Made available by Hasselt University Library in https://documentserver.uhasselt.be

Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial

Peer-reviewed author version

VRANCKX, Pascal; Valgimigli, Marco; Juni, Peter; Hamm, Christian; Steg, Philippe Gabriel; Heg, Dik; van Es, Gerrit Anne; McFadden, Eugene P.; Onuma, Yoshinobu; van Meijeren, Cokky; Chichareon, Ply; BENIT, Edouard; Mollmann, Helge; Janssens, Luc; Ferrario, Maurizio; Moschovitis, Aris; Zurakowski, Aleksander; Dominici, Marcello; Van Geuns, Robert Jan; Huber, Kurt; Slagboom, Ton; Serruys, Patrick W. & Windecker, Stephan (2018) Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. In: LANCET, 392(10151), p. 940-949.

DOI: 10.1016/S0140-6736(18)31858-0
Handle: http://hdl.handle.net/1942/27691

Ticagrelor monotherapy beyond one month vs. standard dual antiplatelet therapy following drug eluting stent implantation: A randomised multicentre superiority trial.

Pascal Vranckx, MD, PhD;* Prof. Marco Valgimigli, MD, PhD;† Prof. Peter Jüni, MD; ‡ Prof. Christian Hamm, MD PhD;§ Prof. Philippe Gabriel Steg, MD;¶ Dik Heg, PhD;Ψ Gerrit Anne van Es, PhD;Ω Eugène P. Mc Fadden, MD;# Yoshinobu Onuma MD, PhD;Δ ¥ Cokky van Meijeren, PhD;¥ Ply Chichareon, MD;Φ Edouard Benit, MD;* Prof. Helge Möllmann, MD;§ Luc Janssens MD;‡ Maurizio Ferrario, MD;** Aris Moschovitis, MD;† Aleksander Zurakowski, MD;†† Marcello Dominici, MD;‡‡ Prof. Robert Jan Van Geuns MD, PhD;Δ Prof. Kurt Huber, MD;§§ Ton Slagboom, MD;¶¶ Prof. Patrick W. Serruys MD, PhD;ΨΨ Prof. Stephan Windecker ,MD.† on behalf of the GLOBAL LEADERS Investigators

* Jessa Ziekenhuis, Faculty of Medicine and Life Sciences at the Hasselt University, Hasselt, Belgium. Stadsomvaart 11, 3500 Hasselt, Belgium.

† Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Freiburgstrasse 18, 3010 Bern, Switzerland.

‡ Applied Health Research Centre, Li Ka Shing Knowledge Institute of St. Michael's Hospital, Department of Medicine and Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada. Yonge street 250, Toronto, ON M5G1B1, Canada

§ Kerckhoff Heart and Thorax Center, Bad Nauheim, Germany. Benekestrasse 2-8, 61231 Bad Nauheim, Germany.

¶ Université Paris-Diderot, Hôpital Bichat, Assistance Publique–Hôpitaux de Paris, INSERM U-1148, FACT (French Alliance for Cardiovascular Trials) Paris, France, National Heart and Lung Institute, Royal Brompton Hospital, Imperial College, London, United Kingdom. Rue Henri Huchard 46, 75877 Paris, France.

Ψ Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland. Mittelstrasse 43, CH-3012 Bern, Switzerland.

Ω The European Cardiovascular Research Institute, Rotterdam, The Netherlands. Westblaak 98, 3012 KM Rotterdam, The Netherlands.

Cork University Hospital, Cork, Ireland. Cork University Hospital, Wilton, Cork, Ireland

∆ Erasmus Medical Center, Rotterdam, The Netherlands. Dr. Doctor Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

¥ Cardialysis, Rotterdam, The Netherlands. Westblaak 98, 3012 KM Rotterdam, The Netherlands.

Φ Academic Medical Center of Amsterdam, Amsterdam, Netherlands. Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.

ǂ Imeldaziekenhuis, Bonheiden, Belgium. Imeldalaan 9, 2820 Bonheiden, Belgium.

** UOC Cardiologia, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.

†† American Heart of Poland, Center for Cardiovascular Research and Development, Katowice, Poland. Francuska 34, 40-028 Katowice, Poland.

‡‡ Azienda Ospedaliera S. Maria, Terni, Italy. Viale Tristano di Joannuccio, 05100 Terni TR, Italy

§§ 3rd Department of Medicine, Cardiology and Intensive Care Medicine, Wilhelminenhospital and Sigmund Freud University, Medical Faculty, Vienna, Austria. Mariahilfer Strasse 49, 1060 Vienna, Austria

¶¶ Onze Lieve vrouwe Gasthuis, Amsterdam, The Netherlands. Oosterpark 9, 1091 AC Amsterdam, The Netherlands.

ΨΨ Imperial College London, London, UK. Office: Westblaak 98, 3012 KM Rotterdam, The Netherlands.

Drs. Vranckx and Valgimigli and Drs. Serruys and Windecker contributed equally to this article.

Corresponding authors:
Patrick Serruys
Emeritus Professor of Medicine, Erasmus University
Email: patrick.w.j.c.serruys@gmail.com

Stephan Windecker, MD
Professor and Chairman
Department of Cardiology
Bern University Hospital - INSELSPITAL
3010 Bern, Switzerland
Tel: +41 31 632 4497
Mail: stephan.windecker@insel.ch

Background

We hypothesized that ticagrelor, in combination with aspirin for 1 month, followed by ticagrelor alone improves outcomes after percutaneous coronary intervention as compared with standard antiplatelet regimens.

Methods

In this randomised multicentre open label superiority trial, patients undergoing percutaneous coronary intervention with biolimus A9-eluting stent platform were allocated 1:1 using concealed, stratified and blocked web-based central randomization to 1-month aspirin and ticagrelor, followed by 23 months ticagrelor alone or standard treatment with 1-year dual antiplatelet therapy, followed by aspirin alone. The primary endpoint was a composite of 2-year all-cause mortality or non-fatal, centrally adjudicated, new Q-wave myocardial infarction.

Findings

Out of a total of 15,991 patients who were assigned to the experimental (7980) or standard treatment (7988), the primary end-point event at 2 years occurred in 304 patients (3·81 %) in the experimental and in 349 patients (4·37%) in the standard treatment groups (rate ratio, 0·87 [95% confidence interval, 0·75-1·01; P=0·073]). There was no evidence for a difference in treatment effects for the primary endpoint across prespecified subgroups of acute coronary syndromes and stable coronary artery disease (p=0·99). All-cause mortality occurred in 224 patients (2·81%) in the experimental group and in 253 patients in the standard treatment group (3·17%) (rate ratio, 0·88 [95% confidence interval, 0·74-1·06], P= 0·186), whereas the incidence of new Q-wave myocardial infarction was 83 (1·04%) vs. 103 (1·29%), respectively (rate ratio, 0·80 [95% confidence interval, 0·60-1·07], P= 0·142). Major bleeding occurred

in 163 in the experimental and 169 in the standard treatment groups (2·04% vs. 2·12%, rate ratio 0.97 [95% CI, 0·78-1·20]; P=0·766).

Interpretation

Ticagrelor, in combination with aspirin for 1 month, followed by ticagrelor alone was not superior to 1-year standard dual antiplatelet therapy followed by aspirin alone in the prevention of all-cause mortality or new Q-wave myocardial infarction at 2 years following percutaneous coronary intervention.

Funding Astra Zeneca, Biosensors and The Medicines Company.

Trial registration: ClinicalTrials.gov number, NCT01813435.)

.

Introduction

Dual antiplatelet therapy reduces the risk of stent-related and spontaneous recurrent ischemic events among patients with acute coronary syndromes or stable coronary artery disease undergoing percutaneous coronary intervention.[1–4] However, dual antiplatelet therapy increases the risk of bleeding which may thus offset the anticipated benefit on ischemic events.[1–3,5] Therefore, an abbreviated dual antiplatelet therapy regimen followed by adenosine diphosphate receptor P2Y12 receptor antagonist monotherapy may favourably impact the balance between bleeding risk and ischemic benefit.[6]

Ticagrelor is a reversible and direct-acting oral antagonist of the P2Y12 receptor that provides faster, greater, and more consistent platelet inhibition than clopidogrel.[7] In the Platelet Inhibition and Patient Outcomes (PLATO) trial, treatment with ticagrelor as compared with clopidogrel (both given in combination with aspirin) reduced the rate of major adverse cardiac events and all-cause mortality.[7] It has been hypothesized that ticagrelor combined with acetylsalicylic acid (aspirin) at a maintenance dose above 150mg daily may attenuate the therapeutic effect of ticagrelor. Accordingly, it has been suggested that the potent P2Y12 inhibitor ticagrelor may be used without concomitant aspirin while preserving ischemic protection and potentially avoid bleeding complications.[8]

The GLOBAL LEADERS trial was designed to compare the benefits and risks of 2 years of treatment with ticagrelor 90mg twice daily, in combination with aspirin for the first month versus conventional 1-year dual antiplatelet therapy, followed by aspirin alone, in patients undergoing percutaneous coronary intervention with uniform use of

an intravenous direct thrombin inhibitor and biodegradable polymer biolimus-eluting stents.[9]

Methods

Study Design and Patients

The design of this randomized open-label multicentre superiority trial was described previously and summarized in the Supplementary Web-appendix.[9] An independent data and safety monitoring committee oversaw the safety of all patients. The institutional review board at each participating institution approved the trial.

The study population consisted of patients scheduled to undergo percutaneous coronary intervention for stable coronary artery disease or acute coronary syndromes requiring dual antiplatelet therapy, unless oral anticoagulation was indicated.[9] Percutaneous coronary intervention was standardized by uniform implantation of biodegradable polymer-based biolimus-eluting stent(s) and bivalirudin administration whenever indicated or feasible. There was no restriction on the number of treated lesions or vessels, on lesion length or number of stents used. Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix.

The study adhered to the ethical principles of the Declaration of Helsinki, to specifications of the International Conference of Harmonization, and to Good Clinical Practice. All participants provided written informed consent at the time of enrolment. The trial is registered with ClinicalTrials.gov, number NCT01813435.

Treatment and Follow-up

After diagnostic coronary angiography but before percutaneous coronary intervention, patients were centrally randomized in a 1:1 ratio using a web-based system stratified by centre and clinical presentation (stable coronary artery disease vs acute coronary syndrome) and blocked using randomly varied block sizes of 2 and 4. The experimental strategy consisted of aspirin 75-100mg once daily in combination with ticagrelor 90mg twice daily for one month followed by ticagrelor 90 mg twice daily alone for 23 months irrespective of clinical presentation. The standard treatment consisted of 1 year dual antiplatelet therapy with aspirin 75-100mg daily in combination with either with clopidogrel 75mg once daily in patients with stable coronary artery disease or ticagrelor 90mg twice daily in patients with acute coronary syndromes followed by aspirin 75-100mg once daily alone for the remaining 12 months (Figure 1).[9]

Global Leaders was an open label trial. We anticipated the potential implications of an unblinded trial towards drug adherence. Trial medications were dispensed at 3-month time intervals during direct patient contact. Adherence was assessed by direct pill counts and self-reporting. Adherence counselling by the study team was the default strategy to improve drug adherence.

Follow-up visits were scheduled at 30 days, 3, 6, 12, 18 and 24 months after the index procedure. The protocol mandated that a 12-lead electrocardiogram was obtained at discharge, 3 months and 2 years, and intercurrently in case of revascularization procedures or suspected ischemic events. Electrocardiogram analyses were performed in a central core laboratory (Cardialysis BV, Rotterdam, the Netherlands). Core laboratory staff were unaware of study group assignments. The electronic case report form was revised and implemented on August 28, 2013 to enable ascertainment of reasons of non-adherence to the allocated strategy during all visits. The

8545 consecutive patients who underwent the 30 day follow-up visit after this date contributed to the analysis of reasons of non-adherence.

Endpoints

The primary endpoint was a composite of all-cause death or new Q-wave myocardial infarction within 730 days of the index procedure. Deaths from any cause were ascertained without adjudication.[10] Q-wave myocardial infarction was defined 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 (see the Supplementary Appendix).[11,12] The key secondary safety endpoint was site reported bleeding assessed according to the Bleeding Academic Research Consortium criteria (grade 3 or 5).[13] Other secondary endpoints of the study included the individual components of the primary endpoint, the composite endpoint of all-cause death, new Q-wave myocardial infarction and stroke; myocardial infarction; stroke; target vessel and any revascularization; and definite stent thrombosis.[9] Up to 7 on-site monitoring visits were performed at individual sites with 20% of reported events checked against source documents. In addition, the trial was monitored for event underreporting and event definition consistency; no independent event adjudication was implemented. More detailed definitions of the endpoints are provided in the Supplementary Web-appendix.

Statistical Analysis

The rate of the primary endpoint at 2 years in the reference group was assumed to be 5% based on the results of the LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial.[14] The Study of Platelet Inhibition and Patient Outcomes (PLATO) trial reported a reduction in all-cause mortality in favour of ticagrelor (4·5%, vs. 5·9% with clopidogrel; HR 0·78, 95%CI 0·69-0·89, P<0·001).[7] We anticipated that the difference could be the same or even larger based on a potential interaction of aspirin dose and ticagrelor and used a 20% RRR as a conservative and clinically relevant margin.[8] A sample size of 8,000 patients per group would provide 84% power to detect a 20% relative risk reduction at a two-sided α of 0.05.

The primary endpoint was analysed according to the intention-to-treat principle using the Mantel-Cox method based on time to occurrence of death or diagnosis of new Q-wave myocardial infarction, reporting rate ratios with 95% confidence intervals. Prespecified landmark analyses used cut-off points at 30 days (corresponding to the planned dates of discontinuation of aspirin in the experimental group) and 1 year (corresponding to the planned dates of discontinuation of a P2Y12 receptor antagonist in the reference group) after the index procedure with risk ratios calculated separately for events up to and beyond the landmark. We performed subgroup analyses of the primary endpoint with tests for treatment-by-subgroup interaction by prespecified baseline characteristics, and by type of reference treatment (use of ticagrelor versus clopidogrel) as a post-hoc criterion. Then, we performed post-hoc subgroup analyses on the same characteristics for the key secondary safety endpoint of Bleeding Academic Research Consortium grade 3 or 5 events.

Secondary efficacy endpoints were analysed according to the intention-to-treat principle in the intent-to-treat population using the Mantel-Cox log-rank method up to the time-point when the first of this type of event occurred ("time-to-first-event analyses"), ignoring any events of the same type the patient experienced after the first event.

Categorical variables were compared with the use of the chi-square test or Fisher's exact test. Continuous variables were compared with use of Student's t-test or the Wilcoxon rank-sum test for non-normally distributed data. Lesion level data were analysed with mixed models accounting for lesions nested within patients. All statistical analyses were performed with Stata software, version 14.2.

Role of the funding source

GLOBAL LEADERS was an investigator-initiated trial sponsored by the European Clinical Research Institute (www.ECRI-trials.com), which received funding from one device (Biosensors International Ltd, Europe) and two drug manufacturers (Astra Zeneca; Cambridge United Kingdom; The Medicines Company, Parsippany; United States of America). The steering committee was responsible for the design, conduct, analysis and reporting of the data. The stent and drug manufacturers who funded the trial had no contributing roles in any aspect of the trial.

The first three and last two authors wrote the first draft of the manuscript had full access to the data, and vouch for the integrity of the analyses presented and for the fidelity of this report to the trial protocol. All co-authors participated in subsequent revisions of the manuscript.

Results

We recruited 15,991 patients from 130 sites in 18 countries from July 2013 through November 2015. Subsequently, 23 patients withdrew consent and requested deletion of their data from the database, leaving 7,980 patients in the experimental group and 7,988 patients in the reference group for the final analysis (Figure 1. A total of 7,782 patients (97·5%) in the experimental group and 7,767 patients (97·2%) in the reference group received the allocated treatment regimen.

The baseline clinical and procedural characteristics of patients are presented in Tables 1 and 2. Acute coronary syndromes were present in 46·9% of patients (unstable angina 12·7%, Non-ST-segment elevation myocardial infarction 21·1%, ST-segment elevation myocardial infarction 13·1%). The mean age was 64·5±10·3 years, and 23·3% of patients were female. Bivalirudin assisted percutaneous coronary intervention was performed in 13,870 patients (87%), biolimus A9-eluting stents were used in 19,415 lesions (94·6%), and staged procedures performed in 1,455 patients (9·1%).

At 2-year follow-up, vital status information was available in 15,960 patients (99·9%). Electrocardiograms were analysable in 14,857 patients at 3 months (93·7% of patents alive at 3 months) and in 14,357 patients at 24 months (92·7% of patients alive at 24 months) (see Figure 1).

Adherence to the allocated antiplatelet treatment at discharge, 30 days, 3, 6, 12, 18 and 24 months are shown in Figure S1 and Table S1 in the Supplementary Web-appendix. At 2 years, 76·6% of patients in the experimental group and 93·1% of patients in the reference group adhered to the protocol mandated antiplatelet treatment strategy. Reasons for non-adherence at 30 days, 12 and 24 months in

8545 consecutive patients are shown in Table S3 in the Supplementary Web-appendix. Dyspnea was considerably more frequent as a reason for non-adherence at all three timepoints (p≤0.005).

Efficacy Outcomes

At 2-year follow-up, a primary endpoint event – a composite of all-cause mortality or new Q-wave myocardial infarction – had occurred in 304 patients (3·81%) in the experimental group and in 349 patients (4·37%) in the reference group (rate ratio, 0·87 [95% confidence interval, 0·75-1·01; P=0·073], Table 3, Figure 2). The subclassification of the new Q-wave myocardial infarction according to the Minnesota code is provided in Figure S2 in the Supplementary Web-appendix. A total of 224 patients (2·81%) in the experimental arm and 253 patients (3·17%) in the reference group died (rate ratio, 0·88 [95% confidence interval, 0·74-1·06]). A new Q-wave myocardial infarction was recorded in 83 patients (1·04%) in the experimental group and in 103 patients (1·29%) in the reference group (rate ratio, 0·80 [95% confidence interval, 0·60-1·07], P= 0·142). The composite of all-cause death, new Q-wave myocardial infarction and stroke occurred in 362 patients (4·54%) in the experimental group and in 416 patients (5·21%) in the reference group (rate ratio, 0·87 [95% confidence interval, 0·76-1·00], P= 0·056). Definite stent thrombosis occurred at similar rates (64, 0·80%) in both treatment groups throughout the study period.

Safety Outcomes

The rate of investigator reported Bleeding Academic Research Consortium grade 3 or 5 events did not differ between treatment groups (163 patients (2·04%) in the ex-

perimental group vs. 169 patients (2·12%) in the reference group; rate ratio 0·97 [95% CI, 0·78-1·20], P= 0·766) (Table 3). Additional bleeding endpoints are provided in Table S2 in the Supplementary Web-Appendix. Dyspnea was more common in the ticagrelor treated patients than in patients treated with other P2Y12-receptor antagonist (13·8% vs. 6·5%).

Additional Analyses

Subgroup analyses of the primary endpoint are shown in Figure 3. There was no evidence for variation in treatment effects for the primary endpoint by pre-specified baseline characteristics, or by type of reference treatment (use of ticagrelor versus clopidogrel) as a post-hoc criterion. Figure S3 presents exploratory subgroup analyses specified post-hoc of the key secondary safety endpoint of Bleeding Academic Research Consortium grade 3 or 5 events. There was evidence for a treatment-by-subgroup interaction for type of indication (Acute Coronary Syndromes versus stable coronary artery disease, p for interaction=0.0068), which appeared partially explained by a treatment-by-subgroup interaction for type of reference treatment (p for interaction=0.016), with an advantage of the experimental strategy in patients with Acute Coronary Syndromes and compared against a ticagrelor-based reference strategy, and a disadvantage in patients with stable coronary artery disease and compared against a clopidogrel-based reference strategy. Landmark analyses are presented in Table S4 in the Supplementary Web-appendix. The primary endpoint occurred in 270 patients (3.40%) in the experimental group and 307 patients (3.87%; rate ratio 0.88 [95% CI, 0.74-1.03], P=0.115) in the reference group between 30 days and 2 years. Rates of mortality, myocardial infarction, definite stent thrombosis and Bleeding Academic Research Consortium grade 3 or 5 events were similar in both groups from 30

days onwards. Beyond 1 year, deaths from any cause were observed in 116 patients (1·48%) in the experimental arm and 122 patients (1·56%) in the reference group (rate ratio 0·95 [95% CI, 0·74-1·22], P=0·913), see table S5 in the Supplementary Web-appendix). Table S4 presents results for post-hoc composite outcomes, including net clinical benefit.

Discussion

Ticagrelor, in combination with aspirin for 1 month, followed by ticagrelor alone was not superior to standard 1-year dual antiplatelet therapy followed by aspirin monotherapy in terms of the composite of all-cause mortality or new Q-wave myocardial infarction after percutaneous coronary intervention.

When the components of the primary endpoint were individually analysed, there were numerical, but not statistically significant differences in favour of the experimental strategy. The rates of definite or probable stent thrombosis were similar between the two study groups. Rates of major bleeding according to the Academic Research Consortium were similar in both antiplatelet strategies and comparable with those reported for the Prospective validation of the Bleeding Academic Research Consortium classification in the all-comer (PRODIGY) all-comers percutaneous coronary intervention trial.[17] While our study was not designed to assess the non-inferiority of the experimental treatment strategy as compared to current standard of care, the upper boundary of the 95 percent confidence interval of the primary endpoint was close to unity suggesting no excessive safety signal attributable to the experimental strategy. In post-hoc subgroup analyses of bleeding events, we found some evidence for a treatment-by-subgroup interaction for type of indication, which appeared partially explained by an interaction with type of reference treatment, with an advantage of the experimental strategy in patients with ACS and compared against a ticagrelor-based reference strategy. These exploratory findings would need to be confirmed in future trials in patients with Acute Coronary Syndromes.

GLOBAL LEADERS is the largest trial to date testing one-month of dual antiplatelet therapy versus a more prolonged dual antiplatelet regimen after drug eluting stent

implantation and had a unique design as it mandated the sole use of ticagrelor, a P2Y12 receptor antagonist as an antiplatelet regimen and not aspirin alone after cessation of dual anti-platelet therapy. Hence, our results cannot be extrapolated to patients receiving 1-month duration of dual antiplatelet therapy followed by aspirin monotherapy.

The duration of dual antiplatelet therapy in the reference arm was determined according to professional guidelines at the time of the planning of the study design. We recognize that a shorter duration of dual antiplatelet therapy of 6 months is recommended in the most recent guidelines for patients with stable coronary artery disease undergoing elective percutaneous coronary intervention, although consideration to an extension during the period between 6-12 months remains an option in the absence of bleeding complications.[18]

Multiple studies have shown that a prolonged duration of dual antiplatelet therapy is associated with a trade-off between ischemic and bleeding risks.[1–3,5,19,20] In the dual antiplatelet therapy (DAPT) study, prolonging treatment for an additional 18 months beyond 1 year significantly reduced major adverse cardiovascular events and stent thrombosis. However, all-cause mortality and rates of moderate and severe bleeding were increased.[1] There was an interaction between stent types and major adverse cardiovascular events, suggesting limited incremental benefit of extended dual antiplatelet therapy in patients receiving new generation drug eluting stents.[1]

Unlike the DAPT trial, our protocol mandated the uniform use biolimus A9-eluting stent platform that provides similar safety and efficacy compared with newer generation durable polymer drug eluting stents.[21] The use of a uniform stent platform avoids difficulties in interpretation resulting from differences in treatment effects observed

across different stent platforms, but retains generalizability in view of the similar performance of our stent platform compared with best in class new generation drug-eluting stent.[22]

In the prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin (PEGASUS) trial, in patients with history of myocardial infarction one year or more before, who had one or more additional high-risk feature(s), ticagrelor at 60mg or 90 mg twice daily reduced the risk of the composite of cardiovascular death, myocardial infarction or stroke at the expense of an increased risk of major bleeding.[2] In an attempt to further enhance the risk-benefit ratio of ticagrelor, the present trial investigated ticagrelor in combination with aspirin for the first month followed by long-term ticagrelor alone. Our trial failed to show the superiority of the experimental treatment strategy. However, it provided reassuring information with respect to the safety and efficacy of ticagrelor monotherapy. Our trial failed to show the superiority of the experimental treatment strategy. The clinical risk profile of patients included in The GLOBAL LEADERS trial was lower than in PEGASUS. A PEGASUS like patient population will be studied in the ongoing Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention (TWILIGHT) trial.[23]

Although the rate of serious adverse events did not differ significantly between the two treatment regimens, discontinuation of the study regimen was more common among patients in the experimental group. The rate of study regimen discontinuation compared favourably to premature study drug discontinuation rates reported in other large outcome trials testing ticagrelor across a variety of indications. [2,7, 24,25] Non-adherence to ticagrelor in the first year in the GLOBAL LEADERS trial was 18% in the experimental group (1378/7550) patients and 15% in the standard treatment

group (575/3890 patients pre-treated with potent P2Y12inhibitor, or patients with an acute coronary syndrome at baseline) vs. 23% (2186/9333 patients) in the PLATO trial.[7] The observed imbalance interruption between the experimental and reference treatment groups after the first year may stem from the fact that aspirin constitutes the default (background) therapy for patients with established atherothrombotic cardiovascular disease, whereas the experimental treatment strategy has not been established. We cannot exclude that pleiotropic effects of aspirin other than the antiplatelet effect may be beneficial and may have contributed to the outcome of the trial.[4]

Our trial should be interpreted in the light of several limitations: Global Leaders was an open-label trial without masking of the components of the treatment strategy. In pragmatic trials, the randomly assigned group is commonly not masked. Efforts that were made to minimize biases included the focus on major, objective outcomes (i.e. all-cause death and Q-wave myocardial infarction diagnosed by blinded staff at a core lab in the GLOBAL LEADERS trial). All-cause mortality is a reliable endpoint that does not require adjudication. Vital status was obtained in all but eight patients. The appearance of a new Q-wave on a 12-lead electrocardiogram, scrutinized by a dedicated core laboratory (using the Minnesota Classification) is associated with an increased risk of all-cause death and heart failure among affected patients. [26–28] Non-fatal, new Q-wave myocardial infarctions constituted approximately 34% of the total number of site-reported myocardial infarctions in the trial. The rate of 3-month and 2-year electrocardiograms that could not be analysed was higher than anticipated (5%), but balanced between both groups. Investigator reporting was used without central adjudication to ascertain secondary outcomes. Bias and random misclassification can therefore not be excluded for these outcomes. However, our trial was

monitored for event underreporting and consistency of event definitions. The rate of all-cause mortality as well as the rate of the composite primary endpoint at two years was lower than expected, limiting the power of the trial. Our original sample size calculation was based on the LEADERS trial in which clopidogrel was used in all patients.[14] In the present study, clopidogrel use was limited to patients with stable coronary artery disease with planned elective percutaneous coronary intervention.[14,23] The lower rates for all-cause mortality in the reference arm may reflect the treatment benefit seen with ticagrelor over clopidogrel in patients with a planned invasive strategy in the PLATO trial.[30] Central adjudication and inclusion of all investigator-reported myocardial infarctions in the primary composite outcome might have increased the power of the trial, and an event driven sample size consideration could have compensated for the lower than expected event rate, but resource limitations prevented us from using either of these two approaches.

In conclusion, in patients undergoing percutaneous coronary intervention, an antiplatelet regimen consisting of one month of ticagrelor in combination with low dose aspirin followed by 23 months of ticagrelor alone was not superior to standard treatment in the reducing the 2-year rate of all-cause mortality and non-fatal, new Q-wave myocardial infarction.

Acknowledgments

Dr. Jüni is a Tier 1 Canada Research Chair in Clinical Epidemiology of Chronic Diseases. This research was completed, in part, with funding from the Canada Research Chairs Programme.

Contributors

PV, MV, PWS, and SW participated in the study design, data gathering, and interpretation, writing the first draft and all revisions of the manuscript. PJ participated in the study design, data analysis and interpretation, writing the first draft and all revisions of the manuscript. CH, and GS participated in the data gathering, and interpretation, writing the first draft and all revisions of the manuscript. DH was involved in the data analysis and revision of the report. GAVE participated in the trial design and data gathering. EMF, YO, CVM, PC participated in the data gathering and cleaning. EB, HM, LJ, MF, AM, AZ, MD, KH, and TS participated in the data gathering and revision of the manuscript.

Conflict of interest

Dr. Pascal Vranckx discloses the following relationships: personal fees from AstraZeneca and the Medicines Company during the conduct of the study; personal fees from Bayer Health Care, Terumo and Daiichi-Sankyo outside the submitted work.

Dr. Marco Valgimigli discloses the following relationships: personal fees from Abbott, personal fees from Chiesi, personal fees from Bayer, personal fees from Daiichi Sankyo, personal fees from Terumo, personal fees from CID, personal fees from Amgen, grants from Swiss National Foundation, grants from Terumo, grants from

Medicure, grants from Abbott, grants from Astra Zeneca, personal fees from Astra Zeneca, outside the submitted work; .

Dr. Peter Jüni discloses the following relationships: Research grants to the institution from Astra Zeneca, Biotronik, Biosensors International, Eli Lilly and The Medicines Company, outside the submitted work; and Dr. Peter Jüni is a Tier 1 Canada Research Chair in Clinical Epidemiology of Chronic Diseases, this research was completed in part, with funding from the Canada Research Chairs Programme. Peter Jüni serves as unpaid member of the steering group of trials funded by Astra Zeneca, Biotronik, Biosensors, St. Jude Medical and The Medicines Company.

Dr. Christian Ham discloses the following relationships: Personal fees from AstraZeneca outside the submitted work.

Dr. Ph Gabriel Steg discloses the following relationships: Research grant from Bayer/Janssen, grants and personal fees from Merck, Sanofi, Amarin, personal fees from Amgen, Bristol-Myers-Squibb, Boehringer-Ingelheim, Pfizer, Novartis, Regeneron, Lilly, AstraZeneca, grants, personal fees and non-financial support from Servier, outside the submitted work.

Dik Heg discloses the following relationships: Dik 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 organizations. In particular, pharmaceutical and medical device companies provide direct funding to some of these studies. For an up-to-date list of CTU Bern's conflicts of interest see

http://www.ctu.unibe.ch/research/declaration_of_interest/index_eng.html

Dr. Eugène P Mc Fadden discloses the following relationships: personal fees from ECRI, Rotterdam , Netherlands, during the conduct of the study; grants from Astra Zeneca, personal fees from Abbott Vascular, personal fees from Daiichi Sankyo, non-financial support from Menarini Ireland, grants from Bayer, grants from Terumo, outside the submitted work.

Dr. Yoshinobu Onuma discloses the following relationships: Consultancy fees from Abbott Vascular.

Dr. Helge Möllmann discloses the following relationships: personal fees from Astra Zeneca, Bayer, Bristol-Myers-Squibb, Boehringer Ingelheim, Daiichi Sankyo, Pfizer

Dr. Van Geuns reports grants and personal fees from Abbott Vascular, grants from Boston Scientific outside the sy

Dr. Kurt Huber discloses the following relationships: personal fees from Astra Zeneca, Sanofi Aventis and Biosensors outside the submitted work.

Dr. Serruys reports personal fees from Abbot Laboratories, Astra Zeneca, Biotronik, Cardialysis, GLG Research, Medtronic, Sino Medical Sciences Technology, Société Europa Digital Publishing, Stentys France, Svelte Medical Systems, Philips/Volcano, St Jude Medical, Qualimed, Xeltis, outside the submitted work.

Dr. Stephan Windecker discloses the following relationships: research contracts to the institution from Abbott, Amgen Inc., Bayer AG, Biotronik, Boston Scientific, Edwards Lifesciences, Medtronic, St Jude Medical, Symetis SA and Terumo Inc. outside the submitted work.

The remaining authors declare no competing interests.

References

1. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. The New England journal of medicine. 2014;371(23):2155-66.

2. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. The New England journal of medicine. 2015;372(19):1791-800.

3. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). European heart journal. 2018;39(3):213-60.

4. Capodanno D, Mehran R, Valgimigli M, Baber U, Windecker S, Vranckx P, et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. Nature reviews Cardiology. 2018;15(8):480-96.

5. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, et al. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. Circulation. 2012;125(16):2015-26.

6. Gargiulo G, Windecker S, Vranckx P, Gibson CM, Mehran R, Valgimigli M. A Critical Appraisal of Aspirin in Secondary Prevention: Is Less More? Circulation. 2016;134(23):1881-906.

7. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. The New England journal of medicine. 2009;361(11):1045-57.

8. Mahaffey KW, Wojdyla DM, Carroll K, Becker RC, Storey RF, Angiolillo DJ, et al. Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) trial. Circulation. 2011;124(5):544-54.

9. 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 : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2016;12(10):1239-45.

10. Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, et al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. Journal of the American College of Cardiology. 2018;71(9):1021-34.

11. Prineas R.J. CRS, Blackburn H. The Minnesota Code Manual of Electrocardiographic Findings John Wright–PSG, Littleton, MA; 1982.

12. Prineas R.J. CRS, Zhang Z.-M. . The Minnesota Code Manual of Electrocardiographic Findings Springer Science & Business Media, London; 2009.

13. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus

report from the Bleeding Academic Research Consortium. Circulation. 2011;123(23):2736-47.

14. Klauss V, Serruys PW, Pilgrim T, Buszman P, Linke A, Ischinger T, et al. 2-year clinical follow-up from the randomized comparison of biolimus-eluting stents with biodegradable polymer and sirolimus-eluting stents with durable polymer in routine clinical practice. JACC Cardiovascular interventions. 2011;4(8):887-95.

15. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function--measured and estimated glomerular filtration rate. The New England journal of medicine. 2006;354(23):2473-83.

16. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. The New England journal of medicine. 1985;312(14):932-6.

17. Vranckx P, Leonardi S, Tebaldi M, Biscaglia S, Parrinello G, Rao SV, et al. Prospective validation of the Bleeding Academic Research Consortium classification in the all-comer PRODIGY trial. European heart journal. 2014;35(37):2524-9.

18. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). European heart journal. 2018;39(3):213-60.

19. Navarese EP, Andreotti F, Schulze V, Kolodziejczak M, Buffon A, Brouwer M, et al. Optimal duration of dual antiplatelet therapy after percutaneous coronary

intervention with drug eluting stents: meta-analysis of randomised controlled trials. BMJ (Clinical research ed). 2015;350:h1618.

20. Costa F, van Klaveren D, James S, Heg D, Raber L, Feres F, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet (London, England). 2017;389(10073):1025-34.
21. Navarese EP, Tandjung K, Claessen B, Andreotti F, Kowalewski M, Kandzari DE, et al. Safety and efficacy outcomes of first and second generation durable polymer drug eluting stents and biodegradable polymer biolimus eluting stents in clinical practice: comprehensive network meta-analysis. BMJ (Clinical research ed). 2013;347:f6530.
22. El-Hayek G, Bangalore S, Casso Dominguez A, Devireddy C, Jaber W, Kumar G, et al. Meta-Analysis of Randomized Clinical Trials Comparing Biodegradable Polymer Drug-Eluting Stent to Second-Generation Durable Polymer Drug-Eluting Stents. JACC Cardiovascular interventions. 2017;10(5):462-73.
23. Baber U, Dangas G, Cohen DJ, Gibson CM, Mehta SR, Angiolillo DJ, Pocock SJ, et al. Ticagrelor with aspirin or alone in high-risk patients after coronary intervention: Rationale and design of the TWILIGHT study. Am Heart J. 2016 Dec;182:125-134.
24. Hiatt WR, Fowkes FG, Heizer G, Berger JS, Baumgartner I, Held P, et al. Ticagrelor versus Clopidogrel in Symptomatic Peripheral Artery Disease. The New England journal of medicine. 2017;376(1):32-40.

25. Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, et al. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. The New England journal of medicine. 2016;375(1):35-43.
26. Qureshi WT, Zhang ZM, Chang PP, Rosamond WD, Kitzman DW, Wagenknecht LE, et al. Silent Myocardial Infarction and Long-Term Risk of Heart Failure: The ARIC Study. Journal of the American College of Cardiology. 2018;71(1):1-8.
27. Stone GW, Mehran R, Dangas G, Lansky AJ, Kornowski R, Leon MB. Differential impact on survival of electrocardiographic Q-wave versus enzymatic myocardial infarction after percutaneous intervention: a device-specific analysis of 7147 patients. Circulation. 2001;104(6):642-7.
28. Zhang ZM, Rautaharju PM, Prineas RJ, Rodriguez CJ, Loehr L, Rosamond WD, et al. Race and Sex Differences in the Incidence and Prognostic Significance of Silent Myocardial Infarction in the Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2016;133(22):2141-8.
29. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet (London, England). 2008;372(9644):1163-73.
30. Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuelsson H, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. Lancet (London, England). 2010;375(9711):283-93.

31. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. The New England journal of medicine. 2017;377(14):1319-30.
32. Ohman EM, Roe MT, Steg PG, James SK, Povsic TJ, White J, et al. Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind, multicentre, randomised trial. Lancet (London, England). 2017;389(10081):1799-808.

Legends to figures

Figure 1: Consort Diagram

Figure 2: Cumulative incidence of all-cause mortality within 2-years (blue: experimental strategy group; red: reference strategy group).

Figure 3: Subgroup analyses of the primary endpoint.

Panel research in context

Evidence before this study

We searched PubMed and ISI Web of Science from January 1, 2008 to May 1, 2018 for all-comers percutaneous coronary intervention trials (See table S6 in the Supplementary Web-Appendix) to allow a comparison for baseline clinical and angiographic characteristics). The baseline angiographic risk of patients included in the GLOBAL LEADERS trial is comparable with that of other all-comers percutaneous coronary intervention outcome studies.

We searched the PubMed database (inception – July 2018) for complete reports of comparative effectiveness studies comparing an established antiplatelet strategy against a ticagrelor based strategy. We did not find any randomized longterm outcome trial comparing standard dual antiplatelet therapy against an experimental strategy using ticagrelor, or any other potent P2Y12 receptor antagonist without aspirin in patients following drug eluting stent implantation. We identified 4 randomised large outcome trials using ticagrelor alone or in combination with aspirin across a wide range of cardiovascular indications, with a patient follow-up ranging from 90-days to 3 years:

The Study of Platelet Inhibition and Patient Outcomes (PLATO) trial tested a dual antiplatelet strategy of clopidogrel vs. ticagrelor against the background of aspirin in 18,624 patients with acute coronary syndromes, with or without ST-segment elevation.[7] The primary end point, a composite of death from cardiovascular causes or cerebrovascular causes or any death without another known cause, occurred significantly less often in the ticagrelor group than in the clopidogrel group (in 9·8% of patients vs. 11·7% at 12 months; hazard ratio, 0·84; 95% confidence interval [CI],

0·77 to 0·92; P<0·001). This pattern was also reflected in a reduction in the rate of death from any cause in favour of ticagrelor (4·5%, vs. 5·9% with clopidogrel; P<0·001). While the overall risk of major bleeding was equal, there was an increase in non-Coronary Artery Bypass Grafting associated bleeding in the ticagrelor group at 12-months (4·5% and 3·8%, respectively; P=0·03).

The prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial tested two doses of ticagrelor (60mg and 90mg) vs. aspirin in 21,162 high-risk patients (e.g., diabetes, renal disease, multivessel disease, and recurrent myocardial infarction) with a myocardial infarction more than 1-year previously.[2] As compared with placebo, either dose of ticagrelor was associated with a 15% decrease in the rate of the primary end point of death from cardiovascular causes, myocardial infarction, or stroke. However, ticagrelor treatment also increased clinically significant bleeding complications by a factor of 2·3 to 2·7 and transfusions by a factor of 3·1 to 3·8.

In the Examining Use of Ticagrelor in Peripheral Artery Disease (EUCLID) in 13,885 patients with symptomatic peripheral artery disease, ticagrelor alone was not shown to be superior to clopidogrel alone for the reduction of cardiovascular events, the composite of cardiovascular death, myocardial infarction, or ischemic stroke (10·8% vs. 10·6%; hazard ratio, 1·02; 95% confidence interval, 0·92 to 1·13; P=0·65).[21] Major bleeding occurred at similar rates (1·6%) among the patients in the two trial groups (hazard ratio, 1·10; 95% CI, 0·84 to 1·43; P=0·49).

The Acute Stroke or Transient Ischaemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial, in 13,199 patients with a non-severe

ischemic stroke or high-risk transient ischemic attack who had not received intravenous or intra-arterial thrombolysis and were not considered to have had a cardioembolic stroke, failed to establish superiority of ticagrelor over aspirin in reducing the rate of stroke, myocardial infarction, or death at 90 days.[22] Again, major bleeding occurred at similar rates (0.5%) in the two treatment groups (hazard ratio, 0.83; 95% CI, 0.52 to 1.44).

The rate of study regimen discontinuation in GLOBAL LEADERS compared favourably to premature study drug discontinuation rates reported in these double-blind outcome trials testing ticagrelor across a variety of indications.[2,7,21,22,24]

Other trials investigating an aspirin-free strategy in patients not on oral anticoagulants include GEMINI-ACS-1 (the Study to Compare the Safety of Rivaroxaban Versus Acetylsalicylic Acid in Addition to Either Clopidogrel or Ticagrelor in Participants With Acute Coronary Syndrome) and COMPASS (the Cardiovascular Outcomes for People Using Anticoagulation Strategies).[31,32] GEMINI and COMPASS omitted aspirin while replacing it with a direct Factor-Xa inhibitor rather than a potent P2Y12 inhibitor. GEMINI-ACS-1 was a phase II trial with a primary bleeding endpoint. COMPASS was conducted in the context of secondary prevention in high-risk patients.

Added value of this study

GLOBAL LEADERS is the largest trial to date testing one-month of dual antiplatelet therapy versus a more prolonged dual antiplatelet regimen after drug eluting stent implantation and had a unique design as it mandated the sole use of ticagrelor, a P2Y12 receptor antagonist as an antiplatelet regimen and not aspirin alone after cessation of dual anti-platelet therapy. GLOBAL LEADERS is the only randomized

trial with randomisation at the timepoint of percutaneous coronary intervention, comparing two antiplatelet strategies and reporting 2-years of follow-up.

Implications of the added evidence

While our study was not designed to assess the non-inferiority of the experimental treatment strategy as compared to current standard of care, the upper boundary of the 95 percent confidence interval of the primary endpoint was close to unity suggesting no excessive safety signal attributable to the experimental strategy.

Data sharing

The study protocol and statistical analysis plan underlying this manuscript will be available with the journal at the Lancet.com. The GLOBAL LEADERS trial is an investigator-initiated trial. Multiple sub-studies are predefined. Internal investigators, who actively participated in the study, and who provide a methodological sound study proposal will be granted priority access to the study data for a period of 60 months.

After 60 month's this option may be extended to external investigators, not affiliated to the trial, whose proposed use of the data has been approved by an independent review committee identified by the steering committee for this purpose. Study proposals may be filed at global.leaders@cardialyis.nl.

Tables

Table-1: Baseline characteristics of randomized patients.

	·	**Standard Treatment Strategy**
Total number of patients	N = 7980	N = 7988
Age (years)	n = 7980, 64·5 ± 10·3	n = 7988, 64·6 ± 10·3
Females	n = 7980, 1865 (23·4%)	n = 7988, 1849 (23·1%)
Body Mass Index (kg/m²)	n = 7979, 28·2 ± 4·6	n = 7987, 28·2 ± 4·6
Medical history		
Diabetes mellitus	n = 7974, 2049 (25·7%)	n = 7983, 1989 (24·9%)
Insulin-dependent Diabetes mellitus	n = 7955, 606 (7·6%)	n = 7966, 617 (7·7%)
Hypertension	n = 7954, 5882 (73·7%)	n = 7960, 5833 (73·0%)
Hypercholesterolemia	n = 7718, 5345 (67·0%)	n = 7747, 5423 (67·9%)
Current smoker	n = 7980, 2066 (25·9%)	n = 7988, 2103 (26·3%)
Peripheral vascular disease	n = 7904, 476 (6.0%)	n = 7918, 529 (6·6%)
Chronic obstructive pulmonary disease	n = 7947, 404 (5·1%)	n = 7949, 417 (5·2%)
Previous major bleeding	n = 7968, 46 (0·6%)	n = 7979, 52 (0·7%)
Impaired renal function[b]	n = 7934, 1099 (13·8%)	n = 7949, 1072 (13·4%)
Previous stroke	n = 7967, 210 (2·6%)	n = 7978, 211 (2·6%)
Previous myocardial infarction	n = 7956, 1831 (22·9%)	n = 7966, 1879 (23·5%)
Previous percutaneous coronary intervention	n = 7974, 2609 (32·7%)	n = 7980, 2612 (32·7%)
Previous coronary artery bypass grafting	n = 7974, 448 (5·6%)	n = 7981, 495 (6·2%)
Clinical presentation		
Stable coronary artery disease	n = 7980, 4230 (53·0%)	n = 7988, 4251 (53·2%)
Acute coronary syndrome	n = 7980, 3750 (47·0%)	n = 7988, 3737 (46·8%)
Unstable angina	n = 7980, 1004 (12·6%)	n = 7988, 1018 (12·7%)
Non ST-segment elevation myocardial infarction	n = 7980, 1684 (21·1%)	n = 7988, 1689 (21·1%)
ST-segment elevation myocardial infarction	n = 7980, 1062 (13·3%)	n = 7988, 1030 (12·9%)

Depicted are sample size (n); and counts (%), mean ± standard deviation or median (25%-75% interquartile range).

[b] Based on creatinine-Estimated Glomerular Filtration Rate (eGFR) clearance of <60 ml/min/1.73 m2, using the Modification of Diet in Renal Disease (MDRD) formula.[15]

Table 2: Baseline angiographic Characteristics of randomized patients.

	Experimental Treatment Strategy	Standard Treatment Strategy	p-value
Total number of patients	N = 7980	N = 7988	
Percutaneous coronary performed[a]	n = 7980, 7943 (99·5%)	n = 7988, 7940 (99·4%)	0·277
Vascular access site*			
Radial	n = 7943, 5872 (73·9%)	n = 7940, 5889 (74·2%)	0·731
Femoral	n = 7943, 2090 (26·3%)	n = 7940, 2072 (26·1%)	0·759
Brachial	n = 7943, 46 (0·6%)	n = 7940, 47 (0·6%)	0·918
Number of lesions treated per patient	n = 7907,	n = 7911,	0·284
One lesion	5895 (74·6%)	5910 (74·7%)	
Two lesions	1618 (20·5%)	1569 (19·8%)	
Three or more lesions	394 (5·0%)	432 (5·5%)	
Total number of treated lesions	n = 10403	n = 10438	
Lesions treated in vessel(s)**	n = 10403	n = 10438	0·611
Left main coronary artery	197 (1·9%)	190 (1·8%)	
Left anterior descending artery	4283 (41·2%)	4383 (42·0%)	
Left circumflex artery	2524 (24·3%)	2553 (24·5%)	
Right coronary artery	3284 (31·6%)	3206 (30·7%)	
Bypass graft****	115 (1.1%)	106 (1·0%)	
Total number of stented lesions	n = 10241	n = 10283	
Index percutaneous coronary intervention			
No of stents per lesion**	n = 10241, 1·2 ± 0.5	n = 10283, 1·2 ± 0·5	0·820
Type of stent*			
Biolimus-eluting stent***	n = 10241, 9708 (94·8%)	n = 10283, 9707 (94·4%)	0·602
Other stent	n = 10241, 654 (6·4%)	n = 10283, 685 (6·7%)	
Total stent length per lesion (mm)**	n = 10241, 24·8 ± 13·9	n = 10283, 24·8 ± 14·0	0·932
Average stent diameter per lesion (mm)*	n = 10241, 3·0 ± 0·5	n = 10283, 3·0 ± 0·5	0·887
Direct stenting per lesion**	n = 10241, 3334 (32.6%)	n = 10283, 3350 (32·6%)	0·932
Bifurcation per lesion**	n = 10403, 1251 (12·0%)	n = 10438, 1265 (12·1%)	0·646
Thrombus aspiration performed per lesion*	n = 10403, 483 (4·6%)	n = 10438, 551 (5·3%)	0·040
TIMI flow pre-procedure*	n = 9837,	n = 9888,	0·708
0 or 1	1296 (13·2%)	1314 (13·3%)	
2	1187 (12·1%)	1173 (11·9%)	
3	7354 (74·8%)	7401 (74·8%)	
TIMI flow post-procedure*	n = 10064,	n = 10145,	0·324
0 or 1	41 (0·4%)	32 (0·3%)	
2	50 (0·5%)	46 (0·5%)	
3	9973 (99·1%)	10067 (99·2%)	

Depicted are sample size (n); and counts (%) or means ± standard deviations. TIMI denotes thrombolysis in myocardial infarction.[16]

[a] N = 85 patients did not undergo percutaneous coronary intervention: medical treatment only (n=31 experimental arm, n=33 reference arm), underwent urgent surgery (n=6 experimental arm, n=15 reference arm).

TIMI flow denotes thrombolysis in myocardial infarction flow.[16]

*More than one access site possible.

**Calculated per lesion and analysed using general or generalized 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=79 experimental arm lesions, n=68 reference group lesions).

****Grafts counted as one separate vessel (n=221).

Table 3: Primary and pre-specified secondary outcomes.

	Experimental Treatment Strategy	Standard Treatment Strategy	Risk Ratio (95% CI)	p-value
Total number of patients	N=7980	N=7988		
All-cause mortality or new Q-wave myo-cardial infarction [c]	304 (3·81)	349 (4·37)	0·87 (0·75-1·01)	0·073
All-cause mortality	224 (2·81)	253 (3·17)	0.88 (0·74-1·06)	0·18
New Q-wave myocardial infarction[e]	83 (1·04)	103 (1·29)	0·80 (0·60-1·07)	0·14
Composite of all-cause mortality, stroke or new Q-wave myocardial infarction	362 (4.54)	416 (5.21)	0.87 (0.76-1.00)	0.056
Myocardial infarction	248 (3·11)	250 (3·13)	1.00 (0·84-1·19)	0·98
Stroke	80 (1·00)	82 (1·03)	0·98 (0·72-1·33)	0·90
Ischemic stroke	63 (0·79)	68 (0·85)	0·93 (0·66-1·31)	0·68
Haemorrhagic stroke	13 (0·16)	9 (0·11)	1·45 (0·62-3·39)	0·39
Undetermined stroke	6 (0·08)	5 (0·06)	1·21 (0·37-3.95)	0·76
Revascularisation	739 (9·26)	793 (9·93)	0·93 (0·84-1·03)	0·17
Target Vessel Revascularization	389 (4·87)	442 (5·53)	0·88 (0·77-1·01)	0·068
Definite stent thrombosis	64 (0·80)	64· (0·80)	1·00 (0·71-1·42)	0·98
BARC 3 or 5 bleeding[b]	163 (2·04)	169 (2·12)	0·97 (0·78-1·20)	0·77
BARC 5 bleeding	22 (0·28)	24 (0·30)	0·92 (0·52-1·64)	0·78
BARC 5b bleeding	15 (0·19)	18 (0·23)	0.84 (0.42-1.66)	0·61
BARC 5a bleeding	7 (0·09)	6 (0·08)	1·17 (0·39-3·49)	0·78
BARC 3 bleeding	150 (1·88)	159 (1.99)	0·95 (0.76-1.18)	0·63
BARC 3c bleeding	35 (0.44)	25 (0.31)	1.41 (0.84-2.35)	0·19
BARC 3b bleeding	53 (0.66)	74 (0.93)	0.72 (0.51-1.02)	0·065
BARC 3a bleeding	77 (0.96)	70 (0.88)	1.10 (0.80-1.53)	0·55

BARC denotes bleeding academic research consortium.[13] 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 percutaneous coronary intervention). Percentage of all patients.

[b] Key safety endpoint.

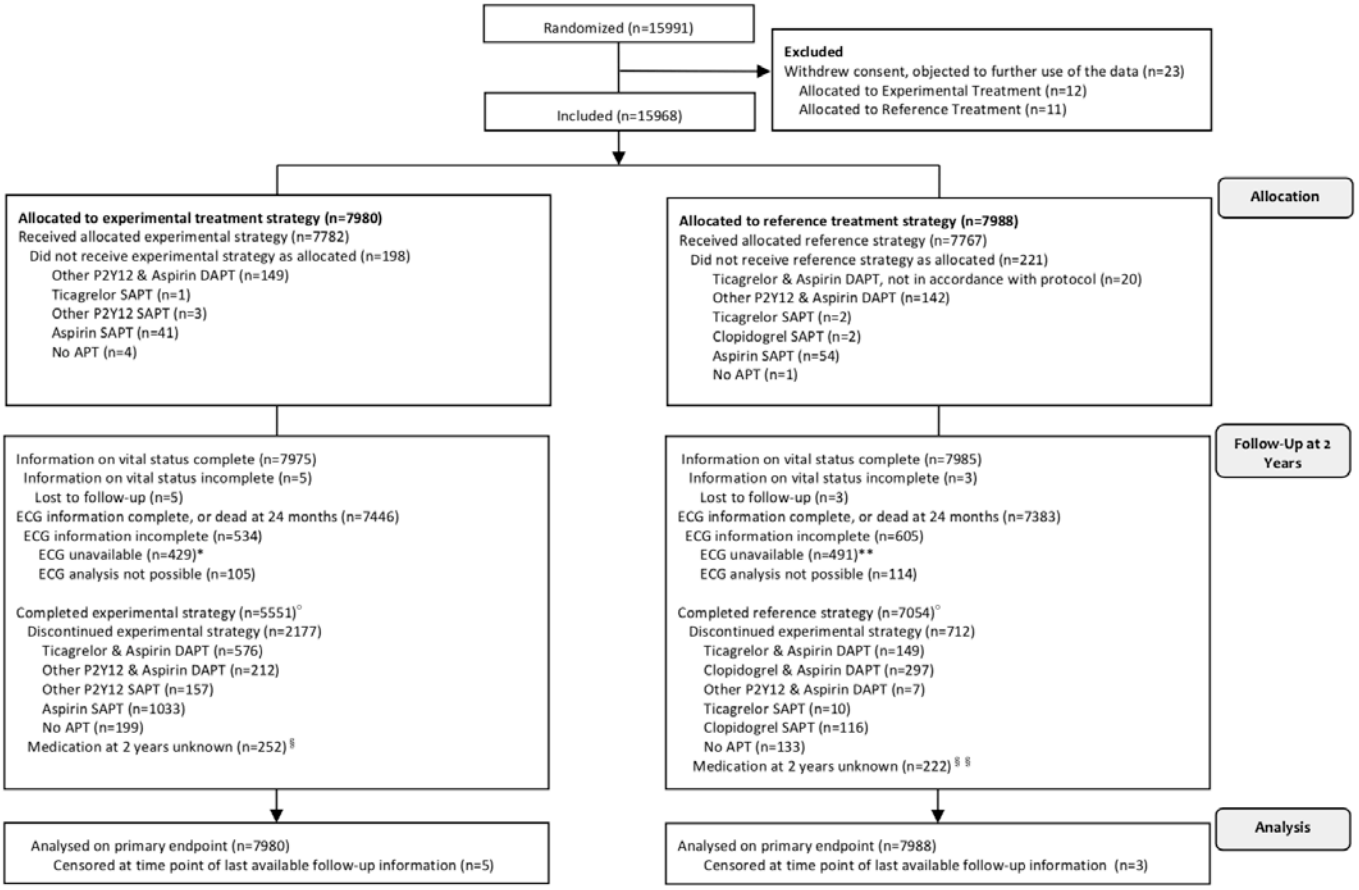
[c] Primary efficacy endpoint

.[d] 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.

[e] New Q-wave or equivalent left bundle branch block (n=3) as adjudicated by the independent cardiologist.

Figures

Figure 1



DAPT denotes dual antiplatelet treatment; SAPT, single antiplatelet treatment; APT, antiplatelet treatment. In patients with repeat revascularization, the allocated initial DAPT regimen could be resumed for 30 days after revascularization in patients allocated to experimental treatment strategy and for 365 days after revascularization in patients allocated to reference treatment strategy.

*Electrocardiogram missing for patients allocated to experimental strategy (n=429): 2-year visit performed but no electrocardiogram (n=195); no 2-year visit performed (n=229); lost to follow-up (n=5).

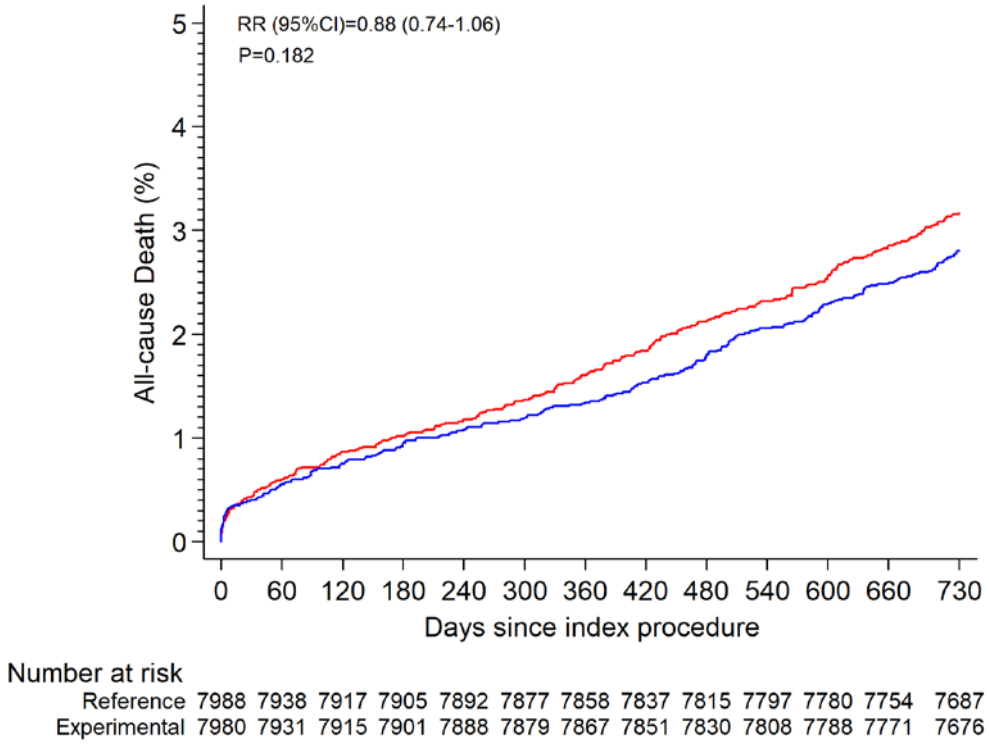
**Electrocardiogram missing for patients allocated to reference strategy (n=491): 2-year visit performed but no electrocardiogram (n=295); no 2-year visit performed (n=193); lost to follow-up (n=3).

° Patients adherent to experimental strategy at 24 months or at last visit before their death.

§Information on vital status complete (n=247), lost to follow-up (n=5).

§§ Information on vital status complete (n=219), lost to follow-up (n=3).

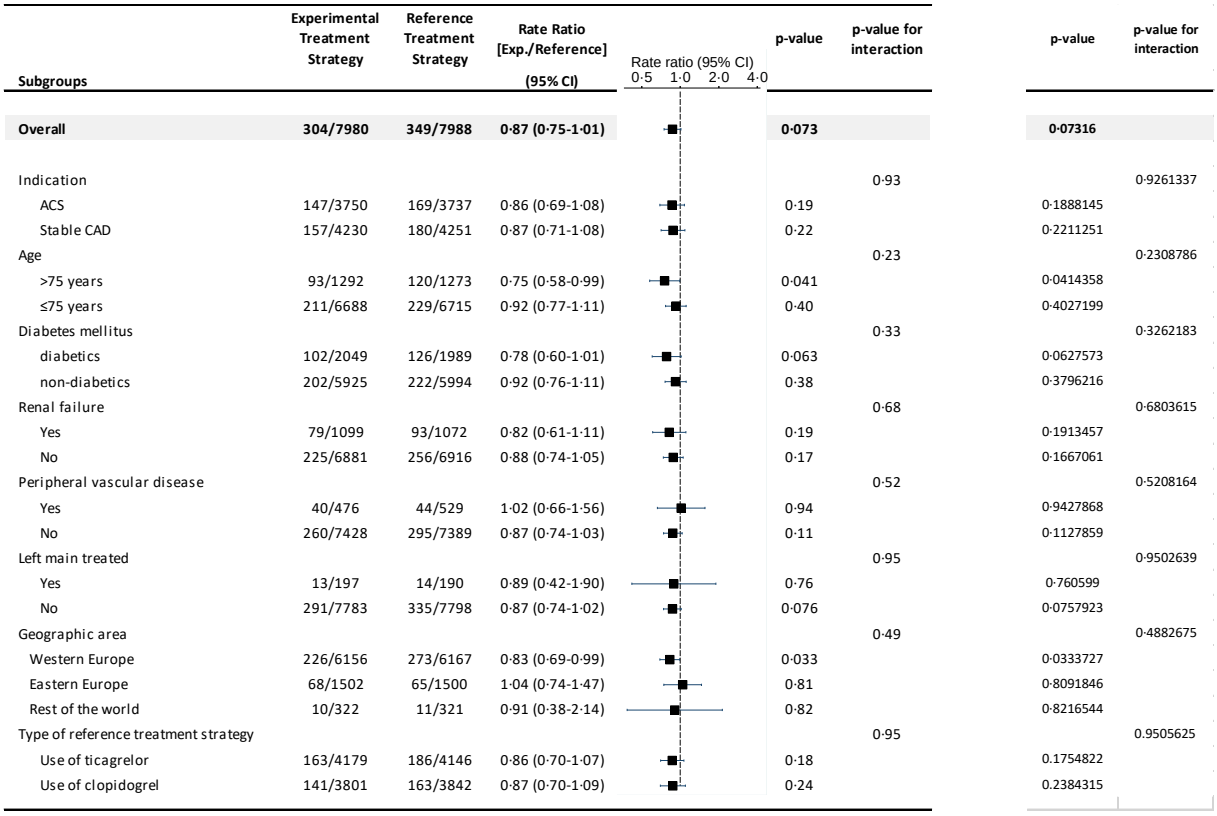
Figure 2



Number at risk

Reference	7988	7938	7917	7905	7892	7877	7858	7837	7815	7797	7780	7754	7687
Experimental	7980	7931	7915	7901	7888	7879	7867	7851	7830	7808	7788	7771	7676

Figure 3



Subgroups	Experimental Treatment Strategy	Reference Treatment Strategy	Rate Ratio [Exp./Reference] (95% CI)	p-value	p-value for interaction	p-value	p-value for interaction
Overall	**304/7980**	**349/7988**	**0·87 (0·75-1·01)**	**0·073**		**0·07316**	
Indication					0·93		0·9261337
ACS	147/3750	169/3737	0·86 (0·69-1·08)	0·19		0·1888145	
Stable CAD	157/4230	180/4251	0·87 (0·71-1·08)	0·22		0·2211251	
Age					0·23		0·2308786
>75 years	93/1292	120/1273	0·75 (0·58-0·99)	0·041		0·0414358	
≤75 years	211/6688	229/6715	0·92 (0·77-1·11)	0·40		0·4027199	
Diabetes mellitus					0·33		0·3262183
diabetics	102/2049	126/1989	0·78 (0·60-1·01)	0·063		0·0627573	
non-diabetics	202/5925	222/5994	0·92 (0·76-1·11)	0·38		0·3796216	
Renal failure					0·68		0·6803615
Yes	79/1099	93/1072	0·82 (0·61-1·11)	0·19		0·1913457	
No	225/6881	256/6916	0·88 (0·74-1·05)	0·17		0·1667061	
Peripheral vascular disease					0·52		0·5208164
Yes	40/476	44/529	1·02 (0·66-1·56)	0·94		0·9427868	
No	260/7428	295/7389	0·87 (0·74-1·03)	0·11		0·1127859	
Left main treated					0·95		0·9502639
Yes	13/197	14/190	0·89 (0·42-1·90)	0·76		0·760599	
No	291/7783	335/7798	0·87 (0·74-1·02)	0·076		0·0757923	
Geographic area					0·49		0·4882675
Western Europe	226/6156	273/6167	0·83 (0·69-0·99)	0·033		0·0333727	
Eastern Europe	68/1502	65/1500	1·04 (0·74-1·47)	0·81		0·8091846	
Rest of the world	10/322	11/321	0·91 (0·38-2·14)	0·82		0·8216544	
Type of reference treatment strategy					0·95		0.9505625
Use of ticagrelor	163/4179	186/4146	0·86 (0·70-1·07)	0·18		0.1754822	
Use of clopidogrel	141/3801	163/3842	0·87 (0·70-1·09)	0·24		0.2384315	

Type of reference treatment strategy was a post-hoc criterion for subgroup analysis. Number of first events and percentages are reported. Rate ratios (95% confidence interval) are estimated using the Mantel-Cox method with two-sided p-values from log-rank test. All events were censored beyond 730 days. P-values for interactions were obtained with approximate $\chi 2$ tests for unequal Rate Ratio's in the subgroups (df=1, except geographic area df=4).

Renal failure = estimated creatinine-estimated glomerular filtration ratio (GFR) of less than 60 ml/min using the Modification of Diet in Renal Disease (MDRD) formula. (3) Assumed no risk in case of missing data: diabetes (n=11), renal failure (n=85), peripheral vascular disease (n=146).

SUPPLEMENTARY APPENDIX

TABLE OF CONTENTS

1 Appendix A: Committees, Leadership and Investigators

1.1 Steering Committee Members:

1. Pascal Vranckx (Jesse Ziekenhuis, Faculty of Medicine and Life Sciences at the Hasselt University, Hasselt, Belgium) (Co-principal investigator)
2. Marco Valgimigli (Inselspital, University Hospital Bern, Bern, Switzerland) (Co-principal investigator)
3. 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)
4. Chris Hamm (University of Giessen and Kerckhoff Heart and Thorax Center, University of Giessen, Bad Nauheim, Germany) (member)
5. Gabriel Steg (Hospital Bichat-Claude Bernard, Paris, France) (member)
6. Gerrit-Anne van Es (ECRI-Trials B.V., Rotterdam, The Netherlands) (Sponsor)
7. Patrick W. Serruys (International Centre for Circulatory Health, NHLI, Imperial College London, London, United Kingdom) (Co-principal investigator)
8. Stephan Windecker (Inselspital, University Hospital Bern, Bern, Switzerland) (Co-principal investigator)

1.2 Country Leaders

Olivier Bertrand (Institut universitaire de cardiologie et de pneumologie de Québec, Québec, Canada), Pawel Buszman (Upper-Silesian Heart Centre, Silesian University

Medical School, Katowice, Poland), Dr. Lene Holmvang (Rigshospitalet, Copenhagen, Denmark), Antonio Colombo (Centro Cuore Emodinamica, Fondazione San Raffaele, Milano, Italy), Kurt Huber (III Department of Medicine and Cardiology, Wilhelminenspital Wien, Vienna, Austria), Tian Hai Koh (National Heart Centre Singapore, Mistri Wing, Singapore), Pedro Lemos (Incor Hospital, São Paulo, Brazil), François Mach (Division of Cardiology, University of Geneva, Geneva, Switzerland), Chris Hamm (Department of Cardiology, Kerckhoff Klinik GmbH, Nauheim, Germany), Gabriel Steg (Département de Cardiologie, C.H.U. Bichat - Claude Bernard, Paris, France), Manel Sabate (Hospital Clínic de Barcelona, Barcelona, Spain), Rod Stables (Liverpool Heart and Chest Hospital, Liverpool, United Kingdom), Robert Jan van Geuns (Erasmus University Medical Center, Rotterdam, The Netherlands), Mathias Vrolix (Ziekenhuis Oost-Limburg, Genk, Belgium), Ivo Petrov (City Clinic, Sofia, Bulgaria), Attila Thury (Szent-Györgyi Albert Klinikai Központ, Szeged, Hungary), Rui Cruz Ferreira (Centro Hospitalar de Lisboa Central, Lisbon, Portugal), Rod Stables (Liverpool Heart and Chest Hospital, Liverpool, UK), Peter Barlis (The Northern hospital, Melbourne, Australia).

1.3 Data and Safety Monitoring Board

Jan G.P.Tijssen (Academic Research Center, Amsterdam, The Netherlands), Laura Mauri (Harvard Clinical Research Institute, Boston, MA, U.S.A.), Freek W.A. Verheugt (Chairman, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands).

1.4 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)

1.5 Electrocardiography Core Laboratory

Lali Sikarulidze (Senior Analyst, Cardialysis, Rotterdam, The Netherlands), Martin Muurling (Senior Analyst, Cardialysis, Rotterdam, The Netherlands), Esther Velthuizen (Senior Analyst, Cardialysis, Rotterdam, The Netherlands), Addy ter Weele (Senior Analyst, Cardialysis, Rotterdam, The Netherlands), Tone de Vreede (Senior Analyst, Cardialysis, Rotterdam, The Netherlands), Maarten Witsenburg (Department of Cardiology, Erasmus University Medical Center, Electrocardiography Core Laboratory Supervisor, Cardialysis, Rotterdam, The Netherlands).

1.6 Angiographic Core Laboratory

Tone de Vreede (Senior Analyst, Cardialysis, Rotterdam, The Netherlands), Annemarie Hugense (Senior Analyst, Cardialysis, Rotterdam, The Netherlands), Ina Hoekman (Senior Analyst, Cardialysis, Rotterdam, The Netherlands), Yvonne Kreuger(Senior Analyst, Cardialysis, Rotterdam, The Netherlands), Coby

Bouwman (Senior Analyst, Cardialysis, Rotterdam, The Netherlands), Lynn Dijksma(Senior Analyst, Cardialysis, Rotterdam, The Netherlands), Yoshinobu Onuma (Angiography Core Laboratory Supervisor, Cardialysis, Rotterdam, The Netherlands).

1.7 Blinded Independent Cardiologist

Eugene McFadden (Department of Cardiology, Cork University Hospital, Cork, Ireland).

1.8 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)

1.9 Statistical Analysis

Dik Heg (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).

1.10 Study Monitors

Yoshinobu Onuma (Cardialysis, Rotterdam, The Netherlands), Ana Guimarães (Cardialysis, Rotterdam, The Netherlands).

1.11 Academic Research Team (Chair: Prof. Patrick W. Serruys)

Ply Chichareon (Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands), Taku Asano (Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands), Chun Chin Chang (Erasmus Medical Center, Erasmus University, Rotterdam, the Netherlands), Yuki Katagiri (Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands), Rodrigo Modolo (Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands), Carlos Collet (Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands), Kuniaki Takahashi (Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands), Norihiro Kogame (Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands), Yosuke Miyazaki (Erasmus Medical Center, Erasmus University, Rotterdam, the Netherlands), Yoshinobu Onuma (Cardialysis, Rotterdam, The Netherlands)

1.12 Classification of reasons of non-adherence (Chair: Prof. Peter Jüni)

Giuseppe Gargiulo (Inselspital, Bern University Hospital, University of Bern),
Felice Gragnano (Inselspital, Bern University Hospital, University of Bern), Negar Manavifar (Inselspital, Bern University Hospital, University of Bern).

1.13 Site Monitoring

Cokky van Meijeren (Clinical Trial Manager, Cardialysis, Rotterdam, The Netherlands), Judith de Bot (Senior Clinical Research Associate, Cardialysis, Rotterdam, The Netherlands), Dorien Hillen (Clinical Research Associate, Cardialysis, Rotterdam, The Netherlands), Pieter Heijke (Clinical Research Associate, Cardialysis, Rotterdam, The Netherlands).

1.14 List of Investigators by Country

Principal Investigator	Country	City	Hospital	Number of patients
Dr. Olivier F. Bertrand	Canada	Quebec	Quebec Heart-Lung Institute	62
Dr Sylvain Plante	Canada	Newmarket, Ontario	Southlake Regional Health Centre	108
Prof. R.J. (Robert Jan) van Geuns	Netherlands	Rotterdam	ErasmusMC	432
Dr. S.H. (Sjoerd) Hofma	Netherlands	Leeuwarden	Medisch Centrum Leeuwarden	32
Dr. K.J. (Kees-Jan) Royaards	Netherlands	Rotterdam	Maasstadziekenhuis	159
Dr. T. (Ton) Slagboom	Netherlands	Amsterdam	OLVG	304

Prof. Dr. Harry Suryapranata	Netherlands	Nijmegen	UMC St Radboud	30
Dr. V.A.W.M. (Victor) Umans	Netherlands	Alkmaar	Medisch Centrum Alkmaar	74
Dr. Benno Rensing	Netherlands	Nieuwegein	Sint Antonius ziekenhuis	23
Dr. Pim van der Harst	Netherlands	Groningen	University Medical Centre Groningen (UMCG)	16
Dr. Michael Magro	Netherlands	Tilburg	TweeSteden ziekenhuis	92
Dr. E. (Emanuel) Barbato	Belgium	Aalst	Onze Lieve Vrouw Ziekenhuis	3
Dr. Adel Aminian	Belgium	Charleroi	CHU de Charleroi	266
Dr. Edouard Benit	Belgium	Hasselt	Virga Jesse	920
Dr. Luc Janssens	Belgium	Bonheiden	Imelda Ziekenhuis	535
Dr. Mathias Vrolix	Belgium	Genk	Ziekenhuis Oost-Limburg	257
Dr. I. (Ian) Buysschaert	Belgium	Aalst	Algemeen stedelijk ziekehuis	206
Prof Dr. G. (Gabriel) Steg	France	Paris	Hôpital Bichat	91

Prof. Didier Carrie	France	Toulouse	Rangueil Hospital	170
Dr. Pascal Barraud	France	Clermont-Ferrand	Clinique des Dômes	9
Prof. Emmanuel Teiger	France	Paris / Creteil	University Hospital Mondor (CHU Mondor)	15
Dr. R. (René) Koning	France	Rouen	Clinique-saint hilaire	24
Prof. Beygui Farzin	France	Caen	CHU de Caen	93
Dr. Jean-francois Morelle	France	Caen	Clinique St. Martin	93
Prof. Karl Isaaz	France	Etienne	Saint Etienne university hopsital	84
Dr. Luc Maillard	France	Aix en Provence	Clinique Axium	40
Dr. Mohamed Abdellaoui	France	Grenoble Cedex	Groupe Hospitalier Mutualiste de Grenoble	117
Dr. Philippe Brunel	France	Dijon	Clinique de Fontaine	95

Dr. Michael Angioi	France	Nancy (Essey Les Nancy)	Clinique Louis Pasteur	9
Dr. Pierre Lantelme	France	Lyon	Hôpital de la Croix-Rousse	9
Dr. Manel Sabate	Spain	Barcelona	Clinic Hospital Barcelona	216
Dr. Agustin Albarran Gonzalez-Trevilla	Spain	Madrid	Hospital 12 Octobre	
Dr. Angel Cequier	Spain	Barcelona	Bellvitge Hospital	198
Dr. Andres Iñiguez	Spain	Vigo	Hospital Meixoeiro Vigo	30
Dr. Antonio Serra Peñaranda	Spain	Barcelona	Hospital Sant Pau	99
Dr. Carlos Macaya Miguel	Spain	Madrid	Clinico Universitario San Carlos	132
Dr. Jose Francisco Diaz	Spain	Huelva	Hospital Juan Ramón Jimenez	25
Dr. Rosa Ana Hernández Antolin	Spain	Madrid	Hospital Ramón y Cajal	106

Dr. Javier Goicolea	Spain	Madrid	Hospital Universitario Puerta de Hierro	45
Dr. Vasco Gama Ribeiro	Portugal	Gaia	Centro Hospitalar de Vila Nova de Gaia/ Espinho	9
Dr. Pedro Canas da Silva	Portugal	Lisbon	Centro Hospitalar de Lisboa Norte - Hospital de Santa Maria	29
Dr. Rui Cruz Ferreira	Portugal	Lisbon	Centro Hospitalar de Lisboa Central - Hospital Santa Marta	62
Dr. Manuel Almeida	Portugal	Carnaxide	Centro Hospitalar de Lisboa Ocidental - Hospital Santa Cruz	13
Dr. Imre Ungi	Hungary	Szeged	Szent-Györgyi Albert Klinikai Központ	120
Dr. Bela Merkely	Hungary	Budapest	Semmelweis University	157
Dr. Geza Fontos	Hungary	Budapest	Gottsegen György Országos Kardiológiai Intézet (National Health institue)	13
Dr. Iván Horváth MD	Hungary	Pécs	University of Pécs (Pécsi Tudományegyetem)	30

Dr. Zsolt Kőszegi	Hungary	Nyíregyháza	Szabolcs-Szatmár-Bereg Megyei Kórházak és Egyetmi Oktatókórház, Jósa András Oktató Kórház County Hospitals and University Teaching Hospital	31
Dr. Zoltán Jambrik	Hungary	Gyula	Békés Megyei Pándy Kálmán Kórház County Hospital	105
Prof. Dr. István Édes	Hungary	Debrecen	University of Debrecen / Debreceni Egyetem Klinikai Központ	17
Dr. Faluközy József	Hungary	Balatonfüred,	Állami Szívkórház State Hospital for Cardiology	54
Prof. Antonio Colombo	Italy	Milano	San Raffaele	45
Dr. Leonardo Bolognese	Italy	Arezzo	Ospedale S. Donato	281
Dr. Maurizio Ferrario	Italy	Pavia	Policlinico San Matteo	479

Dr. Carlo Tumscitz	Italy	Ferrara	University Hospital of Ferrara	274
Prof. Marcello Dominici	Italy	Terni	Azienda Ospedaliera S. Maria	405
Salvatore Curello	Italy	Brescia	Ospedali Civili di Brescia	94
Prof. Marco Roffi	Switzerland	Geneva	University Hospital-Hôpitaux Universitaires de Genève - HUG – Service de Cardiologie Interventionnelle	17
Prof. Eric Eeckhout	Switzerland	Lausanne	CHUV, Centre Hospitalier Universitaire Vaudois,	34
Prof. Tiziano Moccetti	Switzerland	Lugano	CardioCentro Ticino	51
Prof. Stephan Windecker	Switzerland	Bern	Bern University Hospital (Inselspital, Universitätsspital Bern)	468
Dr. med. Aris Moschovitis	Switzerland	Bern	Tiefenauspital	59
Dr. med. Gregor Leibundgut	Switzerland	Liestal	Kantonsspital Baselland, Standort Liestal	76

Prof. Kurt Huber	Austria	Vienna	Wilhelminenspital	309
Prof. Bernhard Frey (Previous PI: Prof. Georg Delle Karth)	Austria	Vienna	University Hospital AKH	62
Prof. Dr. med Guy Friedrich	Austria	Innsbruck	Medical University Innsbruck	74
Prof. Dr. Clemens Steinwender	Austria	Linz	General Hospital Linz (AKH-Linz)	143
Prof. Dr. Robert Zweiker	Austria	Graz	Medical University Hospital Graz	84
Prof. Rod H Stables	UK	Liverpool	Liverpool Heart and Chest Hospital	
Dr. Richard Anderson	UK	Cardiff	Universtiy Hospital of Wales	204
Dr. Saqib Chowdhary	UK	Manchester	University Hospital South Manchester (Wythenshawe)	161
Dr. Scot Garg	UK	Blackburn	Royal Blackburn Hospital	250
Dr. David Hildick-Smith	UK	Brighton	Royal Sussex County Hospital	

Dr. Farzin Fath-Ordoubadi	UK	Manchester	Central Manchester University Hospitals NHS Foundation Trust, Manchester Royal Infirmary	212
Prof. Keith G. Oldroyd	UK	Glasgow	Golden Jubilee National Hospital	203
Dr. Gavin Galasko	UK	Blackpool	Lancashire Heart Centre, Victoria Hospital	77
Dr. Neville Kukreja	UK	Stevenage	Hertfordshire Cardiac Centre Lister Hospital	122
Prof. Azfar Zaman	UK	Newcastle	Freeman Hospital	62
Dr. E. (Eduardas) Subkovas	UK	Rhyl	Glan Clwyd Hospital	51
Prof. Nick Curzen	UK	Southampton	University Hospital Southampton	58
Dr. Stephen Hoole	UK	Cambridge	Papworth Hospital	69
Dr. Suneel Talwar	UK	Bournemouth	Royal Bournemouth Hospital	50
Dr. Simon Walsh	UK	Belfast	Belfast Trust	30

Dr. David Adlam	UK	Leicester	University of Leicester and University Hospitals Leicester	19
Dr. James Cotton	UK	Wolverhampton	New Cross Hospital	25
Dr. Simon Walsh	UK	Belfast	Royal Victoria	20
Dr. Lene Holmvang	Denmark	Copenhagen	Copenhagen University Hospital - Rigshospitalet	52
Dr. Michael Munndt Ottesen	Denmark	Roskilde	Roskilde University Hospital	79
Prof. Paweł Buszman	Poland	Dabrowa Gornicza	PAKS Dabrowa	295
Dr. Aleksander Zurakowski	Poland	Chrzanow	PAKS Chrzanów	461
Dr. Grzegorz Galuszka MD	Poland	Ustroń	PAKS Ustron	58

Dr. Janusz Prokopczuk MD, PhD	Poland	Kedzierzyn-Kozle	PAKS Kozle	236
Prof. Krzysztof Żmudka	Poland	Krakov	Krakowski Szpital Specjalistyczny im. Jana Pawła II	272
Dr Pawel Jasionowicz	Poland	Nysa	Polsko-Amerykanskie Kliniki Serca	236
Dr Adam Młodziankowski	Poland	Mielec	Polsko-Amerykanskie Kliniki Serca; Szpital Powiatowy	90
Prof. Dr. med. C. (Christian) Hamm	Germany	Giessen	University of Giessen	134
Dr. Christoph Liebetrau Dr. Helge Möllman	Germany	Bad Nauheim	Kerckhoff Heart Center	653
PD Dr. med. Christoph Kurt Naber	Germany	Essen	Elisabeth Krankenhaus Essen	247
Prof. Franz-Josef Neumann	Germany	Bad Krozingen	Universitäts-Herzzentrum Freiburg Bad Krozingen	111

Prof. Dr. Volker Schächinger	Germany	Fulda	Klinikum Fulda gAG	160
Dr. Tim Seidler	Germany	Göttingen	University Medical Center Goettingen	73
Dr. Karim Ibrahim	Germany	Dresden	University Hospital, Med. Fakultät Carl Gustav Carus	132
PD Dr. med. Bernhard Zrenner	Germany	Landshut Achdorf	Klinikum Landshut-Achdorf	157
Prof. Dr. med. Tommaso Gori	Germany	Mainz	Universitätsmedizin der Joh. Gutenberg-Universität Mainz	65
Prof. Dr. med. Nikos Werner	Germany	Bonn	Uniklinikum Bonn	20
PD Dr. med. Ibrahim Akin	Germany	Mannheim	Med. Fakult. Mannheim der Univ. Heidelberg	23
Prof. Dr. Tobias Geisler	Germany	Tübingen	Uniklinikum Tübingen	137

Prof. Dr. med. Jürgen vom Dahl	Germany	Mönchengladbach	Kliniken Maria Hilf	144
Prof. Dr. Michael Haude	Germany	Neuss	Städtische Kliniken Neuss, Lukaskrankenhaus GmbH	55
Dr. med. Ingo Eitel, MD	Germany	Lübeck	Universitatsklinikum Schleswig-Holstein / Campus Lübeck	88
Dr. F. (Florian) Krackhardt	Germany	Berlin	Charite, Campus Virchow	16
Prof. Dr. Werner Jung	Germany	Villingen-Schwenningen	Schwarzwald-Baar Klinikum	54
DR. Pedro Alves Lemos Neto	LAM - Brazil	Sao Paulo	INCOR - HCFMUSP	134
Dr. Amanda Sousa	LAM - Brazil	Sao Paulo	Instituto Dante Pazzanese de Cardiologia	61
Edgard Freitas Quintella	LAM - Brazil	Rio de Janeiro	Instituto Estadual Cardiologia Aloisio De Castro	15
Dr. Sergio Leandro	LAM - Brazil	Rio de Janeiro	Instituto Nacional De Cardiologia	1

Dr. Roberto Botelho	LAM - Brazil	Uberlândia	Instituto Do Coracao Do Triangulo Mineiro	37
Dr. Christopher Raffel	Australia	Brisbane	Prince Charles Hospital (state: Queensland)	37
Prof. Peter Barlis	Australia	Melbourne	The Northern hospital (state: Victoria)	39
Prof. Peter Barlis	Australia	Fitzroy,Melbourne	St. Vincent's Hospital (state: Victoria)	7
Prof. Koh Tian Hai	Singapore	Singapore	National Heart Center Singapore	62
Dr. Paul Ong	Singapore	Singapore	Tan Tock Seng Hospital	80
Dr. Ivo Petrov	Bulgaria	Sofia	City Clinic	252
Dr. Mariana Konteva	Bulgaria	Burgas	Heart Center "Pontica"	94
Dr. Vasil Velchev	Bulgaria	Sofia	St. Anna Sofia	112
Dr. Valeri Gelev	Bulgaria	Sofia	Tokuda Hospital	98
Gincho Tonev	Bulgaria	Plovdiv	UMBAL St. George	145
Veselin Valkov	Bulgaria	Varna	"St. Marina" University Hospital	144

Dr. Dobrin Vassilev	Bulgaria	Sofia	Alexandrovska hospital	68
Diana Trendafilova-Lazarova	Bulgaria	Sofia	"St. Ekaterina" university Hospital	32

1.15 Data coordinating centers:

Cardialysis: Westblaak, Rotterdam, KM, 3012, The Netherlands

Theorem: 1016 West Ninth Avenue, King of Prussia, PA, 19406, United States of America

2 Appendix B: supplemental methods

2.1 Study oversight

Data cleaning and preparation was performed by the Cadialysis data management group (Cardialysis, Rotterdam, The Netherlands). Tasks included building and maintenance of the electronic clinical record form (e-CRF) and study database, checks completeness and consistency of e-CRF data, in particular with respect to protocol compliance, review of investigator-reported endpoints for consistency and completeness. After database lock, the database was housed for statistical analysis at an academic Clinical Trials Unit (CTU Bern, Department of Clinical Research, University of Bern, Switzerland).

3 Appendix C: inclusion and exclusion criteria

3.1 Patient selection criteria

3.1.1 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 millimetre.

3.1.2 EXCLUSION CRITERIA.

Drug related

1. Known intolerance to aspirin, P2Y12 receptor antagonists, bivalirudin, stainless steel or biolimus
2. Known intake of a strong cytochrome P3A4 inhibitor (eg, 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 coronar intervention unless dual antiplatelet therapy is maintained throughout the peri-surgical period
	7.	Need for oral anti-coagulation 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 ischemic or unknown cause within last 30 days
General	12.	Known pregnancy at time of randomization
	13.	Inability to provide informed consent
	14.	Currently participating in another trial before reaching primary endpoint

4 Appendix D: Study procedures and follow-up

4.1 Percutaneous coronary intervention

Oral antiplatelet therapy was started as early as possible and no later than 2 hours after the index procedure.

Loading and switching of $P2Y_{12}$-receptor-inhibitors in the Global Leaders trial is detailed elsewhere.[1] In case of ticagrelor discontinuation due to adverse effects other than bleeding (i.e. atrio-ventricular 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 ischemia 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 randomization, 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 antagonist. 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 for a uniform anticoagulation with bivalirudin (The Medicines Company) (dose adjusted per local drug label) in those countries were 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 3 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 ischemic complications (i.e., no reflow or giant thrombus) after stenting. The use of unfractionated heparin (up to an arbitrary set maximum of 4000IU) during the index diagnostic angiogram was left at the discretion of the investigator.[1] The use of other medications was per applicable professional guidelines.

4.2 Patient follow-up

During study follow-up visits, patients were questioned about whether they had had a myocardial infarction, had been hospitalized for a subsequent cardiovascular presentation, had undergone revascularization or cardiac testing, or had seen a cardiologist, and what medications they were taking. If a patient reported a hospitalization that was possibly related to cardiac causes, the hospital records were reviewed by the local research nurse. 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 by the local research nurse 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.

5 Appendix E: Endpoint definitions

Research nurses screened for clinical end-point 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.[2]

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:

5.1 Myocardial infarction

Myocardial infarction was defined according to the Third Universal Myocardial Infarction definition as study specific myocardial infarction criteria.[3] The term acute myocardial infarction was used when there was evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. 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 ischemia
    - 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 ischemia and presumed new ischemic 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 (>5 x 99th 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 are stable or falling. In addition, either:
    - symptoms suggestive of myocardial ischemia or
    - new ischemic 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 ischemia 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 (>10 x 99th 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
  - angiographic documented new graft or new native coronary artery occlusion, or
  - imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

5.2 Q wave myocardial Infarction Ascertainment and Definition

Resting 12-lead electrocardiograms at hospital discharge, 3-months follow-up, and the 24-months end-of-trial visit and any available intercurrent electrocardiograms, related to suspected ischemic events, were inspected for quality and technical errors and analysed by an independent electrocardiography-core laboratory (Cardialysis, Rotterdam, The Netherlands). Serial comparison of sequential tracings was performed to identify patients with new appearance of Q waves (major

Q-QS wave abnormalities 1-1-1 to 1-2-8 according to the Minnesota Code 2009).[4]

Where new Q-waves, with respect to the immediately preceding electrocardiogram (first reference electrocardiogram is at discharge), were identified an independent cardiologist confirmed or rejected the myocardial as a new Q wave myocardial infarction, and if confirmed also assigned a date, based on review of the reported adverse events to the new Q-wave myocardial infarction. [1] Where no clinical correlate was identified, the date of the new silent Q-wave myocardial infarction was arbitrarily assigned to the date of the qualifying electrocardiogram. In case electrocardiograms remained missing after review of all documentation (e.g. death before 2 years of follow-up) it will be assumed no new Q-wave myocardial infarction occurred since the last obtained electrocardiogram.

The electrocardiogram-core laboratory also identified new left bundle branch block on serial electrocardiograms. Where a new left bundle branch block was identified, the independent cardiologist determined, from electronic clinical record form extracts supplemented where necessary with additional source documents, whether a likely ischemic event (prolonged ischemic chest pain, significant rise in cardiac biomarkers or imaging evidence of loss of viable myocardium) occurred. A new left bundle branch block counted as a new Q-wave myocardial infarction only where a qualifying ischemic event was identified. The new Q-wave myocardial infarction was assigned to the date of the qualifying ischemic event.

Core laboratory staff and the independent cardiologist were unaware of the study-group assignments.

5.3 Stent thrombosis

Stent thrombosis was classified as per the Academic Research Consortium Definition.[5]

DEFINITE STENT THROMBOSIS – was considered to have occurred by either angiographic or pathological confirmation.

- The presence of thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent *and presence of at least 1 of the following criteria within a 48-hour window* (The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms was not considered a confirmed stent thrombosis silent occlusion):
    - Acute onset of ischemic symptoms at rest
    - New ischemic electrocardiographic changes that suggest acute ischemia
    - Typical rise and fall in cardiac biomarkers that represent a spontaneous myocardial infarction.

- Non-occlusive Thrombus: Intracoronary thrombus defined as a (sphere shaped, ovoid, or irregular) non-calcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or visible embolization of intraluminal material downstream.

        - Occlusive Thrombus: Thrombolysis in Myocardial Infarction **(**TIMI**)** flow grading 0 or 1 intra-stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch)
    - Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

5.4 Bleeding

Bleeding was assessed according to the Bleeding Academic Research Consortium (BARC) definition.[6] 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, hospitalization, or treatment by a health-care professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health-care professional.
- Type 2: Any overt, actionable sign of hemorrhage (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 nonsurgical, medical intervention by a health-care professional,

  - leading to hospitalization 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 h,

        - 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-h period,
        - Chest tube output more than or equal to 2L within a 24-h 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

6 Appendix G: Supplemental results

6.1 Compliance

Study drug intake was assessed at discharge; 1 month, 3 months, 6 months, 9 months, 1 year, 18 months and 2 years of follow-up (see Table S1).

At 2 years there were 2.6% of patients in the experimental group and 1.99% in the reference groups reported with no antiplatelet therapy. Reasons for absence of any antiplatelet therapy at the 2 years follow-up visit are detailed in table S2.

7 Appendix H: Supplementary Figures and Tables

TABLES

7.1.1 Supplementary table 1: Adherence to the allocated antiplatelet regimen at discharge, 30 days, 3, 6, 12, 18, 24 months of follow up.

	Experimental Treatment Strategy	**Reference Treatment Strategy**	**p-value**
Total number of patients	N = 7980	N = 7988	
During Index PCI			
Bivalirudin	6944 (87·4%)	6926 (87·2%)	0·721
Unfractionated heparin	2913 (36·7%)	2900 (36·5%)	0·856
Enoxaparin	145 (5·7%)	145 (5·8%)	0·952
Glycoprotein IIb/IIIa antagonists	205 (2·6%)	203 (2·6%)	0·960
Ticagrelor	6088 (76·6%)	2903 (36·6%)	<0·001
Clopidogrel	619 (7·8%)	2694 (33·9%)	<0·001
Prasugrel	167 (2·1%)	171 (2·2%)	0·826
Post-PCI Bivalirudin			
Bivalirudin continued	3668 (46·2%)	3651 (46·0%)	0·811
Bivalirudin administration time (hours)	1·84 ± 1·39	1·89 ± 1·47	0·272
Bivalirudin administration time >4 hours	24 (1·0%)	37 (1·6%)	0·121
At Discharge	**n = 7957**	**n = 7967**	
Ticagrelor monotherapy	4 (0·1%)	0 (0·0%)	0·062
Clopidogrel monotherapy	0 (0·0%)	7 (0·1%)	0·016
Other P2Y12 receptor antagonist monotherapy	3 (0·0%)	6 (0·1%)	0·508
Aspirin monotherapy	38 (0·5%)	46 (0·6%)	0·444
Ticagrelor and Aspirin	7761 (97·5%)	3999 (50·2%)	<0·001
Clopidogrel and Aspirin	69 (0·9%)	3835 (48·1%)	<0·001
Other antiplatelet drug and Aspirin	77 (1·0%)	70 (0·9%)	0·563
No antiplatelet therapy, but oral anticoagulation	0 (0·0%)	0 (0·0%)	
Neither antiplatelet therapy nor oral anticoagulation	1 (0·0%)	3 (0·0%)	0·625
Statin	7363 (92·8%)	7338 (92·4%)	0·346
Angiotensin converting enzyme inhibitor	4760 (60·1%)	4813 (60·7%)	0·465
Angiotensin receptor blocker	1343 (17·0%)	1314 (16·6%)	0·510
β Blocker	6269 (79·1%)	6310 (79·6%)	0·505
Proton-pump inhibitor	4037 (51·0%)	4005 (50·6%)	0·634

At 1 Month*¥	**n = 7755**	**n = 7779**	
Ticagrelor monotherapy	19 (0·2%)	11 (0·1%)	0·149
Clopidogrel monotherapy	7 (0·1%)	13 (0·2%)	0·263
Other P2Y12 receptor antagonist monotherapy	1 (0·0%)	2 (0·0%)	1·000
Aspirin monotherapy	36 (0·5%)	32 (0·4%)	0·629
Ticagrelor and Aspirin	7479 (96·4%)	3877 (49·8%)	<0·001
Clopidogrel and Aspirin	159 (2·1%)	3771 (48·5%)	<0·001
Other antiplatelet drug and Aspirin	53 (0·7%)	72 (0·9%)	0·106
No antiplatelet therapy, but oral anticoagulation	0 (0·0%)	0 (0·0%)	
Neither antiplatelet therapy nor oral anticoagulation	1 (0·0%)	1 (0·0%)	1·000
Statin	7249 (93·6%)	7252 (93·2%)	0·401
Angiotensin converting enzyme inhibitor	4697 (60·6%)	4811 (61·9%)	0·118
Angiotensin receptor blocker	1298 (16·8%)	1242 (16·0%)	0·193
β Blocker	6176 (79·7%)	6256 (80·4%)	0·296
Proton-pump inhibitor	4003 (51·7%)	4027 (51·8%)	0·898
At 3 Months	**n = 7648**	**n = 7678**	
Ticagrelor monotherapy	6558 (85·7%)	37 (0·5%)	<0·001
Clopidogrel monotherapy	58 (0·8%)	32 (0·4%)	0·006
Other P2Y12 receptor antagonist monotherapy	38 (0·5%)	9 (0·1%)	<0·001
Aspirin monotherapy	37 (0·5%)	63 (0·8%)	0·012
Ticagrelor and Aspirin	489 (6·4%)	3658 (47·6%)	<0·001
Clopidogrel and Aspirin	308 (4·0%)	3777 (49·2%)	<0·001
Other antiplatelet drug and Aspirin	145 (1·9%)	96 (1·3%)	0·001
No antiplatelet therapy, but oral anticoagulation	1 (0·0%)	2 (0·0%)	1·000
Neither antiplatelet therapy nor oral anticoagulation	7 (0·1%)	3 (0·0%)	0·226
Statin	7122 (93·0%)	7131 (92·8%)	0·593
Angiotensin converting enzyme inhibitor	4558 (59·6%)	4686 (61·0%)	0·072
Angiotensin receptor blocker	1339 (17·5%)	1277 (16·6%)	0·156
β Blocker	6070 (79·3%)	6112 (79·6%)	0·660
Proton-pump inhibitor	3896 (51·0%)	3990 (52·0%)	0·196
At 6 Months	**n = 7596**	**n = 7611**	
Ticagrelor monotherapy	6429 (84·6%)	45 (0·6%)	<0·001
Clopidogrel monotherapy	80 (1·1%)	53 (0·7%)	0·019
Other P2Y12 receptor antagonist monotherapy	52 (0·7%)	17 (0·2%)	<0·001
Aspirin monotherapy	64 (0·8%)	72 (0·9%)	0·547
Ticagrelor and Aspirin	332 (4·4%)	3517 (46·2%)	<0·001
Clopidogrel and Aspirin	449 (5·9%)	3773 (49·6%)	<0·001
Other antiplatelet drug and Aspirin	163 (2·1%)	119 (1·6%)	0·008

No antiplatelet therapy, but oral anticoagulation	9 (0·1%)	3 (0·0%)	0·092
Neither antiplatelet therapy nor oral anticoagulation	8 (0·1%)	12 (0·2%)	0·503
Statin	7038 (92·7%)	7056 (92·6%)	0·926
Angiotensin converting enzyme inhibitor	4433 (58·4%)	4575 (60·1%)	0·038
Angiotensin receptor blocker	1414 (18·6%)	1326 (17·4%)	0·052
β Blocker	5976 (78·7%)	6057 (79·5%)	0·224
Proton-pump inhibitor	3791 (50·0%)	3978 (52·3%)	0·004
At 1 Year*¥	**n = 7550**	**n = 7533**	
Ticagrelor monotherapy	6155 (81·5%)	39 (0·5%)	<0·001
Clopidogrel monotherapy	114 (1·5%)	77 (1·0%)	0·009
Other P2Y12 receptor antagonist monotherapy	39 (0·5%)	10 (0·1%)	<0·001
Aspirin monotherapy	176 (2·3%)	239 (3·2%)	0·002
Ticagrelor and Aspirin	368 (4·9%)	3370 (44·7%)	<0·001
Clopidogrel and Aspirin	577 (7·6%)	3692 (49·0%)	<0·001
Other antiplatelet drug and Aspirin	78 (1·0%)	80 (1·1%)	0·873
No antiplatelet therapy, but oral anticoagulation	20 (0·3%)	15 (0·2%)	0·499
Neither antiplatelet therapy nor oral anticoagulation	20 (0·3%)	8 (0·1%)	0·036
Statin	6966 (92·2%)	6910 (91·5%)	0·121
Angiotensin converting enzyme inhibitor	4348 (57·6%)	4455 (59·0%)	0·070
Angiotensin receptor blocker	1471 (19·5%)	1408 (18·7%)	0·199
β Blocker	5876 (77·8%)	5915 (78·4%)	0·366
Proton-pump inhibitor	3753 (49·7%)	3849 (51·1%)	0·111
At 1·5 Years	**n = 7453**	**n = 7367**	
Ticagrelor monotherapy	5846 (78·4%)	11 (0·1%)	<0·001
Clopidogrel monotherapy	131 (1·8%)	108 (1·5%)	0·171
Other P2Y12 receptor antagonist monotherapy	24 (0·3%)	0 (0·0%)	<0·001
Aspirin monotherapy	834 (11·2%)	6483 (88·0%)	<0·001
Ticagrelor and Aspirin	256 (3·4%)	162 (2·2%)	<0·001
Clopidogrel and Aspirin	210 (2·8%)	476 (6·5%)	<0·001
Other antiplatelet drug and Aspirin	12 (0·2%)	20 (0·3%)	0·160
No antiplatelet therapy, but oral anticoagulation	94 (1·3%)	74 (1·0%)	0·141
Neither antiplatelet therapy nor oral anticoagulation	46 (0·6%)	33 (0·4%)	0·176
Statin	6828 (91·3%)	6665 (90·1%)	0·014
Angiotensin converting enzyme inhibitor	4200 (56·2%)	4227 (57·2%)	0·215
Angiotensin receptor blocker	1497 (20·0%)	1453 (19·7%)	0·579
β Blocker	5722 (76·5%)	5695 (77·0%)	0·460
Proton-pump inhibitor	3749 (50·1%)	3579 (48·5%)	0·042
At 2 Years* ¥	**n = 7488**	**n = 7498**	

Ticagrelor monotherapy	5429 (72·5%)	7 (0·1%)	<0·001
Clopidogrel monotherapy	125 (1·7%)	110 (1·5%)	0·325
Other P2Y12 receptor antagonist monotherapy	21 (0·3%)	0 (0·0%)	<0·001
Aspirin monotherapy	1015 (13·6%)	6727 (89·7%)	<0·001
Ticagrelor and Aspirin	518 (6·9%)	92 (1·2%)	<0·001
Clopidogrel and Aspirin	175 (2·3%)	421 (5·6%)	<0·001
Other antiplatelet drug and Aspirin	11 (0·1%)	15 (0·2%)	0·557
No antiplatelet therapy, but oral anticoagulation	119 (1·6%)	92 (1·2%)	0·061
Neither antiplatelet therapy nor oral anticoagulation	75 (1·0%)	34 (0·5%)	<0·001
Statin	6778 (90·6%)	6731 (89·7%)	0·055
Angiotensin converting enzyme inhibitor	4135 (55·3%)	4230 (56·4%)	0·177
Angiotensin receptor blocker	1503 (20·1%)	1486 (19·8%)	0·653
β Blocker	5676 (75·9%)	5757 (76·7%)	0·241
Proton-pump inhibitor	3733 (50·0%)	3677 (49·0%)	0·253

[¥] The drug counts at the 1 month, 1 year and 2 year time points reflect patient adherence before the protocol mandated change in antiplatelet regimen.

Depicted are counts (%) or means with standard deviations. The bold numbers show the number of patients with medication information obtained. Exact dates of changes to other P2Y12 receptor antagonists were not always obtainable, in which case the more potent P2Y12 receptor antagonists used in the period from the last visit up to the current visit is listed.

*Because patients were expected to switch P2Y12 receptor antagonists around these visits, a stop from 25 days since index percutaneous coronary intervention onwards for the 1 month visit was counted as compliant, a stop from 335 days since index percutaneous coronary intervention onwards for the 1 year visit was counted as compliant, a stop from 700 days since index percutaneous coronary intervention onwards for the 2 year visit was counted a compliant.

7.1.2 Supplementary table 2: BARC bleeding endpoints per allocated treatment strategy group.

	Experimental Treatment Strategy	**Reference Treatment Strategy**	**Rate Ratio (95% CI)**	**p-value**
Total number of patients	N=7980	N=7988		
Composite of Cardiovascular mortality, Stroke or MI	407 (5·10)	421 (5·27)	0·97 (0·85-1·11)	0,685
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

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 percutaneous coronary intervention). 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.

7.1.3 Supplementary table 3: Reasons of non-adherence to allocated strategy

	Experimental Treatment Strategy	Reference Treatment Strategy	p-value
	N = 4254	N = 4291	
1 month Follow-up			
Adherent to treatment strategy	n = 4244,	n = 4275,	
Yes	4021 (95%)	4113 (96%)	
No	223 (5%)	162 (4%)	
Reason of non-adherence			
Allergic Reaction	3 (1%)	7 (4%)	0·103
Atrial Fibrillation leading to OAC	17 (8%)	8 (5%)	0·402
Bleeding	29 (13%)	19 (12%)	0·756
Cerebrovascular Accident	2 (1%)	0 (0%)	0·511
Diarrhea	1 (0%)	1 (1%)	1·000
Dizziness	1 (0%)	1 (1%)	1·000
Dyspnea	78 (35%)	30 (19%)	<0·001
Interference With Other Drugs	4 (2%)	4 (2%)	0·725
Logistical Issues	2 (1%)	1 (1%)	1·000
Medical Decision	4 (2%)	5 (3%)	0·501
Myocardial Infarction	0 (0%)	1 (1%)	0·421
New Medical Condition	2 (1%)	1 (1%)	1·000
OAC, no specification of reason	5 (2%)	5 (3%)	0·748
Other Signs	0 (0%)	0 (0%)	
Other Symptoms	3 (1%)	1 (1%)	0·642
Patient Unwilling To Take Medication	0 (0%)	2 (1%)	0·176
Percutaneous Coronary Intervention	13 (6%)	14 (9%)	0·316
Skin Reaction	2 (1%)	9 (6%)	0·010
Surgery	5 (2%)	5 (3%)	0·748
Thromboembolic Event leading to OAC	4 (2%)	4 (2%)	0·725
Trauma	1 (0%)	0 (0%)	1·000
Upper Gi Complaints	2 (1%)	1 (1%)	1·000
Reason unclear	45 (20%)	43 (27%)	0·176
12 month Follow-up			
Adherent to treatment strategy	n = 4119,	n = 4111,	
Yes	3353 (81%)	3669 (89%)	

No	766 (19%)	442 (11%)	
Reason of non-adherence			
Allergic Reaction	10 (1%)	9 (2%)	0·344
Atrial Fibrillation leading to OAC	38 (5%)	27 (6%)	0·428
Bleeding	138 (18%)	84 (19%)	0·700
Cerebrovascular Accident	4 (1%)	3 (1%)	0·711
Diarrhea	8 (1%)	2 (0%)	0·342
Dizziness	6 (1%)	1 (0%)	0·433
Dyspnea	234 (31%)	102 (23%)	0·005
Interference With Other Drugs	3 (0%)	2 (0%)	1·000
Logistical Issues	3 (0%)	1 (0%)	1·000
Medical Decision	14 (2%)	17 (4%)	0·038
Myocardial Infarction	4 (1%)	4 (1%)	0·474
New Medical Condition	9 (1%)	4 (1%)	0·778
OAC, no specification of reason	14 (2%)	18 (4%)	0·025
Other Signs	5 (1%)	0 (0%)	0·165
Other Symptoms	12 (2%)	8 (2%)	0·816
Patient Unwilling To Take Medication	8 (1%)	7 (2%)	0·428
Percutaneous Coronary Intervention	107 (14%)	22 (5%)	<0·001
Skin Reaction	7 (1%)	13 (3%)	0·010
Surgery	21 (3%)	19 (4%)	0·181
Thromboembolic Event leading to OAC	9 (1%)	4 (1%)	0·778
Trauma	1 (0%)	2 (0%)	0·558
Upper GI Complaints	8 (1%)	9 (2%)	0·204
Reason unclear	103 (13%)	84 (19%)	0·013
24 month Follow-up			
Adherent to treatment strategy	n = 4043,	n = 4049,	
Yes	3145 (78%)	3776 (93%)	
No	898 (22%)	273 (7%)	
Reason of non-adherence			
Allergic Reaction	10 (1%)	2 (1%)	0·743
Atrial Fibrillation leading to OAC	48 (5%)	29 (11%)	0·007
Bleeding	191 (21%)	44 (16%)	0·070
Cerebrovascular Accident	6 (1%)	3 (1%)	0·442
Diarrhea	8 (1%)	0 (0%)	0·210
Dizziness	6 (1%)	0 (0%)	0·346
Dyspnea	233 (26%)	8 (3%)	<0·001
Interference With Other Drugs	4 (0%)	3 (1%)	0·208
Logistical Issues	4 (0%)	0 (0%)	0·579
Medical Decision	24 (3%)	14 (5%)	0·051

Myocardial Infarction	3 (0%)	3 (1%)	0·142
New Medical Condition	6 (1%)	3 (1%)	0·442
OAC, no specification of reason	14 (2%)	17 (6%)	<0·001
Other Signs	5 (1%)	2 (1%)	0·667
Other Symptoms	12 (1%)	2 (1%)	0·541
Patient Unwilling To Take Medication	9 (1%)	3 (1%)	1·000
Percutaneous Coronary Intervention	128 (14%)	50 (18%)	0·102
Skin Reaction	9 (1%)	1 (0%)	0·469
Surgery	35 (4%)	4 (1%)	0·054
Thromboembolic Event leading to OAC	15 (2%)	1 (0%)	0·139
Trauma	5 (1%)	0 (0%)	0·596
Upper GI Complaints	7 (1%)	6 (2%)	0·089
Reason unclear	116 (13%)	78 (29%)	<0·001

* Patients included in the adherence sub-study (n=8545) were those who were assessed using the new version of the eCRF at 1 month Follow-up and later, so reasons for non-adherence could be entered into the system. Percentages and two-sided P-values from Fisher's exact test for reasons of non-adherence refer to the denominator of non-adherent patients at 1, 12 and 24 months.

Reasons of non-adherence were classified in accordance with the Non-adherence Academic Research Consortium document. [9]

OAC: oral anticoagulation medication; GI: gastro-intestinal

7.1.4 Supplementary table 4: Additional outcomes at 2 years follow-up

	Experimental Treatment Strategy	Reference Treatment Strategy	Rate Ratio (95% CI)	p-value
Total nr of patients	N=7980	N=7988		
Composite of All-cause mortality, Stroke, Myocardial infarction, 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 Myocardial Infarction	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 percutaneous coronary intervention). 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.

7.1.5 Supplementary table 5: Landmark analysis

A: Clinical Outcomes up to 30 days; and from 31 days to 2 Years of Follow-up

	Experimental Treatment Strategy	Reference Treatment Strategy	Risk Ratio (95% CI)	p-value
Total number of patients	N=7980	N=7988		
At 30 days				
All-cause mortality or new Q-wave myocardial infarction[c]	34 (0·43)	42 (0·53)	0·81 (0·52-1·27)	0·360
All-cause mortality	32 (0·40)	35 (0·44)	0·92 (0·57-1·48)	0·717
New Q-wave myocardial infarction	2 (0·03)	8 (0·10)	0·25 (0·05-1·18)	0·058
Composite of all-cause mortality, stroke or new Q-wave myocardial infarction	45 (0·56)	59 (0·74)	0·76 (0·52-1·13)	0,172
Myocardial infarction	83 (1·04)	69 (0·86)	1·21 (0·88-1·66)	0·250
Stroke	16 (0·20)	18 (0·23)	0·89 (0·45-1·75)	0·735
Ischemic stroke	11 (0·14)	15 (0·19)	0·73 (0·34-1·60)	0·435
Haemorrhagic stroke	5 (0·06)	1 (0·01)	5·01 (0·58-42·87)	0·102
Undetermined stroke	0 (0·00)	2 (0·03)		
Revascularisation	112 (1·40)	142 (1·78)	0·79 (0·62-1·01)	0·060
Target vessel revascularization	73 (0·91)	93 (1·16)	0·79 (0·58-1·07)	0·122
Definite stent thrombosis	30 (0·38)	29 (0·36)	1·04 (0·62-1·73)	0,892
BARC 3 or 5 bleeding[b]	51 (0·64)	48 (0·60)	1·06 (0·72-1·58)	0·755
BARC 5 bleeding	10 (0·13)	8 (0·10)	1·25 (0·49-3·17)	0·635
BARC 5b bleeding	8 (0·10)	7 (0·09)	1·15 (0·41-3·16)	0·794
BARC 5a bleeding	2 (0·03)	1 (0·01)	2·00 (0·18-22·08)	0·563
BARC 3 bleeding	43 (0·54)	43 (0·54)	1·00 (0·66-1·53)	0·992
BARC 3c bleeding	6 (0·08)	6 (0·08)	1·00 (0·32-3·11)	0·997
BARC 3b bleeding	16 (0·20)	20 (0·25)	0·80 (0·42-1·55)	0·508
BARC 3a Bleeding	23 (0·29)	19 (0·24)	1·21 (0·66-2·23)	0·532
From 30 days to 2 Years (landmark)				
All-cause mortality or new Q-wave myocardial infarction[c]	270 (3·40)	307 (3·87)	0·88 (0·74-1·03)	0·115
All-cause mortality	192 (2·42)	218 (2·74)	0·88 (0·72-1·07)	0·196
New Q-wave myocardial infarction[e]	81 (1·02)	95 (1·20)	0·85 (0·63-1·15)	0·286
Composite of all-cause mortality, stroke or new Q-wave myocardial infarction	317 (4·02)	357 (4·52)	0·89 (0·76-1·04)	0·130
Myocardial infarction	165 (2·11)	181 (2·31)	0·92 (0·74-1·13)	0·427

Stroke	64 (0·81)	64 (0·81)	1·00 (0·71-1·42)	0·979
Ischemic stroke	52 (0·66)	53 (0·67)	0·99 (0·67-1·45)	0·941
Haemorrhagic stroke	8 (0·10)	8 (0·10)	1·01 (0·38-2·68)	0·992
Undetermined stroke	6 (0·08)	3 (0·04)	2·01 (0·50-8·04)	0·314
Revascularisation	627 (8·05)	651 (8·37)	0·96 (0·86-1·08)	0·509
Target vessel revascularization	316 (4·04)	349 (4·46)	0·91 (0·78-1·06)	0·205
Definite stent thrombosis	34 (0·43)	35 (0·44)	0·98 (0·61-1·57)	0·925
BARC 3 or 5 bleeding[b]	112 (1·43)	121 (1·54)	0·93 (0·72-1·20)	0·576
BARC 5 bleeding	12 (0·15)	16 (0·20)	0·75 (0·36-1·59)	0·458
BARC 5b bleeding	7 (0·09)	11 (0·14)	0·64 (0·25-1·65)	0·351
BARC 5a bleeding	5 (0·06)	5 (0·06)	1·01 (0·29-3·47)	0·993
BARC 3 bleeding	107 (1·36)	116 (1·47)	0·93 (0·71-1·20)	0·567
BARC 3c bleeding	29 (0·37)	19 (0·24)	1·54 (0·86-2·74)	0·143
BARC 3b bleeding	37 (0·47)	54 (0·68)	0·69 (0·45-1·05)	0·078
BARC 3a bleeding	54 (0·69)	51 (0·65)	1·06 (0·73-1·56)	0·750

The first event per event type for each patient only is depicted (disregards multiple events of the same type within the same patient and censoring at 730 days since index percutaneous coronary intervention). Percentage of patients at risk.

[b]Secondary safety endpoint.

[c]Primary efficacy endpoint.

[d]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.

[e]New Q-wave or equivalent Left bundle branch block as adjudicated by the independent cardiologist.

B: **Clinical Outcomes up to 1 year; and from 366 days to 2 Years of Follow-up**

	Experimental Treatment Strategy	**Reference Treatment Strategy**	**Risk Ratio (95% CI)**	**p-value**
Total number of patients	N=7980	N=7988		
At 1 year				
All-cause mortality or new Q-wave myocardial infarction[c]	156 (1·95)	197 (2·47)	0·79 (0·64-0·98)	0·028
All-cause mortality	108 (1·35)	131 (1·64)	0·82 (0·64-1·06)	0·138
New Q-wave myocardial infarction[e]	48 (0·60)	69 (0·86)	0·70 (0·48-1·00)	0·052
Composite of all-cause mortality, stroke or new Q-wave myocardial infarction	197 (2·47)	238 (2·98)	0·83 (0·69-1·00)	0·052
Myocardial infarction	179 (2·24)	158 (1·98)	1·14 (0·92-1·41)	0·233

Stroke	52 (0·65)	49 (0·61)	1·07 (0·72-1·57)	0,750
Ischemic stroke	40 (0·50)	41 (0·51)	0·98 (0·63-1·51)	0·926
Haemorrhagic stroke	10 (0·13)	5 (0·06)	2·01 (0·69-5·88)	0·194
Undetermined stroke	2 (0·03)	3 (0·04)	0·67 (0·11-4·00)	0·658
Revascularisation	518 (6·49)	549 (6·87)	0·94 (0·84-1·07)	0·355
Target vessel revascularization	268 (3·36)	306 (3·83)	0·88 (0·74-1·03)	0·118
Definite stent thrombosis	53 (0·66)	41 (0·51)	1·30 (0·86-1·95)	0·210
BARC 3 or 5 bleeding[b]	117 (1·47)	136 (1·70)	0·86 (0·67-1·11)	0·243
BARC 5 bleeding	14 (0·18)	16 (0·20)	0·88 (0·43-1·80)	0·722
BARC 5b bleeding	9 (0·11)	11 (0·14)	0·82 (0·34-1·98)	0·659
BARC 5a bleeding	5 (0·06)	5 (0·06)	1·00 (0·29-3·47)	0·995
BARC 3 bleeding	107 (1·34)	128 (1·60)	0·84 (0·65-1·08)	0·179
BARC 3c bleeding	23 (0·29)	16 (0·20)	1·44 (0·76-2·73)	0·256
BARC 3b bleeding	43 (0·54)	62 (0·78)	0·70 (0·47-1·03)	0·067
BARC 3a bleeding	52 (0·65)	57 (0·71)	0·92 (0·63-1·33)	0·648
From 1 Year to 2 Years (landmark)	148 (1·89)	152 (1·95)	0·97 (0·77-1·22)	0·790
All-cause mortality or new Q-wave myocardial infarction[c]	116 (1·47)	122 (1·55)	0·95 (0·74-1·22)	0·687
All-cause mortality	35 (0·45)	34 (0·44)	1·03 (0·64-1·65)	0·913
New Q-wave myocardial infarction[e]	165 (2·15)	178 (2·32)	0·93 (0·75-1·15)	0·491
Composite of all-cause mortality, stroke or new Q-wave myocardial infarction	69 (0·91)	92 (1·21)	0·75 (0·55-1·03)	0·076
Myocardial infarction	28 (0·36)	33 (0·43)	0·85 (0·51-1·41)	0·533
Stroke	23 (0·30)	27 (0·35)	0·86 (0·49-1·49)	0·581
Ischemic stroke	3 (0·04)	4 (0·05)	0·75 (0·17-3·37)	0·710
Haemorrhagic stroke	4 (0·05)	2 (0·03)	2·01 (0·37-10·97)	0·411
Undetermined stroke	221 (3·05)	244 (3·37)	0·90 (0·75-1·08)	0·279
Revascularisation	121 (1·62)	136 (1·82)	0·89 (0·70-1·14)	0·344
Target vessel revascularization	11 (0·14)	23 (0·30)	0·48 (0·23-0·99)	0·041
Definite stent thrombosis	46 (0·60)	33 (0·43)	1·40 (0·89-2·19)	0·140
BARC 3 or 5 bleeding[b]	8 (0·10)	8 (0·10)	1·00 (0·38-2·68)	0·992
BARC 5 bleeding	6 (0·08)	7 (0·09)	0·86 (0·29-2·56)	0·788
BARC 5b bleeding	2 (0·03)	1 (0·01)	2·01 (0·18-22·11)	0·561
BARC 5a bleeding	43 (0·56)	31 (0·40)	1·39 (0·88-2·21)	0·159
BARC 3 bleeding	12 (0·16)	9 (0·12)	1·34 (0·57-3·18)	0·504
BARC 3c bleeding	10 (0·13)	12 (0·16)	0·83 (0·36-1·93)	0·673
BARC 3b bleeding	25 (0·32)	13 (0·17)	1·93 (0·99-3·77)	0·050
BARC 3a bleeding	25 (0·32)	13 (0·17)	1·93 (0·99-3·77)	0·050

The first event per event type for each patient only is depicted (disregards multiple events of the same type within the same patient and censoring at 730 days since index percutaneous coronary intervention).Percentage of patients at risk.

[b]Secondary safety endpoint.

[c]Primary efficacy endpoint.

[d]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.

[e]New Q-wave or equivalent Left bundle branch block as adjudicated by the independent cardiologist.

7.1.6 Supplementary table 6: Baseline (a) and procedural (b) characteristics of patients included in major all-comer percutaneous coronary intervention trials.

A Baseline characteristics

	LEADERS[7]		RESOLUTE[8]		AIDA[9]		COMPARE[10]		COMPARE II [11]		DUTCH PEER[12]		BIOSCIENCE[13]		DESSOLVE III[14]		BIORESORT[15]		
	Biolimus-eluting stent (n=857)	Sirolimus-eluting stent (n=850)	Zotarolimus-Eluting Stent (n=1140)	Everolimus-Eluting Stent (n=1152)	Scaffold (n=924)	Stent (n=921)	Everolimus-eluting stent (n=897)	Paclitaxel-eluting stent (n=903)	Biolimus-eluting stent (n=1795)	Everolimus-eluting stent (n=912)	Zotarolimus-eluting stent (n=906)	Everolimus-eluting stent (n=905)	Biodegradable polymer SES (n=1063)	Durable polymer EES (n=1056)	MiStent SES (n=703)	Xience EES (n=695)	Everolimus-eluting stent (n=1172)	Zotarolimus-eluting stent (n=1173)	Sirolimus-eluting stent (n=1169)
Age (years)	64·6 ±10·8	64·5±10·7	64·4± 10·9	64·2± 10·8	64·3± 10·6	64·0± 10·5	62·9 (55·4–71·1)	63·6 (55·7–72·9)	63±11·1	62·7± 11	64 (56–72)	65 (57–72)	66·1± 11·6	65·9±11·4	66·4 ±10·7	66·3±10·7	64± 10·7	63·6±10·9	64·2±10·7
Females	25	25,4	23,3	22,8	27,5	24	31	28	25,6	25,7	27	27	23	22,7	30	26	28	28	27
Body Mass Index (kg/m²)	.	.	.	.	.	.	.	.	.	.	27·1 (25·0–30·0)	27·2 (24·9–30·5)	27·8± 4·5	27·5±4·5	27·9 ±4·4	28·1±4·5	27·6±4·2	27·3±4	27·4±4·2
Medical history																			
Diabetes mellitus	26	22,5	23,5	23,4	18,5	16,6	17	19	21,8	21,6	18	17	24,2	21,7	27	27	17	18	18
Insulin-dependent Diabetes mellitus	9,5	9,1	·	·	7	4,9	·	·	·	·	7	6	8,4	6,7	9	9	·	·	·
Hypertension	73,5	72,7	71,1	71,3	50,9	50,5	46	50	54,8	56,3	55	53	68,5	66,9	72	75	44	47	47
Hypercholesterolemia	65,3	68,2	63,9	67,7	37,6	38,3	53	50			46	48	67	67,8	61	60	36	38	40
Current smoker	24	25,2	26,5	26,5	28,6	31,7	33	29	30,8	27,4	24	26	29,1	28,5	27	26	30	31	30

Peripheral Vascular Disease	.	.	.	.	.	.	.	.	7,6	5,6	.	.	8,9	7,7	9	11	.	.	.
Chronic obstructive pulmonary disease	.	.	.	.	.	.	.	.	8	8	.	.	.	.	.	.	.	.	.
Previous major bleeding	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Chronic renal failure	.	.	.	.	7,6	9,9	3	3	4,3	4,4	4	3	15	13,1	7	7	3	3	4
Previous stroke	.	.	.	.	5	6,3	.	.	5,3	5,3	.	.	3,7	5,4	.	.	6	7	7
Previous myocardial infarction	32,3	32,6	28,9	30,4	18	18,7	15	18	20,3	1,8	23	21	21	19,3	27	28	16	21	18
Previous Percutaneous coronary intervention	36,4	36,7	31,8	32,1	21,9	20	13	14	17,8	17	20	18	30,6	27,7	34	36	18	17	18
Previous coronary artery bypass grafting	10,5	12,6	10	9,5	4,1	2,8	7	6	5,9	5,7	9	10	10,6	9,3	7	10	8	8	7
Clinical presentation																			
Stable coronary artery disease	45,2	44,4	33,5	36,1	39,1	40,2	37	39	38,9	38,9	41	42	30,6	31,3	41	41	30	31	30
Acute coronary syndrome																			
Unstable angina	22,2	21,2	19,4	18,9	7,6	9,4	12	12	10,8	9,7	12	15	7,3	7	23	24	16	19	18
Non-ST segment elevation myocardial infarction	16,9	18	15,1	12,7	20	20,8	22	24	26,4	26,5	27	22	27,1	26,9	21	19	21	23	20
ST-segment elevation myocardial infaction	15,8	16,5	13,7	16,1	26	24,4	27	23	20,7	21,6	19	22	19,9	18,6	15	16	32	28	32

Data are percentage or mean ± standard deviation or median (Inter Quartal Range), unless otherwise indicated

. = not reported

B Procedural characteristics

	LEADERS		RESOLUTE		AIDA		COMPARE		COMPARE II		DUTCH PEER		BIOSCIENCE		DESSOLVE III		BIORESORT		
	Biolimus-eluting stent (n=857)	Sirolimus-eluting stent (n=850)	Zotarolimus-Eluting Stent (n=1140)	Everolimus-Eluting Stent (n=1152)	Scaffold (n=924)	Stent (n=921)	Everolimus-eluting stent (n=897)	Paclitaxel-eluting stent (n=903)	Biolimus-eluting stent (n=1795)	Everolimus-eluting stent (n=912)	Zotarolimus-eluting stent (n=906)	Everolimus-eluting stent (n=905)	Biodegradable polymer SES (n=1063)	Durable polymer EES (n=1056)	MiStent SES (n=703)	Xience EES (n=695)	Everolimus-eluting stent (n=1172)	Zotarolimus-eluting stent (n=1173)	Sirolimus-eluting stent (n=1169)
Percutaneos coronary intervention performed	.	.	.	.	.	.	.	.	.	.	.	.	99,9	100	99	99,3	.	.	.
Vascular access site																			
Radial	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	45	46	45
Femoral	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Brachial	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Lesions treated																			
One lesion	63	68,6	.	.	.	.	.	.	.	.	74	76	64,3	65,2	.	.	.	.	.
Two lesions	28,9	21,9	.	.	.	.	.	.	.	.	21	20	25	25,3	.	.	.	.	.
Three or more lesions	8,1	9,5	.	.	.	.	.	.	.	.	5	4	10,7	9,5	.	.	.	.	.
Treated vessel(s)																			
Left main coronary artery	1,6	1,2	2,2	2,5	0,5	0,7	2	2	1,6	1,2	2	2	1,8	1,7	2	1	2	2	2
Left anterior descending artery	37,2	39,7	52,6	48,6	42	44	40	37	40,9	39,7	41	40	40,7	43,9	41	40	40	37	44
Left circumflex artery	28	23,6	33	32,9	24	26	23	26	22,8	25,7	25	24	23,2	22,1	26	26	23	25	22
Right coronary artery	30,7	32,9	37,3	41,3	32	29	33	33	33,4	32,3	31	33	31,7	29,3	30	32	33	34	31
Bypass graft	2,5	2,6	2,5	2,4	0,5	0,6	2	2	1,34	1,2	2	3	2,6	3	<1	1	2	2	2

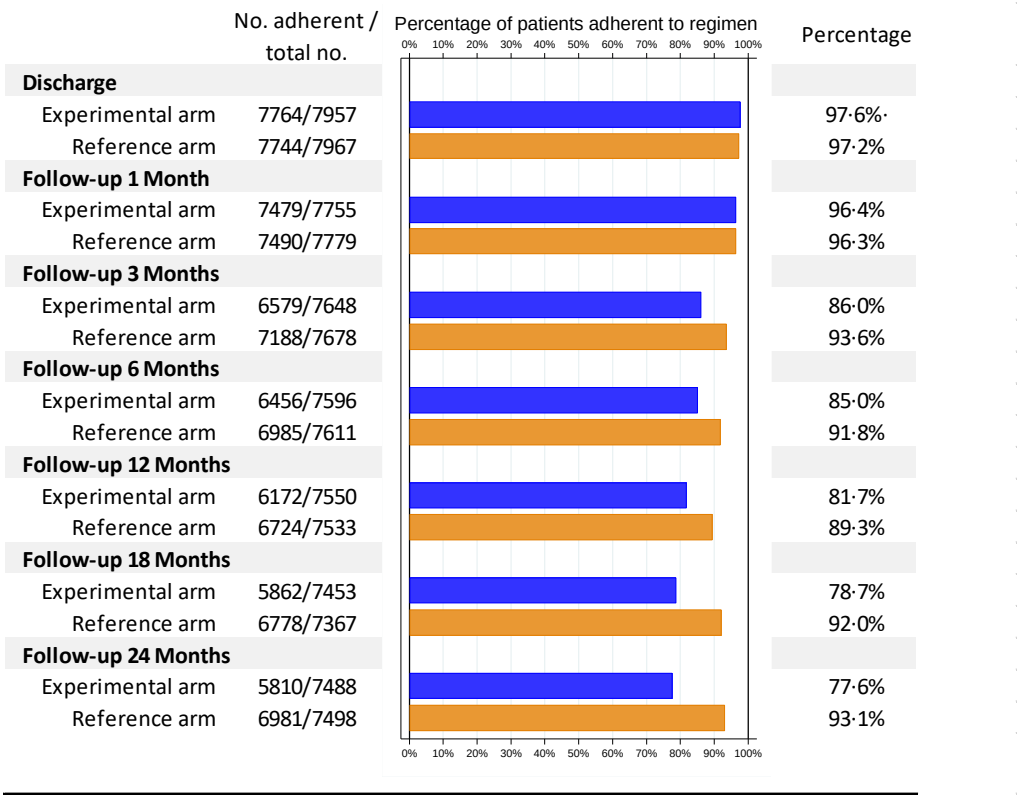
Index PCI																		
No of stents per lesion	1.3±0.7	1.3±0.7	1.15±0.42	1.18±0.45	1.15±0.40	1.11±0.34	1.7±0.9	1.6±0.9	1.4±0.78	1.4±0.75	1.35±0.68	1.36±0.7	1.31±0.61	1.34±0.64	1.23±0.56	1.23±0.6	.	.	.
Type of stent																		
Implantation of study stent only	97,5	95,7	98	96,9	93	98,8	.	.	94,2	97,9	99	100	98,9	99,4	.	.	99	98	98
Other stent	2,5	4,3	2	3,1	7	1,2	.	.	5,8	2,1	1	0	1,1	0,6	.	.	.	.	.
Total stent length per lesion (mm)	24.7±15.5	24.6±14.8	.	.	19.9±5.6	20.3±7.3	28 (18–46)	28 (18–44)	.	.	22 (18–36)	24 (16–38)	25.91±15.4	27.45±16.77	24.2±12.8	25±14.9	.	.	.
Average stent diameter per lesion (mm)	.	.	.	.	3.07±0.37	3.05±0.40	.	.	.	.	.	.	.	.	.	.	.	.	.
Direct stenting	40,4	39,9					34	35	37,5	40,7	29	28	28,2	29,6	.	.	18	15	18
Bifurcation	.	.	16,9	17,7	5	6	17	18	6,4	6,5	23	21	16,5	16,9	7	7	29	8	29
Thrombus aspiration performed	.	.	.	.	.	.	.	.	.	.	.	.	9,2	8,1	3	4	.	.	.
Thrombolysis in myocardial infarction flow pre-procedure(16)																		
0 or 1	15,4	15,1	.	.	.	.	21	20	13,6	14,3	18	16	20	19,1	12	12	.	.	.
2	4,3	4,4	.	.	.	.	7	8	7,4	6,6	11	11	14,1	14,8	18	16	.	.	.
3	80,2	80,5	.	.	.	.	73	71	75,2	75,6	72	73	65,9	66,1	62	64	.	.	.
Thrombolysis in myocardial infarction flow post-procedure(16)																		
0 or 1	.	.	.	.	.	.	.	.	.	.	.	.	0,3	0,4	1	<1	.	.	.
2	.	.	.	.	.	.	.	.	.	.	.	.	1,3	0,8	1	2	.	.	.
3	.	.	.	.	.	.	.	.	.	.	.	.	98,5	98,8	93	92	.	.	.

Data are percentage or mean± standard deviation or median (Inter Quartal Range), unless otherwise indicated

. = not reported

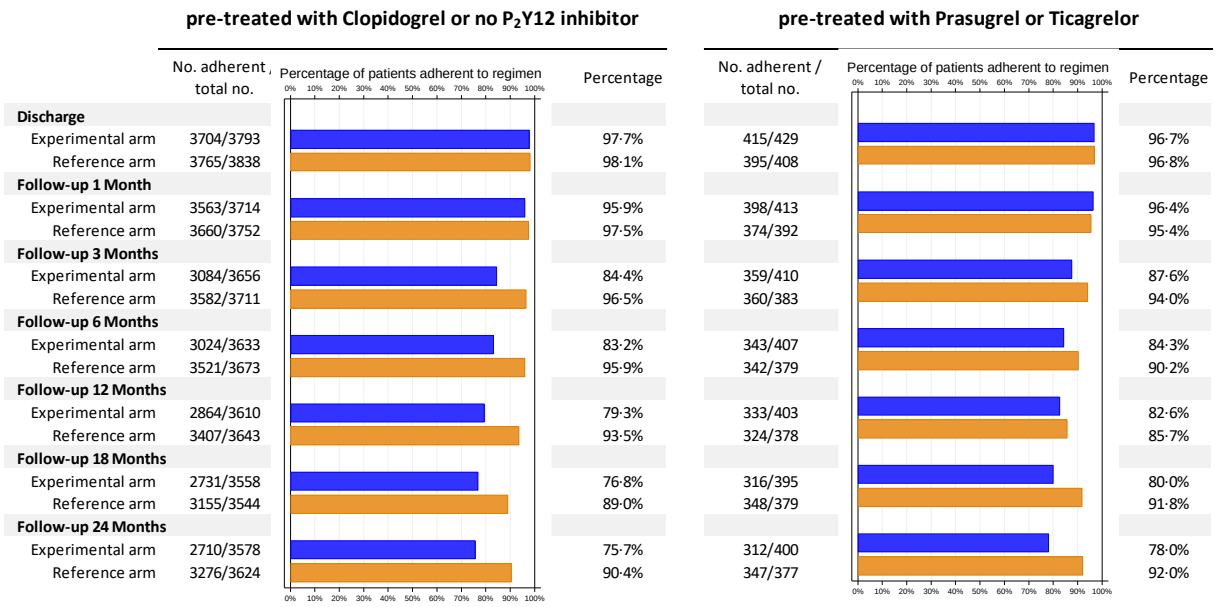
FIGURES

7.1.7 Supplementary Figure 1 Distribution of patient adherence to the allocated antiplatelet treatment strategies over the 2-year trial period.



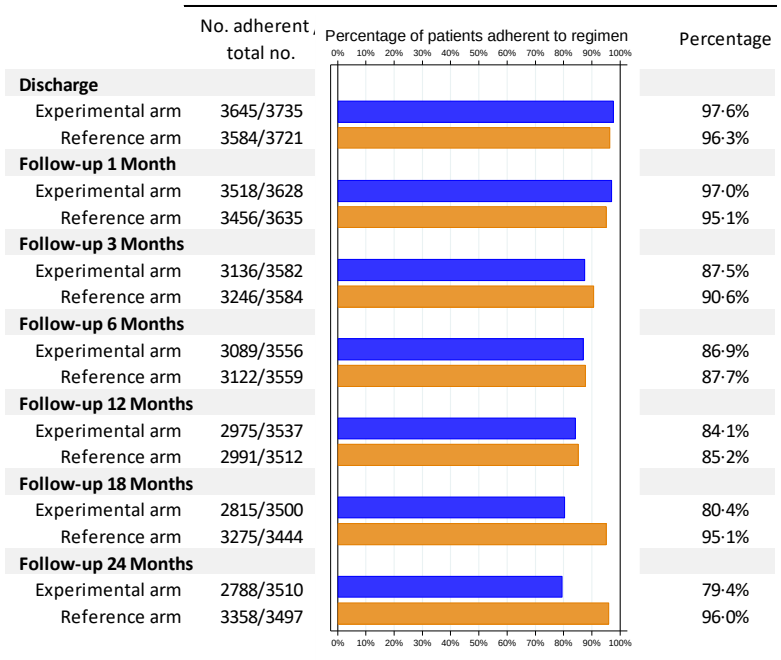
The drug counts at the 1 month, 1 year and 2-year time points reflect patient adherence before the protocol mandated change in antiplatelet regimen. Revascularizations and per-protocol restart of DAPT allowed: i) ticagrelor and aspirin for 30 days in the experimental treatment strategy group, ii) dual antiplatelet therapy with ticagrelor and aspirin (acute coronary syndrome, stable coronary artery disease patients already on ticagrelor or prasugrel), clopidogrel and aspirin (stable coronary artery patients) for 365 days in the standard treatment strategy group.

Panel B: Adherence to treatment strategies for stable coronary artery patients with elective procedures pre-treatment with potent P2Y12 receptor antagonists*.



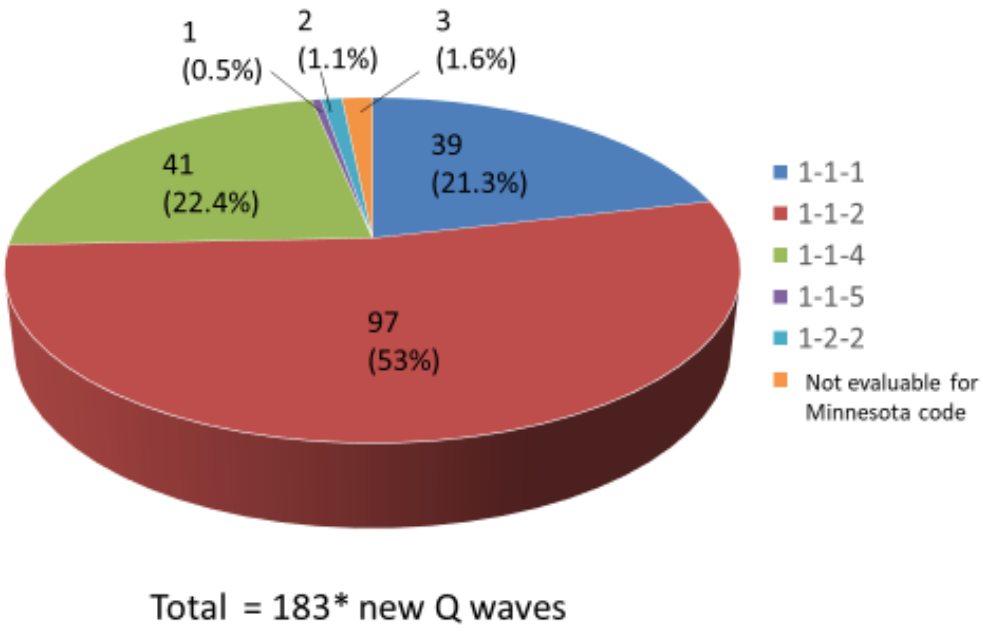
***** Patients with stable coronary artery disease, pre-treated with prasugrel or ticagrelor, who were allocated to the reference strategy, received dual antiplatelet therapy with aspirin and ticagrelor.
Revascularizations and per-protocol restart of DAPT allowed: i) ticagrelor and aspirin for 30 days in the experimental treatment strategy group, ii) dual antiplatelet therapy with ticagrelor and aspirin (acute coronary syndrome, stable coronary artery disease patients already on ticagrelor or prasugrel), clopidogrel and aspirin (stable coronary artery patients) for 365 days in the standard treatment strategy group.

Panel C: Adherence to treatment strategies for Acute Coronary Syndrome patients.



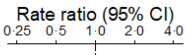
***** Patients with stable coronary artery disease, pre-treated with prasugrel or ticagrelor, who were allocated to the reference strategy, received dual antiplatelet therapy with aspirin and ticagrelor.

7.1.8 Supplementary Figure 2 Classification of new Q-wave myocardial infarction according to the Minnesota code



7.1.9 SUPPLEMENTARY FIGURE 3: Subgroup analyses of the key secondary safety endpoint of Bleeding Academic Research Consortium grade 3 or 5 events

Subgroups	Experimental Treatment Strategy	Reference Treatment Strategy	Rate Ratio [Exp./Reference] (95% CI)	p-value	p-value for interaction
Overall	**163/7980**	**169/7988**	**0·97 (0·78-1·20)**	**0·77**	
Indication					0·0068
ACS	73/3750	100/3737	0·73 (0·54-0·98)	0·037	
Stable CAD	90/4230	69/4251	1·32 (0·97-1·81)	0·081	
Age					0·057
>75 years	65/1292	50/1273	1·29 (0·89-1·86)	0·18	
≤75 years	98/6688	119/6715	0·83 (0·63-1·08)	0·17	
Diabetes mellitus					0·53
diabetics	52/2049	47/1989	1·07 (0·72-1·59)	0·72	
non-diabetics	111/5925	122/5994	0·92 (0·71-1·19)	0·54	
Renal failure					0·48
Yes	43/1099	38/1072	1·10 (0·71-1·71)	0·66	
No	120/6881	131/6916	0·92 (0·72-1·18)	0·53	
Peripheral vascular disease					0·99
Yes	15/476	17/529	0·98 (0·49-1·97)	0·96	
No	148/7428	150/7389	0·98 (0·78-1·24)	0·89	
Left main treated					0·44
Yes	9/197	6/190	1·43 (0·51-4·03)	0·49	
No	154/7783	163/7798	0·95 (0·76-1·18)	0·64	
Geographic area					0·20
Western Europe	143/6156	141/6167	1·02 (0·81-1·29)	0·87	
Eastern Europe	17/1502	27/1500	0·63 (0·34-1·15)	0·13	
Rest of the world	3/322	1/321	3·00 (0·31-28·84)	0·32	
Type of reference treatment strategy					0·016
Use of ticagrelor	84/4179	108/4146	0·77 (0·58-1·02)	0·071	
Use of clopidogrel	79/3801	61/3842	1·32 (0·95-1·84)	0·10	



Type of reference treatment strategy was a post-hoc criterion for subgroup analysis. Number of first events and percentages are reported. Rate ratios (95% confidence interval) are estimated using the Mantel-Cox method with two-sided p-values from log-rank test. All events were censored beyond 730 days. P-values for interactions were obtained with approximate $\chi 2$ tests for unequal Rate Ratio's in the subgroups (df=1, except geographic area df=4).

Renal failure = estimated creatinine-estimated glomerular filtration ratio (GFR) of less than 60 ml/min using the Modification of Diet in Renal Disease (MDRD) formula. (3) Assumed no risk in case of missing data: diabetes (n=11), renal failure (n=85), peripheral vascular disease (n=146).

8 References:

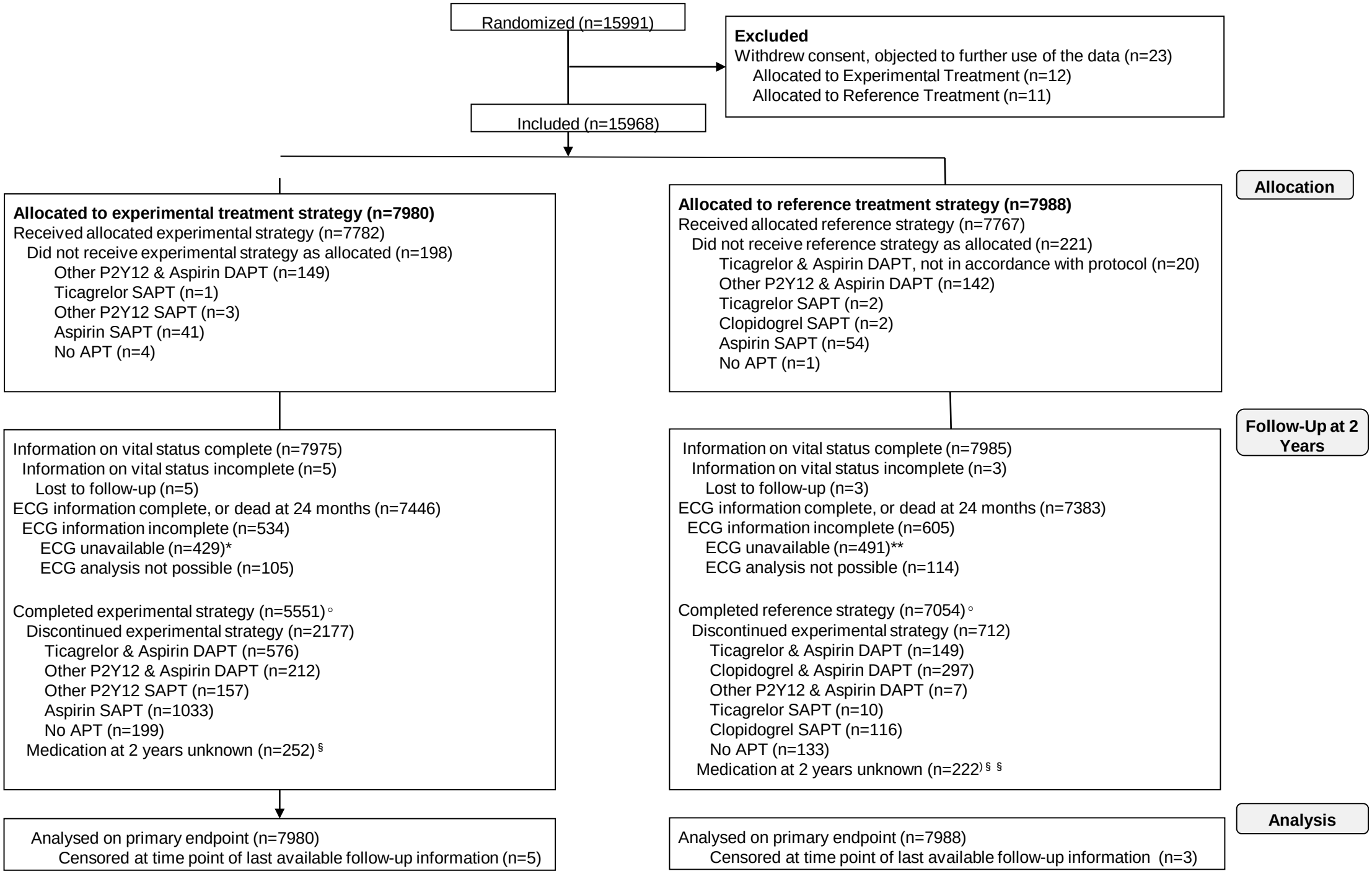
1. Vranckx P, Valgimigli M, Windecker S, Steg PG, Hamm C, Juni P, et al. Long-term ticagrelor monotherapy versus standard dual antiplatelet therapy followed by aspirin monotherapy in patients undergoing biolimus-eluting stent implantation: rationale and design of the GLOBAL LEADERS trial. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2016;12(10):1239-45.
2. Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, et al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. Journal of the American College of Cardiology. 2018;71(9):1021-34.
3. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. European heart journal. 2012;33(20):2551-67.
4. Prineas R.J. CRS, Zhang Z.-M. . The Minnesota Code Manual of Electrocardiographic Findings Springer Science & Business Media, London; 2009.
5. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007;115(17):2344-51.
6. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a

consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123(23):2736-47.

7. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet (London, England). 2008;372(9644):1163-73.
8. Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. The New England journal of medicine. 2010;363(2):136-46.
9. Wykrzykowska JJ, Kraak RP, Hofma SH, van der Schaaf RJ, Arkenbout EK, AJ IJ, et al. Bioresorbable Scaffolds versus Metallic Stents in Routine PCI. The New England journal of medicine. 2017;376(24):2319-28.
10. Kedhi E, Joesoef KS, McFadden E, Wassing J, van Mieghem C, Goedhart D, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet (London, England). 2010;375(9710):201-9.
11. Smits PC, Hofma S, Togni M, Vazquez N, Valdes M, Voudris V, et al. Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent (COMPARE II): a randomised, controlled, non-inferiority trial. Lancet (London, England). 2013;381(9867):651-60.
12. von Birgelen C, Sen H, Lam MK, Danse PW, Jessurun GA, Hautvast RW, et al. Third-generation zotarolimus-eluting and everolimus-eluting stents in

all-comer patients requiring a percutaneous coronary intervention (DUTCH PEERS): a randomised, single-blind, multicentre, non-inferiority trial. Lancet (London, England). 2014;383(9915):413-23.

13. Pilgrim T, Heg D, Roffi M, Tuller D, Muller O, Vuilliomenet A, et al. Ultrathin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation (BIOSCIENCE): a randomised, single-blind, non-inferiority trial. Lancet (London, England). 2014;384(9960):2111-22.
14. de Winter RJ, Katagiri Y, Asano T, Milewski KP, Lurz P, Buszman P, et al. A sirolimus-eluting bioabsorbable polymer-coated stent (MiStent) versus an everolimus-eluting durable polymer stent (Xience) after percutaneous coronary intervention (DESSOLVE III): a randomised, single-blind, multicentre, non-inferiority, phase 3 trial. Lancet (London, England). 2018;391(10119):431-40.
15. von Birgelen C, Kok MM, van der Heijden LC, Danse PW, Schotborgh CE, Scholte M, et al. Very thin strut biodegradable polymer everolimus-eluting and sirolimus-eluting stents versus durable polymer zotarolimus-eluting stents in allcomers with coronary artery disease (BIO-RESORT): a three-arm, randomised, non-inferiority trial. Lancet (London, England). 2016;388(10060):2607-17.
16. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. The New England journal of medicine. 1985;312(14):932-6.


Randomized (n=15991)
Excluded
Withdrew consent, objected to further use of the data (n=23)
Allocated to Experimental Treatment (n=12)
Allocated to Reference Treatment (n=11)
Included (n=15968)
Allocation
Allocated to experimental treatment strategy (n=7980)
Received allocated experimental strategy (n=7782)
Did not receive experimental strategy as allocated (n=198)
Other P2Y12 & Aspirin DAPT (n=149)
Ticagrelor SAPT (n=1)
Other P2Y12 SAPT (n=3)
Aspirin SAPT (n=41)
No APT (n=4)
Allocated to reference treatment strategy (n=7988)
Received allocated reference strategy (n=7767)
Did not receive reference strategy as allocated (n=221)
Ticagrelor & Aspirin DAPT, not in accordance with protocol (n=20)
Other P2Y12 & Aspirin DAPT (n=142)
Ticagrelor SAPT (n=2)
Clopidogrel SAPT (n=2)
Aspirin SAPT (n=54)
No APT (n=1)
Follow-Up at 2 Years
Information on vital status complete (n=7975)
Information on vital status incomplete (n=5)
Lost to follow-up (n=5)
ECG information complete, or dead at 24 months (n=7446)
ECG information incomplete (n=534)
ECG unavailable (n=429)*
ECG analysis not possible (n=105)
Completed experimental strategy (n=5551)◦
Discontinued experimental strategy (n=2177)
Ticagrelor & Aspirin DAPT (n=576)
Other P2Y12 & Aspirin DAPT (n=212)
Other P2Y12 SAPT (n=157)
Aspirin SAPT (n=1033)
No APT (n=199)
Medication at 2 years unknown (n=252)§
Information on vital status complete (n=7985)
Information on vital status incomplete (n=3)
Lost to follow-up (n=3)
ECG information complete, or dead at 24 months (n=7383)
ECG information incomplete (n=605)
ECG unavailable (n=491)**
ECG analysis not possible (n=114)
Completed reference strategy (n=7054)◦
Discontinued experimental strategy (n=712)
Ticagrelor & Aspirin DAPT (n=149)
Clopidogrel & Aspirin DAPT (n=297)
Other P2Y12 & Aspirin DAPT (n=7)
Ticagrelor SAPT (n=10)
Clopidogrel SAPT (n=116)
No APT (n=133)
Medication at 2 years unknown (n=222)§§
Analysis
Analysed on primary endpoint (n=7980)
Censored at time point of last available follow-up information (n=5)
Analysed on primary endpoint (n=7988)
Censored at time point of last available follow-up information (n=3)

	Experimental Treatment Strategy	Reference Treatment Strategy	Rate Ratio [Exp./Reference]		p-value	p-value for interaction
Subgroups			(95% CI)			
Overall	163/7980	169/7988	0·97 (0·78-1·20)		0·77	
Indication						0·0068
ACS	73/3750	100/3737	0·73 (0·54-0·98)		0·037	
Stable CAD	90/4230	69/4251	1·32 (0·97-1·81)		0·081	
Age						0·057
>75 years	65/1292	50/1273	1·29 (0·89-1·86)		0·18	
≤75 years	98/6688	119/6715	0·83 (0·63-1·08)		0·17	
Diabetes mellitus						0·53
diabetics	52/2049	47/1989	1·07 (0·72-1·59)		0·72	
non-diabetics	111/5925	122/5994	0·92 (0·71-1·19)		0·54	
Renal failure						0·48
Yes	43/1099	38/1072	1·10 (0·71-1·71)		0·66	
No	120/6881	131/6916	0·92 (0·72-1·18)		0·53	
Peripheral vascular disease						0·99
Yes	15/476	17/529	0·98 (0·49-1·97)		0·96	
No	148/7428	150/7389	0·98 (0·78-1·24)		0·89	
Left main treated						0·44
Yes	9/197	6/190	1·43 (0·51-4·03)		0·49	
No	154/7783	163/7798	0·95 (0·76-1·18)		0·64	
Geographic area						0·20
Western Europe	143/6156	141/6167	1·02 (0·81-1·29)		0·87	
Eastern Europe	17/1502	27/1500	0·63 (0·34-1·15)		0·13	
Rest of the world	3/322	1/321	3·00 (0·31-28·84)		0·32	
Type of reference treatment strategy						0·016
Use of ticagrelor	84/4179	108/4146	0·77 (0·58-1·02)		0·071	
Use of clopidogrel	79/3801	61/3842	1·32 (0·95-1·84)		0·10	

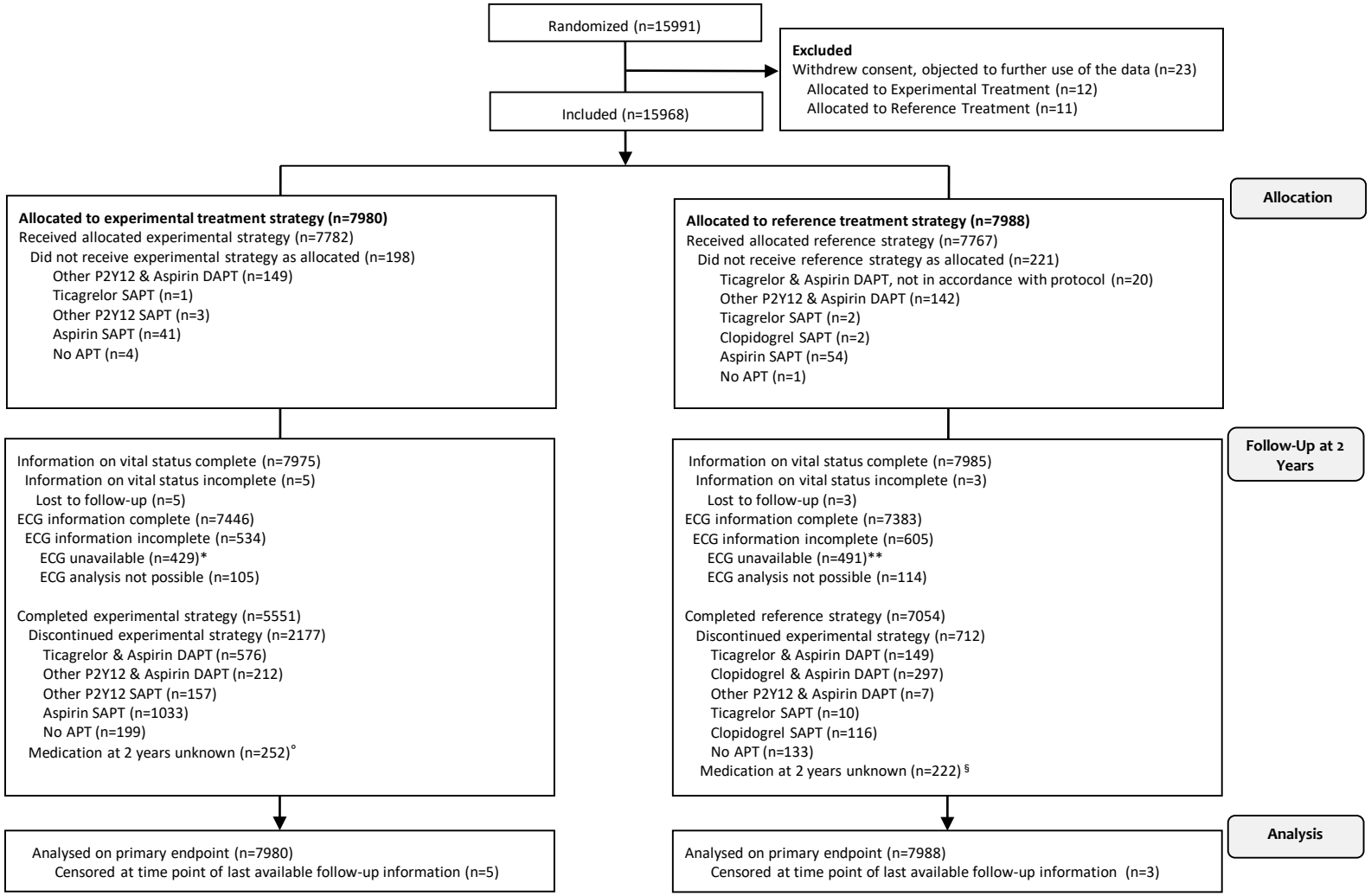


Figure 1. Flowchart of the Global LEADERS randomized clinical trial.

DAPT, dual antiplatelet treatment; SAPT, single antiplatelet treatment; APT, antiplatelet treatment. Restart of appropriate DAPT was allowed for 30 days in experimental arm and 365 days in reference arm after any revascularization; in case of death last medication taken.
*ECG missing for patients allocated to experimental strategy (n=429): 2 year visit performed but no ECG (n=195); no 2 year visit performed (n=228); lost to follow-up (n=6). **ECG missing for patients allocated to reference strategy (n=491): 2 year visit performed but no ECG (n=295); no 2 year visit performed (n=193); lost to follow-up (n=3). ° Information on vital status complete (n=247), lost to follow-up (n=5). § Information on vital status complete (n=219), lost to follow-up (n=3).