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Title: Impact of Ticagrelor Monotherapy on Two-Year Clinical Outcomes in Patients with Long Stenting: A Post Hoc Analysis of the Global Leaders Trial.

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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

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Running title: Ticagrelor monotherapy in relation to long stents

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Abstract

[Aims]

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, multi-centre, open-label, randomised trial, investigating the impact of the experimental strategy (one-month dual antiplatelet regimen [DAPT] followed by 23-month ticagrelor monotherapy) versus the reference regimen (12-month DAPT followed by 12-month aspirin monotherapy) in patients with Biolimus A9-eluting stent (BES). The primary endpoint was the composite of the 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, and the fourth quartile group was at significantly higher ischemic risk at two years. In that stratum (TSL≥ 46mm), 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).

[Conclusion]

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

Condensed abstract

The present post-hoc study of the Global Leaders trial (n=15,450) evaluated the ischemic efficacy and bleeding safety of the experimental strategy (1-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 increasing total stent length (TSL). The experimental strategy showed a significantly reduced risk of the primary endpoint (composite of all-cause death and new Q-wave myocardial infarction) in patients with TSL≥46mm, but not in those with TSL<46mm, while maintaining a similar risk of BARC type 3 or 5 bleeding at two years.

[Keywords]

Stable angina; ACS/ NSTE-ACS; drug-eluting stent; Adjunctive pharmacotherapy

[Abbreviations list]

BARC=Bleeding Academic Research Consortium;

CAD=coronary artery disease;

NACE=net adverse clinical event;

POCE=patient-oriented composite endpoint;

TSL=total stent length;

Introduction

Increase in total lesion length or number of lesions treated result 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 revascularization (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 randomized controlled trials (RCT) has demonstrated that, compared with an abbreviated dual antiplatelet therapy (DAPT) regimen (3 or 6 months), prolonged (>12 months) DAPT significantly reduced major adverse cardiac events (MACE, the 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> 60mm[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 P2Y12 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-ischemic efficacy[9, 10]. Two recent randomized controlled trials (RCT), the STOPDAPT-2 and SMART-CHOICE, showed that, compared to 12-month DAPT, one- or three-month DAPT followed by P2Y12 inhibitor monotherapy was superior for bleeding and non-inferior for the composite ischemic endpoint at one-year follow-up. The aim

of this study is to evaluate the impact of 1-month DAPT followed by 23-month ticagrelor monotherapy vs. 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, multi-center, open-label, RCT (NCT01813435). Details of the study design and protocol have been reported previously[11]. In summary, the trial randomized patients undergoing PCI by default with BES (BioMatrix, Biosensors, Europe) in a 1:1 ratio to either (i) the experimental strategy consisting of 1-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, respectively.

The trial was approved by the institutional review board at each center 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 4.0mm with a stent length of 8, 11, 14, 18, 24, 28, 33, and 36mm. To evaluate the association between stent length and outcomes, groups are compared in quartiles according to a given TSL (quartile 1: 8 to 16mm; quartile 2: 18 to 27mm; quartile 3: 28 to 45mm; quartile 4: ≥ 46mm) 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 revascularization, 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 (ischemic and haemorrhagic), any MI (periprocedural or spontaneous with ST-elevation MI [STEMI] or Non-ST-elevation MI [NSTEMI]), and any revascularization (repeated PCI or coronary artery bypass grafting [CABG] surgery in target or non-target vessel). The third universal definition of MI was the recommended criteria 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 were assessed by an independent ECG core lab.

Statistical analysis

The analyses were performed according to 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 ratio (HR) with 95% confidence intervals (CI) was estimated using an unadjusted Cox regression model. The treatment effect of the experimental vs. the reference strategy between the subgroups was estimated using an unadjusted Cox regression model. To confirm whether the treatment effect of the experimental strategy vs. the reference regimen was significantly modified according to the longer TSL, we performed a multivariate analysis based on a cox proportional hazard regression model for the primary endpoint through the inclusion of randomized 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 vs. stable CAD) [12].

In addition, the one-year landmark analysis was reported using the pre-specified timepoint of one year (at the time of the planned cessation of a P2Y12 inhibitor in the reference strategy). The pre-specified stratified analysis according to clinical presentation (stable CAD or ACS) was performed since a different P2Y12 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 deviations (SD) or median and interquartile range (IQR), and were compared using Student's *t* tests or Mann-Whitney U test, respectively. Categorical variables were reported as percentages and numbers, and were compared using Chi-square or Fisher's exact test as appropriate. No adjustment was performed for multiple testing due to a post-hoc nature of the analysis [14]. All tests were two-

sided and a p-value of <0.05 is considered to be statistically significant. All statistical analyses were performed using SPSS Statistics, version 25 (IBM Corp., Armonk, 281 N.Y., USA).

Results

Patients

Between 1st July 2013 and 9th November 2015, at 130 hospitals in 18 countries (Europe, Asia, Brazil, Australia and Canada), the Global Leaders trial randomized a total of 15,991 patients, of whom 15,450 (96.6%) patients were included in this analysis. Among them, the cohort was subsequently divided into quartiles according to TSL per patient (**Figure 1, 2**). Cumulative frequency of TSL is presented in **Online Figure 1.**

Baseline characteristics and clinical outcomes according to TSL

Baseline characteristics according to the quartiles are presented in **Online Table 1**. Patients in quartile 4 were more likely to be male, and had a higher prevalence of diabetes and hypercholesterolemia 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 more prevalence of bifurcation and a greater number of stents implanted, which resulted in a greater TSL per patient.

Two-year clinical outcomes according to quartiles are presented in **Figure 3** and **Online Table 2**. There was a non-significant higher risk of the primary endpoint according to quartiles (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 quartiles (log-rank p=0.077).

Impact of the experimental strategy in patients with the longer TSL

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

Two-year efficacy and safety outcomes according to the randomized treatment allocation in patients with the longer TSL are presented in **Figure 4 and Online Table 3.** The treatment effect of the experimental strategy vs. 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 favor 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≥ 46mm. 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 the longer TSL.

The multivariable analysis confirmed that there was a significant interaction of the experimental strategy vs. 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 ischemic and bleeding endpoints in the second year (**Online Table 3**).

Stratified analysis according to clinical presentation

In stable CAD patients with the 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-ischemic 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) (**Online Table 4**).

Conversely, in ACS patients with the 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) (**Online Table 5**).

Discussion

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

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

(2) In patients with TSL≥ 46mm, 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 RCTs and large registries have shown that newer generations of DES have significantly reduced the risk of restenosis and the need for repeat revascularization. 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 revascularization (**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, malaposition, and overlapping, all of which may lead to incomplete endothelization and enhancing the stent-related ischemic risk [15]. Second, patients who require more and longer stents represent a more advanced state of CAD, which often results in incomplete revascularization with a subsequently increased risk of recurrent thrombotic events and 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 ischemic 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 revascularization modality either PCI or CABG. Specifically, the risk of repeated revascularization and recurrent MI should be weighed against the risk of stroke. Once PCI is considered as a preferred revascularization strategy, all the 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 received longer stents irrespective of the type of DES, optimal medical therapy for secondary prevention remains of paramount importance.

Currently, the ESC guidelines support a personalized approach regarding antiplatelet therapy after PCI [13]. In particular, prolonged (>12 months) DAPT may be a preferred strategy in patients with stent-driven ischemic risks such as long stenting[13]. However, due to the systemic effect of an antiplatelet therapy, this anti-ischemic efficacy is achieved at the expense of a significantly higher risk of bleeding[8], suggesting that an optimal antiplatelet regimen that can balance ischemic and bleeding risk is warranted in this high ischemic risk population. In the present study, the experimental strategy has demonstrated a more potent anti-ischemic 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 regimens. Specifically, in the experimental treatment group, patients with ACS had a state of high platelet reactivity[17], which could be neutralized 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 normalized, 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 benefits of ticagrelor monotherapy was confined to ACS patients with long stenting.

Limitations

The present results need to be interpreted in light of the following limitations. First, this sub-study was not pre-defined in the protocol of the trial. Together with the inherent limitations of sub-analyses including multiple testing[14], the study findings should be considered as hypothesis-generating only and call for confirmatory randomized 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 was not available in our dataset. However, a previous study has reported that overlap of second-generation DES was no longer associated with a higher risk of ischemic 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 center, 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.

Conclusion

Patients with long stenting (defined as TSL≥ 46mm) was associated with an increased risk of ischemic events. In these patients, compared to standard of care, 1-month DAPT followed by 23-month ticagrelor monotherapy could result in a significant reduction in the primary endpoint and POCE with a similar risk of BARC type 3 or 5 bleeding, thereby

maximizing 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≥ 46mm) had a significantly higher risk of POCE, predominantly driven by all-cause death, any MI, and any revascularization. In that stratum (TSL≥ 46mm), 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.

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

	Longer TSL (TSL≥ 46mm)		
	Experimental strategy	Reference strategy	p-value
Age (year)	64.9±10.3	64.8±10.0	0.742
Gender			0.516
Male	79.5 (1533/1929)	80.3 (1570/1955)	
Female	20.5 (396/1929)	19.7 (385/1955)	
Body mass index (kg/m^2)	28.2±4.6	28.2±4.7	0.747
Diabetes	28.9 (557/1927)	25.1 (491/1953)	0.008
Insulin dependent diabetes mellitus	8.5 (164/1923)	7.7 (151/1949)	0.379
Hypertension	75.5 (1451/1923)	73.5 (1432/1947)	0.184
Hypercholesterolemia	70.4 (1324/1882)	71.4 (1361/1906)	0.497
Current smoker	26.8 (517/1929)	26.7 (522/1955)	0.971
Peripheral vascular disease	6.1 (117/1917)	7.4 (144/1936)	0.109
Chronic obstructive pulmonary disease	5.3 (102/1924)	6.1 (118/1947)	0.331
Previous major bleeding	0.7 (13/1926)	0.6 (12/1952)	0.844
Impaired renal function	13.7 (264/1923)	14.6 (283/1944)	0.461
Previous stroke	2.7 (51/1924)	3.0 (59/1951)	0.500
Previous myocardial infarction	20.9 (402/1923)	23.3 (454/1946)	0.075
Previous percutaneous coronary intervention	28.9 (558/1929)	29.6 (578/1952)	0.647
Previous coronary artery bypass grafting	4.9 (94/1928)	5.8 (113/1954)	0.225
Clinical presentation			0.485
Stable coronary artery disease	50.3 (970/1929)	51.4 (1005/1955)	
Acute coronary syndrome	49.7 (959/1929)	48.6 (950/1955)	
Overall			0.499
Unstable angina	11.2 (216/1929)	10.6 (208/1955)	
Non-ST-elevation myocardial infarction	23.5 (454/1929)	22.1 (432/1955)	

ST-elevation myocardial infarction	15.0 (289/1929)	15.9 (310/1955)	
Vascular access site			
Femoral	28.4 (548/1929)	29.8 (582/1955)	0.358
Brachial	0.6 (12/1929)	0.8 (16/1955)	0.570
Radial	77.6 (1496/1929)	75.6 (1478/1955)	0.161
Lesions treated per patient			0.406
One lesion	23.5 (453/1929)	23.2 (453/1955)	
Two lesions	46.3 (894/1929)	44.7 (874/1955)	
Three or more lesions	30.2 (582/1929)	32.1 (628/1955)	
Treated lesions			0.598
Left main coronary artery	2.0 (82/4180)	2.0 (85/4286)	
Left anterior descending artery	39.2 (1640/4180)	38.1 (1634/4286)	
Left circumflex artery	22.7 (950/4180)	23.4 (1003/4286)	
Right coronary artery	35.4 (1478/4180)	36.0 (1542/4286)	
Bypass graft	0.7 (30/4180)	0.5 (22/4286)	
Mean stents per lesion	1.4±0.7	1.4±0.7	0.726
Biolimus A9-eluting stent	91.9 (3842/4180)	90.4 (3873/4286)	0.013
Other stent	10.2 (426/4180)	11.7 (502/4286)	0.026
Mean total stent length per lesion	32.5±18.3	32.4±18.3	0.706
Mean stent diameter per lesion	2.9±0.4	3.0±0.5	0.119
Direct stenting per lesion	25.2 (1053/4180)	25.1 (1076/4286)	0.940
Bifurcation involved	14.9 (624/4180)	13.9 (597/4286)	0.194
Thrombus aspiration	3.2 (134/4180)	4.4 (190/4286)	0.004
TIMI flow			
Pre-procedure			0.158
0 or 1	14.7 (475/3230)	15.5 (518/3339)	
2	10.5 (339/3230)	11.3 (376/3339)	
3	74.8 (2416/3230)	73.2 (2445/3339)	

Post-procedure			0.570
0 or 1	0.2 (6/3316)	0.2 (6/3468)	
2	0.7 (24/3316)	0.6 (21/3468)	
3	99.1 (3286/3316)	99.2 (3441/3468)	

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 legends

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 36mm). Colours indicate the quartile 1 (blue):8 to 16mm; quartile 2 (green):18 to 27mm; quartile 3 (orange):28 to 45mm; and quartile 4 (red): ≥ 46mm. Data are not shown in patients with total stent length >100 mm.

Figure 3. Clinical outcomes in quartiles according to TSL.

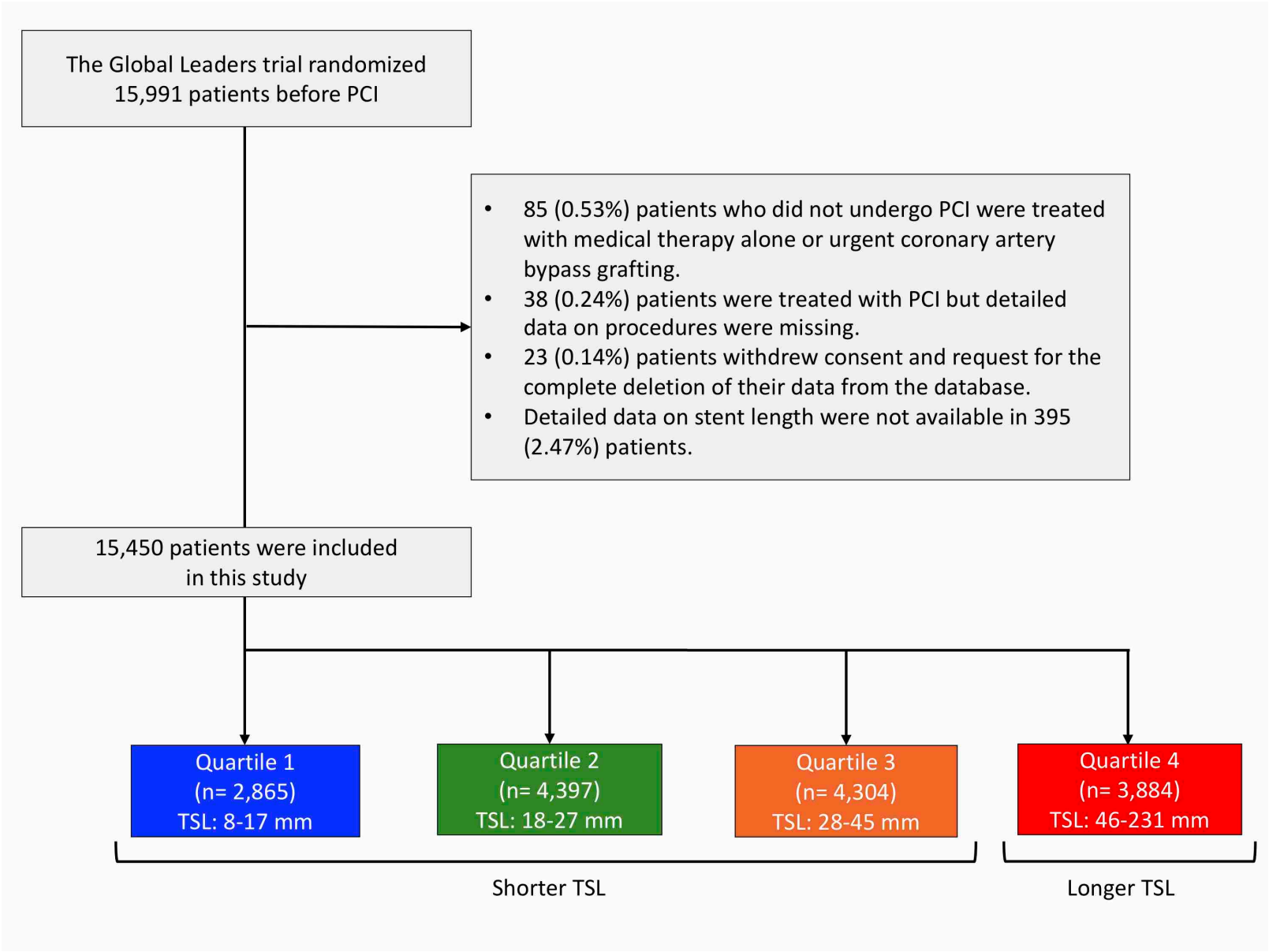
(A) POCE, (B) all-cause mortality, (C) any stroke, (D) any MI, (E) any revascularization (F) BARC type 3 or 5 bleeding.

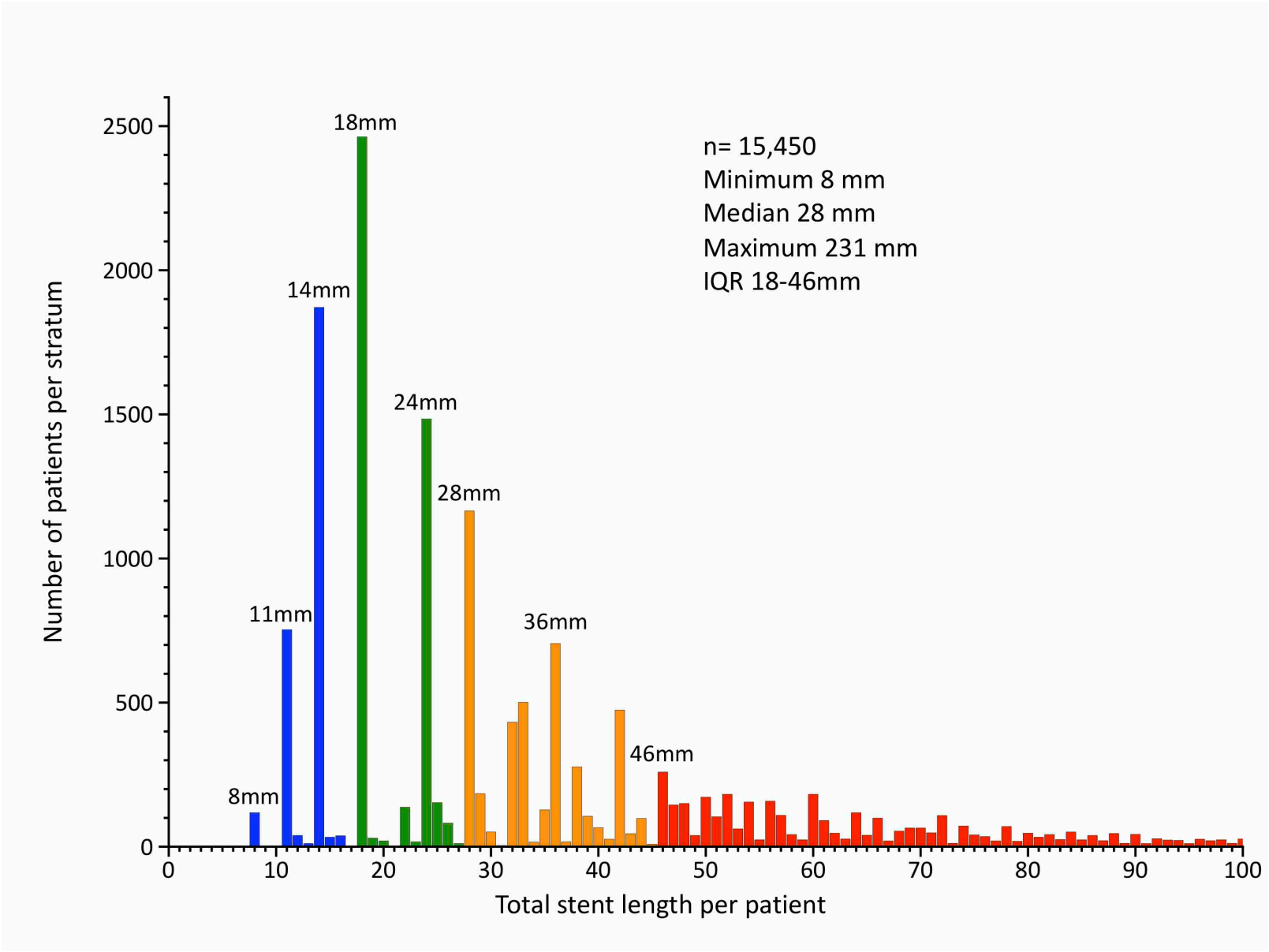
Figure 4. Clinical outcomes of the experimental strategy vs. the reference regimen in patients with the longer TSL.

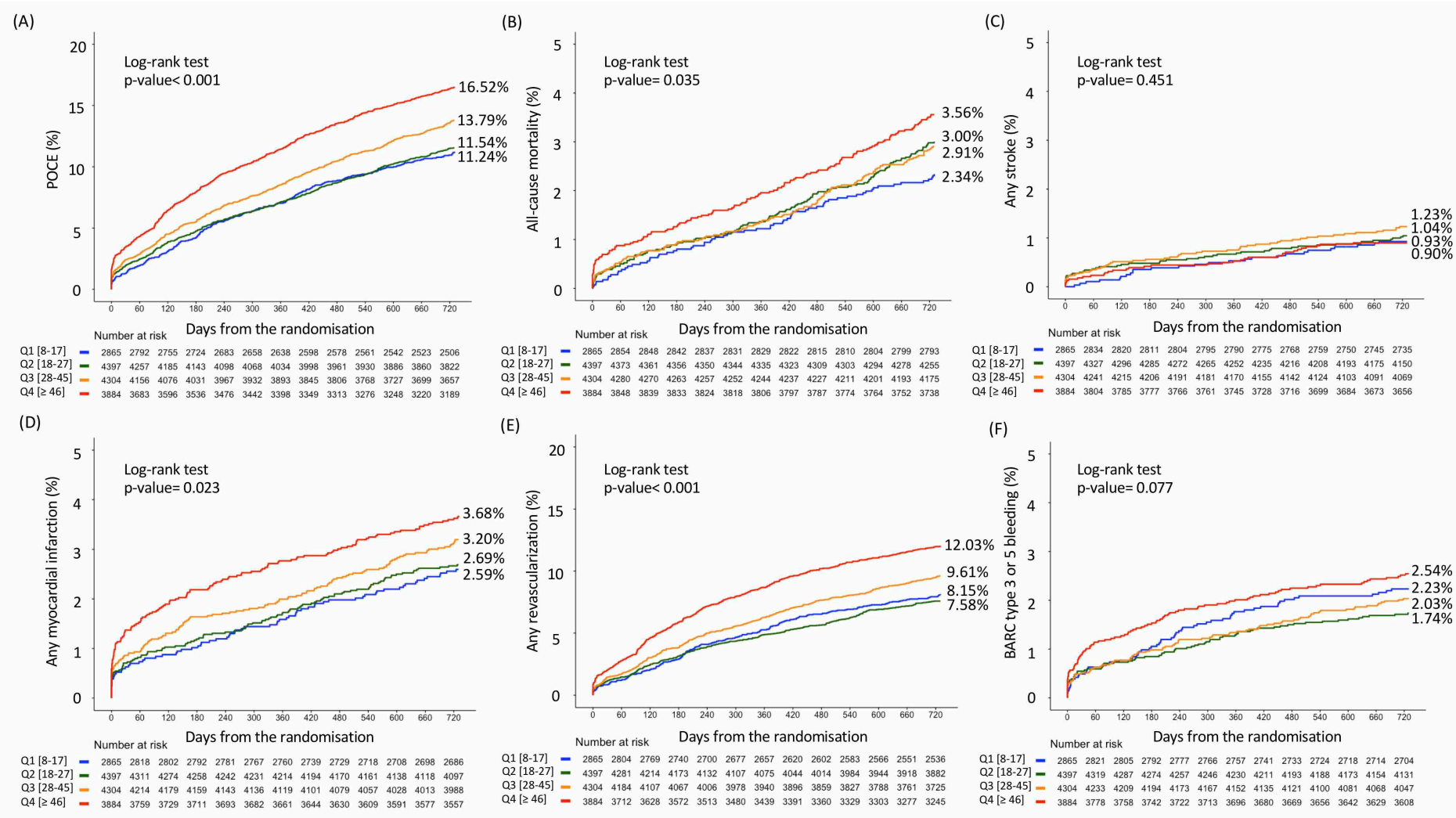
(A) POCE, (B) all-cause mortality, (C) any stroke, (D) any MI, (E) any revascularization (F) BARC type 3 or 5 bleeding.

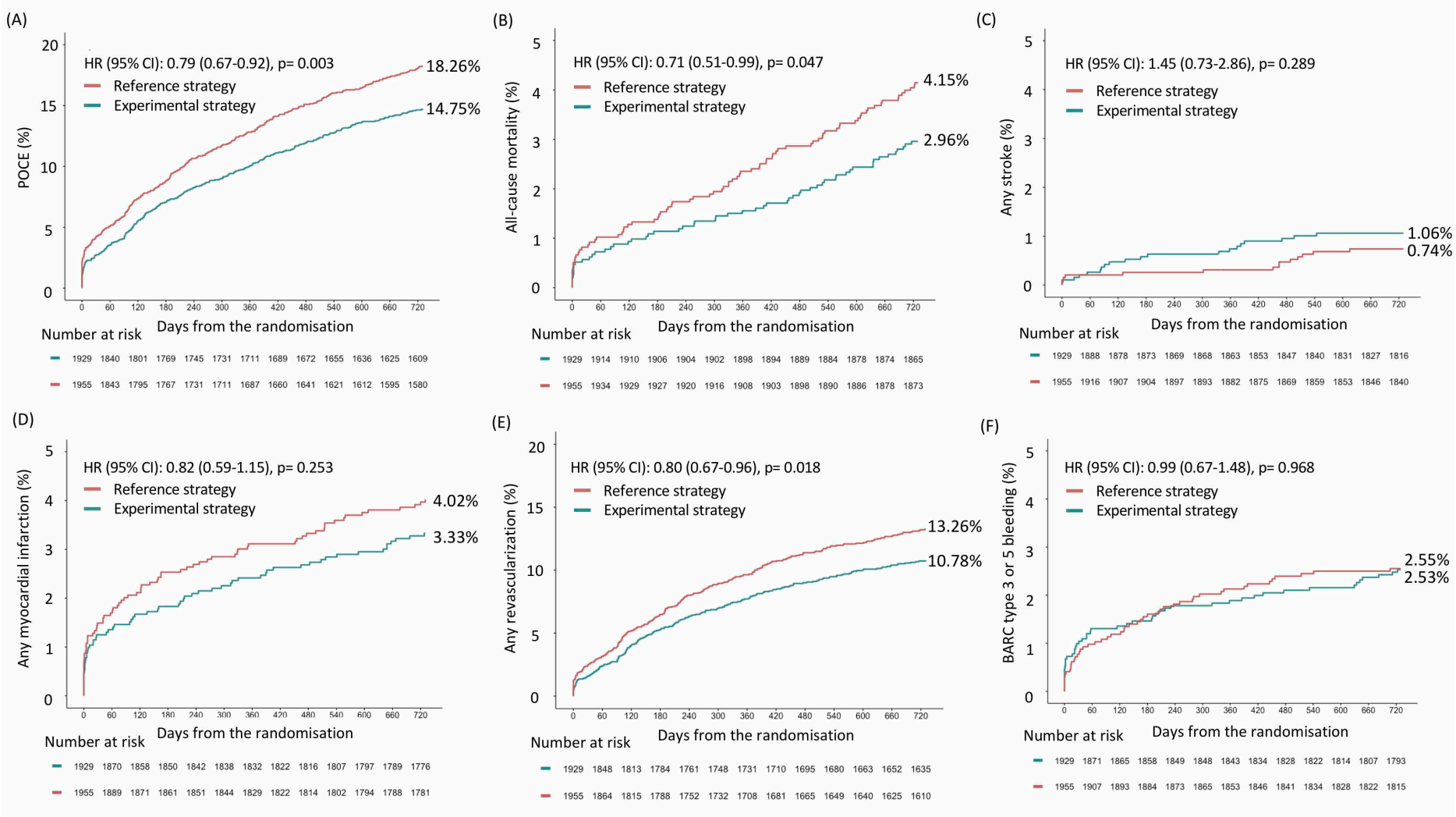
Figure 5. The treatment effect of the experimental strategy vs. the reference regimen stratified by TSL.

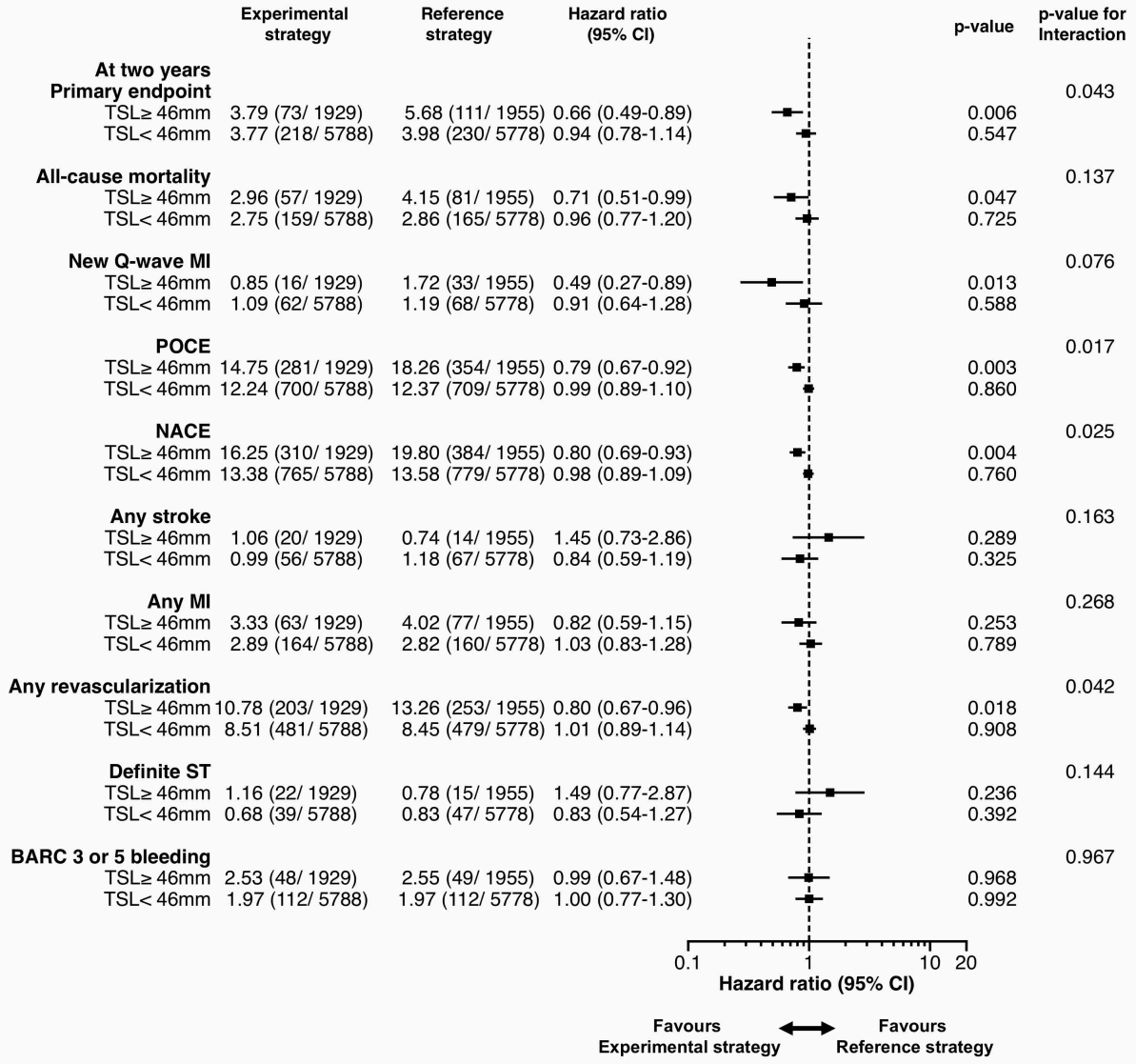
The favourable treatment effect of the experimental strategy was observed in terms of POCE, NACE, and any revascularization at two years in favour of patients with TSL≥ 46mm.











Online supplement

Figure legend

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

IQR: interquartile range.

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

	Quartile 1 [8≤ TSL≤ 16] (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
Randomized treatment					0.788
Experimental	49.9 (1431/ 2865)	49.6 (2180/ 4397)	50.6 (2177/ 4304)	49.7 (1929/ 3884)	
Reference	50.1 (1434/ 2865)	50.4 (2217/ 4397)	49.4 (2127/ 4304)	50.3 (1955/ 3884)	
Age (year)	65.29± 10.31	63.85± 10.4	64.4± 10.26	64.89± 10.15	<0.001
Gender					<0.001
Male	72.9 (2089/ 2865)	75.9 (3337/ 4397)	77.0 (3314/ 4304)	79.9 (3103/ 3884)	
Female	27.1 (776/ 2865)	24.1 (1060/ 4397)	23.0 (990/ 4304)	20.1 (781/ 3884)	
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/ 2863)	23.5 (1035/ 4395)	24.6 (1057/ 4301)	27.0 (1048/ 3880)	0.002
Insulin dependent diabetes mellitus	7.8 (224/ 2857)	7.2 (316/ 4382)	7.4 (317/ 4293)	8.1 (315/ 3872)	0.386
Hypertension	74.7 (2130/ 2853)	71.8 (3146/ 4380)	73.7 (3165/ 4293)	74.5 (2883/ 3870)	0.016
Hypercholesterolemia	70.7 (1929/ 2730)	67.8 (2893/ 4264)	69.9 (2921/ 4180)	70.9 (2685/ 3788)	0.014
Current smoker	22.8 (654/ 2865)	26.8 (1177/ 4397)	27.1 (1166/ 4304)	26.8 (1039/ 3884)	<0.001
PVD	6.3 (179/ 2842)	5.9 (258/ 4351)	6.2 (264/ 4261)	6.8 (261/ 3853)	0.465
COPD	4.7 (134/ 2853)	5.4 (237/ 4379)	4.5 (193/ 4280)	5.7 (220/ 3871)	0.054
Previous major bleeding	0.5 (15/ 2859)	0.5 (22/ 4394)	0.8 (34/ 4298)	0.6 (25/ 3878)	0.320

Impaired renal function*	14.1 (403/ 2849)	13 (571/ 4376)	13.6 (583/ 4275)	14.1 (547/ 3867)	0.438
Current smoker	3.1 (89/ 2861)	2.4 (107/ 4392)	2.2 (96/ 4299)	2.8 (110/ 3875)	0.088
Previous MI	24.2 (692/ 2856)	22.0 (965/ 4389)	24.3 (1041/ 4291)	22.1 (856/ 3869)	0.015
Previous PCI	36.8 (1054/ 2861)	30.8 (1351/ 4393)	34.1 (1467/ 4301)	29.3 (1136/ 3881)	<0.001
Previous CABG	6.3 (179/ 2861)	6.0 (262/ 4395)	6.0 (256/ 4300)	5.3 (207/ 3882)	0.403
Clinical presentation					<0.001
Stable CAD	59.5 (1705/ 2865)	51.4 (2258/ 4397)	52.3 (2252/ 4304)	50.8 (1975/ 3884)	
ACS	40.5 (1160/ 2865)	48.6 (2139/ 4397)	47.7 (2052/ 4304)	49.2 (1909/ 3884)	
Overall					<0.001
UA	14.5 (416/ 2865)	13.0 (573/ 4397)	12.8 (550/ 4304)	10.9 (424/ 3884)	
NSTEMI	18.2 (521/ 2865)	21.4 (939/ 4397)	21.7 (933/ 4304)	22.8 (886/ 3884)	
STEMI	7.8 (223/ 2865)	14.3 (627/ 4397)	13.2 (569/ 4304)	15.4 (599/ 3884)	
Vascular access site					
Femoral	27.8 (797/ 2865)	24.9 (1094/ 4355)	27.1 (1165/ 4304)	29.1 (1130/ 3884)	<0.001
Brachial	0.6 (17/ 2865)	0.6 (25/ 4397)	0.8 (35/ 4304)	0.7 (28/ 3884)	0.502
Radial	72.5 (2076/ 2865)	75.3 (3312/ 4397)	74.2 (3195/ 4239)	76.6 (2974/ 3884)	0.001
Lesions treated per patient					<0.001
One lesion	99.7 (2857/ 2865)	95.4 (4194/ 4397)	63.3 (2726/ 4304)	23.3 (904/ 3884)	
Two lesions	0.3 (8/ 2865)	4.5 (200/ 4397)	34.5 (1484/ 4304)	45.7 (1776/ 3884)	
Three or more lesions	0 (0/ 2865)	0.1 (3/ 4397)	2.2 (94/ 4304)	31.0 (1204/ 3884)	
Target lesions					<0.001
Left main	2.4 (69/ 2873)	1.5 (67/ 4603)	1.8 (107/ 5978)	2.0 (167/ 8466)	
LAD	40.7 (1169/ 2873)	44.0 (2024/ 4603)	42.5 (2538/ 5978)	38.7 (3274/ 8466)	
LCX	28.3 (812/ 2873)	25.1 (1154/ 4603)	24.2 (1447/ 5978)	23.1 (1953/ 8466)	
RCA	27.1 (778/ 2873)	28.1 (1294/ 4603)	30.6 (1830/ 5978)	35.7 (3020/ 8466)	
Bypass graft	1.6 (45/ 2873)	1.4 (64/ 4603)	0.9 (56/ 5978)	0.6 (52/ 8466)	
Biolimus A9-eluting stent	95.4 (2742/ 2873)	96.2 (4428/ 4603)	94.2 (5629/ 5978)	91.1 (7715/ 8466)	<0.001

Other stent	4.6 (131/ 2873)	4.0 (182/ 4603)	6.9 (413/ 5978)	11.0 (928/ 8466)	<0.001
Direct stenting	47.1 (1354/ 2873)	37.7 (1735/ 4603)	32.8 (1961/ 5978)	25.1 (2129/ 8466)	<0.001
Bifurcation	7.7 (222/ 2873)	11.0 (507/ 4603)	11.8 (708/ 5978)	14.4 (1221/ 8466)	<0.001
Thrombus aspiration	3.7 (105/ 2873)	6.3 (288/ 4603)	4.9 (294/ 5978)	3.8 (324/ 8466)	<0.001
TIMI flow					
Pre-procedure					<0.001
0 or 1	7.4 (205/ 2769)	13.6 (590/ 4354)	12.6 (680/ 5409)	15.1 (993/ 6569)	
2	12.4 (342/ 2769)	12.7 (554/ 4354)	12.5 (676/ 5409)	10.9 (715/ 6569)	
3	80.2 (2222/ 2769)	73.7 (3210/ 4354)	74.9 (4053/ 5409)	74 (4861/ 6569)	
Post-procedure					<0.001
0 or 1	0.04 (1/ 2812)	0.05 (2/ 4438)	0.05 (3/ 5538)	0.2 (12/ 6784)	
2	0.1 (2/ 2812)	0.3 (14/ 4438)	0.4 (23/ 5538)	0.7 (45/ 6784)	
3	99.9 (2809/ 2812)	99.6 (4422/ 4438)	99.5 (5512/ 5538)	99.2 (6727/ 6784)	

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 trial; UA: unstable angina.

Online Table 2. Two-year efficacy and safety outcomes and treatment effect of quartiles according to increasing TSL (Quartile 1: 8≤ TSL≤ 16; 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		
Quartile1	3.60 (103/ 2865)		Reference	
Quartile2	4.12 (181/ 4397)		1.15 (0.90-1.46)	0.266
Quartile3	3.81 (164/ 4304)		1.06 (0.83-1.36)	0.638
Quartile4	4.74 (184/ 3884)		1.33 (1.04-1.69)	0.021
All-cause mortality		0.035		
Quartile1	2.34 (67/ 2865)		Reference	
Quartile2	3.00 (132/ 4397)		1.29 (0.96-1.73)	0.093
Quartile3	2.91 (125/ 4304)		1.24 (0.92-1.67)	0.149
Quartile4	3.56 (138/ 3884)		1.53 (1.14-2.05)	0.004
New Q-wave MI		0.445		
Quartile1	1.35 (38/ 2865)		Reference	
Quartile2	1.18 (51/ 4397)		0.88 (0.58-1.33)	0.539
Quartile3	0.97 (41/ 4304)		0.72 (0.46-1.12)	0.144
Quartile4	1.28 (49/ 3884)		0.96 (0.63-1.47)	0.851
POCE		<0.001		
Quartile1	11.24 (319/ 2865)		Reference	
Quartile2	11.54 (502/ 4397)		1.03 (0.89-1.18)	0.688
Quartile3	13.79 (588/ 4304)		1.24 (1.09-1.43)	0.002
Quartile4	16.52 (635/ 3884)		1.53 (1.34-1.75)	<0.001
NACE		<0.001		
Quartile1	12.82 (364/ 2865)		Reference	
Quartile2	12.48 (543/ 4397)		0.97 (0.85-1.11)	0.674
Quartile3	14.94 (637/ 4304)		1.18 (1.04-1.34)	0.013
Quartile4	18.04 (694/ 3884)		1.46 (1.29-1.66)	<0.001

Any stroke		0.451		
Quartile1	0.93 (26/ 2865)		Reference	
Quartile2	1.04 (45/ 4397)		1.13 (0.70-1.84)	0.609
Quartile3	1.23 (52/ 4304)		1.34 (0.84-2.14)	0.227
Quartile4	0.90 (34/ 3884)		0.97 (0.58-1.62)	0.916
Any MI		0.023		
Quartile1	2.59 (73/ 2865)		Reference	
Quartile2	2.69 (116/ 4397)		1.04 (0.78-1.39)	0.799
Quartile3	3.20 (135/ 4304)		1.24 (0.93-1.65)	0.142
Quartile4	3.68 (140/ 3884)		1.44 (1.08-1.91)	0.012
Any revascularization		<0.001		
Quartile1	8.15 (229/ 2865)		Reference	
Quartile2	7.58 (326/ 4397)		0.93 (0.78-1.10)	0.393
Quartile3	9.61 (405/ 4304)		1.19 (1.01-1.40)	0.036
Quartile4	12.03 (456/ 3884)		1.52 (1.30-1.78)	<0.001
Definite ST		0.068		
Quartile1	0.46 (13/ 2865)		Reference	
Quartile2	0.74 (32/ 4397)		1.61 (0.84-3.06)	0.149
Quartile3	0.97 (41/ 4304)		2.11 (1.13-3.93)	0.019
Quartile4	0.97 (37/ 3884)		2.12 (1.12-3.98)	0.020
BARC type 3 or 5 bleeding		0.077		
Quartile1	2.23 (63/ 2865)		Reference	
Quartile2	1.74 (75/ 4397)		0.78 (0.56-1.09)	0.140
Quartile3	2.03 (86/ 4304)		0.91 (0.66-1.26)	0.563
Quartile4	2.54 (97/ 3884)		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.

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

	Longer TSL (≥ 46mm) (n= 3,884)				Shorter TSL (< 46mm) (n= 11,566)				
	Experimental strategy (n= 1929)	Reference Strategy (n= 1955)	Hazard ratio (95% CI)	p-value	Experimental strategy (n= 5788)	Reference Strategy (n= 5778)	Hazard ratio (95% CI)	p-value	p-value for interaction
At one year*									
Primary endpoint	2.13 (41/ 1929)	3.48 (68/ 1955)	0.61 (0.41-0.89)	0.012	1.85 (107/ 5788)	2.15 (124/ 5778)	0.86 (0.66-1.11)	0.256	0.141
All-cause mortality	1.56 (30/ 1929)	2.35 (46/ 1955)	0.66 (0.42-1.04)	0.075	1.26 (73/ 5788)	1.42 (82/ 5778)	0.89 (0.65-1.22)	0.464	0.292
New Q-wave MI	0.58 (11/ 1929)	1.24 (24/ 1955)	0.46 (0.23-0.94)	0.034	0.59 (34/ 5788)	0.75 (43/ 5778)	0.79 (0.50-1.24)	0.301	0.214
POCE	10.10 (193/ 1929)	12.87 (250/ 1955)	0.77 (0.64-0.93)	0.007	7.83 (449/ 5788)	7.55 (434/ 5778)	1.04 (0.91-1.18)	0.585	0.011
NACE	11.40 (218/ 1929)	14.47 (281/ 1955)	0.78 (0.65-0.93)	0.005	8.74 (501/ 5788)	8.67 (498/ 5778)	1.01 (0.89-1.14)	0.898	0.017
Any stroke	0.74 (14/ 1929)	0.31 (6/ 1955)	2.36 (0.91-6.15)	0.078	0.61 (35/ 5788)	0.73 (42/ 5778)	0.83 (0.53-1.31)	0.428	0.053
Any MI	2.42 (46/ 1929)	3.11 (60/ 1955)	0.77 (0.53-1.14)	0.189	2.05 (117/ 5788)	1.54 (88/ 5778)	1.34 (1.01-1.76)	0.041	0.024
Any revascularization	7.77 (147/ 1929)	9.69 (186/ 1955)	0.79 (0.64-0.98)	0.034	5.68 (323/ 5788)	5.40 (308/ 5778)	1.05 (0.90-1.23)	0.528	0.037
Definite ST	0.94 (18/ 1929)	0.46 (9/ 1955)	2.03 (0.91-4.51)	0.083	0.56 (32/ 5788)	0.54 (31/ 5778)	1.03 (0.63-1.69)	0.898	0.159
BARC type 3 or 5 bleeding	1.89 (36/ 1929)	2.13 (41/ 1955)	0.89 (0.57-1.39)	0.610	1.37 (78/ 5788)	1.56 (89/ 5778)	0.88 (0.65-1.19)	0.398	0.958
BARC type 5	0.16 (3/ 1929)	0.31 (6/ 1955)	0.51 (0.13-2.02)	0.334	0.17 (10/ 5788)	0.17 (10/ 5778)	1.00 (0.42-2.40)	0.996	0.415
BARC type 3	1.73 (33/ 1929)	1.98 (38/ 1955)	0.88 (0.55-1.40)	0.592	1.26 (72/ 5788)	1.47 (84/ 5778)	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/ 1886)	2.28 (43/ 1886)	0.74 (0.47-1.17)	0.202	1.96 (111/ 5677)	1.88 (106/ 5653)	1.04 (0.80-1.36)	0.758	0.209
All-cause mortality	1.42 (27/ 1897)	1.83 (35/ 1908)	0.77 (0.47-1.28)	0.318	1.51 (86/ 5711)	1.46 (83/ 5695)	1.03 (0.76-1.40)	0.831	0.334
New Q-wave MI	0.27 (5/ 1886)	0.48 (9/ 1886)	0.56 (0.19-1.66)	0.293	0.49 (28/ 5677)	0.44 (25/ 5653)	1.12 (0.65-1.91)	0.689	0.263
POCE	5.15 (88/ 1709)	6.17 (104/ 1685)	0.83 (0.63-1.10)	0.202	4.77 (251/ 5263)	5.20 (275/ 5292)	0.92 (0.77-1.09)	0.319	0.563
NACE	5.46 (92/ 1685)	6.22 (103/ 1655)	0.88 (0.66-1.16)	0.353	5.07 (264/ 5209)	5.37 (281/ 5228)	0.94 (0.80-1.12)	0.491	0.657
Any stroke	0.32 (6/ 1861)	0.43 (8/ 1881)	0.76 (0.26-2.19)	0.609	0.37 (21/ 5603)	0.45 (25/ 5605)	0.84 (0.47-1.50)	0.559	0.866
Any MI	0.93 (17/ 1831)	0.93 (17/ 1828)	1.00 (0.51-1.96)	0.999	0.85 (47/ 5526)	1.29 (72/ 5563)	0.66 (0.45-0.95)	0.025	0.284
Any revascularization	3.24 (56/ 1728)	3.93 (67/ 1706)	0.82 (0.58-1.17)	0.280	2.97 (158/ 5319)	3.20 (171/ 5345)	0.93 (0.75-1.15)	0.499	0.568
Definite ST	0.22 (4/ 1855)	0.32 (6/ 1879)	0.68 (0.19-2.40)	0.545	0.12 (7/ 5602)	0.28 (16/ 5615)	0.44 (0.18-1.07)	0.069	0.584
BARC type 3 or 5 bleeding	0.65 (12/ 1841)	0.43 (8/ 1853)	1.51 (0.62-3.70)	0.366	0.61 (34/ 5566)	0.41 (23/ 5566)	1.48 (0.87-2.52)	0.145	0.971
BARC type 5	0.11 (2/ 1871)	0.11 (2/ 1886)	1.01 (0.14-7.15)	0.994	0.11 (6/ 5632)	0.11 (6/ 5639)	1.00 (0.32-3.11)	0.995	0.997
BARC type 3	0.65 (12/ 1841)	0.43 (8/ 1853)	1.51 (0.62-3.70)	0.366	0.56 (31/ 5566)	0.38 (21/ 5567)	1.48 (0.85-2.58)	0.165	0.969
At two years									
Primary endpoint	3.79 (73/ 1929)	5.68 (111/ 1955)	0.66 (0.49-0.89)	0.006	3.77 (218/ 5788)	3.98 (230/ 5778)	0.94 (0.78-1.14)	0.547	0.043
All-cause mortality	2.96 (57/ 1929)	4.15 (81/ 1955)	0.71 (0.51-0.99)	0.047	2.75 (159/ 5788)	2.86 (165/ 5778)	0.96 (0.77-1.20)	0.725	0.137
New Q-wave MI	0.85 (16/ 1929)	1.72 (33/ 1955)	0.49 (0.27-0.89)	0.018	1.09 (62/ 5788)	1.19 (68/ 5778)	0.91 (0.64-1.28)	0.588	0.076
POCE	14.75 (281/ 1929)	18.26 (354/ 1955)	0.79 (0.67-0.92)	0.003	12.24 (700/ 5788)	12.37 (709/ 5778)	0.99 (0.89-1.10)	0.860	0.017
NACE	16.25 (310/ 1929)	19.80 (384/ 1955)	0.80 (0.69-0.93)	0.004	13.38 (765/ 5788)	13.58 (779/ 5778)	0.98 (0.89-1.09)	0.760	0.025

Any stroke	1.06 (20/ 1929)	0.74 (14/ 1955)	1.45 (0.73-2.86)	0.289	0.99 (56/ 5788)	1.18 (67/ 5778)	0.84 (0.59-1.19)	0.325	0.163
Any MI	3.33 (63/ 1929)	4.02 (77/ 1955)	0.82 (0.59-1.15)	0.253	2.89 (164/ 5788)	2.82 (160/ 5778)	1.03 (0.83-1.28)	0.789	0.268
Any revascularization	10.78 (203/ 1929)	13.26 (253/ 1955)	0.80 (0.67-0.96)	0.018	8.51 (481/ 5788)	8.45 (479/ 5778)	1.01 (0.89-1.14)	0.908	0.042
Definite ST	1.16 (22/ 1929)	0.78 (15/ 1955)	1.49 (0.77-2.87)	0.236	0.68 (39/ 5788)	0.83 (47/ 5778)	0.83 (0.54-1.27)	0.392	0.144
BARC type 3 or 5 bleeding	2.53 (48/ 1929)	2.55 (49/ 1955)	0.99 (0.67-1.48)	0.968	1.97 (112/ 5788)	1.97 (112/ 5778)	1.00 (0.77-1.30)	0.992	0.967
BARC type 5	0.26 (5/ 1929)	0.42 (8/ 1955)	0.63 (0.21-1.93)	0.421	0.28 (16/ 5788)	0.28 (16/ 5778)	1.00 (0.50-2.00)	0.996	0.493
BARC type 3	2.38 (45/ 1929)	2.40 (46/ 1955)	0.99 (0.66-1.49)	0.963	1.82 (103/ 5788)	1.84 (105/ 5778)	0.98 (0.75-1.29)	0.898	0.975

Data are presented as percentage (number of events).

Abbreviations are as in **Online Table 2.**

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

	Longer TSL (≥ 46mm)				Shorter TSL (< 46mm)				
	Experimental strategy (n= 970)	Reference Strategy (n= 1005)	Hazard ratio (95% CI)	p-value	Experimental strategy (n= 3114)	Reference Strategy (n= 3101)	Hazard ratio (95% CI)	p-value	p-value for interaction
At two years									
Primary endpoint	3.92 (38/ 970)	5.48 (55/ 1005)	0.71 (0.47-1.07)	0.103	3.54 (110/ 3114)	3.94 (122/ 3101)	0.90 (0.69-1.16)	0.410	0.342
All-cause mortality	3.09 (30/ 970)	3.58 (36/ 1005)	0.86 (0.53-1.40)	0.546	2.35 (73/ 3114)	2.68 (83/ 3101)	0.88 (0.64-1.20)	0.407	0.955
New Q-wave MI	0.85 (8/ 970)	2.02 (20/ 1005)	0.41 (0.18-0.94)	0.034	1.24 (38/ 3114)	1.34 (41/ 3101)	0.92 (0.59-1.43)	0.721	0.089
POCE	14.64 (140/ 970)	18.73 (187/ 1005)	0.76 (0.61-0.95)	0.014	12.13 (373/ 3114)	12.43 (382/ 3101)	0.98 (0.85-1.13)	0.773	0.056
NACE	16.19 (155/ 970)	19.63 (196/ 1005)	0.81 (0.65-0.998)	0.047	13.47 (414/ 3114)	13.57 (417/ 3101)	1.00 (0.87-1.14)	0.967	0.098
Any stroke	0.74 (7/ 970)	0.61 (6/ 1005)	1.22 (0.41-3.62)	0.723	0.85 (26/ 3114)	1.08 (33/ 3101)	0.79 (0.47-1.32)	0.363	0.479
Any MI	3.05 (29/ 970)	3.63 (36/ 1005)	0.83 (0.51-1.36)	0.466	2.45 (75/ 3114)	2.43 (74/ 3101)	1.02 (0.74-1.40)	0.921	0.508
Any revascularization	10.58 (100/ 970)	14.19 (140/ 1005)	0.73 (0.56-0.94)	0.016	8.80 (268/ 3114)	8.70 (265/ 3101)	1.01 (0.86-1.2)	0.870	0.034
Definite ST	1.15 (11/ 970)	0.71 (7/ 1005)	1.64 (0.64-4.23)	0.307	0.65 (20/ 3114)	0.65 (20/ 3101)	1.00 (0.54-1.86)	0.999	0.389
BARC type 3 or 5 bleeding	2.63 (25/ 970)	1.52 (15/ 1005)	1.74 (0.92-3.31)	0.088	2.06 (63/ 3114)	1.67 (51/ 3101)	1.24 (0.86-1.79)	0.258	0.360
BARC type 5	0 (0/ 970)	0.30 (3/ 1005)	0.02 (0-171.31)	0.382	0.23 (7/ 3114)	0.26 (8/ 3101)	0.87 (0.32-2.41)	0.796	0.978
BARC type 3	2.63 (25/ 970)	1.32 (13/ 1005)	2.01 (1.03-3.94)	0.041	1.90 (58/ 3114)	1.51 (46/ 3101)	1.26 (0.86-1.86)	0.237	0.236

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

	Longer TSL (≥ 46mm)				Shorter TSL (< 46mm)				
	Experimental strategy (n= 959)	Reference strategy (n= 950)	Hazard ratio (95% CI)	p-value	Experimental strategy (n= 2674)	Reference Strategy (n= 2677)	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/ 2674)	4.04 (108/ 2677)	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/ 2674)	3.06 (82/ 2677)	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/ 2674)	1.02 (27/ 2677)	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/ 2674)	12.30 (327/ 2677)	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/ 2674)	13.61 (362/ 2677)	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/ 2674)	1.29 (34/ 2677)	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/ 2674)	3.28 (86/ 2677)	1.04 (0.78-1.40)	0.780	0.358
Any revascularization	10.99 (103/ 959)	12.26 (113/ 950)	0.89 (0.68-1.16)	0.380	8.17 (213/ 2674)	8.15 (214/ 2677)	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/ 2674)	1.02 (27/ 2677)	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/ 2674)	2.31 (61/ 2677)	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/ 2674)	0.30 (8/ 2677)	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/ 2674)	2.23 (59/ 2677)	0.76 (0.52-1.13)	0.174	0.462

Online Figure 1.