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Patient-oriented composite endpoints and net adverse clinical events with ticagrelor monotherapy following percutaneous coronary intervention: insights from the randomised GLOBAL LEADERS trial

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KEYWORDS

- adjunctive pharmacotherapy
- ACS/NSTE-ACS
- clinical trials
- stable angina

Abstract

Aims: The aim of this study was to evaluate the impact of 23-month ticagrelor monotherapy following one-month dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) on the rates of patient-oriented composite endpoints (POCE) and net adverse clinical events (NACE).

Methods and results: The rates of site-reported Academic Research Consortium (ARC)-2 defined POCE (all-cause death, any stroke, any myocardial infarction or any revascularisation) and NACE (POCE or bleeding type 3 or 5 according to the Bleeding ARC [BARC]) were reported up to two years by intention-to-treat principle in the randomised, multicentre, open-label GLOBAL LEADERS study comparing two antiplatelet strategies in 15,991 patients undergoing PCI. The experimental strategy consisted of aspirin with ticagrelor for one month followed by ticagrelor monotherapy for 23 months, whereas the reference treatment consisted of 12-month DAPT followed by 12-month aspirin monotherapy. At two years, POCE occurred in 1,050 (13.2%) patients in the experimental group and in 1,131 (14.2%) in the reference group (HR 0.93, 95% CI: 0.85-1.01, p=0.085). NACE occurred in 1,145 (14.4%) patients in the experimental group and in 1,237 (15.5%) patients in the reference group (HR 0.92, 95% CI: 0.85-1.00, p=0.057). In pre-specified subgroup analyses, no significant treatment-by-subgroup interactions were found for either POCE or NACE at two years.

Conclusions: The experimental treatment strategy of one-month DAPT followed by 23 months of ticagrelor alone did not result in a significant reduction in the rates of site-reported POCE or NACE, when compared to the reference treatment. ClinicalTrials.gov Identifier: NCT01813435

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Abbreviations

ACS	acute coronary syndromes
ARC	Academic Research Consortium
BARC	Bleeding Academic Research Consortium
CAD	coronary artery disease
CEC	clinical events committee
CI	confidence interval
DAPT	dual antiplatelet therapy
HR	hazard ratio
MI	myocardial infarction
NACE	net adverse clinical events
PCI	percutaneous coronary interventions
POCE	patient-oriented composite endpoints

Introduction

Acetylsalicylic acid-free antiplatelet strategies consisting of more potent $P2Y_{12}$ receptor antagonists have been advocated to ensure an increased net benefit for individual patients, given the expected reduction in the bleeding risk without a trade-off in anti-ischaemic efficacy[1,2].

In the randomised open-label all-comers GLOBAL LEADERS study, the experimental treatment strategy of ticagrelor monotherapy, following one-month dual antiplatelet therapy (DAPT) with aspirin, was not superior to standard DAPT in reducing the primary endpoint consisting of all-cause mortality or core lab-adjudicated new Q-wave myocardial infarction (MI) among patients undergoing percutaneous coronary interventions (PCI)[3]. However, no excess safety signal attributable to this treatment strategy was detected, given the fact that the upper boundary of the 95% confidence interval (CI) of the primary endpoint was close to unity[3].

According to the recent Academic Research Consortium (ARC)-2 consensus, the overall cardiovascular outcomes from the patient perspective, including all-cause death, any type of stroke, MI, and any repeat revascularisation, namely patient-oriented composite endpoints (POCE), should constitute the basis for evaluating novel coronary devices or pharmacotherapeutic agents[4]. The combination of clinically relevant events linked by common elements of pathophysiology may be expected to provide additional statistical power[4]. It has been argued that composite endpoints built on site-reported events may allow detection of benefit and risk signals with potentially superior sensitivity[5-7].

Furthermore, given the strong association between bleeding and mortality risk, attempts to quantify the net adverse clinical events (NACE) incorporating safety-related bleeding events aside from ischaemic complications, may provide incremental insights into the understanding of the benefit-risk ratio of an evaluated treatment strategy.

Given this background, and to complement the interpretation of the GLOBAL LEADERS study results, we analysed the impact of the experimental treatment strategy on the rates of ARC-2 defined site-reported POCE and NACE up to two years after PCI in this randomised, multicentre, open-label study, being so far the first trial comparing two antiplatelet treatment strategies with randomisation done at the time of PCI[1,3].

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Methods

STUDY DESIGN AND POPULATION

GLOBAL LEADERS was an open-label, randomised, multicentre, superiority trial that enrolled a total of 15,991 patients at 130 sites in 18 countries[1]. The rationale, design and methodology of the GLOBAL LEADERS study (ClinicalTrials.gov number NCT01813435) have been detailed elsewhere[1].

In brief, the study population comprised patients scheduled to undergo PCI for stable coronary artery disease (CAD) or acute coronary syndromes (ACS), who required DAPT, on condition that oral anticoagulation was not indicated. There were no restrictions on the number of treated lesions or vessels, on lesion length or number of stents used. All types of lesion were allowed, including left main, bifurcations, chronic total occlusions, interventions on grafted vessels, etc.[1]. Detailed inclusion and exclusion criteria have been described previously[1] and are presented in **Supplementary Appendix 1**.

Patients were randomly allocated either to an experimental strategy of one-month aspirin and ticagrelor, followed by 23 months of ticagrelor alone, or to the reference strategy with one-year DAPT consisting of 75-100 mg aspirin daily in combination with either 75 mg clopidogrel daily (for patients with stable CAD) or 90 mg ticagrelor twice daily (for patients with ACS), followed by 75-100 mg aspirin alone for another 12 months[1]. Antiplatelet therapy was initiated before or at the time of the index procedure. PCI was standardised by uniform implantation of biodegradable polymer-based biolimus A9-eluting stents and bivalirudin administration, the periprocedural anticoagulation by default, except for those countries (Bulgaria, Poland) where the drug was not available **(Supplementary Appendix 2)**.

The primary endpoint was a composite of all-cause death or new Q-wave MI within 730 days of the index procedure. Deaths from any cause were ascertained without adjudication but a search for vital status was conducted through public domains in national and municipal registries among the 18 countries involved in the trial. Q-wave MI was centrally adjudicated and described according to 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[3].

In the present exploratory analysis, we evaluated the efficacy and safety of the experimental versus the reference treatment strategy in reducing the rates of the composite endpoints of POCE and NACE up to two years after PCI in the overall GLOBAL LEADERS study cohort, as well as across different patient subgroups pre-specified in the study protocol.

COMPOSITE ENDPOINT DEFINITIONS

Composite endpoints analysed in the present investigation involved site-reported secondary clinical endpoints[1,3]. POCE were defined as a composite of all-cause mortality, any stroke, any MI or any revascularisation, as specified by the ARC-2 consensus, whereas NACE included POCE and bleeding type 3 or 5, according to the Bleeding Academic Research Consortium

(BARC) definitions. A detailed description of the study endpoint definitions, follow-up and study overview has been provided in **Supplementary Appendix 3**. Composite endpoints were reported up to two years according to the time-to-first-event principle. In addition, the pre-specified landmark analyses were performed corresponding to the planned dates of discontinuation of aspirin at 30 days in the experimental group or of a $P2Y_{12}$ receptor antagonist at one year in the reference group after the index procedure.

STATISTICAL ANALYSIS

Statistical analyses for the primary and secondary endpoints in the GLOBAL LEADERS study have been described in detail previously[1,3].

For the purpose of the current *post hoc* analysis, the composite endpoints of POCE and NACE involving the secondary efficacy and safety endpoints were evaluated using the Mantel-Cox log-rank method up to the time point when the first event occurred, reporting hazard ratios (HR) with 95% CI. Two landmark analyses at 30 days and one year after randomisation were performed.

In addition, we performed predefined subgroup analyses of the POCE and NACE at two years with interaction tests for treatment effect.

All analyses were performed following the intention-to-treat definition using SPSS software, Version 25 (IBM Corp., Armonk, NY, USA). A two-sided p-value of <0.05 was considered statistically significant.

Results

Between July 2013 and November 2015 the GLOBAL LEADERS study enrolled and randomised 15,991 patients[3]. Except for 31 patients (0.19%: 23 patients who withdrew consent and formally requested their data deletion and eight patients with survival information missing despite additional search through public domains in national and municipal registries), there were data from 7,980 patients in the experimental group and 7,988 in the reference group available for analysis **(Figure 1)**.

The baseline clinical and procedural characteristics were well balanced between the experimental and reference treatment strategy **(Supplementary Table 1, Supplementary Table 2)**.

At two-year follow-up, POCE occurred in 1,050 (13.2%) patients in the experimental group and in 1,131 (14.2%) patients in the reference treatment strategy group (HR 0.93, 95% CI: 0.85-1.01, p=0.085 **(Figure 1)**.

NACE had occurred in 1,145 (14.4%) patients in the experimental group and in 1,237 (15.5%) in the reference group (HR 0.92, 95% CI: 0.85-1.00, p=0.057) **(Figure 2, Supplementary Table 3)**.

There were no between-group differences in each individual component of the composite endpoints, all-cause mortality, any stroke, any MI, any revascularisation, or bleeding BARC 3 or 5 type **(Supplementary Table 3)**.

LANDMARK ANALYSES

Following landmark analysis at 30 days, there were no significant differences between the experimental and the reference group in the rates of POCE (11.2% vs 11.8%, HR 0.95, 95% CI: 0.86-1.04, p=0.249) and NACE (12.0% vs 12.8%, HR 0.94, 95% CI: 0.86-1.02, p=0.149) occurring between 30 days and two years post randomisation.

Similarly, following landmark analysis at one year, there were no significant differences between the treatment groups in the rates of POCE (4.9% vs 5.4%, HR 0.91, 95% CI: 0.78-1.05, p=0.180) and NACE (5.2% vs 5.6%, HR 0.93, 95% CI: 0.81-1.08, p=0.341) occurring between one and two years post randomisation **(Figure 3, Supplementary Table 4)**.

SUBGROUP ANALYSES

At two-year follow-up, among ACS patients POCE occurred in 492 (13.1%) patients in the experimental group and in 519 (13.9%) patients in the reference treatment strategy group (HR 0.94, 95%

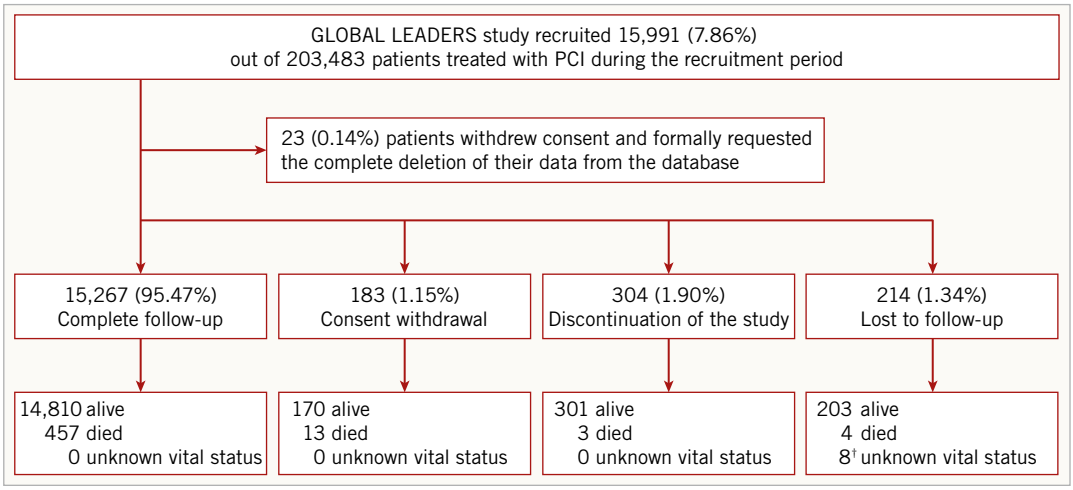

Figure 1. *The GLOBAL LEADERS study flow diagram. † Four patients were in the experimental group and the others were in the reference group.*

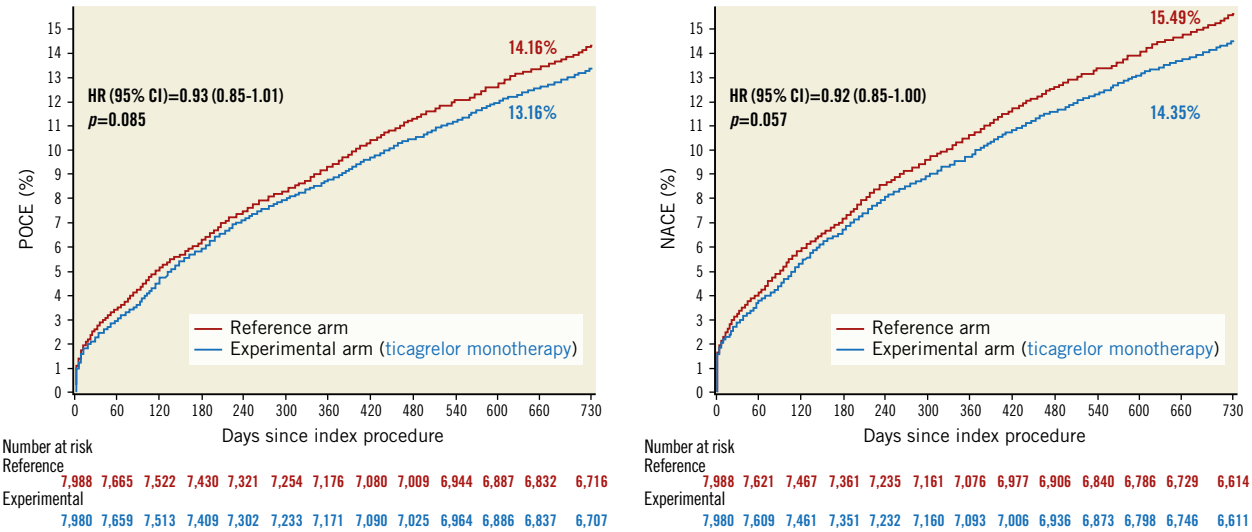

Figure 2. *Kaplan-Meier estimate of patient-oriented composite endpoints (POCE) and net adverse clinical events (NACE) at two years. CI: confidence interval; HR: hazard ratio*

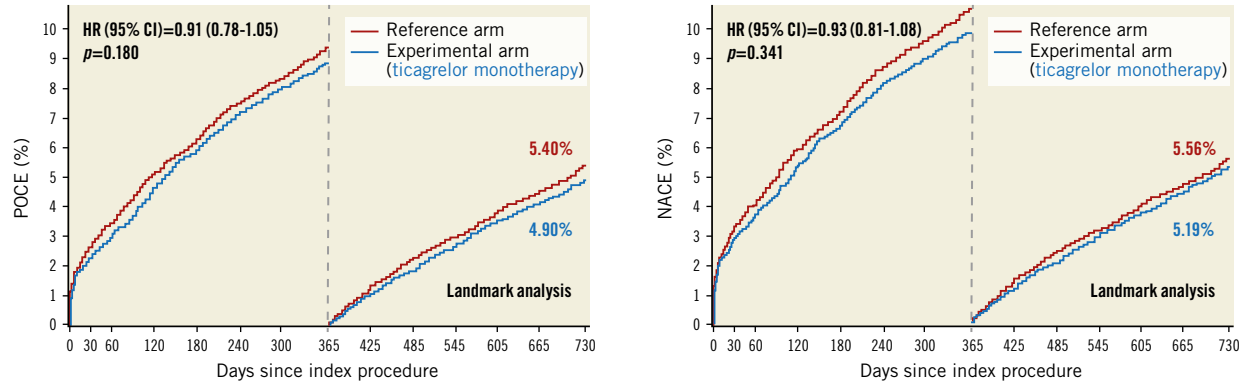

Figure 3. *Landmark analysis at one year for patient-oriented composite endpoints (POCE) and net adverse clinical events (NACE). CI: confidence interval; HR: hazard ratio*

CI: 0.83-1.07, p=0.336), whereas in stable CAD patients POCE occurred in 557 (13.2%) patients in the experimental group and in 613 (14.4%) patients in the reference group (HR 0.91, 95% CI: 0.81-1.02, p=0.108) (p for interaction=0.700).

Among ACS patients, NACE occurred in 531 (14.2%) patients in the experimental group and in 578 (15.5%) in the reference group (HR 0.91, 95% CI: 0.81-1.02, p=0.110), whereas in stable CAD patients NACE occurred in 613 (14.5%) patients in the experimental group and in 660 (15.5%) patients in the reference group (HR 0.93, 95% CI: 0.83-1.04, p=0.205) (p for interaction=0.754).

The remaining subgroup analyses according to pre-specified clinical characteristics and type of treatment also did not demonstrate significant treatment effects, as statistically ascertained by non-significant tests for treatment effect for POCE **(Figure 4, Supplementary Table 5)** and NACE two years after PCI **(Figure 5, Supplementary Table 6)**.

In the experimental versus the reference arm, the rates of patients who adhered to the randomised treatment regimen at discharge, 3, 12, and 24 months were, respectively: 97.6% vs 97.2%, 86.0% vs 93.6%, 81.7% vs 89.3% and 77.6% vs 93.1%.

Discussion

This is the first contemporary all-comers PCI trial reporting site-reported POCE rates according to the new ARC-2 definition which, at variance with the previously reported three-component endpoint (all-cause death, any MI, any revascularisation), also includes stroke as a highly relevant clinical outcome from the individual patient's perspective[4,8].

The experimental strategy did not reduce the risk of POCE when compared to the reference treatment. In addition, no significant differences were seen in the rates of NACE between the treatment groups (p=0.057), though numerical NACE were less frequently observed in the experimental arm. There was no treatment effect for any of the pre-specified subgroups. These findings, in line with the primary study results, do not support a change in clinical practice consisting of standard DAPT followed by aspirin monotherapy.

	Experimental treatment strategy (n=7,980)	Reference treatment strategy (n=7,988)	HR [Exp./Ref] (95% CI)	p	p for interaction
Indication					**0.714**
ACS	492/3,750	518/3,737	0.95 (0.84-1.07)	0.366	
Stable CAD	558/4,230	613/4,251	0.92 (0.82-1.03)	0.131	
Age					**0.134**
>75 years	207/1,292	248/1,273	0.82 (0.68-0.98)	0.032	
≤75 years	843/6,688	883/6,715	0.96 (0.87-1.05)	0.381	
Diabetes mellitus					**0.445**
diabetics	338/2,049	369/1,989	0.88 (0.76-1.02)	0.096	
non-diabetics	711/5,925	761/5,994	0.95 (0.86-1.05)	0.291	
Renal failure					**0.406**
Yes	194/1,099	219/1,072	0.86 (0.71-1.04)	0.128	
No	847/6,881	908/6,916	0.94 (0.86-1.04)	0.218	
Peripheral vascular disease					**0.377**
Yes	101/476	108/529	1.05 (0.80-1.37)	0.736	
No	942/7,428	1,010/7,389	0.92 (0.84-1.01)	0.069	
Left main treated					**0.348**
Yes	37/197	45/190	0.76 (0.49-1.18)	0.217	
No	1,013/7,783	1,086/7,798	0.94 (0.86-1.02)	0.124	
Geographic area					**0.357**
Western Europe	833/6,156	925/6,167	0.90 (0.82-0.99)	0.028	
Eastern Europe	190/1,502	171/1,500	1.12 (0.91-1.38)	0.279	
Rest of the world	27/322	35/321	0.75 (0.45-1.24)	0.261	
Type of reference treatment strategy					**0.273**
Use of ticagrelor	556/4,179	567/4,146	0.97 (0.87-1.09)	0.635	
Use of clopidogrel	494/3,801	564/3,842	0.89 (0.78-1.00)	0.047	

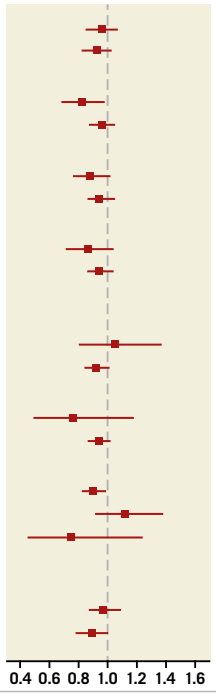

Figure 4. *Subgroup analysis for patient-oriented composite endpoints (POCE) at two years, according to the pre-specified baseline variables. Number of first events and percentages are reported. ACS: acute coronary syndrome; CAD: coronary artery disease; HR: hazard ratio; CI: confidence interval*

	Experimental treatment strategy (n=7,980)	Reference treatment strategy (n=7,988)	HR [Exp./Ref] (95% CI)	p	p for interaction
Indication					**0.728**
ACS	531/3,750	577/3,737	0.91 (0.81-1.03)	0.123	
Stable CAD	614/4,230	660/4,251	0.94 (0.84-1.05)	0.249	
Age					**0.487**
>75 years	245/1,292	276/1,273	0.88 (0.74-1.04)	0.128	
≤75 years	900/6,688	961/6,715	0.94 (0.86-1.03)	0.168	
Diabetes mellitus					**0.544**
diabetics	366/2,049	397/1,989	0.89 (0.77-1.02)	0.103	
non-diabetics	778/5,925	839/5,994	0.94 (0.85-1.03)	0.196	
Renal failure					**0.696**
Yes	219/1,099	239/1,072	0.89 (0.74-1.07)	0.228	
No	917/6,881	993/6,916	0.93 (0.85-1.02)	0.115	
Peripheral vascular disease					**0.506**
Yes	109/476	120/529	1.01 (0.78-1.31)	0.943	
No	1,029/7,428	1,103/7,389	0.92 (0.85-1.00)	0.055	
Left main treated					**0.445**
Yes	42/197	49/190	0.79 (0.53-1.20)	0.272	
No	1,103/7,783	1,188/7,798	0.93 (0.86-1.01)	0.081	
Geographic area					**0.404**
Western Europe	916/6,156	1,014/6,167	0.90 (0.83-0.99)	0.025	
Eastern Europe	200/1,502	188/1,500	1.07 (0.88-1.30)	0.512	
Rest of the world	29/322	35/321	0.81 (0.49-1.32)	0.395	
Type of reference treatment					**0.651**
Use of ticagrelor	602/4,179	631/4,146	0.94 (0.84-1.05)	0.293	
Use of clopidogrel	543/3,801	606/3,842	0.91 (0.81-1.02)	0.099	

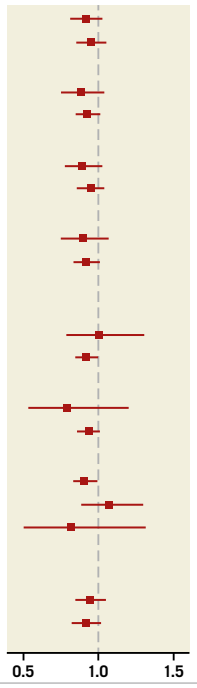

Figure 5. *Subgroup analysis for net adverse clinical events (NACE) at two years, according to the pre-specified baseline variables. Number of first events and percentages are reported. ACS: acute coronary syndrome; CAD: coronary artery disease; HR: hazard ratio; CI: confidence interval*

These observations, however, need to be interpreted in light of the significantly lower treatment adherence in the experimental versus the reference group, that was different in particular between the first and the second year of observation. Although any plausible explanation for these findings would be considered speculative, it cannot be excluded that the lower adherence to the experimental treatment could have partially contributed to the loss of statistical significance for the difference in the rates of the primary endpoint between the two treatment groups at two years, compared with the rates found at one year. In the GLOBAL LEADERS adherence substudy, conducted among 8,545 consecutive patients in whom both the stop and restart dates of the allocated treatment have been recorded after the modification of the electronic case report form (eCRF), the main reasons for non-adherence at two years were dyspnoea (233 [26%] vs 8 [3%], p=0.001), bleeding (191 [21%] vs 44 [16%], p=0.070) and repeat PCI (128 [14%] vs 50 [18%], p=0.102) in the experimental versus the reference group, respectively[3].

SITE-REPORTED vs CEC-ADJUDICATED ENDPOINTS

In the GLOBAL LEADERS study no formal clinical events committee (CEC) procedures were performed for the following reasons. First, the study aimed to be a pragmatic trial to increase generalisability of results and facilitate the adoption of new treatment strategies in clinical practice. Second, limited resources of this investigator-initiated study precluded formal event adjudication in the overall cohort. In addition, the main component of the primary endpoint – all-cause mortality – by definition does not require adjudication and was available in all but eight patients out of 15,991 patients enrolled in the study. The new Q-wave MIs were adjudicated by a dedicated core laboratory using the Minnesota Classification. The study was monitored for event underreporting and event definition consistency, with as many as seven on-site monitoring visits carried out at individual sites; one fifth of events underwent verification against the source documentation.

The role of an independent CEC has been challenged on several occasions with the suggestion that site-reported events may provide sufficient accuracy for reporting[5,6,9,10], especially in pharmacological trials. Both the rate of events and therapeutic effects have been shown to vary after adjudication; a meta-analysis of trials with cardiovascular outcomes failed to detect any effect of event adjudication on study conclusions[6,9,11-13].

Beyond MI, the clinical endpoint of bleeding has been considered one of those outcomes that requires central adjudication in order to avoid potential event misclassification by investigators. Nevertheless, the superiority of such an approach over the investigator-reported events has not been sufficiently documented[14]. "Objective" adjudication of bleeding may not change the overall trial results, though it is associated with a significant increment in study cost, as demonstrated in the PROTECT study[14].

Use of site-reported endpoints is a valid methodology in clinical research, especially involving large cohorts and with highly reliable endpoints (e.g., all-cause mortality). The degree of concordance in detailed or complex endpoints (e.g., universal definition of MI or BARC-defined bleeding categories) between sites and a central CEC is an area of ongoing research, where reproducibility of adjudication has been given increasing attention[6,7]. Of note, well-defined and restricted categories within a classification (e.g., BARC-defined bleeding type 3 to 5 as compared with types 1 and 2) are expected to provide higher concordance among sites and a central CEC, as well as a higher reproducibility. In addition, the risk of missing a serious adverse event by the CEC due to non-comprehensive triggering or lack of full site monitoring has been emphasised[5]. Therefore, public reporting of both site-reported and adjudicated data is an approach that might become the best practice to present and interpret trial results[6,7].

GLOBAL LEADERS STUDY EVENT ADJUDICATION: OPPORTUNITIES AND RISKS OF THE GLASSY SUBSTUDY

At the present time, it is still unclear whether central adjudication or inclusion of all investigator-reported events in the primary composite outcome might have increased or decreased the power and the sensitivity of the trial. To that end, the GLOBAL LEADERS Adjudication Sub-Study – GLASSY – has been designed (ClinicalTrials.gov Identifier: NCT03231059). The GLASSY study aims to re-evaluate, with the use of standard CEC adjudication procedures, the clinical outcomes in a selection of patients recruited in the highest recruiting centres in the GLOBAL LEADERS study. The study will assess the non-inferiority of the experimental versus reference treatment strategy with respect to CEC-adjudicated death, non-fatal MI, non-fatal stroke or urgent target vessel revascularisation (TVR) in addition to the superiority in preventing the adjudicated BARC 3 or 5 bleeding (as a co-primary safety endpoint) at two years. The scope of the study resembles previous attempts at trial event re-evaluation[5]. Importantly, the design of the GLASSY study has been published in the public domain prior to completion of the GLOBAL LEADERS trial, and the database was locked prior to the final results being known. Efforts have been made to ensure blinded endpoint analysis by the CEC members. Some inherent limitations of adjudication of the site-reported endpoints in the highest-recruiting centres of the GLOBAL LEADERS cohort potentially reside in the foreknowledge of the main study results, and in the reduction of the total number of patients involved in this major analysis, thereby potentially affecting the statistical power[1,15]. Furthermore, additional search strategies and enquiries sent to the participating sites may trigger additional endpoint reporting which may also interfere with the final study results and contrast with the originally reported study outcomes. Notwithstanding these risks, the adjudication of secondary endpoints in the GLASSY study will provide valuable data for the clinical community.

ASPIRIN-FREE ANTIPLATELET STRATEGIES IN THE FUTURE

To prove the mechanistically sound concept of aspirin-free strategies, any future randomised clinical trials will have to design novel treatment schemes and specific study endpoints[2].

The true two-year all-cause mortality (2.99%) observed in the present trial was markedly lower than the assumed all-cause mortality (4.5%) derived from the LEADERS trial, potentially underpowering the trial[3]. It appears that additional patient selection and enrichment of the cardiovascular risk in the evaluated population may be needed to detect treatment effects, i.e., with the use of simple prediction tools such as the PARIS or the PRECISE DAPT score[16,17].

Sole ticagrelor use after three months of DAPT comprising ticagrelor and aspirin is currently being evaluated in the TWILIGHT study (ClinicalTrials.gov Identifier: NCT02270242). In contrast to the GLOBAL LEADERS study, TWILIGHT has selected bleeding BARC 2, 3 or 5 type as the composite primary endpoint for the superiority analysis and the composite secondary endpoint of ischaemic events (all-cause death, non-fatal MI, or stroke) for the non-inferiority analysis. An even more drastic approach to acetylsalicylic acid elimination from the antiplatelet regimen is being tested in the ASET trial in which, after successful and optimal PCI for stable CAD, patients receive three-month prasugrel monotherapy followed by aspirin monotherapy (or DAPT). This proof-of-concept, feasibility and safety study is not regulated by formal statistics but conducted in accordance with a stopping rule based on the limited occurrence of definite stent thrombosis – the trial will be terminated if more than three patients experience a definite stent thrombosis within four months of follow-up (ClinicalTrials.gov Identifier: NCT03469856).

Limitations

First and foremost, no central independent adjudication of clinical events was implemented in this open-label study and the currently reported composite endpoints solely involved the site-reported events, carrying the risk of event misclassification. The methodology of reported endpoints based on the electronic report form with description and definition of them in the eCRF could have limited this latter bias. Notwithstanding, with meticulous and continuous monitoring of event underreporting and event definition consistency including as many as seven onsite monitoring visits carried out at individual sites and 20% of reported events checked against the source documents, the clinical events reported by investigators represent a source of valuable data for the global cardiology community.

Secondly, the composite clinical endpoints reported in the present study, though advocated by leading academic and regulatory authorities[4,18], were not pre-specified in the study protocol as formal secondary endpoints. Nevertheless, every component of these clinically relevant endpoints was pre-specified in the study protocol and meaningful. Thirdly, revascularisation has been included in the composite endpoint to increase the sensitivity to detect hidden stent thrombosis or MI, which could have potentially been reported by investigators as only repeat revascularisation. However, it has to be acknowledged that the revascularisation component could also have introduced some noise which is not directly attributable to the treatment effect of antiplatelet therapy. Fourthly, MI has been reported by investigators in this trial according to the third universal definition, applicable at the time of the study design and conduct. Therefore, it cannot be excluded that MI reported according to the new MI definition could be somewhat different.

Finally, the definitions and methodology for the most accurate assessment of net clinical benefit have still not been standardised, and the optimal approach for the benefit-risk balance measurement in an attempt to conclude which therapy may be pursued and which abandoned still remains to be established.

Conclusions

The experimental treatment consisting of one-month DAPT, aspirin and ticagrelor, followed by 23 months of ticagrelor alone, was not associated with statistically significant differences in terms of POCE – the composite of all-cause mortality, any MI, any stroke, and any revascularisation – and NACE – the composite of POCE and any BARC 3 or 5 type bleeding – at two years, when compared to the reference treatment comprising 12-month DAPT, followed by aspirin monotherapy for 12 months. Adjudication of the trial may bring new insights into the tested antiplatelet regimens, though judicious interpretation of these results would be warranted.

Impact on daily practice

The novel antiplatelet regimen of 23-month ticagrelor monotherapy following one-month dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) did not reduce the risk of POCE or NACE when compared to the reference treatment strategy. Although these findings, in line with the primary study results, do not support a change in clinical practice consisting of standard DAPT followed by aspirin monotherapy, further studies evaluating aspirin-free antiplatelet strategies after PCI are warranted.

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Guest Editor

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

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Conflict of interest statement

P.W. Serruys has received personal fees from AstraZeneca, Biotronik, Cardialysis, GLG Research, Medtronic, Sino Medical Sciences Technology, Société Europa Digital & Publishing, Stentys France, Svelte Medical Systems, Philips/Volcano, St. Jude Medical, Qualimed, and Xeltis, outside the submitted work. E. Spitzer reports institutional grants from the European Cardiovascular Research Institute, during the conduct of the study. M. Tomaniak has received lecture fees from AstraZeneca. P. Chichareon has received a research grant from Biosensors. R. Modolo has received research grants from Biosensors. D. Adlam reports grants from the British Heart Foundation, grants from the NIHR Rare Diseases Translational Research Collaboration, grants and non-financial support from NIHR Leicester Biomedical Research Centre, grants from Beat SCAD, grants from Abbott Vascular, and non-financial support from AstraZeneca, during the conduct of the study. J. Tijssen reports personal fees from Cardialysis, for DSMB membership of the GLOBAL LEADERS trial during the conduct of the study. P.G. Steg reports grants and personal fees from Bayer/Janssen, Merck, Sanofi, Amarin, and Servier, personal fees from Amgen, Bristol-Myers Squibb, Boehringer-Ingelheim, Pfizer, Novartis, Regeneron, Lilly, and AstraZeneca, outside the submitted work. C. Hamm reports personal fees from AstraZeneca during the conduct of the study and personal fees from AstraZeneca outside the submitted work. P. Jüni has received research grants to the institution from AstraZeneca, Biotronik, Biosensors International, Eli Lilly and The Medicines Company, outside the submitted work, and is a Tier 1 Canada Research Chair in Clinical Epidemiology of Chronic Diseases (the GLOBAL LEADERS study was completed in part, with funding from the Canada Research Chairs Programme). P. Jüni serves as unpaid member of the steering group of trials funded by AstraZeneca, Biotronik, Biosensors, St. Jude Medical and The Medicines Company. P. Vranckx has received personal fees from AstraZeneca and The Medicines Company during the conduct of the study and personal fees from Bayer HealthCare, Terumo, and Daiichi Sankyo outside the submitted work. Y. Onuma has received consultancy fees from Abbott Vascular outside the submitted work. F. Verheugt reports personal fees from AstraZeneca during the conduct of the study. The other authors have no conflicts of interest to declare. The Guest Editor is a consultant for Edwards Lifesciences.

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Supplementary data

Supplementary Appendix 1. Inclusion and exclusion criteria.

Supplementary Appendix 2. Study procedures and follow-up.

Supplementary Appendix 3. Clinical endpoint definitions.

Supplementary Appendix 4. List of the GLOBAL LEADERS trial investigators.

Supplementary Table 1. Baseline characteristics.

Supplementary Table 2. Procedural characteristics.

Supplementary Table 3. Clinical outcomes at two years of follow-up.

Supplementary Table 4. Clinical outcomes at one year, and with landmark, from one year to two years of follow-up.

Supplementary Table 5. Exploratory subgroup analyses for patient-oriented composite endpoint (POCE) at two years.

Supplementary Table 6. Exploratory subgroup analyses for net adverse clinical events (NACE) at two years.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00202

Supplementary data

Supplementary Appendix 1. Inclusion and exclusion criteria

INCLUSION CRITERIA
For inclusion in the study patients must fulfil the following criteria:

1. Age ≥18 years.
2. Patients with any clinical indication for percutaneous coronary intervention.
3. Presence of one or more coronary artery stenosis of 50% or more in a native coronary artery or in a saphenous venous or arterial bypass conduit suitable for coronary stent implantation in a vessel with a reference vessel diameter of at least 2.25 millimetres.

EXCLUSION CRITERIA

Drug related

1. Known intolerance to aspirin, $P2Y_{12}$ inhibitors, bivalirudin, stainless steel or biolimus.
2. Known intake of a strong cytochrome P3A4 inhibitor (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir), as co-administration may lead to a substantial increase in exposure to ticagrelor.
3. Use of fibrinolytic therapy within 24 hours of percutaneous coronary intervention.
4. Known severe hepatic impairment.

Treatment related

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

Medical

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

General

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

Supplementary Appendix 2. Study procedures and follow-up

Percutaneous coronary intervention

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

Loading and switching of $P2Y_{12}$ receptor inhibitors in the GLOBAL LEADERS trial is detailed elsewhere (Vranckx P, Valgimigli M, Windecker S, Steg PG, Hamm C, Juni P, et al. Long-term ticagrelor monotherapy versus standard dual antiplatelet therapy followed by aspirin monotherapy in patients undergoing biolimus-eluting stent implantation: rationale and design of the GLOBAL LEADERS trial. EuroIntervention. 2016;12(10):1239-45). In case of ticagrelor discontinuation due to adverse effects other than bleeding (i.e., atrioventricular block, dyspnoea), patients could be switched to a standard dose of prasugrel in both study arms. The use of clopidogrel was restricted to patients undergoing elective stenting for stable lesions (cardiac biomarker negative, no clinical signs or symptoms of ongoing myocardial ischaemia lasting more than 20 minutes). In case of definite stent thrombosis patients were treated according to best clinical practice. Patients who required systemic oral anticoagulation after randomisation were treated according to local practice guidelines. Triple therapy was to be prescribed for the shortest necessary duration with frequent INR measurement (target INR 2–2.5) with clopidogrel as the default $P2Y_{12}$ receptor inhibitor. For patients not previously receiving aspirin, a loading dose of 325 mg is preferred (160-500 mg allowed). In the case of staged PCI or in case of unplanned reintervention (other than for definite stent thrombosis or ST-segment elevation myocardial infarction) in the study treatment arm, the 30-day treatment period with aspirin was re-started at the time of the staged procedure or reintervention.

The GLOBAL LEADERS trial protocol mandated a uniform anticoagulation with bivalirudin (The Medicines Company) (dose adjusted per local drug label) in those countries where the drug was approved for use during the procedure and uniform stent platform (Biolimus-A9™ eluting stent; Biosensors Interventional Technologies) use during the index procedure (including staged procedures) and any unplanned or inter-current repeat percutaneous coronary intervention. Balloon angioplasty and stent implantation were performed according to standard techniques; direct stenting (without previous balloon dilatation) was allowed. Staged procedures were permitted within three months after the index procedure; all the stents used were of the assigned type. Glycoprotein IIb/IIIa receptor inhibitors were to be administered only in patients who had periprocedural ischaemic complications (i.e., no reflow or giant thrombus) after stenting. The use of unfractionated heparin (up to an arbitrary set maximum of 4,000 IU) during the index diagnostic angiogram was left to the discretion of the investigator. The use of other medications was per applicable professional guidelines.

Patient follow-up

During study follow-up visits, patients were questioned about whether they had had a myocardial infarction, had been hospitalised for a subsequent cardiovascular presentation, had undergone revascularisation or cardiac testing, or had seen a cardiologist, and what medications they were taking. If a patient reported a hospitalisation that was possibly related to cardiac causes, the hospital records were reviewed. Adverse events were confirmed by means of a review of the records. If the patients or secondary contacts were unavailable, records at the presenting and neighbouring hospitals were reviewed to determine whether there had been repeat visits. Patients who withdrew consent to participate in the study were

included up to the date of withdrawal, with the exception of the analysis of death from any cause, in which we included information from all the patients for whom vital status could be determined from public records at the end of the study.

Study oversight

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

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

Ethics

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

Supplementary Appendix 3. Clinical endpoint definitions

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

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

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

Myocardial infarction
Myocardial infarction was defined according to the third universal definition of myocardial infarction, applicable at the time of study conduct, as study-specific myocardial infarction criteria (Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Eur Heart J. 2012;33:2551-67).

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

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
    - symptoms of ischaemia
    - new or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB)
    - development of pathological Q-waves on the ECG
    - imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
    - identification of an intracoronary thrombus by angiography or autopsy
- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic electrocardiographic changes or new left bundle branch block, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased
- Percutaneous coronary intervention-related myocardial infarction was arbitrarily defined by elevation of cardiac troponin values (>5x99th of the percentile upper reference limit) in patients with normal baseline values (≤99th percentile of the upper reference limit) or a rise of cardiac troponin values >20% if the baseline values were elevated and were stable or

falling. In addition, either:
symptoms suggestive of myocardial ischaemia or

- new ischaemic electrocardiographic changes or
- angiographic findings consistent with a procedural complication, or
- imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality was required.

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

Coronary artery bypass grafting-related myocardial infarction is arbitrarily defined by elevation of cardiac biomarker values (>10x99th percentile of the upper reference limit) in patients with normal baseline cardiac troponin values (≤99th percentile of the upper reference limit). In addition, either:

- new pathological Q-waves or new left bundle branch block, or
- angiographically documented new graft or new native coronary artery occlusion, or
- imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Revascularisation

Revascularisation included target and non-target vessel revascularisations.

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

- Type 0: No evidence of bleeding.
- Type 1: Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalisation, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional.
- Type 2: Any overt, actionable sign of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria:
    - requiring non-surgical, medical intervention by a healthcare professional,
    - leading to hospitalisation or increased level of care, or
    - prompting evaluation
- Type 3: Clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare provider responses, as listed below:
    - Type 3a:

        - overt bleeding plus haemoglobin drop of 3 to <5 g/dL (provided haemoglobin drop is related to bleed)
        - any transfusion with overt bleeding
    - Type 3b:
        - overt bleeding plus haemoglobin drop ≥5 g/dL (provided haemoglobin drop is related to bleed),
        - cardiac tamponade,
        - bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid),
        - bleeding requiring intravenous vasoactive agents
    - Type 3c:
        - intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation, does include intraspinal)
        - subcategories confirmed by autopsy or imaging or lumbar puncture,
        - intraocular bleed compromising vision.
- Type 4: coronary artery bypass grafting-related bleeding
    - perioperative intracranial bleeding within 48 hrs,
    - reoperation after closure of sternotomy for the purpose of controlling bleeding
    - transfusion of ≥5 U whole blood or packed red blood cells within a 48-hr period,
    - chest tube output more than or equal to 2L within a 24-hr period
- Type 5: fatal bleeding
    - Type 5a:
        - probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
    - Type 5b:
        - definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

Supplementary Appendix 4. List of the GLOBAL LEADERS trial investigators.

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Belgium	Virga Jesse	Dr. Edouard Benit
Germany	Kerckhoff Heart Center	Dr. Christoph Liebetrau
Belgium	Imelda	Dr. Luc Janssens
Italy	Lab. Emodinamica	Dr. Maurizio Ferrario
Switzerland	Bern University Hospital (Inselspital, Universitätsspital Bern)	Prof. Stephan Windecker
Poland	PAKS Chrzanów	Dr. Aleksander Żurakowski
Netherlands	Erasmus MC	Prof. Robert Jan van Geuns
Italy	Azienda Ospedaliera S. Maria	Prof. Marcello Dominici
Austria	Wilhelminenspital	Prof. Kurt Huber
Netherlands	OLVG	Dr. Ton Slagboom
Poland	PAKS Dabrowa	Prof. Paweł Buszman
Italy	Ospedale S. Donato	Dr. Leonardo Bolognese
Italy	University Hospital of Ferrara	Dr. Carlo Tumscitz
Poland	Krakowski Szpital Specjalistyczny im. Jana Pawła II	Prof. Krzysztof Żmudka
Belgium	CHU de Charleroi	Dr. Adel Aminian
Belgium	ZOL St. Jan	Dr. Mathias Vrolix
Bulgaria	City Clinic	Dr. Ivo Petrov
UK	Royal Blackburn Hospital	Dr. Scot Garg
Germany	Rhein Ruhr Center	Dr. med. Christoph Kurt Naber
Poland	PAKS Kozle	Dr. Janusz Prokopczuk
Spain	Uni. Hospital Barcelona	Dr. Manel Sabate
UK	Central Manchester University Hospitals NHS Foundation Trust, Manchester Royal Infirmary	Dr. Farzin Fath-Ordoubadi
Belgium	Algemeen stedelijk ziekehuis	Dr. Ian Buysschaert
UK	University Hospital of Wales	Dr. Richard Anderson
UK	Golden Jubilee National Hospital	Prof. Keith G. Oldroyd
Spain	H. Bellvitge	Dr. Angel Cequier
France	Rangueil Hospital	Prof. Didier Carrie
UK	Liverpool Heart and Chest Hospital	Prof. Rod H. Stables
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Netherlands	Maasstad	Dr. Kees-Jan Royaards
Hungary	Semmelweis University	Dr. Bela Merkely
Germany	Klinikum Landshut-Achdorf	Dr. med. Bernhard Zrenner
Bulgaria	UMBAL St. George	Dr. Gincho Tonev

Germany	Kliniken Maria Hilf	Prof. Dr. med. Jürgen vom Dahl
Bulgaria	"St. Marina" University Hospital	Dr. Veselin Valkov
Austria	General Hospital Linz (AKH-Linz)	Prof. Dr. Clemens Steinwender
Germany	Uniklinikum Tübingen	Prof. Dr. Tobias Geisler
Germany	University of Giessen	Prof. Dr. med. Christian Hamm
Brazil	INCOR - HCFMUSP	Dr. Pedro Alves Lemos Neto
Spain	Clinico San Carlos	Dr. Carlos Macaya Miguel
Germany	University Hospital, Med. Fakultät Carl Gustav Carus	Prof. Dr. Ruth H. Strasser Dr. Karim Ibrahim
Poland	Nyskie Centrum Kardiologii	Dr Paweł Jasionowicz
UK	Hertfordshire Cardiac Centre Lister Hospital	Dr. Neville Kukreja
Hungary	Szegedi Tudományegyetem	Dr. Imre Ungi
France	Groupe Hospitalier Mutualiste de Grenoble	Dr. Mohamed Abdellaoui
Bulgaria	St. Anna Sofia	Dr. Vasil Velchev
Germany	Universitäts-Herzzentrum Freiburg Bad Krozingen	Prof. Franz-Josef Neumann
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Spain	H Ramon y Cajal-Madrid	Dr. Rosa Ana Hernández Antolin
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France	Saint Etienne University Hospital	Prof. Karl Isaaz
Austria	Medical University Hospital Graz	Prof. Dr. Robert Zweiker
Singapore	Tan Tock Seng Hospital	Dr. Paul Ong
Denmark	Roskilde University Hospital	Dr. Michael Munndt Ottesen

UK	Lancashire Heart Centre, Victoria Hospital	Dr. Gavin Galasko
Switzerland	Kantonsspital Baselland, Standort Liestal	Dr. med. Gregor Leibundgut
Netherlands	Medisch Centrum Alkmaar	Dr. Victor A.W.M. Umans
Austria	Medical University Innsbruck	Prof. Dr. med Guy Friedrich
Germany	University Medical Center Goettingen	Dr. Tim Seidler
UK	Papworth Hospital	Dr. Stephen Hoole
Bulgaria	Alexandrovska Hospital	Dr. Dobrin Vassilev
Germany	Universitätsmedizin der Joh. Gutenberg-Universität Mainz	Prof. Dr. med. Tommaso Gori
Canada	Quebec Heart-Lung Institute	Dr. Olivier F. Bertrand
Portugal	Hospital St. Marta Lisbon	Dr. Rui Cruz Ferreira
Austria	University Hospital AKH	Prof. Bernhard Frey (Previous PI: Prof. Georg Delle Karth)
UK	Freeman Hospital	Prof. Azfar Zaman
Singapore	National Heart Center Singapore	Prof. Koh Tian Hai
Brazil	Instituto Dante Pazzanese de Cardiologia	Dr. Amanda Sousa
Switzerland	Tiefenauspital	Dr. Aris Moschovitis
UK	University Hospital Southampton	Prof. Nick Curzen
Poland	PAKS Ustron	Dr. Grzegorz Galuszka
Germany	Städtische Kliniken Neuss, Lukaskrankenhaus GmbH	Prof. Dr. Michael Haude
Hungary	State Hospital for Cardiology	Dr. Faluközy József
Germany	Schwarzwald-Baar Klinikum	Prof. Dr. Werner Jung
Denmark	Copenhagen University Hospital - Rigshospitalet	Dr. Lene Holmvang
Switzerland	CardioCentro Ticino	Prof. Tiziano Moccetti
UK	Glan Clwyd Hospital	Dr. Eduardas Subkovas
UK	Royal Bournemouth Hospital	Dr. Suneel Talwar
Spain	Hospital Puerta de Hierro	Dr. Javier Goicolea
Italy	San Raffaele	Prof. Antonio Colombo
France	Clinique Axium	Dr. Luc Maillard
Australia	The Northern Hospital	Prof. Peter Barlis
Brazil	Instituto Do Coracao Do Triangulo Mineiro	Dr. Roberto Botelho
Australia	Prince Charles Hospital	Dr. Christopher Raffel
Switzerland	CHUV, Centre Hospitalier Universitaire Vaudois	Prof. Eric Eeckhout
Netherlands	Medisch Centrum Leeuwarden	Dr. Sjoerd H. Hofma
Bulgaria	"St. Ekaterina" University Hospital	Dr. Diana Trendafilova-Lazarova
Hungary	Szabolcs-Szatmár-Bereg County and Un. Teaching Hospital	Dr. Zsolt Kőszegi
Netherlands	UMC St Radboud	Prof. Dr. Harry Suryapranata

Spain	Hospital Meixoeiro	Dr. Andres Iñiguez
Hungary	University of Pécs	Dr. Iván Horváth
UK	Belfast Health & Social Care Trust	Dr. Simon Walsh
Portugal	Hospital de Santa Maria	Dr. Pedro Canas da Silva
Spain	Hosp Juan Ramon Jiminez	Dr. Jose Francisco Diaz
UK	New Cross Hospital	Dr. James Cotton
France	Clinique Saint-Hilaire	Dr. René Koning
Netherlands	Sint Antonius Ziekenhuis	Dr. Benno Rensing
Germany	Med. Fakult. Mannheim der Univ. Heidelberg	Prof. Dr. med. Ibrahim Akin
Germany	Uniklinikum Bonn	Prof. Dr. med. Nikos Werner
UK	University of Leicester and University Hospitals Leicester	Dr. David Adlam
UK	Royal Sussex County Hospital	Dr. David Hildick-Smith
Hungary	University of Debrecen	Prof. Dr. István Édes
Switzerland	University Hospital-Hôpitaux Universitaires de Genève - HUG – Service de Cardiologie Interventionnelle	Prof. Dr. Marco Roffi
Netherlands	University Medical Centre Groningen (UMCG)	Dr. Pim van der Harst
Germany	Charite, Campus Virchow	Dr. Florian Krackhardt
France	Uni. Hospital Mondor	Prof. Emmanuel Teiger
Brazil	Instituto Estadual Cardiologia Aloisio De Castro	Dr. Edgard Freitas Quintella
Portugal	Hospital St. Cruz Lisbon	Dr. Manuel Almeida
Hungary	Gottsegen György (National Health Institute)	Dr. Geza Fontos
France	Clinique des Domes	Dr. Pascal Barraud
France	Clinique Louis Pasteur	Dr. Michael Angioi
France	Hôpital de la Croix-Rousse	Dr. Pierre Lantelme
Portugal	Centro Hospitalar de Gaia	Dr. Vasco Gama Ribeiro
Australia	St. Vincent’s Hospital (Victoria)	Prof. Peter Barlis
Belgium	OLVZ	Dr. Emanuel Barbato
Brazil	Instituto Nacional De Cardiologia	Dr. Sergio Leandro

Supplementary Table 1. Baseline characteristics.

	Experimental treatment strategy	Reference treatment strategy
Total no. of patients	N=7,980	N=7,988
Age (years)	n=7,980, 64.5±10.3	n=7,988, 64.6±10.3
Females	n=7,980, 1,865 (23.4%)	n=7,988, 1,849 (23.1%)
Body mass index (kg/m²)	n=7,979, 28.2±4·6	n=7,987, 28.2±4.6
Medical history		
Diabetes mellitus	n=7,974, 2,049 (25.7%)	n=7,983, 1,989 (24.9%)
Insulin-dependent diabetes mellitus	n=7,955, 606 (7.6%)	n=7,966, 617 (7.7%)
Hypertension	n=7,954, 5,882 (73.7%)	n=7,960, 5,833 (73.0%)
Hypercholesterolaemia	n=7,718, 5,345 (67.0%)	n=7,747, 5,423 (67.9%)
Current smoker	n=7,980, 2,066 (25.9%)	n=7,988, 2,103 (26.3%)
Peripheral vascular disease	n=7,904, 476 (6.0%)	n=7,918, 529 (6.6%)
Chronic obstructive pulmonary disease	n=7,947, 404 (5.1%)	n=7,949, 417 (5.2%)
Previous major bleeding	n=7,968, 46 (0.6%)	n=7,979, 52 (0.7%)
Impaired renal function*	n=7,934, 1,099 (13.8%)	n=7,949, 1,072 (13.4%)
Previous stroke	n=7,967, 210 (2.6%)	n=7,978, 211 (2.6%)
Previous myocardial infarction	n=7,956, 1,831 (22.9%)	n=7,966, 1,879 (23.5%)
Previous percutaneous coronary intervention	n=7,974, 2,609 (32.7%)	n=7,980, 2,612 (32.7%)
Previous coronary artery bypass grafting	n=7,974, 448 (5.6%)	n=7,981, 495 (6.2%)
Clinical presentation		
Stable coronary artery disease	n=7,980, 4,230 (53.0%)	n=7,988, 4,251 (53.2%)
Acute coronary syndrome	n=7,980, 3,750 (47.0%)	n=7,988, 3,737 (46.8%)
Unstable angina	n=7,980, 1,004 (12.6%)	n=7,988, 1,018 (12.7%)
Non-STEMI	n=7,980, 1,684 (21.1%)	n=7,988, 1,689 (21.1%)
STEMI	n=7,980, 1,062 (13.3%)	n=7,988, 1,030 (12.9%)

Presented are sample sizes (n), and counts (%), means±standard deviations or medians (25%-75% interquartile range).

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

Supplementary Table 2. Procedural characteristics.

	Experimental treatment strategy	Reference treatment strategy	*p*-value
Total no. of patients	N=7,980	N=7,988	
PCI performed[a]	n=7,980, 7,943 (99.5%)	n=7,988, 7,940 (99.4%)	0.277
Vascular access site			
Radial	n=7,943, 5,872 (73.9%)	n=7,940, 5,889 (74.2%)	0.731
Femoral	n=7,943, 2,090 (26.3%)	n=7,940, 2,072 (26.1%)	0.759
Brachial	n=7,943, 46 (0.6%)	n=7,940, 47 (0.6%)	0.918
Number of lesions treated per patient	n=7,907	n=7,911	0.284
One lesion	5,895 (74.6%)	5,910 (74.7%)	
Two lesions	1,618 (20.5%)	1,569 (19.8%)	
Three or more lesions	394 (5.0%)	432 (5.5%)	
Total number of treated lesions	n=10,403	n=10,438	
Lesions treated in vessel(s)*	n=10,403	n=10,438	0.611
Left main coronary artery	197 (1.9%)	190 (1.8%)	
Left anterior descending artery	4,283 (41.2%)	4,383 (42.0%)	
Left circumflex artery	2,524 (24.3%)	2,553 (24.5%)	
Right coronary artery	3,284 (31.6%)	3,206 (30.7%)	
Bypass graft	115 (1.1%)	106 (1.0%)	
Total number of stented lesions	n=10,241	n=10,283	
Index PCI			
No. of stents per lesion*	n=10,241, 1.2±0.5	n=10,283, 1.2±0.5	0.820
Type of stent*			
Biolimus-eluting stent†	n=10,241, 9,708 (94.8%)	n=10,283, 9,707 (94.4%)	0.602
Other stents	n=10,241, 654 (6.4%)	n=10,283, 685 (6.7%)	
Total stent length per lesion (mm)*	n=10,241, 24.8±13.9	n=10,283, 24.8±14.0	0.932
Average stent diameter per lesion (mm)*	n=10,241, 3.0±0.5	n=10,283, 3.0±0.5	0.887

Direct stenting per lesion*	n=10,241, 3,334 (32.6%)	n=10,283, 3,350 (32.6%)	0.932
Bifurcation per lesion*	n=10,403, 1,251 (12.0%)	n=10,438, 1,265 (12.1%)	0.646
Thrombus aspiration performed per lesion*	n=10,403, 483 (4.6%)	n=10,438, 551 (5.3%)	0.040
TIMI flow pre procedure*	n=9,837	n=9,888	0.708
0 or 1	1,296 (13.2%)	1,314 (13.3%)	
2	1,187 (12.1%)	1,173 (11.9%)	
3	7,354 (74.8%)	7,401 (74.8%)	
TIMI flow post procedure*	n=10,064	n=10,145	0.324
0 or 1	41 (0.4%)	32 (0.3%)	
2	50 (0.5%)	46 (0.5%)	
3	9,973 (99.1%)	10,067 (99.2%)	

Presented are sample size (n), and counts (%) or means±standard deviations.

[a] N=85 patients did not receive PCI: medical treatment only (n=33 reference arm, n=31 experimental arm), transferred to urgent surgery (n=15 reference arm, n=6 experimental arm), died before PCI (n=0).

* Calculated per lesion and analysed using general or generalised linear mixed effects models with a random effect of the patient to account for multiple lesions treated within patients.

† Per-protocol BioMatrix family stent used. In n=147 lesions both BioMatrix family stent(s) and other stent(s) were implanted (n=68 reference arm lesions, n=79 experimental arm lesions).

Supplementary Table 3. Clinical outcomes at two years of follow-up.

	Experimental treatment strategy	Reference treatment strategy	Hazard ratio (95% CI)	*p*-value
Total no. of patients	N=7,980	N=7,988		
POCE - death, stroke, MI or revascularisation	1,050 (13.16)	1,131 (14.16)	0.93 (0.85-1.01)	0.085
NACE - death, stroke, MI, revascularisation, BARC 3 or 5 bleeding	1,145 (14.35)	1,237 (15.49)	0.92 (0.85-1.00)	0.057
All-cause mortality	224 (2.81)	253 (3.17)	0.88 (0.74-1.06)	0.180
Stroke	80 (1.00)	82 (1.03)	0.98 (0.72-1.33)	0.900
Myocardial infarction	248 (3.11)	250 (3.13)	1.00 (0.84-1.19)	0.980
Revascularisation	739 (9.26)	793 (9.93)	0.93 (0.84-1.03)	0.170
Target vessel revascularisation	389 (4.87)	442 (5.54)	0.88 (0.77-1.01)	0.068
BARC 2, 3, 4 or 5 bleeding	535 (6.70)	536 (6.71)	1.00 (0.89-1.13)	0.986
BARC 2, 3, or 5 bleeding	529 (6.63)	532 (6.66)	1.00 (0.88-1.12)	0.962
BARC 3 or 5 bleeding	163 (2.04)	169 (2.12)	0.97 (0.78-1.20)	0.766
BARC 5	22 (0.28)	24 (0.30)	0.92 (0.52-1.64)	0.778
BARC 5b	15 (0.19)	18 (0.23)	0.84 (0.42-1.66)	0.609
BARC 5a	7 (0.09)	6 (0.08)	1.17 (0.39-3.49)	0.776
BARC 3	150 (1.88)	159 (1.99)	0.95 (0.76-1.18)	0.630
BARC 3c	35 (0.44)	25 (0.31)	1.41 (0.84-2.35)	0.190
BARC 3b	53 (0.66)	74 (0.93)	0.72 (0.51-1.02)	0.065
BARC 3a	77 (0.96)	70 (0.88)	1.10 (0.80-1.53)	0.546
BARC 2	393 (4.92)	392 (4.91)	1.01 (0.87-1.16)	0.932
Composite of all-cause mortality, stroke, MI, or BARC 3 or 5 bleeding	616 (7.72)	653 (8.17)	0.95 (0.85-1.06)	0.336
Composite of cardiovascular mortality, stroke or MI	407 (5.10)	421 (5.27)	0.97 (0.85-1.11)	0.685
Composite of MI or definite stent thrombosis	271 (3.40)	269 (3.37)	1.01 (0.86-1.20)	0.880

Depicted are the first event per event type for each patient only (disregards multiple events of the same type within the same patient and censoring at 730 days since index PCI). Percentage of all patients. Exact censoring days used at each follow-up, i.e., events occurring up to n days are used for the first events: 2 years=730 days.

Cardiovascular mortality includes unclear causes of death.

MI: myocardial infarction

Supplementary Table 4. Clinical outcomes at one year, and with landmark, from one year to two years of follow-up.

	Experimental treatment strategy	Reference treatment strategy	Hazard ratio (95% CI)	*p*-value
Total no. of patients	N=7,980	N=7,988		
At 1 year				
POCE - death, stroke, MI or revascularisation	699 (8.76)	744 (9.31)	0.94 (0.85-1.04)	0.246
NACE - death, stroke, MI, revascularisation, BARC 3 or 5 bleeding	777 (9.74)	844 (10.57)	0.92 (0.84-1.02)	0.098
All-cause mortality	108 (1.35)	131 (1.64)	0.82 (0.64-1.06)	0.140
Stroke	52 (0.65)	49 (0.61)	1.07 (0.72-1.57)	0.750
Myocardial infarction	179 (2.24)	158 (1.98)	1.14 (0.92-1.41)	0.230
Revascularisation	518 (6.49)	549 (6.87)	0.94 (0.84-1.07)	0.350
Target vessel revascularisation	268 (3.36)	306 (3.83)	0.88 (0.74-1.03)	0.118
BARC 2, 3, 4 or 5 bleeding	402 (5.04)	444 (5.56)	0.91 (0.79-1.04)	0.162
BARC 2, 3, or 5 bleeding	397 (4.97)	440 (5.51)	0.90 (0.79-1.04)	0.149
BARC 3 or 5 bleeding	117 (1.47)	136 (1.70)	0.86 (0.67-1.11)	0.243
BARC 5	14 (0.18)	16 (0.20)	0.88 (0.43-1.80)	0.722
BARC 5b	9 (0.11)	11 (0.14)	0.82 (0.34-1.98)	0.659
BARC 5a	5 (0.06)	5 (0.06)	1.00 (0.29-3.47)	0.995
BARC 3	107 (1.34)	128 (1.60)	0.84 (0.65-1.08)	0.179
BARC 3c	23 (0.29)	16 (0.20)	1.44 (0.76-2.73)	0.256
BARC 3b	43 (0.54)	62 (0.78)	0.70 (0.47-1.03)	0.067
BARC 3a	52 (0.65)	57 (0.71)	0.92 (0.63-1.33)	0.648
BARC 2	298 (3.73)	324 (4.06)	0.92 (0.79-1.08)	0.318
Composite of all-cause mortality, stroke, MI, or BARC 3 or 5 bleeding	402 (5.04)	424 (5.31)	0.95 (0.83-1.09)	0.484

Composite of cardiovascular mortality, stroke or MI	277 (3.47)	267 (3.34)	1.04 (0.88-1.23)	0.623
Composite of MI or definite stent thrombosis	195 (2.44)	177 (2.22)	1.11 (0.90-1.36)	0.326
From 1 year to 2 years (landmark)				
POCE - death, stroke, MI or revascularisation	351 (4.90)	387 (5.40)	0.91 (0.78-1.05)	0.180
NACE - death, stroke, MI, revascularisation, BARC 3 or 5 bleeding	368 (5.19)	393 (5.56)	0.93 (0.81-1.08)	0.341
All-cause mortality	116 (1.47)	122 (1.55)	0.95 (0.74-1.22)	0.690
Stroke	28 (0.36)	33 (0.43)	0.85 (0.51-1.41)	0.530
Myocardial infarction	69 (0.91)	92 (1.21)	0.75 (0.55-1.03)	0.076
Revascularisation	221 (3.05)	244 (3.37)	0.90 (0.75-1.08)	0.280
Target vessel revascularisation	11 (0.14)	23 (0.30)	0.48 (0.23-0.99)	0.041
BARC 2, 3, 4 or 5 bleeding	133 (1.80)	92 (1.25)	1.45 (1.11-1.89)	0.006
BARC 2, 3, or 5 bleeding	132 (1.79)	92 (1.25)	1.44 (1.10-1.88)	0.007
BARC 3 or 5 bleeding	46 (0.60)	33 (0.43)	1.40 (0.89-2.19)	0.140
BARC 5	8 (0.10)	8 (0.10)	1.00 (0.38-2.68)	0.992
BARC 5b	6 (0.08)	7 (0.09)	0.86 (0.29-2.56)	0.788
BARC 5a	2 (0.03)	1 (0.01)	2.01 (0.18-22.11)	0.561
BARC 3	43 (0.56)	31 (0.40)	1.39 (0.88-2.21)	0.159
BARC 3c	12 (0.16)	9 (0.12)	1.34 (0.57-3.18)	0.504
BARC 3b	10 (0.13)	12 (0.16)	0.83 (0.36-1.93)	0.673
BARC 3a	25 (0.32)	13 (0.17)	1.93 (0.99-3.77)	0.050
BARC 2	95 (1.27)	68 (0.91)	1.40 (1.03-1.91)	0.033
Composite of all-cause mortality, stroke, MI, or BARC 3 or 5 bleeding	214 (2.87)	229 (3.06)	0.94 (0.78-1.13)	0.502
Composite of cardiovascular mortality, stroke or MI	130 (1.72)	154 (2.03)	0.85 (0.67-1.07)	0.170
Composite of MI or definite stent thrombosis	76 (1.00)	92 (1.21)	0.83 (0.61-1.13)	0.233

Presented are the first event per event type for each patient only (disregards multiple events of the same type within the same patient and censoring at 730 days since index PCI). Percentage of all patients. Exact censoring days used at each follow-up, i.e., events occurring up to n days are used for the first events: 2 years=730 days.

Cardiovascular mortality includes unclear causes of death.

MI: myocardial infarction

Supplementary Table 5. Exploratory subgroup analyses for patient-oriented composite endpoint (POCE) at two years.

	Experimental treatment strategy (n=7,980)	Reference treatment strategy (n=7,988)	Hazard ratio (95% CI)	*p*-value	*p* for interaction
Gender					0.453
Female	243/1,865	273/1,849	0.88 (0.74-1.04)	0.136	
Male	807/6,115	858/6,139	0.95 (0.86-1.04)	0.253	
BMI (kg/m²)					0.830
≥27	598/4,477	645/4,516	0.94 (0.84-1.05)	0.247	
<27	452/3,503	486/3,472	0.92 (0.81-1.05)	0.198	
Insulin-dependent diabetes mellitus					0.779
Diabetics	118/606	132/617	0.90 (0.70-1.15)	0.396	
Non-diabetics	929/7,374	995/7,371	0.93 (0.70-1.15)	0.396	
Current smoking					0.786
Yes	257/2,066	277/2,103	0.95 (0.80-1.12)	0.532	
No	793/5,914	854/5,885	0.92 (0.84-1.02)	0.100	
Previous stroke (>30 days)					0.451
Yes	43/210	52/211	0.80 (0.53-1.20)	0.274	
No	1,007/7,770	1,079/7,777	0.94 (0.86-1.02)	0.122	
Previous MI					0.782
Yes	287/1,831	311/1,879	0.95 (0.81-1.11)	0.517	
No	763/6,149	820/6,109	0.92 (0.84-1.02)	0.114	
Previous PCI					0.342
Yes	392/2,609	444/2,612	0.88 (0.77-1.01)	0.069	
No	656/5,371	685/5,376	0.96 (0.86-1.07)	0.441	
Previous CABG					0.224
Yes	111/448	114/495	1.09 (0.84-1.41)	0.524	
No	938/7,532	1,016/7,493	0.92 (0.84-1.00)	0.057	

CABG: coronary artery bypass grafting; 95% CI: 95% confidence interval; MI: myocardial infarction; PCI: percutaneous coronary intervention

Supplementary Table 6. Exploratory subgroup analyses for net adverse clinical events (NACE) at two years.

	Experimental treatment strategy (n=7,980)	Reference treatment strategy (n=7,988)	Hazard ratio (95% CI)	*p*-value	*p* for interaction
Gender					0.717
Female	277/1,865	303/1,849	0.90 (0.77-1.06)	0.211	
Male	868/6,115	934/6,139	0.93 (0.85-1.02)	0.139	
BMI (kg/m²)					0.899
≥27	644/4,477	699/4,516	0.93 (0.84-1.03)	0.179	
<27	501/3,503	538/3,472	0.92 (0.81-1.04)	0.178	
Insulin-dependent diabetes mellitus					0.933
Diabetics	129/606	140/617	0.94 (0.74-1.19)	0.579	
Non-diabetics	1,013/7,374	1,093/7,371	0.92 (0.85-1.01)	0.071	
Current smoking					0.926
Yes	276/2,066	302/2,103	0.93 (0.79-1.10)	0.388	
No	869/5,914	935/5,885	0.92 (0.84-1.01)	0.087	
Previous stroke (>30 days)					0.414
Yes	45/210	55/211	0.79 (0.53-1.17)	0.235	
No	1,097/7,770	1,179/7,777	0.93 (0.86-1.01)	0.088	
Previous MI					0.884
Yes	305/1,831	334/1,879	0.94 (0.80-1.09)	0.398	
No	834/6,149	894/6,109	0.92 (0.84-1.01)	0.094	
Previous PCI					0.485
Yes	422/2,609	473/2,612	0.89 (0.78-1.02)	0.085	
No	721/5,371	761/5,376	0.95 (0.85-1.05)	0.283	
Previous CABG					0.231
Yes	115/448	119/495	1.08 (0.84-1.39)	0.564	
No	1,029/7,532	1,116/7,493	0.92 (0.84-1.00)	0.039	

CABG: coronary artery bypass grafting; 95% CI: 95% confidence interval; MI: myocardial infarction; PCI: percutaneous coronary intervention