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ORIGINAL RESEARCH

Ticagrelor Monotherapy or Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation: Per-Protocol Analysis of the GLOBAL LEADERS Trial

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BACKGROUND: In the GLOBAL LEADERS trial, ticagrelor monotherapy beyond 1 month compared with standard antiplatelet regimens after coronary stent implantation did not improve outcomes at intention-to-treat analysis. Considerable differences in treatment adherence between the experimental and control groups may have affected the intention-to-treat results. In this reanalysis of the GLOBAL LEADERS trial, we compared the experimental and control treatment strategies in a per-protocol analysis of patients who did not deviate from the study protocol.

METHODS AND RESULTS: Baseline and postrandomization information were used to classify whether and when patients were deviating from the study protocol. With logistic regressions, we derived time-varying inverse probabilities of nondeviation from protocol to reconstruct the trial population without protocol deviation. The primary end point was a composite of all-cause mortality or nonfatal Q-wave myocardial infarction at 2 years. At 2-year follow-up, 1103 (13.8%) of 7980 patients in the experimental group and 785 (9.8%) of 7988 patients in the control group qualified as protocol deviators. At per-protocol analysis, the rate ratio for the primary end point was 0.88 (95% CI, 0.75–1.03; *P*=0.10) on the basis of 274 versus 325 events in the experimental versus control group. The rate ratio for the key safety end point of major bleeding was 1.00 (95% CI, 0.79–1.26; *P*=0.99). The per-protocol and intention-to-treat effect estimates were overall consistent.

CONCLUSIONS: Among patients who complied with the study protocol in the GLOBAL LEADERS trial, ticagrelor plus aspirin for 1 month followed by ticagrelor monotherapy was not superior to 1-year standard dual antiplatelet therapy followed by aspirin alone at 2 years after coronary stenting.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01813435.

Key Words: DAPT ■ intention-to-treat ■ $P2Y_{12}$ inhibitor monotherapy ■ per-protocol ■ ticagrelor

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CLINICAL PERSPECTIVE

What Is New?

- This per-protocol analysis of the GLOBAL LEADERS trial assessed the per-protocol effect of ticagrelor combined with aspirin for 1 month followed by ticagrelor monotherapy compared with standard antiplatelet therapy after drug-eluting stent implantation.
- Protocol deviators were older and had more often a history of cardiovascular, renal, and pulmonary disease compared with the overall randomized population.
- After censoring data from protocol deviators, the frequency of the primary end point of all-cause mortality or new Q-wave myocardial infarction did not differ significantly between study groups. The same effect was observed for the key safety end point of major bleeding.

What Are the Clinical Implications?

- The per-protocol and intention-to-treat effect estimates for the primary and secondary end points were overall consistent, such that these findings lend support to the validity of the initial interpretation of trial results and their implications for clinical practice.

Nonstandard Abbreviations and Acronyms

DAPT	dual antiplatelet therapy
NACE	net adverse clinical event

Among patients undergoing coronary stent implantation, dual antiplatelet therapy (DAPT) reduces the risk of ischemic events compared with aspirin alone.[1–3] However, a sustained course of DAPT increases the risk of bleeding, which may offset the anticipated ischemic benefit.[4–8] The use of an abbreviated DAPT (1–3 months) followed by P2Y$_{12}$ inhibitor monotherapy after percutaneous coronary intervention (PCI) has been shown to mitigate bleeding risk without apparent loss of efficacy for ischemic prevention.[9–13]

Among available studies, GLOBAL LEADERS is the largest trial and the only one that prespecified the superiority of ticagrelor plus aspirin for 1 month followed by ticagrelor monotherapy for 23 months compared with 1-year DAPT followed by aspirin alone for all-cause mortality or nonfatal centrally adjudicated Q-wave myocardial infarction.[14–18] At intention-to-treat analysis, the experimental strategy failed to show superiority for the primary end point at 2 years (rate ratio [RR], 0.87; 95% CI, 0.75–1.01; P=0.073).[15] In view of the statistical trend toward the benefit associated with the experimental strategy and the high rates of nonadherence to the allocated regimens, particularly in the experimental arm, the intention-to-treat results may have underestimated the true effect of the study treatments.[15,19–22]

In this prespecified analysis of the GLOBAL LEADERS trial, we performed a per-protocol analysis to describe the effect of ticagrelor monotherapy beyond 1 month of DAPT compared with standard antiplatelet regimens among patients who complied with the study protocol through 2-year follow-up.

METHODS

Data Sharing Statement

The statistical analysis plan and study protocol are available from the corresponding author. The GLOBAL LEADERS trial is an investigator-initiated trial. Multiple substudies are predefined. Internal investigators who actively participated in the study and provide a valid study proposal will be granted priority access to the data for 60 months. After 60 months, this option might be extended to external investigators not affiliated with the trial, whose proposed use of the data has been approved by an independent review committee identified by the steering committee. Study proposals can be filed at global.leaders@cardialyis.nl.

Study Design

This is a prespecified per-protocol analysis of the multicenter, open-label, randomized GLOBAL LEADERS trial.[14,15] The study compared 2 antiplatelet strategies in all-comer patients undergoing PCI with uniform use of biodegradable polymer-based biolimus A9-eluting stents and procedural bivalirudin-assisted anticoagulation.[14,15] After diagnostic coronary angiography, but before PCI, patients were randomly assigned to receive the experimental strategy, consisting of 1 month of DAPT (75–100 mg of aspirin plus 90 mg of ticagrelor twice daily) followed by 23 months of ticagrelor monotherapy, or the control strategy, consisting of 12 months of DAPT (75–100 mg of aspirin plus 75 mg of clopidogrel for chronic coronary syndromes or 90 mg of ticagrelor twice daily for acute coronary syndromes) followed by 12 months of aspirin alone. The randomization sequence was concealed via a web-based system, stratified by center and clinical presentation (acute versus chronic coronary syndromes), and blocked using randomly varied block sizes. The study adhered to the principles of the Declaration of Helsinki and Good Clinical Practice. The institutional review board at each participating institution approved the trial, and all participants provided written informed consent.

Study Patients and Procedures

The methods and intention-to-treat results of the trial have been reported previously.[15] This per-protocol analysis was designed to quantify the treatment effect of the randomly allocated antiplatelet strategies among patients who fulfilled all enrollment criteria and did not deviate from medication decisions as planned in the study protocol—the per-protocol treatment effect.[19–21] To determine patients' eligibility, study inclusion and exclusion criteria were assessed, and patients were excluded if any violation had occurred (Table S1). As we anticipated the potential of an unblinded study in terms of drug adherence, medications were dispensed at 3-month time intervals during direct patient contact, and adherence was assessed by direct pill counts and self-reporting at discharge; 30 days; and 3, 6, 12, 18, and 24 months. Adherence counseling by the study team was the default strategy to improve adherence. The investigators systematically collected reasons for nonadherence at 30 days and at months 12 and 24. Two trained clinicians blinded to assignment group and outcomes (F.G., G.G.) independently reviewed adherence data, classified reasons for nonadherence following a hierarchical approach,[23] and categorized the time to protocol deviation on a monthly basis according to the clinical information available in the electronic case report forms. In the case of controversy, senior investigators (S.W., M.V.) were invited to arrive at a consensus. Certain changes of medications for medical reasons were anticipated in the study protocol and were not classified as protocol deviation (Table S2). Specifically, when clinically meaningful events required or indicated the interruption of the allocated treatment (ie, adverse effects, new medical conditions), patients were not classified as protocol deviators (ie, protocol allowed). Conversely, patients qualified as protocol deviators, after a given time point, if nonadherence to study treatment occurred under the following circumstances: (1) high perceived thrombotic risk; (2) high perceived bleeding risk; (3) medical decision without evident clinical reasons; (4) patients unwilling to take study medications; (5) prescription error; (6) logistical issues; or (7) unspecified reasons. This approach is consistent with the recommendations provided by the Non-Adherence Academic Research Consortium.[23]

Study End Points

The primary end point was a composite of all-cause mortality or new Q-wave myocardial infarction at 2 years. Deaths from any cause were ascertained without adjudication. Q-wave myocardial infarction was defined according to 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 protocol required the collection of 12-lead ECGs at discharge, 3 months, and 2 years, and intercurrently in case of revascularization or ischemic events. ECG analysis was performed in a central core laboratory (Cardialysis BV, Rotterdam, the Netherlands) with staff unaware of group assignments. Apart from new Q-wave myocardial infarction, end point events were investigator-reported. The key safety end point was site-reported Bleeding Academic Research Consortium type 3 or 5 bleeding.[24] Other secondary end points included all-cause mortality, myocardial infarction, stroke, target vessel revascularization, definite stent thrombosis, and net adverse clinical events (NACEs). NACE was defined post hoc as the composite of all-cause death, any myocardial infarction, stroke, any revascularization, and Bleeding Academic Research Consortium type 3 or 5 bleeding. The trial was monitored for event underreporting and event definition consistency. Up to 7 on-site monitoring visits were performed at individual sites, with 20% of reported events checked against source documents.

Statistical Analysis

We performed a per-protocol analysis that accounts for the deviation of trial participants from protocol-mandated medications. We estimated and compared the occurrence of the study outcomes in the 2 trial arms as if all patients had followed the trial protocol. Using the information on recorded adverse events and protocol-mandated medications assessed at different time points during the 2-year follow-up, we defined for each participant if and when for the first time (in months after randomization) he/she was nonadherent to the study protocol. At this time point, a nonadherent participant was artificially censored. This artificial censoring introduced selection bias.[19–21] We accounted for this by using time-varying censoring weights.[25] For the calculation of the censoring weights, we restructured the data set such that each subject provided monthly observation periods. At each monthly time period, time-varying month-specific information and baseline information from the trial start was included in the data set. If a patient was no longer protocol adherent at a given month, information of all later months was no longer used for the analysis, including whether he or she experienced an event of interest. We used logistic regression for the remaining uncensored patients (at the monthly period) to calculate the censoring weights. This regression included the following baseline information: age; sex; history of diabetes, hypercholesterolemia, hypertension, stroke, myocardial infarction, vascular disease, chronic obstructive pulmonary disease, and major bleeding; coronary revascularization; alcohol consumption; smoking status; and cardiac arrest at presentation. Additionally, the regression included time-updated information on any adverse event and the number of

recorded adverse events. The data set also included whether the event of interest occurred until the end of the monthly time period for the analysis of primary and secondary outcomes. For outcome analysis, we conducted—in the monthly structured data set—a weighted pooled logistic regression including a flexible spline for the change of the monthly discrete hazard (for the analyzed outcome) and randomization group. This pooled logistic regression represents a proportional hazards model with monthly discrete hazards and the baseline hazards explicitly modeled. The results of that model can be seen as providing a common RR over the whole 2-year follow-up.[26] To account for the weighting used in the analysis, robust standard errors as implemented in STATA statistical software (version 16.1; StataCorp, College Station, TX) were used to derive 95% confidence intervals (CI) and *P* values. *P* values were not adjusted for analyzing multiple end points.

RESULTS

Study Population

In GLOBAL LEADERS, 15 991 patients were recruited and randomly allocated to treatment strategies, but 23 patients withdrew consent and were excluded from data analysis. Thus, 15 968 patients remained eligible for the intention-to-treat analysis. In the experimental group, comprising 7980 patients, 795 (10.0%) and 1103 (13.8%) were classified as protocol deviators at 1-year and 2-year follow-up, respectively. In the control group, consisting of 7988 patients, 523 (6.5%) and 785 (9.8%) patients deviated from the protocol at 1-year and 2-year follow-up, respectively (Figure 1 and Table S3). Reasons for changing study medications determining protocol deviation are detailed in Table S4. The proportion of patients deviating from the study protocol differed between groups and was greater in the experimental than the control group through the entire follow-up period. This difference emerged early and was maintained with slight variation over time, amounting to 4% on an absolute scale at 2-year follow-up.

Baseline Characteristics

Tables 1 and 2 summarize the baseline and procedural characteristics of the study population and protocol deviators at 1-year and 2-year follow-up. In the experimental group, compared with the overall randomized group, protocol deviators were ≈2 years older and

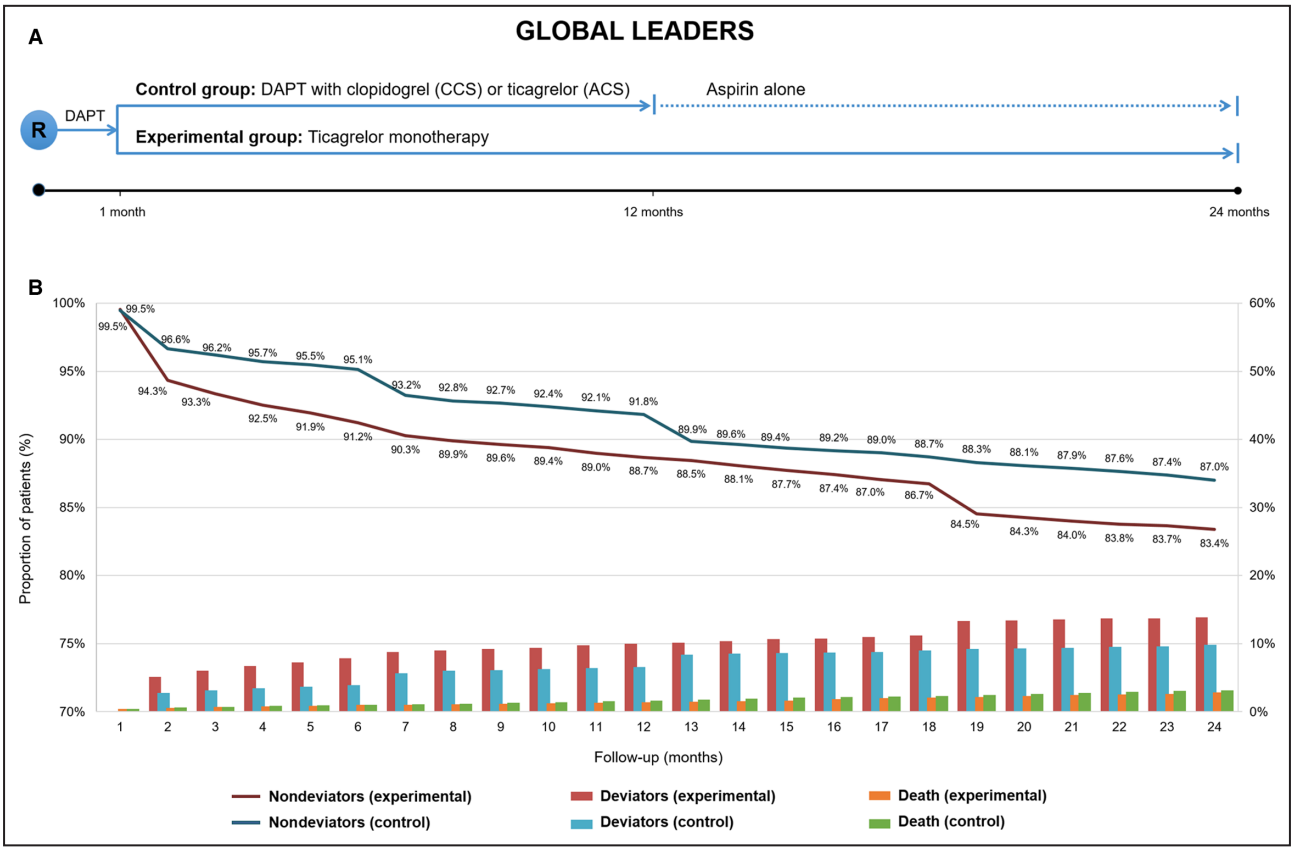

Figure 1. Distribution of protocol deviators and nondeviators in GLOBAL LEADERS at 2 years.
A, Design of the GLOBAL LEADERS trial. **B**, Time trend of protocol deviators (bar graphs), nondeviators (lines), and deaths (bar graphs) at 2 years stratified by treatment strategy. ACS indicates acute coronary syndrome; CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy; and R, randomization.

Table 1. Baseline Characteristics of the Overall Study Population and Protocol Deviators

	Experimental treatment group				Control group			
	Overall randomized patients (n=7980)	Protocol deviators at month 12* (n=795)	Protocol deviators at month 24* (n=1103)	*P* value	Overall randomized patients (n=7988)	Protocol deviators at month 12* (n=523)	Protocol deviators at month 24* (n=785)	*P* value
Age, y	64.5 (10.3)	66.2 (10.4)	66.2 (10.4)	<0.001	64.6 (10.3)	66.4 (10.6)	66.3 (10.5)	<0.001
Male sex	6115 (76.6)	574 (72.2)	823 (74.6)	0.004	6139 (76.9)	384 (73.4)	591 (75.3)	0.13
Female sex	1865 (23.4)	221 (27.8)	280 (25.4)		1849 (23.1)	139 (26.6)	194 (24.7)	
Body mass index, kg/m^2	28.2 (4.6)	28.1 (4.7)	28.2 (4.6)	0.78	28.2 (4.6)	28.1 (4.8)	28.2 (4.7)	0.86
Medical history								
Diabetes	2049 (25.7)	226 (28.4)	295 (26.7)	0.13	1989 (24.9)	133 (25.4)	212 (27.0)	0.10
Insulin-dependent	606 (7.6)	75 (9.4)	95 (8.6)	0.11	617 (7.7)	29 (5.5)	64 (8.2)	<0.001
Hypertension	5882 (73.7)	585 (73.6)	813 (73.7)	0.91	5833 (73.0)	382 (73.0)	581 (74.0)	0.46
Hypercholesterolemia	5345 (67.0)	523 (65.8)	733 (66.5)	0.73	5423 (67.9)	335 (64.1)	538 (68.5)	0.003
Current smoker	2066 (25.9)	193 (24.3)	280 (25.4)	0.46	2103 (26.3)	117 (22.4)	173 (22.0)	0.021
Peripheral vascular disease	476 (6.0)	60 (7.5)	78 (7.1)	0.12	529 (6.6)	51 (9.8)	90 (11.5)	<0.001
COPD	404 (5.1)	57 (7.2)	74 (6.7)	0.012	417 (5.2)	37 (7.1)	54 (6.9)	0.076
Previous major bleeding	46 (0.6)	7 (0.9)	9 (0.8)	0.48	52 (0.7)	3 (0.6)	4 (0.5)	0.96
Impaired renal function†	1099 (13.8)	131 (16.5)	179 (16.2)	0.011	1072 (13.4)	89 (17.0)	126 (16.1)	0.035
Previous stroke	210 (2.6)	20 (2.5)	29 (2.6)	0.87	211 (2.6)	20 (3.8)	28 (3.6)	0.16
Previous myocardial infarction	1831 (22.9)	206 (25.9)	278 (25.2)	0.10	1879 (23.5)	127 (24.3)	206 (26.2)	0.034
Previous PCI	2609 (32.7)	284 (35.7)	385 (34.9)	0.15	2612 (32.7)	165 (31.5)	291 (37.1)	<0.001
Previous CABG	448 (5.6)	69 (8.7)	95 (8.6)	<0.001	495 (6.2)	44 (8.4)	78 (9.9)	<0.001
Clinical presentation								
Stable coronary artery disease	4230 (53.0)	451 (56.7)	611 (55.4)	0.085	4251 (53.2)	199 (38.0)	423 (53.9)	<0.001
Acute coronary syndrome	3750 (47.0)	344 (43.3)	492 (44.6)		3737 (46.8)	324 (62.0)	362 (46.1)	
Unstable angina	1004 (12.6)	88 (11.1)	124 (11.2)	0.24	1018 (12.7)	101 (19.3)	114 (14.5)	<0.001
NSTEMI	1684 (21.1)	159 (20.0)	229 (20.8)	0.42	1689 (21.1)	153 (29.3)	174 (22.2)	<0.001
STEMI	1062 (13.3)	97 (12.2)	139 (12.6)	0.62	1030 (12.9)	70 (13.4)	74 (9.4)	<0.001

Data are n/N (%) or mean (SD) unless otherwise specified. *P* values are based on analyzing 3 mutually exclusive groups of never deviators, deviators during the first 12 months, and deviators during 13–24 months. CABG indicates coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

*Alive at given month.

†Defined as an 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. Procedural Characteristics of the Overall Study Population and Protocol Deviators

	Experimental treatment group				Control group			
	Overall randomized patients (n=7980)	Protocol deviators at month 12* (n=795)	Protocol deviators at month 24* (n=1103)	*P* value	Overall randomized patients (n=7988)	Protocol deviators at month 12* (n=523)	Protocol deviators at month 24* (n=785)	*P* value
PCI done	7943 (99.5)	769 (96.7)	1078 (97.7)	<0.001	7940 (99.4)	501 (95.8)	760 (96.8)	<0.001
Vascular access site	n=7943	n=769	n=1078		n=7940	n=501	n=760	
Radial	5872 (73.9)	503 (65.4)	715 (66.3)	<0.001	5889 (74.2)	363 (72.5)	543 (71.5)	0.042
Femoral	2090 (26.3)	265 (34.5)	365 (33.9)	<0.001	2072 (26.1)	143 (28.5)	222 (29.2)	0.034
Brachial	46 (0.6)	4 (0.5)	4 (0.4)	0.35	47 (0.6)	0 (0.0)	3 (0.4)	0.11
Lesions treated per patient	n=7907	n=752	n=1061		n=7911	n=494	n=752	
1 lesion	5895 (74.5)	558 (74.2)	783 (73.8)	0.51	5910 (74.7)	365 (73.9)	552 (73.4)	0.79
2 lesions	1618 (20.5)	164 (21.8)	231 (21.8)		1569 (19.8)	100 (20.2)	157 (20.9)	
≥3 lesions	394 (5.0)	30 (4.0)	47 (4.4)		432 (5.5)	29 (5.9)	43 (5.7)	
Treated lesions	n=10 403	n=981	n=1394		n=10 438	n=658	n=1004	
Left main coronary artery	197 (1.9)	18 (1.8)	28 (2.0)	0.74	190 (1.8)	9 (1.4)	23 (2.3)	<0.001
Left anterior descending artery	4283 (41.2)	397 (40.5)	563 (40.4)		4383 (42.0)	274 (41.6)	407 (40.5)	
Left circumflex artery	2524 (24.2)	244 (24.9)	342 (24.5)		2553 (24.5)	156 (23.7)	248 (24.7)	
Right coronary artery	3284 (31.6)	307 (31.3)	440 (31.6)		3206 (30.7)	204 (31.0)	302 (30.1)	
Bypass graft	115 (1.1)	15 (1.5)	21 (1.5)		106 (1.0)	15 (2.3)	24 (2.4)	
Stented lesions at index PCI	n=10 241	n=953	n=1362		n=10 283	n=642	n=982	
Mean stents per lesion	1.2 (0.5)	1.2 (0.5)	1.2 (0.5)	0.87	1.2 (0.5)	1.2 (0.5)	1.2 (0.5)	0.76
Biolimus A9-eluting stent	9708 (94.8)	911 (95.6)	1297 (95.2)	0.50	9707 (94.4)	610 (95.0)	923 (94.0)	0.082
Other stent	654 (6.4)	56 (5.9)	82 (6.0)	0.74	685 (6.7)	43 (6.7)	74 (7.5)	0.12
Mean total stent length per lesion	24.8 (13.9)	24.6 (13.9)	24.4 (13.9)	0.078	24.8 (14.0)	24.4 (13.6)	24.1 (13.3)	0.26
Mean stent diameter per lesion	3.0 (0.5)	3.0 (0.5)	3.0 (0.5)	0.28	3.0 (0.5)	3.0 (0.5)	3.0 (0.5)	0.17
Direct stenting per lesion	3334 (32.6)	303 (31.8)	426 (31.3)	0.39	3350 (32.6)	201 (31.3)	285 (29.0)	0.007
Bifurcation per lesion	1251/10 403 (12.0)	97/981 (9.9)	134/1394 (9.6)	0.021	1265/10 438 (12.1)	82/658 (12.5)	124/1004 (12.4)	0.92
Thrombus aspiration done per lesion	483/10 403 (4.6)	36/981 (3.7)	56/1394 (4.0)	0.30	551/10 438 (5.3)	38/658 (5.8)	41/1004 (4.1)	0.003

Data are n/N (%) or mean (SD) unless otherwise specified. *P* values are based on analyzing 3 mutually exclusive groups of never deviators, deviators during the first 12 months, and deviators during 13–24 months. PCI indicates percutaneous coronary intervention.

*Alive at given month.

more frequently women; had more often a history of chronic obstructive pulmonary disease, chronic kidney disease, and coronary artery bypass grafting; and underwent more often elective rather than urgent/emergent coronary stenting. In the control group, compared with the overall randomized group, protocol deviators were also older but did not differ with respect to sex; showed more frequently a history of peripheral artery disease, chronic obstructive pulmonary disease, chronic kidney disease, and myocardial infarction; reported a higher prevalence of prior coronary revascularization; and underwent coronary stenting more often for acute than chronic coronary syndromes.

Clinical Outcomes

At 2-year follow-up, after censoring patients at the time they deviated from the study protocol, a primary end point event had occurred in 274 patients in the experimental group and 325 patients in the control group, resulting in a per-protocol RR of 0.88 (95% CI, 0.75–1.03; *P*=0.10) (Figure 2 and Table 3). Based on 202 and 239 deaths from any cause in the experimental and control groups, respectively, the per-protocol RR for mortality was 0.86 (95% CI, 0.72–1.04; *P*=0.12) (Figure 3). Based on 138 versus 142 Bleeding Academic Research Consortium type 3 or 5 bleeding events in the experimental versus control group, the per-protocol RR was 1.00 (95% CI, 0.79–1.26; *P*=0.99). A total of 1002 and 1148 NACEs occurred in the experimental and control groups, respectively, resulting in a per-protocol RR of 0.90 (95% CI, 0.83–0.97; *P*=0.008). The per-protocol RR of target vessel revascularization was in favor of the experimental strategy. In contrast, the RRs of myocardial infarction, stroke, and definite stent thrombosis did not differ significantly between study groups (Table 3).

The per-protocol and intention-to-treat treatment effect estimates for primary and secondary study end points were overall consistent (Table 3). Because of the artificial censoring of protocol deviators, the number of end point events counted in the per-protocol analysis was lower than the intention-to-treat analysis, resulting in a slightly wider 95% CI, yet similar point estimates for the treatment effects.

DISCUSSION

In this per-protocol analysis of the GLOBAL LEADERS, we assessed the per-protocol effect of ticagrelor combined with aspirin for 1 month followed by ticagrelor monotherapy compared with standard

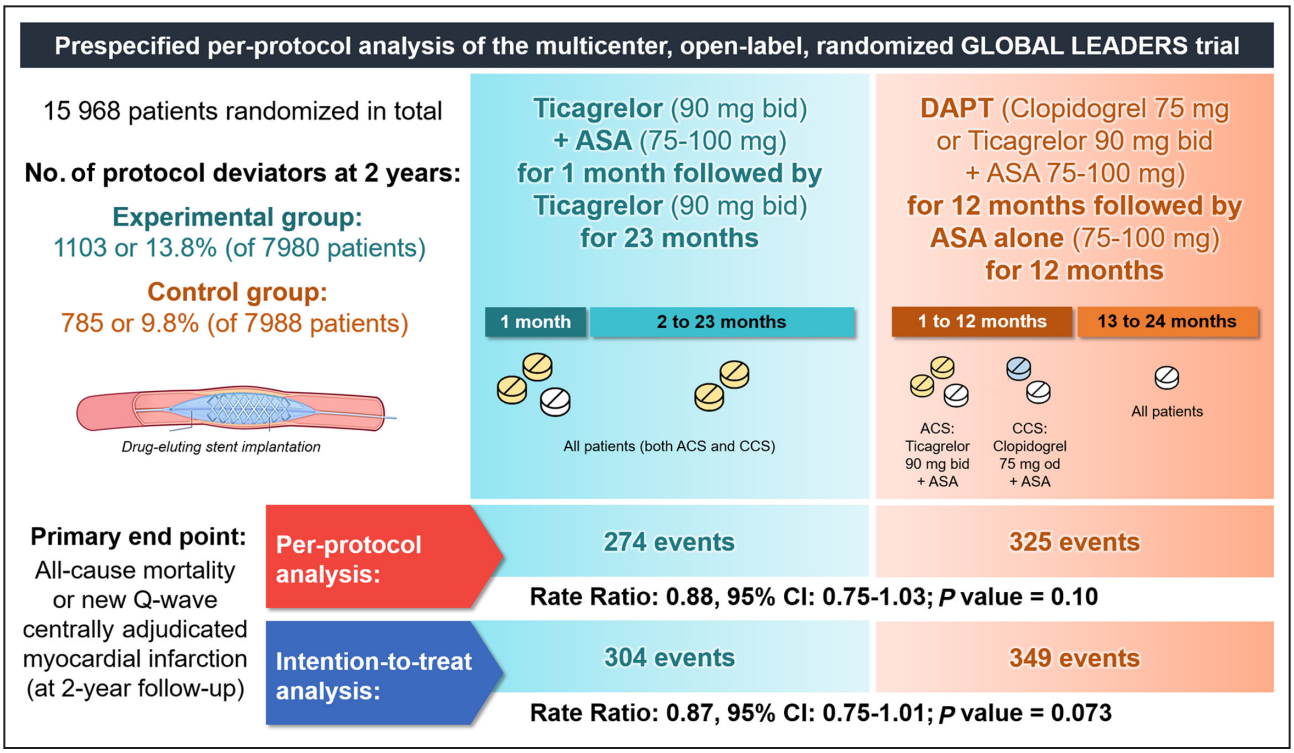

Figure 2. Per-protocol and intention-to-treat effect of ticagrelor monotherapy from 1 month vs standard antiplatelet regimens after coronary stent implantation.
Among patients who complied with the study protocol in the GLOBAL LEADERS, ticagrelor plus aspirin for 1 month followed by ticagrelor monotherapy was not superior to 1-year standard DAPT followed by aspirin alone 2 years after coronary stenting. The per-protocol and intention-to-treat effect estimates were overall consistent. ACS indicates acute coronary syndrome; ASA, acetylsalicylic acid; bid, bis in die (twice daily); CCS, chronic coronary syndrome; and DAPT, dual antiplatelet therapy.

Table 3. Clinical Outcomes in the Intention-to-Treat and Per-Protocol Analysis of the GLOBAL LEADERS Trial at 2 Years

	Intention-to-treat analysis (*Lancet* 2018)			Per-protocol analysis		
	No. of events experimental/ control groups	Rate ratio (95% CI)	*P* value	No. of events experimental/ control groups	Rate ratio (95% CI)	*P* value
Primary end point*	304/349	0.87 (0.75–1.01)	0.073	274/325	0.88 (0.75–1.03)	0.10
All-cause mortality	224/253	0.88 (0.74–1.06)	0.18	202/239	0.86 (0.72–1.04)	0.12
Myocardial infarction	248/250	1.00 (0.84–1.19)	0.98	207/225	0.94 (0.78–1.13)	0.49
Stroke	80/82	0.98 (0.72–1.33)	0.90	69/71	1.00 (0.72–1.40)	0.96
Target vessel revascularization	389/442	0.88 (0.77–1.01)	0.068	341/420	0.83 (0.72–0.96)	0.010
Definite stent thrombosis	64/64	1.00 (0.71–1.42)	0.98	53/59	0.90 (0.62–1.30)	0.57
BARC type 3 or 5 bleeding	163/169	0.97 (0.78–1.20)	0.77	138/142	1.00 (0.79–1.26)	0.99
NACE†	1145/1237	0.92 (0.85–1.00)	0.057	1002/1148	0.90 (0.83–0.97)	0.008

In 8 participants, vital status information was not available at 2 years, and they were censored at the last available month. BARC indicates Bleeding Academic Research Consortium; and NACE, net adverse clinical event.

*The primary end point was the composite of all-cause mortality and new Q-wave centrally adjudicated myocardial infarction.

†NACE end point included death, any myocardial infarction, stroke, or any revascularization.

antiplatelet therapy after drug-eluting stent implantation in patients who complied with the study protocol at the time of 2-year follow-up. The main findings are the following:

1. The proportion of patients deviating from the study protocol was greater in the experimental group (13.8%) than in the control group (9.8%). This difference emerged early, was maintained over time, and amounted to 4% at 2 years.
2. In general, protocol deviators were older; had more often a history of cardiovascular, renal, and pulmonary disease; and reported a higher prevalence of prior coronary revascularization compared with the overall randomized population.
3. After censoring data from protocol deviators, the frequency of the primary end point of all-cause mortality or new Q-wave myocardial infarction did not differ significantly between study groups; the same effect was observed for the key safety end point of investigator-reported major bleeding. Yet the experimental strategy significantly reduced the rate of NACEs in the per-protocol analysis.
4. The per-protocol and intention-to-treat treatment effect estimates for the primary and secondary end points were consistent. Due to the lower number

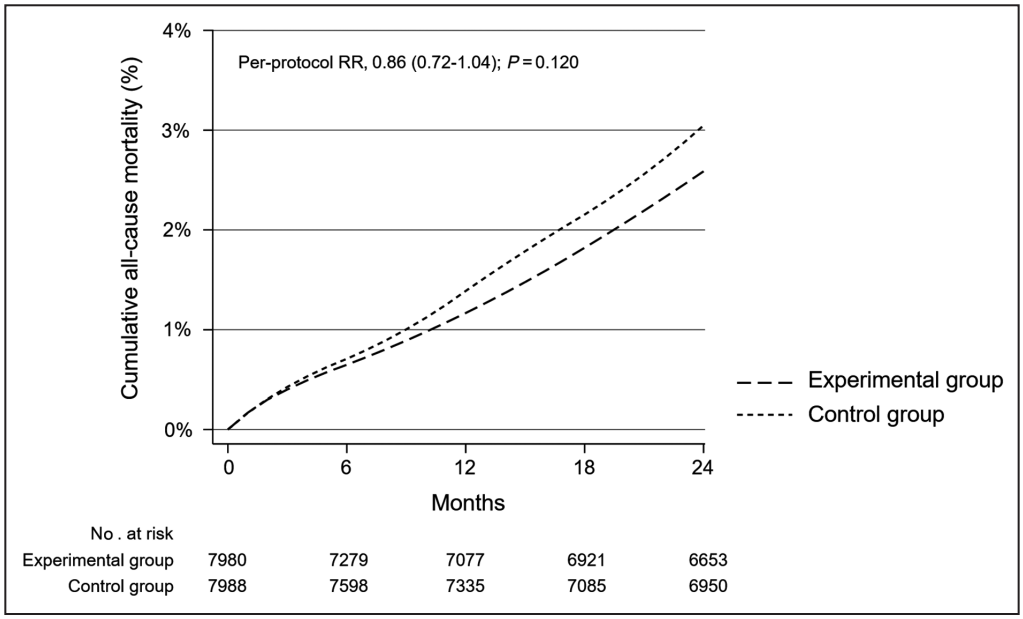

Figure 3. Cumulative incidence of all-cause mortality at 2 years in the per-protocol population.
RR indicates rate ratio.

of events, CIs appeared slightly wider in the per-protocol analysis.

The intention-to-treat analysis of the GLOBAL LEADERS trial showed that the experimental treatment was not superior to the control treatment in the prevention of all-cause mortality or new Q-wave myocardial infarction 2 years after PCI.[15] Yet, the RR estimate of the primary end point showed a nonsignificant trend toward the benefit with the experimental strategy, with the upper boundary of the 95% CI being close to the unit.[15] The intention-to-treat principle represents the gold standard for randomized trial analysis to minimize the risk of bias, but it carries some drawbacks.[19–21] First, this analytical approach offers an estimate of the effect of the treatment assignment—and not of the treatment itself. Second, this strategy is agnostic about postrandomization decisions. Third, it may be affected by incomplete adherence to treatment, particularly if differences across groups exist.[19–21] Therefore, the uncritical reliance on the intention-to-treat results may be problematic and potentially misleading. In the GLOBAL LEADERS, a considerable proportion of participants did not adhere to the study treatment, particularly in the experimental arm.[15] In this scenario, the intention-to-treat analysis might have underestimated the true treatment effect of the experimental strategy, potentially biasing trial results and interpretation.[15,19–21]

We performed a per-protocol analysis of the trial to evaluate the effect of the treatment strategies in patients who had adhered to the protocol—the so-called per-protocol effect. As a consequence of the observational nature of any per-protocol analysis, the validity of the per-protocol effect estimates requires proper adjustment for confounding.[20] For this reason, we refrained from conducting a naïve per-protocol analysis (ie, with no adjustment), which has been previously reported for other clinical trials but relies on incorrect assumptions and leads to biased conclusions.[19–21] We performed an adjusted per-protocol analysis using an inverse-probability weighting model to account for prognostic factors that predicted adherence and provide robust effect estimates.[20] After censoring information from protocol deviators and implementing an extensive adjustment model for pre- and postrandomization confounding, the experimental strategy was not superior to the control strategy for the prevention of all-cause mortality or new Q-wave myocardial infarction at 2 years. These findings lend support to the validity of the initial trial results and interpretation.[15] The per-protocol and intention-to-treat effect estimates for the primary and secondary end points were overall consistent and CIs largely overlapping. This is in line with other trials comparing $P2Y_{12}$ inhibitor monotherapy and standard DAPT after PCI, in whom per-protocol analyses were confirmatory of the intention-to-treat findings.[10–12]

At variance from the intention-to-treat estimates, the rate of NACEs was significantly lowered with the experimental strategy in the per-protocol population. In view of the neutral results for the primary end point, the post hoc definition of this end point, and the multiple comparisons for secondary end points, these findings should be interpreted cautiously. In general, these results appear supportive although nonconclusive for the use of ticagrelor monotherapy shortly after coronary stenting and consistent with those from other studies investigating $P2Y_{12}$ inhibitor monotherapy on composite end points of ischemic and bleeding events.[10,11,13]

This per-protocol analysis also addressed the criticism regarding a relatively high rate of nonadherence to the experimental strategy in the GLOBAL LEADERS trial. In a previous though incomplete adherence subanalysis of the trial, comprising about half of the study population, nonadherence to treatment amounted to 22% in the experimental group and 7% in the control group throughout 2 years,[15] which appeared high but comparable to previous trials investigating ticagrelor for coronary, cerebral, or peripheral artery disease.[27–30] As the trial protocol allowed study drug interruption if clinically indicated, treatment discontinuation did not invariably qualify as a protocol deviation. Accordingly, to select the per-protocol population, we scrutinized adherence information in the overall study cohort and classified participants as protocol deviators if they prematurely interrupted treatment without apparent clinical reasons. We found that the proportion of protocol deviators in the experimental arm was 13.8% at 2 years, suggesting that a relevant proportion of patients in this group discontinued treatment for clinically meaningful reasons rather than for discretionary compliance to the protocol. At the same time point, the rate of protocol deviators in the control group was 9.8% and close to our previous estimates.[15] These findings suggest that the proportion of patients deviating from the trial protocol in the 2 study groups was similar and rather modest. The observed difference in frequency of protocol deviators between the experimental and control groups was relatively low (about 4% through 2-year follow-up) and therefore had a negligible impact on trial results. The differences in adherence are possibly related to the fact that aspirin historically constitutes the default therapy for patients with coronary artery disease, while the experimental strategy has not been established yet. Protocol deviation in the experimental arm, but not in the control group, occurred more frequently among women, who may derive a greater benefit from $P2Y_{12}$ inhibitor monotherapy compared with DAPT.[13] In the context of an open-label trial, these findings may indicate a sex disparity in adhering to study protocols or managing experimental therapies, possibly attributable to the differential behaviors of study personnel, treating physicians, patients, or their relatives. These

data deserve attention and warrant further investigations in view of the potential implications for clinical research and practice.

Limitations of the GLOBAL LEADERS trial also apply to this prespecified per-protocol analysis and have to be considered. This was an open-label trial, and thus patients and investigators were not masked to the treatment strategy. As potential issues in adherence related to the open label were anticipated, adherence was systematically assessed by direct pill counts and self-reporting, and the study team performed counseling to improve adherence. Deviation from the study protocol was categorized and analyzed on a monthly basis. The secondary end point events were investigator reported and not centrally adjudicated. However, the trial was monitored for event underreporting and consistency of event definitions. Also, multiple secondary end points were analyzed and 95% CI and *P* values were not adjusted for multiplicity.[31] Finally, per-protocol analysis of randomized trials are observational studies and can be challenged by confounding.

In conclusion, among patients who complied with the study protocol in the GLOBAL LEADERS trial, ticagrelor combined with aspirin for 1 month followed by ticagrelor monotherapy for 23 months was not superior to 1-year standard DAPT followed by aspirin alone in the prevention of all-cause mortality or new Q-wave myocardial infarction at 2 years after drug-eluting coronary stent implantation. The per-protocol and intention-to-treat treatment effect estimates provided consistent results for primary and secondary end points, though CIs were slightly wider in the per-protocol analysis because of the lower number of events.

APPENDIX

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Supplemental Material

Tables S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. GLOBAL LEADERS trial enrolment criteria.

INCLUSION CRITERIA	
1. Age ≥18 years	
2. Patients with any clinical indication for percutaneous coronary intervention	
3. Presence of one or more coronary artery stenosis of 50% or more in a native coronary artery or in a saphenous venous or arterial bypass conduit suitable for coronary stent implantation in a vessel with a reference vessel diameter of at least 2.25 mm	
EXCLUSION CRITERIA	
Drug-related	1. Known intolerance to aspirin, P2Y12 receptor antagonists, bivalirudin, stainless steel or biolimus 2. Known intake of a strong cytochrome P3A4 inhibitor (i.e., ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir), as co-administration may lead to a substantial increase in exposure to ticagrelor 3. Use of fibrinolytic therapy within 24 hours of percutaneous coronary intervention 4. Known severe hepatic impairment
Treatment-related	5. Planned coronary artery bypass grafting as a staged procedure (hybrid) within 12 months of the index procedure 6. Planned surgery within 12 months of percutaneous coronary intervention unless dual antiplatelet therapy is maintained throughout the peri-surgical period 7. Need for oral anticoagulation therapy 8. PCI for a priori known stent thrombosis
Medical	9. Known overt major bleeding 10. Known history of intracranial hemorrhage 11. Known stroke from ischemic or unknown cause within last 30 days
General	12. Known pregnancy at the time of randomization 13. Inability to provide informed consent 14. Currently participating in another trial before reaching the primary endpoint

Table S2. Reasons for changing medical therapy not determining protocol deviation during the study.

List of reasons
1. Allergic reaction
2. Anemia
3. Atrial fibrillation
4. Bleeding
5. Cerebrovascular accident
6. Chest pain
7. Decreased renal function
8. Diarrhea
9. Dizziness
10. Dyspnea
11. Gout
12. Interference with other drugs
13. Myocardial infarction
14. Neoplasm
15. New medical condition
16. Oral anticoagulation
17. Other signs (in the presence of evident medical reasons)
18. Other symptoms (in the presence of evident medical reasons)
19. Percutaneous coronary intervention
20. Skin reaction
21. Surgery
22. Thromboembolic event
23. Trauma
24. Upper gastrointestinal complaints

Table S3. Protocol deviators and non-deviators by month 24.

Months	Experimental group (n=7,980)			Control group (n=7,988)			Δ deviators experimental vs. control
	Non-deviators	Deviators	Deaths	Non-deviators	Deviators	Deaths	
1	7,943 (99.5%)	5 (0.1%)	32 (0.4%)	7,944 (99.5%)	10 (0.1%)	34 (0.4%)	0.0%
2	7,527 (94.3%)	409 (5.1%)	44 (0.6%)	7,720 (96.6%)	220 (2.8%)	48 (0.6%)	2.4%
3	7,448 (93.3%)	478 (6.0%)	54 (0.7%)	7,683 (96.2%)	248 (3.1%)	57 (0.7%)	2.9%
4	7,384 (92.5%)	536 (6.7%)	60 (0.8%)	7,646 (95.7%)	273 (3.4%)	69 (0.9%)	3.3%
5	7,337 (91.9%)	577 (7.2%)	66 (0.9%)	7,625 (95.5%)	290 (3.6%)	73 (0.9%)	3.6%
6	7,279 (91.2%)	623 (7.8%)	78 (1.0%)	7,598 (95.1%)	308 (3.9%)	82 (1.0%)	4.0%
7	7,203 (90.3%)	697 (8.7%)	80 (1.0%)	7,447 (93.2%)	452 (5.7%)	89 (1.1%)	3.1%
8	7,174 (89.9%)	718 (9.0%)	88 (1.1%)	7,415 (92.8%)	479 (6.0%)	94 (1.2%)	3.0%
9	7,153 (89.6%)	736 (9.3%)	91 (1.1%)	7,401 (92.7%)	485 (6.0%)	102 (1.3%)	3.2%
10	7,134 (89.4%)	749 (9.4%)	97 (1.2%)	7,379 (92.4%)	500 (6.3%)	109 (1.3%)	3.1%
11	7,100 (89.0%)	776 (9.7%)	104 (1.3%)	7,358 (92.1%)	509 (6.4%)	121 (1.5%)	3.4%
12	7,077 (88.7%)	795 (10.0%)	108 (1.3%)	7,335 (91.8%)	523 (6.6%)	130 (1.6%)	3.4%
13	7,059 (88.5%)	807 (10.1%)	114 (1.4%)	7,178 (89.9%)	669 (8.4%)	141 (1.7%)	1.7%
14	7,029 (88.1%)	826 (10.3%)	125 (1.6%)	7,158 (89.6%)	679 (8.5%)	151 (1.9%)	1.9%
15	6,999 (87.7%)	850 (10.7%)	131 (1.6%)	7,138 (89.4%)	686 (8.6%)	164 (2.0%)	2.1%
16	6,975 (87.4%)	859 (10.8%)	146 (1.8%)	7,122 (89.2%)	694 (8.7%)	172 (2.1%)	2.1%
17	6,946 (87.0%)	875 (11.0%)	159 (2.0%)	7,109 (89.0%)	700 (8.8%)	179 (2.2%)	2.2%
18	6,921 (86.7%)	894 (11.2%)	165 (2.1%)	7,085 (88.7%)	717 (9.0%)	186 (2.3%)	2.2%
19	6,745 (84.5%)	1,064 (13.4%)	171 (2.1%)	7,054 (88.3%)	738 (9.2%)	196 (2.5%)	4.1%
20	6,723 (84.3%)	1,072 (13.4%)	185 (2.3%)	7,035 (88.1%)	742 (9.3%)	211 (2.6%)	4.1%
21	6,702 (84.0%)	1,082 (13.5%)	196 (2.5%)	7,018 (87.9%)	750 (9.4%)	220 (2.7%)	4.2%
22	6,685 (83.8%)	1,093 (13.7%)	202 (2.5%)	7,000 (87.6%)	758 (9.5%)	230 (2.9%)	4.2%
23	6,676 (83.7%)	1,096 (13.7%)	208 (2.6%)	6,979 (87.4%)	767 (9.6%)	242 (3.0%)	4.1%
24	6,653 (83.4%)	1,103 (13.8%)	224 (2.8%)	6,950 (87.0%)	785 (9.8%)	253 (3.2%)	4.0%

Table S4. Reasons for patients to be classified as protocol deviators in the experimental and control groups by month 12 and 24.

	Experimental group		Control group	
List of reasons	**By month 12**	**By month 24**	**By month 12**	**By month 24**
Total	795	1,103	523	785
Perceived high bleeding risk	2	3	0	2
Perceived high thrombotic risk	1	1	0	0
Logistical issues	3	4	2	1
Medical decision without clinical reason	16	27	17	30
Patients unwilling to take study drugs	8	11	7	9
Prescription error	1	4	0	0
No specific information	643	886	402	574
Unclear	121	167	95	169