Received: 11 May 2019 | Revised: 10 July 2019 | Accepted: 27 July 2019

DOI: 10.1002/ccd.28428

ORIGINAL STUDIES

WILEY

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

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Funding information
AstraZeneca; Biosensors International Group; Medicines company

Abstract

Background: The aim of this study was to investigate the impact of ticagrelor monotherapy following 1-month dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) for bifurcation lesions.

Methods: GLOBAL LEADERS was a randomized, superiority, all-comers trial comparing 1-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. The primary endpoint was a composite of all-cause death or new Q-wave myocardial infarction (MI) at 2 years.

Results: Among the 15,845 patients included in this subgroup analysis, 2,498 patients (15.8%) underwent PCI for at least one bifurcation lesion. The incidence of the primary endpoint was similar between the bifurcation and nonbifurcation groups (4.7 vs. 4.0%, $p = .083$). The experimental treatment had no significant effect on the primary endpoint according to the presence/absence of a bifurcation lesion (bifurcation: hazard ratio [HR]: 0.74, 95% confidence interval [CI]: 0.51–1.07; nonbifurcation: HR: 0.90, 95% CI: 0.76–1.07, p for interaction = .343), but was associated with significant reduction in definite or probable stent thrombosis (p for interaction = .022) and significant excess of stroke (p for interaction = .018) when compared with the reference treatment.

Conclusions: After PCI for bifurcation lesions using 1-month of DAPT followed by ticagrelor monotherapy for 23 months did not demonstrate explicit benefit regarding all-cause death or new Q-wave MI as in the overall trial.

KEYWORDS

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

1 | INTRODUCTION

Bifurcation lesions are associated with a lower rate of procedural success and a higher risk of complications compared to nonbifurcation 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, this provisional side branch stenting strategy is the recommended treatment of bifurcation lesions with a Class IA recommendation in current guidelines.[3] In 5–25% of cases, a second stent for the side branch may be needed[4–6]; however, the best two-stent technique to use in these situations remains debatable.[3]

The complexity and the numerous subtypes of two-stent techniques render their comparison difficult. For that reason, the European bifurcation club introduced the Main, Across, Distal, Side (MADS) classification to standardize reports that allow comparison between studies and facilitate interpretation of published results in the evolving literature.[7,8] 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 a cohort stratified for the presence of bifurcation lesions within a large contemporary PCI trial.[9]

In terms of antiplatelet therapy, although the increased complexity of PCI including two-stent technique for bifurcation lesions represent a driver for favoring more prolonged dual antiplatelet therapy (DAPT), the evidence regarding the optimal duration of DAPT based on the 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 inhibitors after bifurcation PCI is uncertain.

In this prespecified subgroup analysis of the primary endpoint such as all-cause death and new Q-wave myocardial infarction (MI) from the GLOBAL LEADERS trial,[12] we sought to investigate the impact of ticagrelor monotherapy following 1-month DAPT after bifurcation PCI.

2 | METHODS

2.1 | 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 1-month DAPT with aspirin and ticagrelor followed by 23 months of ticagrelor monotherapy (experimental treatment), 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 (reference treatment). Regarding the primary endpoint of all-cause death or new Q-wave MI at 2 years, the overall trial failed to demonstrate the superiority of experimental treatment compared with the reference treatment (3.81% in the experimental treatment vs. 4.37% in the reference treatment,

p = .073), although at 1 year, the superiority of experimental treatment was demonstrated (1.95 vs. 2.47%, p = .028).

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. The trial is registered with ClinicalTrials.gov, number NCT01813435.

2.2 | Study population and data collection

According to the all-comers concept, only a limited number of inclusion and exclusion criteria were applied in the GLOBAL LEADERS trial (Data S1).

In this prespecified subgroup analysis of primary endpoint, 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 PCIs were classified whether treated with one- or two-stent technique using the results of the MADS classification. Three-stent techniques such as "extended V" and "trouser legs and seat" were included in the two-stent technique. The stenting technique for trifurcation lesion is not covered by the MADS classification, therefore trifurcation was identified according to the definition of SYNTAX score.[14] The choice of bifurcation treatment technique was left to the discretion of the operators.

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 underreporting and event definition consistency. However, no overall central independent adjudication of clinical events was implemented.

2.3 | Endpoint definitions

The primary endpoint was the composite of all-cause death or new Q-wave MI up to 2 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 secondary endpoints included individual components of the primary endpoint (all-cause death and new Q-wave MI); composite of all-cause death, stroke, or new Q-wave MI; any stroke; ischemic stroke; any MI; any revascularization; target vessel revascularization (TVR); definite stent thrombosis (ST); definite or probable ST[16]; and bleeding defined according to the Bleeding Academic Research Consortium criteria (type 3 or 5) up to 2 years.[17]

The third universal definition of MI was the recommended criteria to report MI.[18] Composite endpoints were analyzed hierarchically. Individual components were reported nonhierarchically.[19]

2.4 | Statistical analysis

Clinical outcomes were compared between patients treated for at least one bifurcation lesion versus patients not treated for any bifurcation lesion (bifurcation vs. nonbifurcation).

Thereafter, the effect of experimental versus reference antiplatelet therapy on clinical outcomes according to presence/absence of bifurcation PCI was estimated with a Cox regression model.

Eventually, we did a subgroup analysis of the primary endpoint only in patients treated for at least one bifurcation lesion with tests for treatment–by subgroup interaction according to the prespecified baseline characteristics and the type of stenting technique such as one-stent and two-stent techniques. Due to the absence of classification for trifurcation PCI according to the MADS classification, patients with trifurcation PCI were excluded from the analysis comparing one- versus two-stent technique.

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 nonnormally 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 PCI or 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 cutoffs at 30 days (at the time of the planned date of discontinuation of aspirin in the experimental treatment) and 1 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 .05 was considered to indicate statistical significance. All statistical analyses were done in SPSS (version 25.0.0, IBM, New York, NY).

3 | RESULTS

The GLOBAL LEADERS trial recruited a total of 15,991 patients,[13] of whom 146 patients were excluded from this analysis (Figure 1), leaving 15,845 patients of which 2,498 patients (15.7%) underwent PCI for at least one bifurcation lesion and 7 patients (0.04%) at least one trifurcation lesion. Among the patients with at least one bifurcation lesion, 2002 (80.1%) were treated with PCI using a one-stent technique and 489 (19.6%) using a two-stent technique (Figure 1).

3.1 | Clinical outcomes: Bifurcation versus nonbifurcation groups

Patients in the nonbifurcation group had a higher body mass index and higher prevalence of diabetes mellitus or previous revascularization, whereas patients in the bifurcation group more often presented with acute coronary syndrome (Table 1). In terms of procedural characteristics, patients in the bifurcation group as expected had more lesions, stents, and longer total stent length per patient.

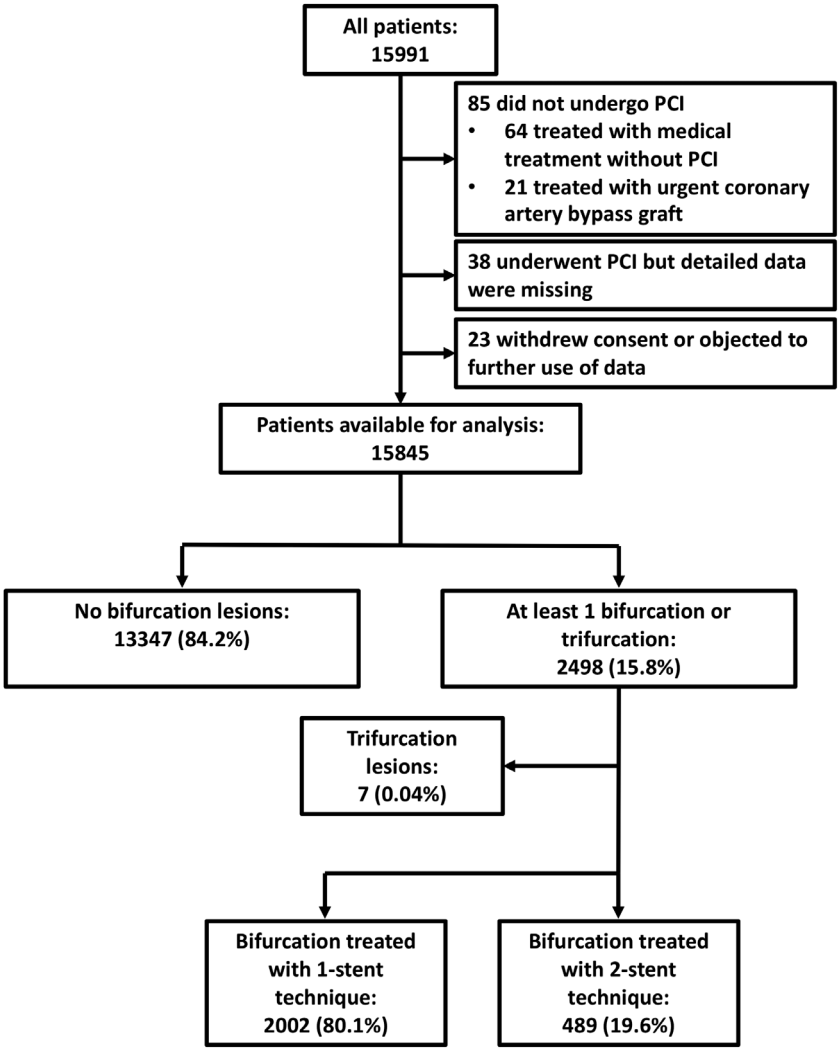

FIGURE 1 Study flow chart

In terms of the primary endpoint (a composite of all-cause death or new Q-wave MI) at 2 years, there was a trend toward a higher incidence in the bifurcation group compared with the nonbifurcation group (4.72 vs. 3.98%, hazard ratio (HR): 1.19, 95% confidence interval [95% CI]: 0.98–1.46, $p = .083$), a difference driven by the significantly higher incidence of new Q-wave MI in the bifurcation group (1.84 vs. 1.04%, HR: 1.78, 95% CI: 1.27–2.48, $p = .001$) (Table 2). The incidences of any revascularization at 2 years were higher in the bifurcation group versus nonbifurcation group (11.21 vs. 9.19%, HR: 1.24, 95% CI: 1.09–1.41, $p = .001$), as well as TVR at 2 years (6.69 vs. 4.83%, HR: 1.40, 95% CI: 1.18–1.66, $p < .001$) (Table 2). These differences in any revascularization and TVR were also observed at 30-day and 1-year follow-up, but not in the landmark analysis at 1 year.

3.2 | Treatment effect of antiplatelet therapy according to presence/absence of bifurcation lesions

There were no significant differences in baseline characteristics between experimental and reference groups stratified by presence/absence of bifurcation lesions (Table S1).

The results for the experimental versus reference antiplatelet treatment in the bifurcation and nonbifurcation groups are reported in Figure 2 and Table S2. Compared to the reference strategy, the experimental strategy did not reduce the primary endpoint at 2 years in patients undergoing PCI irrespective of the presence or absence of a bifurcation lesion (bifurcation: HR: 0.74, 95% CI: 0.51–1.07; nonbifurcation: HR: 0.90, 95% CI: 0.76–1.07, p for interaction = .343); however, it did result in a significant reduction in rates of definite or probable ST at 2 years in patients in the bifurcation group (HR: 0.46, 95% CI: 0.22–0.97) versus nonbifurcation group (HR: 1.20, 95% CI: 0.85–1.69, p for interaction = .022) (Figure S1a). The same trend was observed on 1-year definite or probable ST (p for interaction = .027), whereas this significant benefit of ticagrelor monotherapy against aspirin monotherapy subsided beyond 1 year (p for interaction = .482) (Figure S1b). In terms of the 2-year incidence of stroke, the experimental strategy showed a negative effect in patient undergoing bifurcation PCI against the reference strategy (bifurcation: HR: 2.72, 95% CI: 1.06–6.94 in Figure S2a; nonbifurcation: HR: 0.82, 95% CI: 0.58–1.14, p for interaction = .018). This negative effect was observed at 1 year follow-up (p for interaction = .021), but not at 30 days (p for interaction = .480) and beyond 1 year (p for interaction = .479). In patients undergoing bifurcation PCI, the majority of stroke was ischemic (experimental

TABLE 1 Baseline and procedural characteristics

	Bifurcation, *n* = 2,498	Nonbifurcation, *n* = 13,347	*p* Value
Age (years)	64.4 ± 10.4	64.6 ± 10.3	.601
Male	1950/2498 (78.1)	10,205/13347 (76.5)	.082
Body mass index (kg/m^2)	28.0 ± 4.5	28.2 ± 4.6	.034
Medical history			
Diabetes mellitus	590/2495 (23.6)	3414/13339 (25.6)	.040
Insulin-dependent diabetes mellitus	169/2490 (6.8)	1043/13308 (7.8)	.071
Hypertension	1856/2491 (74.5)	9774/13300 (73.5)	.289
Hypercholesterolemia	1722/2429 (70.9)	8965/12915 (69.4)	.146
Current smoker	638/2498 (25.5)	3501/13347 (26.2)	.471
Peripheral vascular disease	137/2469 (5.5)	857/13230 (6.5)	.082
Chronic obstructive pulmonary disease	109/2482 (4.4)	702/13292 (5.3)	.065
Previous major bleeding	15/2498 (0.6)	83/13326 (0.6)	.896
Impaired renal function[a]	322/2488 (12.9)	1836/13273 (13.8)	.236
Previous stroke	70/2497 (2.8)	348/13325 (2.6)	.584
Previous myocardial infarction	554/2494 (22.2)	3125/13305 (23.5)	.167
Previous percutaneous coronary intervention	774/2498 (31.0)	4407/13333 (33.1)	.043
Previous coronary artery bypass grafting	108/2498 (4.3)	830/13334 (6.2)	<.001
Clinical presentation			
Stable coronary artery disease	1277/2498 (51.1)	7127/13347 (53.4)	.036
Acute coronary syndrome	1221/2498 (48.9)	6220/13347 (46.6)	.036
Unstable angina	348/2498 (13.9)	1659/13347 (12.4)	.038
Non-ST-elevation myocardial infarction	559/2498 (22.4)	2797/13347 (21.0)	.110
ST-elevation myocardial infarction	314/2498 (12.6)	1764/13347 (13.2)	.380
Procedural characteristics			
Vascular access site			
Femoral	679/2458 (27.6)	3589/13188 (27.2)	.675
Brachial	15/2458 (0.6)	91/13188 (0.7)	.658
Radial	1872/2458 (76.2)	9827/13188 (74.5)	.085
Number of lesions treated	1.7 ± 0.9	1.4 ± 0.7	<.001
Number of stents	2.2 ± 1.4	1.6 ± 1.0	<.001
Total stent length	47.3 ± 31.6	33.2 ± 23.2	<.001
Randomization of antiplatelet therapy			
Experimental treatment (1-month DAPT followed by 23-month ticagrelor monotherapy)	1240/2498 (49.6)	6683/13347 (50.1)	.692
Reference treatment (12-month DAPT followed by 12-month aspirin monotherapy)	1258/2498 (50.4)	6664/13347 (49.9)	

Note: Data are mean ± SD or counts (percentage).
Abbreviations: DAPT, dual antiplatelet therapy; ST, stent thrombosis.
[a]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.

group: 13/16 [81.2%], reference group: 6/6 [100%]), and the incidence of ischemic stroke was not different between groups (experimental group: 1.0% vs. reference group: 0.5%, HR 2.21, 95% CI: 0.84–5.80, p = .109 in Figure S2b). Only three hemorrhagic strokes occurred in patient undergoing bifurcation PCI, two occurred in the first year (days 135 and 139) and the third one beyond 1 year (day 596) (experimental group: 0.2% vs. reference group: 0.0%, p = .081 in Figure S2c).

3.3 | Subgroup analysis of the primary endpoint in patients treated for at least one bifurcation lesion

The subgroup analysis in patients with bifurcation PCI demonstrated no variation in treatment effects for the primary endpoint according to prespecified baseline characteristics as well as stenting technique (one- vs. two-stent technique) (Figure 3). In patients treated with two-

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

	Bifurcation, *n* = 2,498	Nonbifurcation, *n* = 13,347	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)	.340
All-cause death	13 (0.52%)	54 (0.40%)	1.29 (0.70–2.36)	.412
New Q-wave MI	2 (0.08%)	8 (0.06%)	1.34 (0.28–6.30)	.712
Composite of all-cause death, stroke or new Q-wave MI	18 (0.72%)	86 (0.64%)	1.12 (0.67–1.86)	.665
Stroke	3 (0.12%)	31 (0.23%)	0.52 (0.16–1.69)	.267
Ischemic stroke	3 (0.12%)	23 (0.17%)	0.70 (0.21–2.32)	.554
Any MI	38 (1.52%)	112 (0.84%)	1.82 (1.26–2.63)	.001
Any revascularization	55 (2.20%)	189 (1.42%)	1.56 (1.16–2.11)	.003
TVR	35 (1.40%)	124 (0.93%)	1.51 (1.04–2.20)	.030
Definite ST	10 (0.40%)	49 (0.37%)	1.09 (0.55–2.15)	.802
Definite or probable ST	16 (0.64%)	69 (0.52%)	1.24 (0.72–2.14)	.439
BARC type 3 or 5 bleeding	16 (0.64%)	82 (0.61%)	1.04 (0.61–1.78)	.876
1-Year outcomes				
All-cause death or new Q-wave MI	67 (2.68%)	284 (2.13%)	1.27 (0.97–1.65)	.082
All-cause death	40 (1.60%)	197 (1.48%)	1.09 (0.77–1.53)	.630
New Q-wave MI	28 (1.12%)	89 (0.67%)	1.69 (1.10–2.58)	.015
Composite of all-cause death, stroke, or new Q-wave MI	80 (3.20%)	352 (2.64%)	1.22 (0.95–1.55)	.112
Stroke	15 (0.60%)	85 (0.64%)	0.94 (0.54–1.63)	.833
Ischemic stroke	13 (0.52%)	67 (0.50%)	1.04 (0.57–1.88)	.905
Any MI	64 (2.56%)	266 (1.99%)	1.29 (0.98–1.70)	.064
Any revascularization	216 (8.65%)	828 (6.20%)	1.41 (1.22–1.64)	<.001
TVR	125 (5.00%)	433 (3.24%)	1.55 (1.27–1.90)	<.001
Definite ST	17 (0.68%)	77 (0.58%)	1.18 (0.70–2.00)	.535
Definite or probable ST	24 (0.96%)	101 (0.76%)	1.27 (0.81–1.98)	.291
BARC type 3 or 5 bleeding	50 (2.00%)	202 (1.51%)	1.33 (0.97–1.81)	.073
2-Year outcomes				
All-cause death or new Q-wave MI	118 (4.72%)	531 (3.98%)	1.19 (0.98–1.46)	.083
All-cause death	75 (3.00%)	399 (2.99%)	1.01 (0.79–1.29)	.964
New Q-wave MI	46 (1.84%)	139 (1.04%)	1.78 (1.27–2.48)	.001
Composite of all-cause death, stroke or new Q-wave MI	138 (5.52%)	634 (4.75%)	1.17 (0.97–1.40)	.100
Stroke	22 (0.88%)	138 (1.03%)	0.85 (0.54–1.34)	.483
Ischemic stroke	19 (0.76%)	110 (0.82%)	0.92 (0.57–1.50)	.746
Any MI	81 (3.24%)	405 (3.03%)	1.07 (0.85–1.36)	.559
Any revascularization	280 (11.21%)	1,227 (9.19%)	1.24 (1.09–1.41)	.001
TVR	167 (6.69%)	645 (4.83%)	1.40 (1.18–1.66)	<.001
Definite ST	24 (0.96%)	104 (0.78%)	1.23 (0.79–1.92)	.353
Definite or probable ST	32 (1.28%)	132 (0.99%)	1.30 (0.88–1.91)	.188
BARC type 3 or 5 bleeding	62 (2.48%)	269 (2.02%)	1.23 (0.94–1.63)	.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)	.134
All-cause death	62 (2.50%)	345 (2.60%)	0.96 (0.73–1.26)	.776
New Q-wave MI	44 (1.77%)	131 (0.99%)	1.80 (1.28–2.54)	.001
Composite of all-cause death, stroke, or new Q-wave MI	120 (4.86%)	548 (4.15%)	1.17 (0.96–1.43)	.110

(Continues)

TABLE 2 (Continued)

	Bifurcation, *n* = 2,498	Nonbifurcation, *n* = 13,347	HR (95% CI)	*p* Value
Stroke	19 (0.77%)	107 (0.81%)	0.95 (0.58–1.54)	.831
Ischemic stroke	16 (0.65%)	87 (0.66%)	0.98 (0.58–1.67)	.948
Any MI	43 (1.76%)	293 (2.23%)	0.79 (0.57–1.09)	.145
Any revascularization	225 (9.29%)	1,038 (7.96%)	1.18 (1.02–1.36)	.025
TVR	132 (5.40%)	521 (3.98%)	1.37 (1.13–1.66)	.001
Definite ST	14 (0.57%)	55 (0.42%)	1.36 (0.76–2.45)	.301
Definite or probable ST	16 (0.65%)	63 (0.48%)	1.36 (0.78–2.35)	.275
BARC type 3 or 5 bleeding	46 (1.87%)	187 (1.42%)	1.32 (0.96–1.82)	.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)	.500
All-cause death	35 (1.43%)	202 (1.54%)	0.93 (0.65–1.33)	.676
New Q-wave MI	18 (0.74%)	50 (0.38%)	1.94 (1.13–3.32)	.014
Composite of all-cause death, stroke, or new Q-wave MI	58 (2.43%)	282 (2.20%)	1.10 (0.83–1.46)	.492
Stroke	7 (0.29%)	53 (0.41%)	0.70 (0.32–1.55)	.382
Ischemic stroke	6 (0.25%)	43 (0.33%)	0.75 (0.32–1.75)	.498
Any MI	17 (0.72%)	139 (1.09%)	0.65 (0.40–1.08)	.097
Any revascularization	64 (2.88%)	399 (3.28%)	0.87 (0.67–1.14)	.318
TVR	42 (1.82%)	212 (1.69%)	1.07 (0.77–1.50)	.672
Definite ST	7 (0.29%)	27 (0.21%)	1.39 (0.60–3.18)	.440
Definite or probable ST	8 (0.33%)	31 (0.24%)	1.38 (0.63–3.00)	.419
BARC type 3 or 5 bleeding	12 (0.50%)	67 (0.52%)	0.96 (0.52–1.78)	.897

Note: Data are counts (percentage).
Abbreviations: BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; POCE, patient-oriented composite endpoint; ST, stent thrombosis; TVR, target vessel.

stent technique, the experimental treatment was associated with a numerically lower incidence of the primary endpoint at 2 years when compared with the reference treatment, but not statistically significant (4.6 vs. 9.1%, HR: 0.50, 95%CI: 0.24–1.02, $p = .056$).

4 | DISCUSSION

The main findings of the study are following:

1. PCI for bifurcation lesions with a biolimus A9-eluting stent was not associated with higher incidence of primary endpoint of all-cause death or new Q-wave MI compared with PCI for nonbifurcation lesions, whereas significant difference was observed in new Q-wave MI, any revascularization, and TVR at 2 years between groups.
2. In patients who underwent bifurcation PCI, 1-month of DAPT with aspirin and ticagrelor followed by 23-month ticagrelor monotherapy had no impact on the primary endpoint but was associated with significant reduction in the risk of definite or probable ST and significant excess of stroke compared with 12-month standard DAPT followed by 12-month aspirin monotherapy.

4.1 | Bifurcation group versus nonbifurcation group

In terms of the primary endpoint of death or new Q-wave MI, the result of the study is in line with previously published data from all-comers trials.[1,20] In contrast, the higher rate of new Q-wave MI in the bifurcation group over the nonbifurcation group was observed consistently at 1- and 2-year follow-ups and in the landmark analysis at 1 year, whereas the incidence of any MI was similar between groups. In the bifurcation subanalysis of the Resolute all-comers trial, 2-year Q-wave MI rates in bifurcation and nonbifurcation groups were similar to the present trial, but there was no significant difference due to less sample size (1.6% in bifurcation vs. 0.6% in nonbifurcation, $p = .097$, $n = 2{,}265$).[20] Therefore, this finding may suggest that bifurcation PCI can be associated with the occurrence of more severe MI up to 2 years when compared with nonbifurcation PCI.

4.2 | Optimal duration of DAPT for patients undergoing bifurcation PCI

The evidence for the optimal antiplatelet strategy after bifurcation PCI is scarce, especially for potent antiplatelet drugs such as ticagrelor and prasugrel. Recent pooled patient-level analysis demonstrated that short DAPT of 3 or 6 months is associated with a higher incidence of

1-year major adverse cardiac events mainly driven by MI, when compared with prolonged DAPT of more than 1 year in patients undergoing PCI for complex lesions including bifurcation lesions treated with a two-stent technique.[10] In addition, a 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 (≥12 months) versus shorter DAPT group (<12 months) after bifurcation PCI with drug-eluting stent (DES).[21] From these results, it seems that patients undergoing bifurcation PCI need at least 12 months of DAPT. The present study also shows no benefit of 1-month DAPT followed by ticagrelor monotherapy on the primary endpoint when compared with 12-month DAPT.

4.3 | ST and stroke after bifurcation PCI

Previously coronary bifurcation lesions were reported as an independent risk factor for ST[22–24] as consequence of several factors. Firstly, bifurcation stenting modifies local hemodynamics and creates low endothelial shear stress and stagnant areas that could result in local thrombogenicity.[25] Secondly, pathological studies demonstrated that the flow divider zone was associated with a high percentage of uncovered struts and fibrin deposition several months after DES implantation, which could represent a substrate for ST.[26] Thirdly, two-stent strategies have been suspected of inducing overlapping device segments that could result in local thrombogenicity.[27] Finally, bifurcation stenting could also encourage stent malapposition due to vessel dimension variation along the different segments and promote future thrombotic events.[28] In the present trial, the incidence of ST did not statistically differ between bifurcation and nonbifurcation groups. However, ticagrelor monotherapy following 1-month DAPT demonstrated significant treatment effect on definite or probable ST at 2 years compared with conventional aspirin monotherapy following 12-month DAPT. This benefit was observed up to 1 year and subsided beyond, although theoretically this benefit should be derived from the comparison between ticagrelor monotherapy versus aspirin monotherapy beyond 1 year. In addition, overall incidence of ST was quite low, and the treatment effect of the experimental strategy on ST went into opposite directions in bifurcation and nonbifurcation groups.

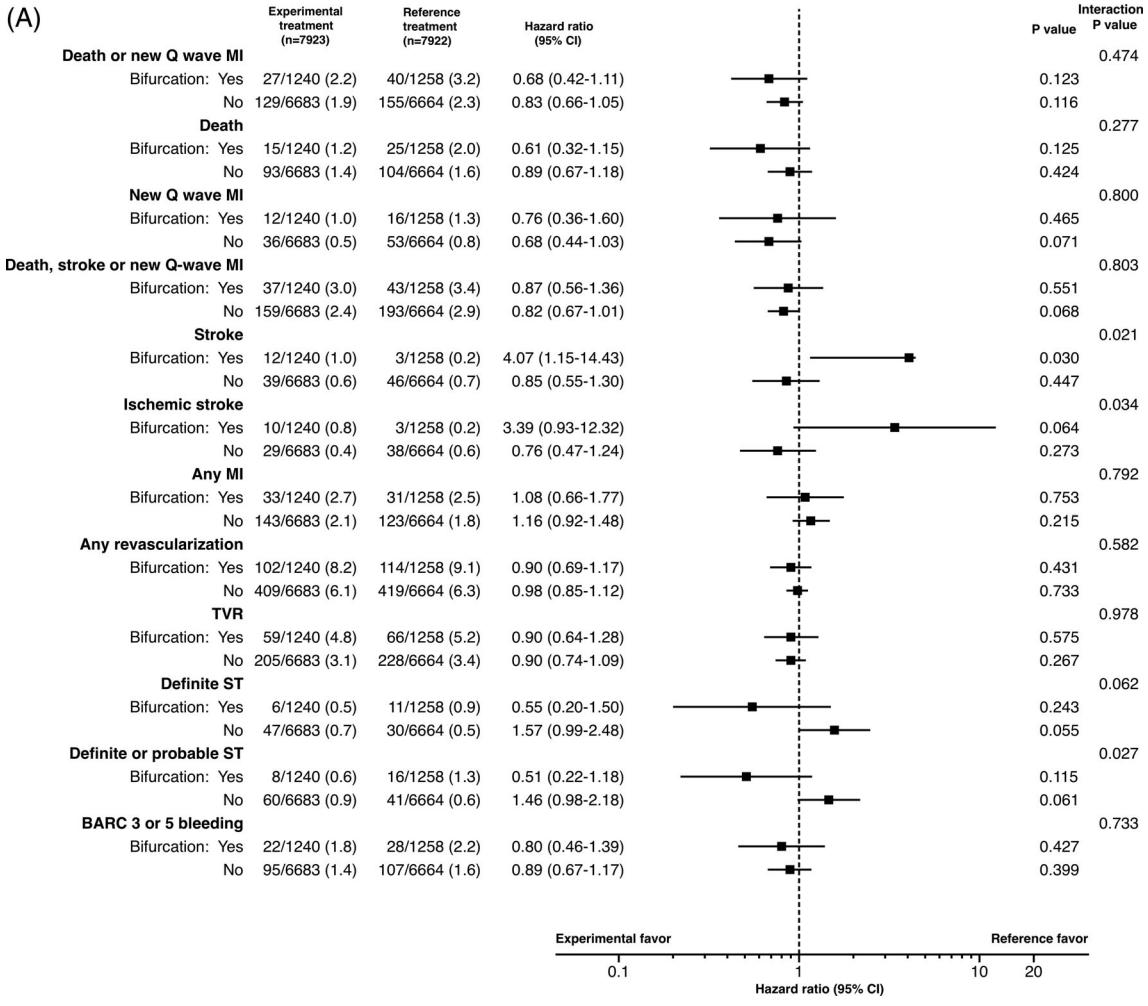

FIGURE 2 Treatment comparison of experimental versus reference antiplatelet strategy in randomized patients with versus without bifurcation PCI at 1 year (A) and 2 years (B) follow-up. BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; PCI, percutaneous coronary intervention; ST, stent thrombosis; TVR, target vessel revascularization

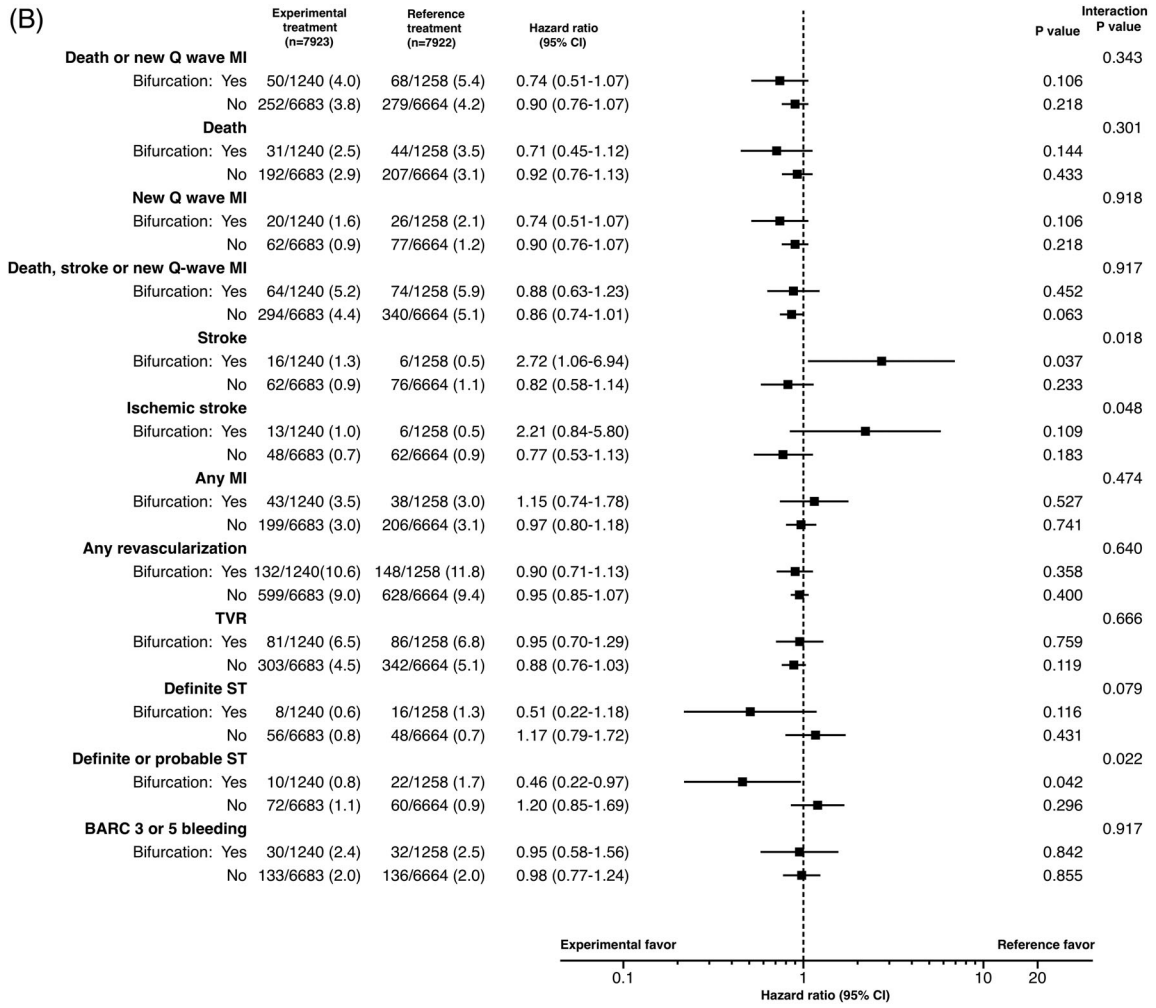

FIGURE 2 (Continued)

Consequently, these significant findings regarding ST can be considered as a play of chance.

On the other hand, in patients who underwent bifurcation PCI, harmful effect of experimental treatment in 2-year stroke was observed compared with reference treatment. This difference in stroke was mainly derived from the result between 30 days and 1 year. Therefore, procedure itself was probably not associated with the occurrence of stroke. These findings may suggest that DAPT is associated with lower incidence of stroke up to 1 year compared with monotherapy of ticagrelor. However, overall incidence of stroke was quite low, and the treatment effect of the experimental strategy on stroke went into opposite directions in bifurcation and nonbifurcation groups. Consequently, these apparently significant findings regarding stroke can be also considered as a play of chance similar to ST.

Regarding composite hard endpoint of all-cause death, stroke, or new Q-wave MI at 2 years, there was no significant difference between groups in patients undergoing bifurcation PCI, which suggests that early discontinuation of aspirin at 30 days after bifurcation PCI followed by ticagrelor monotherapy may be as safe as conventional 12-month DAPT followed by aspirin monotherapy.

Further evidence from dedicated bifurcation trial testing 1-month DAPT followed by P2Y12 monotherapy is warranted in order to further elucidate that possible duality of effect (such as possible prevention of ST and possible increase in stroke) in patients undergoing bifurcation PCI.

4.4 | Study limitations

This prespecified subgroup analysis of primary endpoint has several limitations.

Firstly, in the context of the overall trial in which the primary endpoint was not met, these findings need to be considered as hypothesis generating.

Secondly, although this subgroup analysis of primary endpoint was prespecified and information of bifurcation was prospectively collected,[12] no formal power calculation was performed. In addition, there exist limitations inherent in subgroup analysis such as diminished power to detect real differences and increasing statistical likelihood of false finding when many subgroups are examined with

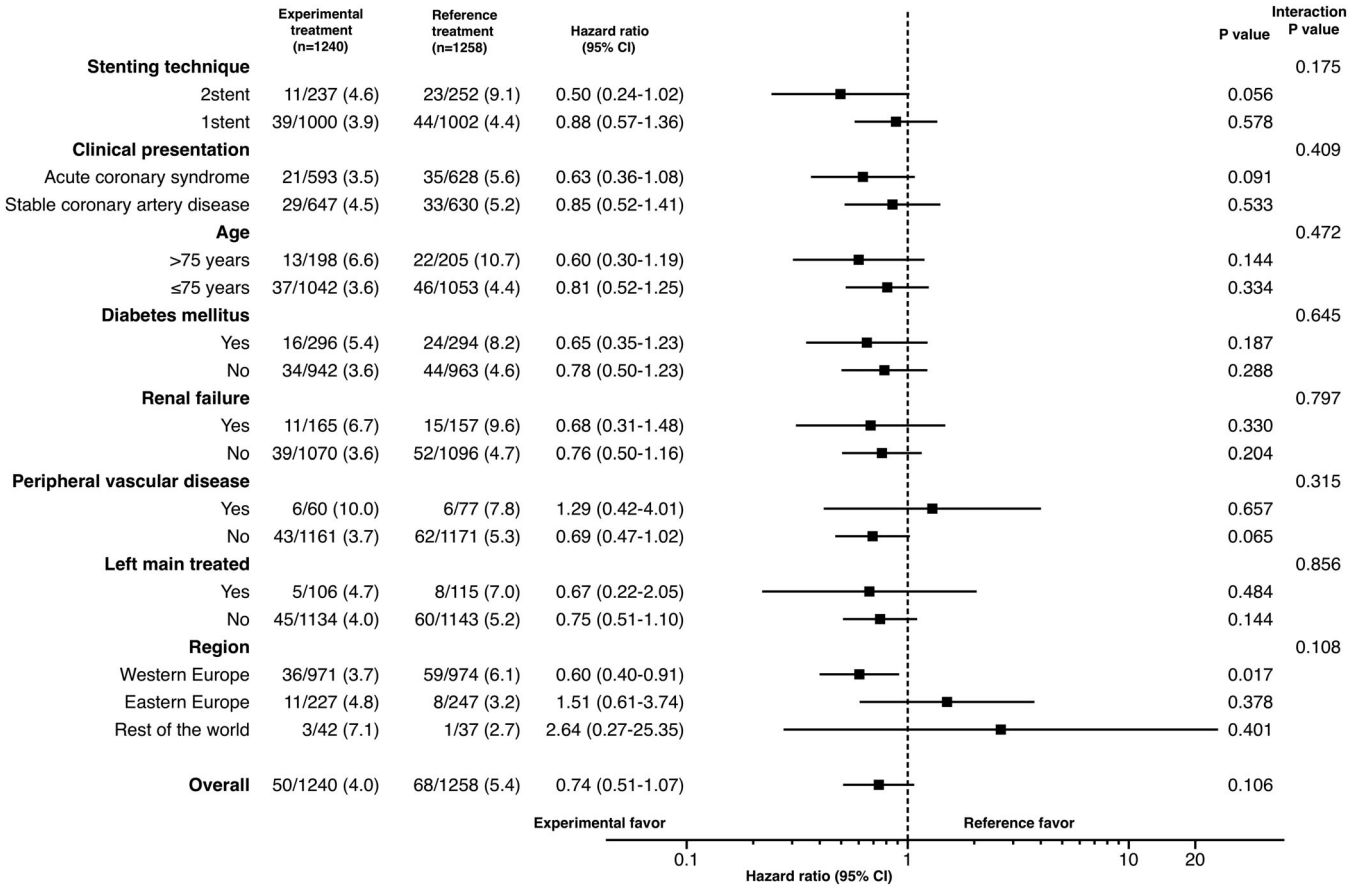

FIGURE 3 Subgroup analysis of all-cause death or new Q-wave MI at 2 years in patients treated for at least one bifurcation lesion. CI, confidence interval, MI, myocardial infarction

multiple testing. Therefore, the study findings should be considered as hypothesis generating.[29]

Thirdly, 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 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. Nevertheless, the result of secondary endpoint should cautiously be interpreted in conjunction with the individual components of the primary endpoint.

Fourthly, the analysis for comparing two- versus one-stent technique was postrandomization and nonprespecified analysis; therefore, the findings are likely influenced by unmeasured confounders.

Fifthly, we did not collect the anatomic SYNTAX score including Medina classification in all the patients, which limited the analysis regarding anatomical complexity of each bifurcation lesion.

Finally, a biolimus A9-eluting stent has a relatively thicker strut of 120 μm compared with other current-generation DES. This might result in worse outcomes in bifurcation lesions treated with two-stent technique using a biolimus A9-eluting stent due to the overlap of relatively thicker struts. A meta-analysis published in 2018 showed that DES with ultrathin struts (strut thickness < 70 μm) reduced the incidence of target lesion failure compared with that of contemporary stents with thicker struts.[30] 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.

5 | CONCLUSIONS

After PCI for bifurcation lesions, using 1-month of DAPT followed by ticagrelor monotherapy for 23 months did not demonstrate explicit benefit regarding all-cause death or new Q-wave MI as in the overall trial.

DISCLOSURE OF INTERESTS

Dr Ph Gabriel Steg reports research grant from Amarin, Bayer, Merck, Sanofi, and Servier, speaking or consulting fees from Amarin, Amgen, AstraZeneca, Bayer/Janssen, Boehringer-Ingelheim, Bristol-Myers-Squibb, Idorsia, Lilly, Merck, Novartis, Novo-Nordisk, Pfizer, Regeneron, Sanofi, Servier. 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. The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

N.K., P.C., Y.O., and P.W.S. analyzed the data and drafted the manuscript. K.D.W., A.C., A.C., S.G., Y.L., P.J., P.G.S., C.H., and L.J. contributed to data collection and to revise the manuscript critically for important intellectual content. K.T., R.M., C.C.C., M.T., H.K., and H.P.S. contributed to revise the manuscript critically for important intellectual content. P.V., M.V., S.W., and P.W.S. contributed to the conception and design of the study. P.W.S. gave final approval of the manuscript submitted.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Kogame N, Chichareon P, De Wilder K, et al. Clinical relevance of ticagrelor monotherapy following 1-month dual antiplatelet therapy after bifurcation percutaneous coronary intervention: Insight from GLOBAL LEADERS trial. *Catheter Cardiovasc Interv*. 2019;1–12. https://doi.org/10.1002/ccd.28428