thrombogenicity (28). Finally, bifurcation stenting could also induce stent malapposition due to vessel dimension variation along the different segments and promote future thrombotic events (29).

In the present study, ticagrelor monotherapy following very short one-month DAPT demonstrated significant treatment effect on definite or probable stent thrombosis compared with conventional aspirin monotherapy following 12-month DAPT. This benefit was observed up to 1 year and subsided beyond 1 year. Therefore, the effect of ticagrelor monotherapy on definite or probable stent thrombosis may superior to conventional DAPT between 1 and 12 months without increase of major bleeding events. However, similar impact on the composite of all-cause death and new Q-wave MI so called “hard endpoint” was not observed.

In terms of early discontinuation of aspirin at 30 days in patients undergoing bifurcation PCI, a landmark analysis at 30 days demonstrated that the incidences of all clinical endpoints were similar between two antiplatelet strategies without any statistically differences in

patients with bifurcation PCI (Table 3). This finding may suggest that aspirin can be stopped at 30 days without safety concerns even in patients undergoing bifurcation PCI.

Study limitations

This prespecified subgroup analysis has several limitations.

Firstly, no formal power calculation was performed and there was numerical mismatch between groups. Together with the inherent limitations of sub-analyses including multiple testing, the study findings should be considered as hypothesis-generating (30).

Secondly, clinical outcomes were not adjudicated by an independent clinical event committee. All events were identified and confirmed by the investigators of each hospital. There might be inaccuracies in determining cause of death (cardiac versus noncardiac) or target vessel MI. Therefore, we chose all-cause death or new Q-wave MI centrally adjudicated by core lab instead of cardiac death or target vessel MI as the primary outcome.

Thirdly, a biolimus A9-eluting stent has a relatively thicker strut of 120 μm compared with other current generation DES. This might result in the worse outcomes in bifurcation lesions treated with 2-stent technique using a biolimus A9-eluting stent due to the overlap of relatively thicker struts. However, in the present study, all patients were exclusively treated with a biolimus A9-eluting stent, and this makes the effect of antiplatelet drug more likely.

Finally, in the context of a trial in which the primary endpoint was not met, these findings need to be considered as hypothesis generating and further investigations are warranted in future specific trials on bifurcation PCI.

Conclusion

In the present study, bifurcation PCI with a biolimus A9 eluting stent was associated with worse clinical outcomes at 2 years compared with non-bifurcation PCI in all-comers

462 population. Ticagrelor in combination with aspirin for 1 month followed by ticagrelor alone
463 for 23months was more beneficial on definite or probable stent thrombosis compared with
464 12-month standard DAPT followed by 12-month aspirin monotherapy without increase of
465 major bleeding events. However, the experimental strategy did not show any benefit on hard
466 endpoint such as a composite of all-cause mortality or new Q-wave MI when compared with
467 the reference strategy in patients undergoing bifurcation PCI.
468

Perspectives

What is known?

The evidence regarding optimal DAPT duration after bifurcation PCI is limited. These limited evidences suggested that patients undergoing bifurcation PCI need at least 12-month DAPT. However, the role of potent P2Y12 inhibitor after bifurcation PCI is uncertain.

What is new?

The present all-comer study included the largest cohort exclusively treated with a biolimus A9 eluting stent. One-month DAPT followed by 23-month potent P2Y12 inhibitor demonstrated clinical benefit on stent thrombosis but not on a composite of all-cause death or new Q-wave MI when compared with 12-month standard DAPT followed by 12-month aspirin monotherapy without increase of major bleeding events.

What is next?

Very short DAPT followed by monotherapy of potent P2Y12 inhibitor to optimize outcomes after bifurcation PCI may warrant prospective randomized investigation.

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583 **Figure legends**

584

585 **Figure 1. Study flow chart.**

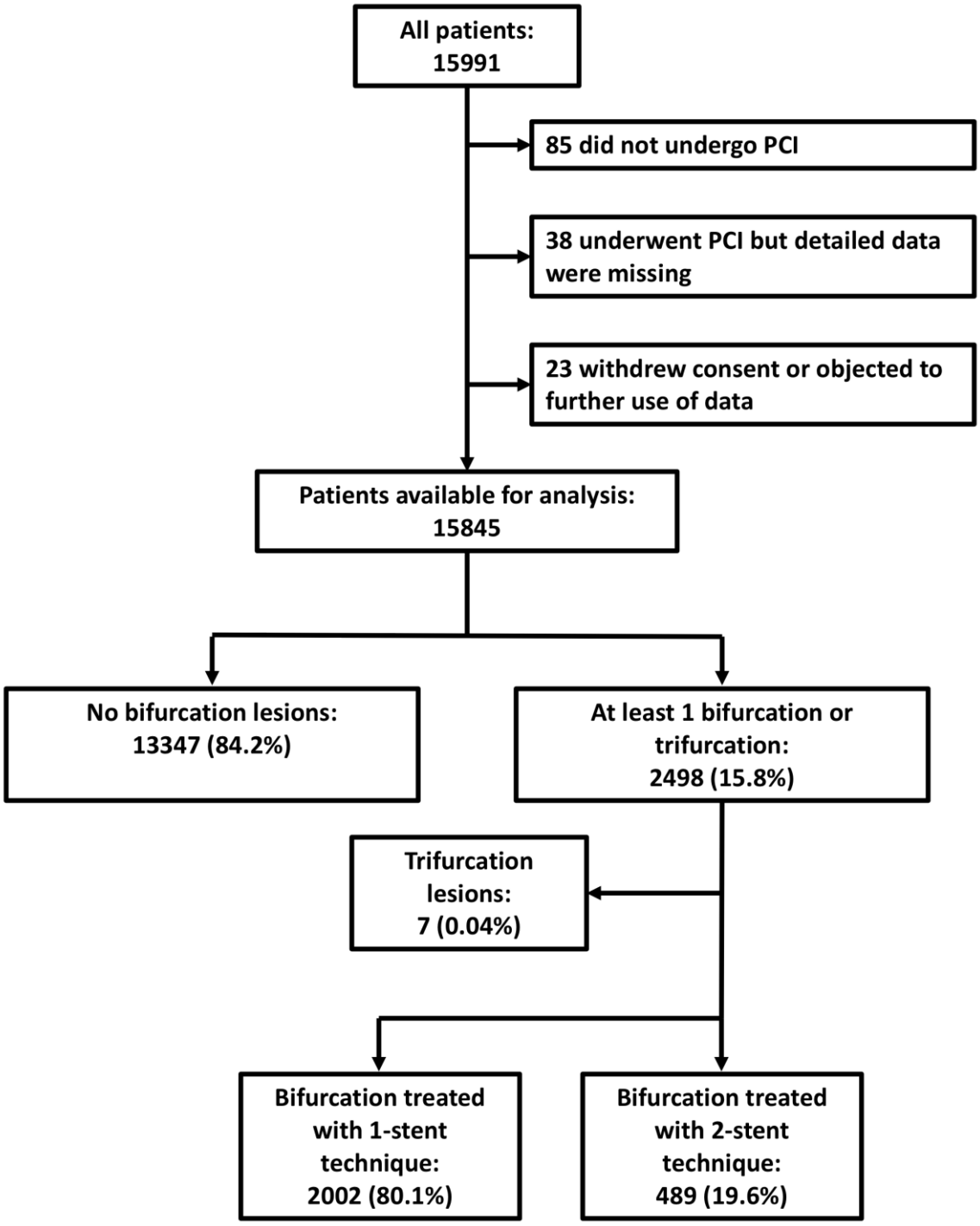

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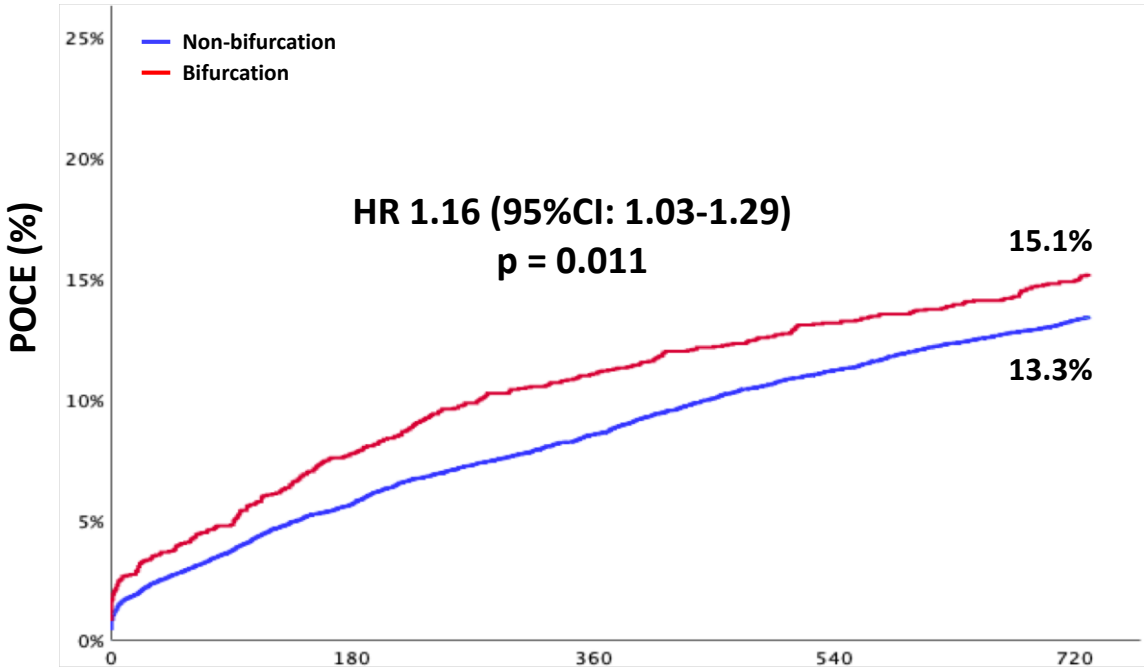
Figure 2. Kaplan–Meier estimates for clinical endpoints over 730 days of follow-up among patients with or without bifurcation PCI.

Kaplan–Meier curves show the cumulative incidence of patient oriented composite endpoint (POCE) -a composite of all-cause death, stroke, any myocardial infarction, or any revascularization- (Panel A); all-cause death (Panel B); stroke (Panel C); any myocardial infarction (Panel D); any revascularization (Panel E).

A

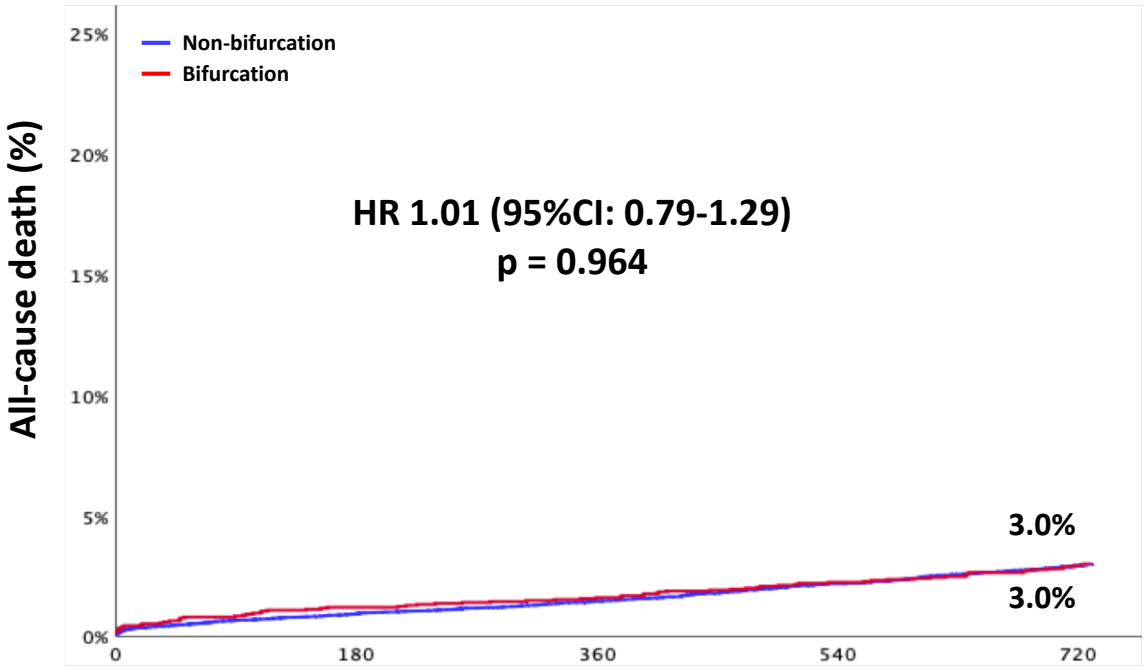


No. at risk

Non-bifurcation	13347	12735	12452	12232	12064	11832	11678	11512	11278
Bifurcation	2498	2358	2281	2225	2193	2165	2136	2113	2069

593

B

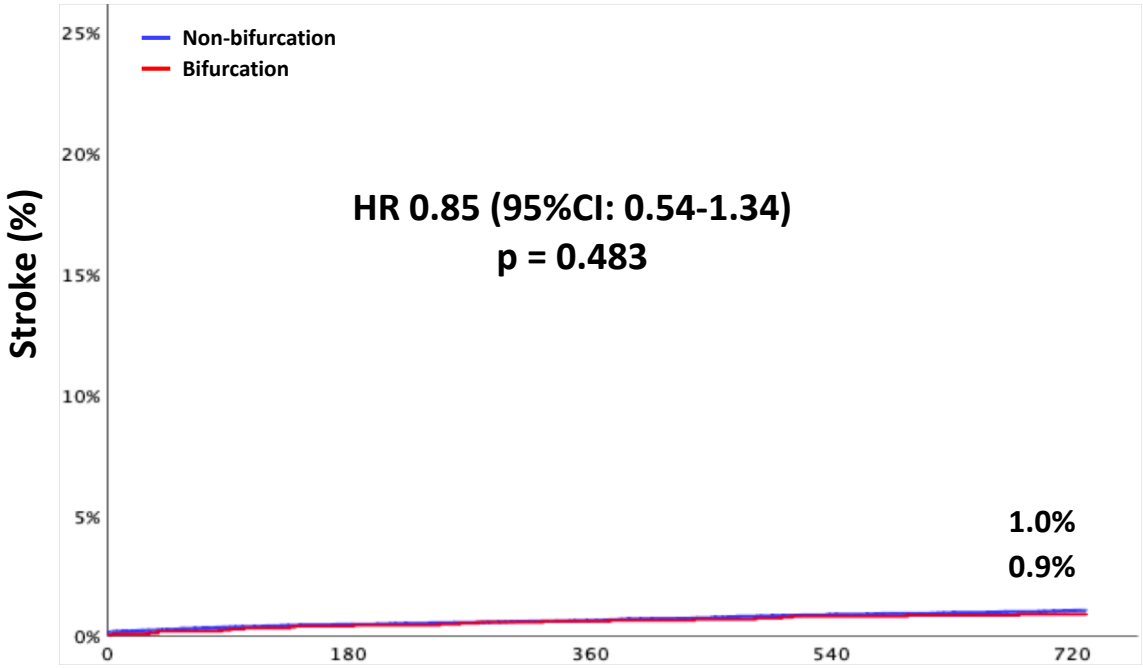


No. at risk

Non-bifurcation	13347	13251	13212	13184	13144	13093	13043	12987	12842
Bifurcation	2498	2476	2466	2461	2456	2448	2439	2429	2403

594

C

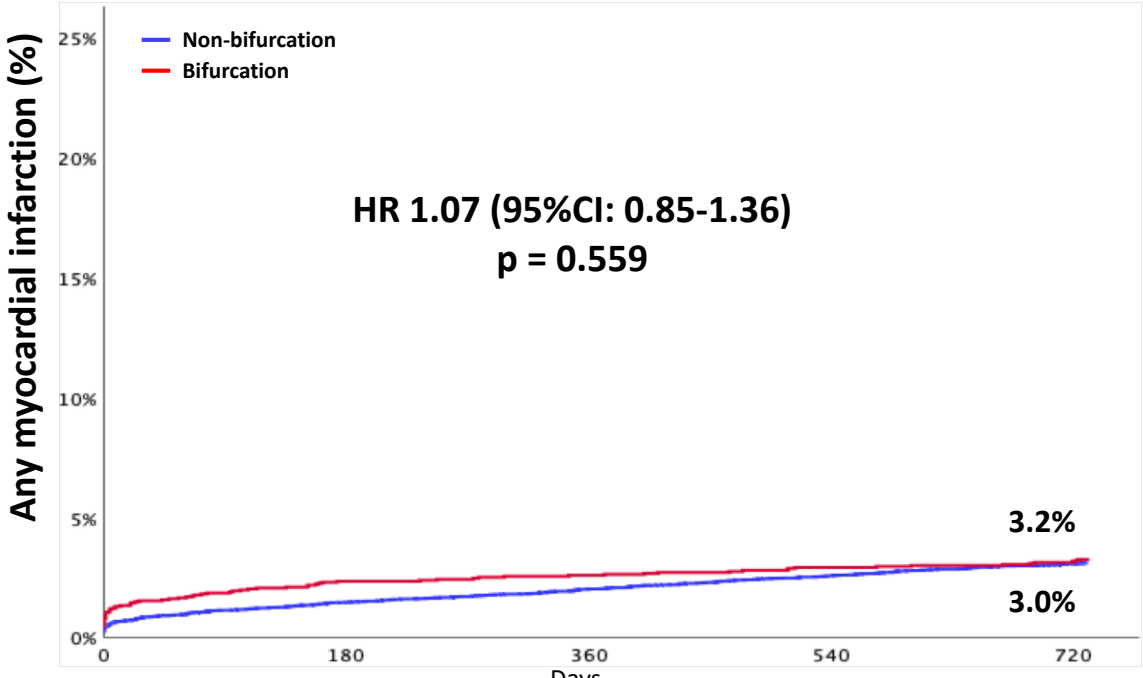


No. at risk

Non-bifurcation	13347	13089	13018	12972	12916	12834	12769	12691	12524
Bifurcation	2498	2455	2436	2425	2417	2405	2391	2377	2350

595

D



No. at risk

Non-bifurcation	13347	12993	12891	12822	12743	12637	12551	12453	12274
Bifurcation	2498	2416	2389	2379	2370	2360	2344	2329	2298

596

E

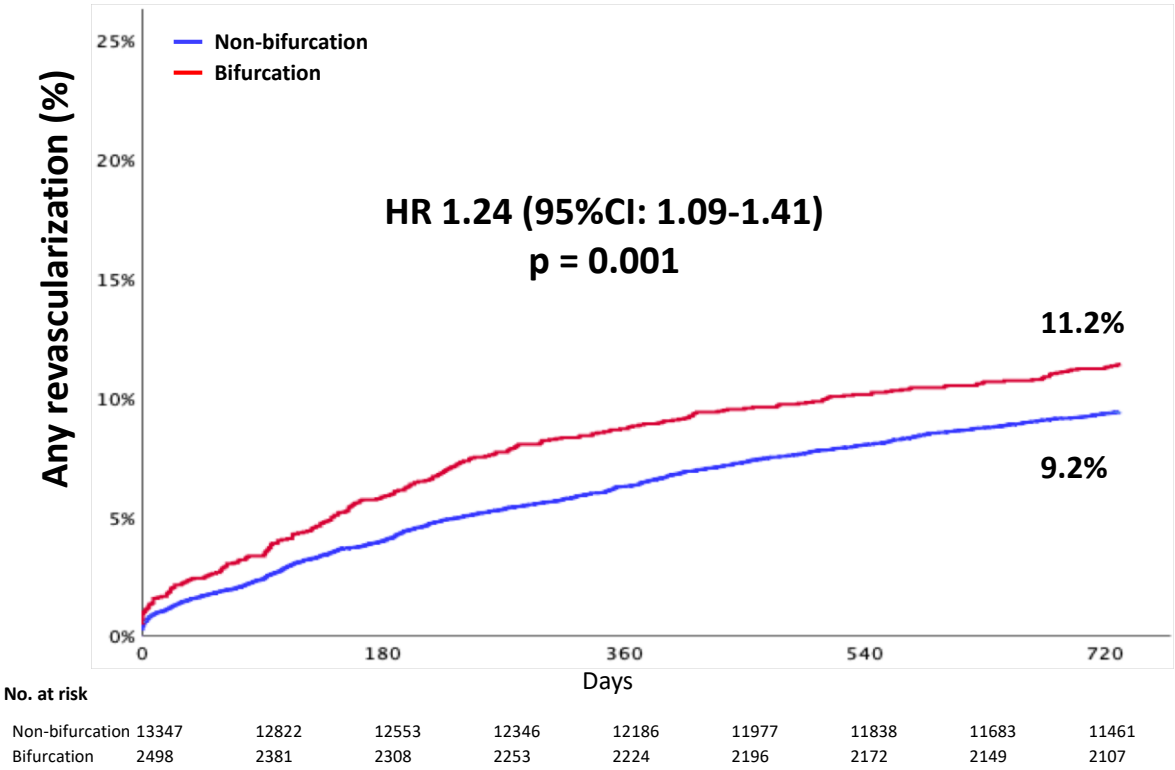
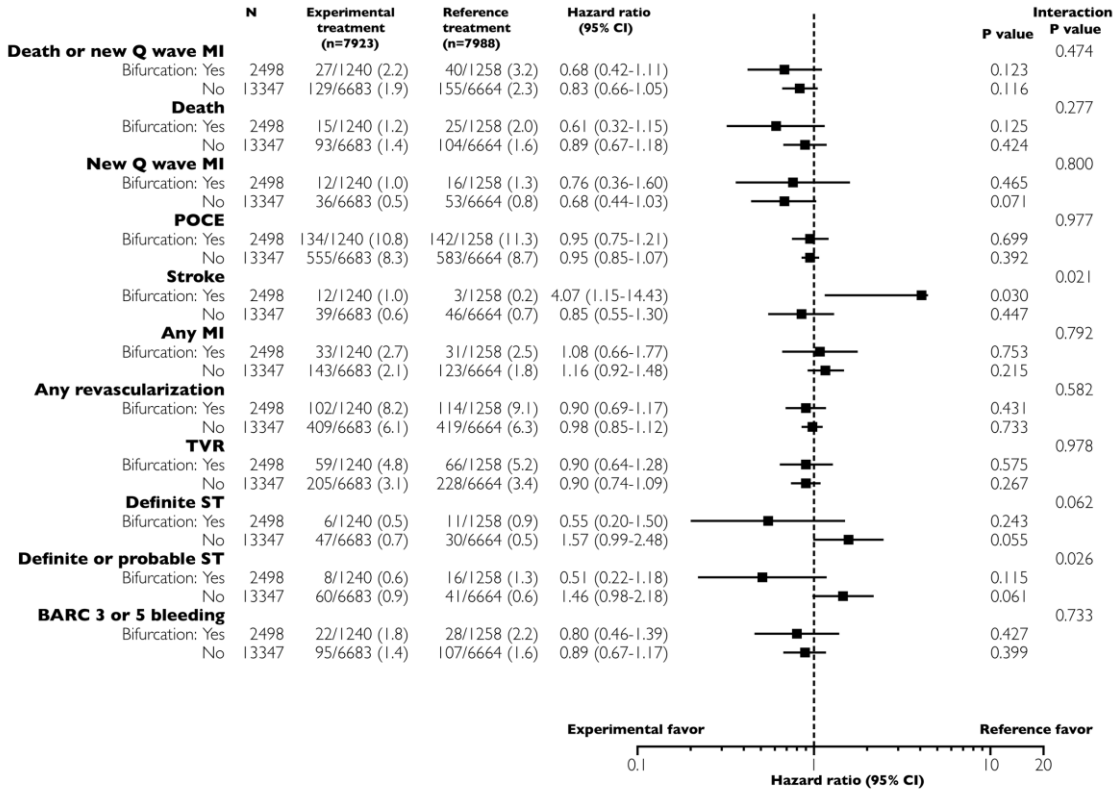


Figure 3. Treatment comparison of experimental versus reference antiplatelet strategy in randomized patients with versus without bifurcation PCI at 1 year (A) and 2 years (B) follow-up

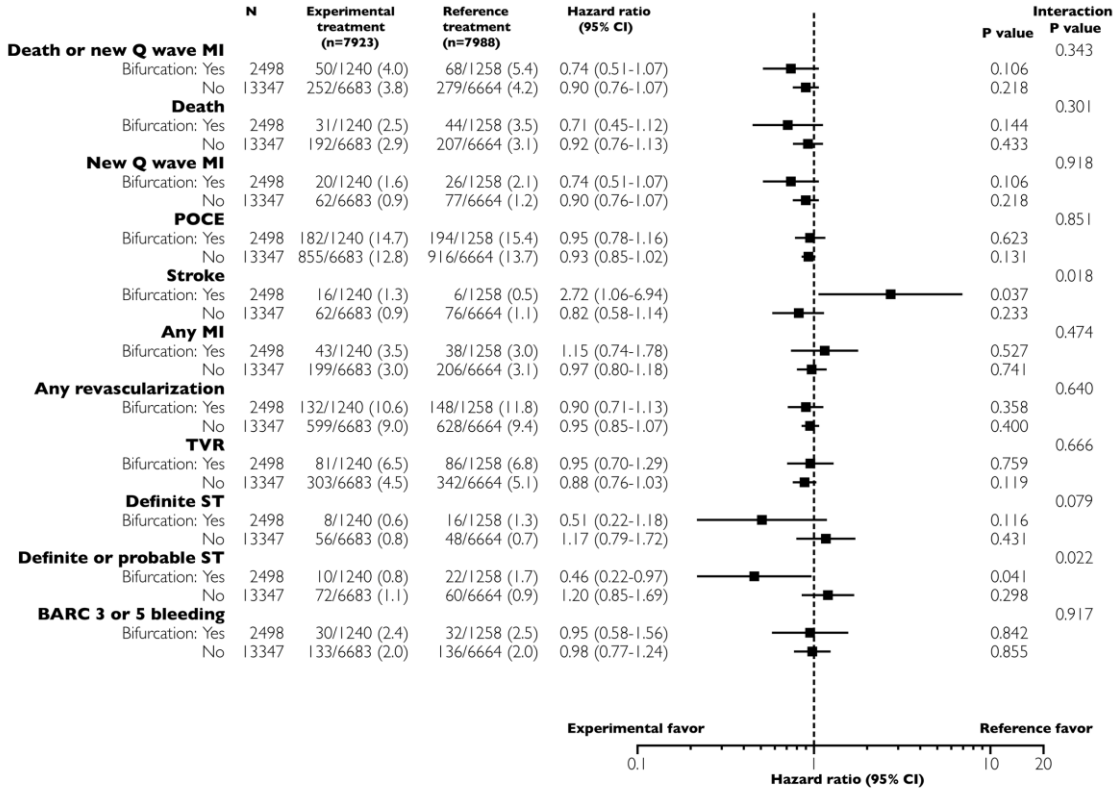
*POCE was defined as a composite of all-cause death, any stroke, any MI, and any revascularization.

#Values were compared with Fisher's exact test.

BARC = Bleeding Academic Research Consortium; MI = myocardial infarction; POCE = patient-oriented composite endpoint; ST = stent thrombosis; TVR = target vessel revascularization.


N
Experimental treatment (n=7923)
Reference treatment (n=7988)
Hazard ratio (95% CI)
P value
Interaction P value
Death or new Q wave MI 0.474
Bifurcation: Yes 2498 27/1240 (2.2) 40/1258 (3.2) 0.68 (0.42-1.11) 0.123
No 13347 129/6683 (1.9) 155/6664 (2.3) 0.83 (0.66-1.05) 0.116
Death 0.277
Bifurcation: Yes 2498 15/1240 (1.2) 25/1258 (2.0) 0.61 (0.32-1.15) 0.125
No 13347 93/6683 (1.4) 104/6664 (1.6) 0.89 (0.67-1.18) 0.424
New Q wave MI 0.800
Bifurcation: Yes 2498 12/1240 (1.0) 16/1258 (1.3) 0.76 (0.36-1.60) 0.465
No 13347 36/6683 (0.5) 53/6664 (0.8) 0.68 (0.44-1.03) 0.071
POCE 0.977
Bifurcation: Yes 2498 134/1240 (10.8) 142/1258 (11.3) 0.95 (0.75-1.21) 0.699
No 13347 555/6683 (8.3) 583/6664 (8.7) 0.95 (0.85-1.07) 0.392
Stroke 0.021
Bifurcation: Yes 2498 12/1240 (1.0) 3/1258 (0.2) 4.07 (1.15-14.43) 0.030
No 13347 39/6683 (0.6) 46/6664 (0.7) 0.85 (0.55-1.30) 0.447
Any MI 0.792
Bifurcation: Yes 2498 33/1240 (2.7) 31/1258 (2.5) 1.08 (0.66-1.77) 0.753
No 13347 143/6683 (2.1) 123/6664 (1.8) 1.16 (0.92-1.48) 0.215
Any revascularization 0.582
Bifurcation: Yes 2498 102/1240 (8.2) 114/1258 (9.1) 0.90 (0.69-1.17) 0.431
No 13347 409/6683 (6.1) 419/6664 (6.3) 0.98 (0.85-1.12) 0.733
TVR 0.978
Bifurcation: Yes 2498 59/1240 (4.8) 66/1258 (5.2) 0.90 (0.64-1.28) 0.575
No 13347 205/6683 (3.1) 228/6664 (3.4) 0.90 (0.74-1.09) 0.267
Definite ST 0.062
Bifurcation: Yes 2498 6/1240 (0.5) 11/1258 (0.9) 0.55 (0.20-1.50) 0.243
No 13347 47/6683 (0.7) 30/6664 (0.5) 1.57 (0.99-2.48) 0.055
Definite or probable ST 0.026
Bifurcation: Yes 2498 8/1240 (0.6) 16/1258 (1.3) 0.51 (0.22-1.18) 0.115
No 13347 60/6683 (0.9) 41/6664 (0.6) 1.46 (0.98-2.18) 0.061
BARC 3 or 5 bleeding 0.733
Bifurcation: Yes 2498 22/1240 (1.8) 28/1258 (2.2) 0.80 (0.46-1.39) 0.427
No 13347 95/6683 (1.4) 107/6664 (1.6) 0.89 (0.67-1.17) 0.399
Experimental favor
Reference favor
0.1
1
10
20
Hazard ratio (95% CI)

607

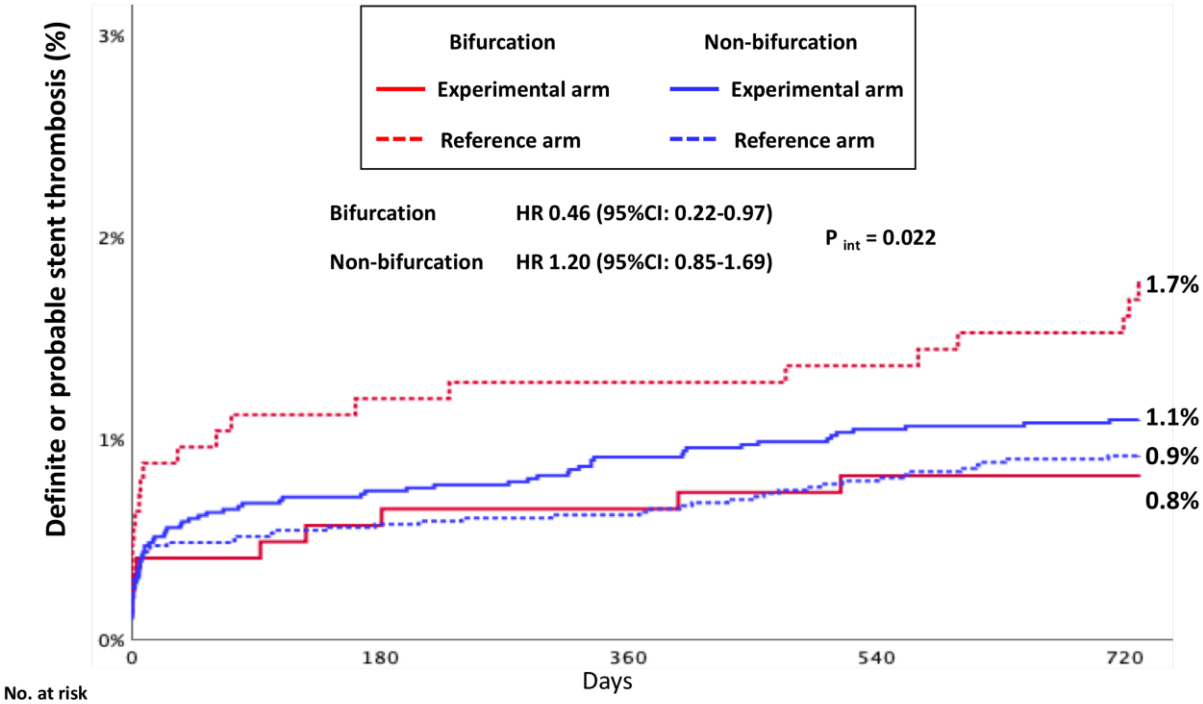

N
Experimental treatment (n=7923)
Reference treatment (n=7988)
Hazard ratio (95% CI)
P value
Interaction P value
Death or new Q wave MI 0.343
Bifurcation: Yes 2498 50/1240 (4.0) 68/1258 (5.4) 0.74 (0.51-1.07) 0.106
No 13347 252/6683 (3.8) 279/6664 (4.2) 0.90 (0.76-1.07) 0.218
Death 0.301
Bifurcation: Yes 2498 31/1240 (2.5) 44/1258 (3.5) 0.71 (0.45-1.12) 0.144
No 13347 192/6683 (2.9) 207/6664 (3.1) 0.92 (0.76-1.13) 0.433
New Q wave MI 0.918
Bifurcation: Yes 2498 20/1240 (1.6) 26/1258 (2.1) 0.74 (0.51-1.07) 0.106
No 13347 62/6683 (0.9) 77/6664 (1.2) 0.90 (0.76-1.07) 0.218
POCE 0.851
Bifurcation: Yes 2498 182/1240 (14.7) 194/1258 (15.4) 0.95 (0.78-1.16) 0.623
No 13347 855/6683 (12.8) 916/6664 (13.7) 0.93 (0.85-1.02) 0.131
Stroke 0.018
Bifurcation: Yes 2498 16/1240 (1.3) 6/1258 (0.5) 2.72 (1.06-6.94) 0.037
No 13347 62/6683 (0.9) 76/6664 (1.1) 0.82 (0.58-1.14) 0.233
Any MI 0.474
Bifurcation: Yes 2498 43/1240 (3.5) 38/1258 (3.0) 1.15 (0.74-1.78) 0.527
No 13347 199/6683 (3.0) 206/6664 (3.1) 0.97 (0.80-1.18) 0.741
Any revascularization 0.640
Bifurcation: Yes 2498 132/1240 (10.6) 148/1258 (11.8) 0.90 (0.71-1.13) 0.358
No 13347 599/6683 (9.0) 628/6664 (9.4) 0.95 (0.85-1.07) 0.400
TVR 0.666
Bifurcation: Yes 2498 81/1240 (6.5) 86/1258 (6.8) 0.95 (0.70-1.29) 0.759
No 13347 303/6683 (4.5) 342/6664 (5.1) 0.88 (0.76-1.03) 0.119
Definite ST 0.079
Bifurcation: Yes 2498 8/1240 (0.6) 16/1258 (1.3) 0.51 (0.22-1.18) 0.116
No 13347 56/6683 (0.8) 48/6664 (0.7) 1.17 (0.79-1.72) 0.431
Definite or probable ST 0.022
Bifurcation: Yes 2498 10/1240 (0.8) 22/1258 (1.7) 0.46 (0.22-0.97) 0.041
No 13347 72/6683 (1.1) 60/6664 (0.9) 1.20 (0.85-1.69) 0.298
BARC 3 or 5 bleeding 0.917
Bifurcation: Yes 2498 30/1240 (2.4) 32/1258 (2.5) 0.95 (0.58-1.56) 0.842
No 13347 133/6683 (2.0) 136/6664 (2.0) 0.98 (0.77-1.24) 0.855
Experimental favor
Reference favor
0.1
1
10
20
Hazard ratio (95% CI)

608

Figure 4. Kaplan–Meier estimates of cumulative incidence of definite or probable stent thrombosis for experimental versus reference antiplatelet strategy in patients with or without bifurcation up to 730 days (A) and up to 365 days and landmark analysis at 365 days (B)

Kaplan–Meier curves show the cumulative incidence of definite or probable stent thrombosis.

A

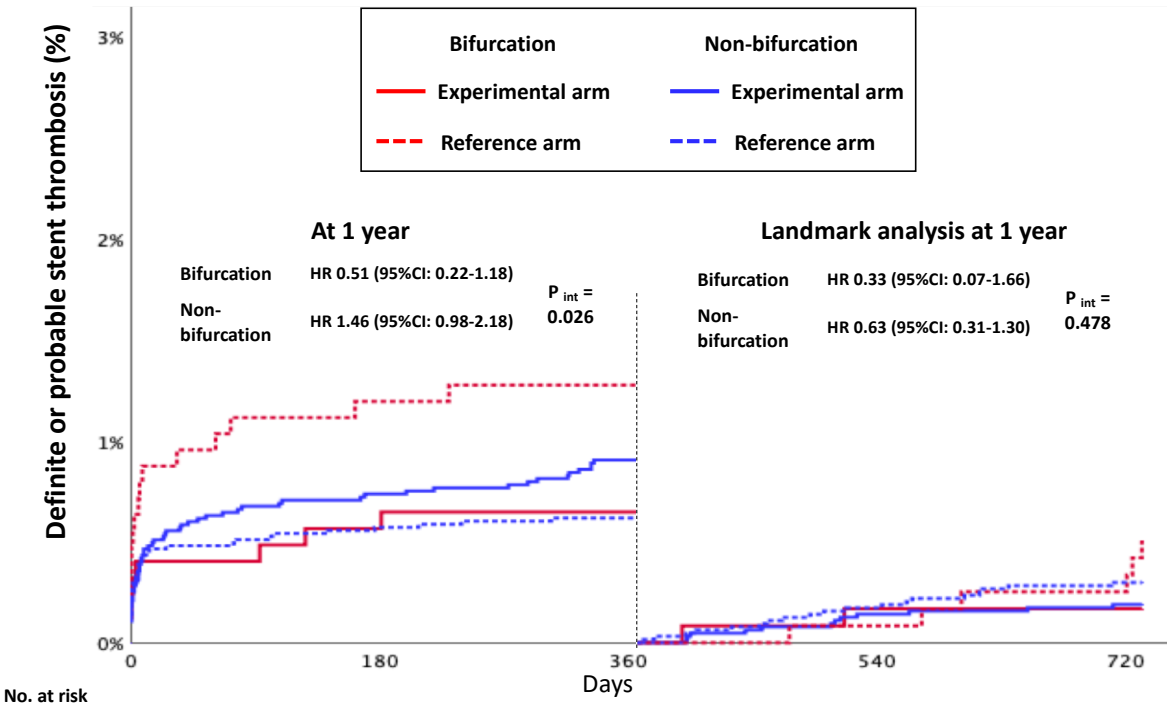


No. at risk

Bifur-Exp	1240	1225	1216	1214	1212	1206	1200	1196	1191
Bifur-Ref	1258	1234	1226	1221	1219	1214	1207	1198	1191
Non-B-Exp	6683	6547	6517	6498	6476	6444	6408	6381	6353
Non-B-Ref	6664	6564	6531	6510	6483	6444	6423	6387	6363

614

B



No. at risk

Bifur-Exp	1240	1225	1216	1214	1212	1206	1200	1196	1191
Bifur-Ref	1258	1234	1226	1221	1219	1214	1207	1198	1191
Non-B-Exp	6683	6547	6517	6498	6476	6444	6408	6381	6353
Non-B-Ref	6664	6564	6531	6510	6483	6444	6423	6387	6363

615

Table 1. Baseline and procedural characteristics

	Bifurcation n = 2498	Non-bifurcation n = 13347	p Value
Age, years	64.4 ± 10.4	64.6 ± 10.3	0.601
Male	1950/2498 (78.1)	10205/13347 (76.5)	0.082
Body-mass index, kg/m2	28.0 ± 4.5	28.2 ± 4.6	0.034
Medical history			
Diabetes mellitus	590/2495 (23.6)	3414/13339 (25.6)	0.040
Insulin-dependent diabetes mellitus	169/2490 (6.8)	1043/13308 (7.8)	0.071
Hypertension	1856/2491 (74.5)	9774/13300 (73.5)	0.289
Hypercholesterolemia	1722/2429 (70.9)	8965/12915 (69.4)	0.146
Current smoker	638/2498 (25.5)	3501/13347 (26.2)	0.471
Peripheral vascular disease	137/2469 (5.5)	857/13230 (6.5)	0.082
Chronic obstructive pulmonary disease	109/2482 (4.4)	702/13292 (5.3)	0.065
Previous major bleeding	15/2498 (0.6)	83/13326 (0.6)	0.896
Impaired renal function*	322/2488 (12.9)	1836/13273 (13.8)	0.236
Previous stroke	70/2497 (2.8)	348/13325 (2.6)	0.584
Previous myocardial infarction	554/2494 (22.2)	3125/13305 (23.5)	0.167
Previous percutaneous coronary intervention	774/2498 (31.0)	4407/13333 (33.1)	0.043
Previous coronary artery bypass grafting	108/2498 (4.3)	830/13334 (6.2)	<0.001
Clinical presentation			
Stable coronary artery disease	1277/2498 (51.1)	7127/13347 (53.4)	0.036
Acute coronary syndrome	1221/2498 (48.9)	6220/13347 (46.6)	0.036
Unstable angina	348/2498 (13.9)	1659/13347 (12.4)	0.038
Non-ST-elevation myocardial infarction	559/2498 (22.4)	2797/13347 (21.0)	0.110
ST-elevation myocardial infarction	314/2498 (12.6)	1764/13347 (13.2)	0.380
Procedural characteristics			
Vascular access site			
Femoral	679/2458 (27.6)	3589/13188 (27.2)	0.675
Brachial	15/2458 (0.6)	91/13188 (0.7)	0.658
Radial	1872/2458 (76.2)	9827/13188 (74.5)	0.085
Number of lesions treated	1.7 ± 0.9	1.4 ± 0.7	<0.001
Number of stents	2.2 ± 1.4	1.6 ± 1.0	<0.001
Total stent length	47.3 ± 31.6	33.2 ± 23.2	<0.001
Randomization of antiplatelet therapy			
Experimental treatment (one-month DAPT followed by 23-month ticagrelor monotherapy)	1240/2498 (49.6)	6683/13347 (50.1)	0.692
Reference treatment (12-month DAPT followed by 12-month aspirin monotherapy)	1258/2498 (50.4)	6664/13347 (49.9)	

Data are mean ± SD or counts (percentage).

*Impaired renal function is defined as estimated glomerular filtration rate of creatinine clearance of 60 mL/min per 1.73 m^2 based on the Modification of Diet in Renal Disease formula.

Table 2. Clinical outcomes at 30 days, one, two years follow-up and landmark analysis at 30 days and 1 year stratified by presence or absence of bifurcation.

	Bifurcation n = 2498	Non-bifurcation n = 13347	HR (95%CI)	p Value
30-day outcomes				
All-cause death or new Q-wave MI	15 (0.60%)	61 (0.46%)	1.32 (0.75-2.31)	0.340
All-cause death	13 (0.52%)	54 (0.40%)	1.29 (0.70-2.36)	0.412
New Q-wave MI	2 (0.08%)	8 (0.06%)	1.34 (0.28-6.30)	0.712
POCE*	86 (3.44%)	311 (2.33%)	1.49 (1.17-1.89)	0.001
Stroke	3 (0.12%)	31 (0.23%)	0.52 (0.16-1.69)	0.267
Any MI	38 (1.52%)	112 (0.84%)	1.82 (1.26-2.63)	0.001
Any revascularization	55 (2.20%)	189 (1.42%)	1.56 (1.16-2.11)	0.003
TVR	35 (1.40%)	124 (0.93%)	1.51 (1.04-2.20)	0.030
Definite ST	10 (0.40%)	49 (0.37%)	1.09 (0.55-2.15)	0.802
Definite or probable ST	16 (0.64%)	69 (0.52%)	1.24 (0.72-2.13)	0.438
BARC 3 or 5 bleeding	16 (0.64%)	82 (0.61%)	1.04 (0.61-1.78)	0.876
1-year outcomes				
All-cause death or new Q-wave MI	67 (2.68%)	284 (2.13%)	1.27 (0.97-1.65)	0.082
All-cause death	40 (1.60%)	197 (1.48%)	1.09 (0.77-1.53)	0.630
New Q-wave MI	28 (1.12%)	89 (0.67%)	1.69 (1.10-2.58)	0.015
POCE*	276 (11.05%)	1138 (8.53%)	1.32 (1.15-1.50)	<0.001
Stroke	15 (0.60%)	85 (0.64%)	0.94 (0.54-1.63)	0.833
Any MI	64 (2.56%)	266 (1.99%)	1.29 (0.98-1.70)	0.064
Any revascularization	216 (8.65%)	828 (6.20%)	1.41 (1.22-1.64)	<0.001
TVR	125 (5.00%)	433 (3.24%)	1.55 (1.27-1.90)	<0.001
Definite ST	17 (0.68%)	77 (0.58%)	1.18 (0.70-2.00)	0.535
Definite or probable ST	24 (0.96%)	101 (0.76%)	1.27 (0.81-1.98)	0.292
BARC 3 or 5 bleeding	50 (2.00%)	202 (1.51%)	1.33 (0.97-1.81)	0.073
2-year outcomes				
All-cause death or new Q-wave MI	118 (4.72%)	531 (3.98%)	1.19 (0.98-1.46)	0.083
All-cause death	75 (3.00%)	399 (2.99%)	1.01 (0.79-1.29)	0.964
New Q-wave MI	46 (1.84%)	139 (1.04%)	1.78 (1.27-2.48)	0.001
POCE*	376 (15.05%)	1771 (13.27%)	1.16 (1.03-1.29)	0.011
Stroke	22 (0.88%)	138 (1.03%)	0.85 (0.54-1.34)	0.483
Any MI	81 (3.24%)	405 (3.03%)	1.07 (0.85-1.36)	0.559
Any revascularization	280 (11.21%)	1227 (9.19%)	1.24 (1.09-1.41)	0.001
TVR	167 (6.69%)	645 (4.83%)	1.40 (1.18-1.66)	<0.001
Definite ST	24 (0.96%)	104 (0.78%)	1.23 (0.79-1.92)	0.353
Definite or probable ST	32 (1.28%)	132 (0.99%)	1.29 (0.88-1.90)	0.189

BARC 3 or 5 bleeding	62 (2.48%)	269 (2.02%)	1.23 (0.94-1.63)	0.134
Landmark analysis at 30 days				
All-cause death or new Q-wave MI	103 (4.15%)	470 (3.54%)	1.18 (0.95-1.46)	0.134
All-cause death	62 (2.50%)	345 (2.60%)	0.96 (0.73-1.26)	0.776
New Q-wave MI	44 (1.77%)	131 (0.99%)	1.80 (1.28-2.54)	0.001
POCE*	290 (12.08%)	1460 (11.26%)	1.08 (0.96-1.23)	0.210
Stroke	19 (0.77%)	107 (0.81%)	0.95 (0.58-1.54)	0.831
Any MI	43 (1.76%)	293 (2.23%)	0.79 (0.57-1.09)	0.145
Any revascularization	225 (9.29%)	1038 (7.96%)	1.18 (1.02-1.36)	0.025
TVR	132 (5.40%)	521 (3.98%)	1.37 (1.13-1.66)	0.001
Definite ST	14 (0.57%)	55 (0.42%)	1.36 (0.76-2.45)	0.301
Definite or probable ST	16 (0.65%)	63 (0.48%)	1.35 (0.78-2.35)	0.276
BARC 3 or 5 bleeding	46 (1.87%)	187 (1.42%)	1.32 (0.96-1.82)	0.092
Landmark analysis at 1 year				
All-cause death or new Q-wave MI	51 (2.10%)	247 (1.89%)	1.11 (0.82-1.50)	0.500
All-cause death	35 (1.43%)	202 (1.54%)	0.93 (0.65-1.33)	0.676
New Q-wave MI	18 (0.74%)	50 (0.38%)	1.94 (1.13-3.32)	0.014
POCE*	100 (4.56%)	633 (5.25%)	0.86 (0.70-1.07)	0.171
Stroke	7 (0.29%)	53 (0.41%)	0.70 (0.32-1.55)	0.382
Any MI	17 (0.72%)	139 (1.09%)	0.65 (0.40-1.08)	0.097
Any revascularization	64 (2.88%)	399 (3.28%)	0.87 (0.67-1.14)	0.318
TVR	42 (1.82%)	212 (1.69%)	1.07 (0.77-1.50)	0.672
Definite ST	7 (0.29%)	27 (0.21%)	1.39 (0.60-3.18)	0.440
Definite or probable ST	8 (0.33%)	31 (0.24%)	1.38 (0.63-2.99)	0.419
BARC 3 or 5 bleeding	12 (0.50%)	67 (0.52%)	0.96 (0.52-1.78)	0.897

Data are counts (percentage).

*POCE was defined as a composite of all-cause death, any stroke, any MI, and any revascularization.

BARC = Bleeding Academic Research Consortium; MI = myocardial infarction; POCE = patient-oriented composite endpoint; ST = stent thrombosis; TVR = target vessel revascularization

Table 3. Clinical outcomes in all patients according to prevalence of bifurcation and allocated antiplatelet regimen at 30days, and Landmark analysis at 30 days and 1 year

	Bifurcation				Non-bifurcation				
	Experimental treatment	Reference treatment	HR (95%CI)	p value	Experimental treatment	Reference treatment	HR (95%CI)	p value	p for interaction
30 days									
All-cause death or new Q-wave MI	3/1240 (0.2)	12/1258 (1.0)	0.25 (0.07-0.90)	0.033	31/6683 (0.5)	30/6664 (0.5)	1.03 (0.62-1.70)	0.906	0.043
All-cause death	3/1240 (0.2)	10/1258 (0.8)	0.30 (0.08-1.10)	0.070	29/6683 (0.4)	25/6664 (0.4)	1.16 (0.68-1.98)	0.592	0.060
New Q-wave MI	0/1240 (0.0)	2/1258 (0.2)	NA	0.254[#]	2/6683 (0.02)	6/6664 (0.1)	0.33 (0.07-1.65)	0.177	NA
POCE*	34/1240 (2.7)	52/1258 (4.1)	0.66 (0.43-1.02)	0.060	151/6683 (2.3)	160/6664 (2.4)	0.94 (0.75-1.18)	0.592	0.153
Stroke	2/1240 (0.2)	1/1258 (0.1)	2.02 (0.18-22.33)	0.565	14/6683 (0.2)	17/6664 (0.3)	0.82 (0.41-1.67)	0.587	0.480
Any MI	21/1240 (1.7)	17/1258 (1.4)	1.25 (0.66-2.38)	0.488	61/6683 (0.9)	51/6664 (0.8)	1.19 (0.82-1.73)	0.349	0.897
Any revascularization	17/1240 (1.4)	38/1258 (3.0)	0.45 (0.25-0.80)	0.006	93/6683 (1.4)	96/6664 (1.4)	0.97 (0.73-1.29)	0.815	0.019
TVR	11/1240 (0.9)	24/1258 (1.9)	0.46 (0.23-0.95)	0.035	61/6683 (0.9)	63/6664 (0.9)	0.97 (0.68-1.37)	0.848	0.070
Definite ST	3/1240 (0.2)	7/1258 (0.6)	0.43 (0.11-1.68)	0.227	27/6683 (0.4)	22/6664 (0.3)	1.22 (0.70-2.15)	0.480	0.165
Definite or probable ST	5/1240 (0.4)	11/1258 (0.9)	0.46 (0.16-1.33)	0.150	37/6683 (0.6)	32/6664 (0.5)	1.15 (0.72-1.85)	0.553	0.120
BARC 3 or 5 bleeding	8/1240 (0.6)	8/1258 (0.6)	1.01 (0.38-2.70)	0.978	43/6683 (0.6)	39/6664 (0.6)	1.10 (0.71-1.70)	0.664	0.881
Landmark at 30 days									
All-cause death or new Q-wave MI	47/1236 (3.8)	56/1246 (4.5)	0.84 (0.57-1.24)	0.390	221/6651 (3.3)	249/6632 (3.8)	0.88 (0.74-1.06)	0.177	0.835
All-cause death	28/1236 (2.3)	34/1248 (2.7)	0.83 (0.50-1.37)	0.464	163/6653 (2.5)	182/6637 (2.7)	0.89 (0.72-1.10)	0.291	0.791
New Q-wave MI	20/1236 (1.6)	24/1246 (1.9)	0.84 (0.46-1.52)	0.561	60/6651 (0.9)	71/6632 (1.1)	0.84 (0.60-1.19)	0.325	0.992
POCE*	148/1198 (12.4)	142/1202 (11.8)	1.06 (0.84-1.33)	0.638	704/6497 (10.8)	756/6474 (11.7)	0.93 (0.84-1.03)	0.157	0.313
Stroke	14/1228 (1.1)	5/1243 (0.4)	2.86 (1.03-7.93)	0.044	48/6602 (0.7)	59/6591 (0.9)	0.81 (0.56-1.19)	0.289	0.024
Any MI	22/1209 (1.8)	21/1228 (1.7)	1.07 (0.59-1.94)	0.829	138/6556 (2.1)	155/6559 (2.4)	0.89 (0.71-1.12)	0.333	0.584
Any revascularization	115/1214 (9.5)	110/1209 (9.1)	1.05 (0.81-1.36)	0.718	506/6523 (7.8)	532/6515 (8.2)	0.95 (0.84-1.07)	0.414	0.501
TVR	70/1220 (5.7)	62/1223 (5.1)	1.14 (0.81-1.61)	0.441	242/6555 (3.7)	279/6546 (4.3)	0.87 (0.73-1.03)	0.101	0.154
Definite ST	5/1227 (0.4)	9/1239 (0.7)	0.56 (0.19-1.68)	0.303	29/6587 (0.4)	26/6588 (0.4)	1.12 (0.66-1.90)	0.677	0.267

Definite or probable ST	5/1231 (0.4)	11/1241 (0.9)	0.46 (0.16-1.32)	0.147	35/6598 (0.5)	28/6598 (0.4)	1.25 (0.76-2.06)	0.376	0.091
BARC 3 or 5 bleeding	22/1223 (1.8)	24/1238 (1.9)	0.93 (0.52-1.66)	0.804	90/6579 (1.4)	97/6576 (1.5)	0.93 (0.70-1.24)	0.612	0.999
Landmark at 1Y									
All-cause death or new Q-wave MI	23/1211 (1.9)	28/1218 (2.3)	0.82 (0.47-1.43)	0.490	123/6549 (1.9)	124/6507 (1.9)	0.99 (0.77-1.26)	0.907	0.562
All-cause death	16/1223 (1.3)	19/1233 (1.5)	0.85 (0.44-1.65)	0.625	99/6585 (1.5)	103/6558 (1.6)	0.96 (0.73-1.26)	0.754	0.740
New Q-wave MI	8/1211 (0.7)	10/1218 (0.8)	0.80 (0.32-2.03)	0.642	26/6549 (0.4)	24/6507 (0.4)	1.08 (0.62-1.88)	0.791	0.593
POCE*	48/1087 (4.4)	52/1106 (4.7)	0.94 (0.63-1.39)	0.755	300/6039 (5.0)	333/6018 (5.5)	0.90 (0.77-1.05)	0.168	0.826
Stroke	4/1196 (0.3)	3/1220 (0.2)	1.36 (0.30-6.08)	0.686	23/6460 (0.4)	30/6452 (0.5)	0.77 (0.45-1.32)	0.336	0.479
Any MI	10/1175 (0.9)	7/1195 (0.6)	1.46 (0.56-3.84)	0.442	56/6363 (0.9)	83/6377 (1.3)	0.68 (0.48-0.95)	0.023	0.140
Any revascularization	30/1108 (2.7)	34/1115 (3.0)	0.89 (0.54-1.45)	0.636	190/6096 (3.1)	209/6084 (3.4)	0.91 (0.74-1.10)	0.325	0.942
TVR	22/1150 (1.9)	20/1163 (1.7)	1.12 (0.61-2.05)	0.721	98/6296 (1.6)	114/6271 (1.8)	0.86 (0.65-1.12)	0.258	0.432
Definite ST	2/1200 (0.2)	5/1214 (0.4)	0.41 (0.08-2.09)	0.280	9/6448 (0.1)	18/6466 (0.3)	0.50 (0.23-1.12)	0.091	0.818
Definite or probable ST	2/1211 (0.2)	6/1219 (0.5)	0.33 (0.07-1.66)	0.180	12/6475 (0.2)	19/6482 (0.3)	0.63 (0.31-1.30)	0.214	0.478
BARC 3 or 5 bleeding	8/1188 (0.7)	4/1198 (0.3)	2.02 (0.61-6.71)	0.251	38/6411 (0.6)	29/6403 (0.5)	1.31 (0.81-2.13)	0.272	0.512

Data are counts (percentage).

*POCE was defined as a composite of all-cause death, any stroke, any MI, and any revascularization.

#Values were compared with Fisher's exact test.

BARC = Bleeding Academic Research Consortium; MI = myocardial infarction; NA = not available; POCE = patient-oriented composite endpoint; ST = stent thrombosis; TVR = target vessel revascularization.