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

Pascal Vranckx, Marco Valgimigli*, Peter Jüni*, Christian Hamm, Philippe Gabriel Steg, Dik Heg, Gerrit Anne van Es, Eugene P McFadden, Yoshinobu Onuma, Cokky van Meijeren, Ply Chichareon, Edouard Benit, Helge Möllmann, Luc Janssens, Maurizio Ferrario, Aris Moschovitis, Aleksander Zurakowski, Marcello Dominici, Robert Jan Van Geuns, Kurt Huber, Ton Slagboom, Patrick W Serruys, Stephan Windecker, on behalf of the GLOBAL LEADERS Investigators*

Summary

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

Methods GLOBAL LEADERS was a randomised, open-label superiority trial at 130 sites in 18 countries. Patients undergoing percutaneous coronary intervention with a biolimus A9-eluting stent for stable coronary artery disease or acute coronary syndromes were randomly assigned (1:1) to 75–100 mg aspirin daily plus 90 mg ticagrelor twice daily for 1 month, followed by 23 months of ticagrelor monotherapy, or standard dual antiplatelet therapy with 75–100 mg aspirin daily plus either 75 mg clopidogrel daily (for patients with stable coronary artery disease) or 90 mg ticagrelor twice daily (for patients with acute coronary syndromes) for 12 months, followed by aspirin monotherapy for 12 months. Randomisation was concealed, stratified by centre and clinical presentation (stable coronary artery disease *vs* acute coronary syndrome), and blocked, with randomly varied block sizes of two and four. The primary endpoint at 2 years was a composite of all-cause mortality or non-fatal centrally adjudicated new Q-wave myocardial infarction as assessed by a core lab in a blinded manner. The key secondary safety endpoint was site-reported bleeding assessed according to the Bleeding Academic Research Consortium criteria (grade 3 or 5). Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01813435, and is closed to new participants, with follow-up completed.

Findings Between July 1, 2013, and Nov 9, 2015, 15 968 participants were randomly assigned, 7980 to the experimental group and 7988 to the control group. At 2 years, 304 (3·81%) participants in the experimental group had died or had a non-fatal centrally adjudicated new Q-wave myocardial infarction, compared with 349 (4·37%) participants in the control group (rate ratio 0·87 [95% CI 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=0·93). Grade 3 or 5 bleeding occurred in 163 participants in the experimental group and 169 in the control group (2·04% *vs* 2·12%; rate ratio 0·97 [95% CI 0·78–1·20]; p=0·77).

Interpretation Ticagrelor in combination with aspirin for 1 month followed by ticagrelor alone for 23 months was not superior to 12 months of standard dual antiplatelet therapy followed by 12 months of aspirin alone in the prevention of all-cause mortality or new Q-wave myocardial infarction 2 years after percutaneous coronary intervention.

Funding AstraZeneca, Biosensors, and The Medicines Company.

Introduction

Dual antiplatelet therapy reduces the risk of stent-related and spontaneous recurrent ischaemic 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 could offset the anticipated benefits of a reduction in ischaemic events.[1–3,5] An abbreviated dual antiplatelet therapy regimen followed by P2Y12-receptor-antagonist monotherapy could favourably affect the balance between bleeding risks and ischaemic benefits.[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 PLATO trial, treatment with ticagrelor as compared

Published **Online** August 27, 2018 http://dx.doi.org/10.1016/S0140-6736(18)31858-0

See **Online/Comment** http://dx.doi.org/10.1016/S0140-6736(18)31884-1

*These authors contributed equally

Jessa Ziekenhuis, Faculty of Medicine and Life Sciences at the Hasselt University, Hasselt, Belgium (P Vranckx MD, E Benit MD)**; Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland** (Prof M Valgimigli MD, A Moschovitis MD, Prof S Windecker MD)**; 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, ON, Canada** (Prof P Jüni MD)**; Kerckhoff Heart and Thorax Center, Bad Nauheim, Germany** (Prof C Hamm MD, Prof H Möllmann MD)**; Université Paris-Diderot, Hôpital Bichat, Assistance Publique–Hôpitaux de Paris, INSERM U-1148, French Alliance for Cardiovascular Trials, Paris, France** (Prof P G Steg MD)**; National Heart and Lung Institute, Royal Brompton Hospital, Imperial College London, London, UK** (Prof P G Steg)**; Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland** (D Heg PhD)**; European Cardiovascular Research Institute, Rotterdam, Netherlands** (G A van Es PhD)**; Cork University Hospital, Cork,**

Ireland (E P McFadden MD); **Erasmus Medical Center, Rotterdam, Netherlands** (Y Onuma MD, Prof R J Van Geuns MD, Prof P W Serruys MD); **Cardialysis, Rotterdam, Netherlands** (Y Onuma, C van Meijeren PhD); **Academic Medical Center of Amsterdam, Amsterdam, Netherlands** (P Chichareon MD, Prof P W Serruys); **Imeldaziekenhuis, Bonheiden, Belgium** (L Janssens MD); **UOC Cardiologia, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy** (M Ferrario MD); **American Heart of Poland, Center for Cardiovascular Research and Development, Katowice, Poland** (A Zurakowski MD); **Azienda Ospedaliera S Maria, Terni, Italy** (M Dominici MD); **3rd Department of Medicine, Cardiology and Intensive Care Medicine, Wilhelminenhospital and Sigmund Freud University, Medical Faculty, Vienna, Austria** (Prof K Huber MD); **and Onze Lieve vrouwe Gasthuis, Amsterdam, Netherlands** (T Slagboom MD)

Correspondence to:
Prof Patrick W Serruys, Erasmus Medical Center, Dr Molewaterplein 40, 3015 GD Rotterdam, Netherlands
patrick.w.j.c.serruys@gmail.com
or
Prof Stephan Windecker, Department of Cardiology, Bern University Hospital—Inselspital, 3010 Bern, Switzerland
stephan.windecker@insel.ch

Research in context

Evidence before this study

We searched PubMed and ISI Web of Science with the terms (("All-comer patients" OR, "all-comers") AND "percutaneous coronary intervention") OR ((ticagrelor OR clopidogrel OR antiplatelet OR aspirin) AND "secondary prevention")) for reports published in English before July 1, 2018, of all-comers percutaneous coronary intervention trials and comparative effectiveness studies in which an established antiplatelet strategy was compared with a ticagrelor-based strategy (appendix). We did not find any randomised long-term outcome trials comparing standard dual antiplatelet therapy with an experimental ticagrelor regimen or any other potent P2Y12 receptor antagonist without aspirin in patients after implantation of a drug-eluting stent. We identified four randomised large outcome trials of ticagrelor alone or in combination with aspirin across a wide range of cardiovascular indications, with follow-up ranging from 90 days to 3 years. In PLATO, clopidogrel plus aspirin was compared with ticagrelor plus aspirin in 18 624 patients with acute coronary syndromes, with or without ST-segment elevation. The primary endpoint, 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 (9·8% *vs* 11·7% at 12 months; hazard ratio [HR] 0·84 [95% CI 0·77–0·92]; p<0·001). The overall risk of major bleeding did not differ significantly between groups, but bleeding associated with non-coronary artery bypass grafting was significantly more common in the ticagrelor group than in the clopidogrel group at 12 months (4·5% *vs* 3·8%; p=0·03). In PEGASUS-TIMI 54, two doses of ticagrelor (60 mg and 90 mg) were compared with aspirin in 21 162 high-risk patients (eg, patients with diabetes, renal disease, multivessel disease, or recurrent myocardial infarction) who had a myocardial infarction at least 1 year before the trial. Compared with placebo, both doses of ticagrelor were associated with at least a 15% decrease in the frequency of the primary endpoint of death from cardiovascular causes, myocardial infarction, or stroke (p=0·008 for the 90 mg dose and p=0·004 for the 60 mg dose). However, ticagrelor treatment also increased the frequency of clinically significant bleeding complications by a factor of 2·3–2·7 (p<0·001 for each dose *vs* placebo). In EUCLID, a trial of 13 885 patients with symptomatic peripheral artery disease, ticagrelor monotherapy was not superior to clopidogrel monotherapy for the reduction of cardiovascular events—a composite of cardiovascular death, myocardial infarction, or ischaemic stroke (10·8% *vs* 10·6%; HR 1·02 [95% CI 0·92–1·13]; p=0·65). Major bleeding occurred at a similar frequency in both groups (HR 1·10 [95% CI 0·84–1·43]; p=0·49). In the SOCRATES trial of 13 199 patients with a non-severe ischaemic stroke or high-risk transient ischaemic attack who had not received intravenous or intra-arterial thrombolysis and were not judged to have had a cardioembolic stroke, ticagrelor was not superior to aspirin in reducing the rate of stroke, myocardial infarction, or death at 90 days. Again, the frequency of major bleeding occurred was similar in the two treatment groups (HR 0·83 [95% CI 0·52–1·44]). Other trials investigating an aspirin-free strategy in patients not on oral anticoagulants include GEMINI-ACS-1 and COMPASS, in which aspirin was replaced with a direct factor Xa inhibitor rather than a potent P2Y12 inhibitor.

Added value of this study

To our knowledge, GLOBAL LEADERS is the largest trial so far of 1 month of dual antiplatelet therapy with aspirin and ticagrelor followed by ticagrelor monotherapy versus a standard dual antiplatelet regimen after implantation of a drug-eluting stent. The sole use of ticagrelor, a P2Y12 receptor antagonist, as an antiplatelet regimen rather than aspirin after cessation of dual anti-platelet therapy was a unique aspect of the study. GLOBAL LEADERS is the only randomised trial so far in which randomisation was done at percutaneous coronary intervention and in which two antiplatelet strategies were compared, with up to 2 years of follow-up.

Implications of all the available evidence

Ticagrelor in combination with aspirin for 1 month followed by ticagrelor alone was not superior to 1 year of standard dual antiplatelet therapy followed by aspirin alone in the prevention of all-cause mortality or new Q-wave myocardial infarction at 2 years after percutaneous coronary intervention. The frequency of major bleeding according to the Bleeding Academic Research Consortium criteria was similar between groups. Overall, our data do not support a change to standard clinical practice.

with clopidogrel (both given in combination with aspirin) significantly reduced the rate of major adverse cardiac events and all-cause mortality.[7] It has been suggested by Mahaffey and colleagues[8] that a daily aspirin dose of 150 mg or higher could attenuate the therapeutic effect of ticagrelor. We hypothesised that the use of ticagrelor without concomitant aspirin could preserve ischaemic protection while potentially avoiding bleeding complications.

The GLOBAL LEADERS trial was designed to compare the benefits and risks of 2 years of treatment with 90 mg ticagrelor twice daily (in combination with aspirin for the first month) with 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]

See Online for appendix

Methods

Study design and participants

GLOBAL LEADERS was an open-label, randomised superiority trial done at 130 sites in 18 countries, the design of which was described previously (appendix).[9] The study population consisted of patients scheduled to undergo percutaneous coronary intervention for stable coronary artery disease or acute coronary syndromes

who required dual antiplatelet therapy, unless oral anticoagulation was indicated.[9] The full inclusion and exclusion criteria are in the appendix. The trial was approved by the institutional review board at each participating institution. The study adhered to the ethical principles of the Declaration of Helsinki, to specifications of the International Conference of Harmonisation, and to Good Clinical Practice. All participants provided written informed consent at enrolment. An independent data and safety monitoring committee oversaw the safety of all patients. Our trial protocol is in the appendix.

Randomisation and masking

After diagnostic coronary angiography but before percutaneous coronary intervention, eligible patients were centrally randomised (1:1) to either the experimental treatment or the control treatment. Randomisation was concealed via a locked web-based system from study nurses and physicians enrolling patients. The allocation sequence was computer generated by an external programmer who was not otherwise involved in the trial, stratified by centre and clinical presentation (stable coronary artery disease *vs* acute coronary syndrome), and blocked, with randomly varied block sizes of two and four. GLOBAL LEADERS was an open-label trial.

Procedures

After diagnostic coronary angiography, percutaneous coronary intervention was standardised by uniform implantation of biodegradable polymer-based biolimus A9-eluting stents and bivalirudin administration whenever indicated or feasible. There were no restrictions on the number of treated lesions or vessels, lesion length, or number of stents used. Antiplatelet therapy was started before or at the time of the index procedure. Patients in the experimental treatment group took 75–100 mg aspirin

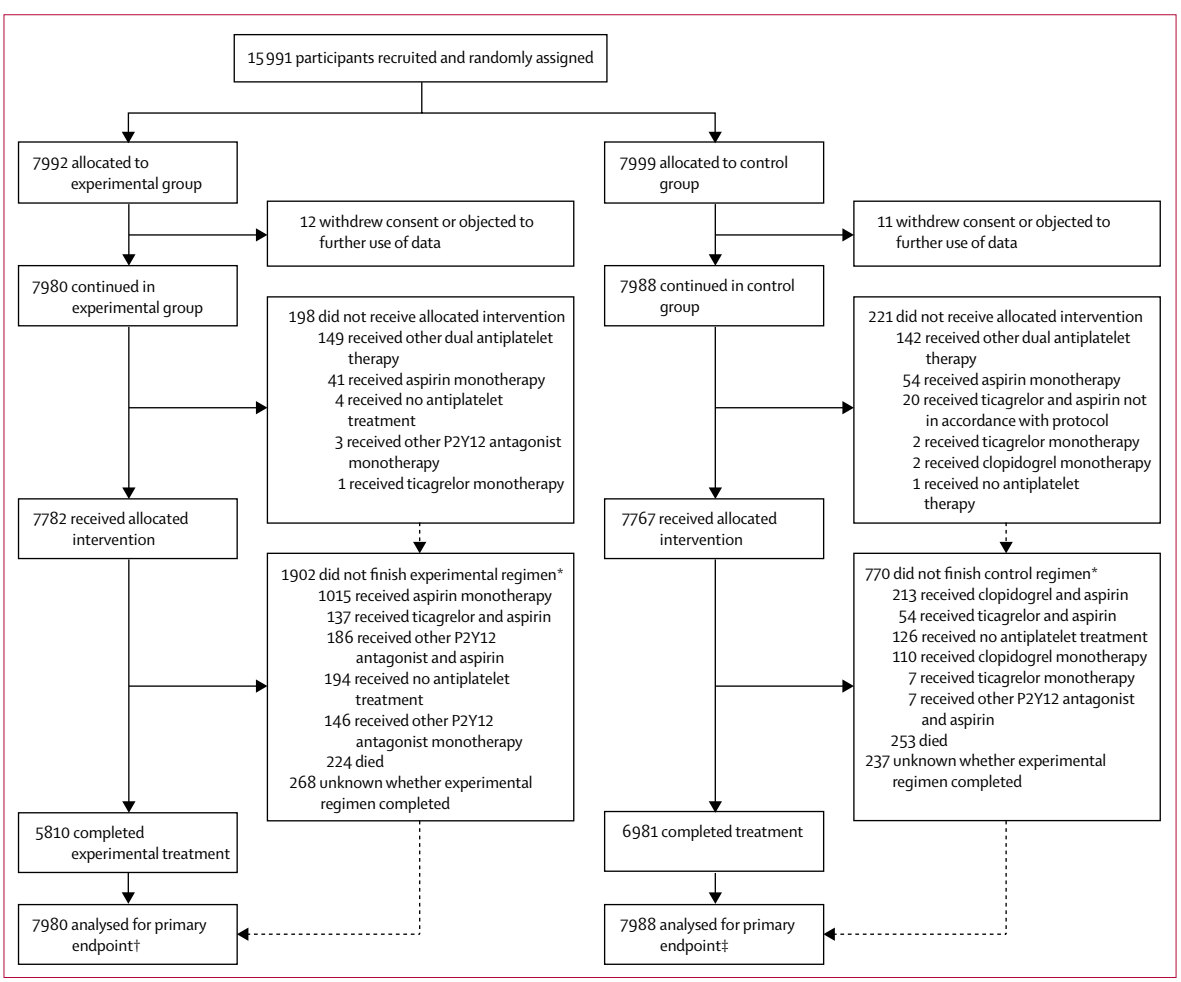

Figure 1: **Trial profile**

In patients with repeat revascularisation, the allocated initial dual antiplatelet regimen could be resumed for 30 days after revascularisation in patients allocated to the experimental treatment group and for 365 days after revascularisation in patients allocated to the control group. *Includes people who did not receive the correct allocated intervention. †Includes five participants for whom vital status information was not available at 2 years (these patients were censored at timepoint of last available follow-up). ‡Includes three participants for whom vital status information was not available at 2 years (these patients were censored at timepoint of last available follow-up).

daily in combination with 90 mg ticagrelor twice daily for 1 month, followed by 90 mg ticagrelor twice daily for 23 months, irrespective of clinical presentation. Patients in the control group received standard treatment: 12 months of dual antiplatelet therapy consisting of 75–100 mg aspirin daily in combination with either 75 mg clopidogrel daily (for patients with stable coronary artery disease) or 90 mg ticagrelor twice daily (for patients with acute coronary syndromes), followed by 75–100 mg aspirin daily for 12 months. Loading doses were given as previously described.[9] Trial medications were dispensed every 3 months 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 and 3, 6, 12, 18, and 24 months after the index procedure. The protocol mandated that a 12-lead electrocardiogram (ECG) was obtained at discharge, 3 months, and 2 years, and intercurrently in the case of revascularisation procedures or suspected ischaemic events. ECG analyses were done in a central core laboratory (Cardialysis, Rotterdam, Netherlands) by staff who were unaware of group assignments. The electronic case report form was revised and implemented on Aug 28, 2013, to enable ascertainment of reasons for non-adherence to the allocated strategy during all visits.

	Experimental intervention group (N=7980)	Control group (N=7988)
Mean age, years (SD)	64·5 (10·3)	64·6 (10·3)
Sex		
Male	6115/7980 (76·6%)	6139/7988 (76·9%)
Female	1865/7980 (23·4%)	1849/7988 (23·1%)
Mean body-mass index, kg/m² (SD)*	28·2 (4·6)	28·2 (4·6)
Medical history		
Diabetes mellitus	2049/7974 (25·7%)	1989/7983 (24·9%)
Insulin-dependent diabetes mellitus	606/7955 (7·6%)	617/7966 (7·7%)
Hypertension	5882/7954 (74·0%)	5833/7960 (73·3%)
Hypercholesterolaemia	5345/7718 (69·3%)	5423/7747 (70·0%)
Current smoker	2066/7980 (25·9%)	2103/7988 (26·3%)
Peripheral vascular disease	476/7904 (6.0%)	529/7918 (6·7%)
Chronic obstructive pulmonary disease	404/7947 (5·1%)	417/7949 (5·2%)
Previous major bleeding	46/7968 (0·6%)	52/7979 (0·7%)
Impaired renal function†	1099/7934 (13·9%)	1072/7949 (13·5%)
Previous stroke	210/7967 (2·6%)	211/7978 (2·6%)
Previous myocardial infarction	1831/7956 (23·0%)	1879/7966 (23·6%)
Previous percutaneous coronary intervention	2609/7974 (32·7%)	2612/7980 (32·7%)
Previous coronary artery bypass grafting	448/7974 (5·6%)	495/7981 (6·2%)
Clinical presentation		
Stable coronary artery disease	4230/7980 (53·0%)	4251/7988 (53·2%)
Acute coronary syndrome		
Overall	3750/7980 (47·0%)	3737/7988 (46·8%)
Unstable angina	1004/7980 (12·6%)	1018/7988 (12·7%)
Non-ST-elevation myocardial infarction	1684/7980 (21·1%)	1689/7988 (21·1%)
ST-elevation myocardial infarction	1062/7980 (13·3%)	1030/7988 (12·9%)

Data are n/N (%), unless otherwise specified. Denominators vary because medical history data were incomplete. *N=7979 in the intervention group and 7987 in the control group. †Defined as an estimated glomerular filtration rate of creatinine clearance of <60 mL/min per 1·73 m² based on the Modification of Diet in Renal Disease formula.[15]

Table 1: **Baseline characteristics of randomly assigned patients**

Outcomes

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 centrally adjudicated and 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 (appendix).[11,12] The key secondary safety endpoint was site-reported bleeding assessed according to the Bleeding Academic Research Consortium (BARC) criteria (grade 3 or 5).[13] Other secondary endpoints included the individual components of the primary endpoint; a composite endpoint of all-cause death, new Q-wave myocardial infarction, or stroke; myocardial infarction; stroke; target vessel or any revascularisation; and definite stent thrombosis.[9] As many as seven on-site monitoring visits were done at individual sites, with 20% of reported events checked against source documents. Additionally, the trial was monitored for event under-reporting and event definition consistency. No independent adjudication of clinical events was implemented. Detailed definitions of the endpoints are in the appendix.

Statistical analysis

The rate of the primary endpoint at 2 years in the control group was assumed to be 5% on the basis of the results of the LEADERS trial.[14] The PLATO trial showed a significant reduction in all-cause mortality with ticagrelor compared with clopidogrel (4·5% *vs* 5·9%; hazard ratio 0·78 [95% CI 0·69–0·89]; p<0·001).[7] We anticipated that the difference in our trial could be similar or even larger because of the potential interaction of aspirin and ticagrelor, and used a 20% relative risk reduction as a conservative and clinically relevant margin.[8] We estimated that a sample size of 8000 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 by intention to treat with the Mantel-Cox method based on time to occurrence of death or diagnosis of new Q-wave myocardial infarction, and was reported as rate ratios with 95% CIs. Prespecified landmark analyses with cutoffs at 30 days (corresponding to the planned date 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 rate ratios calculated separately for events up to and beyond the landmarks. We did 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 *vs* clopidogrel) as a post-hoc criterion. We then did post-hoc subgroup analyses on the same characteristics for the key secondary safety endpoint of BARC grade 3 or 5 events. Secondary efficacy endpoints were analysed by intention to treat with the Mantel-Cox log-rank method up to the timepoint when the first event occurred (time-to-first-event analyses). Any subsequent events of the same type in the same patient were disregarded.

Categorical variables were compared with the χ^2 test or Fisher's exact test. Continuous variables were compared with Student's *t* test or the Wilcoxon rank-sum test for non-normally distributed data. Lesion data were analysed with mixed models accounting for lesions nested within patients. All statistical analyses were done in Stata (version 14.2). The trial is registered with ClinicalTrials.gov, number NCT01813435.

Role of the funding source

The study funders had no role in trial design; data collection, analysis, or interpretion; or writing of the report. PV, MV, PJ, PWS, and SW had full access to all study data and had final responsibility for the decision to submit for publication.

Results

Between July 1, 2013, and Nov 9, 2015, we recruited and randomly assigned 15 991 participants, but 23 patients subsequently withdrew consent and requested deletion of their data from the database. Thus, 15 968 patients remained, 7980 in the experimental group and 7988 in the control group (figure 1). 7782 patients (97·5%) in the experimental group and 7767 (97·2%) in the control group received the allocated treatment regimen. Baseline clinical and procedural characteristics were well matched between groups (tables 1, 2). Overall 7487 (46·8%) of patients had acute coronary syndromes (table 1). Mean age was 64·5 years (SD 10·3), and 3714 (23·3%) patients were female (table 1). Bivalirudin-assisted percutaneous coronary intervention was done in 6944 (87·4%) of 7943 patients in the experimental treatment group and 6926 (87·2%) of 7940 patients in the control group. Biolimus A9-eluting stents were used in 19 415 (94·6%) of 20 524 lesions, and staged procedures were done in 1455 patients (9·1%). At 2-year follow-up, vital status information was available for 7975 patients in the experimental group and 7985 patients in the control group (99·9% overall). ECGs were analysable in 14 857 (93·7%) of 15 856 patients alive at 3 months and in 14 357 (92·7%) of 15 491 patients alive at 24 months (appendix).

Adherence to the allocated antiplatelet treatment at discharge, 30 days, and 3, 6, 12, 18, and 24 months is shown in the appendix. In the first year of our trial, 1378 (18%) of 7550 participants in the experimental group and 575 (15%) of the 3890 participants in the control group who had an acute coronary syndrome at baseline and were treated with ticagrelor did not adhere to tiacagrelor. At 2 years, 5810 (77·6%) of 7488 patients in the experimental group and 6981 (93·1%) of 7498 patients

	Experimental intervention group (N=7980)	Control group (N=7988)
Percutaneous coronary intervention done*	7943 (99·5%)	7940 (99·4%)
Vascular access site†		
n	7943	7940
Radial	5872 (73·9%)	5889 (74·2%)
Femoral	2090 (26·3%)	2072 (26·1%)
Brachial	46 (0·6%)	47 (0·6%)
Lesions treated per patient		
n	7907	7911
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%)
Treated lesions‡		
n (lesions)	10 403	10 438
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%)
Stented lesions		
Index percutaneous coronary intervention		
n (stented lesions)	10 241	10 283
Mean stents per lesion (SD)‡	1·2 (0·5)	1·2 (0·5)
Biolimus A9-eluting stent¶	9708 (94·8%)	9707 (94·4%)
Other stent	654 (6·4%)	685 (6·7%)
Mean total stent length per lesion, mm (SD)‡	24·8 (13·9)	24·8 (14·0)
Mean stent diameter per lesion, mm (SD)†	3·0 (0·5)	3·0 (0·5)
Direct stenting per lesion‡	3334 (32·6%)	3350 (32·6%)
Bifurcation per lesion‡	1251/10 403 (12·0%)	1265/10 438 (12·1%)
Thrombus aspiration done per lesion†	483/10 403 (4·6%)	551/10 438 (5·3%)
TIMI flow‡		
Pre-procedure		
n	9837	9888
0 or 1	1296 (13·2%)	1314 (13·3%)
2	1187 (12·1%)	1173 (11·9%)
3	7354 (74·8%)	7401 (74·8%)
Post-procedure		
n	10 064	10 145
0 or 1	41 (0·4%)	32 (0·3%)
2	50 (0·5%)	46 (0·5%)
3	9973 (99·1%)	10 067 (99·2%)

Data are n (%) or n/N (%), unless otherwise specified. TIMI=thrombolysis in myocardial infarction.[16] *85 patients did not undergo percutaneous coronary intervention: 64 received medical treatment only (31 in the experimental group and 33 in the control group) and 21 underwent urgent surgery (six in the experimental group and 15 in the control group). †More than one access site possible. ‡Calculated per lesion and analysed with general or generalised linear mixed-effects models with a random effect for patients to account for multiple lesions treated within patients. §Grafts counted as one separate vessel (n=221). ¶Per-protocol biolimus A9-eluting stent used; for 147 lesions (79 in the experimental group and 68 in the control group), both biolimus A9-eluting and other stents were implanted.

Table 2: **Baseline angiographic characteristics of randomly assigned patients**

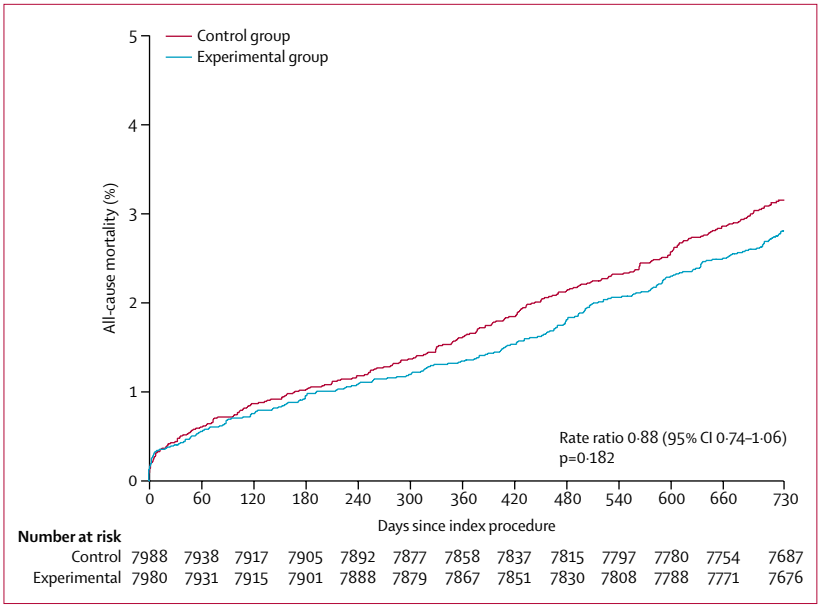

Figure 2: **Cumulative incidence of all-cause mortality at 2 years**

in the reference group adhered to the protocol-mandated antiplatelet treatment strategy. Data for 8545 consecutive patients who underwent the 30-day follow-up visit after the protocol amendment were used in the analysis of non-adherence. Reasons for non-adherence at 30 days, 12 months, and 24 months are in the appendix. At all three timepoints, dyspnoea was a significantly more common reason for non-adherence in the experimental group than in the control group (p≤0·005; appendix).

At 2-year follow-up, a primary endpoint event—ie, all-cause mortality or new Q-wave myocardial infarction—had occurred in 304 (3·81%) participants in the experimental group and 349 (4·37%) in the control group (rate ratio 0·87 [95% CI 0·75–1·01]; p=0·073; figure 2; table 3). Subclassification of new Q-wave myocardial infarctions according to the Minnesota code is in the appendix. The frequency of all-cause mortality, new Q-wave myocardial infarction, definite stent thrombosis, or investigator-reported BARC grade 3 or 5 events did not differ significantly between groups (table 3). Additional data for bleeding endpoints are in the appendix. The composite of all-cause death, new Q-wave myocardial infarction, or stroke occurred in 362 (4·54%) participants in the experimental group and 416 (5·21%) in the control group (rate ratio 0·87 [95% CI 0·76–1·00]; p=0·056; table 3). Dyspnoea was more common among patients who ever received ticagrelor (1642 [13·8%] first episodes among 11 936 patients ever on ticagrelor) than among patients who ever received clopidogrel or other P2Y12-receptor antagonists (360 [6·5%] first episodes among 5578 patients; p<0·0001).

Subgroup analyses showed no variation in treatment effects for the primary endpoint by prespecified baseline characteristics, or by type of reference treatment (use of ticagrelor *vs* clopidogrel) as a post-hoc criterion (figure 3). Exploratory post-hoc subgroup analyses of BARC grade 3 or 5 events are in the appendix. A treatment-by-subgroup interaction was noted for type of indication (acute coronary syndromes *vs* stable coronary artery disease; $p_{interaction}$=0·0068), which seemed to be partly accounted for by a treatment-by-subgroup interaction for type of reference treatment ($p_{interaction}$=0·016), with an advantage for 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 in the appendix. The primary endpoint occurred in 270 patients (3·40%) in the experimental group and 307 patients (3·87%) in the control group between 30 days and 2 years (rate ratio 0·88 [95% CI 0·74–1·03]; p=0·115). Rates of mortality, myocardial infarction, definite stent thrombosis, and BARC grade 3 or 5 events were similar in both groups from 30 days onwards (appendix). Beyond 1 year, deaths from any cause were observed in 116 (1·48%) participants in the experimental group and 122 (1·56%) in the control group (rate ratio 0·95 [95% CI 0·74–1·22]; p=0·913; appendix). The appendix includes data for post-hoc composite outcomes, including net clinical benefit.

Discussion

In our multicentre randomised trial, ticagrelor in combination with aspirin for 1 month followed by ticagrelor alone for 23 months was not superior to standard 1-year dual antiplatelet therapy followed by aspirin monotherapy in terms of the composite endpoint of all-cause mortality or new Q-wave myocardial infarction after percutaneous coronary intervention. When the components of the primary endpoint were individually analysed, they did not differ significantly between groups. Rates of definite or probable stent thrombosis and major bleeding according to BARC criteria were similar between the groups. Rates of major bleeding were similar to those reported for the PRODIGY allcomers percutaneous coronary intervention trial.[17]

Although our study was not designed to assess the non-inferiority of the experimental treatment strategy compared with the current standard of care, the upper boundary of the 95% CI of the primary endpoint was close to unity, suggesting no relevant safety signal of the experimental strategy. In post-hoc subgroup analyses of bleeding events, we noted some evidence for a treatment-by-subgroup interaction for type of indication, which seemed to be partly explained by an interaction with type of reference treatment, with an advantage for the experimental strategy in patients with acute coronary syndrome 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 so far testing 1 month of dual antiplatelet therapy versus a more prolonged dual antiplatelet regimen after implantation of a drug-eluting stent. It had a unique design, in that it mandated monotherapy with ticagrelor, a P2Y12 receptor antagonist, as an antiplatelet regimen and not aspirin alone after cessation of dual antiplatelet therapy. Thus, our results cannot be extrapolated to patients receiving 1 month of dual antiplatelet therapy followed by aspirin monotherapy. The duration of dual antiplatelet therapy in the control group was based on professional guidelines at the time of study design. We recognise that a shorter duration of dual antiplatelet therapy of 6 months is recommended in the 2017 European Society of Cardiology guidelines for patients with stable coronary artery disease undergoing elective percutaneous coronary intervention, although an extension of treatment for another 6 months remains an option in the absence of bleeding complications.[18]

Several studies have shown that prolonged dual antiplatelet therapy is associated with a trade-off between ischaemic and bleeding risks.[1–3,5,19,20] In the dual antiplatelet therapy study,[1] prolongation of 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 increased.[1] There was an interaction between stent type and major adverse cardiovascular events, suggesting limited incremental benefit of extended dual antiplatelet therapy in patients receiving new-generation drug-eluting stents.[1] In our protocol, we mandated the uniform use of biolimus A9-eluting stent platform, which is as safe and efficacious as newer generation durable polymer drug-eluting stents.[21] The use of a uniform stent avoids difficulties in interpretation resulting from differences in treatment effects with different stents, but retains generalisability in view of the similar performance of our stent to that of the best new-generation drug-eluting stents.[22]

In the PEGASUS trial,[2] in patients with a history of myocardial infarction at least 1 year before randomisation and at least one additional high-risk feature, 60 mg or 90 mg ticagrelor twice daily significantly reduced the risk of the composite endpoint of cardiovascular death, myocardial infarction, or stroke (p=0·004 and p=0·008, respectively) but increased the risk of major bleeding (p<0·001 for both doses) compared with placebo. In an attempt to improve the risk–benefit ratio of ticagrelor, we 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 compared with standard therapy. However, it provided reassuring information with respect to the safety and efficacy of ticagrelor monotherapy. The clinical risk profile of patients included in GLOBAL LEADERS was lower than that of patients included in PEGASUS. A PEGASUS-like patient population is under investigation in the TWILIGHT trial[23] of ticagrelor with aspirin or alone in high-risk patients after coronary intervention.

	Experimental treatment group (N=7980)	Control group (N=7988)	Rate ratio (95% CI)	p value
All-cause mortality or new Q-wave myocardial infarction	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)	0·182
New Q-wave myocardial infarction*	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				
Overall	80 (1·00%)	82 (1·03%)	0·98 (0·72–1·33)	0·90
Ischaemic	63 (0·79%)	68 (0·85%)	0·93 (0·66–1·31)	0·68
Haemorrhagic	13 (0·16%)	9 (0·11%)	1·45 (0·62–3·39)	0·39
Undetermined	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 revascularisation	389 (4·87%)	442 (5·54%)	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				
BARC 3 or 5 bleeding	163 (2·04%)	169 (2·12%)	0·97 (0·78–1·20)	0·77
BARC 5 bleeding				
Any	22 (0·28%)	24 (0·30%)	0·92 (0·52–1·64)	0·78
5b bleeding	15 (0·19%)	18 (0·23%)	0·84 (0·42–1·66)	0·61
5a bleeding	7 (0·09%)	6 (0·08%)	1·17 (0·39–3·49)	0·78
BARC 3 bleeding				
Any	150 (1·88%)	159 (1·99%)	0·95 (0·76–1·18)	0·63
3c bleeding	35 (0·44%)	25 (0·31%)	1·41 (0·84–2·35)	0·19
3b bleeding	53 (0·66%)	74 (0·93%)	0·72 (0·51–1·02)	0·065
3a bleeding	77 (0·96%)	70 (0·88%)	1·10 (0·80–1·53)	0·55

Shown are the first event per event type for each patient only. Multiple events of the same type within the same patient are disregarded. Data were censored 730 days after index percutaneous coronary intervention. BARC=Bleeding Academic Research Consortium.[13] *New Q-wave or equivalent left bundle branch block (n=3) as adjudicated by the core laboratory.

Table 3: **Primary and prespecified secondary outcomes**

Although the rate of serious adverse events did not differ significantly between the two groups, discontinuation of the treatment regimen was more common in the experimental group than in the control group. The rate of discontinuation of the experimental regimen in our trial compared favourably to those reported in other large outcome trials testing ticagrelor for various indications.[2,7,24,25] In the first year of our trial, non-adherence to ticagrelor was noted in 1953 (17%) of 11 440 patients, compared with 2186 (23%) of 9333 patients in the PLATO trial.[7] The observed differences in rates of regimen interruption between the experimental and reference treatment groups after the first year could 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. Additionally, we cannot exclude that pleiotropic effects

	Experimental treatment group	Control group	Rate ratio (95% CI)	p value	$p_{interaction}$
Indication					
Acute coronary syndrome	147/3750	169/3737	0·86 (0·69–1·08)	0·19	0·93
Stable coronary artery disease	157/4230	180/4251	0·87 (0·71–1·08)	0·22	
Age					
>75 years	93/1292	120/1273	0·75 (0·58–0·99)	0·041	0·23
≤75 years	211/6688	229/6715	0·92 (0·77–1·11)	0·40	
Diabetes mellitus					
Yes	102/2049	126/1989	0·78 (0·60–1·01)	0·063	0·33
No	202/5925	222/5994	0·92 (0·76–1·11)	0·38	
Renal failure					
Yes	79/1099	93/1072	0·82 (0·61–1·11)	0·19	0·68
No	225/6881	256/6916	0·88 (0·74–1·05)	0·17	
Peripheral vascular disease					
Yes	40/476	44/529	1·02 (0·66–1·56)	0·94	0·52
No	260/7428	295/7389	0·87 (0·74–1·03)	0·11	
Left main treated					
Yes	13/197	14/190	0·89 (0·42–1·90)	0·76	0·95
No	291/7783	335/7798	0·87 (0·74–1·02)	0·076	
Region					
Western Europe	226/6156	273/6167	0·83 (0·69–0·99)	0·033	0·49
Eastern Europe	68/1502	65/1500	1·04 (0·74–1·47)	0·81	
Rest of the world	10/322	11/321	0·91 (0·38–2·14)	0·82	
Type of reference treatment strategy					
Use of ticagrelor	163/4179	186/4146	0·86 (0·70–1·07)	0·18	0·95
Use of clopidogrel	141/3801	163/3842	0·87 (0·70–1·09)	0·24	
Overall	**304/7980**	**349/7988**	**0·87 (0·75–1·01)**	**0·073**	

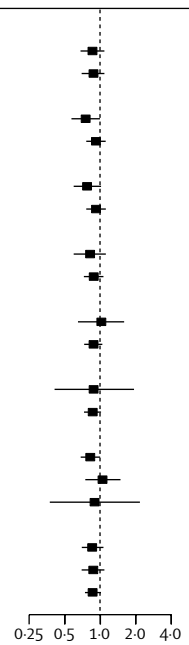

Figure 3: **Subgroup analyses of all-cause mortality or non-fatal centrally adjudicated new Q-wave myocardial infarction at 2 years**
Type of reference treatment strategy was a post-hoc criterion for subgroup analysis. Rate ratios and 95% CIs were estimated with the Mantel-Cox method with two-sided p-values from the log-rank test. All events were censored beyond 730 days. $p_{interaction}$ values were calculated with approximate χ^2 tests for unequal rate ratios in the subgroups. Assumed no risk in case of missing data: diabetes (n=11), renal failure (n=85), peripheral vascular disease (n=146).

of aspirin other than the antiplatelet effect could be beneficial and could have affected the outcome of our trial.[4]

Our trial has several limitations. GLOBAL LEADERS was an open-label trial, and thus participants and investigators were not masked to the components of the treatment strategy. Efforts that were made to minimise biases included a focus on major, objective outcomes (ie, all-cause death and centrally adjudicated Q-wave myocardial infarction diagnosed by blinded staff at a core lab). 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 ECG, scrutinised by staff at 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 186 (37%) of the 498 site-reported myocardial infarctions in the trial (table 3). The proportion of 3-month and 2-year ECGs 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 under-reporting and consistency of event definitions. The rate of all-cause mortality and the composite primary endpoint at 2 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 our study, clopidogrel was given only to patients with stable coronary artery disease with planned elective percutaneous coronary intervention.[14,23] The lower rates for all-cause mortality in the control group could reflect the treatment benefit noted for ticagrelor compared with clopidogrel in patients with a planned invasive strategy in the PLATO trial.[29] 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 approaches.

In conclusion, the results of the GLOBAL LEADERS trial do not support a change to practice at this time. Several trials of shortened regimens of dual antiplatelet therapy after stenting are underway (eg, NCT03023020, NCT03355742, NCT03344653, NCT03462498). In some of these trials, simple, validated risk scores (eg, the PRECISE-DAPT score[20] used in Master DAPT [NCT03023020]) have been implemented to reduce the risk of bleeding and establish the optimal intensity and duration of antiplatelet therapy.

Contributors

PV, MV, PWS, and SW designed the study, gathered and interpreted data, wrote the first draft of the Article, and contributed to all revisions. PJ designed the study, analysed and interpreted data, wrote the first draft of the Article, and contributed to all revisions. CH and PGS gathered and interpreted data, wrote the first draft of the Article, and contributed to all revisions. DH analysed data and contributed to revision of the Article. GAvE designed the study and gathered data. EPM, YO, CvM, and PC gathered and cleaned data. EB, HM, LJ, MF, AM, AZ, MD, RJVG, KH, and TS gathered data and contributed to revision of the Article.

Declaration of interests

PV has received personal fees from AstraZeneca and the Medicines Company during the conduct of the study and personal fees from Bayer Health Care, Terumo, and Daiichi-Sankyo outside the submitted work. MV has received personal fees from Abbott, AstraZeneca, Chiesi, Bayer, Daiichi Sankyo, Terumo, Alvi Medical, and Amgen, and grants from the Swiss National Foundation, Terumo, Medicure, Abbott, and AstraZeneca, outside the submitted work. PJ's institution has received research grants from AstraZeneca, Biotronik, Biosensors International, Eli Lilly, and the Medicines Company, outside the submitted work. PJ has served as an unpaid member of the steering group of trials funded by AstraZeneca, Biotronik, Biosensors, St Jude Medical, and the Medicines Company. CH has received personal fees from AstraZeneca outside the submitted work. PGS has received research grants from Bayer/Janssen, grants and personal fees from Merck, Sanofi, and Amarin, personal fees from Amgen, Bristol-Myers Squibb, Boehringer Ingelheim, Pfizer, Novartis, Regeneron, Lilly, and AstraZeneca, and grants, personal fees, and non-financial support from Servier, all outside the submitted work. DH is affiliated with Clinical Trials Unit Bern at the University of Bern, which has a staff policy of not accepting honoraria or consultancy fees. However, it is involved in the design, conduct, or analysis of clinical studies funded by not-for-profit and for-profit organisations, including pharmaceutical and medical device companies. An up-to-date list of Clinical Trials Unit Bern's conflicts of interest is available online. EPM has received personal fees from the European Clinical Research Institute during the conduct of the study, grants from AstraZeneca, personal fees from Abbott Vascular and Daiichi Sankyo, non-financial support from Menarini Ireland, and grants from Bayer and Terumo outside the submitted work. YO has received consultancy fees from Abbott Vascular. HM has received personal fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, and Pfizer. RJVG has received grants and personal fees from Abbott Vascular, grants from Boston Scientific outside the submitted work. KH has received personal fees from AstraZeneca, Sanofi Aventis, and Biosensors outside the submitted work. PWS has received personal fees from Abbot Laboratories, AstraZeneca, Biotronik, Cardialysis, GLG Research, Medtronic, Sino Medical Sciences Technology, Société Europa Digital Publishing, Stentys France, Svelte Medical Systems, Philips/Volcano, St Jude Medical, Qualimed, and Xeltis, outside the submitted work. SW's institution has research contracts with Abbott, Amgen, Bayer, Biotronik, Boston Scientific, Edwards Lifesciences, Medtronic, St Jude Medical, Symetis SA, and Terumo outside the submitted work. All other authors declare no competing interests.

Data sharing

GLOBAL LEADERS trial is an investigator-initiated trial. Multiple substudies are predefined. Internal investigators, who actively participated in the study, and who provide a methodologically sound study proposal will be granted priority access to the study data for 60 months. After 60 months, this option might 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 can be filed at global.leaders@cardialyis.nl.

Acknowledgments

GLOBAL LEADERS was sponsored by the European Clinical Research Institute, which received funding from Biosensors International, AstraZeneca, and the Medicines Company. PJ 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.

References

1 Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014; **371:** 2155–66.
2 Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015; **372:** 1791–800.
3 Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018; **39:** 213–60.
4 Capodanno D, Mehran R, Valgimigli M, et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. *Nat Rev Cardiol* 2018; **15:** 480–96.
5 Valgimigli M, Campo G, Monti M, et al. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. *Circulation* 2012; **125:** 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:** 1881–906.
7 Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; **361:** 1045–57.
8 Mahaffey KW, Wojdyla DM, Carroll K, et al. Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation* 2011; **124:** 544–54.
9 Vranckx P, Valgimigli M, Windecker S, et al. Long-term ticagrelor monotherapy versus standard dual antiplatelet therapy followed by aspirin monotherapy in patients undergoing biolimus-eluting stent implantation: rationale and design of the GLOBAL LEADERS trial. *EuroIntervention* 2016; **12:** 1239–45.
10 Hicks KA, Mahaffey KW, Mehran R, et al. 2017 cardiovascular and stroke endpoint definitions for clinical trials. *J Am Coll Cardiol* 2018; **71:** 1021–34.
11 Prineas RJ, Crow RS, Blackburn H. The Minnesota code manual of electrocardiographic findings. Littleton, MA: John Wright, 1982.
12 Prineas RJ, Crow RS, Zhang Z-M. The Minnesota code manual of electrocardiographic findings. London: Springer Science & Business Media, 2009.
13 Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011; **123:** 2736–47.
14 Klauss V, Serruys PW, Pilgrim 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 Cardiovasc Interv* 2011; **4:** 887–95.
15 Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function—measured and estimated glomerular filtration rate. *N Engl J Med* 2006; **354:** 2473–83.
16 TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. *N Engl J Med* 1985; **312:** 932–36.
17 Vranckx P, Leonardi S, Tebaldi M, et al. Prospective validation of the Bleeding Academic Research Consortium classification in the all-comer PRODIGY trial. *Eur Heart J* 2014; **35:** 2524–29.
18 Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018; **39:** 213–60.
19 Navarese EP, Andreotti F, Schulze V, et al. Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials. *BMJ* 2015; **350:** h1618.
20 Costa F, van Klaveren D, James S, 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* 2017; **389:** 1025–34.

For **Clinical Trials Unit Bern's conflicts of interest** see http://www.ctu.unibe.ch/research/declaration_of_interest/index_eng.html

21 Navarese EP, Tandjung K, Claessen B, 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* 2013; **347:** f6530.

22 El-Hayek G, Bangalore S, Casso Dominguez A, et al. Meta-analysis of randomized clinical trials comparing biodegradable polymer drug-eluting stent to second-generation durable polymer drug-eluting stents. *JACC Cardiovasc Interv* 2017; **10:** 462–73.

23 Baber U, Dangas G, Cohen DJ, 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; **182:** 125–34.

24 Hiatt WR, Fowkes FG, Heizer G, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med* 2017; **376:** 32–40.

25 Johnston SC, Amarenco P, Albers GW, et al. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. *N Engl J Med* 2016; **375:** 35–43.

26 Qureshi WT, Zhang ZM, Chang PP, et al. Silent myocardial infarction and long-term risk of heart failure: the ARIC study. *J Am Coll Cardiol* 2018; **71:** 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:** 642–47.

28 Zhang ZM, Rautaharju PM, Prineas RJ, 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:** 2141–48.

29 Cannon CP, Harrington RA, James S, 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* 2010; **375:** 283–93.