Safety and Efficacy of 1-Month Dual Antiplatelet Therapy (Ticagrelor + Aspirin) Followed by 23-Month Ticagrelor Monotherapy in Patients Undergoing Staged Percutaneous Coronary Intervention (A Sub-Study from GLOBAL LEADERS)

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Safety and Efficacy of 1-month Dual Antiplatelet Therapy Followed by 23-Month Ticagrelor Monotherapy in Patients Undergoing Staged Percutaneous Coronary Intervention

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Structured Abstract

Objectives: To determine if patients undergoing staged percutaneous coronary intervention (SPCI) benefit from a novel aspirin-free antiplatelet regimen compared with standard dual antiplatelet therapy (DAPT).

Methods: The GLOBAL LEADERS is a multi-center, randomized, open-label trial, comparing the experimental strategy of 1-month DAPT (ticagrelor and aspirin) followed by 23-month ticagrelor monotherapy and the reference regimen of 12-month DAPT, followed by 12-month aspirin monotherapy in patients undergoing SPCI and non-SPCI (post hoc analysis). The primary endpoint was the composite of all-cause death or new Q-wave myocardial infarction at 2 years, and the key secondary safety endpoint was Bleeding Academic Research Consortium (BARC)-defined bleeding type 3 or 5.

Results: Of 15,968 randomized patients, a total of 1,651 patients underwent SPCI within 3 months. The rates of the primary and key secondary safety endpoints were similar between the 2 regimens. In CCS patients undergoing SPCI, the experimental strategy tended to increase the risk of all-cause death (4.1% vs 1.7%, HR 2.465; 95% CI 0.888-6.845, p=0.083, $P_{interaction}$=0.042). In ACS patients undergoing SPCI, the experimental strategy decreased the risks of BARC type 3 or 5 (1.8% vs 4.5%, HR 0.387; 95% CI 0.179-0.836, p=0.016, $P_{interaction}$=0.075) and BARC type 2, 3, or 5 bleeding (5.7% vs 11.2%, HR 0.496; 95% CI 0.317-0.776, p=0.002, $P_{interaction}$=0.011).

Conclusions:

In patients undergoing SPCI, one-month DAPT followed by 23-month ticagrelor monotherapy was associated with different safety profile depending on clinical presentation, with an increased risk of all-cause death in CCS and a reduced bleeding rates in ACS, achieved without a trade-off in the risk of ischemic events.

Trial registration number: NCT01813435

Keywords: staged percutaneous coronary intervention, antiplatelet regimen, dual antiplatelet therapy, ticagrelor monotherapy, and bleeding

Condensed Abstract

Optimal antiplatelet treatment regimens in patients undergoing staged percutaneous coronary intervention (SPCI) are debatable. Using the all-comers GLOBAL LEADERS population, whether patients undergoing SPCI benefit from a novel aspirin-free antiplatelet regimen was investigated. In patients undergoing SPCI, one-month dual antiplatelet therapy followed by 23-month ticagrelor monotherapy was associated with different safety profile depending on clinical presentation, with an increased risk of all-cause death in chronic coronary syndrome and a reduced bleeding rates in acute coronary syndrome, achieved without a trade-off in the risk of ischemic events.

Abbreviation:

DAPT: dual antiplatelet therapy

SPCI: staged percutaneous coronary intervention

ACS: acute coronary syndrome

CCS: chronic coronary syndrome

eCRF: electronic case report form

SAE: serious adverse events

MI: myocardial infarction

BARC: Bleeding Academic Research Consortium

POCE: patient-oriented composite endpoint

NACE: net adverse clinical endpoint

ARC: Academic Research Consortium

CABG: coronary artery bypass graft

IQR: interquartile range

HR: hazard ratio

CI: confidence interval

STEMI: ST-elevation myocardial infarction

Introduction

Dual antiplatelet therapy (DAPT) reduces the risk of stent-related and spontaneous recurrent ischemic events among patients undergoing percutaneous coronary intervention (PCI) (1). The potency and duration of DAPT after PCI are currently based mainly on clinical presentation (acute or chronic coronary syndromes) and the estimated bleeding risk (2) (3). An abbreviated DAPT regimen followed by P2Y12-receptor-antagonist monotherapy could favorably affect the balance between bleeding risks and ischemic benefits (4). Ticagrelor is a reversible and direct-acting oral antagonist of the P2Y12 receptor providing faster, greater, and more consistent platelet inhibition than clopidogrel (5).

Up to one-tenth of patients enrolled in PCI trials require more than one procedure to complete an intended percutaneous revascularization strategy due to multivessel coronary disease (6) (7) (8). It would be ideal, both from patient and societal (health care economic) perspectives, that all lesions requiring intervention are treated in a single session. However, there are legitimate clinical and nonclinical reasons that may justify a staged procedure (9). Interestingly, Spitzer et al showed that the time frame for staged procedure after the start of the index procedure defined in the recent randomized clinical trials was different from trial to trial (1 week to 3 month) (10). Extension of the time delay between the index and staged procedure would extend the duration of DAPT if a prespecified duration is imposed by a trial protocol or guidelines following the final staged procedure. In the latest European and American guidelines with regard to the duration of DAPT, there is no description related to staged procedure, and therefore optimal antiplatelet regimens after staged procedure have not yet been specifically evaluated (2) (11).

Our study sought to investigate whether patients undergoing staged procedure might benefit from a novel aspirin-free antiplatelet regimen compared to standard DAPT regimen in the GLOBAL LEADERS trial.

Methods

Study population

This analysis is a planned sub-study in the design paper of the GLOBAL LEADERS trial, a multi-center, prospective, and open-label randomized controlled trial (NCT01813435) (12). Details of the study design and protocol have been reported elsewhere (12). The trial randomly assigned patients before index PCI to either (i) the experimental strategy with 1-month DAPT (aspirin and ticagrelor) followed by 23-month ticagrelor monotherapy, or (ii) the reference regimen with 12-month DAPT (clopidogrel for chronic coronary syndrome [CCS] followed by 12-month aspirin monotherapy or aspirin and either ticagrelor for acute coronary syndrome [ACS], respectively) (13). Of note, patients with planned oral anticoagulation were excluded. All types of anatomic lesions (e.g. saphenous vein grafts, chronic total occlusions, in-stent restenosis etc) were included and treated by default with Biolimus A9-eluting stents (BioMatrix, Biosensors, Europe) of which the use was unrestricted in number, length and diameter.

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 gave written informed consent prior to participation in the trial.

Staged PCI

Staged PCI (SPCI) was defined as an intervention planned at the time of the index study procedure, according to the protocol of the GLOBAL LEADERS trial (**Figure 1**). When SPCI were inevitable for medical or logistic reasons, the reason was documented in the electronic case report form (eCRF) and patient file. In the "index procedure" form of the eCRF, the investigator indicated that the lesion to treat at SPCI was present at the time of the first procedure. The investigator also completed a "SPCI" form. SPCI had to be performed within 3 months of the start of the index procedure, and the patient had to receive the same type of study stent (Biolimus A9-eluting stents).

By design when a SPCI occurred outside the time window of 3 months (90 days) after the start of the index procedure, the procedure was considered to be a reintervention and reported as a revascularization event (**Online Figure 1**). In the case of SPCI in the experimental strategy, the 1-month treatment period with aspirin (and thus DAPT) had to be re-started after the staged procedure. On the other hand, in case of SPCI in the reference regimen, the 12-month DAPT time clock re-started at the time of the final staged procedure. Patients were followed after hospital discharge for up to 2 years after the index procedure (in case of a SPCI: for up to 2 years after the index procedure). This included 6 clinic visits (at 1 month, 3 months, 6 months, 1 year, 1.5 years, and 2 years) to obtain information regarding cardiovascular drug use, hospitalizations and serious adverse events (SAE). An assessment of the cardiovascular drug use and any SAE were recorded during clinical follow-up visits.

Adherence to the allocated antiplatelet treatment

At discharge and at the 6 clinical visits (1 month, 3 months, 6 months, 1 year, 1.5 years, and 2 years), information was requested from the patients regarding their adherence to

medication intake, including the antiplatelet regimen prescribed by the physician and the reason for discontinuation, duration and type of antiplatelet regimen prescribed (14). In addition, remote site monitoring was performed to ensure patient adherence to the protocol. Each six weeks as a minimum, the monitoring organization contacted each site to discuss the adherence to the allocated antiplatelet treatment.

Study endpoints

The primary endpoint was the composite of all-cause death or new Q-wave myocardial infarction (MI) at 2 years. Deaths from any cause were ascertained without adjudication (15). 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. According to the design of the GLOBAL LEADERS, the endpoint of all-cause mortality or new Q-wave MI evaluated by core lab was also assessed between 1 and 12 months. The electrocardiogram was collected at discharge, 3 months and 24 months and analyzed in the core lab. Whenever Q wave MI was detected at 24 months medical records during the study period were reviewed by independent assessor to determine the possible date of Q wave MI.

The key secondary safety endpoint was bleeding according to Bleeding Academic Research Consortium (BARC) criteria type 3 or 5 up to 2 years. Other secondary endpoints included individual components of the primary endpoint (all-cause death and non-fatal new Q-wave MI), any stroke, any MI, any revascularization, and definite stent thrombosis.

In addition, patient-oriented composite endpoint (POCE) and net adverse clinical endpoint (NACE) were evaluated at 2 years according to the Academic Research Consortium

(ARC)-2 definition (16) (17). POCE is defined as the composite of all-cause death, any stroke (ischemic, haemorrhagic or undetermined), any MI (periprocedural or spontaneous MI), and any revascularization (repeated PCI or coronary artery bypass graft [CABG] surgery in target or non-target vessel). MI were reported according to the third universal definition of MI, contemporary at the time of study design (12). NACE is defined as 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 stent thrombosis according to ARC definition (18), were reported non-hierarchically. All endpoints were site-reported, as the trial did not have a clinical adjudication committee for serious adverse events due to limited financial resources.

Statistical analysis

Continuous variables are reported as mean ± standard deviations or median and are compared using Student's *t* tests or Mann-Whitney U test, respectively. Categorical variables are reported as percentages and numbers and are compared using Chi-square or Fisher's exact test as appropriate.

All analyses are performed according to intention-to-treat principle. The cumulative incidence of clinical events up to 2 years is calculated using the Kaplan-Meier method and compared using the log-rank test. Hazard ratio (HR) with 95% confidence interval (CI) is estimated using a Cox proportional regression model. The treatment effect of the experimental strategy versus the reference regimen between the 2 groups is estimated using a Cox regression model. In addition, a pre-specified subgroup analysis according to clinical presentation (CCS or ACS) is performed, since P2Y12 inhibitors in the reference regimen were different according clinical presentation (12).

All tests are two-sided and a p-value of <0.05 is considered to be statistically significant. No adjustment for multiple testing is performed in view of the post-hoc nature of the analysis (19). All data were processed using SPSS version 26.0 (IBM Inc, Armonk, NY, USA).

Results

Participants

The GLOBAL LEADERS trial enrolled 15,991 patients at 130 hospitals in 18 countries between July 2013 and November 2015 in an all-comers design: no restriction regarding the clinical presentation of patients, the complexity of lesions or the number of stents used (20). Flow chart of the present study is shown in **Figure 2**. Twenty-three patients withdrew consent and requested data deletion from the database, leaving 15,968 patients in the present analysis. After randomization, 1,651 patients received SPCI according to the protocol of the trial. Of these, 847 patients were assigned in the experimental strategy and 804 patients were assigned in the reference regimen.

Baseline characteristics in patients undergoing SPCI and non-SPCI

Baseline patient and procedural characteristics in patients undergoing SPCI and non-SPCI were shown in **Online Table 1**. Male gender was more frequently observed in the SPCI group than in the non-SPCI group. Patients in the SPCI group were less likely to have comorbidities (hypercholesterolaemia and a history of MI, PCI, and CABG), whereas they were current smoker more frequently. The frequency of ACS (unstable angina, non-ST-elevation myocardial infarction [NSTEMI], and STEMI) was higher in the SPCI group than the non-SPCI group.

Angiographically, treated lesion numbers and treated lesions were significantly different between the 2 groups. Of note, multivessel treatment and bifurcation treatment were more frequently observed in the SPCI group compared to the non-SPCI group.

Clinical outcomes in patients undergoing SPCI and non-SPCI

Clinical outcomes at 2 years in patients undergoing SPCI and non-SPCI are shown in **Online Table 2**. The risks of the primary and key secondary endpoints were similar between the 2 groups. However, the multivariate Cox regression model demonstrated that the risks of all-cause death (3.5% vs 2.9%, HR 1.437 [95% CI 1.020-2.025, p=0.038), POCE (17.2% vs 13.2%, HR 1.388 [95% CI 1.186-1.625, p<0.001), any revascularization (13.2% vs 9.2%, HR 1.515 [95% CI 1.263-1.817, p<0.001), BARC type 2, 3, or 5 bleeding (8.0% vs 6.5%, HR 1.261 [95% CI 1.006-1.581, p=0.044), and NACE (18.7% vs 14.5%, HR 1.365 [95% CI 1.174-1.588, p<0.001) were higher in the SPCI group than the non-SPCI group.

Baseline patient and procedural characteristics according to the antiplatelet regimen in patients undergoing SPCI

Baseline patient characteristics according to the antiplatelet regimen in patients understanding SPCI are shown in the **Table 1**. There was no significant difference between the 2 regimens.

At index PCI, thrombus aspiration was less frequently used in the experimental strategy than the reference regimen (7.8% vs 11.0%, p=0.011), whereas the frequency of STEMI was numerically higher, but not significantly different, in the experimental strategy (25.5% vs 21.5%, p=0.055) (**Table 2**).

At SPCI, treated lesions were significantly different between the 2 groups (left main coronary artery: 1.8% [experimental strategy] vs 2.6% [reference regimen], left anterior descending artery: 36.7% vs 31.2%, left circumflex artery: 27.9% vs 26.7%, right coronary artery: 33.5% vs 38.9%, and bypass graft: 0.1% vs 0.6%, p=0.009) (**Table 3**).

Adherence during clinical follow-up visits to the allocated antiplatelet regimen between patients undergoing SPCI and non-SPCI

At 3 months of the clinical follow-up visit, adherence rate of the allocated antiplatelet regimen was significantly lower in patients undergoing SPCI with experimental strategy than in those with non-SPCI (77.7% vs 87.0%, p<0.001) (**Table 4**). At the other follow-up visits, there was no difference in adherence rate.

Impact of the experimental strategy in relation to SPCI

The Kaplan-Meier curves of NACE, all-cause death, any MI, any revascularization, BARC type 3 or 5 bleeding, and BARC type 2, 3, or 5 bleeding at 2-year follow up according to the randomized antiplatelet regimen in patients undergoing SPCI are presented in **Online Figure 2**. The treatment effect of the experimental strategy versus the reference regimen in patients undergoing SPCI and non-SPCI is presented in **Online Figure 3**. At 2 years, the risks of the primary and key secondary endpoints were similar between the 2 regimens, as were the risk of all other bleeding and ischemic endpoints.

Stratified analysis according to clinical presentation (CCS or ACS)

In patients undergoing SPCI, irrespective of clinical presentation (CCS or ACS), there was no significant difference in the primary endpoint at 2 years between the two anti-platelet regimens.

However in CCS patients undergoing SPCI, the experimental strategy trended toward an increasing risk of all-cause death (4.1% vs 1.7%, HR 2.465; 95% CI 0.888-6.845, p=0.083), and that numerical difference was not seen in patients with non-SPCI (SPCI vs non-SPCI, $P_{interaction}$=0.042) (**Figure 3**).

In ACS patients undergoing SPCI, the risks of NACE (15.0% vs 20.4%, HR 0.707 [95% CI 0.526-0.951, p=0.022), which was mainly derived from BARC type 3 or 5 bleeding (1.8% vs 4.5%, HR 0.387 [95% CI 0.179-0.836, p=0.016), and BARC type 2, 3, or 5 bleeding (5.7% vs 11.2%, HR 0.496 [95% CI 0.317-0.776, p=0.002) were significantly lower amongst patients receiving the experimental strategy. The treatment effect (reduction of bleeding) was specially prominent for BARC type 2, 3, or 5 bleeding, and the effect was not seen in patients with non-SPCI (SPCI vs non-SPCI, $P_{interaction}$=0.011) (**Figure 4**).

Discussions

The present study compared and assessed 2-year clinical outcomes of patients treated with 1-month DAPT followed by 23-month ticagrelor monotherapy and 12-month DAPT regimen followed by 12-month aspirin monotherapy after SPCI in the GLOBAL LEADERS trial. The main findings of this study can be summarized as follows:

1. In our cohort, patients undergoing SPCI had a higher risk of all-cause death, POCE, any revascularization, BARC type 2, 3, or 5 bleeding, and NACE up to 2 years than patients with non-SPCI.

2. Overall in patients undergoing SPCI, the risks of the primary and key secondary endpoint were similar between the experimental and reference regimen, as were the risks of all other bleeding and ischemic events.
3. When stratified according to clinical presentation, patients with CCS undergoing SPCI tended to have a higher risk of all-cause death in the experimental strategy, whereas ACS patients undergoing SPCI had a significantly lower risk of NACE in the experimental strategy group, mainly due to lower BARC type 3, or 5 bleeding, and BARC type 2, 3, or 5 bleeding.

Given the association between extent and complexity of coronary artery disease and subsequent higher rates of adverse events (7), the need to identify and provide patients at higher-risk of ischemic events with an optimal treatment is of paramount importance. In the present study, at the index procedure, the rate of PCI with complex lesions was higher in patients undergoing SPCI compared with the other patients. This high frequency of complex PCI could inherently affect the 2-year ischemic event rate (21). Although in the randomized EXCEL trial, which compared PCI to CABG in patients with unprotected left main coronary artery disease, SPCI showed a borderline reduction of all-cause death up to 3 years by multivariate analysis (HR 0.14; 95% CI 0.02 to 1.01; p=0.051) (8), it must be emphasised that the sample sizes of patients undergoing SPCI with treated left main artery disease in both trials (EXCEL: 77 patients and GLOBAL LEADERS: 62 patients) are underpowered to draw any valid conclusion.

Regarding bleeding events, well-established predictors of bleeding events such as age, impaired renal function and vascular access were comparable between the staged and non-SPCI group. However, it is conceivable that SPCI led to further bleeding events since at the time of the staged procedure, vascular access had to be re-established while on potent antiplatelet regimen,

either DAPT or ticagrelor monotherapy Of note, in the present study, at 3-month clinical follow-up visit, adherence rate of the experimental strategy was lower in patients undergoing SPCI than those with non-SPCI. In case of ticagrelor discontinuation due to adverse effects other than bleeding (i.e. atrioventricular block, dyspnea), patients could be switched to a standard dose of prasugrel in both antiplatelet regimens (12). As described in the primary publication of the GLOBAL LEADERS trial, dyspnea was a common reason for non-adherence of ticagrelor (20). Besides multifactorial cause for non-adherence to the experimental strategy at 3 months in patients undergoing SPCI, the reintervention itself might also impact the protocol based DAPT duration.

In the present study, the experimental strategy trended toward an increased risk of all-cause death in CCS patients undergoing SPCI versus non-SPCI. One explanation of this result is that the rates of BARC type 3 or 5 bleeding was numerically higher in CCS patients undergoing SPCI. Of note, the THEMIS trial also demonstrated that the incidence of the long-term major bleeding was higher in the ticagrelor plus aspirin group than the aspirin monotherapy group in CCS patients (22). Previous studies have shown that major bleeding is a common adverse event after PCI and is associated with increased morbidity and mortality (23) (24). Bleeding predictors have been described extensively; they are related mostly to the patient's clinical characteristics, the invasiveness of the procedure, and the potency of the antithrombotic regimen. As indicated in the updated European guideline, clopidogrel was recommended and ticagrelor discouraged in CCS patients, regardless of the bleeding risk (2). The present result might suggest that ticagrelor monotherapy for patients with CCS was harmful due to an increased risk of major bleeding, and therefore at staged procedure, the re-instauration of experimental strategy (DAPT with ticagrelor followed by ticagrelor monotherapy) in CCS should be discouraged as well as the antiplatelet

regimen including ticagrelor in CCS at index procedure. However, recent publication reported that ticagrelor 60mg or 90mg twice-daily provided greater and more consistent platelet inhibition on cellular uptake as well as platelet reactivity than clopidogrel in CCS patients undergoing elective PCI (25), and possibly, reduced ticagrelor 60mg twice-daily would be warranted to decrease bleeding events.

On the other hand, in ACS patients undergoing SPCI, the frequency of BARC type 3 or 5 bleeding was significantly lower in the experimental strategy than the reference regimen. Since the duration of DAPT according to the protocol of the GLOBAL LEADERS trial was reset at the final staged procedure (12), irrespective of the timing of staged procedure, execution of SPCI made the duration of DAPT extended both in patients randomized to the experimental or the reference regimen. Several studies reported that long-term DAPT after placement of a drug-eluting stent was associated with an increased risk of bleeding events compared to short-term DAPT (1) (26). Recently, Tomaniak et al have also demonstrated that between 1 month and 12 months after PCI in ACS patients – the time-frames when a direct comparison of aspirin versus aspirin and ticagrelor therapy was possible by the study protocol – aspirin was associated with increased bleeding risk and appeared not to add to the benefit of ticagrelor on ischemic events (27). Ticagrelor monotherapy after 1-month DAPT in ACS patients undergoing SPCI could provide a clinical benefit up to 2 years as a risk reduction of bleeding events, and importantly, this anti-bleeding safety was achieved without a trade-off in an increased risk of ischemic events.

Limitations

The present study has several limitations. First, although planned in the design paper of the GLOBAL LEADERS trial, the study is a post hoc analysis of a neutral randomized

controlled study. Inherent subgroup analysis limitations, including the risk of multiple testing, cannot be excluded. Therefore, our findings should be considered as strictly hypothesis-generating. Further, all secondary clinical endpoints were site-reported; the trial did not have a central clinical adjudication committee for serious adverse events due to limited financial resources. However, seven on-site monitoring visits were performed in each participating center, and 20% of the reported events were checked according to the source documents. In addition, the rate of site reported BARC type 3 bleeding in the GLOBAL LEADERS trial and the rate of adjudicated BARC type 3 bleeding in the GLOBAL LEADERS adjudication sub-study (GLASSY) were similar (28) (29). A fact indicating that any serious issue of reclassification is highly unlikely.

Conclusions

After SPCI, one-month DAPT followed by 23-month ticagrelor monotherapy might be associated with different safety profile depending on the clinical presentation, with an increased risk of all-cause death in CCS and reduced bleeding in ACS, achieved without a trade-off in the risk of ischemic events.

Clinical Perspective:

What is known?

Although all lesions requiring intervention would ideally be treated in a single session both from patient and societal (health care economic) perspectives, SPCI might be necessary due to legitimate clinical and nonclinical reasons. To date, optimal antiplatelet regimens after SPCI have not yet been specifically evaluated.

What is new?

Our study investigated whether patients undergoing SPCI benefit from a novel aspirin-free antiplatelet regimen compared with standard DAPT regimen using the all-comers GLOBAL LEADERS population. One-month DAPT followed by 23-month ticagrelor monotherapy might be associated with different safety profile depending on the clinical presentation, with an increased risk of all-cause death in CCS and reduced bleeding in ACS, achieved without a trade-off in the risk of ischemic events.

What is next?

The results of the present study should be considered hypothesis-generating. Ideally, optimal antiplatelet regimens based on the clinical presentation in patients undergoing SPCI would be prospectively evaluated in an adequately powered randomized trial.

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571 **Table 1. Baseline patient characteristics according to the antiplatelet regimen in patients undergoing staged PCI**

	Overall N=1651	Experimental strategy N=847	Reference regimen N=804	p value
Age	65.0 ± 9.9	65.0 ± 9.9	64.9 ± 9.9	0.885
Male	1315 (79.8%)	650 (80.8%)	665 (78.5%)	0.239
Body mass index, kg/m²	28.1 ± 4.5	28.0 ± 4.4	28.2 ± 4.5	0.342
Medical history				
Diabetes mellitus	431 (26.1%)	195 (24.3%)	236 (27.9%)	0.092
Insulin-dependent diabetes mellitus	140 (8.5%)	62 (7.7%)	78 (9.3%)	0.269
Hypertension	1223 (74.6%)	584 (73.1%)	639 (76.1%)	0.166
Hypercholesterolemia	1060 (67.4%)	508 (66.1%)	552 (68.6%)	0.305
Previous stroke	50 (3.0%)	27 (3.4%)	23 (2.7%)	0.449
Previous myocardial infarction	300 (18.2%)	146 (18.2%)	154 (18.3%)	0.945
Previous PCI	382 (23.2%)	177 (22.0%)	205 (24.2%)	0.298
Previous coronary artery bypass grafting	59 (3.6%)	28 (3.5%)	31 (3.7%)	0.846
Peripheral vascular disease	96 (5.9%)	46 (5.8%)	50 6.0%)	0.857
Chronic obstructive pulmonary disease	74 (4.5%)	37 (4.6%)	37 (4.4%)	0.830
Previous major bleeding	15 (0.9%)	7 (0.9%)	8 (0.9%)	0.873
Current smoker	500 (30.3%)	237 (29.5%)	263 (31.1%)	0.487
Impaired renal function *	219 (13.3%)	94 (11.7%)	125 (14.8%)	0.065
Clinical presentation				
Chronic coronary syndrome	634 (38.4%)	295 (36.7%)	339 (40.0%)	0.164
Acute coronary syndrome	1017 (61.6%)	509 (63.3%)	508 (60.0%)	0.164
Unstable angina	236 (14.3%)	115 (14.3%)	121 (14.3%)	0.992
Non-ST-elevation myocardial infarction	394 (23.9%)	189 (23.5%)	205 (24.2%)	0.740
ST-elevation myocardial infarction	387 (23.4%)	205 (25.5%)	182 (21.5%)	0.055

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573 Values are expressed as n (%) or mean ± standard deviation.

574 * Defined as an estimated glomerular filtration rate of creatinine clearance of <60 mL/min per 1.73 m^2 based on the Modification of

575 Diet in Renal Disease formula.

576 PCI: percutaneous coronary intervention

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589 **Table 2. Procedural characteristics at index procedure in patients undergoing staged PCI**

	Overall N=1651	Experimental strategy N=847	Reference regimen N=804	p value
Access site				0.997
Radial	1198 (72.6%)	614 (72.5%)	584 (72.6%)	
Femoral	451 (27.3%)	232 (27.4%)	219 (27.2%)	
Brachial	2 (0.1%)	1 (0.1%)	1 (0.1%)	
Lesions treated per patient				0.970
One lesion	1173 (72.4%)	602 (72.6%)	571 (72.2%)	
Two lesions	369 (22.8%)	188 (22.7%)	181 (22.9%)	
Three lesions or more	78 (4.8%)	39 (4.7%)	39 (4.9%)	
Treated lesions				0.891
n (lesions)	2157	1103	1054	
Left main coronary artery	20 (0.9%)	10 (0.9%)	10 (0.9%)	
Left anterior descending artery	820 (38.0%)	415 (37.6%)	405 (38.4%)	
Left circumflex artery	523 (24.2%)	267 (24.2%)	256 (24.3%)	
Right coronary artery	780 (36.2%)	402 (36.4%)	378 (35.9%)	
Bypass graft *	14 (0.6%)	9 (0.8%)	5 (0.5%)	
Stented lesions				
Number of stents	1.3 ± 0.6	1.3 ± 0.6	1.3 ± 0.6	0.581
Biolimus A9-eluting stent	2005 (94.8%)	1035 (95.5%)	970 (94.0%)	0.125
Mean total stent length per lesion, mm	2.98 ± 0.44	2.97 ± 0.43	3.00 ± 0.45	0.232
Mean stent diameter per lesion, mm	28.5 ± 15.8	28.6 ± 16.2	28.3 ± 15.5	0.680
Direct stenting per lesion	562 (26.6%)	283 (26.1%)	279 (27.0%)	0.334
Bifurcation per lesion	324 (15.0%)	169 (15.3%)	155 (14.7%)	0.689
Thrombus aspiration done per lesion	202 (9.4%)	86 (7.8%)	116 (11.0%)	0.011

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Values are expressed as n (%) or mean ± standard deviation.

* Grafts counted as one separate vessel.

PCI: percutaneous coronary intervention

608 **Table 3. Procedural characteristics at staged procedure in patients undergoing staged PCI**

	Overall N=1651	Experimental strategy N=847	Reference regimen N=804	p value
Vascular access site				0.781
Radial	1007 (67.7%)	520 (68.2%)	487 (67.3%)	
Femoral	477 (32.1%)	242 (31.7%)	235 (32.5%)	
Brachial	3 (0.2%)	1 (0.1%)	2 (0.3%)	
Lesions treated per patient				0.209
One lesion	1122 (75.9%)	574 (75.5%)	548 (76.2%)	
Two lesions	291 (19.7%)	158 (20.8%)	133 (18.55)	
Three lesions or more	66 (4.5%)	28 (3.7%)	38 (5.3%)	
Treated lesions				0.009
n (lesions)	1916	980	936	
Left main coronary artery	42 (2.2%)	18 (1.8%)	24 (2.6%)	
Left anterior descending artery	652 (34.0%)	360 (36.7%)	292 (31.2%)	
Left circumflex artery	523 (27.3%)	273 (27.9%)	250 (26.7%)	
Right coronary artery	692 (36.1%)	328 (33.5%)	364 (38.9%)	
Bypass graft *	7 (0.4%)	1 (0.1%)	6 (0.6%)	
Stented lesions				
Number of stents	1.2 ± 0.6	1.2 ± 0.7	1.2 ± 0.6	0.579
Biolimus A9-eluting stent	1490 (82.0%)	755 (81.4%)	735 (82.8%)	0.433
Mean total stent length per lesion, mm	2.88 ± 0.44	2.88 ± 0.44	2.89 ± 0.45	0.446
Mean stent diameter per lesion, mm	26.9 ± 15.5	27.1 ± 15.9	26.7 ± 15.2	0.591
Direct stenting per lesion	615 (33.9%)	304 (32.8%)	311 (35.0%)	0.308
Bifurcation per lesion	236 (12.3%)	122 (12.4%)	114 (12.2%)	0.858
Thrombus aspiration done per lesion	12 (0.6%)	4 (0.4%)	8 (0.9%)	0.216

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610 Values are expressed as n (%) or mean ± standard deviation.

611 * Grafts counted as one separate vessel.

612 PCI: percutaneous coronary intervention

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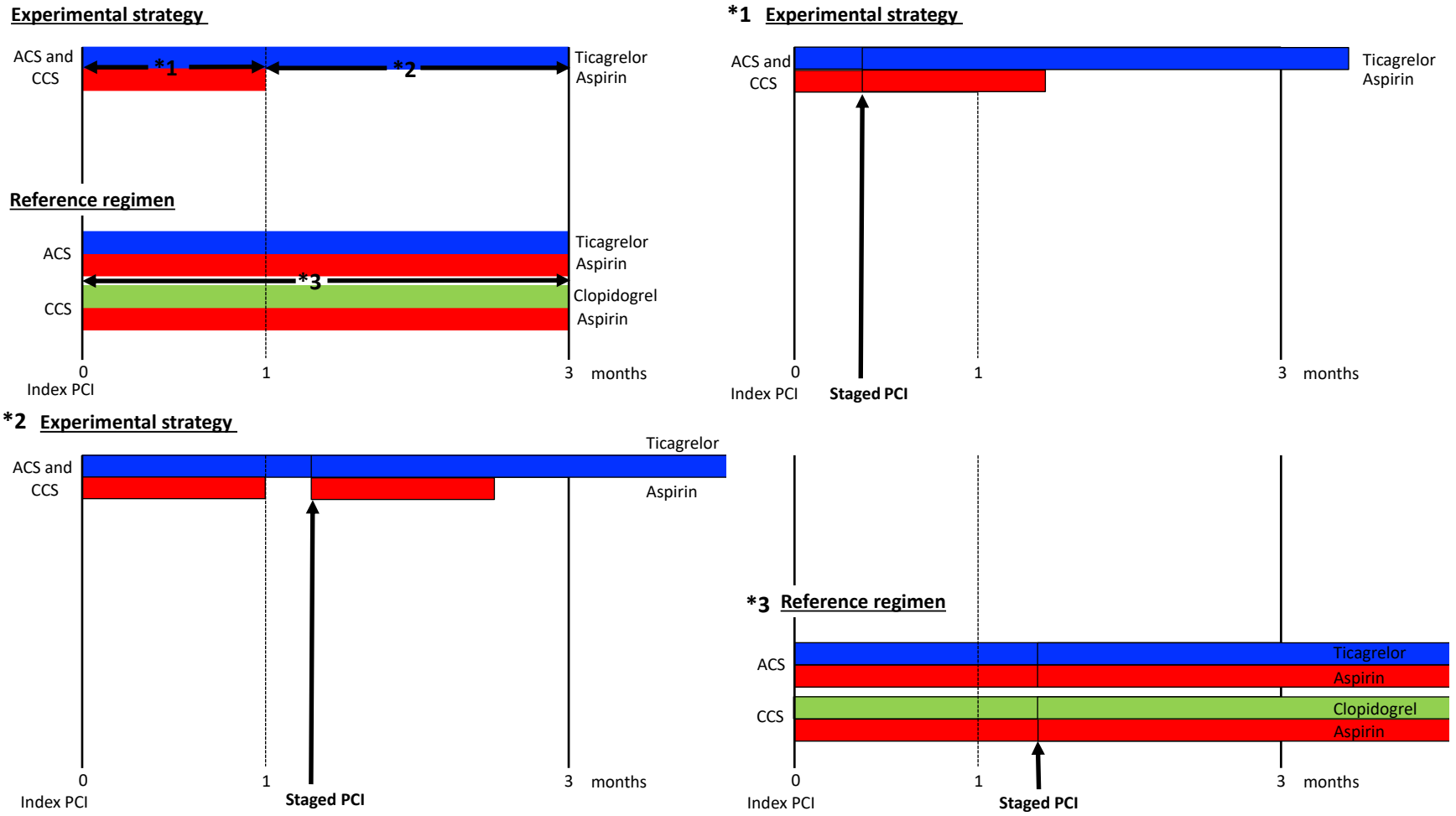
Table 4. Adherence during clinical follow-up visits to the allocated antiplatelet regimen between patients undergoing staged PCI and non-staged PCI

	Experimental strategy			Reference regimen		
	Staged PCI	Non-staged PCI	p value	Staged PCI	Non-staged PCI	p value
At discharge	827 (97.9%)	6937 (97.5%)	0.555	774 (96.5%)	6970 (97.3%)	0.210
At 1 month	801 (96.5%)	6678 (96.4%)	0.915	767 (96.2%)	6723 (96.3%)	0.938
At 3 months	6937 (97.5%)	5943 (87.0%)	<0.001	730 (92.8%)	6458 (93.7%)	0.297
At 6 months	696 (84.8%)	5760 (85.0%)	0.853	709 (91.2%)	6276 (91.8%)	0.573
At 12 months	678 (80.0%)	5494 (77.0%)	0.138	685 (85.2%)	6039 (84.1%)	0.604
At 18 months	636 (75.1%)	5226 (73.3%)	0.445	690 (85.8%)	6088 (84.7%)	0.096
At 24 months	627 (74.0%)	5183 (72.7%)	0.658	697 (86.7%)	6284 (87.5%)	0.666

Values are expressed as n (%).

PCI: percutaneous coronary intervention

Figure 1. Definition of staged PCI according to the protocol of the GLOBAL LEADERS trial



643 **Figure 2. Flow chart**

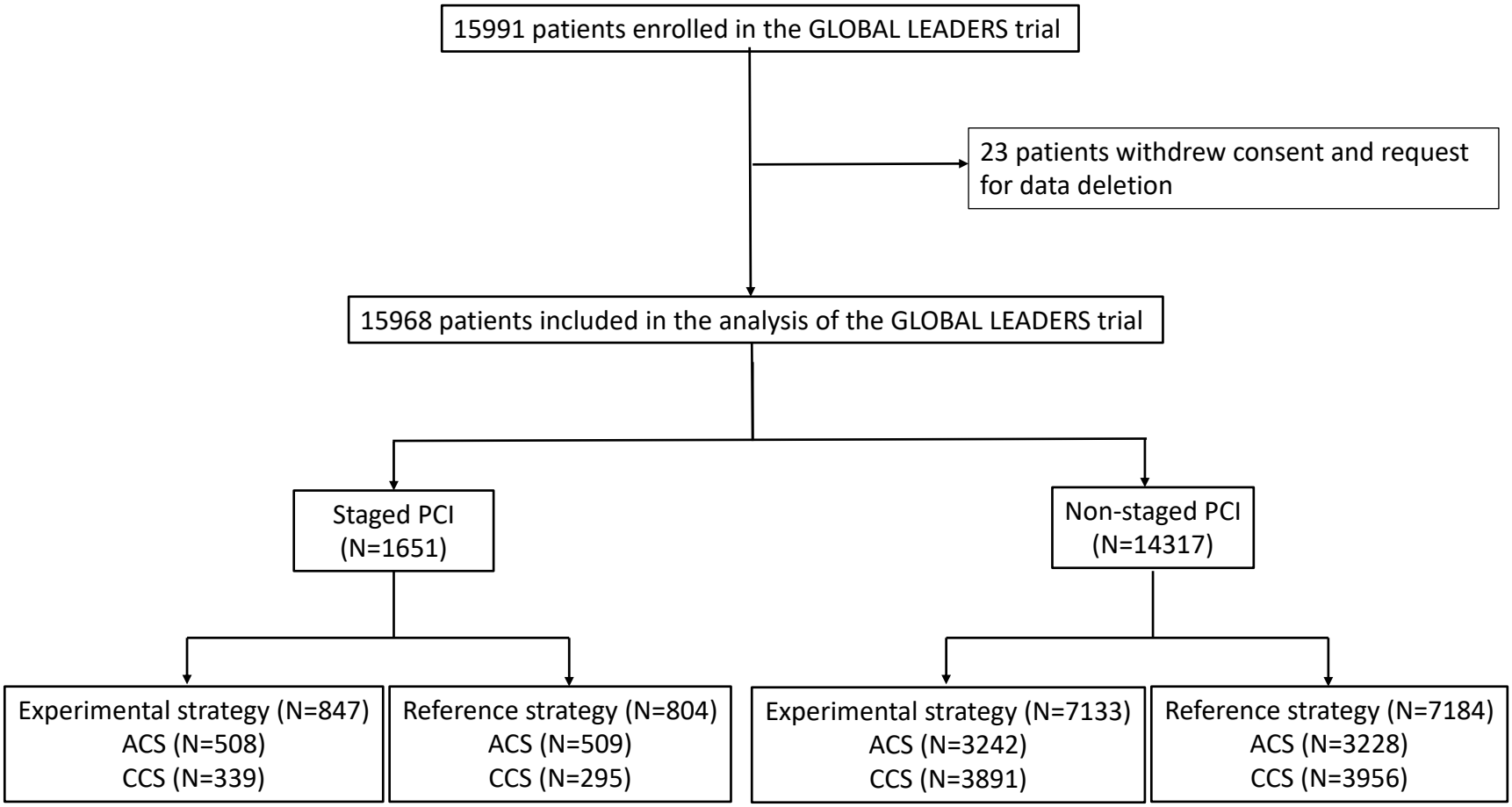


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Figure 3. Treatment effect of the experimental strategy versus the reference regimen in CCS patients undergoing staged PCI

Outcomes at 2 year	Experimental strategy	Reference regimen	HR; exp/ref (95%CI)	p value	P value for interaction
All-cause death or New Q-wave MI					
Staged PCI	19 (5.6%)	9 (3.1%)	1.861 (0.842-4.112)	0.125	0.051
Non-staged PCI	138 (3.5%)	171 (4.3%)	0.818 (0.654-1.024)	0.079	
All-cause death					
Staged PCI	14 (4.1%)	5 (1.7%)	2.465 (0.888-6.845)	0.083	0.042
Non-staged PCI	94 (2.4%)	116 (2.9%)	0.823 (0.627-1.080)	0.160	
New Q-wave MI					
Staged PCI	5 (1.5%)	4 (1.4%)	1.102 (0.296-4.102)	0.885	0.629
Non-staged PCI	45 (1.2%)	58 (1.55)	0.787 (0.533-1.162)	0.228	
BARC type 3 or 5					
Staged PCI	11 (3.2%)	4 (1.4%)	2.440 (0.777-7.663)	0.127	0.269
Non-staged PCI	79 (2.0%)	65 (1.6%)	1.244 (0.896-1.727)	0.193	
POCE					
Staged PCI	63 (18.6%)	58 (19.7%)	0.929 (0.650-1.327)	0.684	0.904
Non-staged PCI	495 (12.7%)	555 (14.0%)	0.908 (0.805-1.025)	0.119	
Any MI					
Staged PCI	10 (2.9%)	11 (3.7%)	0.801 (0.340-1.886)	0.611	0.620
Non-staged PCI	105 2.7%)	107 (2.7%)	1.003 (0.767-1.313)	0.980	
Any stroke					
Staged PCI	1 (0.3%)	1 (0.3%)	0.876 (0.055-14.004)	0.925	0.978
Non-staged PCI	35 (0.9%)	39 (1.0%)	0.917 (0.581-1.448)	0.711	
Any revascularization					
Staged PCI	47 (13.9%)	52 (17.6%)	0.773 (0.521-1.147)	0.200	0.409
Non-staged PCI	356 (9.1%)	393 (9.9%)	0.923 (0.799-1.065)	0.272	
TVR					
Staged PCI	26 (7.7%)	30 (10.2%)	0.745 (0.441-1.260)	0.272	0.394
Non-staged PCI	194 (5.0%)	208 (5.3%)	0.951 (0.782-1.157)	0.618	
Definite ST					
Staged PCI	6 (1.8%)	3 (1.0%)	1.763 (0.441-7.048)	0.423	0.540
Non-staged PCI	26 (0.7%)	24 (0.6%)	1.107 (0.635-1.927)	0.721	
BARC tyoe 2, 3, or 5					
Staged PCI	29 (8.6%)	17 (5.8%)	1.512 (0.831-2.752)	0.176	0.401
Non-staged PCI	251 (6.5%)	222 (5.6%)	1.158 (0.967-1.387)	0.111	
NACE					
Staged PCI	68 (20.1%)	61 (20.7%)	0.960 (0.680-1.357)	0.818	0.860
Non-staged PCI	546 (14.0%)	599 (15.1%)	0.930 (0.828-1.044)	0.218	

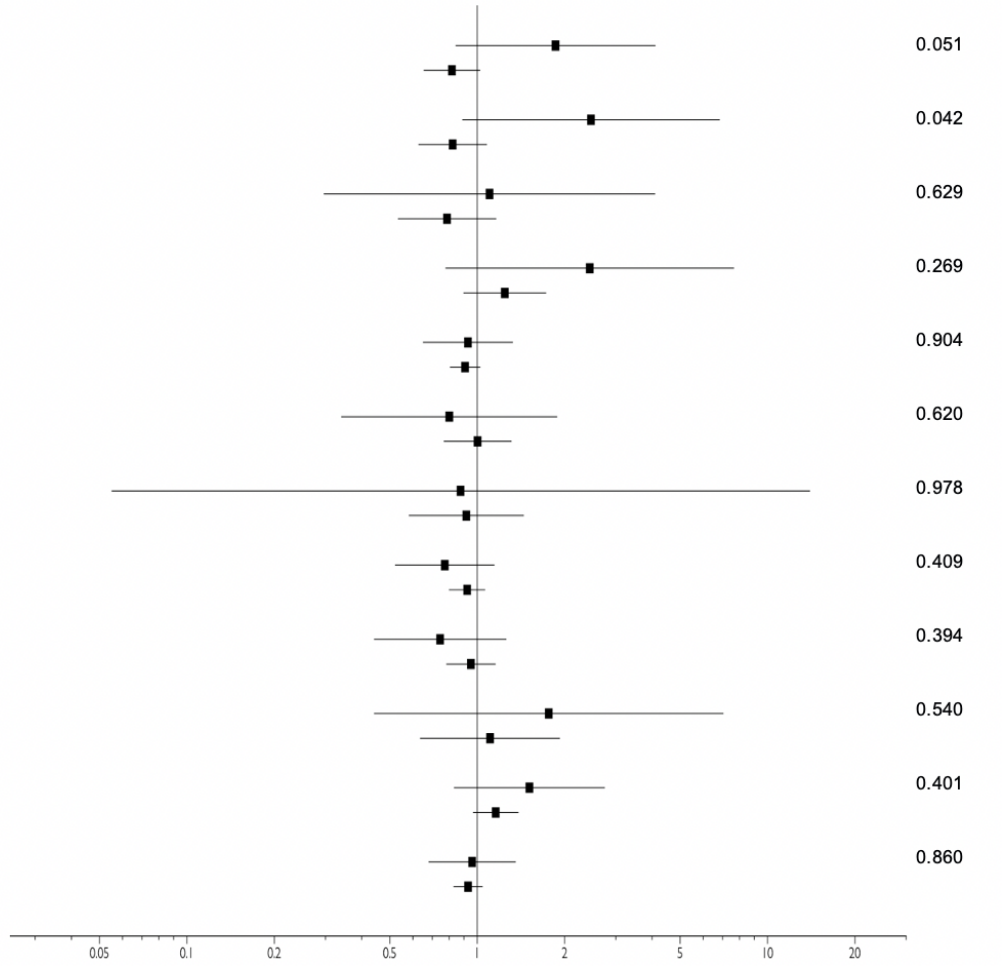

Figure 4. Treatment effect of the experimental strategy versus the reference regimen in ACS patients undergoing staged PCI

Outcomes at 2 year	Experimental strategy	Reference regimen	HR; exp/ref (95%CI)	p value	P value for interaction
All-cause death or New Q-wave MI					
Staged PCI	18 (3.5%)	29 (5.7%)	0.616 (0.342-1.109)	0.106	0.222
Non-staged PCI	129 (4.0%)	140 (4.3%)	0.914 (0.719-1.161)	0.459	
All-cause death					
Staged PCI	15 (3.0%)	24 (4.7%)	0.623 (0.327-1.187)	0.150	0.263
Non-staged PCI	101 (3.1%)	108 (3.3%)	0.929 (0.708-1.218)	0.593	
New Q-wave MI					
Staged PCI	3 (0.6%)	8 (1.6%)	0.902 (0.550-1.480)	0.684	0.219
Non-staged PCI	30 (0.9%)	33 (1.0%)	0.373 (0.099-1.407)	0.145	
BARC type 3 or 5					
Staged PCI	9 (1.8%)	23 (4.5%)	0.387 (0.179-0.836)	0.016	0.075
Non-staged PCI	64 (2.0%)	77 (2.4%)	0.827 (0.594-1.153)	0.263	
POCE					
Staged PCI	72 (14.2%)	91 (17.9%)	0.981 (0.858-1.123)	0.782	0.164
Non-staged PCI	420 (13.0%)	427 (13.2%)	0.774 (0.568-1.055)	0.105	
Any MI					
Staged PCI	20 (3.9%)	23 (4.5%)	1.037 (0.797-1.349)	0.788	0.591
Non-staged PCI	113 (3.5%)	109 3.4%()	0.868 (0.477-1.581)	0.644	
Any stroke					
Staged PCI	4 (0.8%)	5 (1.0%)	1.078 (0.689-1.685)	0.743	0.671
Non-staged PCI	40 (1.2%)	37 (1.1%)	0.797 (0.214-2.969)	0.736	
Any revascularization					
Staged PCI	52 (10.2%)	67 (13.2%)	0.763 (0.531-1.096)	0.143	0.166
Non-staged PCI	284 (8.8%)	281 (8.7%)	1.008 (0.854-1.188)	0.929	
TVR					
Staged PCI	29 (5.7%)	35 (6.9%)	0.825 (0.504-1.350)	0.444	0.995
Non-staged PCI	140 (4.3%)	169 (5.2%)	0.823 (0.658-1.030)	0.089	
Definite ST					
Staged PCI	6 (1.2%)	4 (0.8%)	1.504 (0.425-5.331)	0.527	0.351
Non-staged PCI	26 (0.8%)	33 (1.0%)	0.785 (0.470-1.313)	0.357	
BARC tyoe 2, 3, or 5					
Staged PCI	29 (5.7%)	57 (11.2%)	0.496 (0.317-0.776)	0.002	0.011
Non-staged PCI	220 (6.8%)	236 (7.3%)	0.926 (0.771-1.113)	0.415	
NACE					
Staged PCI	76 (15.0%)	104 (20.4%)	0.707 (0.526-0.951)	0.022	0.063
Non-staged PCI	455 (14.0%)	473 (14.7%)	0.957 (0.841-1.088)	0.500	

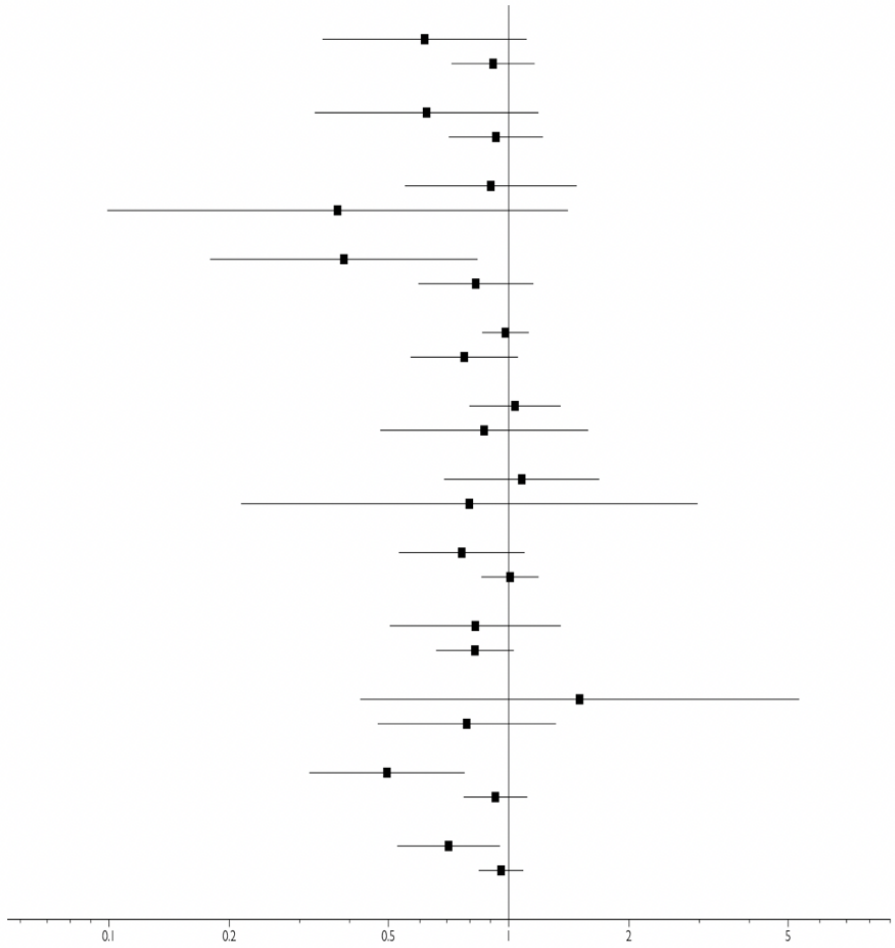

Figure legends

Figure 1. Definition of staged PCI according to the protocol of the GLOBAL LEADERS trial the upper left of the figure describes the experimental strategy and reference regimen from index PCI to 3 months. Staged PCI had to be performed within 3 months of the start of the index procedure according to the protocol of the GLOBAL LEADERS trial. Blue, red, and green lines show prescription of ticagrelor, aspirin, and clopidogrel, respectively.

*1: When in the experimental strategy, the staged PCI was performed within 1 month after the index procedure, DAPT (ticagrelor plus aspirin) was prolonged by one month (upper right of the figure).

*2: When in the experimental strategy, the staged PCI was performed more than 1 month after the index procedure, DAPT (ticagrelor plus aspirin) had to be re-started, at the staged PCI. DAPT was continued for 1 month after the staged PCI (bottom left of the figure).

*3: When in the reference regimen, the staged PCI was performed in ACS patients, DAPT (ticagrelor plus aspirin) was theoretically not interrupted whereas in CCS patients, DAPT with clopidogrel and aspirin continued (bottom right of the figure).

PCI: percutaneous coronary intervention

Figure 2. Flow chart

Figure 3. Treatment effect of the experimental strategy versus the reference regimen in CCS patients undergoing staged PCI

CCS: chronic coronary syndrome, MI: myocardial infarction, PCI: percutaneous coronary intervention, HR: hazard ratio, BARC: Bleeding Academic Research Consortium, POCE: patient-oriented composite endpoint, TVR: target vessel revascularization, ST: stent thrombosis, NACE: net adverse clinical events

675 **Figure 4**. Treatment effect of the experimental strategy versus the reference regimen in ACS
676 patients undergoing staged PCI
677 ACS: acute coronary syndrome, MI: myocardial infarction, PCI: percutaneous coronary
678 intervention, HR: hazard ratio, CI: confidence interval, BARC: Bleeding Academic Research
679 Consortium, POCE: patient-oriented composite endpoint, TVR: target vessel revascularization,
680 ST: stent thrombosis, NACE: net adverse clinical events
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Online Tables and Figures

Online Table 1. Baseline patient and procedural characteristics in patients undergoing staged PCI and non-staged PCI

Online Table 2. Clinical outcomes at 2 years in patients undergoing staged PCI and non-staged PCI

Online Figure 1. The days when staged PCI was undergone after index procedure

Cumulative frequency curve shows when staged PCI was undergone after index procedure

PCI: percutaneous coronary intervention

Online Figure 2. Impact of the experimental strategy versus the reference regimen on 2-year clinical outcomes in patients undergoing staged PCI

Kaplan Meier curves show an incidence rate of (A) NACE, (B) all-cause death, (C) any MI, (D) any revascularization, (E) BARC type 3 or 5 bleeding, and (F) BARC type 2, 3, or 5 bleeding at 2 years in patients undergoing staged PCI.

NACE: net adverse composite events, MI: myocardial infarction, BARC: Bleeding Academic Research Consortium, HR: hazard ratio

Online Figure 3. Treatment effect of the experimental strategy versus the reference regimen in patients undergoing staged PCI and non-staged PCI

MI: myocardial infarction, PCI: percutaneous coronary intervention, HR: hazard ratio, CI: confidence interval, BARC: Bleeding Academic Research Consortium, POCE: patient-oriented composite endpoint, TVR: target vessel revascularization, ST: stent thrombosis, NACE: net adverse clinical events

720 **Online Table 1.** Baseline patient and procedural characteristics in patients undergoing staged PCI and non-staged PCI

	Overall N=15968	**Staged PCI N=1651**	**Non-staged PCI N=14317**	**p value**
Patient characteristics				
Age	64.5 ± 10.3	65.0 ± 9.9	64.5 ± 10.4	0.074
Male	12254 (76.4%)	1315 (79.6%)	10939 (76.7%)	0.003
Body mass index, kg/m²	28.2 ± 4.6	28.1 ± 4.5	28.2 ± 4.6	0.394
Medical history				
Diabetes mellitus	4038 (25.2%)	431 (26.1%)	3607 (25.3%)	0.421
Insulin-dependent diabetes mellitus	1223 (7.6%)	140 (8.5%)	1083 (7.7%)	0.182
Hypertension	11715 (73.5%)	1223 (74.6%)	10492 (73.6%)	0.330
Hypercholesterolemia	10768 (69.9%)	1060 (67.4%)	9708 (69.6%)	0.041
Previous stroke	421 (2.6%)	50 (3.0%)	371 (2.6%)	0.297
Previous myocardial infarction	3710 (23.9%)	300 (18.2%)	3410 (23.3%)	<0.001
Previous PCI	5221 (33.8%)	382 (23.2%)	4839 (32.7%)	<0.001
Previous coronary artery bypass grafting	943 (6.2%)	59 (3.6%)	884 (5.9%)	<0.001
Peripheral vascular disease	1005 (6.4%)	96 (5.9%)	909 (6.4%)	0.386
Chronic obstructive pulmonary disease	821 (5.2%)	74 (4.5%)	747 (5.2%)	0.199
Previous major bleeding	98 (0.5%)	15 (0.1%)	83 (0.6%)	0.105
Current smoker	4169 (25.6%)	500 (30.3%)	3669 (26.1%)	<0.001
Impaired renal function *	2171 (13.7%)	219 (13.3%)	1952 (13.7%)	0.621
Clinical presentation				
Chronic coronary syndrome	8481 (54.8%)	634 (38.4%)	7847 (53.1%)	<0.001
Acute coronary syndrome	7487 (45.2%)	1017 (61.6%)	6470 (46.9%)	<0.001
Unstable angina	2022 (12.5%)	236 (14.3%)	1786 (12.7%)	0.035
	3373 (20.8%)	394 (23.9%)	2979 (21.1%)	0.004
ST-elevation myocardial infarction	2092 (11.9%)	387 (23.4%)	1705 (13.1%)	<0.001
Procedural characteristics				
Vascular access site				0.554
Radial	11702 (73.8%)	1198 (72.6%)	10504 (73.7%)	
Femoral	4162 (26.1%)	451 (27.3%)	3711 (26.2%)	

Brachial	19 (0.1%)	2 (0.1%)	17 (0.1%)	
Lesions treated per patient				0.019
One lesion	11805 (74.9%)	1173 (72.4%)	10632 (74.6%)	
Two lesions	3187 (19.8%)	369 (22.8%)	2818 (20.1%)	
Three lesions or more	826 (5.3%)	78 (4.8%)	748 (5.2%)	
Treated lesions				<0.001
Left main coronary artery	429 (2.6%)	62 (3.8%)	367 (2.7%)	
Left anterior descending artery	8053 (48.3%)	1199 (72.8%)	6854 (50.8%)	
Left circumflex artery	5009 (28.9%)	902 (54.8%)	4107 (31.6%)	
Right coronary artery	5956 (33.9%)	1138 (69.1%)	4818 (37.6%)	
Bypass graft [y]	218 (1.4%)	20 (1.2%)	198 (1.4%)	
Multivessel treatment	3576 (22.6%)	1399 (84.9%)	2177 (15.3%)	<0.001
Bifurcation or trifurcation	2498 (15.8%)	455 (27.6%)	2043 (14.4%)	<0.001

Values are expressed as n (%) or mean ± standard deviation.

* Defined as an estimated glomerular filtration rate of creatinine clearance of <60 mL/min per 1.73 m^2 based on the Modification of Diet in Renal Disease formula. [y] Grafts counted as one separate vessel.

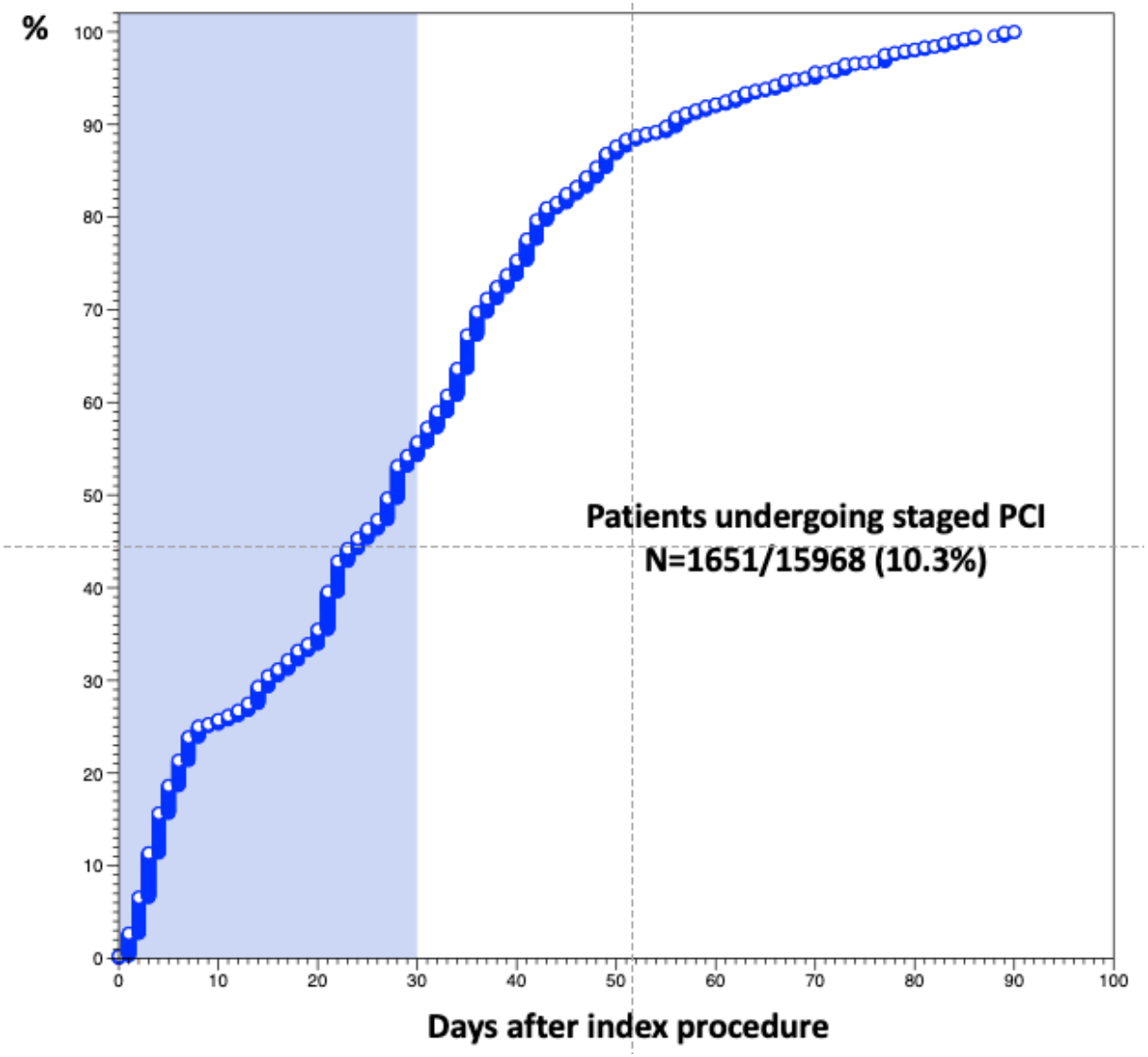
PCI: percutaneous coronary intervention

Online Table 2. Clinical outcomes at 2 years in patients undergoing staged PCI and non-staged PCI

Outcomes at 2 years	Staged PCI	Non-staged PCI	Unadjusted HR; staged PCI /non-staged PCI (95% CI)	P value	Adjusted HR; staged PCI /non-staged PCI (95% CI)	P value
All-cause death or New Q-wave MI	75 (4.5%)	578 (4.0%)	1.129 (0.888-1.436)	0.322	1.284 (0.952-1.732)	0.102
All-cause death	58 (3.5%)	419 (2.9%)	1.203 (0.914-1.583)	0.187	1.437 (1.020-2.025)	0.038
BARC type 3 or 5	47 (2.8%)	285 (2.0%)	1.428 (1.049-1.944)	0.024	1.332 (0.907-1.956)	0.144
New Q-wave MI	20 (1.2%)	166 (1.2%)	1.049 (0.660-1.669)	0.838	1.026 (0.577-1.821)	0.931
POCE	284 (17.2%)	1897 (13.2%)	1.333 (1.177-1.510)	<0.001	1.388 (1.186-1.625)	<0.001
Any MI	64 (3.9%)	434 (3.0%)	1.281 (0.985-1.665)	0.064	1.230 (0.886-1.707)	0.215
Any stroke	11 (0.7%)	151 (1.1%)	0.628 (0.340-1.158)	0.136	0.757 (0.352-1.627)	0.475
Any revascularization	218 (13.2%)	1314 (9.2%)	1.478 (1.280-1.705)	<0.001	1.515 (1.263-1.817)	<0.001
TVR	120 (7.3%)	711 (5.0%)	1.474 (1.214-1.788)	<0.001	1.263 (0.995-1.603)	0.055
Definite ST	19 (1.2%)	109 (0.8%)	1.509 (0.927-2.456)	0.098	1.515 (0.819-2.801)	0.186
BARC type 2, 3, or 5	132 (8.0%)	929 (6.5%)	1.237 (1.030-1.484)	0.022	1.261 (1.006-1.581)	0.044
NACE	309 (18.7%)	2073 (14.5%)	1.331 (1.181-1.499)	<0.001	1.365 (1.174-1.588)	<0.001

MI: myocardial infarction, PCI: percutaneous coronary intervention, HR: hazard ratio, CI: confidence interval, BARC: Bleeding Academic Research Consortium, POCE: patient-oriented composite endpoint, TVR: target vessel revascularization, ST: stent thrombosis, NACE: net adverse clinical events

740 **Online Figure 1**. The days when staged PCI was undergone after index procedure



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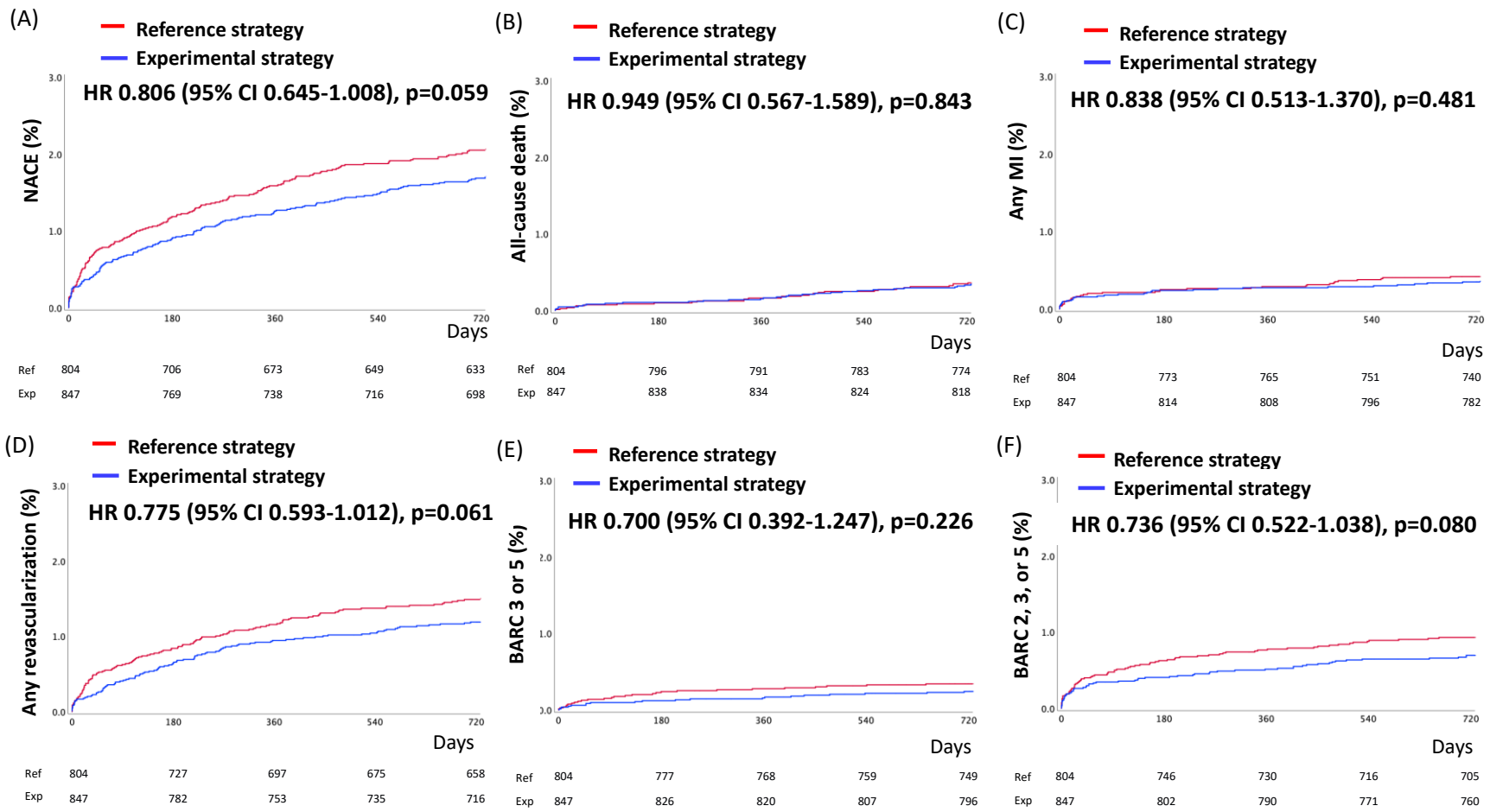
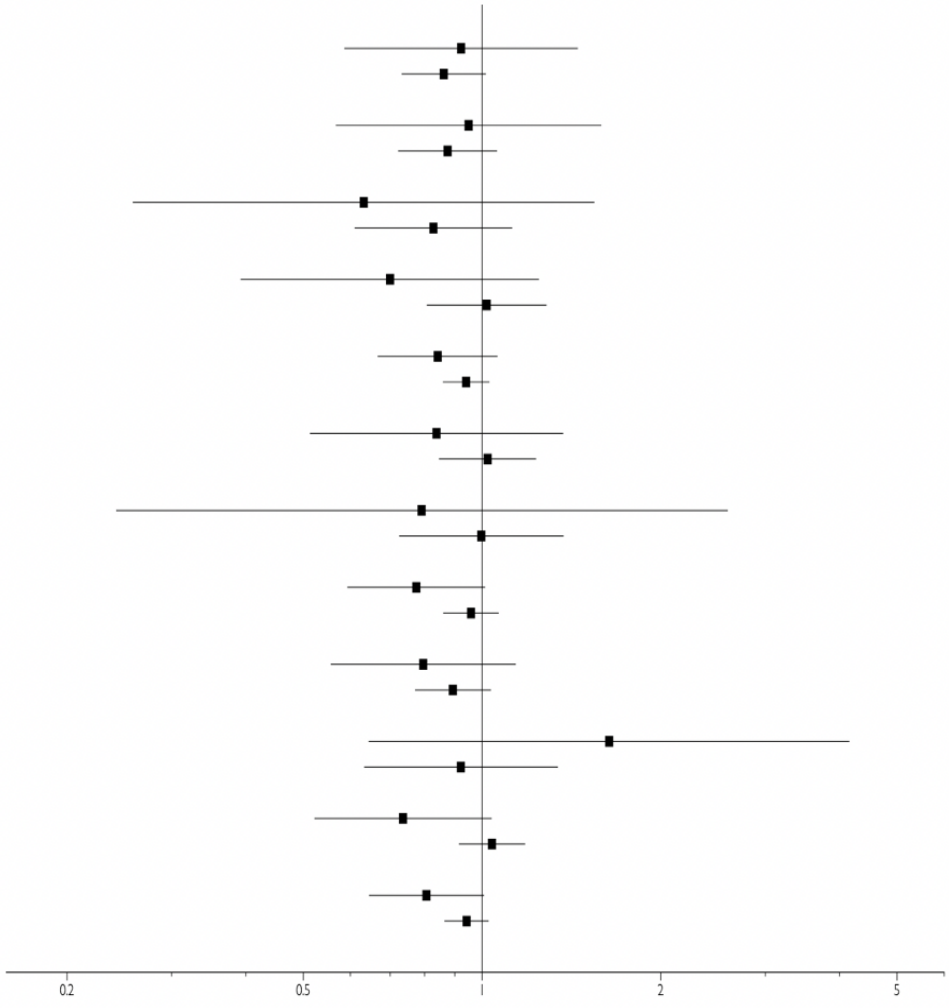
Online Figure 2. Impact of the experimental strategy versus the reference regimen on 2-year clinical outcomes in patients undergoing staged PCI



746 **Online Figure 3.** Treatment effect of the experimental strategy versus the reference regimen in patients undergoing staged PCI and

747 non-staged PCI

Outcomes at 2 year	Experimental strategy	Reference regimen	HR; exp/ref (95%CI)	p value	P value for interaction
All-cause death or New Q-wave MI					
Staged PCI	37 (4.7%)	38 (4.7%)	0.922 (0.586-1.450)	0.725	0.783
Non-staged PCI	267 (3.7%)	311 (4.3%)	0.862 (0.732-1.015)	0.074	
All-cause death					
Staged PCI	29 (3.4%)	29 (3.6%)	0.949 (0.567-1.588)	0.843	0.771
Non-staged PCI	195 (2.7%)	224 (3.1%)	0.875 (0.722-1.060)	0.173	
New Q-wave MI					
Staged PCI	8 (0.9%)	12 (1.5%)	0.632 (0.258-1.546)	0.315	0.575
Non-staged PCI	75 (1.1%)	91 (1.3%)	0.828 (0.610-1.124)	0.226	
BARC type 3 or 5					
Staged PCI	20 (2.4%)	27 (3.4%)	0.700 (0.392-1.247)	0.226	0.238
Non-staged PCI	143 (2.0%)	142 (2.0%)	1.018 (0.807-1.284)	0.883	
POCE					
Staged PCI	135 (15.9%)	149 (18.5%)	0.842 (0.667-1.062)	0.147	0.380
Non-staged PCI	915 (12.8%)	982 (13.7%)	0.940 (0.859-1.029)	0.179	
Any MI					
Staged PCI	30 (3.5%)	34 (4.2%)	0.838 (0.513-1.370)	0.481	0.459
Non-staged PCI	218 (3.1%)	216 (3.0%)	1.022 (0.846-1.233)	0.823	
Any stroke					
Staged PCI	5 (0.6%)	6 (0.7%)	0.791 (0.242-2.593)	0.699	0.712
Non-staged PCI	75 (1.1%)	76 (1.1%)	0.997 (0.725-1.372)	0.987	
Any revascularization					
Staged PCI	99 (11.7%)	119 (14.8%)	0.775 (0.593-1.012)	0.061	0.146
Non-staged PCI	640 (9.0%)	674 (9.4%)	0.958 (0.860-1.067)	0.436	
TVR					
Staged PCI	55 (6.5%)	65 (8.1%)	0.796 (0.556-1.140)	0.214	0.563
Non-staged PCI	334 (4.7%)	377 (5.2%)	0.893 (0.771-1.035)	0.132	
Definite ST					
Staged PCI	12 (1.4%)	7 (0.9%)	1.637 (0.644-4.157)	0.300	0.263
Non-staged PCI	52 (0.7%)	57 (0.8%)	0.921 (0.633-1.342)	0.670	
BARC tyoe 2, 3, or 5					
Staged PCI	58 (6.8%)	74 (9.2%)	0.736 (0.522-1.038)	0.080	0.065
Non-staged PCI	471 (6.6%)	458 (6.4%)	1.039 (0.914-1.182)	0.560	
NACE					
Staged PCI	144 (17.0%)	165 (20.5%)	0.806 (0.645-1.008)	0.059	0.197
Non-staged PCI	1001 (14.0%)	1072 (14.9%)	0.942 (0.864-1.026)	0.171	



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