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Ticagrelor alone or conventional dual antiplatelet therapy in patients with stable or acute coronary syndromes

Anna Franzone[1], MD, PhD; Eugène P. McFadden[2,3], MD; Sergio Leonardi[4], MD, MHS; Raffaele Piccolo[1], MD, PhD; Pascal Vranckx[5], MD, PhD; Patrick W. Serruys[6,7], MD; Christian Hamm[8], MD; Philippe Gabriel Steg[9], MD; Dik Heg[10], PhD; Mattia Branca[10], PhD; Peter Jüni[11], MD; Stephan Windecker[12], MD; Marco Valgimigli[12], MD, PhD; on behalf of the GLASSY Investigators

1. Department of Advanced Biomedical Sciences, Federico II University of Naples, Naples, Italy; 2. Cardialysis Core Laboratories and Clinical Trial Management, Rotterdam, the Netherlands; 3. Department of Cardiology, Cork University Hospital, Cork, Ireland; 4. University of Pavia and Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy; 5. Department of Cardiology and Critical Care Medicine, Hartcentrum Hasselt, Jessa Ziekenhuis, Hasselt, Belgium; 6. Department of Cardiology, Imperial College London, London, United Kingdom; 7. Department of Cardiology, National University of Ireland, Galway, Ireland; 8. German Center for Cardiovascular Research (DZHK), partner site RheinMain, Frankfurt am Main, and Department of Cardiology, Kerckhoff Heart and Thorax Center, Bad Nauheim, Germany; 9. Université de Paris and AP-HP, Paris, France; 10. Institute of Social and Preventive Medicine and Clinical Trials Unit, University of Bern, Bern, Switzerland; 11. Applied Health Research Centre, Li Ka Shing Knowledge Institute of St Michael's Hospital, Department of Medicine, University of Toronto, Ontario, Canada; 12. Department of Cardiology, Inselspital, University of Bern, Bern, Switzerland

A list of study collaborators can be found in the Appendix paragraph.

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KEYWORDS

- ACS/NSTE ACS
- adjunctive pharmacotherapy
- stable angina
- STEMI

Abstract

Aims: The aim of this study was to investigate the effect of ticagrelor monotherapy after one-month dual antiplatelet therapy (DAPT) or conventional DAPT in patients with or without acute coronary syndrome (ACS) in the GLOBAL LEADERS Adjudication Sub-StudY (GLASSY).

Methods and results: Risk estimates were expressed as rate ratios (RR) with 95% confidence intervals (CI). A total of 3,840 ACS and 3,745 stable ischaemic heart disease (SIHD) patients were included. At two years, rates of the co-primary efficacy endpoint, a composite of death, myocardial infarction, stroke or urgent target vessel revascularisation, were 7.94% in the experimental and 9.68% in the control group (RR 0.82, 95% CI: 0.66-1.01) among ACS patients and 6.31% in the experimental and 7.14% in the control group (RR 0.89, 95% CI: 0.69-1.13) among SIHD patients (p_{int}=0.63). Trends for lower and higher risk of BARC 3 or 5 bleeding with the experimental strategy in ACS (2.27% vs 3.00%, RR 0.76, 95% CI: 0.51-1.12) and SIHD (2.70% vs 1.96%, RR 1.39, 95% CI: 0.91-2.12) patients, respectively, were observed with significant interaction testing (p_{int}=0.039). A net clinical benefit endpoint, the composite of both co-primary study endpoints, favoured the experimental treatment among ACS patients only.

Conclusions: Ticagrelor monotherapy after one-month DAPT provided consistent treatment effects on ischaemic endpoints in patients with or without ACS but only the former experienced a net clinical benefit. ClinicalTrials.gov identifier: NCT03231059

**Corresponding author: Swiss Cardiovascular Center Bern, Bern University Hospital, Hochschulstrasse 6, CH-3010 Bern, Switzerland. E-mail: marco.valgimigli@insel.ch*

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Abbreviations

ACS	acute coronary syndrome
ARC	Academic Research Consortium
BARC	Bleeding Academic Research Consortium
CI	confidence interval(s)
DAPT	dual antiplatelet therapy
GLASSY	GLOBAL LEADERS Adjudication Sub-StudY
GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries
IR	investigator-reported
MI	myocardial infarction
NCB	net clinical benefit
PCI	percutaneous coronary intervention
PEGASUS	Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin
PLATO	A Comparison of Ticagrelor and Clopidogrel in Patients With Acute Coronary Syndrome
RR	rate ratio
SIHD	stable ischaemic heart disease
ST	stent thrombosis
TIMI	Thrombolysis In Myocardial Infarction
TVR	target vessel revascularisation

Introduction

Dual antiplatelet therapy (DAPT) is the current standard of care in patients undergoing percutaneous coronary intervention (PCI)[1]. Because of their favourable risk-benefit ratio compared to clopidogrel, potent $P2Y_{12}$ inhibitors in addition to aspirin are currently recommended for one year after PCI for acute coronary syndrome (ACS). Prolonged DAPT mitigates the recurrence of ischaemic events, in particular in patients with prior myocardial infarction (MI) and other high-risk clinical features[2]. However, it confers an increased risk of major bleeding with a relevant impact on mortality, morbidity and costs[3].

Ticagrelor showed superior efficacy, including lower cardiovascular mortality rates, as compared to clopidogrel in patients with ACS but it increased spontaneous bleeding compared to clopidogrel[4]. Evidence regarding the risk/benefit profile of ticagrelor in patients with stable ischaemic heart disease (SIHD) is more limited.

In this study we explored the efficacy and safety of ticagrelor monotherapy from one month after PCI as compared to the current standard of care on adjudicated endpoints among 7,585 patients with or without ACS from the top 20 sites participating in the GLOBAL LEADERS trial (A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation).

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Methods

STUDY DESIGN AND PARTICIPANTS

GLASSY (NCT03231059) was a pre-specified ancillary study of the GLOBAL LEADERS trial (NCT01813435)[5]. Details of the study participants and procedures are provided in **Supplementary Appendix 1-Supplementary Appendix 6**. Ethics committees from each participating institution approved the study protocol and the study was conducted according to the principles of the Declaration of Helsinki and of Good Clinical Practice.

STUDY ENDPOINTS

The co-primary efficacy endpoint was a composite of death, MI, stroke or urgent target vessel revascularisation. The co-primary safety endpoint was a composite of Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding events. Secondary endpoints included each component of the co-primary composite endpoints plus definite, probable or possible stent thrombosis according to the Academic Research Consortium (ARC) classification; bleeding events adjudicated according to BARC, Thrombolysis In Myocardial Infarction (TIMI) and Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) classifications; type of death (cardiovascular, non-cardiovascular). Endpoint definitions are reported in **Supplementary Appendix 7**.

An independent clinical events committee blinded to treatment allocation adjudicated all suspected endpoints based on previously described trigger logics embedded in the case report forms.

STATISTICAL ANALYSIS

The co-primary efficacy and safety endpoints were the composite of death, non-fatal MI, non-fatal stroke, or urgent target vessel revascularisation (TVR) and type 3 or 5 BARC bleeding. A *post hoc* composite endpoint of net clinical benefit (NCB), defined as the composite of both co-primary study endpoints, consisting of all-cause death, non-fatal MI, non-fatal stroke, urgent TVR and BARC 3 or 5 bleeding was also considered. They were analysed by stratifying the population based on ACS versus SIHD, following the intention to treat with the Mantel-Cox method and reported as rate ratios (RR) with 95% confidence intervals (CI). We also performed pre-specified landmark analyses with cut-offs at 30 days and one year after the index procedure, with RRs calculated separately for events up to and beyond the landmarks. Consistency of treatment effect was analysed with treatment-by-subgroup interaction testing by ACS or SIHD at presentation. Secondary endpoints were analysed by intention to treat with the Mantel-Cox log-rank method. Conventional level of significance (p=0.05) was used for all p-values.

There was no adjustment for multiple testing of secondary endpoints. Categorical variables were compared with the chi-square or Fisher's exact test; continuous variables were compared with the Student's t-test or Wilcoxon rank-sum test for non-normally distributed data. All analyses were performed at the Clinical Trials Unit (University of Bern, Bern, Switzerland) in Stata, version 14.2 (StataCorp, College Station, TX, USA).

Results

PATIENTS AND PROCEDURES

From July 2013 to November 2015, 3,840 patients with ACS (1,939 in the experimental arm and 1,901 in the control arm) and 3,745 patients with SIHD (1,855 in the experimental arm and 1,890

in the control arm) were included from 20 sites across 9 countries **(Supplementary Figure 1)**. Baseline clinical and procedural features were balanced between arms within each presentation stratum **(Supplementary Table 1, Supplementary Table 2)**. Adherence to study medications is shown in **Supplementary Figure 2**.

Outcomes

FATAL AND ISCHAEMIC ENDPOINTS

At two years, the co-primary efficacy endpoint occurred in 154 (7.94%) patients in the experimental arm and in 184 (9.68%) patients in the control arm (RR 0.82, 95% CI: 0.66 to 1.01; p=0.065) in the ACS group, and in 117 (6.31%) patients in the experimental arm and in 135 (7.14%) patients in the control arm (RR 0.89, 95% CI: 0.69 to 1.13; p=0.34) in the SIHD group, with non-significant interaction testing (p_{int}=0.63) **(Figure 1, Figure 2, Table 1)**.

A total of 69 (3.56%) patients in the experimental arm and 78 (4.10%) in the control arm (RR 0.87, 95% CI: 0.63 to 1.20; p=0.39) in the ACS group and 42 (2.26%) patients in the experimental arm and 58 (3.07%) patients in the control arm (RR 0.74, 95% CI: 0.50 to 1.10; p=0.14) in the SIHD group died within two years (p_{int}=0.54) **(Table 1, Figure 2)**.

The rates of MI (2.99% vs 4.21%, RR 0.71, 95% CI: 0.51 to 0.99; p=0.046) and urgent TVR (2.27% vs 3.42%, RR 0.66, 95% CI: 0.45 to 0.97; p=0.033) were significantly lower among

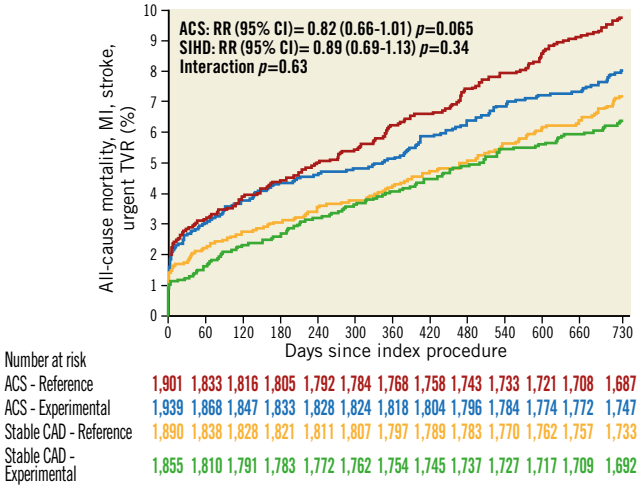

Figure 1. *Kaplan-Meier graphs for the co-primary ischaemic endpoint. Red lines, ACS patients in the reference arm; blue lines, ACS patients with experimental treatment; orange lines, SIHD patients in the reference arm; green lines, SIHD patients with experimental treatment.*

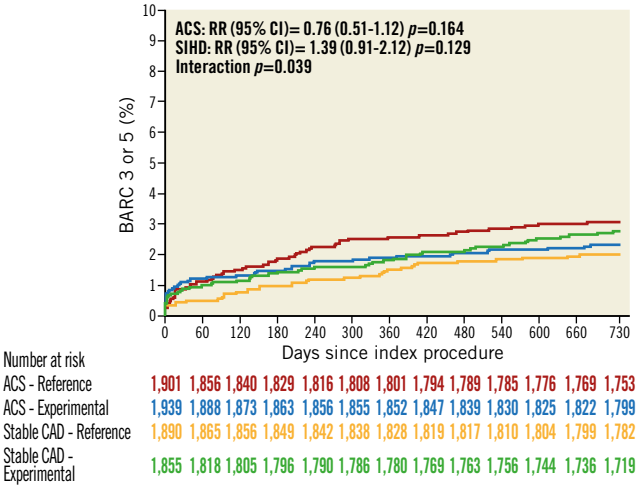

Figure 2. *Kaplan-Meier estimates for the co-primary safety endpoint. Red lines, ACS patients in the reference arm; blue lines, ACS patients with experimental treatment; orange lines, SIHD patients in the reference arm; green lines, SIHD patients with experimental treatment.*

Table 1. Adjudicated clinical outcomes at two years of follow-up.

	Acute coronary syndrome			Stable ischaemic heart disease			Interaction
	Experimental treatment N=1,939	Reference treatment N=1,901	Rate ratio (95% CI)	Experimental treatment N=1,855	Reference treatment N=1,890	Rate ratio (95% CI)	*p*-value
All-cause death, MI, stroke or urgent TVR[a]	154 (7.94)	184 (9.68)	0.82 (0.66-1.01)	117 (6.31)	135 (7.14)	0.89 (0.69-1.13)	0.63
All-cause death	69 (3.56)	78 (4.10)	0.87 (0.63-1.20)	42 (2.26)	58 (3.07)	0.74 (0.50-1.10)	0.54
MI	58 (2.99)	80 (4.21)	0.71 (0.51-0.99)	50 (2.70)	55 (2.91)	0.93 (0.63-1.37)	0.30
Stroke	25 (1.29)	17 (0.89)	1.44 (0.78-2.68)	19 (1.02)	27 (1.43)	0.72 (0.40-1.29)	0.11
Urgent target vessel revascularisation	44 (2.27)	65 (3.42)	0.66 (0.45-0.97)	27 (1.46)	38 (2.01)	0.72 (0.44-1.19)	0.77
BARC 3 or 5[b]	44 (2.27)	57 (3.00)	0.76 (0.51-1.12)	50 (2.70)	37 (1.96)	1.39 (0.91-2.12)	0.039
NCB	185 (9.54)	222 (11.7)	0.81 (0.67-0.99)	155 (8.36)	163 (8.62)	0.97 (0.78-1.21)	0.22

Depicted is 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. Rate ratio from Mantel-Cox time-to-event analyses, *p*-value from log-rank test. [a] Co-primary efficacy endpoint. [b] Co-primary safety endpoint. Censoring at 2 years, i.e., only events considered within and including 730 days since index PCI (or randomisation if no PCI performed).

ACS patients with experimental treatment whereas they did not differ among SIHD patients (2.70% vs 2.91% and 1.46% vs 2.01%, respectively). There was no evidence of interaction for either endpoint. Secondary endpoints are reported in **Supplementary Table 3**.

BLEEDING AND NET ADVERSE CLINICAL ENDPOINTS

Interaction testing for the occurrence of the co-primary safety endpoint of BARC grade 3 or 5 bleeding was significant (p_{int}=0.039), with a lower risk in ACS (2.27% vs 3.00%, RR 0.76, 95% CI: 0.51 to 1.12; p=0.164) and a higher risk in SIHD (2.70% vs 1.96%, RR 1.39, 95% CI: 0.91 to 2.12; p=0.129) patients assigned to the experimental arm, respectively **(Table 1, Figure 2, Figure 3)**.

BARC 2, 3 or 5 bleeding occurred in 147 (7.58%) patients in the experimental arm and in 186 (9.78%) patients in the control arm (RR 0.77, 95% CI: 0.62 to 0.95; p=0.017) in the ACS group and in 174 (9.38%) patients in the experimental arm and in 134 (7.09%) patients in the control arm (RR 1.34, 95% CI: 1.07 to 1.68; p=0.010) in the SIHD group, with significant treatment-by-subgroup interaction (p_{int}<0.001) **(Supplementary Table 3)**.

NCB occurred in 185 (9.54%) patients in the experimental arm and in 222 (11.7%) patients in the control arm (RR 0.81, 95% CI: 0.67 to 0.99; p=0.037) in the ACS group and in 155 (8.36%) patients in the experimental arm and in 163 (8.62%) patients in the control arm (RR 0.97, 95% CI: 0.78 to 1.21; p=0.815) in the SIHD group (p_{int}=0.22) **(Table 1)**. Other secondary endpoints are reported in **Supplementary Table 3**.

LANDMARK ANALYSES

Landmark analysis at 30 days suggested significant interaction according to clinical presentation with respect to all-cause and cardiovascular mortality that was similar in both treatment groups in ACS patients but seemingly lower with experimental therapy in SIHD patients. Some bleeding endpoints, including BARC 2 or 3, were increased with experimental therapy in SIHD but not in ACS patients **(Supplementary Table 4)**.

Landmark analysis from 31 days to one year did not provide evidence of interaction for any of the fatal or ischaemic cardiovascular or cerebrovascular endpoints when stratified based on presenting syndrome, whereas there were strong signals for interaction for multiple bleeding endpoints, including BARC 2 or 3 as well as BARC 2, 3 or 5, owing to the lower risks with the experimental therapy in ACS patients counterbalanced by an opposite trend in SIHD patients **(Supplementary Table 5)**.

Finally, there was no signal for interaction with respect to any ischaemic or bleeding endpoints at landmark analysis from one to two years.

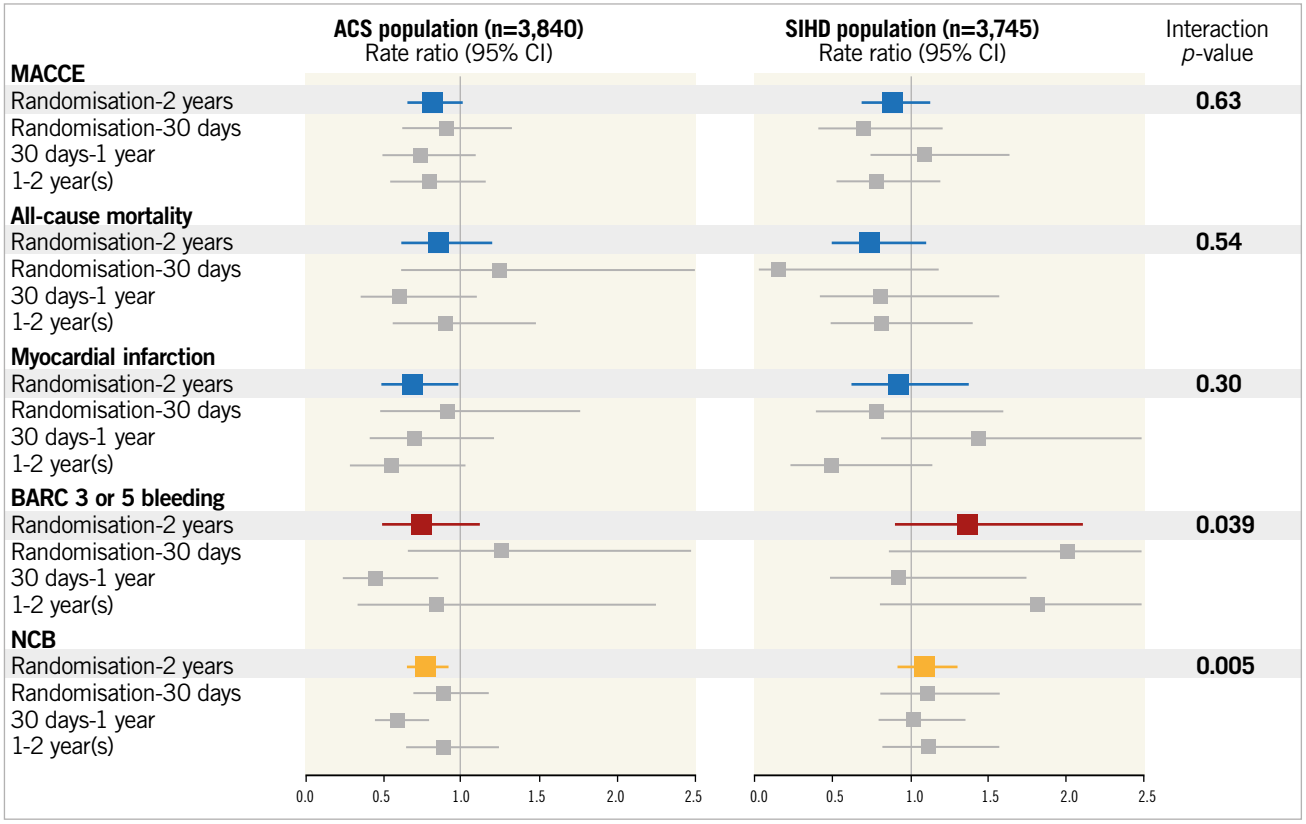

Figure 3. *Rate ratios of co-primary endpoints and other secondary efficacy or safety endpoints at two years and according to landmark analysis at 30 days, from 30 days to one year and beyond one year. Blue, RR and corresponding 95% CI of efficacy endpoints from randomisation to two years. Red, RR and corresponding 95% CI of BARC 3 or 5 bleeding from randomisation to two years. Orange, RR and corresponding 95% CI of NCB from randomisation to two years. Grey, landmark analyses.*

Discussion

This subgroup analysis of centrally adjudicated efficacy and safety endpoints among patients of the GLASSY study presenting with ACS or SIHD showed the following:

1. Ticagrelor monotherapy after one-month DAPT (experimental strategy) provided consistent treatment effects in patients with ACS or SIHD in terms of a composite endpoint of ischaemic events compared to standard DAPT (reference strategy).
2. ACS but not SIHD patients (although with negative interaction testing) experienced nominally significant reductions of MI and urgent TVR at two years with the experimental strategy.
3. There were trends towards lower and higher risk of BARC 3 or 5 bleeding with the experimental strategy in ACS and SIHD patients, respectively.
4. A treatment-by-subgroup interaction was also noted for the composite of the co-primary efficacy endpoint and BARC grade 2, 3 or 5 bleeding with respect to clinical presentation, suggesting an NCB of the experimental strategy among ACS but not among SIHD patients.

Importantly, in GLASSY, randomisation to either the experimental or the reference strategy was stratified by clinical presentation at the index PCI.

Our analysis suggests that, in ACS but not in SIHD patients, ticagrelor monotherapy after one-month DAPT may represent an attractive option as compared to current guideline-recommended treatment.

The search for optimal antiplatelet therapy after PCI is currently focusing on lowering the risk of recurrent ischaemic events while avoiding bleeding. Evidence from the DAPT[2] and PEGASUS[6] trials supports the superior ischaemic protection of prolonged DAPT with aspirin and an oral $P2Y_{12}$ inhibitor across the broad spectrum of coronary artery disease, with a more pronounced effect in post-MI patients. However, both studies identified a sizeable bleeding liability, including major albeit non-fatal bleeding, with prolonged DAPT. In the THEMIS study, a prolonged DAPT regimen consisting of aspirin and ticagrelor at 90 or 60 mg in SIHD patients with diabetes mellitus without a history of MI or stroke conveyed a reduced risk of ischaemic cardiovascular events compared to aspirin monotherapy; however, the incidence of major bleeding was higher with ticagrelor, yielding a lower number needed to treat for harm than for benefit[7,8].

A possible strategy to preserve ischaemic benefit in the early period while mitigating bleeding risk in the longer term was investigated in the TROPICAL-ACS trial in which a stepwise, platelet function testing-guided de-escalation from prasugrel to the less potent clopidogrel, at two weeks after discharge, was non-inferior to standard DAPT[9].

Our current data indicate that ticagrelor monotherapy after one month of DAPT provides similar ischaemic protection, but fewer bleeding hazards, as compared to standard DAPT. The interpretation of our results is challenged by the parent study design: patients allocated to the experimental arm received aspirin and ticagrelor for 30 days irrespective of clinical presentation (as opposed to aspirin and ticagrelor in ACS patients and aspirin and clopidogrel in SIHD patients in the control group) followed by ticagrelor alone from day 31 to two years (as opposed to aspirin and ticagrelor in ACS patients and aspirin and clopidogrel in SIHD patients in the control group from day 31 to one year, followed by aspirin monotherapy during the course of the second year). Therefore, the observed results might reflect the higher risk of bleeding associated with the combined use of ticagrelor and aspirin in stable patients assigned to the experimental arm.

The benefit of dropping aspirin in the experimental strategy was more evident among ACS patients who received more profound and consistent $P2Y_{12}$ inhibition with ticagrelor on top of aspirin. At landmark analysis, the benefit in terms of BARC grade 3 or 5 bleeding with the experimental as opposed to the control arm was greatest from 31 to 365 days. On the other hand, the prevention of MI with the experimental strategy was highest beyond 365 days when both ACS and SIHD patients who were randomised to the experimental arm received ticagrelor instead of aspirin monotherapy.

Our results should be interpreted in the context of the recent double-blind Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention (TWILIGHT) trial, which showed, especially in ACS patients, a remarkable bleeding reduction with ticagrelor monotherapy as compared to aspirin and ticagrelor in PCI patients after a course of three-month DAPT[10]. Consistent results were also recently reported by the ShorT and Optimal Duration of Dual AntiPlatelet Therapy-2 Study (STOPDAPT-2)[11] and by the Smart Angioplasty Research Team: Comparison Between $P2Y_{12}$ Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents (SMART-CHOICE) trial[12], which showed that a $P2Y_{12}$ inhibitor monotherapy, after either one- or three-month DAPT, preserved ischaemic risks but lowered the bleeding hazard as compared to standard DAPT. The present analysis lends additional support to the hypothesis that dropping the less effective antiplatelet agent (aspirin) rather than combining more antiplatelet agents in patients undergoing PCI confers a better safety profile in terms of bleeding, with a similar or better protection against ischaemic events.

Limitations

First, we included consecutive patients from the highest enrolling sites rather than a randomly selected sample from all sites of the parent trial. Nevertheless, we have already shown that there was no evidence for treatment-by-subgroup interaction for the primary study outcome or other key secondary efficacy or safety endpoints between GLASSY and non-GLASSY sites. Second, adherence to allocated treatment was significantly lower in the experimental arm. Nevertheless, discontinuation rates were comparable to other trials investigating ticagrelor. Third, one-year DAPT in the control group across all SIHD and ACS

patients may no longer be perceived as the current standard of care. Fourth, the observed interaction for the type of reference treatment might reflect the higher risk of bleeding associated with the combined use of ticagrelor and aspirin in stable patients in the experimental arm. Fifth, the study had an open-label design and event rates for ischaemic and bleeding endpoints were lower than anticipated, with a consequent impact on the nominal power for the tested hypothesis.

Conclusions

Ticagrelor monotherapy after one-month DAPT, as compared to one-year DAPT followed by aspirin alone, provided consistent ischaemic protection both in patients with and in those without ACS at 24 months. There was, however, evidence for differences in treatment effect for safety with respect to presenting syndrome, such that only patients with ACS derived a bleeding benefit with ticagrelor monotherapy after 12-month DAPT as compared to conventional treatment.

Impact on daily practice

In patients undergoing PCI with new-generation drug-eluting stents, ticagrelor monotherapy after one month of DAPT provides consistent treatment benefit in patients with and in those without ACS as compared to standard therapy with regard to ischaemic events; however, only patients with ACS experienced a bleeding risk reduction and a favourable net clinical benefit with this strategy.

Appendix. Study collaborators

Edouard Benit, MD; *Jessa Hospital, Department of Cardiology, Hasselt, Belgium*. Christoph Liebetrau, MD; *Department of Cardiology, Kerckhoff Heart and Thorax Center, Bad Nauheim, Germany and German Center for Cardiovascular Research (DZHK), partner site RheinMain, Frankfurt am Main, Germany*. Luc Janssens, MD; *Imelda Hospital, Bonheiden, Belgium*. Maurizio Ferrario, MD; *University of Pavia and Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy*. Aleksander Zurakowski, MD; *Center of Cardiovascular Research and Development, American Heart of Poland, Katowice, Poland*. Roberto Diletti, MD, PhD; *Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands*. Marcello Dominici, MD, *S. Maria University-Hospital, Terni, Italy*. Kurt Huber, MD; *3rd Medical Department, Cardiology, Wilhelminen Hospital, and Sigmund Freud University Medical School, Vienna, Austria*. Ton Slagboom, MD; *OLVG Amsterdam, Amsterdam, the Netherlands*. Paweł Buszman, MD; *Center for Cardiovascular Research and Development, American Heart of Poland, Katowice, Poland*. Leonardo Bolognese, MD; *Azienda Usl Toscana Sud Est, Arezzo, Italy*. Carlo Tumscitz, MD; *Cardiology Unit, Sant'Anna Hospital, Ferrara, Italy*. Krzysztof Bryniarski, MD, PhD; *Jagiellonian University Medical College, The John Paul II Hospital, Krakow, Poland*. Adel Aminian, MD; *Department of Cardiology, Centre Hospitalier Universitaire de Charleroi, Charleroi, Belgium*. Mathias Vrolix, MD; *Ziekenhuis Oost Limburg, Genk, Belgium*. Ivo Petrov, MD; *Acibadem City Clinic Cardiovascular Center, Sofia, Bulgaria*. Scot Garg, MD, PhD; *East Lancashire Hospitals NHS Trust, Blackburn, United Kingdom*. Christoph Naber, MD; *Contilia Heart and Vascular Centre, Stadtspital Triemli Zürich, Switzerland*. Janusz Prokopczuk, MD; *PAKS, Kedzierezyn-Kozle, Poland*.

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Conflict of interest statement

S. Leonardi reports grants and personal fees from AstraZeneca, Bayer, and BMS/Pfizer, outside the submitted work. P. Vranckx reports personal fees from AstraZeneca, Daiichi Sankyo, Bayer AG, CLS Behring, and Medscape, outside the submitted work. P.W. Serruys reports personal fees from Abbott, Biosensors, Cardialysis, Medtronic, Sino Medical Sciences, Philips/Volcano, Xeltis, and HeartFlow, outside the submitted work, and personal consultancy fees from Abbott Laboratories, Biosensors, Cardialysis, Medtronic, Sino Medical Sciences Technology, Philips/Volcano, Xeltis, and HeartFlow. 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, AstraZeneca, and Idorsia, outside the submitted work. D. Heg is affiliated with CTU Bern, University of Bern, which has a staff policy of not accepting honoraria or consultancy fees. However, CTU Bern is involved in design, conduct, or analysis of clinical studies funded by not-for-profit and for-profit organisations. In particular, pharmaceutical and medical device companies provide direct funding to some of these studies. S. Windecker reports grants from Amgen, Abbott, Bayer, BMS, Boston Scientific, Biotronik, CSL Behring, Edwards Lifesciences, Medtronic, Polares, and SINOMED, outside the submitted work. P. Jüni serves as unpaid member of the steering group of trials funded by AstraZeneca, Biotronik, Biosensors, St. Jude Medical and The Medicines Company, and has participated in advisory boards and/or consulting from Amgen, Ava and Fresenius, but has not received personal payments by any pharmaceutical company or device manufacturer. M. Valgimigli reports grants and personal fees from Terumo, personal fees from AstraZeneca, Alvimedica/CID, Abbott Vascular, Daiichi Sankyo, Opsens, Bayer, CoreFlow, Idorsia Pharmaceuticals Ltd, Universität Basel / Dept. Klinische Forschung, Vifor, Bristol Myers Squibb SA, iVascular, and Medscape, outside the submitted work. C. Liebetrau reports personal fees from AstraZeneca, outside the submitted work. R. Diletti reports grants from AstraZeneca, outside the submitted work. C. Naber reports personal fees from Abbott, Medtronic, Bionsesors, and Biotronik, outside the submitted work. The other authors have no conflicts of interest to declare.

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The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-00145

Supplementary data

Supplementary Appendix 1. Participating sites

Country	City	Hospital	Number of patients
Belgium	Hasselt	Virga Jesse	920
Germany	Bad Nauheim	Kerckhoff Heart Center	655
Belgium	Bonheiden	Imelda Ziekenhuis	536
Italy	Pavia	Policlinico San Matteo	479
Switzerland	Bern	Uni. Hospital Bern	469
Poland	Chrzanow	PAKS Chrzanów	462
Netherlands	Rotterdam	Erasmus Medical Center	434
Italy	Terni	Ospedaliera S. Maria	405
Austria	Vienna	Wilhelminenspital	309
Netherlands	Amsterdam	OLVG A'dam	304
Poland	Dabrowa Gornicza	PAKS Dabrowa	295
Italy	Arezzo	Ospedale S. Donato	281
Italy	Ferrara	Azienda Ospedaliera di Ferrara	273
Poland	Krakov	JP2 Krakov	272
Belgium	Charleroi	CHU de Charleroi	266
Belgium	Genk	ZOL St.Jan	257
Bulgaria	Sofia	City Clinic Sofia	252
UK	Blackburn	Royal Blackburn	249
Germany	Essen	Rhein Ruhr Center	247
Poland	Kedzierzyn-Kozle	PAKS Kozle	236

Supplementary Appendix 2. Institutional Review Board and Central Ethics Committee approval timelines

Country	Sites	Central ethic committee	Protocol number	Approval date
Austria	4301	Ethikkommision der Stadt Wien	13-064-0413	03-Jul-2017
Belgium	3204-3202-3205-3203	Comité d'Etique LS.P.P.C OM 008	A17/31_23/08	27-Sep-2017
Germany	4902-4903	Ethikkommission des Fachbereichs Medizin- Bfarm	78/13 4038963	21-Jun-2017 15-Aug-2017
Netherlands	3101-3104	Medisch Etische Toetsings Commissie Erasmus MC	NL-43637.678.13	31-May-2017
Italy	3902-3905-3909-3903	Comitato Etico Area Pavia AIFA	20170018252 88004	03-Jul-2017 30-Jul-2017
UK	4404	North-West Liverpool Central Research Ethics Committee	13/NW/0283	26-Jun-2017
Switzerland	4106	Kantonale Ethikkommision Bern	039/13	18-Apr-2017
Poland	4802-4805-4801-4807	PRZEWODNICZACY Komisji Bioetycznej	2013/07/18/02	7-May-2018
Bulgaria	9901	MECTHA ETHYJA KOMHCHR	109-3-010	7-May-2018

Supplementary Appendix 3. Study organisation

Study sponsor: European Clinical Research Institute (ECRI), Rotterdam, the Netherlands
CEC project leader: Anna Franzone, MD, PhD
Principal investigator: Marco Valgimigli, MD, PhD, University of Bern, Bern, Switerland
Study chair: Stephan Windecker, MD, University of Bern, Bern, Switerland

Steering committee members:
Pascal Vranckx (Jesse Ziekenhuis, Faculty of Medicine and Life Sciences at the Hasselt University, Hasselt, Belgium)
Peter Jüni (Applied Health Research Centre, Li Ka Shing Knowledge Institute of St. Michael's Hospital, Department of Medicine, University of Toronto, Toronto, Canada) (Methodologist)
Chris Hamm (University of Giessen and Kerckhoff Heart and Thorax Center, University of Giessen, Bad Nauheim, Germany) (member)
Gabriel Steg (Hospital Bichat-Claude Bernard, Paris, France) (member)

Clinical events committee

Chair: Eugène P. McFadden, MD, Cardialysis Core Laboratories and Clinical Trial Management, Rotterdam, the Netherlands and Department of Cardiology, Cork University Hospital, Cork, Ireland
Co-chair: Sergio Leonardi, MD, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy
Member: Raffaele Piccolo, MD, PhD, Department of Advanced Biomedical Sciences, Federico II University of Naples, Naples, Italy

Data and safety monitoring board
Jan G.P. Tijssen (Academic Research Center, Amsterdam, the Netherlands),
Laura Mauri (Harvard Clinical Research Institute, Boston, MA, USA),
Freek W.A. Verheugt (Chairman, Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands).

Safety reporting
Rick Andreae (Senior Safety Associate, Cardialysis, Rotterdam, the Netherlands), Eva Teurlings (Senior Safety Associate, Cardialysis, Rotterdam, the Netherlands), Boudijn Ladan (Safety Associate, Cardialysis, Rotterdam, the Netherlands), Natalia Vlcek (Safety Officer, Cardialysis, Rotterdam, the Netherlands), Yoshinobu Onuma (Medical Reviewer, Cardialysis, Rotterdam, the Netherlands), Osama I. Soliman (Medical Reviewer, Cardialysis, Rotterdam, the Netherlands), Ernest Spitzer (Safety Medical Coordinator, Cardialysis, Rotterdam, the Netherlands)

Data management
Tessa Rademaker-Havinga (Cardialysis, Rotterdam, the Netherlands), Wietze Lindeboom (Cardialysis, Rotterdam, the Netherlands), Art Ghandilyan (Cardialysis, Rotterdam, the Netherlands), Judith Jonk (Cardialysis, Rotterdam, the Netherlands), Sanne Palsrok (Cardialysis, Rotterdam, the Netherlands), Marco Bressers (Head of Data Management and Statistics, Cardialysis, Rotterdam, the Netherlands)

Statistical analysis
Dik Heg and Mattia Branca (Clinical Trials Unit, Bern, Switzerland), Peter Jüni (Applied Health Research Centre, Li Ka Shing Knowledge Institute of St. Michael's Hospital, Department of Medicine, University of Toronto, Toronto, Canada).

Study monitors
Yoshinobu Onuma (Cardialysis, Rotterdam, the Netherlands), Ana Guimarães (Cardialysis, Rotterdam, the Netherlands).

Supplementary Appendix 4. Clinical events committee operations

Within the selected study patients, all IR events as well as additional potential events (triggers) identified through a systematic analysis of the eCRF were considered for CEC adjudication. Non-IR triggers were assessed after all the relevant source documentation had been requested from and provided by the participating sites and were identified using a comprehensive search strategy that considers keywords logically related to the event. In general, keywords with a clear relationship to the endpoint of interest (e.g., for MI: unstable angina or ischaemic heart disease) triggered a formal CEC review, whereas keywords with a potential relationship (e.g., for MI: asystole, cardiac tamponade, hypertensive crisis) triggered a review by a physician (independent from the CEC members). In the latter case, the event underwent formal CEC review only if the reviewing physician suspected an event. To limit possible reporting bias towards the null hypothesis (i.e., querying for source documentation may stimulate a site to report previously unreported endpoints), only patients who had successfully completed the follow-up, data entry, and all query processes for the parent study were deemed eligible for the GLASSY study. For sites whose first language is not English, a mother tongue MD was involved for source documentation translation.

The first approval for GLASSY occurred on 18 April 2017, and the first adjudication performed on 6 September 2017.

Supplementary Appendix 5. 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, $P2Y_{12}$ receptor antagonists, 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	5.	Planned coronary artery bypass grafting as a staged procedure (hybrid) within 12 months of the index procedure
	6.	Planned surgery within 12 months of percutaneous coronary intervention unless dual antiplatelet therapy is maintained throughout the peri-surgical period
	7.	Need for oral anticoagulation therapy
	8.	PCI for *a priori* known stent thrombosis
Medical	9.	Known overt major bleeding

	10.	Known history of intracranial haemorrhage
	11.	Known stroke from ischaemic or unknown cause within last 30 days
General	12.	Known pregnancy at time of randomisation
	13.	Inability to provide informed consent
	14.	Currently participating in another trial before reaching primary endpoint

Supplementary Appendix 6. Clinical events committee procedures

According to best adjudication practice, GLASSY was conducted according to the following features:

1. Prospective approach to adjudication. The CEC data set was locked before the termination of the parent study. Suspected events (triggers) were assessed during the conduct of the study rather than adjudicating all cases after the study was completed and the primary results were available (i.e., retrospective adjudication). In case of updated entry of suspected events or updated source documentation by the site after request by the CEC team of source documentation, events were re-evaluated for adjudication.

2. Blinding of randomised treatment allocation. According to the PROBE methodology, the CEC was blinded to randomised treatment allocation.

Several steps were undertaken to ensure that the CEC personnel and physicians remained blinded.

First, any reference to treatment assignment contained in the eCRF or source documents that could lead to un-blinding of treatment assignment was obliterated by using a black marker by the site prior to submission to the CEC physician members.

Second, the CEC coordinator and operation personnel obliterated any reference to study drug assignment prior to distribution to the physicians if information was noted during the preparation of the event packet.

Third, if a reviewer noted the treatment assignment during the review of a particular event, the CEC coordinator was notified, and the event was sent for review by the third expert reviewer.

3. Triggering and adjudication of investigator- as well as non-investigator-reported events.

All IR events (death, MI, stroke, bleeding, coronary revascularisation, and stent thrombosis) were recorded by the CEC on dedicated adjudication forms. We also used comprehensive search strategies for potential cardiovascular events that were not reported by the investigator via eCRF dedicated queries. Therefore, we had potential to identify events qualifying for the endpoints of the GLASSY study in patients without IR events or triggers.

It is possible that the request of source documentation may have triggered endpoint reporting (and biased the study towards the null hypothesis). To quantify this, IR endpoints entered after CEC requested source documentation were monitored and reported.

4. Independent voting processes by CEC members with at least three CEC members with knowledge of the geographic variations of care represented in the trial. Each event was reviewed independently by at least two CEC physicians. In case of disagreement, the event was reviewed by all three reviewers with independent votes.

5. Independence from parent study.
To maximise the scientific integrity of GLASSY, CEC personnel operated independently from the data management group of the parent study, including no cross talk on trigger logic specifications, query processes for source documentation and, most importantly, event reporting and adjudication results.

6. Quantification of sufficient evidence for adjudication of non-fatal triggers (NO versus UNKNOWN events).
Finally, we quantified the minimum amount of evidence required for the assessment of non-fatal endpoints. In a randomised trial, a prerequisite to assess whether a suspected non-fatal endpoint has occurred or not is the availability of sufficient evidence for such an assessment, including relevant source documents, tests, and/or laboratory exams. While this is commonly performed for fatal events (death is adjudicated as "unknown" in case of no or insufficient description of death circumstances), it is not generally mandatory for non-fatal events.

In GLASSY, we reported all non-fatal endpoints but for each non-fatal trigger examined an assessment was performed as to whether enough information was available for formal adjudication. This allowed distinguishing triggers that did not meet the endpoint definition (i.e., no event with sufficient documentation present) from triggers for which this was unknown due to insufficient documentation. For each type of non-fatal endpoint, the proportion of events with insufficient evidence indirectly estimated a) the feasibility of GLASSY, b) the quality of endpoint reported by sites, and c) the uncertainty of the evidence related to the studied outcome.

Sufficient evidence for CEC adjudication includes at a minimum a narrative description with at least one pertinent medical documentation, including ECG/biomarkers for MI; angiographic report for stent thrombosis and urgent revascularisation; brain imaging for stroke; and labs and other appropriate testing for bleeding. In case of CRF-only narrative, the evidence was considered insufficient and the case did not undergo CEC adjudication.

7. Quality control of the adjudication process
To evaluate reproducibility, a random sample of ≈5% of adjudicated events was re-reviewed by the complete CEC committee (i.e., three members) who did not have access to the initial adjudication results.

A major disagreement was considered to have occurred if there was a disagreement on whether an event had occurred or not while a minor disagreement was considered present if there was any discordance on the remaining adjudicated fields.

Supplementary Appendix 7. Endpoint definitions

Death
All deaths were categorised as cardiovascular, non-cardiovascular or undetermined based on the definitions below.

1. Cardiovascular death
Cardiovascular death was defined as death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death (immediate) due to cardiovascular (CV) procedures, death due to CV haemorrhage, and death due to other cardiovascular causes.

- Death due to acute myocardial infarction:
  Death by any mechanism (arrhythmia, heart failure, mechanical complication, low output) within 30 days after a myocardial infarction (MI) related to the immediate consequences of the MI, such as progressive congestive heart failure (CHF), inadequate cardiac output, or refractory arrhythmia. If these events occur after a "break" (e.g., a CHF and arrhythmia-free period of at least a week), they should be designated by the immediate cause, even though the MI may have increased the risk of that event (e.g., late arrhythmic death becomes more likely after an acute MI [AMI]). The AMI should be verified to the extent possible by the diagnostic criteria outlined for AMI or by autopsy findings showing recent MI or recent coronary thrombus. Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischaemia, new ST elevation, new left bundle branch block (LBBB), or evidence of fresh thrombus by coronary angiography and/or at autopsy should be considered death resulting from an AMI, even if death occurs before blood samples or 12-lead electrocardiogram (ECG) could be obtained, or at a time before the appearance of cardiac biomarkers

in the blood. Death resulting from a procedure to treat an MI percutaneous coronary intervention (PCI), coronary artery infarction, should also be considered death due to AMI. Death resulting from an elective coronary procedure to treat myocardial ischaemia (i.e., chronic stable angina) or death due to an MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.

- Sudden cardiac death:
  Death that occurs unexpectedly, not following an AMI, and includes the following deaths:
  -Death witnessed and occurring without new or worsening symptoms.
  -Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless documented (i.e., by ECG or other objective) to be due to AMI.
  -Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic [ECG] recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review). Death after unsuccessful resuscitation from cardiac arrest.
  -Death after successful resuscitation from cardiac arrest and without identification of a non-cardiac aetiology.
  -Unwitnessed death without other cause of death (information regarding the patient's clinical status preceding death should be provided, if available).

General considerations: a subject seen alive and clinically stable 24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as "sudden cardiac death". Typical scenarios include:

- Subject well the previous day but found dead in bed the next day.
- Subject found dead at home on the couch with the television on.
- Deaths for which there is no information beyond "Patient found dead at home" may be classified as "death due to other cardiovascular causes".

- Death due to heart failure or cardiogenic shock:
  Death due to congestive heart failure refers to a death in association with clinically worsening symptoms and/or signs of heart failure not following an AMI. Deaths due to heart failure can have various aetiologies, including single or recurrent myocardial infarctions, ischaemic or non-ischaemic cardiomyopathy, hypertension, or valvular disease. Cardiogenic shock not occurring in the context of an AMI or as the consequence of an arrhythmia occurring in the absence of worsening heart failure is defined as systolic blood pressure (SBP) <90 mmHg for greater than one hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:
    cool, clammy skin or
    oliguria (urine output <30 mL/hour) or
    altered sensorium or
    cardiac index <2.2 L/min/m²

  Cardiogenic shock can also be defined if SBP <90 mmHg and increases to ≥90 mmHg in less than one hour with positive inotropic or vasopressor agents alone and/or with mechanical support.

- Death due to stroke refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.
- Death due to cardiovascular procedures refers to death caused by the immediate complications of a cardiac procedure and excludes death resulting from procedures to treat an AMI or the complications resulting from an AMI.
- Death due to cardiovascular haemorrhage refers to death related to haemorrhage such as a non-stroke intracranial haemorrhage, non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or haemorrhage causing cardiac tamponade.
- Death due to other cardiovascular causes: death due to other cardiovascular causes refers to a cardiovascular death not included in the above categories (e.g., pulmonary embolism or peripheral arterial disease).

2. Non-cardiovascular death

Non-cardiovascular death was defined as any death that is not thought to be due to a cardiovascular cause. The following categories may be collected
- Non-malignant causes
- Pulmonary
- Renal
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Non-infectious (e.g., systemic inflammatory response syndrome)
- Haemorrhage*, excluding haemorrhagic strokes and bleeding in the setting of coronary revascularisation
- Non-cardiovascular procedure or surgery
- Accidental (e.g., physical accidents or drug overdose) or trauma
- Suicide
- Prescription drug error (e.g., prescribed drug overdose, use of inappropriate drug, or drug drug interaction)
- Neurological process that is not a stroke or haemorrhage
- Other non-cardiovascular, specify: _____

*Examples: death due to GI bleeding is not considered a CV death. Death due to retroperitoneal haematoma following PCI is considered CV death. Death due to intracerebral haemorrhage is considered CV death.
- Malignant causes

Death results directly from the cancer; OR death results from a complication of the cancer (e.g., infection, complication of surgery/chemotherapy/radiotherapy); OR death results from withdrawal of other therapies because of concerns relating to the poor prognosis associated with the cancer. Cancer deaths may arise from cancers that were present prior to randomisation or which developed subsequently should be further classified (worsening prior malignancy; new malignancy).

3. Undetermined cause of death

Undetermined cause of death refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause, due to absence of any information (e.g., the only available information is “patient died”). The use of this category of death is discouraged and should apply to a minimal number of cases when no information at all on the circumstances of death is available (i.e., found on obituary of local newspaper). In all circumstances the reviewer will use all available information to attribute to one of the categories based on best clinical judgement.

For each death event an assessment will be made as to whether the event was caused, on the basis of the totality of the evidence, by a bleeding (i.e., a fatal bleeding occurred) or not.

Myocardial infarction (MI)

For the primary analysis, MI endpoint will be defined based on the third universal definition of myocardial infarction with the exception of periprocedural MI after PCI, which will be defined according to the SCAI definition.

For secondary analyses, PCI-related MI according to the third universal MI definition (type 4a) will also be adjudicated.

1. Type 1 (Spontaneous MI, >48 hours after intervention)

Symptoms suggestive of ischaemia/infarction in association with ECG, cardiac biomarkers or pathologic evidence of infarction as follows:

• Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin T or I) with at least one value above the 99th percentile upper reference limit 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 LBBB

Development of new Q-waves in the ECG
Evidence of new loss of viable myocardium or new regional wall motion abnormality
Identification of an intracoronary thrombus by angiography or autopsy

Spontaneous MI typically occurs after the periprocedural period and may be secondary to late stent complications or progression of native disease (e.g., non-culprit lesion plaque rupture). Performance of ECG and angiography supports adjudication to either a target or non-target vessel or lesion in most cases.

2. Type 2 MI
In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy/bradyarrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without LVH.

The distinction between type 1 and type 2 MI will be based by consensus on the preponderance of clinical evidence. The diagnosis of type 2 MI requires a predisposing condition as well as an acute trigger of supply/demand imbalance, including acute anaemia, respiratory failure, hypotension, sustained hypertension (with or without left ventricular hypertrophy), prolonged tachyarrhythmias and bradyarrhythmias, coronary embolism, coronary artery spasm. If the evidence is conflicting or unclear, the MI will be classified as type 1.

3. Type 3 MI
Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

4. Type 4a MI (NOT USED for primary analysis; see definition below)
Type 4a MI is defined by elevation of cTn values (>5xURL) occurring within 48 hours of the procedure in patients with normal baseline values (≤URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, at least one of the following is required:

- o symptoms suggestive of myocardial ischaemia
- o new ischaemic ECG changes
- o angiographic findings consistent with a procedural complication
- o imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality

5. Type 4b MI
Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of evidence of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the URL.

6. Type 4c MI
A spontaneous MI where a restenosis is the only angiographic explanation

7. Type 5 MI
Coronary artery bypass grafting (CABG) related MI is defined by elevation of troponin values (>10xURL) occurring within 48 hours of the procedure in patients with normal baseline cTn values (≤URL).
In addition, at least one of the following is required:

- o new pathological Q-waves or new LBBB
- o angiographic documented new graft or new native coronary artery occlusion
- o imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

8. Periprocedural MI after PCI (within 48 hours after PCI)
Periprocedural MI is defined based on the SCAI definitions as follows:
1) In patients with normal baseline CK-MB: the peak CK-MB measured within 48 hours of the procedure rises to ≥10x the local laboratory ULN, or to ≥5xULN with new pathologic Q-waves in ≥2 contiguous leads

or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises to ≥70x the local laboratory ULN, or ≥35xULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB.
2) In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling: the CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level. 3) In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling: the CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

Stroke

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by central nervous system (CNS) vascular injury as a result of haemorrhage or infarction. CNS includes brain, spinal cord and retina.
Classification:
-*Ischaemic stroke*
Ischaemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by CNS infarction. Evidence of infarction is defined as "pathological", imaging, or other objective evidence of acute cerebral, spinal cord, or retinal focal ischaemic injury in a defined vascular distribution; or in absence of the above (i.e., imaging or autopsy unavailable), clinical evidence of cerebral, spinal cord, or retinal focal ischaemic injury is based on symptoms persisting ≥24 hours or until death, and other aetiologies excluded.

Note, haemorrhagic infarction, defined as a parenchymal haemorrhage after CNS infarction, is considered an ischaemic stroke.

-*Cerebral haemorrhage*
Haemorrhages in the CNS are classified as stroke if they are non-traumatic, caused by a vascular event, and result in injury to the CNS. In contrast, traumatic haemorrhages will not be characterised as stroke. Subdural haematoma will not be classified as a stroke. The diagnoses included in this section are intracerebral haemorrhage (intraparenchymal and intraventricular) and subarachnoid haemorrhage (both aneurysmal and non-aneurysmal).

Stroke caused by intracerebral haemorrhage
Rapidly developing clinical signs of neurological dysfunction (focal or global) attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.

-*Stroke caused by subarachnoid haemorrhage*
Rapidly developing signs of neurological dysfunction (focal or global) and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma. Haemorrhages may be further classified according to location (example, supratentorial, subtentorial, etc.)

-*Stroke not otherwise specified*
An episode of acute neurological dysfunction presumed to be caused by ischaemia or haemorrhage, persisting ≥24 hours or until death, but without sufficient evidence to be classified as one of the above.

Urgent target vessel revascularisation (TVR)

It is defined as an urgent coronary revascularisation in a target coronary vessel (i.e., a vessel treated during the index PCI). Urgent coronary revascularisation is defined as follows:
One or more episodes of rest pain, presumed to be ischaemic in origin, which results in either urgent repeat PCI or urgent CABG. In the absence of pain, new ST-segment changes (a new ST segment shift >0.05 mV [0.5 mm] on a 12-lead ECG), indicative of ischaemia, acute pulmonary oedema, ventricular arrhythmias, or

haemodynamic instability presumed to be ischaemic in origin, will constitute sufficient evidence of ischaemia. To be considered urgent, the repeat PCI or CABG will be initiated within 24 hours of the last episode of ischaemia. The episode of ischaemia leading to urgent repeat PCI must occur following completion of the index PCI and guidewire removal. CABG initiated within 24 hours of PCI (index or repeat) due to an unsatisfactory result, even in the absence of documented ischaemia, will also be considered an urgent coronary revascularisation endpoint.

Bleeding

All potential bleeding events will be primarily adjudicated according to Bleeding Academic Research Consortium (BARC) classification as well as according to the TIMI and the GUSTO classification as follows:

1. BARC classification

Type 0. No 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 Types 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 of increased level of care
-Prompting evaluation

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 LP
- Intra-ocular bleed compromising vision

Type 4. CABG-related bleeding
- Perioperative intracranial bleeding within 48 hours
- Reoperation following closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥5 units of whole blood or packed red blood cells within 48-hour period
- Chest tube output ≥2 L within a 24-hour period

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

Obs: platelet transfusions should be recorded and reported, but are not included in these definitions until further information is obtained about the relationship to outcomes.
* Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1 g/dL haemoglobin).

2. TIMI bleeding criteria

Non-CABG-related bleeding
• Major
    o Any intracranial bleeding (excluding microhaemorrhages <10 mm evident only on gradient-echo MRI)
    o Clinically overt signs of haemorrhage associated with a drop in haemoglobin of ≥5 g/dL
    o Fatal bleeding (bleeding that directly results in death within seven days)

• Minor
    o Clinically overt (including imaging), resulting in haemoglobin drop of 3 to <5 g/dL

• Other non-major or minor
    o Any overt bleeding event that does not meet the criteria above

Bleeding in the setting of CABG
• Fatal bleeding (bleeding that directly results in death)
• Perioperative intracranial bleeding
• Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding
• Transfusion of ≥5 U PRBCs or whole blood within a 48-hour period; cell saver transfusion will not be counted in calculations of blood products
• Chest tube output >2 L within a 24-hour period

3. GUSTO bleeding criteria

Severe or life-threatening
    o Intracerebral haemorrhage
    o Resulting in substantial haemodynamic compromise requiring treatment

Moderate
    o Requiring blood transfusion but not resulting in haemodynamic compromise

Mild
    o Bleeding that does not meet the above criteria

Stent thrombosis

Stent thrombosis is defined by the Academic Research Consortium as follows:

Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation:
a. Angiographic confirmation of stent thrombosis
    The presence of a thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least one of the following criteria within a 48-hour time window:
        • Acute onset of ischaemic symptoms at rest
        • New ischaemic ECG changes that suggest acute ischaemia
        • Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI: troponin or CK-MB >99th percentile of URL)

• Non-occlusive thrombus. Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) non-calcified filling defect or lucency surrounded by contrast material (on three sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolisation of intraluminal material downstream
• Occlusive thrombus TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if it originates from the side branch)

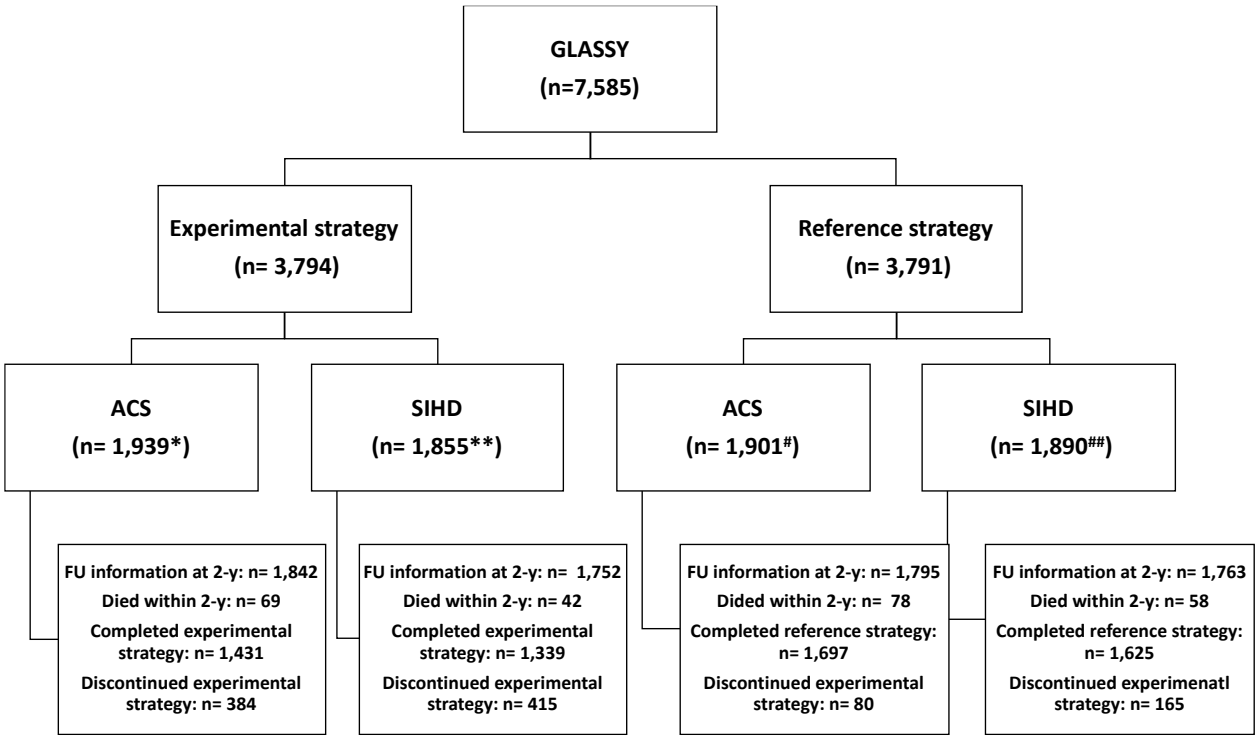
b. Pathological confirmation of stent thrombosis
Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy

The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion)

Probable stent thrombosis:
Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

• Any unexplained death within the first 30 days.
• Irrespective of the time after the index procedure, any myocardial infarction (MI) which is related to documented acute ischaemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.

Possible stent thrombosis:
Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days following intracoronary stenting until the end of trial follow-up.



Supplementary Figure 1. Study profile.

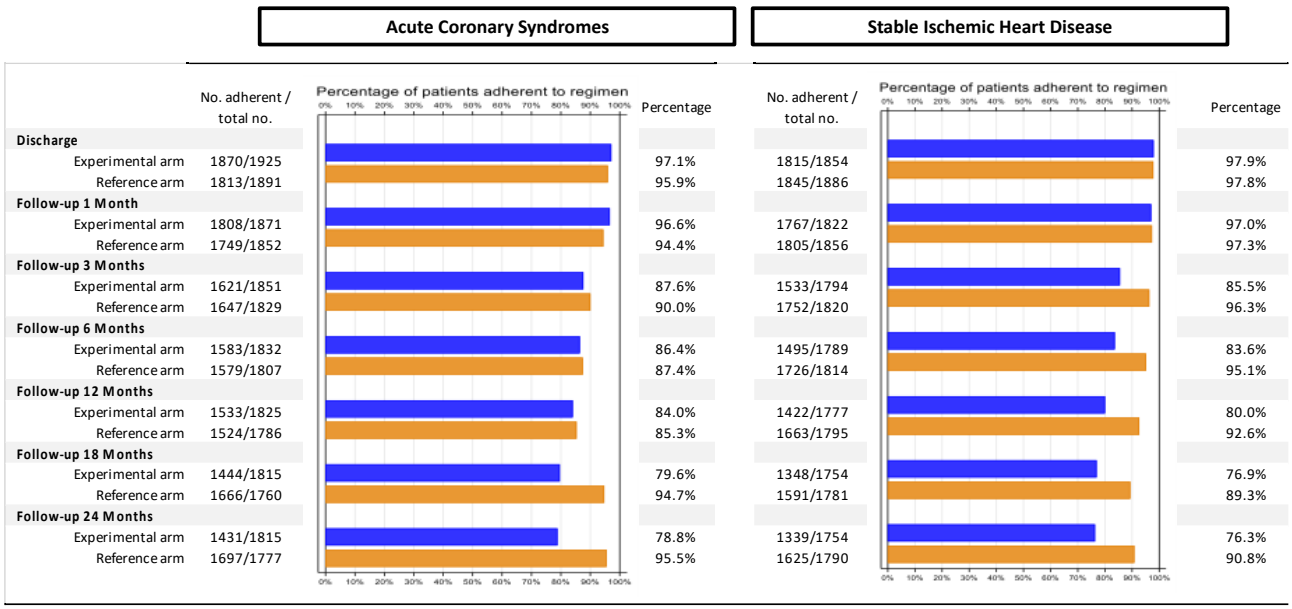
*Received allocated experimental strategy n=1,881
Did not receive experimental strategy as allocated n=58
Other $P2Y_{12}$ and aspirin: n=44
Other $P2Y_{12}$ SAPT: n=1
Aspirin SAPT: n=12
No APT: n=1

** Received allocated experimental strategy n=1,816
Did not receive experimental strategy as allocated n=39
Other $P2Y_{12}$ and aspirin: n=28
Other $P2Y_{12}$ SAPT: n=2
Aspirin SAPT: n=9

#Received allocated reference strategy n=1,820
Did not receive reference strategy as allocated n=81
Other $P2Y_{12}$ and aspirin: n=69
Ticagrelor SAPT: n=1
Aspirin SAPT: n=11

##Received allocated reference strategy n=1,853
Did not receive reference strategy as allocated n=37
Ticagrelor and aspirin, not in accordance with the protocol: n=8
Other $P2Y_{12}$ and aspirin: n=12
Clopidogrel SAPT: n=1
Aspirin SAPT: n=16

ACS: acute coronary syndrome; FU: follow-up; SIHD: stable ischaemic heart disease



Supplementary Figure 2. Adherence to study medications in patients with or without ACS at the time of index PCI.

Supplementary Table 1. Baseline characteristics.

	Acute coronary syndrome		Stable ischaemic heart disease	
	Experimental treatment strategy	**Reference treatment strategy**	**Experimental treatment strategy**	**Reference treatment strategy**
	N=1,939	N=1,901	N=1,855	N=1,890
Age, years	63.8±10.9	63.7±10.9	66.2±9.4	65.9±9.6
Females	468 (24.1%)	428 (22.5%)	442 (23.8%)	461 (24.4%)
Body mass index, kg/m²	27.9±4.5	27.7±4.5	28.0±4.6	28.1±4.5
Medical history				
Diabetes mellitus	401 (20.7%)	373 (19.6%)	522 (28.1%)	526 (27.8%)
Insulin-dependent	102 (5.3%)	105 (5.5%)	161 (8.7%)	163 (8.6%)
Hypertension	1,321 (68.1%)	1,292 (68.0%)	1,431 (77.1%)	1,448 (76.6%)
Hypercholesterolaemia	1,075 (55.4%)	1,080 (56.8%)	1,327 (71.5%)	1,396 (73.9%)
Previous stroke	34 (1.8%)	46 (2.4%)	63 (3.4%)	53 (2.8%)
Current smoker	709 (36.6%)	679 (35.7%)	375 (20.2%)	423 (22.4%)
Previous MI	359 (18.5%)	384 (20.2%)	510 (27.5%)	509 (26.9%)
Previous PCI	438 (22.6%)	468 (24.6%)	798 (43.0%)	818 (43.3%)
Previous CABG	63 (3.2%)	74 (3.9%)	141 (7.6%)	165 (8.7%)
Peripheral vascular disease	115 (5.9%)	129 (6.8%)	138 (7.4%)	171 (9.0%)
Chronic obstructive pulmonary disease	95 (4.9%)	99 (5.2%)	103 (5.6%)	105 (5.6%)
Previous major bleeding	11 (0.6%)	12 (0.6%)	15 (0.8%)	10 (0.5%)
Impaired renal function[b]	264 (13.6%)	231 (12.2%)	246 (13.3%)	264 (14.0%)
Clinical presentation				
Cardiac arrest	17 (0.9%)	12 (0.6%)	8 (0.4%)	8 (0.4%)
Killip II to IV	59 (3.0%)	42 (2.2%)	32 (1.7%)	24 (1.3%)
Stable coronary artery disease			1,855 (100.0%)	1,890 (100.0%)
Acute coronary syndrome	1,939 (100.0%)	1,901 (100.0%)		
Unstable angina	490 (25.3%)	499 (26.2%)		
Non-STEMI	760 (39.2%)	737 (38.8%)		
STEMI	689 (35.5%)	665 (35.0%)		
Time from symptom onset to wire crossing lesion ≤12 hrs	578 (29.8%)	572 (30.1%)		

LVEF pre-PCI (%)	52.3±11.9	52.4±11.4	56.9±11.4	57.1±10.9
Multivessel treatment	257 (13.3%)	273 (14.4%)	283 (15.3%)	285 (15.1%)

[b] 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.
Depicted are sample sizes (n), counts (%), means±standard deviations or medians (25%-75% interquartile range).
CABG: coronary artery bypass grafting; MI: myocardial infarction; PCI: percutaneous coronary intervention

Supplementary Table 2. Procedural characteristics.

	Acute coronary syndrome			Stable ischaemic heart disease		
	Experimental treatment	**Reference treatment**	***p*-value**	**Experimental treatment**	**Reference treatment**	***p*-value**
Total no. of patients	N=1,939	N=1,901		N=1,855	N=1,890	
PCI performed	1,927 (99.4%)	1,894 (99.6%)	0.359	1,849 (99.7%)	1,880 (99.5%)	0.454
Vascular access site						
Femoral	453 (23.5%)	426 (22.5%)	0.465	558 (30.2%)	547 (29.1%)	0.473
Brachial	14 (0.7%)	10 (0.5%)	0.540	16 (0.9%)	25 (1.3%)	0.209
Radial	1,475 (76.5%)	1,466 (77.4%)	0.539	1,281 (69.3%)	1,320 (70.2%)	0.545
Bivalirudin given during procedure	1,848 (95.9%)	1,803 (95.2%)	0.308	1,659 (89.7%)	1,675 (89.1%)	0.558
Total number of lesions treated*	N=2,458	N=2,438		N=2,472	N=2,524	
Lesions treated per patient	n=1,917	n=1,890	0.659	n=1,845	n=1,871	0.814
One lesion	1,487 (77.6%)	1,455 (77.0%)	0.671	1,365 (74.0%)	1,384 (74.0%)	1.000
Two lesions	357 (18.6%)	352 (18.6%)	1.000	374 (20.3%)	371 (19.8%)	0.743
Three or more lesions	73 (3.8%)	83 (4.4%)	0.370	106 (5.7%)	116 (6.2%)	0.580
Treated vessel(s)	n=2,436	n=2,427	<0.001	n=2,462	n=2,505	0.769
Left main coronary artery	47 (1.9%)	54 (2.2%)		53 (2.2%)	54 (2.2%)	
Left anterior descending artery	949 (39.0%)	932 (38.4%)		1,049 (42.6%)	1,039 (41.5%)	
Left circumflex artery	605 (24.8%)	633 (26.1%)		615 (25.0%)	616 (24.6%)	
Right coronary artery	816 (33.5%)	784 (32.3%)		718 (29.2%)	772 (30.8%)	
Bypass graft (saphenous or mammarian)	19 (0.8%)	24 (1.0%)		27 (1.1%)	24 (1.0%)	
Index PCI procedure* **						

≥2 vessels treated	257 (13.3%)	273 (14.4%)	0.326	283 (15.3%)	285 (15.1%)	0.891
No. of stents per lesion	1.2±0.5	1.2±0.5	0.723	1.2±0.5	1.2±0.5	0.416
Type of stent						
Biolimus A9-eluting stent	2,314 (96.3%)	2,302 (96.6%)	0.863	2,288 (94.9%)	2,320 (93.9%)	0.687
Other stent	110 (4.6%)	104 (4.4%)		144 (6.0%)	167 (6.8%)	
Total stent length per lesion (mm)	25.1±13.9	25.2±14.0	0.934	23.5±13.1	23.3±13.1	0.653
Average stent diameter per lesion (mm)	3.0±0.5	3.0±0.5	0.773	2.9±0.5	2.9±0.5	0.588
Direct stenting	908 (37.8%)	942 (39.5%)	0.305	918 (38.1%)	883 (35.7%)	0.281
Bifurcation involved	291 (11.9%)	297 (12.2%)	0.587	273 (11.1%)	279 (11.1%)	0.666
Thrombus aspiration performed	310 (12.7%)	341 (14.1%)	0.164	9 (0.4%)	24 (1.0%)	0.039
IABP	3 (0.2%)	7 (0.6%)	0.223	0 (0.0%)	0 (0.0%)	
TIMI flow pre-procedure	n=2,349	n=2,319	0.705	n=2,312	n=2,354	0.599
0 or 1	590 (25.1%)	596 (25.7%)		118 (5.1%)	131 (5.6%)	
2	347 (14.8%)	324 (14.0%)		279 (12.1%)	305 (13.0%)	
3	1,412 (60.1%)	1,399 (60.3%)		1,915 (82.8%)	1,918 (81.5%)	
TIMI flow post procedure	n=2,421	n=2,422	0.819	n=2,436	n=2,491	0.627
0 or 1	12 (0.5%)	11 (0.5%)		6 (0.2%)	3 (0.1%)	
2	30 (1.2%)	19 (0.8%)		5 (0.2%)	5 (0.2%)	
3	2,379 (98.3%)	2,392 (98.8%)		2,425 (99.5%)	2,483 (99.7%)	

Depicted are sample size (n), counts (%) or means±standard deviations. *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. ***Grafts counted as one separate vessel.

IABP: intra-aortic balloon pump; TIMI: Thrombolysis In Myocardial Infarction

Supplementary Table 3. Additional adjudicated clinical outcomes at two years of follow-up.

	Acute coronary syndrome			Stable ischaemic heart disease			Interaction
	Experimental treatment	**Reference treatment**	**Rate ratio (95% CI)**	**Experimental treatment**	**Reference treatment**	**Rate ratio (95% CI)**	***p*-value**
	N=1,939	N=1,901		N=1,855	N=1,890		
Cardiovascular or unknown mortality	46 (2.37)	48 (2.52)	0.94 (0.63-1.41)	23 (1.24)	40 (2.12)	0.59 (0.35-0.98)	0.16
Unknown mortality	11 (0.57)	12 (0.63)	0.90 (0.40-2.04)	7 (0.38)	12 (0.63)	0.60 (0.24-1.52)	0.52
Non-cardiovascular mortality	23 (1.19)	30 (1.58)	0.75 (0.44-1.30)	19 (1.02)	18 (0.95)	1.08 (0.57-2.06)	0.40
Ischaemic stroke	20 (1.03)	15 (0.79)	1.31 (0.67-2.56)	14 (0.75)	26 (1.38)	0.55 (0.29-1.05)	0.06
Haemorrhagic stroke	5 (0.26)	2 (0.11)	2.45 (0.48-12.6)	4 (0.22)	1 (0.05)	4.10 (0.46-36.9)	0.71
Definite, probable or possible ST	41 (2.11)	51 (2.68)	0.79 (0.52-1.19)	24 (1.29)	31 (1.64)	0.79 (0.46-1.35)	0.99
Definite or probable ST	24 (1.24)	31 (1.63)	0.76 (0.44-1.29)	9 (0.49)	15 (0.79)	0.61 (0.27-1.40)	0.67
Definite ST	18 (0.93)	26 (1.37)	0.68 (0.37-1.24)	9 (0.49)	12 (0.63)	0.77 (0.32-1.82)	0.82
Probable ST	6 (0.31)	7 (0.37)	0.84 (0.28-2.51)	0 (0.00)	3 (0.16)		
Possible ST	17 (0.88)	20 (1.05)	0.83 (0.44-1.59)	15 (0.81)	18 (0.95)	0.85 (0.43-1.69)	0.96
BARC 2, 3 or 5	147 (7.58)	186 (9.78)	0.77 (0.62-0.95)	174 (9.38)	134 (7.09)	1.34 (1.07-1.68)	<0.001

BARC 5	10 (0.52)	4 (0.21)	2.45 (0.77-7.82)	1 (0.05)	3 (0.16)	0.34 (0.04-3.27)	0.10
BARC 5b	9 (0.46)	4 (0.21)	2.21 (0.68-7.17)	1 (0.05)	2 (0.11)	0.51 (0.05-5.64)	0.26
BARC 5a	1 (0.05)	0 (0.00)		0 (0.00)	1 (0.05)		
BARC 4	1 (0.05)	2 (0.11)	0.49 (0.04-5.42)	4 (0.22)	5 (0.26)	0.82 (0.22-3.04)	0.71
BARC 2 or 3	138 (7.12)	183 (9.63)	0.73 (0.59-0.92)	173 (9.33)	131 (6.93)	1.36 (1.09-1.71)	<0.001
BARC 3	35 (1.81)	53 (2.79)	0.65 (0.42-0.99)	49 (2.64)	34 (1.80)	1.48 (0.96-2.29)	0.008
BARC 3c	3 (0.15)	4 (0.21)	0.74 (0.17-3.30)	18 (0.97)	4 (0.21)	4.62 (1.56-13.7)	0.04
BARC 3b	13 (0.67)	26 (1.37)	0.49 (0.25-0.95)	21 (1.13)	20 (1.06)	1.07 (0.58-1.98)	0.008
BARC 3a	20 (1.03)	25 (1.32)	0.79 (0.44-1.41)	10 (0.54)	14 (0.74)	0.73 (0.32-1.64)	0.89
BARC 2	107 (5.52)	138 (7.26)	0.75 (0.59-0.97)	137 (7.39)	101 (5.34)	1.40 (1.08-1.81)	0.001
BARC 1	147 (7.58)	180 (9.47)	0.79 (0.63-0.98)	180 (9.70)	124 (6.56)	1.51 (1.20-1.90)	0.000
TIMI major or minor	41 (2.11)	51 (2.68)	0.79 (0.52-1.19)	39 (2.10)	29 (1.53)	1.38 (0.85-2.23)	0.08
TIMI major	22 (1.13)	29 (1.53)	0.74 (0.43-1.29)	34 (1.83)	19 (1.01)	1.84 (1.05-3.23)	0.02
TIMI minor	21 (1.08)	24 (1.26)	0.86 (0.48-1.54)	5 (0.27)	12 (0.63)	0.43 (0.15-1.21)	0.25
TIMI other	244 (12.58)	300 (15.8)	0.78 (0.66-0.92)	296 (16.0)	223 (11.8)	1.39 (1.17-1.65)	0.000
TIMI CABG-related	1 (0.05)	2 (0.11)	0.49 (0.04-5.42)	3 (0.16)	5 (0.26)	0.61 (0.15-2.56)	0.88
GUSTO severe	20 (1.03)	9 (0.47)	2.19 (1.00-4.81)	22 (1.19)	14 (0.74)	1.61 (0.82-3.15)	0.56
GUSTO moderate	21 (1.08)	35 (1.84)	0.59 (0.34-1.01)	21 (1.13)	21 (1.11)	1.02 (0.56-1.87)	0.18
GUSTO mild	244 (12.58)	307 (16.2)	0.76 (0.64-0.90)	296 (15.96)	224 (11.9)	1.38 (1.16-1.65)	<0.001
All-cause death, MI, stroke, urgent TVR, BARC 2, 3 or 5	272 (14.03)	336 (17.67)	0.78 (0.67-0.92)	265 (14.29)	249 (13.17)	1.10 (0.92-1.31)	0.005
All-cause death, MI, stroke, urgent TVR, TIMI major	164 (8.46)	203 (10.7)	0.79 (0.64-0.97)	144 (7.76)	150 (7.94)	0.98 (0.78-1.24)	0.15
All-cause death, MI, stroke, BARC 3 or 5	169 (8.72)	197 (10.4)	0.84 (0.68-1.03)	143 (7.71)	150 (7.94)	0.98 (0.78-1.23)	0.33

Depicted is 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. Rate ratio from Mantel-Cox time-to-event analyses, p-value from log-rank test-censoring at 2 years, i.e., only events considered within and including 730 days since index PCI (or randomisation if no PCI performed).

MI: myocardial infarction; ST: stent thrombosis; TVR: target vessel revascularisation

Supplementary Table 4. Adjudicated clinical outcomes at 30 days.

	Acute coronary syndrome				Stable ischaemic heart disease				
	Experimental treatment	**Reference treatment**	**Rate ratio (95% CI)**	***p*-value**	**Experimental treatment**	**Reference treatment**	**Rate ratio (95% CI)**	***p*-value**	**Interaction *p*-value***
Total no. of patients	N=1,939	N=1,901			N=1,855	N=1,890			
All-cause death, MI, stroke or urgent TVR[a]	52 (2.68)	56 (2.95)	0.91 (0.62-1.33)	0.623	23 (1.24)	33 (1.75)	0.71 (0.41-1.21)	0.204	0.455
All-cause mortality	18 (0.93)	14 (0.74)	1.26 (0.63-2.54)	0.512	1 (0.05)	7 (0.37)	0.15 (0.02-1.18)	0.036	0.030
Cardiovascular or unknown mortality	18 (0.93)	13 (0.68)	1.36 (0.67-2.78)	0.397	1 (0.05)	7 (0.37)	0.15 (0.02-1.18)	0.036	0.024
Myocardial infarction	18 (0.93)	19 (1.00)	0.93 (0.49-1.77)	0.824	14 (0.75)	18 (0.95)	0.79 (0.39-1.60)	0.512	0.741
Stroke	9 (0.46)	7 (0.37)	1.26 (0.47-3.39)	0.645	7 (0.38)	6 (0.32)	1.19 (0.40-3.54)	0.756	0.937
Ischaemic	6 (0.31)	6 (0.32)	0.98 (0.32-3.04)	0.973	4 (0.22)	6 (0.32)	0.68 (0.19-2.41)	0.546	0.671
Haemorrhagic	3 (0.15)	1 (0.05)	2.95 (0.31-28.4)	0.327	3 (0.16)	0 (0.00)			
Urgent target vessel revascularisation	21 (1.08)	27 (1.42)	0.76 (0.43-1.35)	0.349	6 (0.32)	14 (0.74)	0.44 (0.17-1.13)	0.080	0.323
Definite. probable or possible stent thrombosis	20 (1.03)	17 (0.89)	1.15 (0.60-2.21)	0.664	3 (0.16)	6 (0.32)	0.51 (0.13-2.04)	0.330	0.287
Definite or probable stent thrombosis	20 (1.03)	17 (0.89)	1.15 (0.60-2.21)	0.664	3 (0.16)	6 (0.32)	0.51 (0.13-2.04)	0.330	0.287

Definite stent thrombosis	15 (0.77)	14 (0.74)	1.05 (0.51-2.18)	0.894	3 (0.16)	4 (0.21)	0.76 (0.17-3.41)	0.723	0.706
Probable stent thrombosis	5 (0.26)	3 (0.16)	1.64 (0.39-6.84)	0.496	0 (0.00)	2 (0.11)			
BARC 2, 3 or 5 bleeding	70 (3.61)	69 (3.63)	1.00 (0.71-1.40)	0.995	63 (3.40)	44 (2.33)	1.47 (1.00-2.16)	0.051	0.140
BARC 3 or 5 bleeding[b]	21 (1.08)	16 (0.84)	1.29 (0.67-2.48)	0.442	16 (0.86)	8 (0.42)	2.04 (0.87-4.78)	0.093	0.399
BARC 5 bleeding	5 (0.26)	0 (0.00)			0 (0.00)	2 (0.11)			
BARC 4 bleeding	1 (0.05)	1 (0.05)	0.98 (0.06-15.73)	0.990	2 (0.11)	2 (0.11)	1.02 (0.14-7.23)	0.986	0.983
BARC 2 or 3 bleeding	65 (3.35)	69 (3.63)	0.93 (0.66-1.30)	0.663	63 (3.40)	42 (2.22)	1.54 (1.04-2.28)	0.031	0.056
BARC 3 bleeding	16 (0.83)	16 (0.84)	0.98 (0.49-1.97)	0.961	16 (0.86)	6 (0.32)	2.73 (1.06-6.98)	0.029	0.083
BARC 3c bleeding	1 (0.05)	2 (0.11)	0.49 (0.04-5.42)	0.553	4 (0.22)	1 (0.05)	4.08 (0.46-36.5)	0.173	0.178
BARC 3b bleeding	6 (0.31)	7 (0.37)	0.84 (0.28-2.51)	0.757	9 (0.49)	4 (0.21)	2.30 (0.71-7.47)	0.155	0.216
BARC 3a bleeding	10 (0.52)	8 (0.42)	1.23 (0.48-3.11)	0.665	3 (0.16)	2 (0.11)	1.53 (0.26-9.15)	0.640	0.832
BARC 2 bleeding	50 (2.58)	54 (2.84)	0.91 (0.62-1.34)	0.632	49 (2.64)	36 (1.90)	1.39 (0.90-2.14)	0.133	0.151
BARC 1 bleeding	54 (2.78)	84 (4.42)	0.62 (0.44-0.88)	0.007	105 (5.66)	74 (3.92)	1.46 (1.08-1.98)	0.013	<0.001
TIMI major or minor bleeding	19 (0.98)	14 (0.74)	1.33 (0.67-2.66)	0.412	12 (0.65)	6 (0.32)	2.04 (0.77-5.45)	0.145	0.486
TIMI major bleeding	9 (0.46)	7 (0.37)	1.26 (0.47-3.39)	0.643	10 (0.54)	3 (0.16)	3.40 (0.94-12.4)	0.048	0.226
TIMI minor bleeding	11 (0.57)	8 (0.42)	1.35 (0.54-3.36)	0.516	2 (0.11)	3 (0.16)	0.68 (0.11-4.07)	0.670	0.498
TIMI other bleeding	101 (5.21)	136 (7.15)	0.72 (0.56-0.94)	0.014	153 (8.25)	110 (5.82)	1.44 (1.12-1.85)	0.004	<0.001
TIMI CABG-related	1 (0.05)	1 (0.05)	0.98 (0.06-15.7)	0.990	1 (0.05)	2 (0.11)	0.51 (0.05-5.61)	0.574	0.724
GUSTO severe bleeding	11 (0.57)	3 (0.16)	3.61 (1.00-12.9)	0.035	6 (0.32)	5 (0.26)	1.22 (0.37-4.01)	0.739	0.217

GUSTO moderate bleeding	8 (0.41)	8 (0.42)	0.98 (0.37-2.62)	0.971	7 (0.38)	3 (0.16)	2.38 (0.61-9.20)	0.195	0.294
GUSTO mild bleeding	102 (5.26)	139 (7.31)	0.71 (0.55-0.92)	0.010	154 (8.30)	110 (5.82)	1.45 (1.13-1.86)	0.003	<0.001
All-cause death, MI, stroke, urgent TVR, BARC 3 or 5	67 (3.46)	68 (3.58)	0.97 (0.69-1.36)	0.842	35 (1.89)	38 (2.01)	0.94 (0.59-1.49)	0.786	0.920
All-cause death, MI, stroke, urgent TVR, BARC 2 or 3	112 (5.78)	121 (6.37)	0.91 (0.70-1.18)	0.463	80 (4.31)	72 (3.81)	1.13 (0.82-1.57)	0.441	0.289
All-cause death, MI, stroke, urgent TVR, TIMI major	55 (2.84)	60 (3.16)	0.90 (0.62-1.30)	0.565	29 (1.56)	34 (1.80)	0.87 (0.53-1.43)	0.577	0.915
All-cause death, MI, stroke, BARC 3	56 (2.89)	49 (2.58)	1.12 (0.76-1.65)	0.554	33 (1.78)	32 (1.69)	1.05 (0.64-1.72)	0.840	0.836

Depicted is the first event per event type for each patient only (disregards multiple events of the same type within the same patient). Percentage of all patients. Rate ratio from Mantel-Cox time-to-event analyses, p-value from log-rank test.

[a]Co-primary efficacy endpoint.

[b]Co-primary safety endpoint.

Outcomes with too few events not shown (see Table 1, main article).

*Interaction p-value from approximate chi-square test with df=1, testing for a modifying effect of the period (0-30 days) on the rate ratio comparing the two regimens.

Supplementary Table 5. Adjudicated clinical outcomes from 30 days to one year for ACS and stable CAD patients.

	Acute coronary syndrome				Stable ischaemic heart disease				
	Experimental treatment	**Reference treatment**	**Rate ratio (95% CI)**	***p*-value**	**Experimental treatment**	**Reference treatment**	**Rate ratio (95% CI)**	***p*-value**	**Interaction *p*-value***
Total no. of patients	N=1,939	N=1,901			N=1,855	N=1,890			
All-cause death, MI, stroke or urgent TVR[a]	48 (2.56)	63 (3.43)	0.75 (0.51-1.09)	0.127	52 (2.85)	48 (2.60)	1.11 (0.75-1.64)	0.616	0.156
All-cause mortality	19 (1.00)	30 (1.59)	0.62 (0.35-1.11)	0.104	16 (0.87)	20 (1.07)	0.82 (0.42-1.58)	0.546	0.545
Cardiovascular or unknown mortality	10 (0.52)	18 (0.96)	0.55 (0.25-1.19)	0.121	11 (0.60)	13 (0.69)	0.86 (0.39-1.93)	0.721	0.421
Unknown mortality	3 (0.16)	5 (0.27)	0.59 (0.14-2.47)	0.466	4 (0.22)	4 (0.21)	1.02 (0.26-4.09)	0.974	0.588
Non-cardiovascular mortality	9 (0.47)	12 (0.64)	0.74 (0.31-1.75)	0.490	5 (0.27)	7 (0.37)	0.73 (0.23-2.30)	0.589	0.987
Myocardial infarction	24 (1.27)	33 (1.77)	0.71 (0.42-1.21)	0.208	27 (1.48)	19 (1.02)	1.46 (0.81-2.62)	0.208	0.075
Stroke	10 (0.52)	5 (0.27)	1.97 (0.67-5.77)	0.207	6 (0.33)	10 (0.54)	0.61 (0.22-1.69)	0.338	0.115
Ischaemic stroke	9 (0.47)	5 (0.27)	1.77 (0.59-5.29)	0.298	5 (0.27)	10 (0.54)	0.51 (0.17-1.49)	0.210	0.105

Haemorrhagic stroke	1 (0.05)	0 (0.00)			0 (0.00)	0 (0.00)			
Urgent target vessel revascularisation	11 (0.58)	20 (1.08)	0.54 (0.26-1.12)	0.094	14 (0.76)	11 (0.59)	1.30 (0.59-2.86)	0.518	0.107
Definite, probable or possible stent thrombosis	8 (0.42)	16 (0.86)	0.49 (0.21-1.15)	0.095	13 (0.71)	11 (0.59)	1.21 (0.54-2.69)	0.646	0.129
Definite or probable stent thrombosis	3 (0.16)	5 (0.27)	0.59 (0.14-2.47)	0.466	5 (0.27)	4 (0.21)	1.28 (0.34-4.75)	0.716	0.435
Definite stent thrombosis	2 (0.11)	3 (0.16)	0.66 (0.11-3.93)	0.642	5 (0.27)	3 (0.16)	1.70 (0.41-7.14)	0.461	0.410
Probable stent thrombosis	1 (0.05)	3 (0.16)	0.33 (0.03-3.16)	0.310	0 (0.00)	1 (0.05)			
Possible stent thrombosis	5 (0.26)	11 (0.59)	0.45 (0.16-1.29)	0.126	8 (0.43)	7 (0.37)	1.17 (0.42-3.22)	0.763	0.194
BARC 2, 3 or 5 bleeding	48 (2.60)	96 (5.29)	0.48 (0.34-0.69)	0.000	64 (3.59)	64 (3.49)	1.04 (0.73-1.46)	0.843	0.002
BARC 3 or 5 bleeding[b]	15 (0.79)	32 (1.71)	0.46 (0.25-0.85)	0.011	18 (0.99)	20 (1.07)	0.93 (0.49-1.75)	0.811	0.119
BARC 5 bleeding	1 (0.05)	1 (0.05)	0.99 (0.06-15.8)	0.992	0 (0.00)	0 (0.00)			
BARC 4 bleeding	0 (0.00)	1 (0.05)			2 (0.11)	2 (0.11)	1.02 (0.14-7.27)	0.984	
BARC 2 or 3 bleeding	47 (2.54)	95 (5.23)	0.48 (0.34-0.68)	<0.001	64 (3.59)	64 (3.49)	1.04 (0.73-1.46)	0.843	0.002
BARC 3 bleeding	14 (0.74)	31 (1.66)	0.44 (0.24-0.83)	0.009	18 (0.99)	20 (1.07)	0.93 (0.49-1.75)	0.811	0.105

BARC 3c bleeding	2 (0.10)	2 (0.11)	0.99 (0.14-7.00)	0.989	8 (0.44)	2 (0.11)	4.11 (0.87-19.34)	0.053	0.247
BARC 3b bleeding	5 (0.26)	14 (0.75)	0.35 (0.13-0.97)	0.035	6 (0.33)	12 (0.64)	0.51 (0.19-1.36)	0.173	0.600
BARC 3a bleeding	7 (0.37)	16 (0.85)	0.43 (0.18-1.04)	0.055	4 (0.22)	7 (0.37)	0.58 (0.17-2.00)	0.386	0.691
BARC 2 bleeding	34 (1.83)	71 (3.89)	0.47 (0.31-0.70)	<0.001	49 (2.73)	46 (2.50)	1.10 (0.73-1.64)	0.648	0.003
BARC 1 bleeding	63 (3.39)	86 (4.79)	0.70 (0.51-0.97)	0.034	59 (3.39)	44 (2.44)	1.40 (0.95-2.07)	0.088	0.008
TIMI major or minor bleeding	15 (0.79)	28 (1.50)	0.53 (0.28-0.98)	0.041	16 (0.87)	15 (0.80)	1.10 (0.54-2.22)	0.800	0.125
TIMI major bleeding	8 (0.42)	14 (0.75)	0.56 (0.24-1.34)	0.187	13 (0.71)	11 (0.59)	1.21 (0.54-2.71)	0.634	0.198
TIMI minor bleeding	7 (0.37)	15 (0.80)	0.46 (0.19-1.13)	0.081	3 (0.16)	4 (0.21)	0.77 (0.17-3.42)	0.726	0.563
TIMI other bleeding	92 (5.09)	143 (8.19)	0.61 (0.47-0.80)	<0.001	97 (5.73)	89 (5.04)	1.15 (0.86-1.53)	0.341	0.001
TIMI CABG-related bleeding	0 (0.00)	1 (0.05)			2 (0.11)	2 (0.11)	1.02 (0.14-7.26)	0.984	
GUSTO severe bleeding	4 (0.21)	2 (0.11)	1.98 (0.36-10.8)	0.423	10 (0.54)	6 (0.32)	1.71 (0.62-4.71)	0.294	0.886
GUSTO moderate bleeding	11 (0.58)	23 (1.23)	0.47 (0.23-0.96)	0.034	7 (0.38)	11 (0.59)	0.65 (0.25-1.68)	0.373	0.586

GUSTO mild bleeding	91 (5.03)	146 (8.39)	0.59 (0.46-0.77)	0.000	98 (5.80)	89 (5.04)	1.16 (0.87-1.55)	0.305	0.001
All-cause death, MI, stroke, urgent TVR, BARC 3	60 (3.22)	89 (4.87)	0.66 (0.47-0.91)	0.012	67 (3.70)	65 (3.52)	1.05 (0.75-1.48)	0.759	0.051
All-cause death, MI, stroke, urgent TVR, BARC 2 or 3	88 (4.85)	139 (7.84)	0.61 (0.47-0.80)	<0.001	108 (6.12)	107 (5.91)	1.04 (0.80-1.36)	0.765	0.005
All-cause death, MI, stroke, urgent TVR, TIMI major	55 (2.94)	75 (4.09)	0.72 (0.51-1.02)	0.060	65 (3.58)	58 (3.14)	1.15 (0.81-1.63)	0.446	0.063
All-cause death, MI, stroke, BARC 3	59 (3.15)	87 (4.71)	0.67 (0.48-0.93)	0.015	62 (3.42)	64 (3.46)	0.99 (0.70-1.41)	0.968	0.102

Depicted is the first event per event type for each patient only (disregards multiple events of the same type within the same patient). Percentage of all patients. Rate ratio from Mantel-Cox time-to-event analyses, p-value from log-rank test.

[a] Co-primary efficacy endpoint.

[b] Co-primary safety endpoint.

Outcomes with too few events not shown (see Table 1, main article).

*Interaction p-value from approximate chi-square test with df=1, testing for a modifying effect of the period on the rate ratio comparing the two regimens.