Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

APPENDIX

1. INCLUSION AND EXCLUSION CRITERIA

INCLUSION CRITERIA

For inclusion in the study patients must fulfil the following 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 millimetre.

EXCLUSION CRITERIA

Drug related

1. Known intolerance to aspirin, P2Y12 inhibitors, bivalirudin, stainless steel or biolimus
2. Known intake of a strong cytochrome P3A4 inhibitor (eg, 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

1. Planned coronary artery bypass grafting as a staged procedure (hybrid) within 12 months of the index procedure
2. Planned surgery within 12 months of percutaneous coronar intervention unless dual antiplatelet therapy is maintained throughout the peri-surgical period
3. Need for oral anti-coagulation therapy
4. PCI for a priori known stent thrombosis

Medical

1. Known overt major bleeding
2. Known history of intracranial haemorrhage
3. Known stroke from ischemic or unknown cause within last 30 days

General

1. Known pregnancy at time of randomization
2. Inability to provide informed consent
3. Currently participating in another trial before reaching primary endpoint

2. STUDY PROCEDURES AND FOLLOW UP

2.1 Percutaneous coronary intervention

Oral antiplatelet therapy was started as early as possible and no later than two hours after the index procedure.

Loading and switching of P2Y12-receptor-inhibitors in the Global Leaders trial is presented elsewhere (Vranckx P, Valgimigli M, Windecker S, Steg PG, Hamm C, Juni P, et al. Long-term ticagrelor monotherapy versus standard dual antiplatelet therapy followed by aspirin monotherapy in patients undergoing biolimus-eluting stent implantation: rationale and design of the GLOBAL LEADERS trial. EuroIntervention. 2016;12(10):1239-45.). In case of ticagrelor discontinuation due to adverse effects other than bleeding (i.e. atrio-ventricular block, dyspnoe), patients could be switched to a standard dose of prasugrel in both study arms. The use of clopidogrel was restricted to patients undergoing elective stenting for stable lesions (cardiac biomarker negative, no clinical signs or symptoms of ongoing myocardial ischemia lasting more than 20 minutes). In case of definite stent thrombosis patients were treated according to best clinical practice. Patients who required systemic oral anticoagulation after randomization, were treated according to local practice guidelines. Triple therapy was to be prescribed for the shortest necessary duration with frequent INR measurement (target INR 2–2.5) with clopidogrel as the default P2Y12 receptor inhibitor. For patients not previously receiving aspirin, a loading dose of 325 mg is preferred (160-500 mg allowed). In the case of staged PCI or in case of unplanned reintervention (other than for

definite stent thrombosis or ST- segment elevation myocardial infarction) in the study treatment arm, the 30-day treatment period with aspirin was re-started at the time of the staged procedure or reintervention.

The GLOBAL LEADERS trial protocol mandated for a uniform anticoagulation with bivalirudin (The Medicines Company)(dose adjusted per local drug label) in those countries were the drug was approved for use during the procedure and uniform stent platform (Biolimus-A9TM eluting stent, Biosensors Interventional Technologies) use during the index procedure (including staged procedures) and any unplanned or inter-current repeat percutaneous coronary intervention. Balloon angioplasty and stent implantation were performed according to standard techniques; direct stenting (without previous balloon dilatation) was allowed. Staged procedures were permitted within 3 months after the index procedure; all the stents used were of the assigned type. The use of glycoprotein IIB/IIIA receptor inhibitors was to be administered only in patients who had periprocedural ischemic complications (i.e., no reflow or giant thrombus) after stenting. The use of unfractionated heparin (up to an arbitrary set maximum of 4000IU) during the index diagnostic angiogram was left at the discretion of the investigator. The use of other medications was per applicable professional guidelines.

2.2 Patient follow-up

During study follow-up visits, patients were questioned about whether they had had a myocardial infarction, had been hospitalized for a subsequent

cardiovascular presentation, had undergone revascularization or cardiac testing, or had seen a cardiologist, and what medications they were taking. If a patient reported a hospitalization that was possibly related to cardiac causes, the hospital records were reviewed. Adverse events were confirmed by means of a review of the records. If the patients or secondary contacts were unavailable, records at the presenting and neighboring hospitals were reviewed to determine whether there had been repeat visits. Patients who withdrew consent to participate in the study were included up to the date of withdrawal, with the exception of the analysis of death from any cause, in which we included information from all the patients for whom vital status could be determined from public records at the end of the study.

2.3 Study oversight

The electronic case record form (eCRF) was built to collect detailed information on the individual components of the predefined secondary endpoints (e.g. death, any stroke, MI, revascularization, bleeding). Moreover, textboxes allowed for free text narrative information per event.

The trial was monitored for event under-reporting (onsite and remote monitoring) and event definition consistency. The eCRF (including free text boxes: event narratives) was reviewed by independent medical monitors for consistency with the endpoint definitions and sites queried when considered necessary. In addition, there were seven on-site monitoring visits done at individual sites, with 20% of reported events validated against source documents, but overall no independent central event adjudication was planned.

2.4 Ethics

The study was performed in compliance with the ethical principles of the Declaration of Helsinki, the International Conference of Harmonisation, and Good Clinical Practice. All participants provided written informed consent at enrolment. An independent data and safety monitoring committee oversaw the safety of all patients. The trial was registered with the ClinicalTrials.gov. number NCT01813435.

3. CLINICAL ENPOINT DEFINITIONS

Research nurses screened for clinical end-point events during the follow-up visits. If the patient did not appear and patients or relatives could not be contacted after the nurses had placed repeated telephone calls and mailed a letter, information on the vital status was collected through review of public health records. All-cause death was ascertained without the need for adjudication.

Investigators were instructed during the investigator meetings and site initiation visits on the outcome definitions implemented in the GLOBAL LEADERS trial. Detailed patient based information was collected via the individual electronic case report forms to allow proper classification of all site reported outcome events. Medical monitors (Cardialysis, Rotterdam, The Netherlands) checked the case record forms of site reported endpoints for completeness and consistency against the following definitions

3.1 Stroke

Stroke was defined as an acute onset of focal or global neurological deficit persisting ≥24 hours or <24 hours in case i) therapeutic intervention was required ii) it was confirmed by neuro-imaging or iii) patient's death. Stroke was categorized as either ischemic, haemorrhagic or as of undetermined cause.

3.2 Myocardial infarction

Myocardial infarction was defined according to the Third Universal Myocardial Infarction definition, applicable at the time of study conduct, as study specific myocardial infarction criteria (Thygesen K, Alpert JS, Jaffe AS, Simoons ML,

Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Eur Heart J. 2012;33:2551-67).

The term acute myocardial infarction was used when there was evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria met the diagnosis for myocardial infarction:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
  - o Symptoms of ischemia
  - o New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB)
  - o Development of pathological Q waves on the ECG
  - o Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
  - o Identification of an intracoronary thrombus by angiography or autopsy
- Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic electrocardiographic changes or new left bundle branch block, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased
- Percutaneous coronary intervention related myocardial infarction was arbitrarily defined by elevation of cardiac troponin values (>5 x 99th of the percentile upper reference limit) in patients with normal baseline values (≤99th percentile of the upper reference limit) or a rise of cardiac troponin values

>20% if the baseline values were elevated and are stable or falling. In addition, either:

o symptoms suggestive of myocardial ischemia or o new ischemic electrocardiographic changes or

o angiographic findings consistent with a procedural complication, or o imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality was required

- Stent thrombosis associated with myocardial infarction when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile of the upper reference limit

- Coronary Artery Bypass Grafting- related myocardial infarction is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile of the upper reference limit) in patients with normal baseline cardiac troponin values (≤99th percentile of the upper reference limit). In addition, either:

o new pathological Q waves or new left bundle branch block, or

o angiographic documented new graft or new native coronary artery occlusion, or

o imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

3.3 Q wave myocardial Infarction Ascertainment and Definition

Resting 12-lead electrocardiograms at hospital discharge, 3-months, and the 24-months end-of-trial visit and any available intercurrent electrocardiograms, related to suspected ischemic events, were inspected for quality and technical

errors and analyzed by an independent electrocardiography-core laboratory (Cardialysis, Rotterdam, The Netherlands). Serial comparison of sequential tracings was performed to identify patients with new appearance of Q waves (major Q-QS wave abnormalities 1-1-1 to 1-2-8 according to the Minnesota Code) (Prineas RJ, CRS, Zhang Z-M . The Minnesota Code Manual of Electrocardiographic Findings Springer Science & Business Media, London; 2009).

Where new Q-waves, with respect to the immediately preceding electrocardiogram (first reference electrocardiogram is at discharge), were identified an independent cardiologist confirmed or rejected the myocardial as a new Q wave myocardial infarction, and if confirmed also assigned a date, based on review of the reported adverse events to the new Q-wave myocardial infarction. (Vranckx P, Valgimigli M, Windecker S, Steg PG, Hamm C, Juni P, et al. Long-term ticagrelor monotherapy versus standard dual antiplatelet therapy followed by aspirin monotherapy in patients undergoing biolimus-eluting stent implantation: rationale and design of the GLOBAL LEADERS trial. EuroIntervention. 2016;12:1239-45). Where no clinical correlate was identified, the date of the new silent Q-wave myocardial infarction was arbitrarily assigned to the date of the qualifying electrocardiogram. In case electrocardiograms remained missing after review of all documentation (e.g. death before 2 years of follow-up) it will be assumed no new Q-wave myocardial infarction occurred since the last obtained electrocardiogram.

The electrocardiogram-core laboratory also identified new left bundle branch block on serial electrocardiograms. Where a new left bundle branch block was

identified, the independent cardiologist determined, from electronic clinical record form extracts supplemented where necessary with additional source documents, whether a likely ischemic event (prolonged ischemic chest pain, significant rise in cardiac biomarkers or imaging evidence of loss of viable myocardium) occurred. A new left bundle branch block counted as a new Q-wave myocardial infarction only where a qualifying ischemic event was identified. The new Q-wave myocardial infarction was assigned to the date of the qualifying ischemic event.

Core laboratory staff and the independent cardiologist were unaware of the study- group assignments.

3.4 Revascularization

Revascularization included target and non-target vessel revascularizations

3.5 Stent thrombosis

Stent thrombosis was classified as per the Academic Research Consortium Definition.

Definite stent thrombosis – was considered to have occurred by either angiographic or pathological confirmation.

o The presence of thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour window (The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms was not considered a confirmed stent thrombosis silent occlusion):

• Acute onset of ischemic symptoms at rest

• New ischemic electrocardiographic changes that

suggest acute ischemia

• Typical rise and fall in cardiac biomarkers that

represent a spontaneous myocardial infarction.

▪ Non-occlusive Thrombus: Intracoronary thrombus defined as a (sphere shaped, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or visible embolization of intraluminal material downstream.

▪ Occlusive Thrombus: Thrombolysis in Myocardial Infarction (TIMI) flow grading 0 or 1 intra-stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if

originates from the side branch)

o Evidence of recent thrombus within the stent determined at autopsy

or via examination of tissue retrieved following thrombectomy.

3.6 Bleeding

Bleeding was assessed according to the Bleeding Academic Research Consortium (BARC) definition (Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123:2736-47). We only considered BARC 3 or 5 for the key secondary safety endpoint. These bleedings are clinically meaningful and relatively easy to ascertain.

- Type 0: No evidence of bleeding

- Type 1: Bleeding that is not actionable and does not cause the patient to

seek unscheduled performance of studies, hospitalization, or treatment by a health-care professional; may include episodes leading to self- discontinuation of medical therapy by the patient without consulting a health-care professional.

- Type 2: Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria:

o requiring nonsurgical, medical intervention by a health-care professional,

o leading to hospitalization or increased level of care, or

o prompting evaluation

- Type 3: Clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare provider responses, as listed below: o Type 3a:

▪ Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL (provided hemoglobin drop is related to bleed)

▪ Any transfusion with overt bleeding o Type 3b:

▪ Overt bleeding plus hemoglobin drop ≥5 g/dL (provided hemoglobin drop is related to bleed),

▪ Cardiac tamponade,

▪ Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid),

▪ Bleeding requiring intravenous vasoactive agents

o Type 3c:

▪ Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)

▪ Subcategories confirmed by autopsy or imaging or lumbar

puncture,

▪ Intraocular bleed compromising vision.

o Type 4: Coronary artery bypass grafting-related bleeding

▪ Perioperative intracranial bleeding within 48 h,

▪ Reoperation after closure of sternotomy for the purpose of controlling bleeding

▪ Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-h period,

▪ Chest tube output more than or equal to 2L within a 24-h period

o Type 5: Fatal bleeding

▪ Type 5a:

• Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious ▪ Type 5b:

• Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

eTable 1 Baseline characteristics of patients included in the landmark analysis at 30 days (events between 31 and 365 days)[a].

	Reference (Aspirin + Ticagrelor) (n = 3,712)		Experimental (Ticagrelor) (n = 3,729)		
	N	**%**	**N**	**%**	**p value**
Age > 75 years	537	(14.5)	548	(14.7)	0.78
Sex (female)	846	(22.8)	861	(23.1)	0.76
Acute coronary syndrome type					0.77
Unstable angina	1015	(27.3)	1003	(26.9)	
NSTEMI	1681	(45.3)	1678	(45.0)	
STEMI	1016	(27.4)	1048	(28.1)	
Geographic area					0.54
West Europe	2808	(75.6)	2861	(76.7)	
East Europe	786	(21.2)	752	(20.2)	
Rest of the World	118	(3.2)	116	(3.1)	
Diabetes mellitus	787	(21.2)	803	(21.6)	0.71
Insulin-dependent diabetes mellitus	241	(6.5)	206	(5.5)	0.08
Hypertension	2503	(67.8)	2544	(68.6)	0.46
Hypercholesterolemia	2195	(61.9)	2167	(60.9)	0.37
Previous stroke more than 30 days ago	93	(2.5)	80	(2.1)	0.30
Previous myocardial infarction	691	(18.6)	684	(18.4)	0.77
Previous percutaneous coronary intervention	869	(23.4)	853	(22.9)	0.58
Previous coronary artery bypass grafting	145	(3.9)	129	(3.5)	0.31
Peripheral vascular disease	193	(5.3)	189	(5.1)	0.80
Chronic obstructive pulmonary disease	171	(4.6)	172	(4.6)	0.98
Previous major bleeding	24	(0.6)	24	(0.6)	0.99
Current smoking	1246	(33.6)	1282	(34.4)	0.46
Impaired renal function [b]	459	(12.4)	494	(13.2)	0.26

[a] Baseline characteristics of patients alive after 30 days, not censored prior to this landmark.
Data shown are count and percentages.
NSTEMI – non-ST segment elevation myocardial infarction, STEMI – ST segment elevation myocardial infarction.
[b] 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**.**

eTable 2 Clinical events between 0 and 30 days in acute coronary syndrome patients[a]

	Reference	Experimental	HR (95% CI)	p value
	N=3737	N=3750		
Primary outcome: all-cause death or new Q-wave MI	28 (0.8)	22 (0.6)	0.78 (0.45-1.37)	0.39
Key safety outcome: BARC 3 or 5 bleeding	34 (0.9)	29 (0.77)	0.85 (0.52-1.40)	0.52
BARC 3 bleeding	32 (0.7)	25 (0.67)	0.78 (0.46-1.31)	0.35
BARC 3a bleeding	13 (0.4)	13 (0.4)	1.00 (0.46-2.15)	1.00
BARC 3b bleeding	15 (0.40)	10 (0.27)	0.66 (0.30-1.48)	0.31
BARC 3c bleeding	6 (0.16)	3 (0.08)	0.50 (0.12-1.99)	0.32
BARC 5 bleeding	4 (0.11)	6 (0.16)	1.50 (0.42-5.30)	0.53
BARC 5a bleeding	0 (0.0)	2 (0.05)	-	-
BARC 5b bleeding	4 (0.11)	4 (0.11)	1.00 (0.25-3.99)	1.00
All-cause mortality	24 (0.64)	21 (0.56)	0.87 (0.49-1.57)	0.65
New Q-wave MI	5 (0.13)	1 (0.03)	0.20 (0.02-1.70)	0.10
All-cause mortality, new Q-wave MI[c] or BARC 3 or 5 bleeding	57 (1.5)	45 (1.2)	0.79 (0.53-1.16)	0.23
All-cause mortality, stroke or any MI	70 (1.9)	71 (1.9)	1.01 (0.73-1.41)	0.94
MI (site-reported)	36 (1.0)	46 (1.2)	1.28 (0.82-1.98)	0.27
Stroke [b]	12 (0.3)	11 (0.3)	0.91 (0.40-2.07)	0.83
Ischemic	10 (0.3)	8 (0.2)	0.80 (0.31-2.02)	0.63
Haemorrhagic	1 (0.03)	3 (0.08)	2.99 (0.31-28.76)	0.32
Undetermined	1 (0.03)	0 (0.00)	-	-
Revascularisation	82 (2.2)	62 (1.7)	0.75 (0.54-1.05)	0.09
TVR	51 (1.4)	40 (1.1)	0.78 (0.52-1.18)	0.24
Definite ST	17 (0.5)	18 (0.5)	1.06 (0.54-2.05)	0.87
POCE	129 (3.5)	105 (2.8)	0.81 (0.63-1.05)	0.11
NACE	157 (4.2)	125 (3.3)	0.79 (0.63-1.00)	0.05

HR – hazard ratio, 95%CI – 95% confidence interval, MI - myocardial infarction, ST – stent thrombosis, TVR – target vessel revascularization

BARC – Bleeding Academic Research Consortium. Patient-oriented composite endpoint (POCE) included all-cause mortality or any MI, revascularization or stroke, whereas net adverse clinical events (NACE) comprised POCE, BARC type 3 or 5 bleeding. Patients who were alive at 31 days of follow-up and did not encounter event of the specific type nor were censored prior to the landmark of 30 days have been included in the present analysis.

[a] in these time-frames experimental regimen = ticagrelor plus aspirin, reference regimen = ticagrelor plus aspirin

[b] not including transient ischemic attack

eTable 3 Additional bleeding endpoints between 31 and 365 days[a] in acute coronary syndrome patients

	Reference		Experimental		HR (95% CI)	p value
	(ASA + Ticagrelor)		(Ticagrelor alone)			
	Nr of events /Nr of pt at risk	(%)	Nr of events /Nr of pt at risk	(%)		
BARC 2 bleeding	110/3626	(3.0)	73/3632	(2.0)	0.66 (0.49-0.89)	0.006
BARC 3 bleeding	53/3666	(1.5)	27/3680	(0.7)	0.51 (0.32-0.80)	0.003
BARC 3a bleeding	25/3683	(0.7)	13/3690	(0.4)	0.52 (0.27-1.01)	0.06
BARC 3b bleeding	24/3681	(0.7)	9/3693	(0.2)	0.37 (0.17-0.81)	0.01
BARC 3c bleeding	6/3690	(0.2)	7/3702	(0.2)	1.16 (0.39-3.46)	0.79
BARC 5 bleeding	4/3695	(0.11)	2/3703	(0.05)	0.50 (0.09-2.73)	0.41
BARC 5a bleeding	2/3695	(0.05)	1/3703	(0.03)	0.50 (0.05-5.51)	0.57
BARC 5b bleeding	2/3695	(0.05)	1/3703	(0.03)	0.50 (0.05-5.51)	0.57
BARC 3 or 5 bleeding	54/3666	(1.5)	28/3680	(0.8)	0.52 (0.33-0.81)	0.004
BARC 2,3,5 bleeding	152/3597	(4.2)	97/3611	(2.7)	0.63 (0.49-0.81)	0.001
BARC 2,3,4,5 bleeding	154/3597	(4.3)	97/3609	(2.7)	0.62 (0.48-0.80)	0.001

[a] within these time-frames: experimental regimen = ticagrelor monotherapy, reference regimen = ticagrelor plus aspirin
BARC – Bleeding Academic Research Consortium, HR – hazard ratio, 95% CI – 95% confidence interval

1 **eTable 4 Cumulative rate of one-year clinical outcomes in acute coronary syndrome subgroup**

	Reference	Experimental	HR (95% CI)	p value
	N=3737	N=3750		
Primary outcome: all-cause mortality or new Q-wave MI	103 (2.8)	77 (2.1)	0.74 (0.55-1.00)	0.05
Key safety outcome: BARC 3 or 5 bleeding	88 (2.4)	57 (1.5)	0.64 (0.46-0.90)	0.009
BARC 3 bleeding	85 (2.3)	52 (1.4)	0.61 (0.43-0.86)	0.004
BARC 3a bleeding	38 (1.0)	26 (0.7)	0.68 (0.41-1.12)	0.13
BARC 3b bleeding	39 (1.0)	19 (0.5)	0.49 (0.28-0.84)	0.008
BARC 3c bleeding	12 (0.3)	10 (0.3)	0.83 (0.36-1.92)	0.67
BARC 5 bleeding	8 (0.21)	8 (0.2)	1.00 (0.37-2.66)	0.99
BARC 5a bleeding	2 (0.05)	3 (0.08)	1.50 (0.25-8.96)	0.66
BARC 5b bleeding	6 (0.16)	5 (0.13)	0.83 (0.25-2.73)	0.76
All-cause mortality	75 (2.0)	59 (1.6)	0.78 (0.56-1.10)	0.15
New Q-wave MI	30 (0.8)	18 (0.5)	0.60 (0.33-1.07)	0.08
All-cause mortality, new Q-wave MI or BARC 3 or 5 bleeding	179 (4.8)	126 (3.4)	0.70 (0.56-0.88)	0.002
All-cause mortality, stroke or any MI	174 (4.7)	166 (4.4)	0.95 (0.77-1.18)	0.66
Stroke[a]	26 (0.7)	28 (0.8)	1.07 (0.63-1.83)	0.79
Ischemic	22 (0.6)	21 (0.6)	0.95 (0.52-1.73)	0.87
Haemorrhagic	3 (0.1)	6 (0.2)	1.99 (0.50-7.97)	0.32
Undetermined	1 (0.03)	1 (0.03)	1.00 (0.06-15.92)	0.99
MI (site-reported)	88 (2.4)	96 (2.6)	1.09 (0.82-1.46)	0.56
Revascularisation	254 (6.8)	243 (6.5)	0.95 (0.80-1.14)	0.59
TVR	147 (3.9)	124 (3.3)	0.84 (0.66-1.07)	0.15
Definite ST	23 (0.6)	25 (0.7)	1.08 (0.62-1.91)	0.78
Additional bleeding endpoints				
BARC 2 bleeding	180 (4.8)	145 (3.9)	0.90 (0.73-1.09)	0.27
BARC 2,3,5 bleeding	256 (6.9)	196 (5.2)	0.84 (0.71-1.00)	0.05
BARC 2,3,4,5	258 (6.9)	198 (5.3)	0.84 (0.71-1.00)	0.05
Additional composite endpoints				
Death, new Q-wave MI, stroke	124 (3.3)	95 (2.5)	0.86 (0.70-1.05)	0.14
Cardiac death, MI, stroke	148 (4.0)	150 (4.0)	0.99 (0.82-1.19)	0.92
POCE	358 (9.6)	336 (9.0)	0.93 (0.81-1.08)	0.37
Death, MI, stroke or BARC 3 or 5 bleeding	246 (6.6)	209 (5.6)	0.90 (0.77-1.05)	0.19
NACE	423 (11.3)	373 (9.9)	0.88 (0.76-1.01)	0.06

HR – hazard ratio, 95%CI – 95% confidence interval; BARC – Bleeding Academic Research Consortium; TVR – target vessel revascularization. ST – stent thrombosis. Patient-oriented composite endpoint (POCE) included all-cause mortality or any MI, revascularization or stroke, whereas net adverse clinical events (NACE) comprised POCE, BARC type 3 or 5 bleeding. Patients who were alive at 31 days of follow-up and did not encounter event of the specific type nor were censored prior to the landmark of 30 days have been included in the present analysis.

[a] in these time-frames experimental regimen = ticagrelor plus aspirin, reference regimen = ticagrelor plus aspirin

[b] not including transient ischemic attack.

eTable 5 Exploratory analysis of clinical events between 31 and 365 days[a] in acute coronary syndrome patients who adhered to the randomized treatment[b] (sensitivity analysis)

	Reference		Experimental		HR (95% CI)	p value
	ASA + Ticagrelor		Ticagrelor alone			
	Nr of events /Nr of pt at risk	(%)	Nr of events /Nr of pt at risk	(%)		
Primary endpoint: all-cause death or new Q-wave MI	53/2928	(1.8)	40/2804	(1.4)	0.79 (0.52-1.19)	0.25
Key safety endpoint BARC 3 or 5 bleeding	18/2923	(0.6)	9/2794	(0.3)	0.52 (0.23-1.16)	0.11
BARC 3 bleeding	17/2923	(0.6)	8/2794	(0.3)	0.49 (0.21-1.14)	0.10
BARC 5 bleeding	2/2931	(0.07)	2/2805	(0.04)	1.04 (0.15-7.41)	0.97
All-cause death	33/2897	(1.1)	26/2779	(0.9)	0.82 (0.49-1.38)	0.46
Stroke[c]	10/2926	(0.3)	6/2801	(0.2)	0.63 (0.23-1.72)	0.36
MI (site-reported)	38/2904	(1.3)	17/2778	(0.6)	0.47 (0.26-0.83)	0.009
Revascularization	136/2879	(4.7)	92/2776	(3.3)	0.69 (0.53-0.91)	0.007
TVR	79/2899	(2.7)	39/2784	(1.4)	0.51 (0.35-0.75)	0.001
Definite ST	5/2924	(0.2)	3/2790	(0.1)	0.63 (0.15-2.63)	0.53
Death, new Q-wave MI, stroke	60/2923	(2.1)	42/2800	(1.5)	0.73 (0.49-1.08)	0.12
Cardiac death, MI, stroke	59/2898	(2.0)	33/2774	(1.2)	0.58 (0.38-0.89)	0.01
POCE	174/2862	(6.1)	118/2761	(4.3)	0.70 (0.55-0.88)	0.002
Death, MI, stroke or BARC 3 or 5 bleeding	85/2890	(2.9)	48/2764	(1.7)	0.59 (0.41-0.84)	0.003
NACE	185/2854	(6.5)	123/2751	(4.5)	0.68 (0.54-0.86)	0.001

MI – myocardial infarction, BARC – Bleeding Academic Research Consortium, HR – hazard ratio, 95% CI – 95% confidence interval, ST - stent thrombosis, TVR – target vessel revascularization
The primary outcome was a composite of all-cause mortality or nonfatal, centrally adjudicated, new Q-wave MI. Patient-oriented composite endpoint (POCE) included all-cause mortality or any MI, revascularization or stroke, whereas net adverse clinical events (NACE) comprised POCE, BARC 3 or 5 type bleeding. P values for the log rank test.

[a] In these time-frames experimental regimen = ticagrelor monotherapy, reference regimen = ticagrelor plus aspirin)

[b] as assessed at each follow-up visit up to 365 days (at discharge, 30 days, 90 days, 180 days and 365 days**.** Patients with missing information on adherence at any time point of the follow-up were excluded.

[c] not including transient ischemic attack.

eTable 6 Exploratory analysis of clinical events between 31 and 365 days[a] in acute coronary syndrome patients who underwent complex percutaneous coronary intervention (PCI)[b] (sensitivity analysis)

	Reference		Experimental		HR (95% CI)	p value
	ASA + Ticagrelor		Ticagrelor alone			
	Nr of events /Nr of pt at risk	(%)	Nr of events /Nr of pt at risk	(%)		
Primary outcome: all-cause death or new Q-wave MI	25/1098	(2.3)	12/1103	(1.1)	0.48 (0.24-0.95)	0.04
Key safety endpoint: BARC 3 or 5 bleeding	24/1086	(2.2)	8/1087	(0.7)	0.33 (0.15-0.74)	0.007
BARC 3 bleeding	24/1086	(2.2)	7/1087	(0.6)	0.29 (0.12-0.67)	0.004
BARC 5 bleeding	-	-	-	-	-	-
All-cause death	17/1100	(1.5)	7/1103	(0.6)	0.41 (0.17-0.99)	0.05
Stroke[c]	0/1090	(0.0)	6/1097	(0.5)	-	-
MI (site-reported)	22/1082	(2.0)	17/1088	(1.6)	0.76 (0.41-1.44)	0.40
Revascularization	62/1063	(5.8)	66/1082	(6.1)	1.05 (0.74-1.48)	0.80
TVR	43/1078	(4.0)	32/1090	(2.9)	0.73 (0.46-1.15)	0.18
Definite ST	3/1091	(0.3)	3/1092	(0.3)	1.00 (0.20-4.94)	0.99
Death, new Q-wave MI, stroke	24/1089	(2.2)	16/1097	(1.5)	0.66 (0.35-1.24)	0.20
Cardiac death, MI, stroke	22/869	(2.5)	9/796	(1.1)	0.44 (0.20-0.96)	0.04
POCE	77/1055	(7.3)	79/1079	(7.3)	1.00 (0.73-1.37)	0.99
Death, MI, stroke or BARC 3 or 5 bleeding	58/1070	(5.4)	34/1078	(3.2)	0.58 (0.38-0.88)	0.01
NACE	97/1046	(9.3)	83/1069	(7.8)	0.83 (0.62-1.11)	0.21

MI – myocardial infarction, BARC – Bleeding Academic Research Consortium, HR – hazard ratio, 95% CI – 95% confidence interval, ST - stent thrombosis, TVR – target vessel revascularization
The primary outcome was a composite of all-cause mortality or nonfatal, centrally adjudicated, new Q-wave MI. Patient-oriented composite endpoint (POCE) included all-cause mortality or any MI, revascularization or stroke, whereas net adverse clinical events (NACE) comprised POCE, BARC 3 or 5 type bleeding. P values for the log rank test.
[a] in these time-frames experimental regimen = ticagrelor monotherapy, reference regimen = ticagrelor plus aspirin
[b] PCI was defined as complex PCI when at least one of the following features were met: multivessel PCI, ≥ 3 stents implanted, ≥ 3 lesions treated, bifurcation PCI with ≥ 2 stents, and total stent length > 60 mm. These five high-risk features of complex percutaneous procedure for ischemic events have been described previously (Neumann FJ et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019;40:87-165; Giustino G et al. et al. Efficacy and Safety of Dual Antiplatelet Therapy After Complex PCI. J Am Coll Cardiol. 2016;68:1851-1864). Multivessel PCI was defined as PCI performed to treat two or three separate major coronary territories. An isolated left main lesion was classified as two-vessel disease in the presence of right dominance and three-vessel disease in the presence of left dominance. To calculate the total stent length, the sum of the nominal stent lengths was used as per patient.
[c] not including transient ischemic attack.

eTable 7 Exploratory analysis of clinical events between 31 and 365 days[a] in acute coronary syndrome patients who underwent complex percutaneous coronary intervention (PCI)[b] and adhered to the randomized treatment at each follow-up visit up to 365 days[c] (sensitivity analysis)

	Reference		Experimental		HR (95% CI)	p value
	ASA + Ticagrelor		Ticagrelor alone			
	Nr of events /Nr of pt at risk	(%)	Nr of events /Nr of pt at risk	(%)		
Primary outcome: all-cause death or new Q-wave MI	19/880	(2.2)	7/802	(0.9)	0.40 (0.17-0.96)	0.04
Key safety endpoint: BARC 3 or 5 bleeding	10/876	(1.1)	2/797	(0.3)	0.22 (0.05-0.996)	0.05
BARC 3 bleeding	10/876	(1.1)	1/797	(0.1)	0.11 (0.01-0.85)	0.04
BARC 5 bleeding	-	-	-	-	-	-
All-cause death	11/881	(1.2)	3/802	(0.4)	0.30 (0.08-1.07)	0.06
New Q-wave MI						
Stroke[d]	0/878	(0.0)	1/802	(0.1)	-	-
MI (site-reported)	18/872	(2.1)	6/796	(0.8)	0.36 (0.14-0.91)	0.03
Revascularization	52/857	(6.1)	34/790	(4.3)	0.70 (0.46-1.08)	0.11
TVR	36/867	(4.2)	15/795	(1.9)	0.45 (0.25-0.82)	0.01
Definite ST	2/878	(0.2)	0/797	(0.0)	-	-
Composite endpoints						
Death, new Q-wave MI, stroke	18/877	(2.1)	7/802	(0.9)	0.42 (0.18-1.01)	0.05
Cardiac death, MI, stroke	81/3648	(2.2)	80/3654	(2.2)	0.99 (0.73-1.35)	0.94
POCE	62/852	(7.3)	37/788	(4.7)	0.64 (0.43-0.96)	0.03
Death, MI, stroke or BARC 3/5 bleeding	36/864	(4.2)	10/791	(1.3)	0.30 (0.15-0.60)	0.001
NACE	69/847	(8.1)	37/783	(4.7)	0.57 (0.38-0.85)	0.006

MI – myocardial infarction, BARC – Bleeding Academic Research Consortium, HR – hazard ratio, 95% CI – 95% confidence interval, ST - stent thrombosis, TVR – target vessel revascularization
The primary outcome was a composite of all-cause mortality or nonfatal, centrally adjudicated, new Q-wave MI. Patient-oriented composite endpoint (POCE) included all-cause mortality or any MI, revascularization or stroke, whereas net adverse clinical events (NACE) comprised POCE, BARC 3 or 5 type bleeding. P values for the log rank test.
[a] in these time-frames experimental regimen = ticagrelor monotherapy, reference regimen = ticagrelor plus aspirin
[b] PCI was defined as complex PCI when at least one of the following features were met: multivessel PCI, ≥ 3 stents implanted, ≥ 3 lesions treated, bifurcation PCI with ≥ 2 stents, and total stent length > 60 mm. These five high-risk features of complex percutaneous procedure for ischemic events have been described previously (Neumann FJ et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019;40:87-165; Giustino G et al. et al. Efficacy and Safety of Dual Antiplatelet Therapy After Complex PCI. J Am Coll Cardiol. 2016;68:1851-1864). Multivessel PCI was defined as PCI performed to treat two or three separate major coronary territories. An isolated left main lesion was classified as two-vessel disease in the presence of right dominance and three-vessel disease in the presence of left dominance. To calculate the total stent length, the sum of the nominal stent lengths was used as per patient.

[c] as assessed at each follow-up visit up to 365 days (at discharge, 30 days, 90 days, 180 days and 365 days**).** Patients with missing information on adherence at any time point of the follow-up were excluded.

[d] not including transient ischemic attack.

eTable 8 Exploratory analysis of one-year clinical outcomes in acute coronary syndrome patients who underwent complex percutaneous coronary intervention (PCI)[a] (n = 2,221).

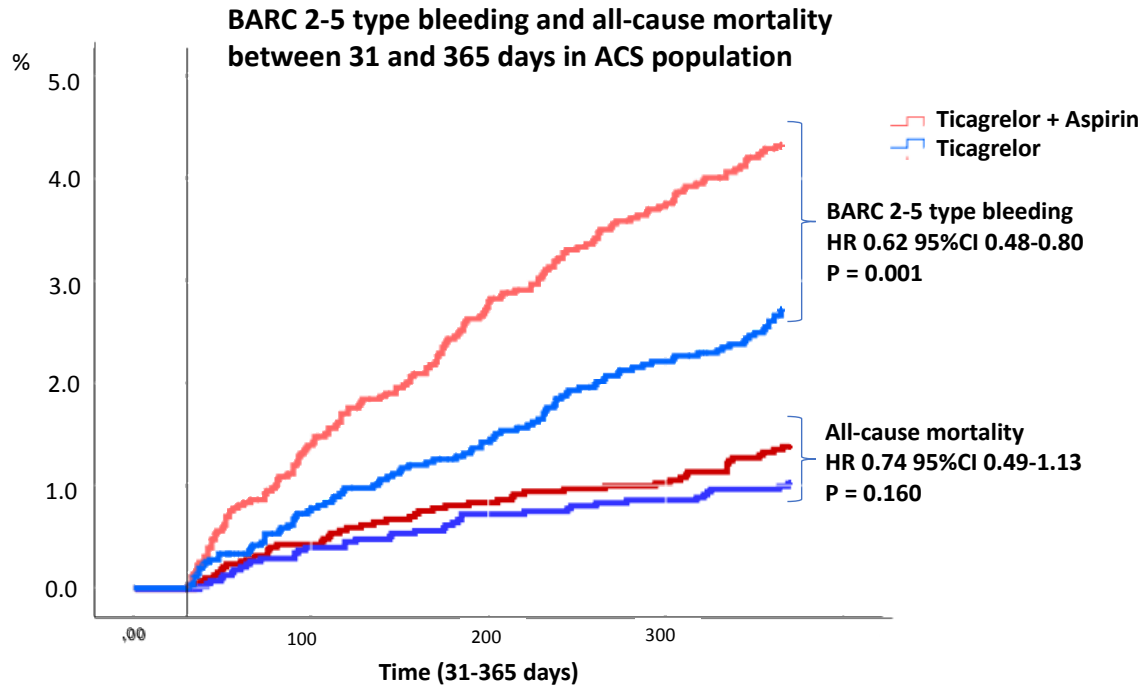
	Reference	Experimental	HR (95%CI)	p value
	(N = 1,112)	(N = 1,109)		
Primary outcome: all-cause death or new Q-wave MI	38 (3.4)	18 (1.6)	0.47 (0.27-0.83)	0.009
Key safety endpoint: BARC 3 or 5 bleeding	34 (3.1)	21 (1.9)	0.61 (0.36-1.06)	0.08
BARC 3 bleeding	33 (3.0)	17 (1.5)	0.51 (0.29-0.91)	0.03
BARC 5 bleeding	3 (0.3)	4 (0.4)	1.34 (0.30-5.96)	0.71
All-cause death	28 (2.5)	13 (1.2)	0.46 (0.24-0.89)	0.02
New Q-wave MI	11 (1.0)	5 (0.5)	0.45 (0.16-1.30)	0.14
Stroke[b]	5 (0.4)	9 (0.8)	1.79 (0.60-5.35)	0.30
MI (site-reported)	35 (3.1)	26 (2.3)	0.74 (0.44-1.22)	0.24
Revascularization	94 (8.5)	81 (7.3)	0.85 (0.63-1.14)	0.28
TVR	60 (5.4)	39 (3.5)	0.64 (0.43-0.96)	0.03
Definite ST	7 (0.6)	8 (0.7)	1.14 (0.41-3.15)	0.80
Composite endpoints				
Death, new Q-wave MI, stroke	43 (3.8)	22 (2.0)	0.52 (0.31-0.87)	0.01
Cardiac death, MI, stroke	55 (4.9)	42 (3.8)	0.76 (0.51-1.13)	0.18
POCE	129 (11.6)	103 (9.3)	0.79 (0.61-1.02)	0.07
Death, MI, stroke or BARC 3/5 bleeding	95 (8.5)	59 (5.3)	0.61 (0.44-0.85)	0.003
NACE	158 (14.2)	117 (10.6)	0.73 (0.57-0.92)	0.008

MI – myocardial infarction, BARC – Bleeding Academic Research Consortium, HR – hazard ratio, 95% CI – 95% confidence interval, ST - stent thrombosis, TVR – target vessel revascularization
The primary outcome was a composite of all-cause mortality or nonfatal, centrally adjudicated, new Q-wave MI. Patient-oriented composite endpoint (POCE) included all-cause mortality or any MI, revascularization or stroke, whereas net adverse clinical events (NACE) comprised POCE, BARC 3 or 5 type bleeding. P values for the log rank test.

[a] PCI was defined as complex PCI when at least one of the following features were met: multivessel PCI, ≥ 3 stents implanted, ≥ 3 lesions treated, bifurcation PCI with ≥ 2 stents, and total stent length > 60 mm. These five high-risk features of complex percutaneous procedure for ischemic events have been described previously (Neumann FJ et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019;40:87-165; Giustino G et al. et al. Efficacy and Safety of Dual Antiplatelet Therapy After Complex PCI. J Am Coll Cardiol. 2016;68:1851-1864). Multivessel PCI was defined as PCI performed to treat two or three separate major coronary territories. An isolated left main lesion was classified as two-vessel disease in the presence of right dominance and three-vessel disease in the presence of left dominance. To calculate the total stent length, the sum of the nominal stent lengths was used as per patient.

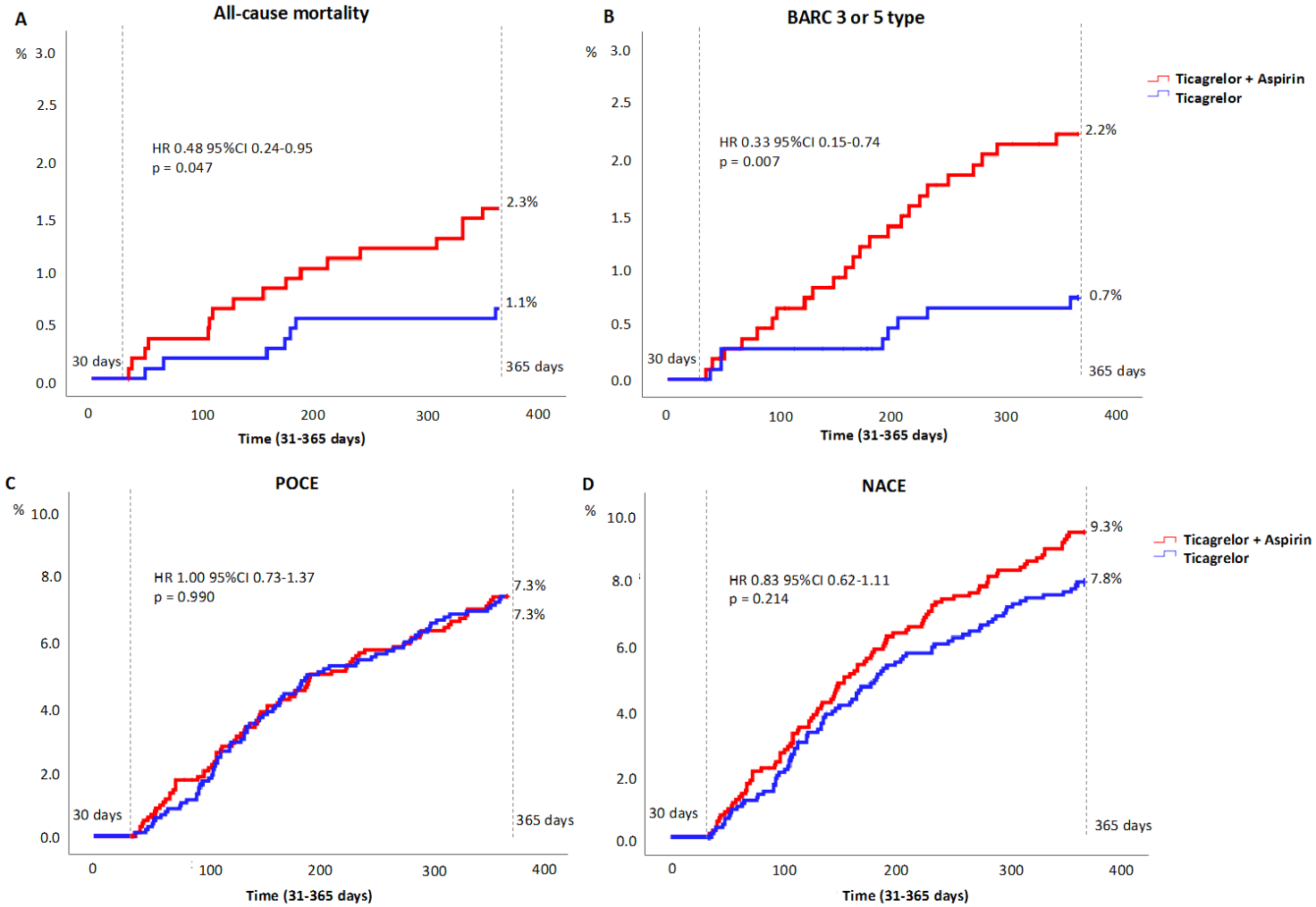
[b] not including transient ischemic attack

eFigure 1 Bleeding Academic Research Consortium (BARC)-defined bleeding type ≥ 2 and all-cause mortality between 31 and 365 days[a] in ACS patients



[a] In these time-frames experimental regimen = ticagrelor monotherapy, reference regimen = ticagrelor plus aspirin
HR – hazard ratio, 95%CI – 95% confidence interval
BARC – Bleeding Academic Research Consortium.

eFigure 2 Exploratory analyses of clinical outcomes between 31 and 365 days[a] in acute coronary syndrome patients who underwent complex percutaneous coronary intervention (PCI)[b] (sensitivity analysis)



HR – hazard ratio, 95%CI – 95% confidence interval

BARC – Bleeding Academic Research Consortium. Patient-oriented composite endpoint (POCE) included all-cause mortality or any MI, revascularization or stroke, whereas net adverse clinical events (NACE) comprised POCE, BARC type 3 or 5 bleeding. Patients who were alive at 31 days of follow-up and did not encounter event of the specific type nor were censored prior to the landmark of 30 days have been included in the present analysis.

[a] Between 31 and 365 days according to the study protocol the experimental regimen = ticagrelor monotherapy, the reference regimen = ticagrelor plus aspirin

[b] PCI was defined as complex PCI when at least one of the following features were met: multivessel PCI, ≥ 3 stents implanted, ≥ 3 lesions treated, bifurcation PCI with ≥ 2 stents, and total stent length > 60 mm. These five high-risk features of complex percutaneous procedure for ischemic events have been described previously (Neumann FJ et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019;40:87-165; Giustino G et al. et al. Efficacy and Safety of Dual Antiplatelet Therapy After Complex PCI. J Am Coll Cardiol. 2016;68:1851-1864). Multivessel PCI was defined as PCI performed to treat two or three separate major coronary territories. An isolated left main lesion was classified as two-vessel disease in the presence of right dominance and three-vessel disease in the presence of left dominance. To calculate the total stent length, the sum of the nominal stent lengths was used as per patient.