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Impact of ticagrelor monotherapy on two-year clinical outcomes in patients with long stenting: a post hoc analysis of the GLOBAL LEADERS trial

Kuniaki Takahashi[1], MD; Ply Chichareon[1,2], MD; Rodrigo Modolo[1,3], MD; Norihiro Kogame[1], MD; Chun Chin Chang[4], MD; Mariusz Tomaniak[4,5], MD; Aris Moschovitis[6], MD; Nick Curzen[7], BM (Hons), PhD; Michael Haude[8], MD; Werner Jung[9], MD; Lene Holmvang[10], MD, DMSci; Scot Garg[11], MD, PhD; Jan G.P. Tijssen[1,12], PhD; Joanna J. Wykrzykowska[1], MD, PhD; Robbert J. de Winter[1], MD, PhD; Christian Hamm[13], MD; Philippe Gabriel Steg[14], MD; Hans-Peter Stoll[15], MD; Yoshinobu Onuma[16], MD, PhD; Marco Valgimigli[17], MD, PhD; Pascal Vranckx[18], MD, PhD; Stephan Windecker[17], MD; Patrick W. Serruys[16]*, MD, PhD

The authors' affiliations can be found in the Appendix paragraph.

GUEST EDITOR: Alec Vahanian, MD, PhD; *Department of Cardiology, Hôpital Bichat-Claude Bernard, and University Paris VII, Paris, France*

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KEYWORDS

- ACS/NSTE-ACS
- adjunctive pharmacotherapy
- drug-eluting stent
- stable angina

Abstract

Aims: The aim of this study was to evaluate the impact of a novel antiplatelet regimen in patients with increasing total stent length (TSL).

Methods and results: This is a *post hoc* analysis of the GLOBAL LEADERS trial, a prospective, multicentre, open-label, randomised trial, investigating the impact of the experimental strategy (one-month dual antiplatelet therapy [DAPT] followed by 23-month ticagrelor monotherapy) versus the reference regimen (12-month DAPT followed by 12-month aspirin monotherapy) in patients with a Biolimus A9-eluting stent (BES). The primary endpoint was the composite of all-cause death and new Q-wave myocardial infarction (MI), and the secondary endpoint was Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding at two years. To investigate the association between total stent length and outcomes, groups were compared in quartiles according to TSL; the fourth quartile group was at significantly higher ischaemic risk at two years. In that stratum (TSL ≥46 mm), the experimental strategy significantly reduced the risk of the primary endpoint (hazard ratio [HR] 0.67, 95% confidence interval [CI]: 0.49-0.90; $p_{interaction}$=0.043), while demonstrating a similar risk of BARC type 3 or 5 bleeding (HR 0.99, 95% CI: 0.66-1.49; $p_{interaction}$=0.975).

Conclusions: Ticagrelor monotherapy could potentially balance ischaemic and bleeding risks, thereby achieving a net clinical benefit in patients with a TSL ≥46 mm with a BES.

**Corresponding author: Department of Cardiology, National University of Ireland, University Road, Galway, H91 TK33, Ireland. E-mail: patrick.w.j.c.serruys@gmail.com*

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Abbreviations

BARC Bleeding Academic Research Consortium
CAD coronary artery disease
NACE net adverse clinical events
POCE patient-oriented cardiovascular events
TSL total stent length

Introduction

An increase in total lesion length or number of lesions treated results in the need for longer total stent length (TSL), which has been associated with an increased risk of major adverse cardiovascular events (MACE) after percutaneous coronary intervention (PCI) with bare metal stents (BMS)[1]. Whilst first-generation drug-eluting stents (DES) significantly reduced neointimal hyperplasia and subsequently improved clinical outcomes as compared with BMS, TSL still remained a significant predictor of target lesion revascularisation (TLR) and stent thrombosis (ST)[2]. Since the advent of the second-generation DES, clinical outcomes in patients with increasing TSL have improved significantly, and TSL is no longer associated with a higher risk of ST[3-7].

To date, data on the effect of different antiplatelet regimens in patients who received longer stents are limited. A prior pooled patient-level analysis from six randomised controlled trials (RCT) has demonstrated that, compared with an abbreviated dual antiplatelet therapy (DAPT) regimen (three or six months), prolonged (>12 months) DAPT significantly reduced MACE (a composite of cardiac death, myocardial infarction [MI], and definite or probable ST) in patients who underwent complex PCI, where one of the criteria was a TSL >60 mm[8]. However, an increased risk of bleeding according to Bleeding Academic Research Consortium (BARC) definition (type 3 or 5) was documented[8]. Given that bleeding is associated with impaired quality of life, morbidity, and mortality, so-called "aspirin-free" strategies (an abbreviated DAPT followed by potent $P2Y_{12}$ monotherapy) have recently been proposed, aiming to reduce an excess of bleeding risk mainly related to the addition of aspirin while maintaining a potent anti-ischaemic efficacy[9,10]. Two recent RCT, STOPDAPT-2 and SMART-CHOICE, showed that, compared to 12-month DAPT, one- or three-month DAPT followed by $P2Y_{12}$ inhibitor monotherapy was superior for bleeding and non-inferior for the composite ischaemic endpoint at one-year follow-up. The aim of this study is to evaluate the impact of one-month DAPT followed by 23-month ticagrelor monotherapy versus 12-month DAPT followed by 12-month aspirin monotherapy on two-year clinical outcomes in patients with increasing TSL.

Methods

STUDY DESIGN

This study is a *post hoc* analysis of the GLOBAL LEADERS trial, a prospective, multicentre, open-label, RCT (NCT01813435). Details of the study design and protocol have been reported previously[11]. In summary, the trial randomised patients undergoing PCI by default with BES (BioMatrix™; Biosensors, Morges, Switzerland) in a 1:1 ratio to either (i) the experimental strategy consisting of one-month DAPT (aspirin and ticagrelor) followed by 23-month ticagrelor monotherapy, or (ii) the reference regimen consisting of 12-month DAPT (aspirin and either ticagrelor for acute coronary syndrome [ACS] or clopidogrel for stable coronary artery disease [CAD]) followed by 12-month aspirin monotherapy.

The trial was approved by the institutional review board at each centre and followed the ethical principles of the Declaration of Helsinki. All the patients provided written informed consent prior to participation in the trial.

TOTAL STENT LENGTH

In the present analysis, nominal stent length is used to calculate TSL as per patient. During the trial, available stent diameters were 2.25 to 4.0 mm with a stent length of 8, 11, 14, 18, 24, 28, 33, and 36 mm. To evaluate the association between stent length and outcomes, groups are compared in quartiles according to a given TSL (quartile 1: 8 to 17 mm; quartile 2: 18 to 27 mm; quartile 3: 28 to 45 mm; quartile 4: ≥46 mm), as in previous studies[2,12]. Given suboptimal outcomes in patients with increasing TSL, a longer and more potent antiplatelet regimen may be useful[13]. Thus, clinical outcomes are further assessed to determine whether the experimental strategy could improve outcomes in patients with long stenting as compared with the reference regimen.

STUDY ENDPOINTS

The primary endpoint was the composite of all-cause death or new Q-wave MI at two years. Deaths from any cause were ascertained without adjudication. Q-wave MI was centrally adjudicated and defined in compliance with the Minnesota classification (new major Q-QS wave abnormalities) or by the appearance of a new left bundle branch block in conjunction with abnormal biomarkers. The key secondary endpoint was bleeding according to the BARC criteria (type 3 or 5) up to two years. Other secondary endpoints included individual components of the primary endpoint, any stroke, any MI, any revascularisation, and definite ST.

In addition, patient-oriented cardiovascular events (POCE) and net adverse clinical events (NACE) were explored up to two years according to the Academic Research Consortium (ARC)-2 definition. POCE is the composite of all-cause death, any stroke (ischaemic and haemorrhagic), any MI (periprocedural or spontaneous with ST-elevation MI [STEMI] or non-ST-elevation MI [NSTEMI]), and any revascularisation (repeat PCI or coronary artery bypass grafting [CABG] surgery in target or non-target vessel). The third universal definition of MI was the recommended criterion to report MI. NACE is the composite of POCE and BARC type 3 or 5 bleeding. Composite endpoints were analysed hierarchically. Individual components of the composite endpoints as well as definite ST according to Academic Research Consortium (ARC) definition were reported non-hierarchically. The endpoints were site-reported with the exception of the primary endpoint, all-cause death and new Q-wave MI, which was assessed by an independent electrocardiogram (ECG) core lab.

STATISTICAL ANALYSIS

The analyses were performed according to the intention-to-treat principle. The cumulative incidence of clinical events during two-year follow-up was calculated using the Kaplan-Meier method and compared using the log-rank test. Hazard ratios (HR) with 95% confidence intervals (CI) were estimated using an unadjusted Cox regression model. The treatment effect of the experimental versus the reference strategy between the subgroups was estimated using an unadjusted Cox regression model. To confirm whether the treatment effect of the experimental strategy versus the reference regimen was significantly modified according to the longer TSL, we performed a multivariate analysis based on a Cox proportional hazards regression model for the primary endpoint through the inclusion of randomised treatment-by-TSL ≥46 mm interaction term as well as the traditional covariates - age, hypertension, diabetes, current smoker, previous MI, previous PCI, and clinical presentation (ACS versus stable CAD)[12].

In addition, the one-year landmark analysis was reported using the pre-specified time point of one year (at the time of the planned cessation of a $P2Y_{12}$ inhibitor in the reference strategy). The pre-specified stratified analysis according to clinical presentation (stable CAD or ACS) was performed since a different $P2Y_{12}$ inhibitor in the reference group was used according to clinical presentation (i.e., clopidogrel for stable CAD or ticagrelor for ACS)[11].

Continuous variables were reported as mean±standard deviation (SD) or median and interquartile range (IQR) and were compared using the Student's t-test or Mann-Whitney U test. Categorical variables were reported as percentages and numbers and were compared using the chi-square test or Fisher's exact test as appropriate. No adjustment was performed for multiple testing due to the *post hoc* nature of the analysis[14]. All tests were two-sided and a p-value of <0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS Statistics, Version 25 (IBM Corp., Armonk, NY, USA).

Results

PATIENTS

Between July 2013 and November 2015, at 130 hospitals in 18 countries (Europe, Asia, Brazil, Australia and Canada), the GLOBAL LEADERS trial randomised a total of 15,991 patients, of whom 15,450 (96.6%) were included in this analysis. This cohort was subsequently divided into quartiles according to TSL per patient **(Figure 1, Figure 2)**. The cumulative frequency of TSL is presented in **Supplementary Figure 1**.

BASELINE CHARACTERISTICS AND CLINICAL OUTCOMES ACCORDING TO TSL

Baseline characteristics according to quartile are presented in **Supplementary Table 1**. Patients in quartile 4 were more likely

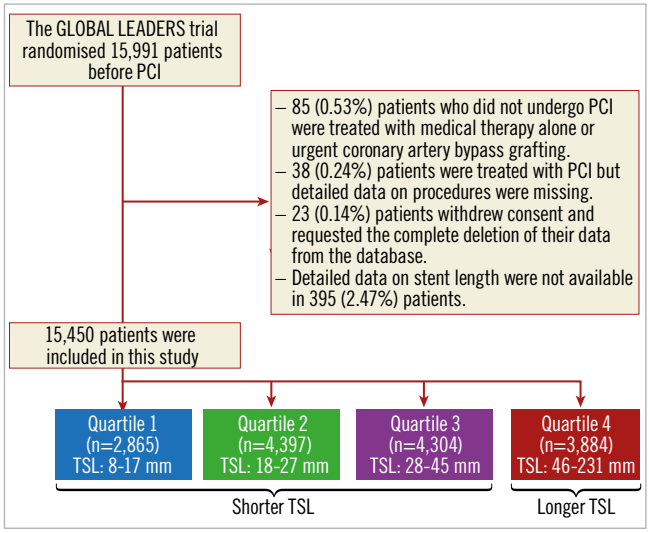

Figure 1. *Patient flow diagram of the present study. PCI: percutaneous coronary intervention; TSL: total stent length*

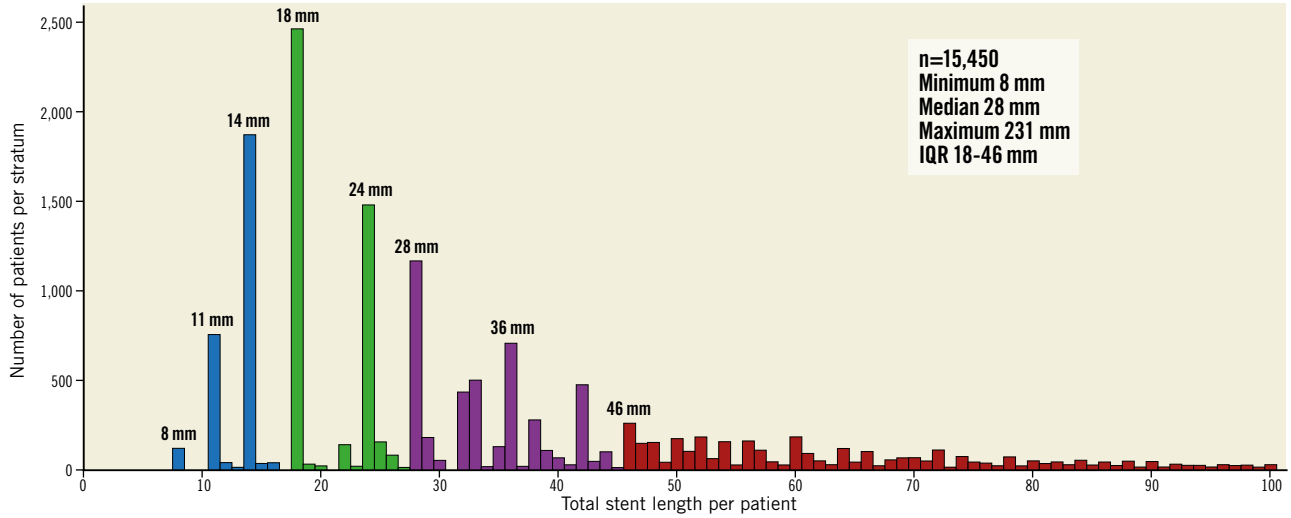

Figure 2. *Distribution of total stent length per patient. The distribution of the total stent length depends on the available nominal stent lengths of BioMatrix stent (8, 11, 14, 18, 24, 28, 33, and 36 mm). Colours indicate the quartile 1 (blue): 8 to 17 mm; quartile 2 (green): 18 to 27 mm; quartile 3 (purple): 28 to 45 mm; and quartile 4 (red): ≥46 mm. Data are not shown in patients with total stent length >100 mm.*

to be male and had a higher prevalence of diabetes and hypercholesterolaemia and a lower prevalence of previous PCI. In terms of angiographic variables, patients in this group were more likely to receive multivessel PCI and less likely to undergo direct stenting. They also had a greater number of treated lesions with a higher prevalence of bifurcation and a greater number of stents implanted, which resulted in a greater TSL per patient.

Two-year clinical outcomes according to quartile are presented in **Figure 3** and **Supplementary Table 2**. There was a non-significant higher risk of the primary endpoint according to quartile (log-rank p=0.073). Increasing TSL resulted in a higher risk of POCE (log-rank p<0.001). The risk of BARC type 3 or 5 bleeding was numerically higher according to quartile (log-rank p=0.077).

IMPACT OF THE EXPERIMENTAL STRATEGY IN PATIENTS WITH LONGER TSL

Baseline characteristics stratified according to antiplatelet regimen in patients with longer TSL (defined as a TSL ≥46 mm) are presented in **Table 1**. All baseline characteristics with the exception of diabetes and the type of stent implanted were statistically similar between groups.

Two-year efficacy and safety outcomes according to the randomised treatment allocation in patients with longer TSL are presented in **Figure 4** and **Supplementary Table 3**. The treatment effect of the experimental strategy versus the reference regimen is presented in **Figure 5**. The experimental strategy led to a significantly reduced risk of the primary endpoint (3.79% vs 5.68%, HR 0.66, 95% CI: 0.49-0.89; p=0.006, $p_{interaction}$=0.043) in favour of the longer TSL group. In addition, the experimental treatment had a significant risk reduction in POCE (14.75% vs 18.26%; HR 0.79, 95% CI: 0.67-0.92; p=0.003, $p_{interaction}$=0.017) in patients with TSL ≥46 mm. The risk of BARC type 3 or 5 bleeding was statistically similar between the two regimens (2.53% vs 2.55%; HR 0.99, 95% CI: 0.66-1.49; p=0.963, $p_{interaction}$=0.975), resulting in a significantly reduced risk of NACE (16.25% vs 19.80%; HR 0.80, 95% CI: 0.69-0.93; p=0.004, $p_{interaction}$=0.025) in patients with longer TSL.

The multivariable analysis confirmed that there was a significant interaction of the experimental strategy versus the reference regimen according to TSL ≥46 mm in terms of the primary endpoint ($p_{interaction}$=0.047).

Based on a landmark analysis at one year, ticagrelor monotherapy, when compared with aspirin monotherapy, had no incremental benefit with respect to any ischaemic and bleeding endpoints in the second year **(Supplementary Table 3)**.

STRATIFIED ANALYSIS ACCORDING TO CLINICAL PRESENTATION

In stable CAD patients with longer TSL, the experimental treatment had a numerically lower risk of the primary endpoint (3.92% vs 5.48%, HR 0.71, 95% CI: 0.47-1.07, p=0.103, $p_{interaction}$=0.342) and a significant risk reduction in POCE (14.64% vs 18.73%; HR 0.76, 95% CI: 0.61-0.95; p=0.014, $p_{interaction}$=0.056). However, its anti-ischaemic efficacy was achieved at the expense of a numerically higher risk of BARC type 3 or 5 bleeding (2.63% vs 1.52%; HR 1.74, 95% CI: 0.92-3.31; p=0.088, $p_{interaction}$=0.360) **(Supplementary Table 4)**.

Conversely, in ACS patients with longer TSL, the experimental treatment had a significantly lower risk of the primary endpoint (3.66% vs 5.90%, HR 0.61, 95% CI: 0.40-0.93, p=0.023, $p_{interaction}$=0.055) and a numerically lower risk of POCE (14.86% vs 17.75%; HR 0.82, 95% CI: 0.66-1.03; p=0.083, $p_{interaction}$=0.143). The risk of BARC type 3 or 5 bleeding was numerically lower in the experimental strategy (2.43% vs 3.67%; HR 0.66, 95% CI: 0.39-1.12; p=0.127, $p_{interaction}$=0.554), which led to a significantly lower risk of NACE (16.32% vs 19.97%; HR 0.80, 95% CI: 0.64-0.98; p=0.036, $p_{interaction}$=0.131) **(Supplementary Table 5)**.

Discussion

The main findings of this study can be summarised as follows.

(1) There was a non-significant higher risk of the primary endpoint according to quartile, whereas increasing TSL resulted in a greater risk of POCE, which was driven by all-cause death, any MI, and any revascularisation.

(2) In patients with a TSL ≥46 mm, the experimental strategy with ticagrelor monotherapy, when compared to the reference regimen, significantly reduced the risk of the primary endpoint as well as POCE with a similar risk of BARC type 3 or 5 bleeding, thereby achieving a significant net clinical benefit at two years. The benefits with the experimental strategy were largely confined to the first year of treatment and ACS patients who underwent long stenting.

Numerous RCT and large registries have shown that newer generations of DES have significantly reduced the risk of restenosis and the need for repeat revascularisation. Nevertheless, even with a second-generation DES, post-stenting reference segment plaque burden has been associated with edge restenosis. Hence, the preferred strategy is full coverage of atherosclerotic lesions, resulting in stents with longer lengths. As of today, there have been a few studies investigating the effect of increasing TSL with a second-generation DES on clinical outcomes[3-7]. Three studies have reported that longer stent lengths were no longer associated with a significant increase in MACE, TLR, and ST in patients who received a second-generation DES[3-5]. However, these studies had relatively small to medium sample sizes (n=730, 1,181 and 2,111, respectively) compared to the present study which included the largest cohort (n=15,450). In the present analysis, the longer TSL group had a significantly higher risk of ARC-2-defined POCE, driven by all-cause death, any MI, and any revascularisation **(Figure 3)**. The pathophysiological foundation for this association may reside in the following facts. First, longer and more stents implanted may increase the likelihood of stent size mismatch, stent underexpansion, malapposition, and overlapping, all of which may lead to incomplete endothelialisation and an enhancement of the stent-related ischaemic risk[15]. Second, patients who require more and longer stents represent a more advanced state of CAD, which often results in incomplete revascularisation with a subsequently increased risk of recurrent thrombotic events and

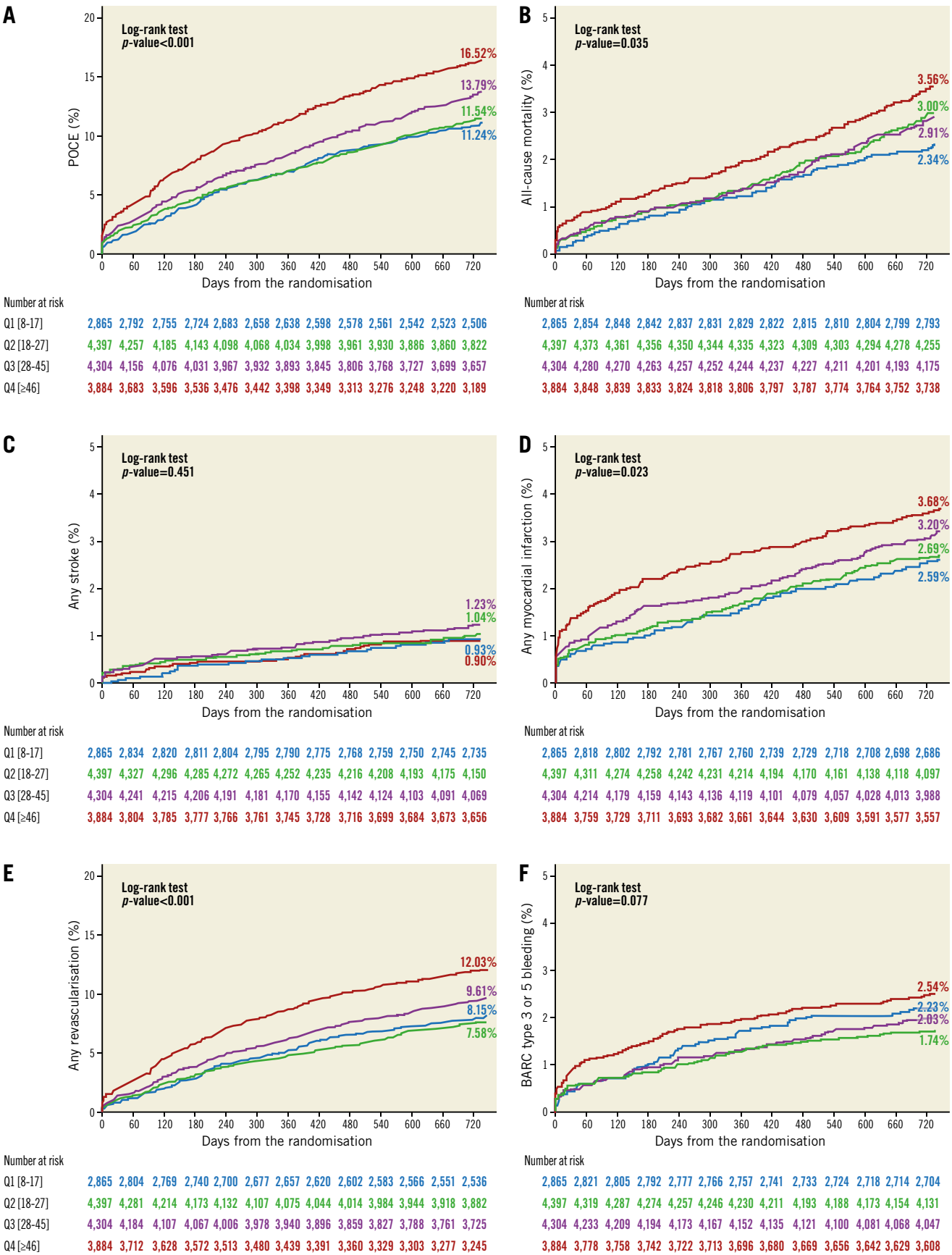

Figure 3. *Clinical outcomes in quartiles according to TSL. A) POCE. B) All-cause mortality. C) Any stroke. D) Any MI. E) Any revascularisation. F) BARC type 3 or 5 bleeding.*

Table 1. Baseline characteristics according to the randomised strategies in patients with longer TSL (≥46 mm).

			Longer TSL (TSL ≥46 mm)		*p*-value
			Experimental strategy	Reference strategy	
Age, years			64.9±10.3	64.8±10.0	0.742
Gender		Male	79.5 (1,533/1,929)	80.3 (1,570/1,955)	
		Female	20.5 (396/1,929)	19.7 (385/1,955)	
Body mass index, kg/m^2			28.2±4.6	28.2±4.7	0.747
Diabetes			28.9 (557/1,927)	25.1 (491/1,953)	0.008
Insulin-dependent diabetes mellitus			8.5 (164/1,923)	7.7 (151/1,949)	0.379
Hypertension			75.5 (1,451/1,923)	73.5 (1,432/1,947)	0.184
Hypercholesterolaemia			70.4 (1,324/1,882)	71.4 (1,361/1,906)	0.497
Current smoker			26.8 (517/1,929)	26.7 (522/1,955)	0.971
Peripheral vascular disease			6.1 (117/1,917)	7.4 (144/1,936)	0.109
Chronic obstructive pulmonary disease			5.3 (102/1,924)	6.1 (118/1,947)	0.331
Previous major bleeding			0.7 (13/1,926)	0.6 (12/1,952)	0.844
Impaired renal function*			13.7 (264/1,923)	14.6 (283/1,944)	0.461
Previous stroke			2.7 (51/1,924)	3.0 (59/1,951)	0.500
Previous myocardial infarction			20.9 (402/1,923)	23.3 (454/1,946)	0.075
Previous percutaneous coronary intervention			28.9 (558/1,929)	29.6 (578/1,952)	0.647
Previous coronary artery bypass grafting			4.9 (94/1,928)	5.8 (113/1,954)	0.225
Clinical presentation					0.485
Stable coronary artery disease			50.3 (970/1,929)	51.4 (1,005/1,955)	
Acute coronary syndrome			49.7 (959/1,929)	48.6 (950/1,955)	
Overall					0.499
Unstable angina			11.2 (216/1,929)	10.6 (208/1,955)	
Non-ST-elevation myocardial infarction			23.5 (454/1,929)	22.1 (432/1,955)	
ST-elevation myocardial infarction			15.0 (289/1,929)	15.9 (310/1,955)	
Vascular access site		Femoral	28.4 (548/1,929)	29.8 (582/1,955)	0.358
		Brachial	0.6 (12/1,929)	0.8 (16/1,955)	0.570
		Radial	77.6 (1,496/1,929)	75.6 (1,478/1,955)	0.161
Lesions treated per patient		One lesion	23.5 (453/1,929)	23.2 (453/1,955)	0.406
		Two lesions	46.3 (894/1,929)	44.7 (874/1,955)	
		Three or more lesions	30.2 (582/1,929)	32.1 (628/1,955)	
Target lesions		Left main coronary artery	2.0 (82/4,180)	2.0 (85/4,286)	0.598
		Left anterior descending artery	39.2 (1,640/4,180)	38.1 (1,634/4,286)	
		Left circumflex artery	22.7 (950/4,180)	23.4 (1,003/4,286)	
		Right coronary artery	35.4 (1,478/4,180)	36.0 (1,542/4,286)	
		Bypass graft	0.7 (30/4,180)	0.5 (22/4,286)	
Mean stents per lesion			1.4±0.7	1.4±0.7	0.726
Biolimus A9-eluting stent			91.9 (3,842/4,180)	90.4 (3,873/4,286)	0.013
Other stent			10.2 (426/4,180)	11.7 (502/4,286)	0.026
Mean total stent length per lesion, mm			32.5±18.3	32.4±18.3	0.706
Mean stent diameter per lesion, mm			2.9±0.4	3.0±0.5	0.119
Direct stenting per lesion			25.2 (1,053/4,180)	25.1 (1,076/4,286)	0.940
Bifurcation involved			14.9 (624/4,180)	13.9 (597/4,286)	0.194
Thrombus aspiration			3.2 (134/4,180)	4.4 (190/4,286)	0.004
TIMI flow	Pre-procedure	0 or 1	14.7 (475/3,230)	15.5 (518/3,339)	0.158
		2	10.5 (339/3,230)	11.3 (376/3,339)	
		3	74.8 (2,416/3,230)	73.2 (2,445/3,339)	
	Post-procedure	0 or 1	0.2 (6/3,316)	0.2 (6/3,468)	0.570
		2	0.7 (24/3,316)	0.6 (21/3,468)	
		3	99.1 (3,286/3,316)	99.2 (3,441/3,468)	

Data are presented as mean±standard deviation or percentage (number). * Based on creatinine-estimated GFR (eGFR) clearance of <60 ml/min/1.73 m^2, using the Modification of Diet in Renal Disease (MDRD) formula. TIMI: Thrombolysis In Myocardial Infarction

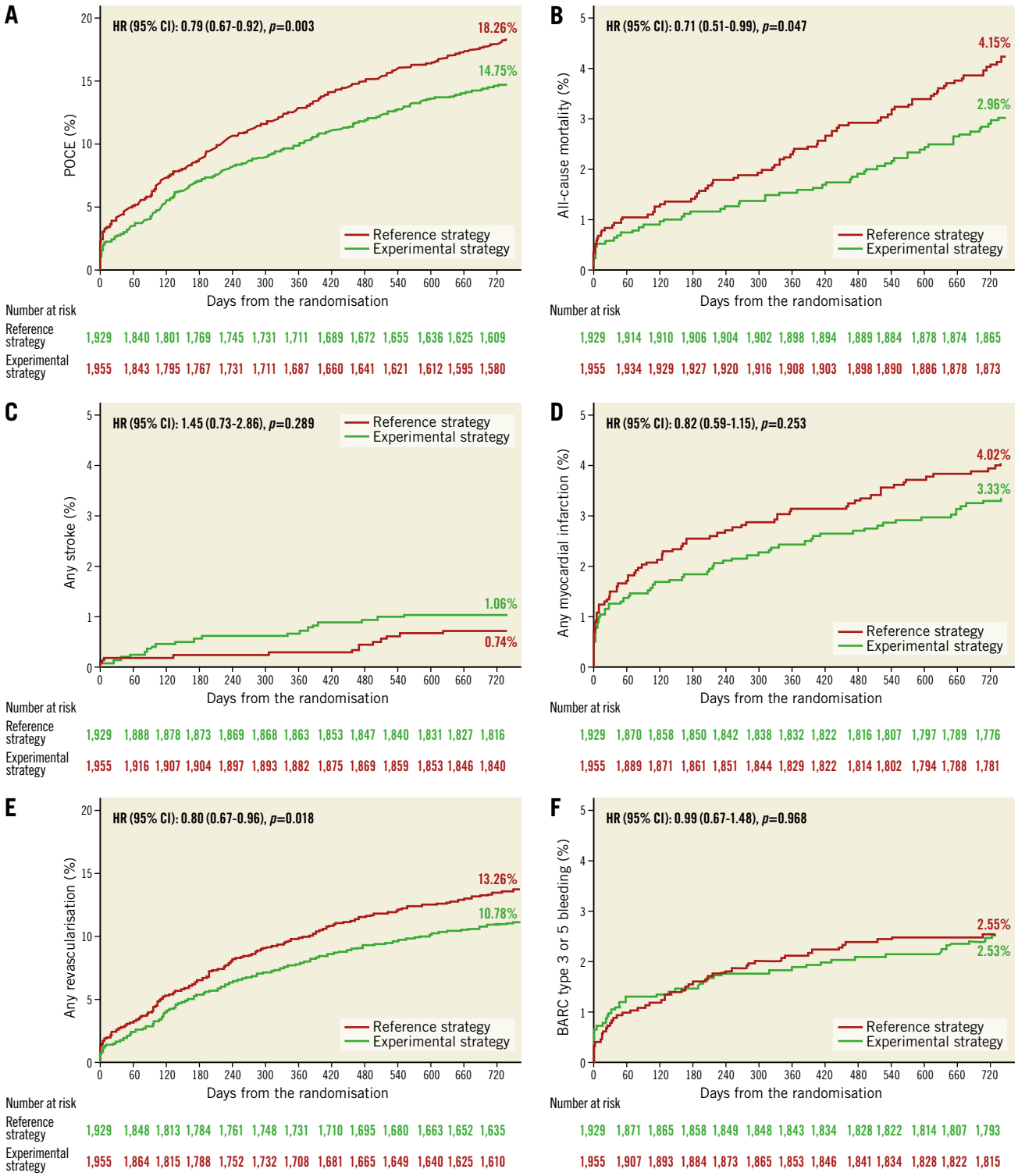

Figure 4. *Clinical outcomes of the experimental strategy versus the reference regimen in patients with longer TSL. A) POCE. B) All-cause mortality. C) Any stroke. D) Any MI. E) Any revascularisation. F) BARC type 3 or 5 bleeding.*

mortality. Third, patients who undergo long stenting tend to have more cardiovascular and non-cardiovascular comorbidities with a greater probability of natural plaque progression followed by thrombotic events (i.e., non-stent-related ischaemic risk)[8].

This limited efficacy of PCI in patients who required a longer TSL reaffirms the need for a dedicated Heart Team approach regarding the best revascularisation modality, either PCI or CABG. Specifically, the risk of repeat revascularisation and recurrent MI

	Experimental strategy	Reference strategy	Hazard ratio (95% CI)	*p*-value	*p*-value for interaction
At two years					
Primary endpoint					0.043
TSL ≥46 mm	3.79 (73/1,929)	5.68 (111/1,955)	0.66 (0.49-0.89)	0.006	
TSL <46 mm	3.77 (218/5,788)	3.98 (230/5,778)	0.94 (0.78-1.14)	0.547	
All-cause mortality					0.137
TSL ≥46 mm	2.96 (57/1,929)	4.15 (81/1,955)	0.71 (0.51-0.99)	0.047	
TSL <46 mm	2.75 (159/5,788)	2.86 (165/5,778)	0.96 (0.77-1.20)	0.725	
New Q-wave MI					0.076
TSL ≥46 mm	0.85 (16/1,929)	1.72 (33/1,955)	0.49 (0.27-0.89)	0.013	
TSL <46 mm	1.09 (62/5,788)	1.19 (68/5,778)	0.91 (0.64-1.28)	0.588	
POCE					0.017
TSL ≥46 mm	14.75 (281/1,929)	18.26 (354/1,955)	0.79 (0.67-0.92)	0.003	
TSL <46 mm	12.24 (700/5,788)	12.37 (709/5,778)	0.99 (0.89-1.10)	0.860	
NACE					0.025
TSL ≥46 mm	16.25 (310/1,929)	19.80 (384/1,955)	0.80 (0.69-0.93)	0.004	
TSL <46 mm	13.38 (765/5,788)	13.58 (779/5,778)	0.98 (0.89-1.09)	0.760	
Any stroke					0.163
TSL ≥46 mm	1.06 (20/1,929)	0.74 (14/1,955)	1.45 (0.73-2.86)	0.289	
TSL <46 mm	0.99 (56/5,788)	1.18 (67/5,778)	0.84 (0.59-1.19)	0.325	
Any MI					0.268
TSL ≥46 mm	3.33 (63/1,929)	4.02 (77/1,955)	0.82 (0.59-1.15)	0.253	
TSL <46 mm	2.89 (164/5,788)	2.82 (160/5,778)	1.03 (0.83-1.28)	0.789	
Any revascularisation					0.042
TSL ≥46 mm	10.78 (203/1,929)	13.26 (253/1,955)	0.80 (0.67-0.96)	0.018	
TSL <46 mm	8.51 (481/5,788)	8.45 (479/5,778)	1.01 (0.89-1.14)	0.908	
Definite ST					0.144
TSL ≥46 mm	1.16 (22/1,929)	0.78 (15/1,955)	1.49 (0.77-2.87)	0.236	
TSL <46 mm	0.68 (39/5,788)	0.83 (47/5,778)	0.83 (0.54-1.27)	0.392	
BARC 3 or 5 bleeding					0.967
TSL ≥46 mm	2.53 (48/1,929)	2.55 (49/1,955)	0.99 (0.67-1.48)	0.968	
TSL <46 mm	1.97 (112/5,788)	1.97 (112/5,778)	1.00 (0.77-1.30)	0.992	

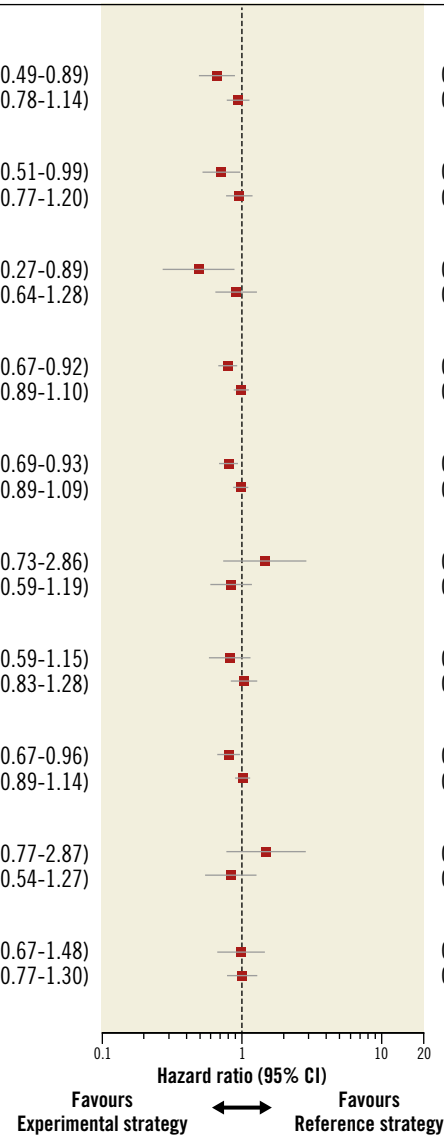

Figure 5. *The treatment effect of the experimental strategy versus the reference regimen stratified by TSL. The favourable treatment effect of the experimental strategy was observed in terms of POCE, NACE, and any revascularisation at two years in favour of patients with TSL ≥46 mm.*

should be weighed against the risk of stroke. Once PCI is considered as the preferred revascularisation strategy, every possible effort should be made to achieve optimal outcomes. One potential strategy in patients with long lesions is intravascular ultrasound-guided PCI[16]. Moreover, when patients receive longer stents, irrespective of the type of DES, optimal medical therapy for secondary prevention remains of paramount importance.

Currently, the ESC guidelines support a personalised approach regarding antiplatelet therapy after PCI[13]. In particular, prolonged (>12 months) DAPT may be a preferred strategy in patients with stent-driven ischaemic risks such as long stenting[13]. However, due to the systemic effect of an antiplatelet therapy, this anti-ischaemic efficacy is achieved at the expense of a significantly higher risk of bleeding[8], suggesting that an optimal antiplatelet regimen that can balance ischaemic and bleeding risk is warranted in this high ischaemic risk population. In the present study, the experimental strategy demonstrated a more potent anti-ischaemic efficacy without a trade-off in the risk of major bleeding in patients with long stenting. This negative result of bleeding was the amalgam between patients with stable CAD and ACS treated with different types of antiplatelet regimen. Specifically, in the experimental treatment group, patients with ACS had a state of high platelet reactivity[17], which could be neutralised by a single potent antiplatelet inhibition with ticagrelor even in the absence of aspirin, whereas in patients with stable CAD, in whom the platelet reactivity was assumed to be normal[17], the use of ticagrelor as monotherapy could lower the level of homeostasis excessively, leading to a borderline excess of bleeding. Conversely, in the reference

treatment group, ACS patients received a combination of ticagrelor and aspirin, and thereby platelet reactivity was certainly normalised, while in stable patients receiving a less potent antiplatelet therapy, namely clopidogrel, the risk of bleeding was not excessive even in conjunction with aspirin. Thus, the real benefit of ticagrelor monotherapy was confined to ACS patients with long stenting.

Limitations

The present results need to be interpreted bearing in mind the following limitations. First, this substudy was not predefined in the protocol of the trial. Together with the inherent limitations of subanalyses including multiple testing[14], the study findings should be considered as hypothesis-generating only and call for confirmatory randomised trials. Second, we did not collect the anatomic SYNTAX score in the whole population, precluding outcome assessment stratified according to the SYNTAX score. Third, data on overlapping were not available in our data set. However, a previous study has reported that overlap of second-generation DES was no longer associated with a higher risk of ischaemic events as compared to first-generation DES[18]. Fourth, secondary endpoints were site-reported, since the trial did not have a clinical adjudication committee for serious adverse events. However, seven on-site monitoring visits were performed in each participating centre, and 20% of reported events were checked according to source documents. In addition, the trial was monitored for event under-reporting and event definition consistency.

Conclusions

Patients with long stenting (defined as a TSL ≥46 mm) were associated with an increased risk of ischaemic events. In these patients, compared to the standard of care, one-month DAPT followed by 23-month ticagrelor monotherapy resulted in a significant reduction in the primary endpoint and POCE with a similar risk of BARC type 3 or 5 bleeding, thereby maximising a significant net clinical benefit at two years. The real benefits of the experimental strategy seem to be related to ACS patients with long stenting.

Impact on daily practice

The present study included the largest cohort (n=15,450) treated by default with Biolimus A9-eluting stents. When patients were divided into quartiles according to TSL per patient, the fourth quartile group (TSL ≥46 mm) had a significantly higher risk of POCE, predominantly driven by all-cause death, any MI, and any revascularisation. In that stratum (TSL ≥46 mm), the experimental strategy, when compared to the reference regimen, had a significantly reduced risk of the primary endpoint as well as POCE without trade-off in the risk of BARC type 3 or 5 bleeding, thereby achieving a significantly lower risk of NACE at two years. These significant benefits were mainly confined to the first year of the treatment and to ACS patients.

Guest Editor

This paper was guest edited by Alec Vahanian, MD, PhD; *Department of Cardiology, Hôpital Bichat-Claude Bernard, and University Paris VII, Paris, France*.

Appendix. Authors' affiliations

1. Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; 2. Division of Cardiology, Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand; 3. Department of Internal Medicine, Cardiology Division, University of Campinas (UNICAMP), Campinas, Brazil; 4. Department of Interventional Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands; 5. First Department of Cardiology, Medical University of Warsaw, Warsaw, Poland; 6. Tiefenauspital, Bern, Switzerland; 7. University Hospital Southampton, Southampton, and Faculty of Medicine, University of Southampton, Southampton, United Kingdom; 8. Städtische Kliniken Neuss, Lukaskrankenhaus GmbH, Neuss, Germany; 9. Schwarzwald-Baar Klinikum, Villingen-Schwenningen, Germany; 10. Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark; 11. Royal Blackburn Hospital, Blackburn, United Kingdom; 12. Cardialysis B.V., Rotterdam, the Netherlands; 13. Kerckhoff Campus, University of Giessen, Bad Nauheim, Germany; 14. FACT (French Alliance for Cardiovascular Trials), Université Paris-Diderot, Paris, France; 15. Biosensors Clinical Research, Morges, Switzerland; 16. Department of Cardiology, National University of Ireland, Galway, Ireland; 17. Department of Cardiology, University of Bern, Inselspital, Bern, Switzerland; 18. Jessa Ziekenhuis, Faculty of Medicine and Life Sciences at the Hasselt University, Hasselt, Belgium.

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Conflict of interest statement

R. Modolo reports research grants from the Sao Paulo Research Foundation (FAPESP grant number 2017/22013-8) and Biosensors. L. Holmvang reports being a local primary investigator in the GLOBAL LEADERS trial and institutional research contracts with AstraZeneca, MicroPort and Biosensors. M. Haude reports institutional grants/research support from Abbott and Biotronik, and honoraria or consultation fees from Biotronik, Cardiac Dimensions, OrbusNeich, and Philips. C. Hamm reports personal fees from AstraZeneca. H.P. Stoll is a full-time employee of Biosensors International. J.G.P. Tijssen reports personal fees from Cardialysis, for DSMB membership of the GLOBAL LEADERS trial during the conduct of the study. R.J. de Winter reports grants from AstraZeneca. M. Valgimigli reports grants and personal fees from Abbott, AstraZeneca and Terumo, and personal fees from Chiesi, Bayer, Daiichi Sankyo, Amgen, Alvimedica, Biosensors and Idorsia, and grants from Medicure, outside the submitted

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Supplementary data

Supplementary Figure 1. Cumulative frequency distribution curves of total stent length per patient.

Supplementary Table 1. Baseline characteristics of quartiles according to TSL per patient.

Supplementary Table 2. Two-year efficacy and safety outcomes and treatment effect of quartiles according to increasing TSL (Quartile 1: 8 ≤TSL ≤17; Quartile 2: 18 ≤TSL ≤27; Quartile 3: 28 ≤TSL ≤45; Quartile 4: 46 ≤TSL ≤231).

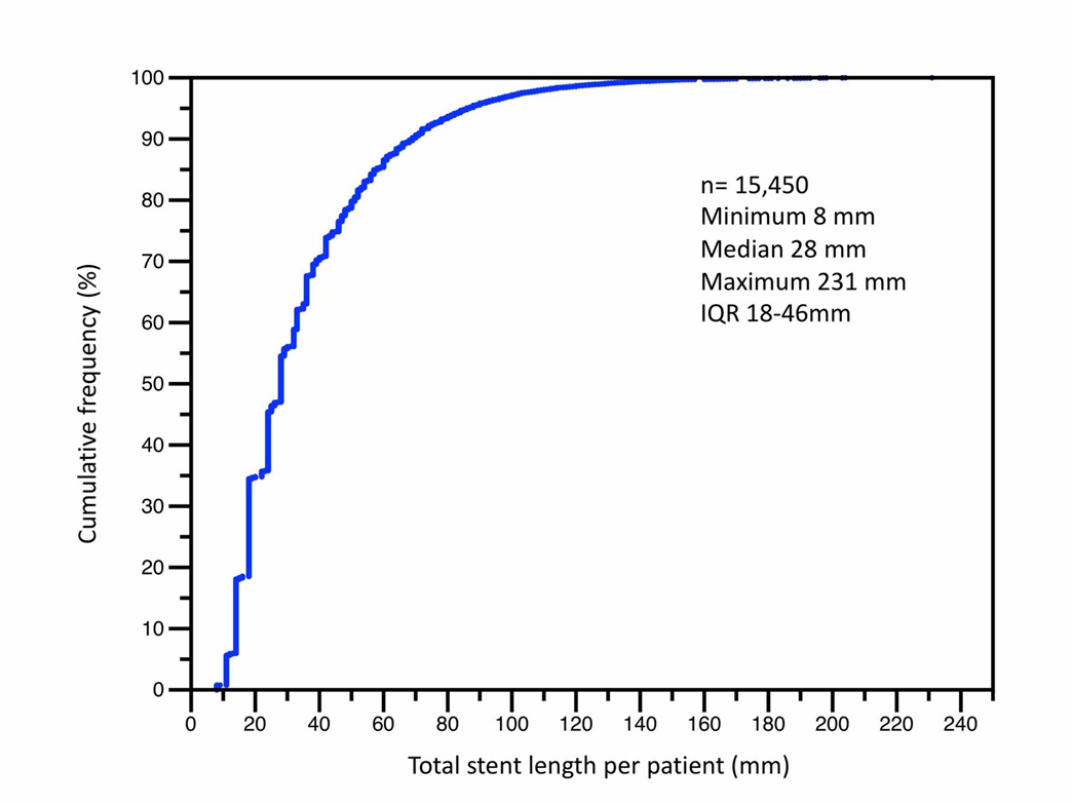
Supplementary Table 3. Clinical outcomes and treatment effect of the experimental versus reference strategy stratified by TSL per patient.

Supplementary Table 4. Clinical outcomes and treatment effect of the experimental versus reference strategy stratified by TSL per patient in patients with stable CAD.

Supplementary Table 5. Clinical outcomes and treatment effect of the experimental versus reference strategy stratified by TSL per patient in patients with ACS.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00498

Supplementary data



Supplementary Figure 1. Cumulative frequency distribution curves of total stent length per patient.

IQR: interquartile range

Supplementary Table 1. Baseline characteristics of quartiles according to TSL per patient.

	Quartile 1 [8 ≤TSL ≤17] (n=2,865)	Quartile 2 [18 ≤TSL ≤27] (n=4,397)	Quartile 3 [28 ≤TSL ≤45] (n=4,304)	Quartile 4 [46 ≤TSL ≤231] (n=3,884)	*p*-value
Randomised treatment					0.788
Experimental	49.9 (1,431/2,865)	49.6 (2,180/4,397)	50.6 (2,177/4,304)	49.7 (1,929/3,884)	
Reference	50.1 (1,434/2,865)	50.4 (2,217/4,397)	49.4 (2,127/4,304)	50.3 (1,955/3,884)	
Age (years)	65.29±10.31	63.85±10.4	64.4±10.26	64.89±10.15	<0.001
Gender					<0.001
Male	72.9 (2,089/2,865)	75.9 (3,337/4,397)	77.0 (3,314/4,304)	79.9 (3,103/3,884)	
Female	27.1 (776/2,865)	24.1 (1,060/4,397)	23.0 (990/4,304)	20.1 (781/3,884)	
BMI (kg/m^2)	28.1±4.5	28.2±4.7	28.2±4.5	28.2±4.6	0.399
Diabetes	25.8 (740/2,863)	23.5 (1,035/4,395)	24.6 (1,057/4,301)	27.0 (1,048/3,880)	0.002
Insulin-dependent diabetes mellitus	7.8 (224/2,857)	7.2 (316/4,382)	7.4 (317/4,293)	8.1 (315/3,872)	0.386
Hypertension	74.7 (2,130/2,853)	71.8 (3,146/4,380)	73.7 (3,165/4,293)	74.5 (2,883/3,870)	0.016
Hypercholesterolaemia	70.7 (1,929/2,730)	67.8 (2,893/4,264)	69.9 (2,921/4,180)	70.9 (2,685/3,788)	0.014
Current smoker	22.8 (654/2,865)	26.8 (1,177/4,397)	27.1 (1,166/4,304)	26.8 (1,039/3,884)	<0.001
PVD	6.3 (179/2,842)	5.9 (258/4,351)	6.2 (264/4,261)	6.8 (261/3,853)	0.465
COPD	4.7 (134/2,853)	5.4 (237/4,379)	4.5 (193/4,280)	5.7 (220/3,871)	0.054
Previous major bleeding	0.5 (15/2,859)	0.5 (22/4,394)	0.8 (34/4,298)	0.6 (25/3,878)	0.320
Impaired renal function*	14.1 (403/2,849)	13 (571/4,376)	13.6 (583/4,275)	14.1 (547/3,867)	0.438
Current smoker	3.1 (89/2,861)	2.4 (107/4,392)	2.2 (96/4,299)	2.8 (110/3,875)	0.088
Previous MI	24.2 (692/2,856)	22.0 (965/4,389)	24.3 (1,041/4,291)	22.1 (856/3,869)	0.015
Previous PCI	36.8 (1,054/2,861)	30.8 (1,351/4,393)	34.1 (1,467/4,301)	29.3 (1,136/3,881)	<0.001
Previous CABG	6.3 (179/2,861)	6.0 (262/4,395)	6.0 (256/4,300)	5.3 (207/3,882)	0.403
Clinical presentation					<0.001
Stable CAD	59.5 (1,705/2,865)	51.4 (2,258/4,397)	52.3 (2,252/4,304)	50.8 (1,975/3,884)	
ACS	40.5 (1,160/2,865)	48.6 (2,139/4,397)	47.7 (2,052/4,304)	49.2 (1,909/3,884)	
Overall					<0.001
UA	14.5 (416/2,865)	13.0 (573/4,397)	12.8 (550/4,304)	10.9 (424/3,884)	
NSTEMI	18.2 (521/2,865)	21.4 (939/4,397)	21.7 (933/4,304)	22.8 (886/3,884)	
STEMI	7.8 (223/2,865)	14.3 (627/4,397)	13.2 (569/4,304)	15.4 (599/3,884)	
Vascular access site					
Femoral	27.8 (797/2,865)	24.9 (1,094/4,355)	27.1 (1,165/4,304)	29.1 (1,130/3,884)	<0.001
Brachial	0.6 (17/2,865)	0.6 (25/4,397)	0.8 (35/4,304)	0.7 (28/3,884)	0.502
Radial	72.5 (2,076/2,865)	75.3 (3,312/4,397)	74.2 (3,195/4,239)	76.6 (2,974/3,884)	0.001

Lesions treated per patient					<0.001
One lesion	99.7 (2,857/2,865)	95.4 (4,194/4,397)	63.3 (2,726/4,304)	23.3 (904/3,884)	
Two lesions	0.3 (8/2,865)	4.5 (200/4,397)	34.5 (1,484/4,304)	45.7 (1,776/3,884)	
Three or more lesions	0 (0/2,865)	0.1 (3/4,397)	2.2 (94/4,304)	31.0 (1,204/3,884)	
Target lesions					<0.001
Left main	2.4 (69/2,873)	1.5 (67/4,603)	1.8 (107/5,978)	2.0 (167/8,466)	
LAD	40.7 (1,169/2,873)	44.0 (2,024/4,603)	42.5 (2,538/5,978)	38.7 (3,274/8,466)	
LCX	28.3 (812/2,873)	25.1 (1,154/4,603)	24.2 (1,447/5,978)	23.1 (1,953/8,466)	
RCA	27.1 (778/2,873)	28.1 (1,294/4,603)	30.6 (1,830/5,978)	35.7 (3,020/8,466)	
Bypass graft	1.6 (45/2,873)	1.4 (64/4,603)	0.9 (56/5,978)	0.6 (52/8,466)	
Biolimus A9-eluting stent	95.4 (2,742/2,873)	96.2 (4,428/4,603)	94.2 (5,629/5,978)	91.1 (7,715/8,466)	<0.001
Other stent	4.6 (131/2,873)	4.0 (182/4,603)	6.9 (413/5,978)	11.0 (928/8,466)	<0.001
Direct stenting	47.1 (1,354/ 2,873)	37.7 (1,735/4,603)	32.8 (1,961/5,978)	25.1 (2,129/8,466)	<0.001
Bifurcation	7.7 (222/2,873)	11.0 (507/4,603)	11.8 (708/5,978)	14.4 (1,221/8,466)	<0.001
Thrombus aspiration	3.7 (105/2,873)	6.3 (288/4,603)	4.9 (294/5,978)	3.8 (324/8,466)	<0.001
TIMI flow					
Pre-procedure					<0.001
0 or 1	7.4 (205/2,769)	13.6 (590/4,354)	12.6 (680/5,409)	15.1 (993/6,569)	
2	12.4 (342/2,769)	12.7 (554/4,354)	12.5 (676/5,409)	10.9 (715/6,569)	
3	80.2 (2,222/2,769)	73.7 (3,210/4,354)	74.9 (4,053/5,409)	74 (4,861/6,569)	
Post-procedure					<0.001
0 or 1	0.04 (1/2,812)	0.05 (2/4,438)	0.05 (3/5,538)	0.2 (12/6,784)	
2	0.1 (2/2,812)	0.3 (14/4,438)	0.4 (23/5,538)	0.7 (45/6,784)	
3	99.9 (2,809/2,812)	99.6 (4,422/4,438)	99.5 (5,512/5,538)	99.2 (6,727/6,784)	

Data are expressed as mean±standard deviation or percentage (number).

* Based on creatinine-estimated GFR (eGFR) clearance of <60 ml/min/1.73 m^2, using the Modification of Diet in Renal Disease (MDRD) formula.

ACS: acute coronary syndrome; BMI: body mass index; CABG: coronary artery bypass graft; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; LM: left main; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; PVD: peripheral vascular disease; RCA: right coronary artery; STEMI: ST-segment elevation myocardial infarction; TIMI: Thrombolysis In Myocardial Infarction; UA: unstable angina

Supplementary Table 2. Two-year efficacy and safety outcomes and treatment effect of quartiles according to increasing TSL (Quartile 1: 8 ≤TSL ≤17; Quartile 2: 18 ≤TSL ≤27; Quartile 3: 28 ≤TSL ≤45; Quartile 4: 46 ≤TSL ≤231).

	Event rates	Log-rank *p*-value	HR (95% CI)	*p*-value
Primary endpoint		0.073		
Quartile 1	3.60 (103/2,865)		Reference	
Quartile 2	4.12 (181/4,397)		1.15 (0.90-1.46)	0.266
Quartile 3	3.81 (164/4,304)		1.06 (0.83-1.36)	0.638
Quartile 4	4.74 (184/3,884)		1.33 (1.04-1.69)	0.021
All-cause mortality		0.035		
Quartile 1	2.34 (67/2,865)		Reference	
Quartile 2	3.00 (132/4,397)		1.29 (0.96-1.73)	0.093
Quartile 3	2.91 (125/4,304)		1.24 (0.92-1.67)	0.149
Quartile 4	3.56 (138/3,884)		1.53 (1.14-2.05)	0.004
New Q-wave MI		0.445		
Quartile 1	1.35 (38/2,865)		Reference	
Quartile 2	1.18 (51/4,397)		0.88 (0.58-1.33)	0.539
Quartile 3	0.97 (41/4,304)		0.72 (0.46-1.12)	0.144
Quartile 4	1.28 (49/3,884)		0.96 (0.63-1.47)	0.851
POCE		<0.001		
Quartile 1	11.24 (319/2,865)		Reference	
Quartile 2	11.54 (502/4,397)		1.03 (0.89-1.18)	0.688
Quartile 3	13.79 (588/4,304)		1.24 (1.09-1.43)	0.002
Quartile 4	16.52 (635/3,884)		1.53 (1.34-1.75)	<0.001
NACE		<0.001		
Quartile 1	12.82 (364/2,865)		Reference	
Quartile 2	12.48 (543/4,397)		0.97 (0.85-1.11)	0.674
Quartile 3	14.94 (637/4,304)		1.18 (1.04-1.34)	0.013
Quartile 4	18.04 (694/3,884)		1.46 (1.29-1.66)	<0.001
Any stroke		0.451		
Quartile 1	0.93 (26/2,865)		Reference	
Quartile 2	1.04 (45/4,397)		1.13 (0.70-1.84)	0.609
Quartile 3	1.23 (52/4,304)		1.34 (0.84-2.14)	0.227
Quartile 4	0.90 (34/3,884)		0.97 (0.58-1.62)	0.916
Any MI		0.023		
Quartile 1	2.59 (73/2,865)		Reference	
Quartile 2	2.69 (116/4,397)		1.04 (0.78-1.39)	0.799

Quartile 3	3.20 (135/4,304)		1.24 (0.93-1.65)	0.142
Quartile 4	3.68 (140/3,884)		1.44 (1.08-1.91)	0.012
Any revascularisation		<0.001		
Quartile 1	8.15 (229/2,865)		Reference	
Quartile 2	7.58 (326/4,397)		0.93 (0.78-1.10)	0.393
Quartile 3	9.61 (405/4,304)		1.19 (1.01-1.40)	0.036
Quartile 4	12.03 (456/3,884)		1.52 (1.30-1.78)	<0.001
Definite ST		0.068		
Quartile 1	0.46 (13/2,865)		Reference	
Quartile 2	0.74 (32/4,397)		1.61 (0.84-3.06)	0.149
Quartile 3	0.97 (41/4,304)		2.11 (1.13-3.93)	0.019
Quartile 4	0.97 (37/3,884)		2.12 (1.12-3.98)	0.020
BARC type 3 or 5 bleeding		0.077		
Quartile 1	2.23 (63/2,865)		Reference	
Quartile 2	1.74 (75/4,397)		0.78 (0.56-1.09)	0.140
Quartile 3	2.03 (86/4,304)		0.91 (0.66-1.26)	0.563
Quartile 4	2.54 (97/3,884)		1.15 (0.83-1.57)	0.398

Data are presented as percentage (number of events).

BARC: Bleeding Academic Research Consortium; CI: confidence interval; HR: hazard ratio; MI: myocardial infarction; NACE: net adverse clinical events; PCI: percutaneous coronary intervention; POCE: patient-oriented composite endpoint; ST: stent thrombosis; TSL: total stent length

Supplementary Table 3. Clinical outcomes and treatment effect of the experimental versus reference strategy stratified by TSL per patient.

	Longer TSL (≥46 mm) (n=3,884)				Shorter TSL (<46 mm) (n=11,566)				
	Experimental strategy (n=1,929)	Reference strategy (n=1,955)	Hazard ratio (95% CI)	*p*-value	Experimental strategy (n=5,788)	Reference strategy (n=5,778)	Hazard ratio (95% CI)	*p*-value	*p*-value for interaction
At one year									
Primary endpoint	2.13 (41/1,929)	3.48 (68/1,955)	0.61 (0.41-0.89)	0.012	1.85 (107/5,788)	2.15 (124/5,778)	0.86 (0.66-1.11)	0.256	0.141
All-cause mortality	1.56 (30/1,929)	2.35 (46/1,955)	0.66 (0.42-1.04)	0.075	1.26 (73/5,788)	1.42 (82/5,778)	0.89 (0.65-1.22)	0.464	0.292
New Q-wave MI	0.58 (11/1,929)	1.24 (24/1,955)	0.46 (0.23-0.94)	0.034	0.59 (34/5,788)	0.75 (43/5,778)	0.79 (0.50-1.24)	0.301	0.214
POCE	10.10 (193/1,929)	12.87 (250/1,955)	0.77 (0.64-0.93)	0.007	7.83 (449/5,788)	7.55 (434/5,778)	1.04 (0.91-1.18)	0.585	0.011
NACE	11.40 (218/1,929)	14.47 (281/1,955)	0.78 (0.65-0.93)	0.005	8.74 (501/5,788)	8.67 (498/5,778)	1.01 (0.89-1.14)	0.898	0.017
Any stroke	0.74 (14/1,929)	0.31 (6/1,955)	2.36 (0.91-6.15)	0.078	0.61 (35/5,788)	0.73 (42/5,778)	0.83 (0.53-1.31)	0.428	0.053
Any MI	2.42 (46/1,929)	3.11 (60/1,955)	0.77 (0.53-1.14)	0.189	2.05 (117/5,788)	1.54 (88/5,778)	1.34 (1.01-1.76)	0.041	0.024
Any revascularisation	7.77 (147/1,929)	9.69 (186/1,955)	0.79 (0.64-0.98)	0.034	5.68 (323/5,788)	5.40 (308/5,778)	1.05 (0.90-1.23)	0.528	0.037
Definite ST	0.94 (18/1,929)	0.46 (9/1,955)	2.03 (0.91-4.51)	0.083	0.56 (32/5,788)	0.54 (31/5,778)	1.03 (0.63-1.69)	0.898	0.159
BARC type 3 or 5 bleeding	1.89 (36/1,929)	2.13 (41/1,955)	0.89 (0.57-1.39)	0.610	1.37 (78/5,788)	1.56 (89/5,778)	0.88 (0.65-1.19)	0.398	0.958
BARC type 5	0.16 (3/1,929)	0.31 (6/1,955)	0.51 (0.13-2.02)	0.334	0.17 (10/5,788)	0.17 (10/5,778)	1.00 (0.42-2.40)	0.996	0.415
BARC type 3	1.73 (33/1,929)	1.98 (38/1,955)	0.88 (0.55-1.40)	0.592	1.26 (72/5,788)	1.47 (84/5,778)	0.86 (0.63-1.18)	0.340	0.929
Between one year and two years (landmark analysis at one year)									
Primary endpoint	1.70 (32/1,886)	2.28 (43/1,886)	0.74 (0.47-1.17)	0.202	1.96 (111/5,677)	1.88 (106/5,653)	1.04 (0.80-1.36)	0.758	0.209
All-cause mortality	1.42 (27/1,897)	1.83 (35/1,908)	0.77 (0.47-1.28)	0.318	1.51 (86/5,711)	1.46 (83/5,695)	1.03 (0.76-1.40)	0.831	0.334
New Q-wave MI	0.27 (5/1,886)	0.48 (9/1,886)	0.56 (0.19-1.66)	0.293	0.49 (28/5,677)	0.44 (25/5,653)	1.12 (0.65-1.91)	0.689	0.263
POCE	5.15 (88/1,709)	6.17 (104/1,685)	0.83 (0.63-1.10)	0.202	4.77 (251/5,263)	5.20 (275/5,292)	0.92 (0.77-1.09)	0.319	0.563
NACE	5.46 (92/1,685)	6.22 (103/1,655)	0.88 (0.66-1.16)	0.353	5.07 (264/5,209)	5.37 (281/5,228)	0.94 (0.80-1.12)	0.491	0.657

Any stroke	0.32 (6/1,861)	0.43 (8/1,881)	0.76 (0.26-2.19)	0.609	0.37 (21/5,603)	0.45 (25/5,605)	0.84 (0.47-1.50)	0.559	0.866
Any MI	0.93 (17/1,831)	0.93 (17/1,828)	1.00 (0.51-1.96)	0.999	0.85 (47/5,526)	1.29 (72/5,563)	0.66 (0.45-0.95)	0.025	0.284
Any revascularisation	3.24 (56/1,728)	3.93 (67/1,706)	0.82 (0.58-1.17)	0.280	2.97 (158/5,319)	3.20 (171/5,345)	0.93 (0.75-1.15)	0.499	0.568
Definite ST	0.22 (4/1,855)	0.32 (6/1,879)	0.68 (0.19-2.40)	0.545	0.12 (7/5,602)	0.28 (16/5,615)	0.44 (0.18-1.07)	0.069	0.584
BARC type 3 or 5 bleeding	0.65 (12/1,841)	0.43 (8/1,853)	1.51 (0.62-3.70)	0.366	0.61 (34/5,566)	0.41 (23/5,566)	1.48 (0.87-2.52)	0.145	0.971
BARC type 5	0.11 (2/1,871)	0.11 (2/1,886)	1.01 (0.14-7.15)	0.994	0.11 (6/5,632)	0.11 (6/5,639)	1.00 (0.32-3.11)	0.995	0.997
BARC type 3	0.65 (12/1,841)	0.43 (8/1,853)	1.51 (0.62-3.70)	0.366	0.56 (31/5,566)	0.38 (21/5,567)	1.48 (0.85-2.58)	0.165	0.969
At two years									
Primary endpoint	3.79 (73/1,929)	5.68 (111/1,955)	0.66 (0.49-0.89)	0.006	3.77 (218/5,788)	3.98 (230/5,778)	0.94 (0.78-1.14)	0.547	0.043
All-cause mortality	2.96 (57/1,929)	4.15 (81/1,955)	0.71 (0.51-0.99)	0.047	2.75 (159/5,788)	2.86 (165/5,778)	0.96 (0.77-1.20)	0.725	0.137
New Q-wave MI	0.85 (16/1,929)	1.72 (33/1,955)	0.49 (0.27-0.89)	0.018	1.09 (62/5,788)	1.19 (68/5,778)	0.91 (0.64-1.28)	0.588	0.076
POCE	14.75 (281/1,929)	18.26 (354/1,955)	0.79 (0.67-0.92)	0.003	12.24 (700/5,788)	12.37 (709/5,778)	0.99 (0.89-1.10)	0.860	0.017
NACE	16.25 (310/1,929)	19.80 (384/1,955)	0.80 (0.69-0.93)	0.004	13.38 (765/5,788)	13.58 (779/5,778)	0.98 (0.89-1.09)	0.760	0.025
Any stroke	1.06 (20/1,929)	0.74 (14/1,955)	1.45 (0.73-2.86)	0.289	0.99 (56/5,788)	1.18 (67/5,778)	0.84 (0.59-1.19)	0.325	0.163
Any MI	3.33 (63/1,929)	4.02 (77/1,955)	0.82 (0.59-1.15)	0.253	2.89 (164/5,788)	2.82 (160/5,778)	1.03 (0.83-1.28)	0.789	0.268
Any revascularisation	10.78 (203/1,929)	13.26 (253/1,955)	0.80 (0.67-0.96)	0.018	8.51 (481/5,788)	8.45 (479/5,778)	1.01 (0.89-1.14)	0.908	0.042
Definite ST	1.16 (22/1,929)	0.78 (15/1,955)	1.49 (0.77-2.87)	0.236	0.68 (39/5,788)	0.83 (47/5,778)	0.83 (0.54-1.27)	0.392	0.144
BARC type 3 or 5 bleeding	2.53 (48/1,929)	2.55 (49/1,955)	0.99 (0.67-1.48)	0.968	1.97 (112/5,788)	1.97 (112/5,778)	1.00 (0.77-1.30)	0.992	0.967
BARC type 5	0.26 (5/1,929)	0.42 (8/1,955)	0.63 (0.21-1.93)	0.421	0.28 (16/5,788)	0.28 (16/5,778)	1.00 (0.50-2.00)	0.996	0.493
BARC type 3	2.38 (45/1,929)	2.40 (46/1,955)	0.99 (0.66-1.49)	0.963	1.82 (103/5,788)	1.84 (105/5,778)	0.98 (0.75-1.29)	0.898	0.975

Data are presented as percentage (number of events).

BARC: Bleeding Academic Research Consortium; CI: confidence interval; HR: hazard ratio; MI: myocardial infarction; NACE: net adverse clinical events; PCI: percutaneous coronary intervention; POCE: patient-oriented composite endpoint; ST: stent thrombosis; TSL: total stent length

Supplementary Table 4. Clinical outcomes and treatment effect of the experimental versus reference strategy stratified by TSL per patient in patients with stable CAD.

	Longer TSL (≥46 mm)				Shorter TSL (<46 mm)				
	Experimental strategy (n=970)	Reference strategy (n=1,005)	Hazard ratio (95% CI)	*p*-value	Experimental strategy (n=3,114)	Reference strategy (n=3,101)	Hazard ratio (95% CI)	*p*-value	*p*-value for interaction
At two years									
Primary endpoint	3.92 (38/970)	5.48 (55/1,005)	0.71 (0.47-1.07)	0.103	3.54 (110/3,114)	3.94 (122/3,101)	0.90 (0.69-1.16)	0.410	0.342
All-cause mortality	3.09 (30/970)	3.58 (36/1,005)	0.86 (0.53-1.40)	0.546	2.35 (73/3,114)	2.68 (83/3,101)	0.88 (0.64-1.20)	0.407	0.955
New Q-wave MI	0.85 (8/970)	2.02 (20/1,005)	0.41 (0.18-0.94)	0.034	1.24 (38/3,114)	1.34 (41/3,101)	0.92 (0.59-1.43)	0.721	0.089
POCE	14.64 (140/970)	18.73 (187/1,005)	0.76 (0.61-0.95)	0.014	12.13 (373/3,114)	12.43 (382/3,101)	0.98 (0.85-1.13)	0.773	0.056
NACE	16.19 (155/970)	19.63 (196/1,005)	0.81 (0.65-0.998)	0.047	13.47 (414/3,114)	13.57 (417/3,101)	1.00 (0.87-1.14)	0.967	0.098
Any stroke	0.74 (7/970)	0.61 (6/1,005)	1.22 (0.41-3.62)	0.723	0.85 (26/3,114)	1.08 (33/3,101)	0.79 (0.47-1.32)	0.363	0.479
Any MI	3.05 (29/970)	3.63 (36/1,005)	0.83 (0.51-1.36)	0.466	2.45 (75/3,114)	2.43 (74/3,101)	1.02 (0.74-1.40)	0.921	0.508
Any revascularisation	10.58 (100/970)	14.19 (140/1,005)	0.73 (0.56-0.94)	0.016	8.80 (268/3,114)	8.70 (265/3,101)	1.01 (0.86-1.2)	0.870	0.034
Definite ST	1.15 (11/970)	0.71 (7/1,005)	1.64 (0.64-4.23)	0.307	0.65 (20/3,114)	0.65 (20/3,101)	1.00 (0.54-1.86)	0.999	0.389
BARC type 3 or 5 bleeding	2.63 (25/970)	1.52 (15/1,005)	1.74 (0.92-3.31)	0.088	2.06 (63/3,114)	1.67 (51/3,101)	1.24 (0.86-1.79)	0.258	0.360
BARC type 5	0 (0/970)	0.30 (3/1,005)	0.02 (0-171.31)	0.382	0.23 (7/3,114)	0.26 (8/3,101)	0.87 (0.32-2.41)	0.796	0.978
BARC type 3	2.63 (25/970)	1.32 (13/1,005)	2.01 (1.03-3.94)	0.041	1.90 (58/3,114)	1.51 (46/3,101)	1.26 (0.86-1.86)	0.237	0.236

Data are presented as percentage (number of events).

BARC: Bleeding Academic Research Consortium; CI: confidence interval; HR: hazard ratio; MI: myocardial infarction; NACE: net adverse clinical events; POCE: patient-oriented composite endpoint; ST: stent thrombosis; TSL: total stent length

Supplementary Table 5. Clinical outcomes and treatment effect of the experimental versus reference strategy stratified by TSL per patient in patients with ACS.

	Longer TSL (≥46 mm)				Shorter TSL (< 46 mm)				
	Experimental strategy (n=959)	Reference strategy (n=950)	Hazard ratio (95% CI)	*p*-value	Experimental strategy (n=2,674)	Reference strategy (n=2,677)	Hazard ratio (95% CI)	*p*-value	*p*-value for interaction
At two years									
Primary endpoint	3.66 (35/959)	5.90 (56/950)	0.61 (0.40-0.93)	0.023	4.04 (108/2,674)	4.04 (108/2,677)	1.00 (0.76-1.30)	0.992	0.055
All-cause mortality	2.82 (27/959)	4.74 (45/950)	0.59 (0.37-0.95)	0.030	3.22 (86/2,674)	3.06 (82/2,677)	1.05 (0.78-1.42)	0.753	0.045
New Q-wave MI	0.85 (8/959)	1.40 (13/950)	0.60 (0.25-1.46)	0.263	0.92 (24/2,674)	1.02 (27/2,677)	0.89 (0.51-1.54)	0.673	0.467
POCE	14.86 (141/959)	17.75 (167/950)	0.82 (0.66-1.03)	0.083	12.37 (327/2,674)	12.30 (327/2,677)	1.00 (0.86-1.17)	0.956	0.143
NACE	16.32 (155/959)	19.97 (188/950)	0.80 (0.64-0.98)	0.036	13.27 (351/2,674)	13.61 (362/2,677)	0.97 (0.84-1.12)	0.691	0.131
Any stroke	1.38 (13/959)	0.87 (8/950)	1.60 (0.66-3.85)	0.298	1.15 (30/2,674)	1.29 (34/2,677)	0.88 (0.54-1.45)	0.625	0.251
Any MI	3.61 (34/959)	4.45 (41/950)	0.81 (0.51-1.28)	0.362	3.40 (89/2,674)	3.28 (86/2,677)	1.04 (0.78-1.40)	0.780	0.358
Any revascularisation	10.99 (103/959)	12.26 (113/950)	0.89 (0.68-1.16)	0.380	8.17 (213/2,674)	8.15 (214/2,677)	1.00 (0.83-1.21)	0.995	0.474
Definite ST	1.17 (11/959)	0.86 (8/950)	1.35 (0.54-3.36)	0.515	0.72 (19/2,674)	1.02 (27/2,677)	0.71 (0.39-1.27)	0.245	0.239
BARC type 3 or 5 bleeding	2.43 (23/959)	3.67 (34/950)	0.66 (0.39-1.12)	0.127	1.87 (49/2,674)	2.31 (61/2,677)	0.80 (0.55-1.17)	0.257	0.554
BARC type 5	0.53 (5/959)	0.54 (5/950)	0.98 (0.28-3.39)	0.978	0.34 (9/2,674)	0.30 (8/2,677)	1.13 (0.44-2.93)	0.802	0.860
BARC type 3	2.12 (20/959)	3.57 (33/950)	0.59 (0.34-1.03)	0.065	1.72 (45/2,674)	2.23 (59/2,677)	0.76 (0.52-1.13)	0.174	0.462

Data are presented as percentage (number of events).

BARC: Bleeding Academic Research Consortium; CI: confidence interval; HR: hazard ratio; MI: myocardial infarction; NACE: net adverse clinical events; POCE: patient-oriented composite endpoint; ST: stent thrombosis; TSL: total stent length