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ORIGINAL RESEARCH

Efficacy and Safety of Ticagrelor Monotherapy by Clinical Presentation: Pre-Specified Analysis of the GLOBAL LEADERS Trial

Pascal Vranckx, MD, PhD;* Marco Valgimigli, MD, PhD;* Ayodele Odutayo, MD, DPhil;* Patrick W. Serruys, MD, PhD; Christian Hamm, MD, PhD; Philippe Gabriel Steg, MD; Dik Heg, PhD; Eugene P. Mc Fadden, MD; Yoshinobu Onuma, MD, PhD; Edouard Benit, MD; Luc Janssens, MD; Roberto Diletti, MD, PhD; Maurizio Ferrario, MD; Kurt Huber, MD; Lorenz Räber, MD; Stephan Windecker, MD; Peter Jüni, MD; on behalf of the GLOBAL LEADERS Investigators

BACKGROUND: The optimal duration of dual antiplatelet therapy after coronary drug-eluting stent placement in adults with stable coronary artery disease (SCAD) versus acute coronary syndromes (ACS) remains uncertain.

METHODS AND RESULTS: This was a prespecified subgroup analysis of the GLOBAL LEADERS trial. Participants were randomly assigned 1:1 to the experimental or reference strategy, stratified by ACS (experimental, n=3750; reference, n=3737) versus SCAD (experimental, n=4230; reference, n=4251). The experimental strategy was 75 to 100 mg aspirin daily plus 90 mg ticagrelor twice daily for 1 month, followed by 23 months of ticagrelor monotherapy. The reference strategy was 75 to 100 mg aspirin daily plus either 75 mg clopidogrel daily (for SCAD) or 90 mg ticagrelor twice daily (for ACS) for 12 months, followed by aspirin monotherapy for 12 months. The primary end point at 2 years was a composite of all-cause mortality or non-fatal centrally adjudicated new Q-wave myocardial infarction. The key secondary safety end point was site-reported Bleeding Academic Research Consortium grade 3 or 5 bleeding. The primary end point occurred in 147 (3.92%) versus 169 (4.52%) patients with ACS (rate ratio [RR], 0.86; 95% CI, 0.69–1.08; *P*=0.189), and in 157 (3.71%) versus 180 (4.23%) patients with SCAD (RR, 0.87; 95% CI, 0.71–1.08; *P*=0.221) with experimental and reference strategy, respectively (*P*-interaction=0.926). Bleeding Academic Research Consortium grade 3 or 5 bleeding occurred in 73 (1.95%) versus 100 (2.68%) patients with ACS (RR, 0.73; 95% CI, 0.54–0.98; *P*=0.037), and in 90 (2.13%) versus 69 (1.62%) patients with SCAD (RR, 1.32; 95% CI, 0.97–1.81; *P*=0.081; *P*-interaction=0.007).

CONCLUSIONS: While there was no evidence for differences in efficacy between treatment strategies by subgroup, the experimental strategy appeared to reduce bleeding risk in patients with ACS but not in patients with SCAD.

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

Key Words: acute coronary syndrome ■ all-comers ■ antiplatelet therapy ■ coronary ■ intervention ■ stable coronary artery disease ■ ticagrelor

Correspondence to: Peter Jüni, MD, Department of, Medicine & Institute of Health Policy, Management and Evaluation, Applied Health Research Centre (AHRC), Li Ka Shing Knowledge Institute of St. Michael's Hospital, Canada Research Chair in Clinical Epidemiology of Chronic Diseases, University of Toronto, 30 Bond Street, Toronto, Ontario, Canada M5B 1W8. E-mail: peter.juni@utoronto.ca

†P. Vranckx, M. Valgimigli and A. Odutayo contributed equally.

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CLINICAL PERSPECTIVE

What Is New?

- In patients with acute coronary syndrome, treatment with ticagrelor and aspirin as dual antiplatelet therapy for 1 month followed by ticagrelor monotherapy reduced Bleeding Academic Research Consortium grade 3 or 5 bleeding with no difference in ischemic outcomes.
- In patients with stable coronary artery disease, treatment with ticagrelor and aspirin as dual antiplatelet therapy for 1 month followed by ticagrelor monotherapy resulted in a non-significant increase in the risk of bleeding compared with guideline recommended treatment with clopidogrel and aspirin.

What Are the Clinical Implications?

- Ticagrelor monotherapy following an abbreviated treatment with dual antiplatelet therapy may provide an optimal balance between ischemic and bleeding risk in patients with acute coronary syndrome but not in stable coronary artery disease.

Nonstandard Abbreviations and Acronyms

BARC	Bleeding Academic Research Consortium
DAPT	dual antiplatelet therapy
SCAD	stable coronary artery disease

Current guidelines recommend dual antiplatelet therapy (DAPT) with aspirin and clopidogrel for a duration of 6 to 12 months following percutaneous coronary intervention (PCI) in patients with stable coronary artery disease (SCAD) and DAPT with aspirin and a potent P2Y12 inhibitor (ticagrelor or prasugrel) for a duration of 12 months in patients with acute coronary syndromes (ACS). Long-term aspirin monotherapy is recommended for all patients.[1–3]

In the advent of potent P2Y12 inhibitors, more evidence is needed on antiplatelet strategies that optimize the balance between bleeding risk and cardiovascular protection in ACS and SCAD. For instance, in the PLATO (Platelet Inhibition and Patient Outcomes) trial, treatment with ticagrelor as compared with clopidogrel (both given in combination with aspirin) reduced the rate of major adverse cardiac events and all-cause mortality in patients with ACS.[4] However, ticagrelor has not been tested in the setting of elective PCI for SCAD.

Likewise, the optimal dose and duration of aspirin therapy in combination with ticagrelor has not been investigated.[5] Indeed, the establishment of aspirin as the main antiplatelet used after PCI stems from studies that are outdated with contemporary practice.[6] Whether monotherapy with more potent antiplatelet medications may obviate the need for combination treatment with aspirin warrants further study in ACS and SCAD.

In the GLOBAL LEADERS trial, the experimental regimen consisting of ticagrelor and aspirin DAPT for 1 month, followed by ticagrelor monotherapy for 23 months was not superior to standard DAPT for 12 months followed by aspirin monotherapy in the prevention of all-cause mortality or new Q-wave myocardial infarction (Q-wave MI) at 2 years after PCI with biodegradable polymer biolimus A9-eluting stents.[7,8] Randomization was stratified according to clinical presentation (ACS versus SCAD). Here we report on a prespecified subgroup analysis according to clinical presentation (ACS versus SCAD),[8] including landmark analyses to examine ischemic and bleeding outcomes up to 30 days, from 31 days to 1 year, and from 1 to 2 years of follow-up.

METHODS

Data Sharing Statement

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

Study Design

The design and the primary end point results of the GLOBAL LEADERS open-label, multicenter superiority trial, were reported previously.[7,8] The trial was approved by the institutional review board at each participating center and all participants provided written informed consent. Sixty months after completion of the primary GLOBAL LEADERS trial, the data underlying this study may be shared with external investigators not affiliated to the trial, whose proposed use of the data has been approved by an independent review committee identified by the steering committee for this purpose.

Study Patients

The study population consisted of patients scheduled to undergo PCI for ACS or symptomatic SCAD,

requiring DAPT.[7,8] PCI was standardized by uniform implantation of biodegradable polymer-based biolimus A9-eluting stent(s) and bivalirudin anticoagulation whenever indicated or feasible. There was no restriction on the number of treated lesions or vessels, on lesion length or number of stents used. The main inclusion and exclusion criteria were previously reported.[7,8] All patients provided written informed consent.

Study Procedures and Randomization

After diagnostic coronary angiography but before PCI, patients were centrally randomized in a 1:1 ratio using a web-based system stratified by center and clinical presentation (ACS versus SCAD) and blocked using randomly varied block sizes of 2 and 4. The experimental strategy consisted of DAPT with aspirin 75 to 100 mg once daily in combination with ticagrelor 90 mg twice daily for 1 month followed by ticagrelor 90 mg twice daily monotherapy for 23 months irrespective of clinical presentation. The reference treatment consisted of 1 year of DAPT with aspirin 75 to 100 mg daily in combination with either clopidogrel 75 mg once daily in patients with SCAD or ticagrelor 90 mg twice daily in patients with ACS and patients with SCAD who had already been on treatment with either ticagrelor or prasugrel, followed by aspirin 75 to 100 mg monotherapy once daily for the remaining 12 months.[7,8] Follow-up visits were scheduled at 30 days, 3, 6, 12, 18, and 24 months after the index procedure. A 12-lead ECG was obtained at discharge, 3 months, and 2 years, and intercurrently in case of revascularization procedures or suspected ischemic events. ECG analyses were performed in a central core laboratory (Cardialysis BV, Rotterdam, the Netherlands). Core laboratory staff were unaware of study arm assignments.[7,8]

End Points

The primary end point was a composite of all-cause death or new Q-wave MI within 730 days of the index procedure.[7,8] Q-wave MI 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.[9,10] The key secondary safety end point was investigator reported bleeding assessed according to the Bleeding Academic Research Consortium criteria (grade 3 or 5).[11] Other secondary end points of the study included the individual components of the primary end point, the composite end point of all-cause death, new Q-wave MI or stroke, myocardial infarction, stroke, target vessel and any revascularization, and stent thrombosis.[8] More detailed definitions of the end points are reported elsewhere.[7,8,12]

Statistical Analysis

Statistical analyses were performed by an academic statistical group led by 2 of the authors (D. H., P. J.), who had access to the full data set. All analyses were performed according to the intention-to-treat principle, including all patients in the analysis according to the clinical presentation. Events up to 730 days post-randomization were considered. We analyzed primary and secondary end points separately for patients with ACS and SCAD, based on time to occurrence of first event using the Mantel−Cox model to derive rate ratios with 95% CIs, and performed treatment-by-subgroup interaction tests. There was no prespecified hierarchical testing of end points. Landmark analyses used prespecified cut-off points at 30 days (corresponding to the planned dates of discontinuation of aspirin in the experimental arm) and 1 year (corresponding to the planned dates of discontinuation of a $P2Y_{12}$ antagonist in the reference arm) after the index procedure with rate ratios (RRs) calculated separately for events up to and beyond the landmark. Categorical variables were compared with the use of the Chi-square test or Fisher exact test. Continuous variables were compared with use of Student *t*-test or the Wilcoxon rank-sum test for non-normally distributed data. Lesion level data were analyzed with mixed models accounting for lesions nested within patients. All statistical analyses were performed with Stata software, version 14.2.

RESULTS

The GLOBAL LEADERS trial enrolled 7487 patients with ACS (experimental n=3750, reference n=3737), and 8481 patients with SCAD (experimental n=4230, reference n=4251) at 130 sites in 18 countries from July 2013 through November 2015 (Figure S1). Complete follow-up for vital status through 730 days was available in 7483 (99.9%) patients with ACS and 8477 (99.9%) patients with SCAD. Baseline clinical and angiographic features were balanced between arms within each presentation stratum (Tables 1 and 2). Patients with ACS were younger, had a lower body mass index, and lower prevalence of cardiovascular risk factors or prior cardiovascular events including stroke, myocardial infarction, or coronary revascularization compared with patients with SCAD (Table 1). Finally, radial access was less frequent, bivalirudin use slightly more common and procedural complexity lower in ACS compared with patients with SCAD (Table 2).

At 1 year, 2975 out of 3537 (84.1%) versus 3122 out of 3512 (85.2%) assessed patients with ACS, and 3197 out of 4013 (79.7%) versus 3733 out of 4021 (92.8%) Patients with SCAD adhered to experimental and reference strategies, respectively. At 2 years, adherence to the experimental strategy was 79.4% (2788 of 3510) in

Table 1. Baseline Characteristics of Randomly Assigned Patients by Clinical Presentation (ACS Versus SCAD)

	Acute coronary syndrome ACS		SCAD		ACS vs SCAD
	Experimental treatment strategy	Reference treatment strategy	Experimental treatment strategy	Reference treatment strategy	
Total no. of patients	n=3750	n=3737	n=4230	n=4251	*P* value
Age, y	63.2±10.8	63.3±10.8	65.6±9.7	65.7±9.7	<0.001
Women	870/3750 (23.2%)	854/3737 (22.9%)	995/4230 (23.5%)	995/4251 (23.4%)	0.523
Body mass index, kg/m^2	28.0±4.5	28.1±4.7	28.3±4.6	28.3±4.6	0.001
Medical history					
Diabetes	809/3746 (21.6%)	795/3736 (21.3%)	1240/4228 (29.3%)	1194/4247 (28.1%)	<0.001
Insulin-dependent	208/3734 (5.6%)	243/3727 (6.5%)	398/4221 (9.4%)	374/4239 (8.8%)	<0.001
Hypertension	2560/3731 (68.6%)	2523/3718 (67.9%)	3322/4223 (78.7%)	3310/4242 (78.0%)	<0.001
Hypercholesterolemia	2178/3580 (60.8%)	2211/3569 (62.0%)	3167/4138 (76.5%)	3212/4178 (76.9%)	<0.001
Current smoker	1288/3750 (34.3%)	1255/3737 (33.6%)	778/4230 (18.4%)	848/4251 (19.9%)	<0.001
Peripheral vascular disease	191/3711 (5.1%)	196/3699 (5.3%)	285/4193 (6.8%)	333/4219 (7.9%)	<0.001
COPD	174/3729 (4.7%)	177/3720 (4.8%)	230/4218 (5.5%)	240/4229 (5.7%)	0.016
Previous Major bleeding	24/3734 (0.6%)	24/3730 (0.6%)	22/4225 (0.5%)	28/4249 (0.7%)	0.686
Impaired renal function*	500/3734 (13.4%)	467/3728 (12.5%)	599/4200 (14.3%)	605/4221 (14.3%)	0.015
Previous stroke	81/3744 (2.2%)	94/3732 (2.5%)	129/4223 (3.1%)	117/4246 (2.8%)	0.029
Previous MI	685/3742 (18.3%)	695/3730 (18.6%)	1146/4214 (27.2%)	1184/4236 (28.0%)	<0.001
Previous PCI	854/3749 (22.8%)	872/3733 (23.4%)	1755/4225 (41.5%)	1740/4247 (41.0%)	<0.001
Previous CABG	130/3750 (3.5%)	145/3735 (3.9%)	318/4224 (7.5%)	350/4246 (8.2%)	<0.001
Type of ACS					
Unstable angina	1004/3750	1018/3737			…
Non–ST-segment–elevation MI	1684/3750	1689/3737			…
ST-segment–elevation MI	1062/3750	1030/3737			…

Depicted are sample sizes (n); and counts (%), means±SDs or medians (25%–75% interquartile range). ACS indicates acute coronary syndrome; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; and SCAD, stable coronary artery disease.

*Based on creatinine-estimated glomerular filtration rate clearance of <60 mL/min per 1.73 m^2, using the Modification of Diet in Renal Disease formula.

ACS and 76.0%; (3022 of 3978) in patients with SCAD and adherence to the reference strategy was 96.0% (3358 of 3497) in ACS and 90.6% (3623 of 4001) in patients with SCAD (Figure S2).

Two-Year Clinical Outcomes

Table 3 presents results for all outcomes at the end of follow-up in patients with ACS and SCAD, Figure 1 provides results for key secondary outcomes. The primary end point of all-cause mortality or new Q-wave MI at 2 years occurred in 147 (3.92%) versus 169 (4.52%) patients with ACS (RR, 0.86; 95% CI, 0.69–1.08; *P*=0.189), and in 157 (3.71%) versus 180 (4.23%) patients with SCAD (RR, 0.87; 95% CI, 0.71–1.08; *P*=0.221) with experimental and reference strategy, respectively (*P* for interaction [*P*-int]=0.926). Both components, all-cause mortality and new-Q-MI, were numerically, but not statistically (*P*≥0.266) lower in the experimental arm of each subgroup, with negative tests for treatment-by-subgroup interaction (*P*-int≥0.884).

Tests for treatment-by-subgroup interaction were negative with respect to myocardial infarction (*P*-int=0.904), stroke (*P*-int=0.662), and definite stent thrombosis (*P*-int=0.356). There was a statistical trend towards less target vessel revascularization in the experimental arm in the ACS (4.51% versus 5.46%; RR, 0.82; 95% CI, 0.67–1.01; *P*=0.061) but not the SCAD subgroup (5.20% versus 5.60%; RR, 0.93; 95% CI, 0.78–1.12; *P*=0.446), but the test for interaction was again negative (*P*-int=0.379).

Bleeding Academic Research Consortium (BARC) grade 3 or 5 bleeding occurred in 73 (1.95%) versus 100 (2.68%) patients with ACS (RR, 0.73; 95% CI, 0.54–0.98; *P*=0.037), and in 90 (2.13%) versus 69 (1.62%) patients with SCAD (RR, 1.32; 95% CI, 0.97–1.81; *P*=0.081; *P*-int=0.007).

Landmark Analyses

Landmark analyses are presented in Figures 2 and 3 and in the appendix (Tables S1 and S2, Figures S3 and

Table 2. Baseline Angiographic Characteristics of Randomly Assigned Patients Stratified by Clinical Presentation (ACS Versus SCAD)

	ACS		SCAD		ACS vs SCAD
	Experimental treatment strategy	Reference treatment strategy	Experimental treatment strategy	Reference treatment strategy	
Total no. of patients	n=3750	n=3737	n=4230	n=4251	*P* value
PCI performed*	3730 (99.5%)	3727 (99.7%)	4213 (99.6%)	4213 (99.1%)	0.038
Vascular access site					
Radial	2886 (77.4%)	2934 (78.7%)	2986 (70.9%)	2955 (70.1%)	<0.001
Femoral	850 (22.8%)	805 (21.6%)	1240 (29.4%)	1267 (30.1%)	<0.001
Brachial	18 (0.5%)	13 (0.3%)	28 (0.7%)	34 (0.8%)	0.009
Bivalirudin during PCI	3299 (88.4%)	3290 (88.3%)	3645 (86.5%)	3636 (86.3%)	<0.001
No. of lesions treated per patient†	n=3719,	n=3715,	n=4188,	n=4196,	<0.001
One lesion	2839 (76.3%)	2841 (76.5%)	3056 (73.0%)	3069 (73.1%)	<0.001
Two lesions	714 (19.2%)	704 (19.0%)	904 (21.6%)	865 (20.6%)	0.002
Three or more lesions	166 (4.5%)	170 (4.6%)	228 (5.4%)	262 (6.2%)	<0.001
Total number of treated lesions	n=4834	n=4818	n=5642	n=5697	
Lesions treated in vessel(s)‡	n=4803,	n=4796,	n=5600,	n=5642,	0.003
Left main coronary artery	76 (1.6%)	86 (1.8%)	121 (2.2%)	104 (1.8%)	
Left anterior descending artery	1916 (39.9%)	1961 (40.9%)	2367 (42.3%)	2422 (42.9%)	
Left circumflex artery	1180 (24.6%)	1209 (25.2%)	1344 (24.0%)	1344 (23.8%)	
Right coronary artery	1581 (32.9%)	1494 (31.2%)	1703 (30.4%)	1712 (30.3%)	
Bypass graft	50 (1.0%)	46 (1.0%)	65 (1.2%)	60 (1.1%)	
Lesions treated per patient	n=4737	n=4725	n=5504	n=5558	
No. of stents per lesion‡	n=4737, 1.2±0.5	n=4725, 1.2±0.5	n=5504, 1.2±0.5	n=5558, 1.2±0.5	0.904
Type of stent‡					
Biolimus-eluting stent§	4523/4737 (95.5%)	4493/4725 (95.1%)	5185/5504 (94.2%)	5214/5558 (93.8%)	0.154
Other stent	267/4737 (5.6%)	283/4725 (6.0%)	387/5504 (7.0%)	402/5558 (7.2%)	
Total stent length per lesion, mm‡	25.2±13.8	25.2±13.7	24.4±14.0	24.5±14.2	<0.001
Average stent diameter per lesion, mm‡	3.01±0.47	3.01±0.48	2.97±0.46	2.97±0.46	<0.001
Direct stenting per lesion‡	1580/4737 (33.4%)	1643/4725 (34.8%)	1754/5504 (31.9%)	1707/5558 (30.7%)	<0.001
Bifurcation per lesion‡	586/4803 (12.2%)	602/4796 (12.6%)	665/5600 (11.9%)	663/5642 (11.8%)	0.22
Thrombus aspiration performed per lesion‡	459/4803 (9.6%)	508/4796 (10.6%)	24/5600 (0.4%)	43/5642 (0.8%)	<0.001
TIMI flow pre-procedure‡	n=4538,	n=4544,	n=5299,	n=5344,	<0.001
0 or 1	985 (21.7%)	994 (21.9%)	311 (5.9%)	320 (6.0%)	
2	641 (14.1%)	593 (13.1%)	546 (10.3%)	580 (10.9%)	
3	2912 (64.2%)	2957 (65.1%)	4442 (83.8%)	4444 (83.2%)	
TIMI flow post-procedure‡	n=4647,	n=4672,	n=5417,	n=5473,	0.625
0 or 1	22 (0.5%)	19 (0.4%)	19 (0.4%)	13 (0.2%)	
2	40 (0.9%)	33 (0.7%)	10 (0.2%)	13 (0.2%)	
3	4585 (98.7%)	4620 (98.9%)	5388 (99.5%)	5447 (99.5%)	

Depicted are sample size (n); and counts (%) or means±SDs. ACS indicates acute coronary syndrome; PCI, percutaneous coronary syndrome; SCAD, stable coronary artery disease; and TIMI, thrombolysis in myocardial infarction.

*Thirty patients with acute coronary syndrome did not receive percutaneous coronary intervention (PCI): medical treatment only (n=5 reference arm, n=16 experimental arm), transferred to urgent surgery (n=5 reference arm, n=4 experimental arm), died before PCI (n=0). Fifty-five stable patients with stable coronary artery disease did not receive PCI: medical treatment only (n=28 reference arm, n=15 experimental arm), transferred to urgent surgery (n=10 reference arm, n=2 experimental arm), died before PCI (n=0).

†Fifty-three patients with acute coronary syndrome did not have information available on the number of treated lesions. Ninety-seven patients did not have information available on the number of treated lesions.

‡Calculated per lesion and analyzed using general or generalized linear mixed-effects models with a random effect of the patient to account for multiple lesions treated within patients.

§Per-protocol BioMatrix family stent used. In n=147 lesions both BioMatrix family stent(s) and other stent(s) were implanted (n=68 reference arm lesions, n=79 experimental arm lesions).

‖Grafts counted as one separate vessel (n=221).

Table 3. Clinical Outcomes at 2 Years Follow-Up by Clinical Presentation (ACS Versus SCAD)

	ACS				SCAD				
Total no. of patients	Experimental treatment strategy n=3750	Reference treatment strategy n=3737	Rate ratio (95% CI)	*P* value	Experimental treatment strategy n=4230	Reference treatment strategy n=4251	Rate ratio (95% CI)	*P* value	Interaction *P* value
All-cause mortality or new Q-wave MI	147 (3.92)	169 (4.52)	0.86 (0.69–1.08)	0.189	157 (3.71)	180 (4.23)	0.87 (0.71–1.08)	0.221	0.926
All-cause mortality	116 (3.09)	132 (3.53)	0.87 (0.68–1.12)	0.286	108 (2.55)	121 (2.85)	0.90 (0.69–1.16)	0.410	0.884
New Q-wave MI*	33 (0.88)	41 (1.10)	0.80 (0.50–1.26)	0.335	50 (1.18)	62 (1.46)	0.81 (0.56–1.18)	0.266	0.964
All-cause mortality, new Q-wave MI or BARC 3 or 5 bleeding	199 (5.31)	243 (6.50)	0.81 (0.67–0.98)	0.029	232 (5.48)	231 (5.43)	1.02 (0.85–1.22)	0.870	0.094
All-cause mortality, stroke or any MI	264 (7.04)	277 (7.41)	0.95 (0.80–1.13)	0.567	244 (5.77)	260 (6.12)	0.95 (0.80–1.13)	0.557	0.980
NACCE	310 (8.27)	342 (9.15)	0.90 (0.77–1.05)	0.188	306 (7.23)	311 (7.32)	1.00 (0.85–1.17)	0.961	0.377
Myocardial infarction	133 (3.55)	132 (3.53)	1.01 (0.79–1.28)	0.955	115 (2.72)	118 (2.78)	0.99 (0.76–1.27)	0.911	0.904
Stroke	44 (1.17)	42 (1.12)	1.04 (0.68–1.59)	0.841	36 (0.85)	40 (0.94)	0.91 (0.58–1.43)	0.681	0.662
Ischemic stroke	35 (0.93)	35 (0.94)	1.00 (0.62–1.59)	0.990	28 (0.66)	33 (0.78)	0.86 (0.52–1.42)	0.549	0.667
Hemorrhagic stroke	7 (0.19)	6 (0.16)	1.16 (0.39–3.46)	0.786	6 (0.14)	3 (0.07)	2.02 (0.51–8.10)	0.309	0.537
Undetermined stroke	2 (0.05)	1 (0.03)	1.99 (0.18–21.98)	0.565	4 (0.09)	4 (0.09)	1.01 (0.25–4.04)	0.987	0.628
Revascularization	336 (8.96)	348 (9.31)	0.96 (0.83–1.12)	0.596	403 (9.53)	445 (10.47)	0.91 (0.80–1.04)	0.175	0.608
Target vessel revascularization	169 (4.51)	204 (5.46)	0.82 (0.67–1.01)	0.061	220 (5.20)	238 (5.60)	0.93 (0.78–1.12)	0.446	0.379
Definite stent thrombosis	32 (0.85)	37 (0.99)	0.86 (0.54–1.39)	0.540	32 (0.76)	27 (0.64)	1.20 (0.72–2.00)	0.490	0.356
BARC 3 or 5 bleeding	73 (1.95)	100 (2.68)	0.73 (0.54–0.98)	0.037	90 (2.13)	69 (1.62)	1.32 (0.97–1.81)	0.081	0.007
BARC 5 bleeding	14 (0.37)	13 (0.35)	1.07 (0.50–2.29)	0.853	8 (0.19)	11 (0.26)	0.73 (0.30–1.83)	0.504	0.528
BARC 5b bleeding	9 (0.24)	10 (0.27)	0.90 (0.36–2.21)	0.814	6 (0.14)	8 (0.19)	0.76 (0.26–2.18)	0.605	0.810
BARC 5a bleeding	5 (0.13)	3 (0.08)	1.66 (0.40–6.96)	0.482	2 (0.05)	3 (0.07)	0.67 (0.11–4.03)	0.663	0.435
BARC 3 bleeding	66 (1.76)	97 (2.60)	0.68 (0.49–0.92)	0.014	84 (1.99)	62 (1.46)	1.37 (0.99–1.91)	0.058	0.002
BARC 3c bleeding	14 (0.37)	18 (0.48)	0.78 (0.39–1.56)	0.474	21 (0.50)	7 (0.16)	3.04 (1.29–7.15)	0.007	0.013
BARC 3b bleeding	21 (0.56)	42 (1.12)	0.50 (0.30–0.84)	0.008	32 (0.76)	32 (0.75)	1.01 (0.62–1.65)	0.967	0.052
BARC 3a bleeding	35 (0.93)	41 (1.10)	0.85 (0.54–1.34)	0.483	42 (0.99)	29 (0.68)	1.46 (0.91–2.35)	0.112	0.103

Depicted are the first event per event type for each patient only (disregards multiple events of the same type within the same patient and censoring at 730 days since index percutaneous coronary intervention). Percentage of patients at risk. Rate ratios (RR) with 95% CI with *P* values from Mantel−Cox log-rank tests. Interaction *P* values from approximate Chi-square test (*df*=1) for unequal RRs, testing for effect modification because of the presentation at percutaneous coronary intervention (acute coronary syndrome vs stable coronary artery disease). ACS indicates acute coronary syndrome; BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; NACCE, composite of all-cause mortality, stroke, any myocardial infarction or, Bleeding Academic Research Consortium 3 or 5 bleeding; and SCAD, stable coronary artery disease.

*New Q-wave or equivalent left bundle branch block as adjudicated by an independent physician.

S4). Analyses up to 30 days, from 31 days to 1 year, and from 1 to 2 years did not show any significant interaction according to clinical presentation with respect to all-cause mortality or ischemic end points. For BARC grade 3 or 5 bleeding, there was evidence for a qualitative treatment-by-subgroup interaction in the landmark analysis up from 31 days to 1 year (*P*-int=0.017), with a benefit of the experimental strategy in patients with ACS, but not in patients with SCAD. Conversely, there was little evidence for a treatment-by-subgroup interaction up to 30 days or from 1 to 2 years (Figure 3 and Tables S1 and S2).

DISCUSSION

In this prespecified subgroup analysis of the GLOBAL LEADERS trial, we analyzed prespecified efficacy and safety end points according to clinical presentation throughout 2 years. For the primary composite end point of all-cause mortality or new Q-Wave MI, we did not find a difference in treatment effects between ACS and patients with SCAD treated with ticagrelor and aspirin DAPT for 1 month followed by ticagrelor monotherapy for 23 months (experimental strategy) or standard DAPT for 12 months followed by aspirin monotherapy (reference strategy). Furthermore, there was no evidence for differences in treatment effects between subgroups in terms of investigator reported myocardial infarction, stroke, or definite stent thrombosis.

Conversely, we found a biologically plausible treatment-by-subgroup interaction for the key secondary safety outcome, BARC-grade 3 or 5 bleeding, with a significantly lower incidence of bleeding with the experimental strategy in patients with ACS, but a non-significant increase in the risk of bleeding with the experimental strategy in patients with SCAD. Using a landmark analysis, this treatment-by-subgroup interaction was most pronounced from 30 days to 1 year. This time period corresponded to ticagrelor monotherapy in the experimental strategy for both ACS and SCAD compared with DAPT with ticagrelor and aspirin in the reference strategy for patients with ACS and clopidogrel and aspirin in the reference strategy for patients with SCAD. Given that aspirin and $P2Y_{12}$ inhibitors exert a synergistic inhibitory effect on platelet activation, the combined use of these agents as compared with monotherapy mainly contributes to bleeding. Our

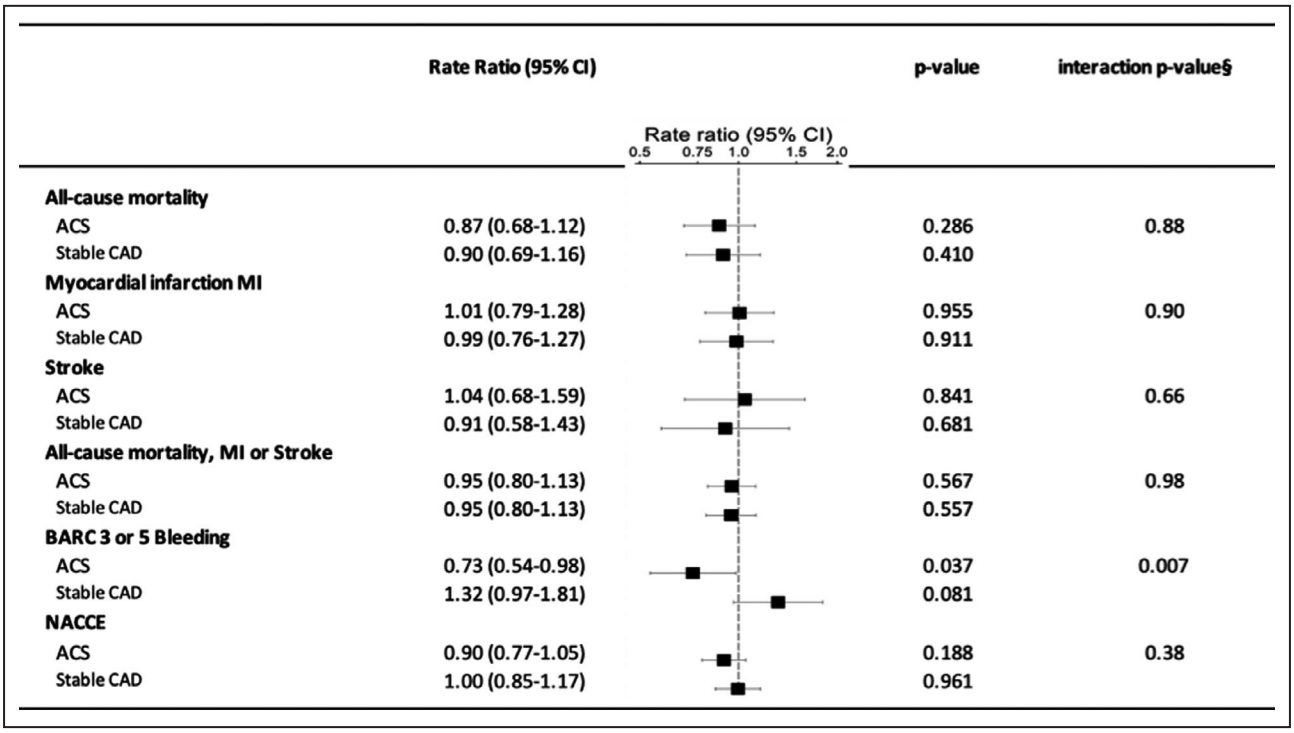
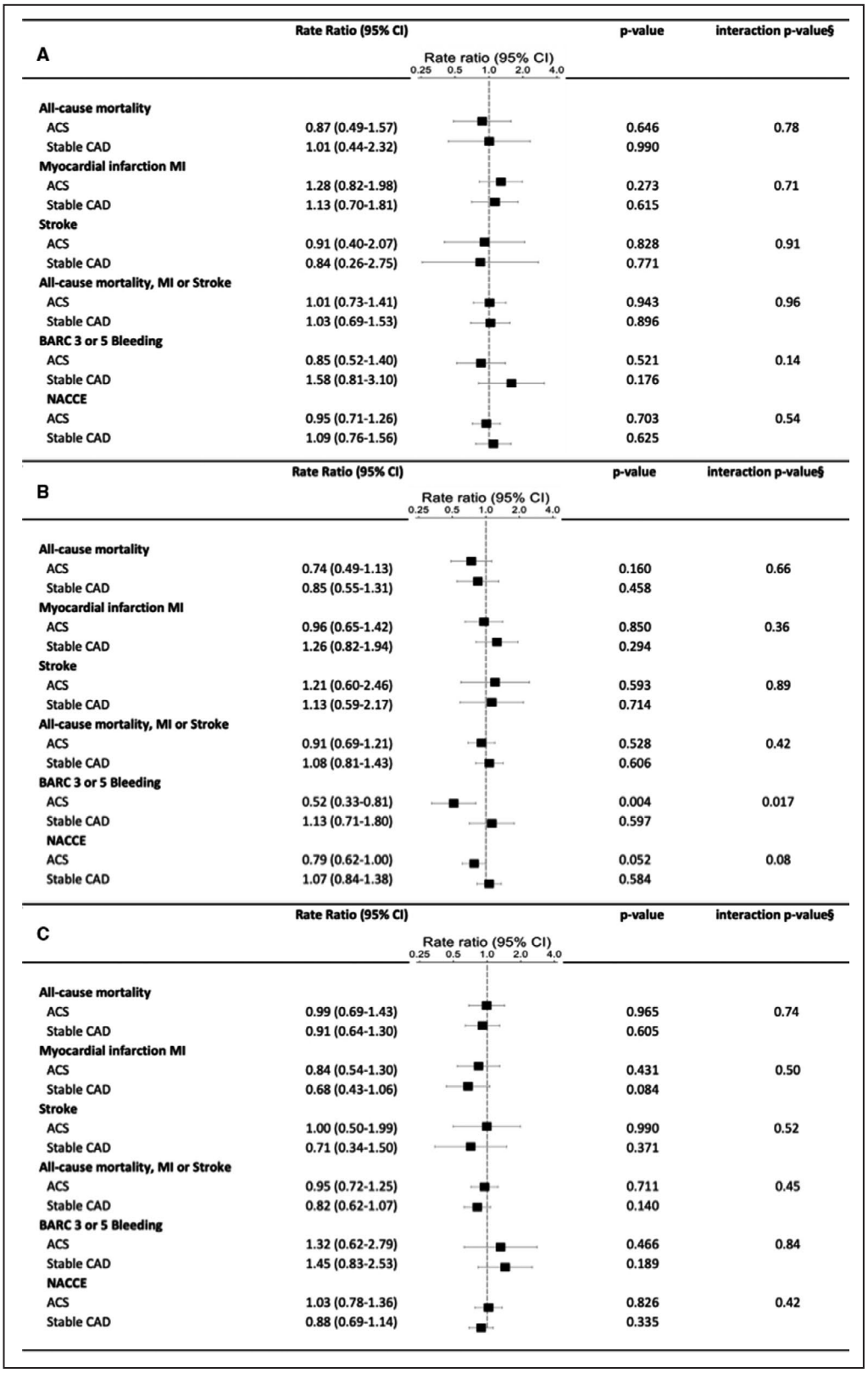


Figure 1. Caterpillar plot for key clinical outcomes by clinical presentation (acute coronary syndrome vs stable coronary artery disease).
Depicted are the first event per event type for each patient only (disregards multiple events of the same type within the same patient and censoring at 730 days since index percutaneous coronary intervention). Percentage of patients at risk. Exact censoring days used at each follow-up, ie, events occurring up to number of days are used for the first events: 2 years=730 days. ACS indicates acute coronary syndrome; BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; NACCE, composite of all-cause mortality, stroke, any myocardial infarction or, Bleeding Academic Research Consortium 3 or 5 bleeding; and SCAD, stable coronary artery disease. §Interaction *P* value of modifying effect of acute coronary syndrome/stable coronary artery disease on the rate ratio comparing experimental vs reference regimen, within the specified period (*df*=1).



analysis therefore suggests that withdrawal of aspirin after a short period of DAPT and continued treatment with ticagrelor monotherapy may represent a safer alternative to the current guideline recommended treatment for reducing recurrent ischemic events in patients with ACS.

Our analysis does not support the experimental strategy in patients with SCAD because of the

Figure 2. Caterpillar plot of landmark analyses for clinical outcomes up to 30 days (A), from 31 days to 1 year (B) and from 1 year to end of follow-up (C) by clinical presentation (acute coronary syndrome vs stable coronary artery disease).
Top panel (**A**) Up to 30 days, middle panel (**B**) 31 days to 1 year and bottom panel (**C**) from 1 year to end of follow-up. Within each landmark period, depicted are the first event per event type for each patient only (disregards multiple events of the same type within the same patient and censoring at 730 days since index percutaneous coronary intervention). Percentage of patients at risk. Exact censoring days used at each follow-up, ie, events occurring up to number of days are used for the first events: 2 years=730 days. ACS indicates acute coronary syndrome; BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; NACCE, composite of all-cause mortality, stroke, any myocardial infarction or, Bleeding Academic Research Consortium 3 or 5 bleeding; and SCAD, stable coronary artery disease. §Interaction *P* value of modifying effect of acute coronary syndrome/ stable coronary artery disease on the rate ratio comparing experimental vs reference regimen, within the specified period (*df*=1).

increased, albeit not statistically significant, incidence of bleeding throughout all landmark periods.[7] Of note, there was no benefit for BARC-grade 3 or 5 bleeding from day 30 to 1 year with the experimental versus reference strategy in patients with SCAD (RR, 1.13; 95% CI, 0.71–1.80). This landmark period corresponds to ticagrelor monotherapy in the experimental strategy and DAPT with clopidogrel and aspirin in the reference strategy. However, the CI for the SCAD subgroup is wide and we cannot rule out a 29% reduction in the incidence of BARC-grade 3 or 5 bleeding. This paradoxical finding may therefore be attributable to chance.

We previously reported on the composites of all-cause mortality or Q-wave MI, and BARC 3 or 5 bleeding for these subgroups for months 1 to 24 combined,[7] and on a post-hoc landmark analysis of months 2 to 12 in patients with ACS.[13] The present analyses now provide the full picture for all relevant investigator reported clinical outcomes over 3 distinct periods characterized by changes in anti-platelet treatment (month 1, months 2–12, and months 13–24), with appropriate tests for interaction between treatment and subgroup. Our results allow a differentiated, mechanistic understanding beyond the grand mean of the negative GLOBAL LEADERS trial.[7]

Beyond the GLOBAL LEADERS trial, there is limited evidence about the efficacy and safety of monotherapy with potent P2Y12 inhibitors. The SMART-CHOICE trial, an open-label non-inferiority study in 2993 patients undergoing PCI, randomized participants to 3 months of DAPT with aspirin and a P2Y12 inhibitor, followed by P2Y12 inhibitor monotherapy, compared with guideline recommended 12 months of treatment with DAPT.[14] In this trial, the experimental strategy was non-inferior to guideline recommended treatment with respect to major adverse cardiac and cerebrovascular events (MACCE) and reduced the incidence of BARC 2 to 5 bleeding.[14] There was also no variation in the treatment effect for MACCE or bleeding when stratified by clinical presentation (ACS versus SCAD) or by type of P2Y12 inhibitor (clopidogrel versus ticagrelor or prasugrel).[14] In comparison to the GLOBAL LEADERS trial, the SMART-CHOICE trial included a lower risk patient population and only 23% of participants received a potent P2Y12 inhibitor such as ticagrelor or prasugrel. Nonetheless, the findings of the SMART-CHOICE trial are complementary to this prespecified analysis of the GLOBAL LEADERS trial, reinforcing the finding that a short period of DAPT followed by P2Y12 monotherapy may provide an optimal balance between ischemic and bleeding risk.

The TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial examined a higher ischemic risk patient population undergoing treatment with ticagrelor monotherapy after 3 months of DAPT compared with DAPT using aspirin and ticagrelor for the duration of 12 months.[15] In the subgroup of patients with ACS, TWILIGHT demonstrated that ticagrelor monotherapy after 3 months of DAPT reduced the incidence of BARC 2, 3, or 5 bleeding by 53% (hazard ratio, 0.47; 95% CI, 0.36–0.61).[15] The results of TWILIGHT are therefore consistent with our subgroup analysis in ACS, which showed a 48% reduction in the incidence BARC 3 or 5 bleeding (RR, 0.52; 95% CI, 0.33–0.81) while preserving efficacy for ischemic outcomes. Taken together, the TWILIGHT trial and our subgroup analysis suggest a role for stopping aspirin within 3 months after PCI in patients with ACS receiving ticagrelor to decrease bleeding risk while preserving efficacy for ischemic end points compared with standard DAPT up to 12 months after implantation of drug-eluting stents. Conversely, our experimental strategy does not seem to convey a benefit when predominantly compared with clopidogrel in patients with SCAD, neither in terms of efficacy nor safety.

TWILIGHT and GLOBAL LEADERS should stimulate the next appropriately powered randomized trial comparing monotherapy with a potent P2Y12 inhibitor against standard DAPT in patients with ACS using an even shorter initial DAPT period than the 1 month used in GLOBAL LEADERS or the 3 months used in TWILIGHT. In view of the biologic half-life of aspirin and the considerable decrease in the risk of ischemic events in patients with ACS beyond 7 to 10 days after stent implantation, a restriction of DAPT to 7 to 10 days or to the period of hospitalization could be considered in such a trial. This restriction may result in an even more optimal balance between protection from recurrent ischemic events and bleeding risk.

On an absolute scale, there is also a strong rationale for further research focused on optimizing the balance between ischemic and bleeding risk after PCI.

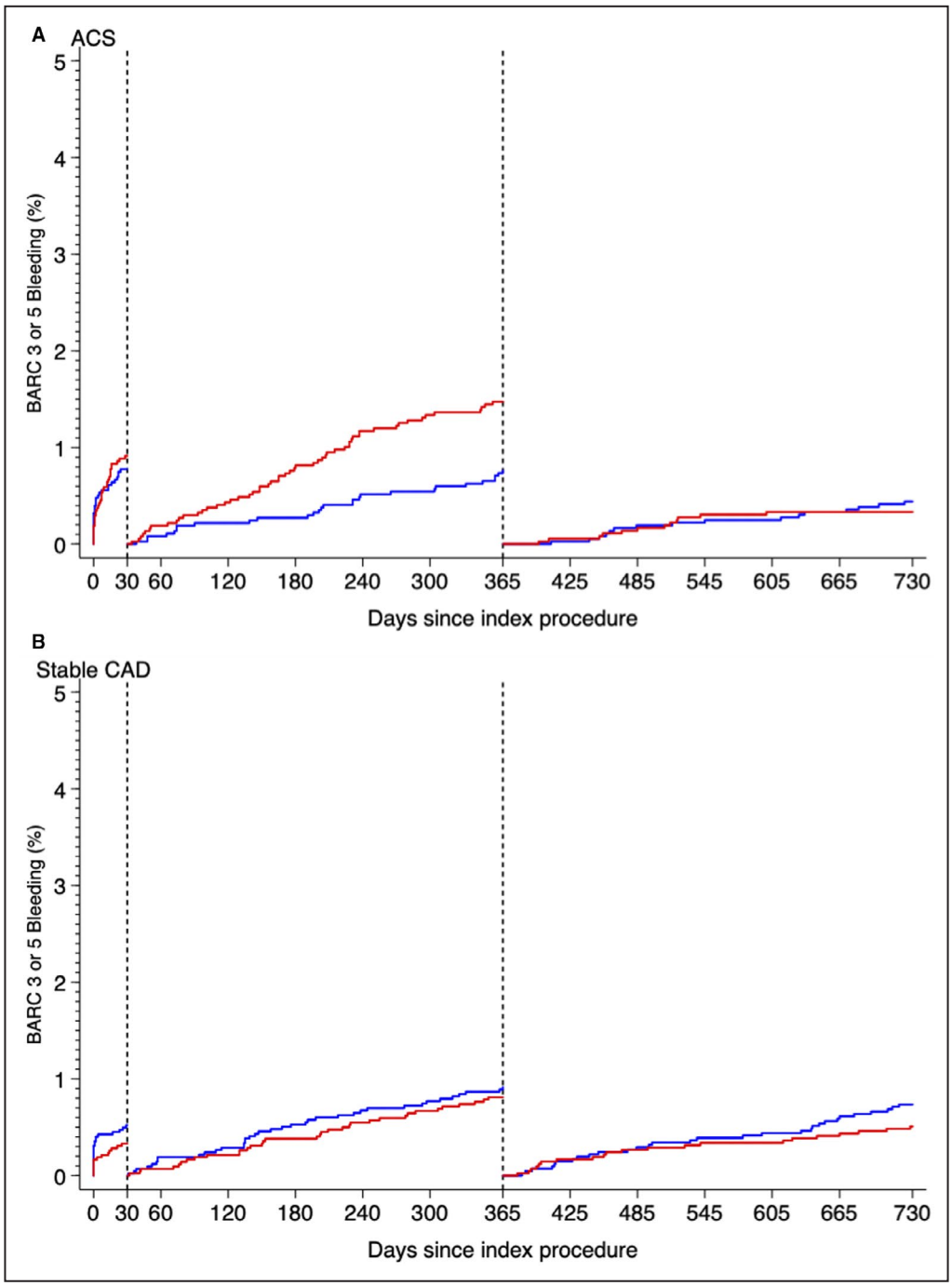


Figure 3. Kaplan–Meier curves of Bleeding Academic Research Consortium 3 or 5 bleeding up to 30 days, from 31 days to 1 year and from 1 year to end of follow-up by clinical presentation (acute coronary syndrome vs stable coronary artery disease).
Within each landmark period, depicted are the first event per event type for each patient only (disregards multiple events of the same type within the same patient and censoring at 730 days since index percutaneous coronary intervention). Top panel: Acute coronary syndrome patients. Cumulative incidence of (**A**) Bleeding Academic Research Consortium 3 or 5 events (acute coronary syndrome), lower panel: (**B**) Bleeding Academic Research Consortium 3 or 5 events (stable coronary artery disease), (blue: experimental strategy arm; red: reference strategy arm). ACS indicates acute coronary syndrome; BARC, Bleeding Academic Research Consortium; and SCAD, stable coronary artery disease.

In our study, the absolute difference in the incidence of BARC 3 or 5 bleeding over 2 years in patients with ACS is 0.73% with the experimental compared with the reference strategy. This corresponds to a number needed to treat 143 adults. For comparison, the absolute risk difference in BARC major bleeding with the

use of radial versus femoral access for PCI was also 0.7%. Further research into the optimal antiplatelet regimen in adults with ACS may be a simple yet effective strategy to further improve clinical outcomes.

Limitations of the GLOBAL LEADERS trial also apply to this prespecified subgroup analysis and need to be considered.[7] First, GLOBAL LEADERS was an open-label trial, and therefore participants and investigators were not masked to the components of the treatment strategy. Efforts that were made to minimize bias included a focus on major, objective primary outcomes, namely all-cause mortality, and adjudicated new Q-wave MI. Investigator reporting for bleeding, MI, stroke, and stent thrombosis was used without central adjudication to ascertain secondary outcomes. Bias and random misclassification can therefore not be excluded for these secondary outcomes. However, GLOBAL LEADERS was monitored for event under-reporting and consistency of event definitions.[7] Second, the ACS and SCAD subgroups varied in important baseline characteristics that may suggest a lower risk of bleeding in adults with ACS. Specifically, adults with ACS were younger and less likely to have hypertension, hypercholesterolemia, and to be active smokers compared with adults with SCAD. Furthermore, PCI in adults with ACS was more often performed using radial access compared with adults with SCAD. These baselines differences would suggest that the incidence of bleeding should be lower in adults with ACS versus SCAD throughout the duration of follow-up. However, our study only identified a treatment-by-subgroup interaction for BARC-grade 3 or 5 bleeding from 30 days to 1 year. Therefore, the withdrawal of aspirin and the continuation of treatment with continuation of ticagrelor monotherapy in adults with ACS likely accounts for the treat-by-subgroup interaction for BARC-grade 3 or 5 bleeding in our study. Third, non-adherence was more common in the experimental strategy than in the control group for both the ACS and SCAD subgroups.[7] This was driven primarily by dyspnea in participants receiving ticagrelor and was largely limited to the first year of treatment.[16] Furthermore, the rate of non-adherence of the experimental regimen in our trial compared favorably with those reported in other large outcome trials involving ticagrelor for various indications.[16] Fourth, PCI in the GLOBAL LEADERS trial was standardized by uniform implantation of biodegradable polymer-based biolimus A9-eluting stents and bivalirudin administration whenever indicated or feasible. Although the choice of anticoagulant and stent in GLOBAL LEADERS may not represent prevalent clinical practice, these treatments were used comparably in the experimental and reference strategy groups and unlikely to bias the results of our study. In addition, guidelines updated since the initiation of the GLOBAL LEADERS trial now recommend 6 months of DAPT after PCI in adults with SCAD versus the 1 year of DAPT that was used in our trial.[3] A shorter duration of DAPT would likely reduce the incidence of bleeding in the reference strategy group and provide further support for avoiding monotherapy with a P2Y12 inhibitor in adults with SCAD. Finally, GLOBAL LEADERS was negative in the main analysis of the primary outcome in the overall population, neither the ACS nor SCAD analysis were powered to detect between-group differences in clinical outcomes or treatment-by-subgroup interactions and there was no formal procedure planned to account for multiple testing. Our results should therefore be considered exploratory in nature. Strength of this subgroup analysis include its prespecified nature, the stratification of randomization by type of presentation, and the large sample size of GLOBAL LEADERS, which means that the analyzed ACS and SCAD populations are larger than the populations included in most randomized trials in patients with coronary artery disease.

In conclusion, this analysis provides novel large-scale randomized evidence to support the use ticagrelor monotherapy following an abbreviated treatment with DAPT to mitigate the risk of bleeding in patients with ACS while preserving efficacy. Ticagrelor monotherapy after PCI in patients with ACS therefore deserves further study.

ARTICLE INFORMATION

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Affiliations

Jessa Ziekenhuis, Faculty of Medicine and Life Sciences at the Hasselt University, Hasselt, Belgium (P.V., E.B.); Department of Cardiology, University of Bern, Inselspital, Bern, Switzerland (M.V., L.R., S.W.); Department of Medicine and Institute of Health Policy, Management and Evaluation, Applied Health Research Centre, Li Ka Shing Knowledge Institute of St. Michael's Hospital, University of Toronto, Canada (A.O., P.J.); Imperial College London, London, United Kingdom (P.W.S.); Kerckhoff Heart and Thorax Center, Bad Nauheim, Germany (C.H.); INSERM U-1148, FACT (French Alliance for Cardiovascular Trials), Hôpital Bichat, Assistance Publique–Hôpitaux de Paris, Université de Paris, France (P.G.S.); National Heart and Lung Institute, Royal Brompton Hospital, Imperial College, London, United Kingdom (P.G.S.); Clinical Trials Unit, University of Bern, Switzerland (D.H.); (E.P.M.F.); and (E.P.M.F.), Cork University Hospital, Wilton, Cork, Ireland; Imeldaziekenhuis, Bonheiden, Belgium (L.J.); Cardialysis, Rotterdam, The Netherlands (Y.O.); Erasmus Medical Center, Rotterdam, The Netherlands (Y.O., R.D.); UOC Cardiologia, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy (M.F.); and 3rd Department of Medicine, Cardiology and Intensive Care Medicine, Medical Faculty, Wilhelminen Hospital and Sigmund Freud University, Vienna, Austria (K.H.).

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Author contributions: Profs. Vranckx, Valgimigli, Serruys, Windecker, Jüni were responsible for the conception and design of the study; All authors were involved in acquisition, analysis, or interpretation of data; Prof. Vranckx, Prof. Valgimigli, Dr. Odutayo, and Prof. Jüni drafted the manuscript; All authors critically revised the manuscript for important intellectual content; Prof. Heg was responsible for the statistical analysis; All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data

analysis; Profs. Vranckx and Jüni are the guarantors of the study results, had full access to the final data, and had final responsibility for content and the decision to submit for publication.

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Supplementary Material

Tables S1–S2
Figures S1–S4

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SUPPLEMENTAL MATERIAL

TABLE S1. Landmark analysis.

Clinical outcomes up to 30 days; and from 31 days to 2 years of Follow up.

	Acute coronary syndrome ACS				Stable CAD				interaction p-value
	Experimental Strategy	Reference Strategy	Rate Ratio (95% CI)	p-value	Experimental Strategy	Reference Strategy	Rate Ratio (95% CI)	p-value	
Total number of patients	N=3750	N=3737			N=4230	N=4251			
At 30 days									
All-cause mortality or new Q-wave MI[c]	22 (0.59)	28 (0.75)	0.78 (0.45-1.37)	0.388	12 (0.28)	14 (0.33)	0.86 (0.40-1.86)	0.704	0.843
All-cause mortality	21 (0.56)	24 (0.64)	0.87 (0.49-1.57)	0.646	11 (0.26)	11 (0.26)	1.01 (0.44-2.32)	0.990	0.784
New Q-wave MI[e]	1 (0.03)	5 (0.13)	0.20 (0.02-1.70)	0.101	1 (0.02)	3 (0.07)	0.34 (0.03-3.22)	0.320	0.742
All-cause mortality, new Q-wave MI[c] or BARC 3 or 5 Bleeding	45 (1.20)	57 (1.53)	0.79 (0.53-1.16)	0.228	29 (0.69)	24 (0.56)	1.22 (0.71-2.09)	0.479	0.200
All-cause mortality, stroke or any MI	71 (1.89)	70 (1.87)	1.01 (0.73-1.41)	0.943	49 (1.16)	48 (1.13)	1.03 (0.69-1.53)	0.896	0.956
NACCE	92 (2.45)	97 (2.60)	0.95 (0.71-1.26)	0.703	63 (1.49)	58 (1.36)	1.09 (0.76-1.56)	0.625	0.536
Myocardial infarction	46 (1.23)	36 (0.96)	1.28 (0.82-1.98)	0.273	37 (0.87)	33 (0.78)	1.13 (0.70-1.81)	0.615	0.707

Stroke	11 (0.29)	12 (0.32)	0.91 (0.40-2.07)	0.828	5 (0.12)	6 (0.14)	0.84 (0.26-2.75)	0.771	0.907
Ischemic stroke	8 (0.21)	10 (0.27)	0.80 (0.31-2.02)	0.633	3 (0.07)	5 (0.12)	0.60 (0.14-2.53)	0.485	0.749
Haemorrhagic stroke	3 (0.08)	1 (0.03)	2.99 (0.31-28.76)	0.319	2 (0.05)	0 (0.00)			
Undetermined stroke	0 (0.00)	1 (0.03)			0 (0.00)	1 (0.02)			
Revascularisation	62 (1.65)	82 (2.19)	0.75 (0.54-1.05)	0.090	50 (1.18)	60 (1.41)	0.84 (0.57-1.22)	0.353	0.675
Target Vessel Revascularization	40 (1.07)	51 (1.36)	0.78 (0.52-1.18)	0.241	33 (0.78)	42 (0.99)	0.79 (0.50-1.25)	0.308	0.973
Definite stent thrombosis	18 (0.48)	17 (0.45)	1.06 (0.54-2.05)	0.873	12 (0.28)	12 (0.28)	1.01 (0.45-2.24)	0.989	0.928
BARC 3 or 5 Bleeding[b]	29 (0.77)	34 (0.91)	0.85 (0.52-1.40)	0.521	22 (0.52)	14 (0.33)	1.58 (0.81-3.10)	0.176	0.142
BARC 5 Bleeding	6 (0.16)	4 (0.11)	1.50 (0.42-5.30)	0.530	4 (0.09)	4 (0.09)	1.01 (0.25-4.03)	0.994	0.678
BARC 5b Bleeding	4 (0.11)	4 (0.11)	1.00 (0.25-3.99)	0.997	4 (0.09)	3 (0.07)	1.34 (0.30-6.00)	0.700	0.776
BARC 5a Bleeding	2 (0.05)	0 (0.00)			0 (0.00)	1 (0.02)			
BARC 3 Bleeding	25 (0.67)	32 (0.86)	0.78 (0.46-1.31)	0.348	18 (0.43)	11 (0.26)	1.65 (0.78-3.49)	0.188	0.106
BARC 3c Bleeding	3 (0.08)	6 (0.16)	0.50 (0.12-1.99)	0.315	3 (0.07)	0 (0.00)			
BARC 3b Bleeding	10 (0.27)	15 (0.40)	0.66 (0.30-1.48)	0.314	6 (0.14)	5 (0.12)	1.21 (0.37-3.96)	0.756	0.412

BARC 3a Bleeding	13 (0.35)	13 (0.35)	1.00 (0.46-2.15)	0.995	10 (0.24)	6 (0.14)	1.68 (0.61-4.62)	0.311	0.421
From 30 days to 2 Years (landmark at 30 days)	125 (3.35)	141 (3.80)	0.88 (0.69-1.12)	0.290	145 (3.44)	166 (3.92)	0.88 (0.70-1.09)	0.244	0.989
All-cause mortality or new Q-wave MI	95 (2.55)	108 (2.91)	0.87 (0.66-1.15)	0.335	97 (2.30)	110 (2.59)	0.89 (0.67-1.16)	0.384	0.942
All-cause mortality	32 (0.86)	36 (0.97)	0.88 (0.55-1.42)	0.604	49 (1.16)	59 (1.39)	0.83 (0.57-1.22)	0.347	0.857
New Q-wave MI	154 (4.18)	186 (5.08)	0.82 (0.66-1.02)	0.069	203 (4.86)	207 (4.92)	0.99 (0.82-1.20)	0.936	0.196
All-cause mortality, new Q-wave MI[c] or BARC 3 or 5 Bleeding	193 (5.28)	207 (5.67)	0.93 (0.77-1.13)	0.479	195 (4.69)	212 (5.07)	0.93 (0.77-1.13)	0.473	0.998
All-cause mortality, stroke or any MI	218 (6.00)	245 (6.76)	0.88 (0.74-1.06)	0.187	243 (5.87)	253 (6.06)	0.97 (0.82-1.16)	0.767	0.457
NACCE	87 (2.38)	96 (2.62)	0.91 (0.68-1.21)	0.506	78 (1.88)	85 (2.03)	0.93 (0.68-1.26)	0.643	0.905
Myocardial infarction	33 (0.89)	30 (0.81)	1.10 (0.67-1.80)	0.714	31 (0.74)	34 (0.81)	0.92 (0.57-1.50)	0.745	0.625
Stroke	27 (0.73)	25 (0.68)	1.08 (0.63-1.86)	0.789	25 (0.60)	28 (0.66)	0.90 (0.53-1.55)	0.711	0.652
Ischemic stroke	4 (0.11)	5 (0.14)	0.80 (0.21-2.97)	0.736	4 (0.10)	3 (0.07)	1.35 (0.30-6.03)	0.693	0.604
Haemorrhagic stroke	2 (0.05)	0 (0.00)			4 (0.10)	3 (0.07)	1.35 (0.30-6.03)	0.694	
Undetermined stroke	274 (7.52)	266 (7.36)	1.02 (0.87-1.21)	0.780	353 (8.52)	385 (9.25)	0.92 (0.80-1.07)	0.273	0.355

Revascularisation	129 (3.52)	153 (4.20)	0.84 (0.66-1.06)	0.137	187 (4.50)	196 (4.69)	0.96 (0.79-1.18)	0.702	0.379
Target Vessel Revascularization	14 (0.38)	20 (0.54)	0.70 (0.35-1.38)	0.301	20 (0.48)	15 (0.36)	1.35 (0.69-2.64)	0.376	0.174
Definite stent thrombosis	44 (1.20)	66 (1.80)	0.66 (0.45-0.97)	0.033	68 (1.63)	55 (1.31)	1.25 (0.88-1.79)	0.211	0.016
BARC 3 or 5 Bleeding	8 (0.22)	9 (0.24)	0.89 (0.34-2.30)	0.804	4 (0.10)	7 (0.17)	0.58 (0.17-1.98)	0.376	0.589
BARC 5 Bleeding	5 (0.14)	6 (0.16)	0.83 (0.25-2.72)	0.759	2 (0.05)	5 (0.12)	0.40 (0.08-2.09)	0.264	0.483
BARC 5b Bleeding	3 (0.08)	3 (0.08)	1.00 (0.20-4.94)	0.998	2 (0.05)	2 (0.05)	1.01 (0.14-7.18)	0.991	0.991
BARC 5a Bleeding	41 (1.11)	65 (1.77)	0.63 (0.42-0.93)	0.018	66 (1.58)	51 (1.21)	1.31 (0.91-1.89)	0.143	0.006
BARC 3 Bleeding	11 (0.30)	12 (0.33)	0.91 (0.40-2.07)	0.828	18 (0.43)	7 (0.17)	2.61 (1.09-6.24)	0.025	0.082
BARC 3c Bleeding	11 (0.30)	27 (0.73)	0.41 (0.20-0.82)	0.009	26 (0.62)	27 (0.64)	0.97 (0.57-1.67)	0.923	0.050
BARC 3b Bleeding	22 (0.60)	28 (0.76)	0.78 (0.45-1.37)	0.390	32 (0.77)	23 (0.55)	1.41 (0.82-2.41)	0.208	0.136
BARC 3a Bleeding	22 (0.60)	28 (0.76)	0.78 (0.45-1.37)	0.390	32 (0.77)	23 (0.55)	1.41 (0.82-2.41)	0.208	0.136

Depicted are the first event per event type for each patient only (disregards multiple events of the same type within the same patient and censoring at 730 days since index PCI). Percentage of patients at risk. NACCE: composite of all-cause mortality, stroke, any myocardial infarction or, BARC 3 or 5 bleeding

Table S2. Clinical outcomes up to 1 year; and from 366 days to 2 years of Follow up.

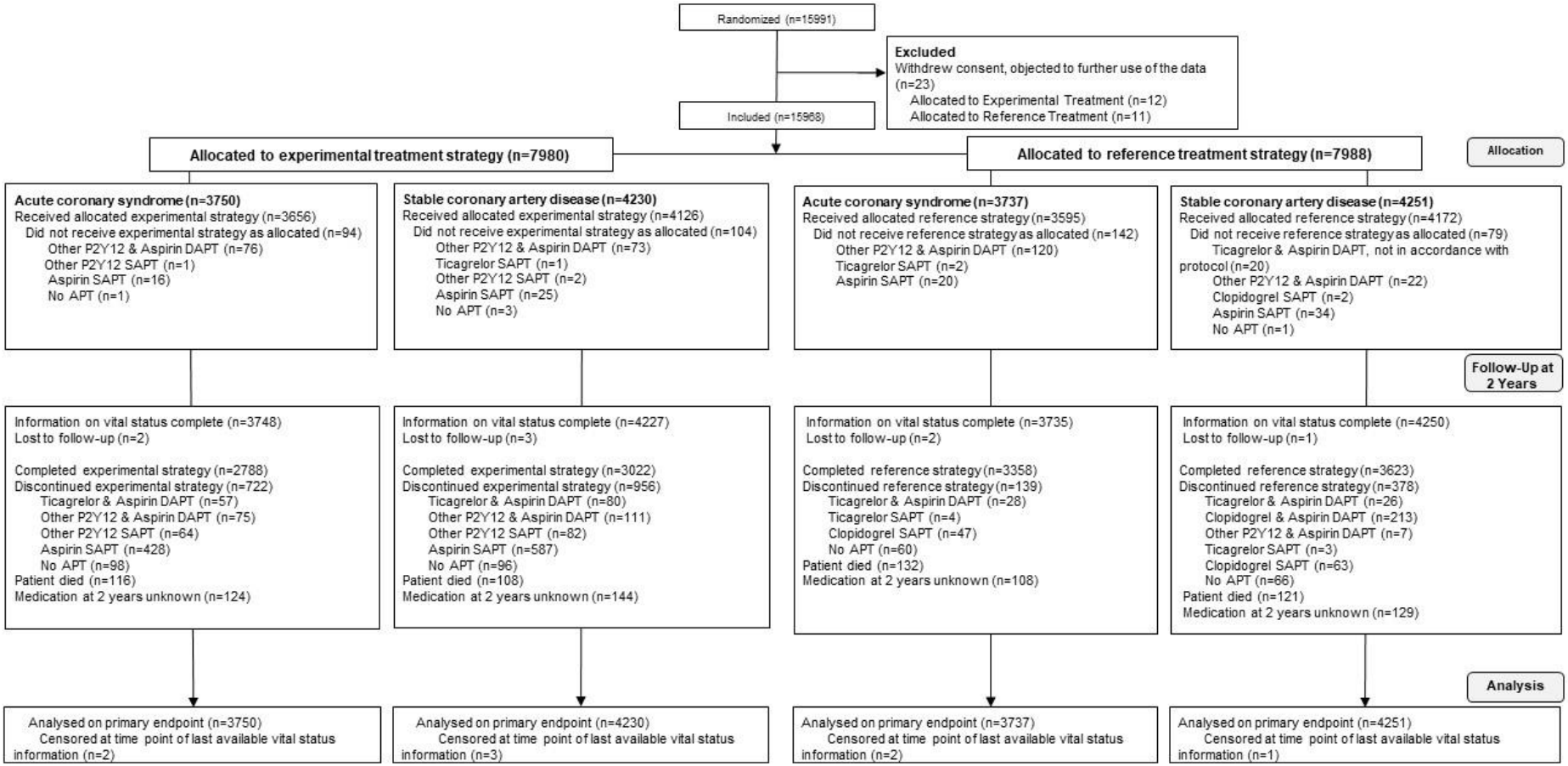
	Acute coronary syndrome ACS				Stable CAD				interaction p-value
	Experi-mental Strategy	Reference Strategy	Rate Ratio (95% CI)	p-value	Experi-mental Strategy	Reference Strategy	Rate Ratio (95% CI)	p-value	
Total No. of patients	N=3750	N=3737			N=4230	N=4251			
At 1 Year									
All-cause mortality or new Q-wave MI	77 (2.05)	103 (2.76)	0.74 (0.55-1.00)	0.047	79 (1.87)	94 (2.21)	0.84 (0.63-1.14)	0.266	0.550
All-cause mortality	59 (1.57)	75 (2.01)	0.78 (0.56-1.10)	0.158	49 (1.16)	56 (1.32)	0.88 (0.60-1.29)	0.513	0.655
New Q-wave MI	18 (0.48)	30 (0.80)	0.60 (0.33-1.07)	0.079	30 (0.71)	39 (0.92)	0.77 (0.48-1.24)	0.287	0.499
All-cause mortality, new Q-wave MI or BARC 3 or 5 Bleeding	126 (3.36)	179 (4.79)	0.70 (0.56-0.88)	0.002	131 (3.10)	133 (3.13)	0.99 (0.78-1.27)	0.963	0.038
All-cause mortality, stroke or any MI	166 (4.43)	174 (4.66)	0.95 (0.77-1.18)	0.662	148 (3.50)	141 (3.32)	1.06 (0.84-1.34)	0.620	0.509
NACCE	208 (5.55)	244 (6.53)	0.85 (0.71-1.02)	0.084	190 (4.49)	178 (4.19)	1.08 (0.88-1.32)	0.466	0.089
Myocardial infarction	96 (2.56)	88 (2.35)	1.09 (0.82-1.46)	0.555	83 (1.96)	70 (1.65)	1.20 (0.87-1.65)	0.266	0.671

Stroke	28 (0.75)	26 (0.70)	1.07 (0.63-1.83)	0.792	24 (0.57)	23 (0.54)	1.05 (0.59-1.87)	0.857	0.961
Ischemic stroke	21 (0.56)	22 (0.59)	0.95 (0.52-1.73)	0.874	19 (0.45)	19 (0.45)	1.01 (0.53-1.91)	0.975	0.896
Haemorrhagic stroke	6 (0.16)	3 (0.08)	1.99 (0.50-7.97)	0.319	4 (0.09)	2 (0.05)	2.02 (0.37-11.04)	0.407	0.991
Undetermined stroke	1 (0.03)	1 (0.03)	1.00 (0.06-15.92)	0.999	1 (0.02)	2 (0.05)	0.50 (0.05-5.56)	0.569	0.714
Revascularisation	243 (6.48)	254 (6.80)	0.95 (0.80-1.14)	0.586	275 (6.50)	295 (6.94)	0.94 (0.80-1.11)	0.450	0.906
Target Vessel Revascularization	124 (3.31)	147 (3.93)	0.84 (0.66-1.07)	0.153	144 (3.40)	159 (3.74)	0.91 (0.73-1.14)	0.424	0.623
Definite stent thrombosis	25 (0.67)	23 (0.62)	1.08 (0.62-1.91)	0.779	28 (0.66)	18 (0.42)	1.57 (0.87-2.84)	0.132	0.376
BARC 3 or 5 Bleeding	57 (1.52)	88 (2.35)	0.64 (0.46-0.90)	0.009	60 (1.42)	48 (1.13)	1.26 (0.86-1.85)	0.225	0.009
BARC 5 Bleeding	8 (0.21)	8 (0.21)	1.00 (0.37-2.66)	0.997	6 (0.14)	8 (0.19)	0.76 (0.26-2.18)	0.603	0.706
BARC 5b Bleeding	5 (0.13)	6 (0.16)	0.83 (0.25-2.73)	0.760	4 (0.09)	5 (0.12)	0.81 (0.22-3.00)	0.747	0.972
BARC 5a Bleeding	3 (0.08)	2 (0.05)	1.50 (0.25-8.96)	0.656	2 (0.05)	3 (0.07)	0.67 (0.11-4.03)	0.663	0.533
BARC 3 Bleeding	52 (1.39)	85 (2.27)	0.61 (0.43-0.86)	0.004	55 (1.30)	43 (1.01)	1.29 (0.87-1.93)	0.204	0.005
BARC 3c Bleeding	10 (0.27)	12 (0.32)	0.83 (0.36-1.92)	0.665	13 (0.31)	4 (0.09)	3.29 (1.07-10.09)	0.027	0.048
BARC 3b Bleeding	19 (0.51)	39 (1.04)	0.49 (0.28-0.84)	0.008	24 (0.57)	23 (0.54)	1.05 (0.59-1.87)	0.856	0.054
BARC 3a Bleeding	26 (0.69)	38 (1.02)	0.68 (0.41-1.12)	0.131	26 (0.61)	19 (0.45)	1.38 (0.77-2.50)	0.281	0.072

From 1 Year to 2 Years									
(landmark at 365 days)									
All-cause mortality or new Q-wave MI	70 (1.91)	66 (1.82)	1.05 (0.75-1.47)	0.781	78 (1.88)	86 (2.07)	0.91 (0.67-1.23)	0.541	0.537
All-cause mortality	57 (1.55)	57 (1.56)	0.99 (0.69-1.43)	0.965	59 (1.41)	65 (1.55)	0.91 (0.64-1.30)	0.605	0.745
New Q-wave MI	15 (0.41)	11 (0.30)	1.35 (0.62-2.95)	0.447	20 (0.48)	23 (0.55)	0.87 (0.48-1.59)	0.655	0.382
All-cause mortality, new Q-wave MI or BARC 3 or 5 Bleeding	73 (2.05)	64 (1.82)	1.13 (0.81-1.58)	0.486	101 (2.50)	98 (2.41)	1.04 (0.79-1.38)	0.761	0.732
All-cause mortality, stroke or any MI	98 (2.78)	103 (2.92)	0.95 (0.72-1.25)	0.711	96 (2.39)	119 (2.93)	0.82 (0.62-1.07)	0.140	0.447
NACCE	102 (2.92)	98 (2.83)	1.03 (0.78-1.36)	0.826	116 (2.92)	133 (3.30)	0.88 (0.69-1.14)	0.335	0.419
Myocardial infarction	37 (1.04)	44 (1.24)	0.84 (0.54-1.30)	0.431	32 (0.79)	48 (1.17)	0.68 (0.43-1.06)	0.084	0.496
Stroke	16 (0.44)	16 (0.44)	1.00 (0.50-1.99)	0.990	12 (0.29)	17 (0.41)	0.71 (0.34-1.50)	0.371	0.521
Ischemic stroke	14 (0.39)	13 (0.36)	1.07 (0.50-2.28)	0.857	9 (0.22)	14 (0.34)	0.65 (0.28-1.50)	0.310	0.384
Haemorrhagic stroke	1 (0.03)	3 (0.08)	0.33 (0.03-3.19)	0.315	2 (0.05)	1 (0.02)	2.03 (0.18-22.39)	0.555	0.265
Undetermined stroke	1 (0.03)	0 (0.00)			3 (0.07)	2 (0.05)	1.52 (0.25-9.09)	0.645	
Revascularisation	93 (2.74)	94 (2.78)	0.98 (0.74-1.31)	0.900	128 (3.33)	150 (3.88)	0.86 (0.68-1.08)	0.198	0.472

Target Vessel Revascularization	45 (1.28)	57 (1.64)	0.78 (0.53-1.15)	0.212	76 (1.91)	79 (1.97)	0.97 (0.71-1.33)	0.847	0.396
Definite stent thrombosis	7 (0.19)	14 (0.39)	0.50 (0.20-1.23)	0.125	4 (0.10)	9 (0.22)	0.45 (0.14-1.47)	0.174	0.896
BARC 3 or 5 Bleeding	16 (0.45)	12 (0.34)	1.32 (0.62-2.79)	0.466	30 (0.74)	21 (0.51)	1.45 (0.83-2.53)	0.189	0.843
BARC 5 Bleeding	6 (0.17)	5 (0.14)	1.20 (0.36-3.92)	0.768	2 (0.05)	3 (0.07)	0.68 (0.11-4.05)	0.665	0.600
BARC 5b Bleeding	4 (0.11)	4 (0.11)	1.00 (0.25-3.98)	0.996	2 (0.05)	3 (0.07)	0.68 (0.11-4.05)	0.665	0.736
BARC 5a Bleeding	2 (0.06)	1 (0.03)	1.99 (0.18-21.97)	0.566	0 (0.00)	0 (0.00)			
BARC 3 Bleeding	14 (0.39)	12 (0.34)	1.15 (0.53-2.50)	0.714	29 (0.71)	19 (0.46)	1.55 (0.87-2.76)	0.135	0.550
BARC 3c Bleeding	4 (0.11)	6 (0.17)	0.66 (0.19-2.35)	0.522	8 (0.20)	3 (0.07)	2.71 (0.72-10.21)	0.125	0.124
BARC 3b Bleeding	2 (0.06)	3 (0.08)	0.66 (0.11-3.96)	0.648	8 (0.20)	9 (0.22)	0.90 (0.35-2.33)	0.824	0.767
BARC 3a Bleeding	9 (0.25)	3 (0.08)	2.98 (0.81-11.02)	0.085	16 (0.39)	10 (0.24)	1.62 (0.74-3.57)	0.226	0.430

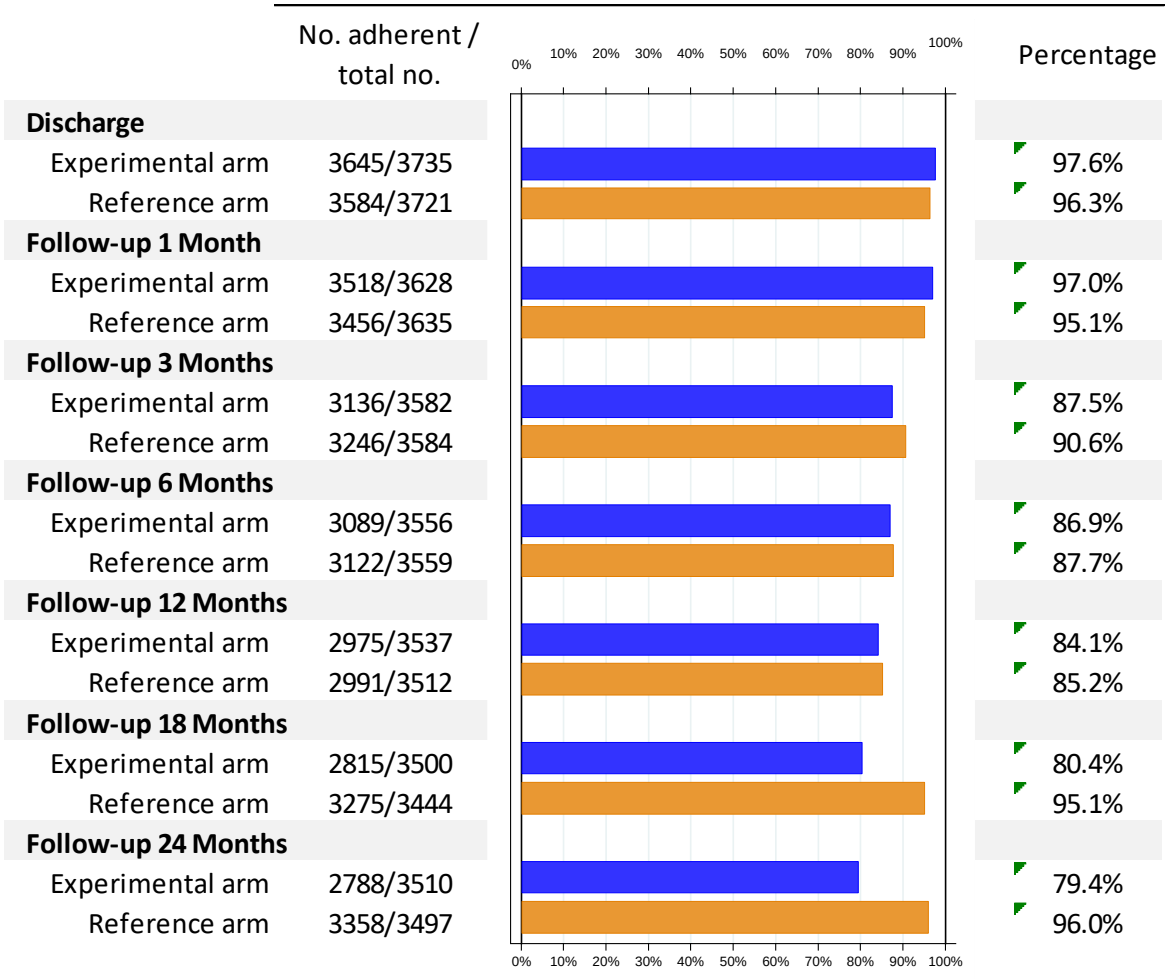
Figure S1. Consort flowchart of the Global LEADERS randomized clinical trial.



DAPT, dual antiplatelet treatment; SAPT, single antiplatelet treatment; APT, antiplatelet treatment. Restart of appropriate DAPT was allowed for 30 days in experimental arm and 365 days in reference arm after any revascularization; in case of death last medication taken.

Figure S2. Distribution of patient adherence to the allocated antiplatelet treatment strategies stratified by clinical presentation over the 2-year trial period.

A: Patients with acute coronary syndromes



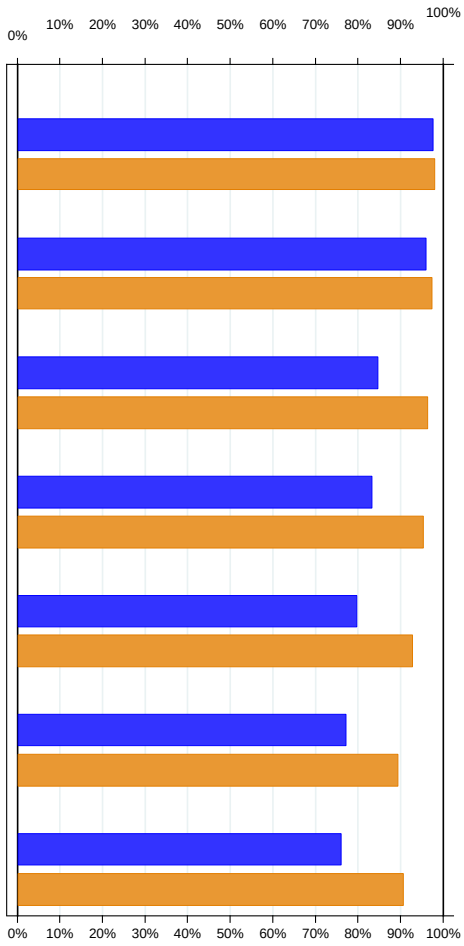
Revascularisations and per-protocol restart of DAPT allowed:

Experimental arm: Ticagrelor & Aspirin allowed for 30 days

Reference arm: Ticagrelor & Aspirin in ACS, and also in Stable CAD patients who were pre-treated with Ticagrelor or Prasugrel, was allowed for 365 days; Clopidogrel & Aspirin was allowed for 365 days in Stable CAD patients who were pre-treated with Clopidogrel or no P2Y12 inhibitor

B: Patients with stable coronary artery disease.

	No. adherent / total no.	Percentage
Discharge		
Experimental arm	4119/4222	97.6%
Reference arm	4160/4246	98.0%
Follow-up 1 Month		
Experimental arm	3961/4127	96.0%
Reference arm	4034/4144	97.3%
Follow-up 3 Months		
Experimental arm	3443/4066	84.7%
Reference arm	3942/4094	96.3%
Follow-up 6 Months		
Experimental arm	3367/4040	83.3%
Reference arm	3863/4052	95.3%
Follow-up 12 Months		
Experimental arm	3197/4013	79.7%
Reference arm	3733/4021	92.8%
Follow-up 18 Months		
Experimental arm	3047/3953	77.1%
Reference arm	3503/3923	89.3%
Follow-up 24 Months		
Experimental arm	3022/3978	76.0%
Reference arm	3623/4001	90.6%

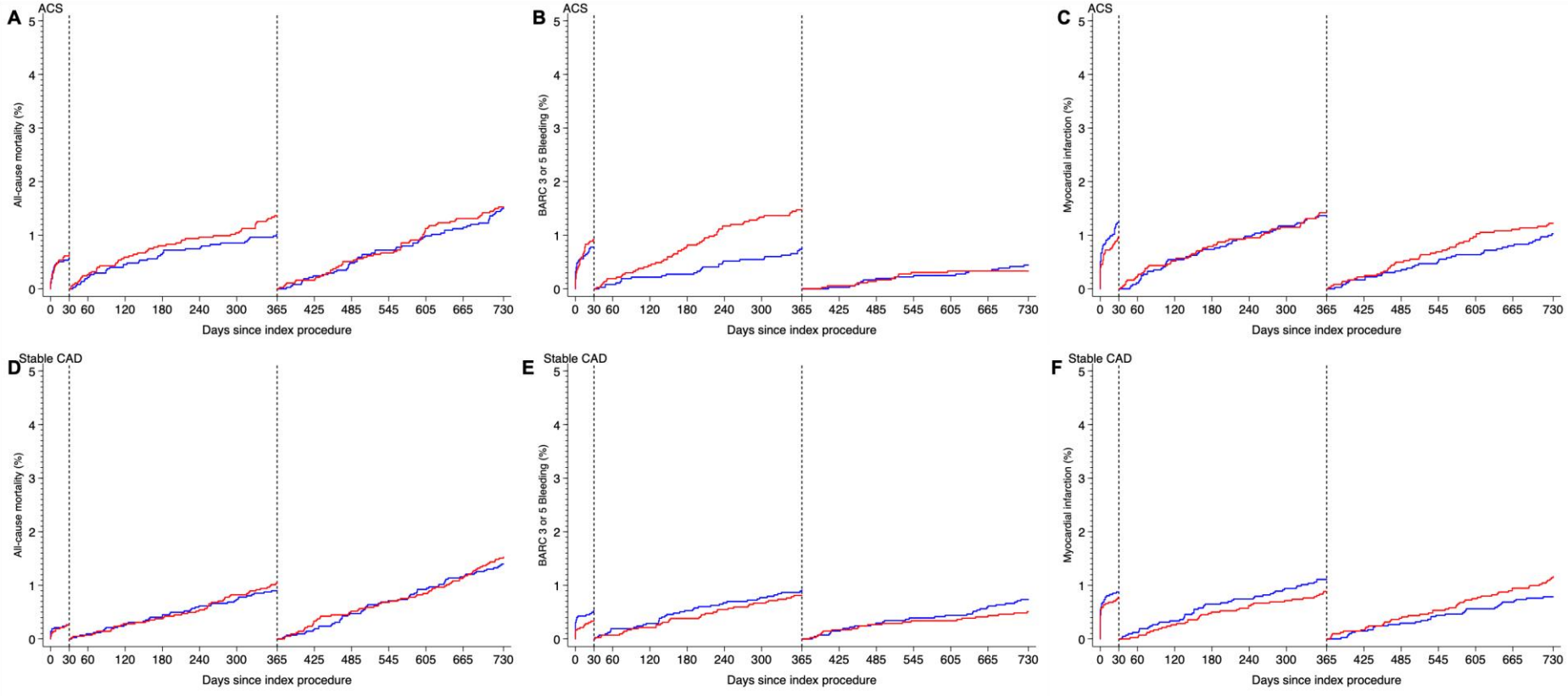


Revascularisations and per-protocol restart of DAPT allowed:

Experimental arm: Ticagrelor & Aspirin allowed for 30 days

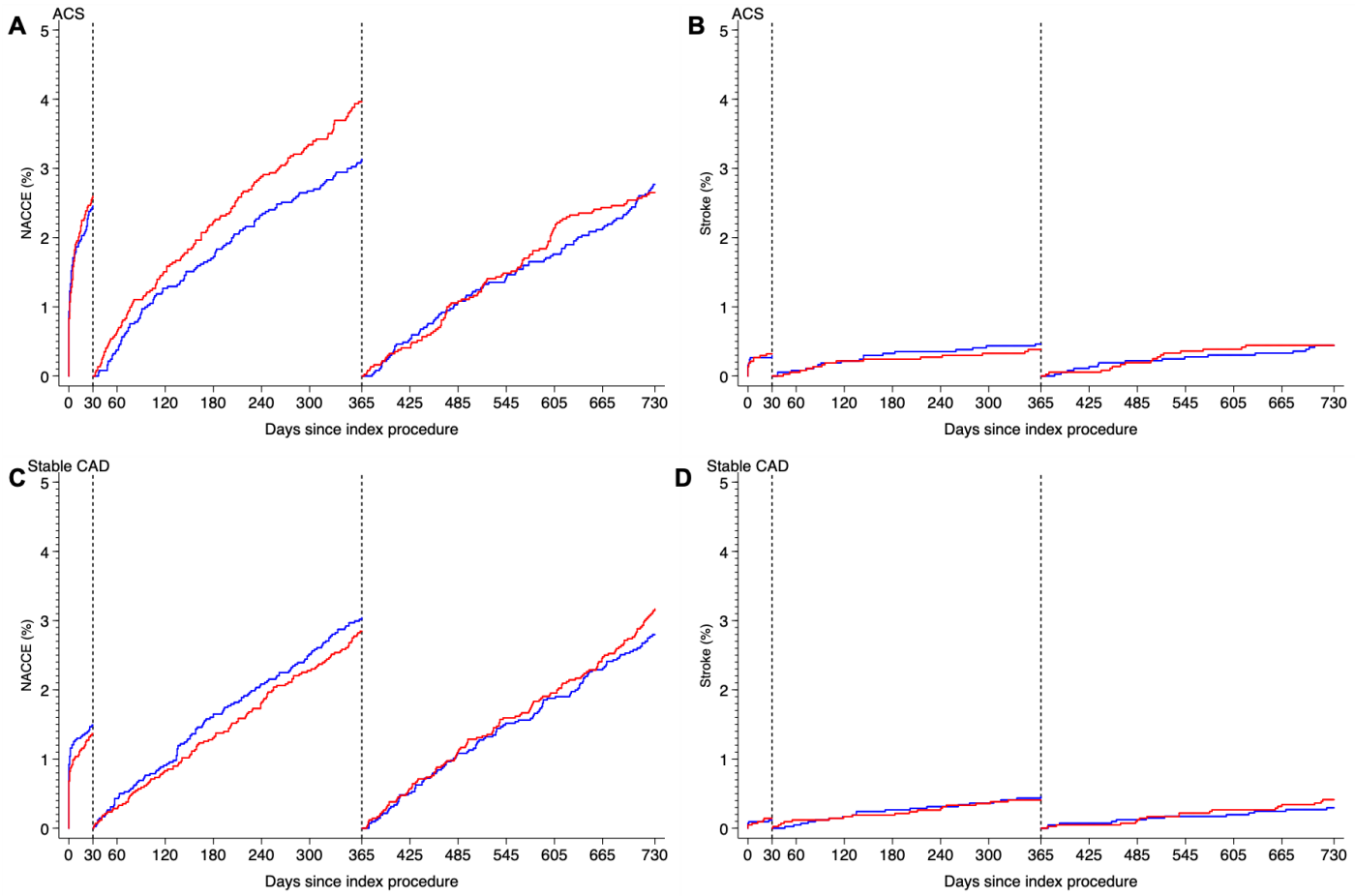
Reference arm: Ticagrelor & Aspirin in ACS, and also in Stable CAD patients who were pre-treated with Ticagrelor or Prasugrel, was allowed for 365 days; Clopidogrel & Aspirin was allowed for 365 days in Stable CAD patients who were pre-treated with Clopidogrel or no P2Y12 inhibitor

Figure S3. Landmark Analysis for All-Cause Mortality, BARC 3 or 5 Bleeding up and Myocardial infarction to 30 days, from 31 days to 1 year and from 1 year to end of follow up Kaplan-Meier graphs of the Endpoints.



Top panels: Acute coronary syndrome patients. Cumulative incidence of A) all-cause mortality (ACS), B) Bleeding Academic Research Consortium 3 or 5 events (ACS), C) investigator reported myocardial infarction (ACS); lower panels: stable coronary artery disease. patients (D-F) (blue: experimental strategy arm; red: reference strategy arm).

Figure S4. Landmark Analysis for NACCE – Net Adverse Clinical and Cerebral Events and stroke up to 30 days, from 31 days to 1 year and from 1 year to end of follow up Kaplan-Meier graphs of the Endpoints.



Within each landmark period, depicted are the first event per event type for each patient only (disregards multiple events of the same type within the same patient and censoring at 730 days since index PCI). Top panels: Acute coronary syndrome patients. Cumulative incidence of A) NACCE - Net Adverse Clinical and Cerebral Events (ACS), B) Stroke (ACS); lower panels: stable coronary artery disease. patients (C-D) (blue: experimental strategy arm; red: reference strategy arm).