# 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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## Reference

**1.** Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014;371:2155-66.
**2.** Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018;39:213-60.
**3.** Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;68:1082-115.
**4.** Gargiulo G, Windecker S, Vranckx P, Gibson CM, Mehran R, Valgimigli M. A Critical Appraisal of Aspirin in Secondary Prevention: Is Less More? Circulation 2016;134:1881-906.
**5.** Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57.
**6.** Wykrzykowska JJ, Kraak RP, Hofma SH, et al. Bioresorbable Scaffolds versus Metallic Stents in Routine PCI. N Engl J Med 2017;376:2319-28.
**7.** Stefanini GG, Serruys PW, Silber S, et al. The impact of patient and lesion complexity on clinical and angiographic outcomes after revascularization with zotarolimus- and everolimus-eluting stents: a substudy of the RESOLUTE All Comers Trial (a randomized comparison of a zotarolimus-eluting stent with an everolimus-eluting stent for percutaneous coronary intervention). J Am Coll Cardiol 2011;57:2221-32.
**8.** Collet C, Modolo R, Banning A, et al. Impact of Staging Percutaneous Coronary Intervention in Left Main Artery Disease: Insights From the EXCEL Trial. JACC Cardiovasc Interv 2019;12:411-2.
**9.** Blankenship JC, Moussa ID, Chambers CC, et al. Staging of multivessel percutaneous coronary interventions: an expert consensus statement from the Society for Cardiovascular Angiography and Interventions. Catheter Cardiovasc Interv 2012;79:1138-52.
**10.** Spitzer E, McFadden E, Vranckx P, et al. Defining Staged Procedures for Percutaneous Coronary Intervention Trials: A Guidance Document. JACC Cardiovasc Interv 2018;11:823-32.
**11.** Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. Circulation 2016;134:e123-55.
**12.** Vranckx P, Valgimigli M, Windecker S, et al. Long-term ticagrelor monotherapy versus standard dual antiplatelet therapy followed by aspirin monotherapy in patients undergoing

biolimus-eluting stent implantation: rationale and design of the GLOBAL LEADERS trial. EuroIntervention 2016;12:1239-45.
**13.** Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2019.
**14.** Valgimigli M, Garcia-Garcia HM, Vrijens B, et al. Standardized classification and framework for reporting, interpreting, and analysing medication non-adherence in cardiovascular clinical trials: a consensus report from the Non-adherence Academic Research Consortium (NARC). Eur Heart J 2019;40:2070-85.
**15.** Hicks KA, Mahaffey KW, Mehran R, et al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. Circulation 2018;137:961-72.
**16.** Garcia-Garcia HM, McFadden EP, Farb A, et al. Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document. Eur Heart J 2018;39:2192-207.
**17.** Serruys PW, Tomaniak M, Chichareon P, et al. Patient-oriented composite endpoints and net adverse clinical events with ticagrelor monotherapy following percutaneous coronary intervention: Insights from the randomized GLOBAL LEADERS trial. EuroIntervention 2019.
**18.** Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-51.
**19.** Li G, Taljaard M, Van den Heuvel ER, et al. An introduction to multiplicity issues in clinical trials: the what, why, when and how. Int J Epidemiol 2017;46:746-55.
**20.** Vranckx P, Valgimigli M, Juni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet 2018;392:940-9.
**21.** Serruys PW, Takahashi K, Chichareon P, et al. Impact of long-term ticagrelor monotherapy following 1-month dual antiplatelet therapy in patients who underwent complex percutaneous coronary intervention: insights from the Global Leaders trial. Eur Heart J 2019;40:2595-604.
**22.** Steg PG, Bhatt DL, Simon T, et al. Ticagrelor in Patients with Stable Coronary Disease and Diabetes. N Engl J Med 2019;381:1309-20.
**23.** Vranckx P, Leonardi S, Tebaldi M, et al. Prospective validation of the Bleeding Academic Research Consortium classification in the all-comer PRODIGY trial. Eur Heart J 2014;35:2524-9.
**24.** Hamon M, Lemesle G, Tricot O, et al. Incidence, source, determinants, and prognostic impact of major bleeding in outpatients with stable coronary artery disease. J Am Coll Cardiol 2014;64:1430-6.
**25.** Orme RC, Parker WAE, Thomas MR, et al. Study of Two Dose Regimens of Ticagrelor Compared with Clopidogrel in Patients Undergoing Percutaneous Coronary Intervention for Stable Coronary Artery Disease (STEEL-PCI). Circulation 2018.
**26.** Lee SY, Hong MK, Palmerini T, et al. Short-Term Versus Long-Term Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation in Elderly Patients: A Meta-Analysis of Individual Participant Data From 6 Randomized Trials. JACC Cardiovasc Interv 2018;11:435-43.
**27.** Tomaniak M, Chichareon P, Onuma Y, et al. Benefit and Risks of Aspirin in Addition to Ticagrelor in Acute Coronary Syndromes: A Post Hoc Analysis of the Randomized GLOBAL LEADERS Trial. JAMA Cardiol 2019.

**28.** Leonardi S, Franzone A, Piccolo R, et al. Rationale and design of a prospective substudy of clinical endpoint adjudication processes within an investigator-reported randomised controlled trial in patients with coronary artery disease: the GLOBAL LEADERS Adjudication Sub-StudY (GLASSY). BMJ Open 2019;9:e026053.
**29.** Franzone A, McFadden E, Leonardi S, et al. Ticagrelor Alone Versus Dual Antiplatelet Therapy From 1 Month After Drug-Eluting Coronary Stenting. J Am Coll Cardiol 2019;74:2223-34.

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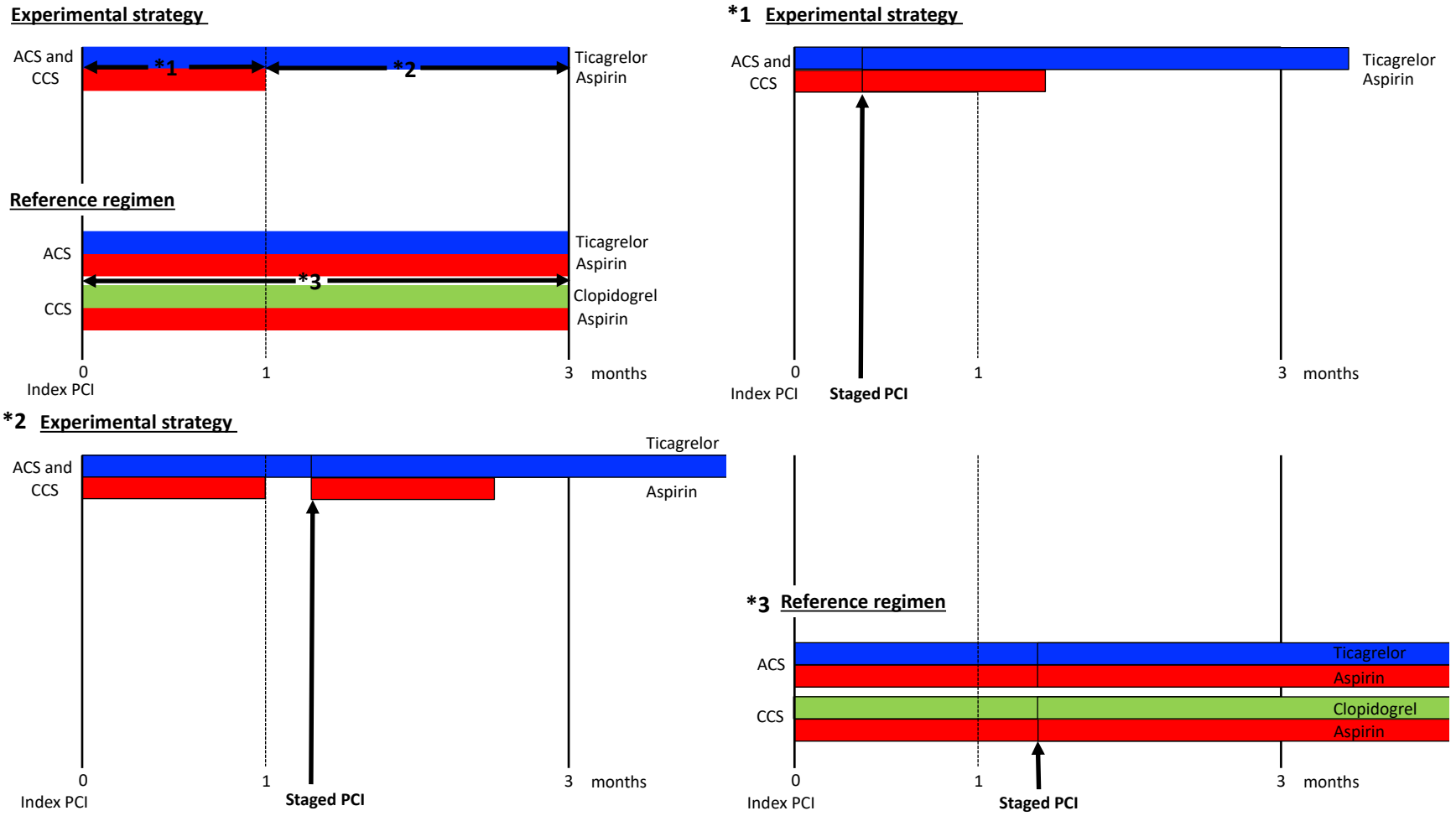
**Table 4. Adherence during clinical follow-up visits to the allocated antiplatelet regimen between patients undergoing staged PCI and non-staged PCI**

| | 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**

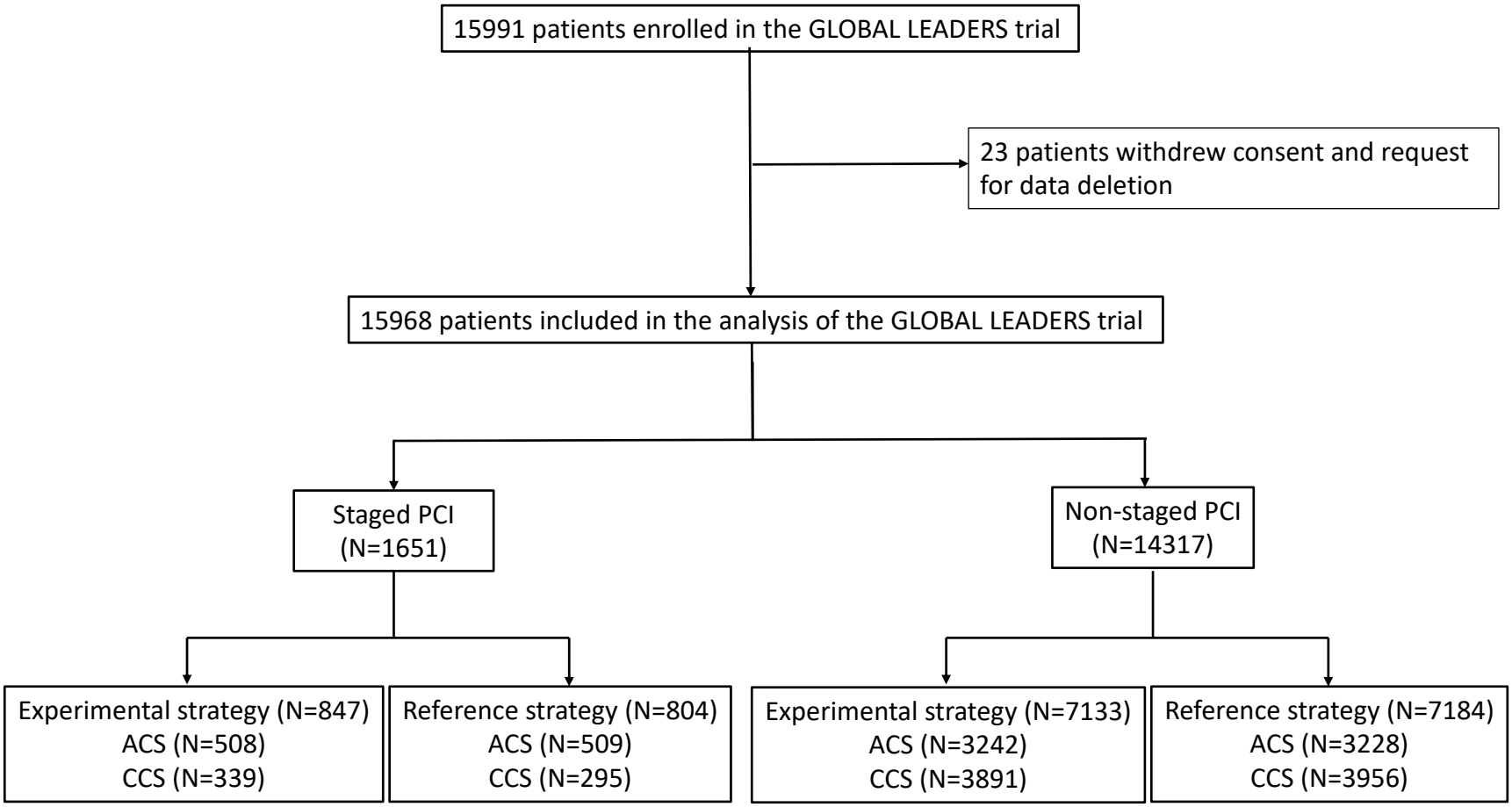



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**Figure 3. Treatment effect of the experimental strategy versus the reference regimen in CCS patients undergoing staged PCI**

| 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 | |

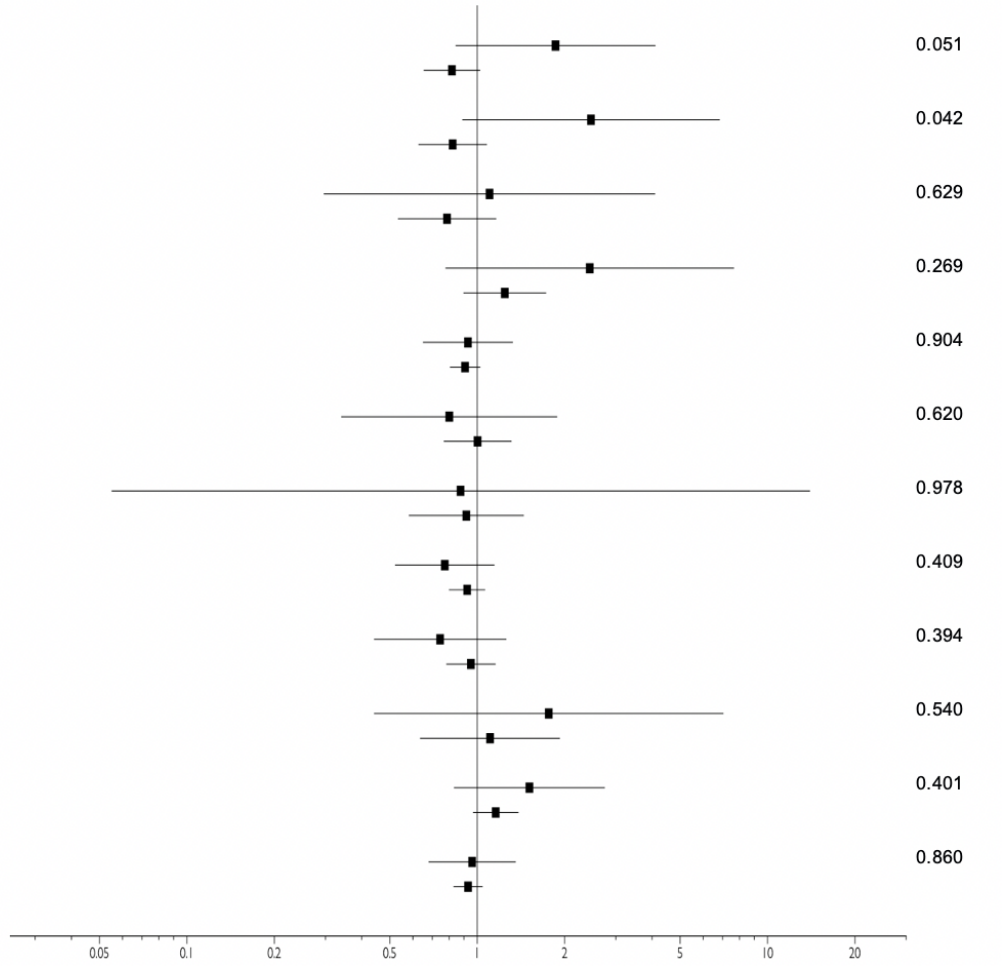
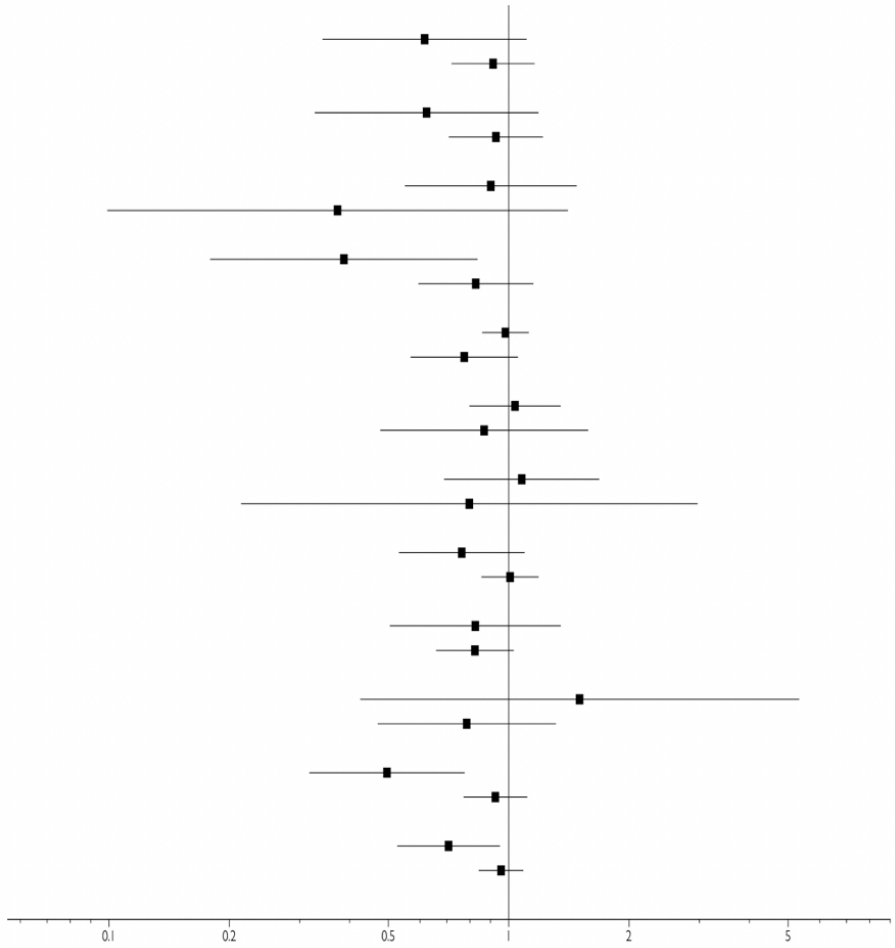


**Figure 4. Treatment effect of the experimental strategy versus the reference regimen in ACS patients undergoing staged PCI**

| 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.

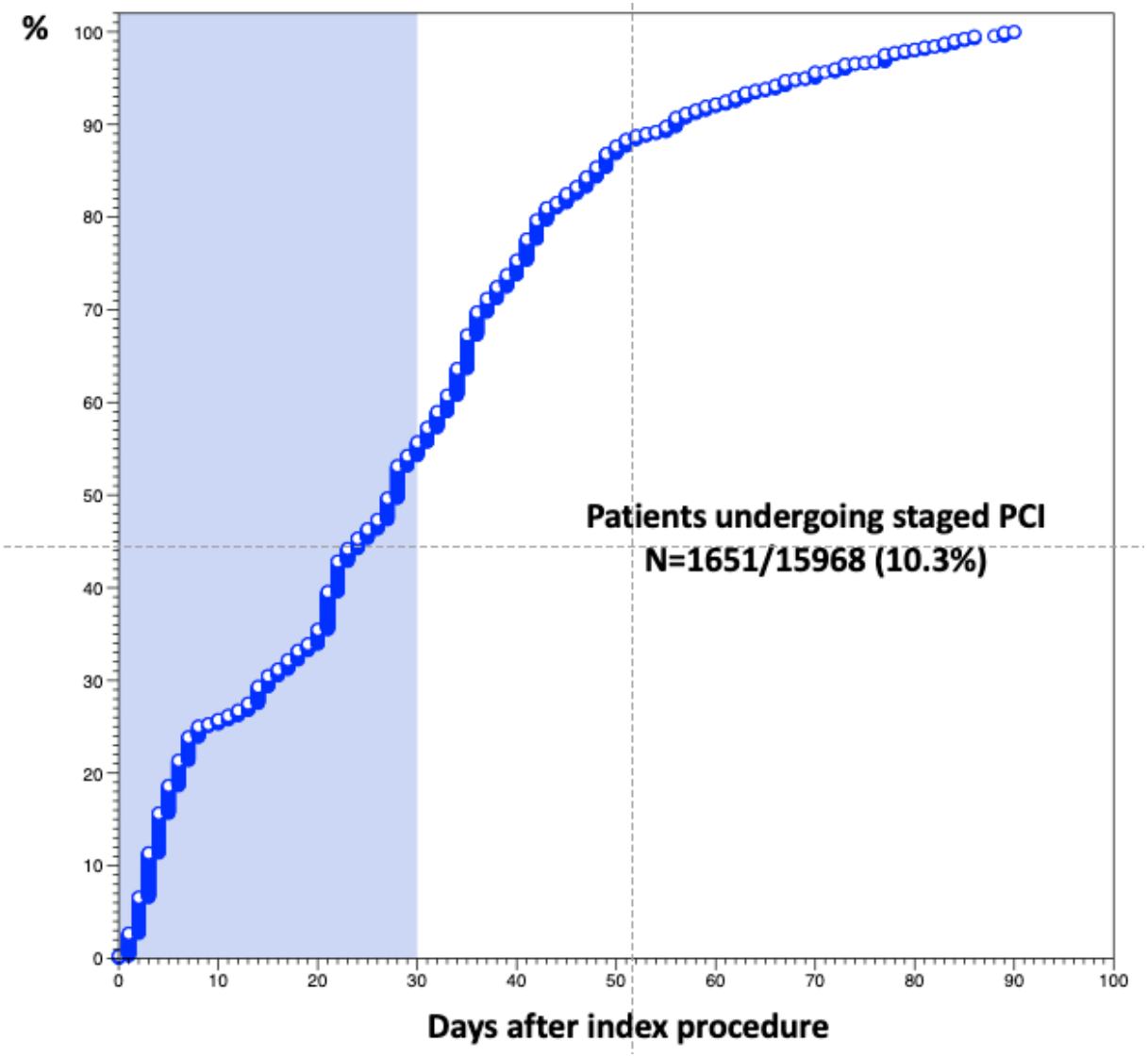
PCI: percutaneous coronary intervention

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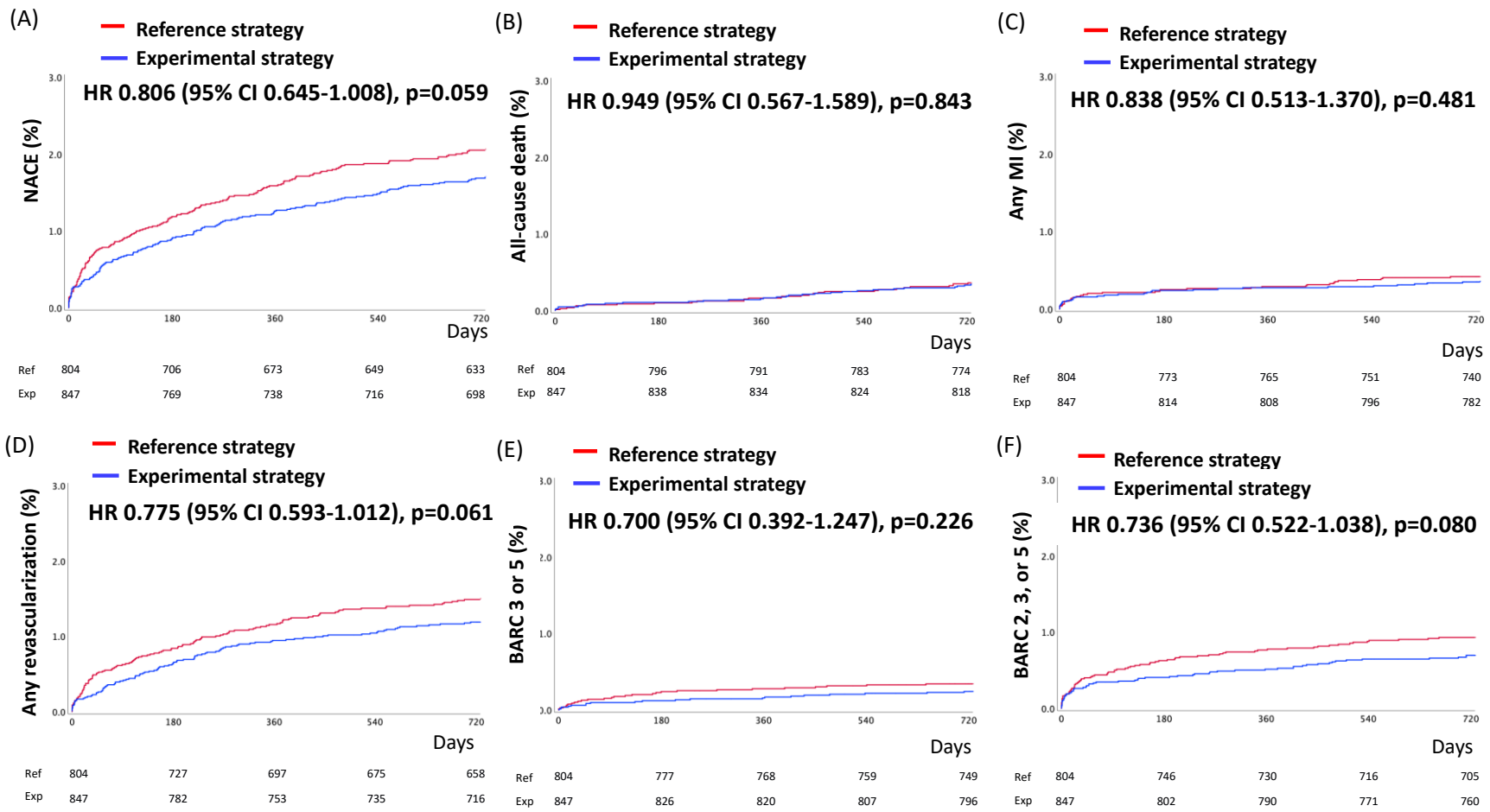
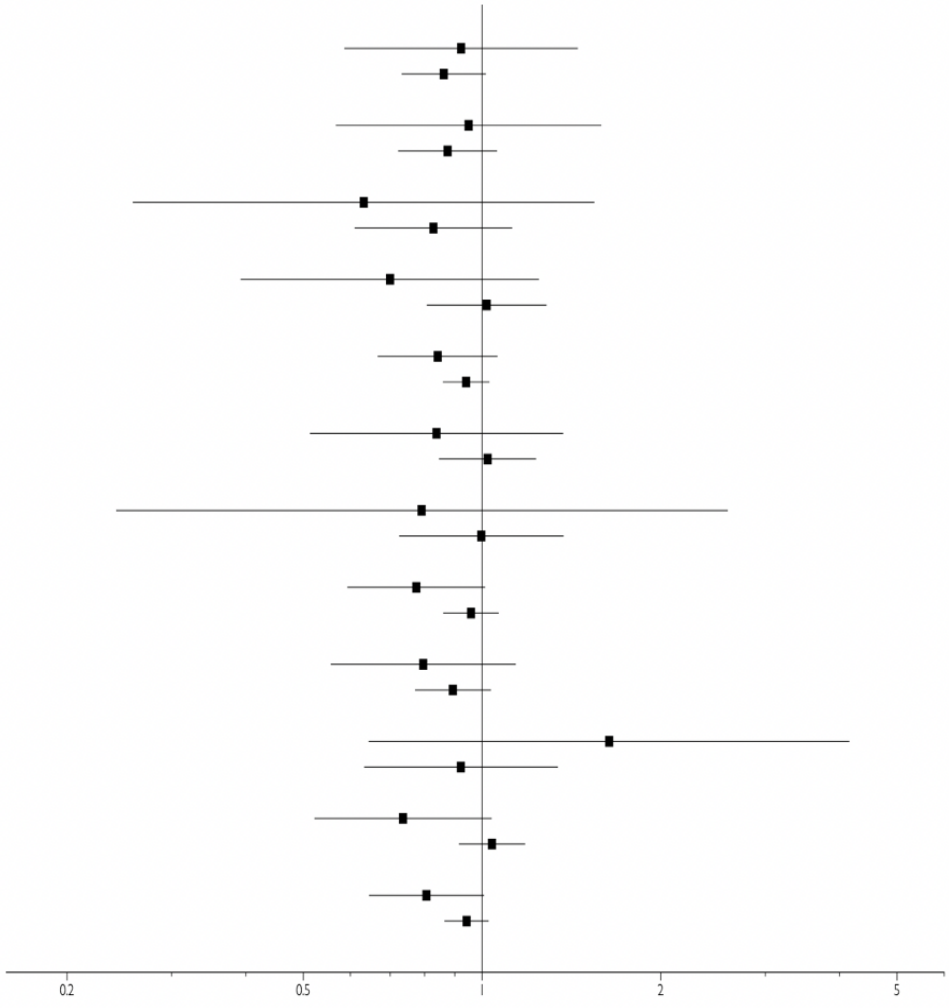
**Online Figure 2.** Impact of the experimental strategy versus the reference regimen on 2-year clinical outcomes in patients undergoing staged PCI



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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