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FASTTRACK CLINICAL RESEARCH
AHA

Randomized trial of ticagrelor vs. aspirin in patients after coronary artery bypass grafting: the TiCAB trial

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Aims The antiplatelet treatment strategy providing optimal balance between thrombotic and bleeding risks in patients undergoing coronary artery bypass grafting (CABG) is unclear. We prospectively compared the efficacy of ticagrelor and aspirin after CABG.

Methods and results We randomly assigned in double-blind fashion patients scheduled for CABG to either ticagrelor 90 mg twice daily or 100 mg aspirin (1:1) once daily. The primary outcome was the composite of cardiovascular death, myocardial infarction (MI), repeat revascularization, and stroke 12 months after CABG. The main safety endpoint was based on the Bleeding Academic Research Consortium classification, defined as BARC ≥4 for periprocedural and hospital stay-related bleedings and BARC ≥3 for post-discharge bleedings. The study was prematurely halted after recruitment of 1859 out of 3850 planned patients. Twelve months after CABG, the primary endpoint occurred in 86 out of 931 patients (9.7%) in the ticagrelor group and in 73 out of 928 patients (8.2%) in the aspirin group [hazard ratio 1.19; 95% confidence interval (CI) 0.87–1.62; $P = 0.28$]. All-cause mortality (ticagrelor 2.5% vs. aspirin 2.6%, hazard ratio 0.96, CI 0.53–1.72; $P = 0.89$),

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cardiovascular death (ticagrelor 1.2% vs. aspirin 1.4%, hazard ratio 0.85, CI 0.38–1.89; $P = 0.68$), MI (ticagrelor 2.1% vs. aspirin 3.4%, hazard ratio 0.63, CI 0.36–1.12, $P = 0.12$), and stroke (ticagrelor 3.1% vs. 2.6%, hazard ratio 1.21, CI 0.70–2.08; $P = 0.49$), showed no significant difference between the ticagrelor and aspirin group. The main safety endpoint was also not significantly different (ticagrelor 3.7% vs. aspirin 3.2%, hazard ratio 1.17, CI 0.71–1.92; $P = 0.53$).

Conclusion In this prematurely terminated and thus underpowered randomized trial of ticagrelor vs. aspirin in patients after CABG no significant differences in major cardiovascular events or major bleeding could be demonstrated.

ClinicalTrials.gov Identifier NCT01755520.

Keywords Coronary artery bypass surgery • Antiplatelet therapy • Ticagrelor • Aspirin

Key points

Question Is platelet inhibition with ticagrelor better than aspirin in preventing major cardiovascular events in the 1st 12 months following coronary artery bypass grafting?

Findings This randomized (1:1) clinical trial was prematurely halted after inclusion of 1859 patients following the advice of the data safety monitoring board. There was no indication that ticagrelor might be better than aspirin.

Meaning These results demonstrate that monotherapy with aspirin remains to be the primary choice for platelet inhibition after coronary artery bypass grafting.

Introduction

It is recommended that patients undergoing coronary artery bypass grafting (CABG) receive aspirin shortly after surgery for secondary prevention of cardiovascular events.[1–4] Despite this measure, clinically relevant complications are reported in more than 10% of patients in the 1st year after CABG.[5–7] Early graft failure, which is predominantly mediated by platelet aggregation, has been identified as a relevant contributing factor in this context.[8,9]

In some patients, the response to aspirin may be attenuated shortly after CABG.[8,10] Interestingly, in CABG patients with graft thrombosis, platelets were found to be more resistant to aspirin as compared to platelets from patients without this complication.[11] Therefore, intensified platelet inhibition may be beneficial for the prevention of ischaemic events in patients after CABG, as long as such treatment does not increase the risk of major bleeding. Guiding to individualized therapy the work of Patrono *et al.*[12] gave comprehensive overview on different antiplatelet strategies evaluating efficacy and safety.

Ticagrelor, an oral, reversibly binding and direct-acting $P2Y_{12}$ receptor antagonist may be an alternative to aspirin as it provides robust and consistent platelet inhibition.[13] Ticagrelor does not require metabolic activation and displays rapid onset of antiplatelet effects even when given to acutely compromised patients,[13–15] e.g. those recovering from major surgery.

Some of the limitations of antiplatelet monotherapy might be overcome by dual antiplatelet therapy (DAPT) after CABG surgery.[1–4] Specifically, the efficacy and safety of adding clopidogrel, a $P2Y_{12}$ receptor antagonist, to aspirin has been tested in this setting in a number of trials.[16–19] However, results of these studies were inconclusive and risk of bleeding was potentially increased.[16–19]

While the majority of CABG patients is treated for stable coronary artery disease ~10–30% present with an acute coronary syndrome (ACS).[20] ACS patients undergoing percutaneous revascularization (PCI) experienced a benefit when treated with DAPT.[21,22] Current guidelines, published after the Ticagrelor in CABG (TiCAB) trial was started, extrapolated these data and now recommend DAPT not only in PCI but likewise in CABG-treated ACS patients.[2,23,24] It is noteworthy, however, that specific and sufficiently large randomized trials with DAPT in CABG patients presenting with ACS are still lacking, which is acknowledged by a level of evidence C (expert consensus) in the most recent document of the Task Force of European Society of Cardiology and European Association for Cardio-Thoracic Surgery.[2,25] Indeed, many cardiovascular surgeons are hesitant in prescribing DAPT to their ACS-CABG patients because of potential bleeding risks.[26]

Data on ticagrelor treatment after CABG are limited. A post-randomization analysis of the *Platelet Inhibition and Patient Outcomes* (PLATO) trial revealed in ACS patients benefits of ticagrelor compared to clopidogrel, as part of a DAPT strategy together with aspirin.[7,27] Specifically, the ticagrelor treated subgroup showed a reduction of total mortality and cardiovascular death by approximately 50%.[7] Moreover, a smaller trial in CABG patients (DACAB) revealed a tendency towards higher graft patency rates with ticagrelor plus aspirin as compared with aspirin monotherapy.[28]

The *TiCAB trial* was designed to test the hypothesis that ticagrelor-monotherapy, as compared to aspirin monotherapy, will result in a lower incidence of cardiovascular events in patients undergoing CABG.[29] We expected in this all-comers study ~25% of participants to present with an ACS.[29]

Methods

The protocol details of this investigator-initiated randomized, double-blind, parallel grouped, and placebo-controlled phase III trial (ClinicalTrials.gov Identifier NCT01755520) have been published before.[29] The protocol is also available in the Supplementary material online, *Appendix*. The trial was sponsored by the Deutsches Herzzentrum München, Munich, Germany. Financial support was provided by AstraZeneca (Mölndal, Sweden). Other than supplying financial support, AstraZeneca was not involved in the study design, study processes,

including site selection and management, or data collection and analysis. The protocol was approved by an independent ethics committee at each participating site and was conducted in accordance with the provisions of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. All patients provided written informed consent.

The trial had a slower than planned recruitment rate. Prior to the protocol amendment, which allowed post-surgical initiation of study medication, 14 patients were recruited per month, after modification of the protocol 54 patients were recruited per month. The anticipated recruitment rate was at 90 patients per month, such that the manufacturer of ticagrelor withdrew the funding in 2016. Recruitment was continued under in-house funding until 2017 and follow-up of all included patients was completed until April 2018. *Per protocol*, review of clinical data by the Data Safety Monitoring Board (DSMB, names and positions are listed in the Supplementary material online, *Appendix*) was planned when approximately half of the intended patient number had complete 1-year follow-up, which was scheduled in March 2018. The recommendations of the DSMB are detailed in the Result section. With the exception of the DSMB, all investigators, the sponsor (Deutsches Herzzentrum München), and AstraZenca remained blinded for the distribution of study medication until closure of the data bank in September 2018. A total number of 1893 patients were randomized and 1859 were available for the final analysis.

The data were collected and held in a blinded fashion at an external site (Institut für Herzinfarktforschung in Ludwigshafen, Germany). An independent, Endpoint Adjudication Committee, whose members were unaware of the trial-group assignments, determined whether investigator-reported events met the endpoint definition with the use of predefined criteria. The database was closed on 20 September 2018 and the data were transferred to and analysed at the ISAResearch Center at the sponsor's institution. The authors are solely responsible for the design and conduct of all analyses and drafting of the manuscript. All authors participated in the interpretation of the data.

Patients and study design

The study population consisted of patients aged 18 years or older with an ACS or stable coronary artery disease [including three-vessel coronary disease or left main stenosis or two-vessel disease with impaired left ventricular function (<50%)] who were scheduled for CABG. About 25% of patients were expected to present with an ACS as outlined in the power calculation within the study protocol. Major exclusion criteria were cardiogenic shock, indication for continued oral anticoagulation or DAPT at the time of randomization, need for concomitant non-coronary surgery (e.g. valve replacement) or reasons precluding the use of aspirin or ticagrelor. For details see the study protocol in the Supplementary material online, *Appendix* or the TiCAB methods paper.[29] Patients who developed atrial fibrillation after CABG were recommended to receive oral anticoagulation in addition to study medication.

The primary efficacy endpoint of the study was a composite of cardiovascular death, myocardial infarction (MI), stroke, and repeat revascularization 12 months after CABG. Secondary endpoints contain the individual components of the primary endpoint as well as all-cause death and major bleeding events. Definitions of the individual endpoint components are provided in Supplementary material online, *Appendix B*.

Procedures

An interactive Web-response system was used for randomization stratified according to the clinical presentation with ACS or stable coronary artery disease. Within the 1st 24 h after surgery, but ideally within 6 h, patients received either aspirin 100 mg and placebo ticagrelor or placebo aspirin and ticagrelor 90 mg. The maintenance doses, aspirin 100 mg once daily or ticagrelor 90 mg twice daily, were recommended for 12 months. The placebo-controlled, double dummy design precluded the identification of study medication.

Patients were evaluated at 3, 6, 9, and 12 months after randomization. Compliance was assessed and defined as regular intake of study medication for more than 80% of days between visits. Follow-ups at 3 and 12 months were planned as inpatient visits, the 6- and 9-month follow-ups were performed by phone contact. Patients were monitored for the occurrence of adverse clinical events including death, MI, stroke, repeat revascularization, and major bleeding. The initial plan had been to administer study medication also prior to surgery, i.e. at days -5 to -3 before the scheduled day of CABG (protocol version 4). However, because of logistic problems with this strategy leading to slow patient recruitment this plan was abandoned with an amendment to the study protocol after inclusion of 245 patients (protocol version 5).[29] The study drug was provided by AstraZeneca and repacked in blisters by Haupt Pharma Wülfing GmbH (Gronau/Leine, Germany). Sufficient blisters were issued at discharge to cover the entire trial period. Other medications could be taken according to the judgement of the treating physician.

Statistical analysis

The calculation of the sample size was based on an expected primary endpoint event rate of 13% in the control group within the 1st 12 months after enrolment.[6] A total of 3760 patients were required to ensure a power of 80% to detect a relative risk reduction of 22.5% in the primary endpoint in the ticagrelor group at a two-sided α level of 0.0492 (to preserve the overall significance level of 0.05 after planned interim analysis). The final sample size was set at 3850 patients assuming a drop-out rate of 2%. Sample size calculation was performed with nQuery Advisor according to the method described by O'Brien and Muller.[30]

Categorical variables such as demographics and medical history data were summarized using frequencies and proportions and were compared using the χ^2 test or Fisher's exact test, as appropriate. Continuous data were summarized using mean ± standard deviation or median (25th–75th percentile) and were compared using either the Student's *t*-test or the non-parametric Wilcoxon rank sum test. Outcomes were compared between treatment and control groups by the use of Cox proportional hazards model effect after checking for fulfilment of the proportional hazard assumption. For composite endpoints time-to-first-event analysis was used. All analyses were performed according to a modified intention-to-treat principle with inclusion of all patients who were randomly assigned to one of the two study groups with the exception of those patients who withdrew their consent before undergoing CABG or did not undergo the planned surgery, and consequently, did not receive any study drug. The primary endpoint of the study was also analysed in various subgroups of interest (age, gender, diabetes, history of a percutaneous coronary intervention, number of arterial, and venous bypass grafts) including those pre-specified as defined by stratification for ACS, after testing for interaction for the treatment effect. All statistical analyses were performed with the use of R v3.5.1 software.

Results

Patients

The TiCAB study was conducted in 26 centres in three countries. The 1st patient was enrolled on 24 April 2013, the last patient on 3 April 2017, such that the 1-year follow-up of about half of the intended patients was completed in March 2018 when a planned interim analysis of the DSMB was scheduled. Based on the event rates

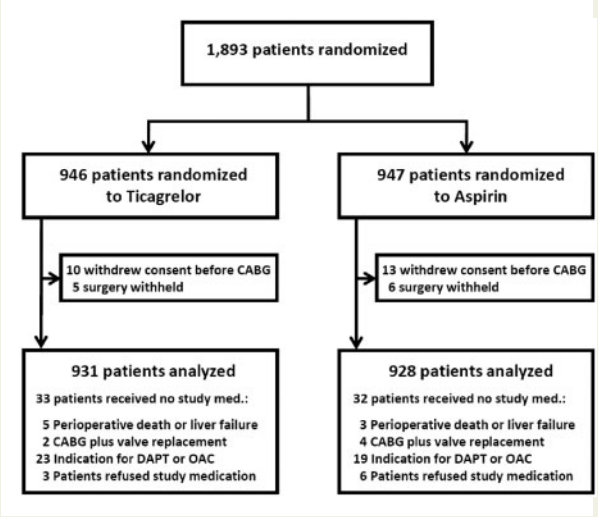


Figure 1 Trial enrolment, randomization, and follow-up.

at this date and an at-first blinded comparison of the groups, the DSMB calculated that the patient population had to be increased beyond the 3760 patients by 1134 patients. The DSMB went on to an unblinded analysis, which revealed that the event rate was higher in the ticagrelor arm. Thus, with respect to testing the hypothesis that ticagrelor is superior to aspirin, the calculated number was likely to be an underestimation. Therefore, and because of withdrawal of funding by the drug manufacturer, the DSMB suggested stopping of the trial.

As a consequence, further recruitment was halted after about half of the intended number of patients was included. *Figure 1* shows the flow of participants through the trial. Of the total number of 1893 patients who were enrolled, 34 patients were excluded from the analysis due to either consent withdrawal before CABG ($n = 23$) or because bypass surgery was not performed ($n = 11$). No study medication was given to these 34 patients. Therefore, 1859 randomly assigned patients were analysed in the ticagrelor and aspirin groups. The groups represent clinical characteristics that are typical for CABG patients and were well matched with respect to relevant baseline data (*Table 1*). Likewise, the periprocedural data showed no significant difference between both groups (*Table 2*). The 1st study drug was given within 24 h of the surgery in 91% of the patients in both groups. Compliance with study drug intake evaluated at 12 months was also similar in both groups (ticagrelor group 86.2% and aspirin group 87.0%).

Efficacy

The primary endpoint occurred in 86 out of 931 patients in the ticagrelor group and in 73 out of 928 patients in the aspirin group, which relates to Kaplan–Meier estimates of 9.7% and 8.2%, respectively [hazard ratio 1.19, 95% confidence interval (CI) 0.87–1.62; $P = 0.28$]. None of the individual components of the primary endpoint showed a significant difference between the two groups, with hazard ratios in the ticagrelor arm of 0.85 (0.38–1.89) for cardiovascular mortality, 0.63 (0.36–1.12) for MI, 1.21 (0.70–2.08) for stroke, and 1.28 (0.82–2.00) for repeat revascularization (*Table 3* and *Figure 2*). Within the 1st 7 days post-surgery 18 and 10 strokes occurred in the ticagrelor and aspirin group, respectively ($P = 0.14$). The rate of atrial fibrillation at discharge did not show significant differences between the ticagrelor (2.4%) vs. aspirin group (2.5%). Likewise, the risks of the combined endpoint of MI, stroke, and cardiovascular death [hazard ratio of 0.99 (0.69–1.42)] as well as all-cause death [hazard ratio of 0.96 (0.53–1.72)] showed no significant differences between the two treatment groups (*Table 3* and *Figure 2*). Individual endpoints are shown in the Supplementary material online, *Figures*. Concerning the components of the primary endpoint we perceived heterogeneity in that the rates of cardiovascular disease and MI were lower in the ticagrelor group but stroke and revascularization were lower in the aspirin group.

The incidence of the primary endpoint was higher in the stratum of patients with ACS, but there was no significant interaction of this condition with treatment outcome in this underpowered analysis (*Figure 3*). The same is true for all other pre-specified subgroups (*Figure 3*).

Safety

We observed no difference with respect to the predefined bleeding endpoint (ticagrelor 3.7% vs. aspirin 3.2%, hazard ratio 1.17, CI 0.71–1.92; $P = 0.53$; *Table 3* and *Figure 2*). The overall bleeding rates type 2–5, as defined by the Bleeding Academic Research Consortium, as well as fatal or life-threatening bleedings were also not significantly different (*Table 3*). Pacemaker implantation was required in a comparable proportion of patients after CABG surgery (ticagrelor group 1.1% vs. aspirin group 1.2%).

Discussion

This randomized trial prospectively compared ticagrelor monotherapy with aspirin monotherapy in the 1st year after CABG. The study was prematurely stopped after about half of the intended patient number was included and did not observe any significant difference between the ticagrelor and aspirin arm with respect to major ischaemic or fatal events as well as potential adverse effects including various forms of bleeding.

In patients undergoing CABG effective antiplatelet therapy is needed in order to lower the risk of ischaemic events, which are mainly caused by early graft occlusion. The benefits of such treatment have to be balanced with the risks of major perioperative bleedings or the need of blood transfusion, both of which adversely affect long-term prognosis. Various studies investigated the effects of DAPT in this respect,[7,16,26,28,31–34] but results were mixed and the implementation rates of DAPT after CABG are low.[34]

Given that aspirin has been found to be less effective with respect to platelet inhibition in some patients after CABG,[10,11] an alternative medication with rapid onset of action may be beneficial.[35,36] Indeed, patients receiving ticagrelor plus aspirin had a higher rate of bypass graft patency as compared with patients treated with aspirin alone.[28] Moreover, a post-randomization analysis of the PLATO trial suggested a survival benefit in patients who were revascularized by

Table 1 Baseline characteristics of the patients[a]

Characteristics	Ticagrelor group ($n = 931$)	Aspirin group ($n = 928$)
Male gender, *n* (%)	794 (85.3)	785 (84.6)
Age (years)	66.4 ± 10.1	67.0 ± 10.2
Heart rate	70.1 ± 12.7	70.5 ± 12.1
Body mass index[b]	28.8 ± 5.2	28.4 ± 4.8
Clinical presentation, *n* (%)		
Stable angina	642 (69.0)	646 (69.6)
Unstable angina	126 (13.5)	117 (12.6)
Non-ST-elevation myocardial infarction	163 (17.5)	165 (17.8)
History of myocardial infarction, *n* (%)	218 (23.4)	204 (22.0)
Recent myocardial infarction (<90 days), *n* (%)	84 (9.0)	82 (8.8)
History of CABG, *n* (%)	6 (0.6)	8 (0.9)
History of PCI, *n* (%)	193 (20.7)	182 (19.6)
History of cardiovascular surgery, *n* (%)	2 (0.2)	2 (0.2)
Angina severity (CCS class),[c] *n* (%)		
I	140 (15.0)	130 (14.0)
II	431 (46.3)	460 (49.6)
III	178 (19.1)	159 (17.1)
IV	182 (19.5)	179 (19.3)
Heart function severity (NYHA class), *n* (%)		
I	241 (25.9)	241 (26.0)
II	430 (46.2)	430 (46.3)
III	243 (26.1)	231 (24.9)
IV	17 (1.8)	26 (2.8)
Cardiovascular risk factors, *n* (%)		
Hypertension	836 (89.8)	836 (90.1)
Hyperlipidaemia	765 (82.2)	754 (81.3)
Smoking status, *n* (%)		
Smoking	200 (21.5)	187 (20.2)
Ex-smoking	320 (34.4)	321 (34.6)
Diabetes, *n* (%)	338 (36.3)	330 (35.6)
Insulin	117 (12.6)	120 (12.9)
Oral antidiabetics	185 (19.9)	180 (19.4)
Diet	36 (3.9)	30 (3.2)
Peripheral vascular disease, *n* (%)	90 (9.7)	80 (8.6)
Cerebrovascular disease, *n* (%)	83 (8.9)	82 (8.8)
Stroke, *n* (%)	38 (4.1)	36 (3.9)
TIA, *n* (%)	18 (1.9)	16 (1.7)
Chronic obstructive pulmonary disease, *n* (%)	82 (8.8)	66 (7.1)
Chronic kidney disease[d], *n* (%)	59 (6.3)	72 (7.8)
LVEF[e]	56.6 ± 12.2	56.4 ± 12.4
<30%, *n* (%)	17 (1.9)	16 (1.8)
30–50%, *n* (%)	225 (24.7)	232 (25.6)
>50%, *n* (%)	659 (72.4)	646 (71.1)
Extent of coronary artery disease, *n* (%)		
Three vessel disease	855 (91.8)	858 (92.5)
Two vessel disease and EF (<50%)	67 (7.2)	60 (6.5)
Left main disease	387 (41.6)	365 (39.3)
Singular left main disease	6 (0.6)	7 (0.8)
EuroSCORE I,[f] *n* (%)	3.9 ± 3.3	4.1 ± 3.2
Low (0–2)	327 (35.1)	303 (32.7)
Medium (3–5)	357 (38.3)	390 (42.0)
High (≥6)	247 (26.5)	235 (25.3)
Lesion characteristics, *n* (%)		
Length (>20 mm)	8 (0.9)	15 (1.6)
Calcified	446 (47.9)	435 (46.9)
Thrombotic	44 (4.7)	35 (3.8)
Restenotic	66 (7.1)	63 (6.8)
Total occlusion	856 (91.9)	858 (92.5)
Poor mobility, *n* (%)	19 (2.0)	17 (1.8)
History of cancer, *n* (%)	34 (3.7)	38 (4.1)
Pulmonary hypertension, *n* (%)	25 (2.7)	27 (2.9)
Medication use, *n* (%)		
Aspirin	727 (78.1)	731 (78.8)
P2Y12-inhibitor	98 (10.5)	81 (8.7)
Ticagrelor	37 (4.0)	26 (2.8)
Prasugrel	4 (0.4)	0 (0.0)
Clopidogrel	57 (6.1)	55 (5.9)
Oral anticoagulant	1 (0.1)	4 (0.4)
β-blockers	635 (68.2)	606 (65.3)
ACEI or ARB	718 (77.1)	711 (76.6)
Calcium antagonist	199 (21.4)	202 (21.8)
Diuretics	286 (30.7)	288 (31.0)
Statins	776 (83.4)	779 (83.9)
Nitrates	50 (5.4)	53 (5.7)
Proton pump inhibitor	304 (32.7)	264 (28.4)

[a]Plus-minus values are means ± SD. There were no significant differences in baseline characteristics between the two groups.
[b]The body mass index is the weight in kilograms divided by the square of the height in meters.
[c]Classes of angina on the CCS scale range from I to IV, with higher classes indicating greater limitations on physical activity owing to angina.
[d]Shown as reported from the partner site.
[e]LVEF data were available for 1818/1859 participants (97.8%).
[f]The EuroSCORE indicate the percent risk of death within 30 days after surgery. The score is calculated with multivariable models that incorporate clinical predictors to estimate the operative mortality for any given patient. The EuroSCORE was developed in 1998 from data on cardiac surgery in eight European countries.
CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction; NYHA, New York Class Association; TIA, transitory ischaemic attack; PCI, percutaneous coronary intervention.

CABG and treated with ticagrelor plus aspirin as compared with patients treated with clopidogrel plus aspirin.[7,27] These findings encouraged us to study ticagrelor monotherapy after CABG.[4]

Table 2 Operative variables[a]

Variables	Ticagrelor group ($n = 931$)	Aspirin group ($n = 928$)
Off pump, *n* (%)	34 (3.5)	32 (3.4)
Number of performed grafts	2.7 ± 0.7	2.6 ± 0.7
1, *n* (%)	11 (1.2)	17 (1.8)
2, *n* (%)	384 (41.2)	393 (42.3)
≥3, *n* (%)	536 (57.6)	518 (55.8)
Number of arterial grafts, *n* (%)		
0	37 (4.0)	39 (4.2)
1	382 (41.0)	403 (43.4)
≥2	512 (55.0)	486 (52.4)
Number of saphenous grafts, *n* (%)		
0	313 (33.6)	313 (33.7)
1	368 (39.5)	350 (37.7)
2	205 (22.0)	223 (24.0)
≥3	45 (4.8)	42 (4.5)
Number of patients receiving blood transfusions, *n* (%)	71 (8.2)	74 (8.6)
Units of transfused packed red cells	0.7 ± 1.1	0.8 ± 1.2
Postoperative length of ICU stay (days)[b]	1 (1–3)	1 (1–3)
Postoperative length of hospital stay (days)[b]	9 (8–12)	9 (7–11)

[a]Plus-minus values are means ± SD. There were no significant differences in operative variables between the two groups.
[b]Presented as median and interquartile range (25th–75th percentile).
ICU, intensive care unit.

However, analysis of about half of the intended patients of the TiCAB trial failed to show beneficial impact on the primary endpoint while opposing trends concerning various secondary endpoints might suggest that ticagrelor and aspirin have diverse efficacy in preventing specific outcomes such as MI or stroke.

There are a number of differences between the post-randomization analysis of the PLATO trial and the present prospective analysis.[7,27] First, PLATO exclusively studied patients requiring bypass grafting in the setting of an ACS. In contrast, in the present trial, the majority of patients had stable coronary artery disease at the time of surgery. This might have translated to differences in total mortality, which was fairly high (9.7%) in the clopidogrel/aspirin arm as compared with the ticagrelor/aspirin arm (4.7%) of the PLATO-CABG study as well as both arms of the present trial (ticagrelor group 2.5% and aspirin group 2.6%). Thus, differences in patient populations may explain the differing outcomes of the two studies. Moreover, for the time being the *post-hoc* subgroup analysis in the PLATO-CABG study still awaits confirmation.

Ticagrelor confers pleiotropic effects which might be advantageous in the early post-operative period. In particular, it has been shown to increase plasma levels of adenosine—via inhibition the nucleoside transporter 1—with beneficial effects on myocardial blood flow and immuno-modulation, which might reduce tissue injury in the setting of major cardiac surgery.[37–39] In light of such platelet-independent drug effects it may be relevant that in PLATO most patients received ticagrelor treatment also prior to surgery, with optimal results when ticagrelor was stopped 3 days before the operation.[7] However, investigators of the present trials were concerned that such strategy may lead to higher transfusion rates[40] such that our initial plan to offer ticagrelor also on days -5 to -3 before surgery proved to be non-feasible and was abandoned by a major protocol amendment after inclusion of only 245 patients into the study.

Dual antiplatelet therapy composed of ticagrelor plus aspirin as used in PLATO or DACAB studies may offer specific benefits in patients undergoing CABG, specifically in the setting of an ACS.[2,4,7,28] By design, our study cannot address this subject. However, pharmacological data had suggested that ticagrelor monotherapy may be more effective than aspirin.[14,15,39] Moreover, a *post-hoc* analysis of the PLATO trial demonstrated that the lower the dose of concomitant aspirin therapy, the greater was the benefit of ticagrelor as compared with clopidogrel.[41] This and other observations[7,40] stimulated a number of studies to explore the merits of ticagrelor monotherapy (TWILIGHT; ClinicalTrials.gov identifier NCT02270242).[28,42,43] Available data from these trials in patients undergoing CABG (DACAB), PCI (GLOBAL LEADERS), conservative management of stroke (SOCRATES), or peripheral arterial disease[44] suggest—like the present study—that ticagrelor-monotherapy is equally effective but not better than other antiplatelet monotherapies.[28,42–44] Thus, further studies need to explore whether a combination of ticagrelor with aspirin may be more advantageous after CABG or in cardiovascular conditions other than ACS. Given the concerns of many surgeons regarding bleeding risks during DAPT after CABG[45] lower dosages or shorter duration of DAPT may offer solutions.

Limitations

The main limitation of the present trial is the premature recruitment stop such that our conclusions are based on only 159 events. The lower than expected event rates would have required inclusion of more than the anticipated patient numbers such that the DSMB recommended discontinuation of patient enrolment, which was further justified by the withdrawal of major funding source. In conjunction, the lower than expected event rate and the premature recruitment stop rendered the study underpowered. Another limitation may be seen in the fact that we did not have the opportunity to study graft patency in this trial.[28]

Conclusions

In this prematurely terminated and thus underpowered randomized trial of ticagrelor vs. aspirin in patients after CABG no significant differences in major cardiovascular events or major bleeding could be demonstrated.

Table 3 Major efficacy and safety endpoints after 12 months[a]

Efficacy outcome measures	Ticagrelor group (*n* = 931)	Aspirin group (*n* = 928)	Hazard ratio (95% CI)	*P*-value
Primary efficacy endpoint,[b] *n* (%)	86 (9.7)	73 (8.2)	1.19 (0.87–1.62)	0.28
Secondary endpoints				
CV-death, *n* (%)	11 (1.2)	13 (1.4)	0.85 (0.38–1.89)	0.68
MI, *n* (%)	19 (2.1)	30 (3.4)	0.63 (0.36–1.12)	0.12
Stroke, *n* (%)	29 (3.1)	24 (2.6)	1.21 (0.70–2.08)	0.49
Haemorrhagic stroke	1 (0.1)	3 (0.3)	0.33 (0.03–3.21)	0.34
Repeat revascularization, *n* (%)	43 (5.0)	34 (3.9)	1.28 (0.82–2.00)	0.28
PCI/stenting	34 (3.7)	31 (3.3)	1.11 (0.68–1.80)	0.69
CV-death, MI, or stroke, *n* (%)	58 (6.3)	59 (6.5)	0.99 (0.69–1.42)	0.94
CV-death or MI, *n* (%)	30 (3.2)	40 (4.3)	0.75 (0.47–1.20)	0.23
CV-death or stroke, *n* (%)	39 (4.2)	36 (3.9)	1.09 (0.69–1.71)	0.72
AC-death, *n* (%)	22 (2.5)	23 (2.6)	0.96 (0.53–1.72)	0.89
AC-death, MI, or stroke, *n* (%)	63 (6.9)	65 (7.2)	0.97 (0.69–1.38)	0.88
Safety outcome measures				
Secondary safety endpoint (BARC 3, 4, 5 bleeding),[c] *n* (%)	34 (3.7)	29 (3.2)	1.17 (0.71–1.92)	0.53
BARC 5, *n*	1	1		
BARC 4, *n*	24	21		
BARC 3, *n*	9	7		
Total bleeding events (BARC 2, 3, 4, 5), *n* (%)	45 (4.9)	44 (4.9)	1.02 (0.67–1.55)	0.92

[a]Percentages are Kaplan–Meier estimates. Hazard ratios with 95% confidence interval and *P*-values are shown for all outcomes at 12 months, starting with the day of surgery. Patients could have had more than one type of event.
[b]Primary efficacy endpoint combines cardiovascular death, myocardial infarction, stroke, and repeat revascularization.
[c]Secondary safety endpoint was defined as BARC class 4 or 5 bleeding over 12 months or class 3 bleeding between discharge and 12 months.
BARC: Bleeding Academic Research Consortium; CV, cardiovascular death; MI, myocardial infarction; PCI, percutaneous coronary intervention.

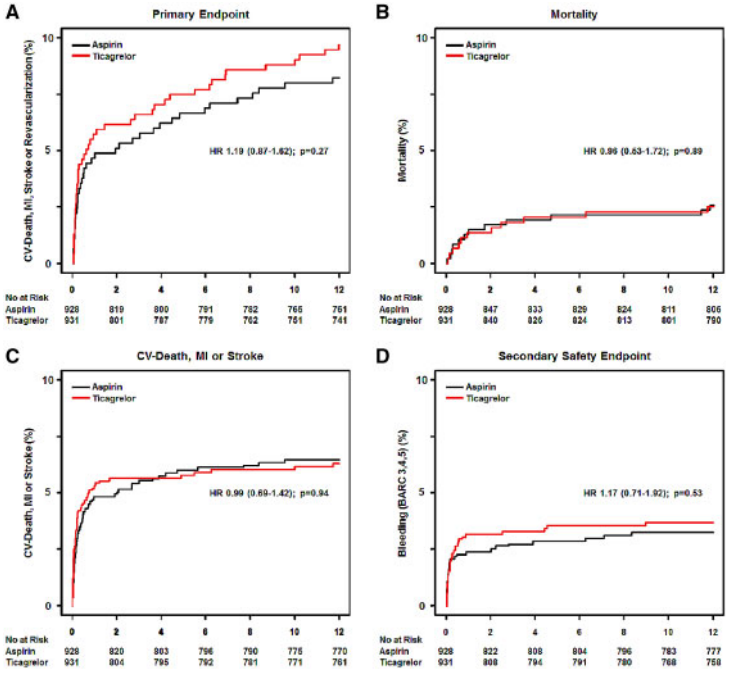


Figure 2 (*A*) Cumulative Kaplan–Meier curves for the primary endpoint (the composite of cardiovascular death, myocardial infarction, repeat revascularization, and stroke). (*B*) Cumulative Kaplan–Meier curves of all-cause death. (*C*) Cumulative Kaplan–Meier curves for the composite of cardiovascular death, myocardial infarction, and stroke. (*D*) Cumulative Kaplan–Meier curves for the secondary safety endpoint (bleeding—BARC 3, 4, or 5).

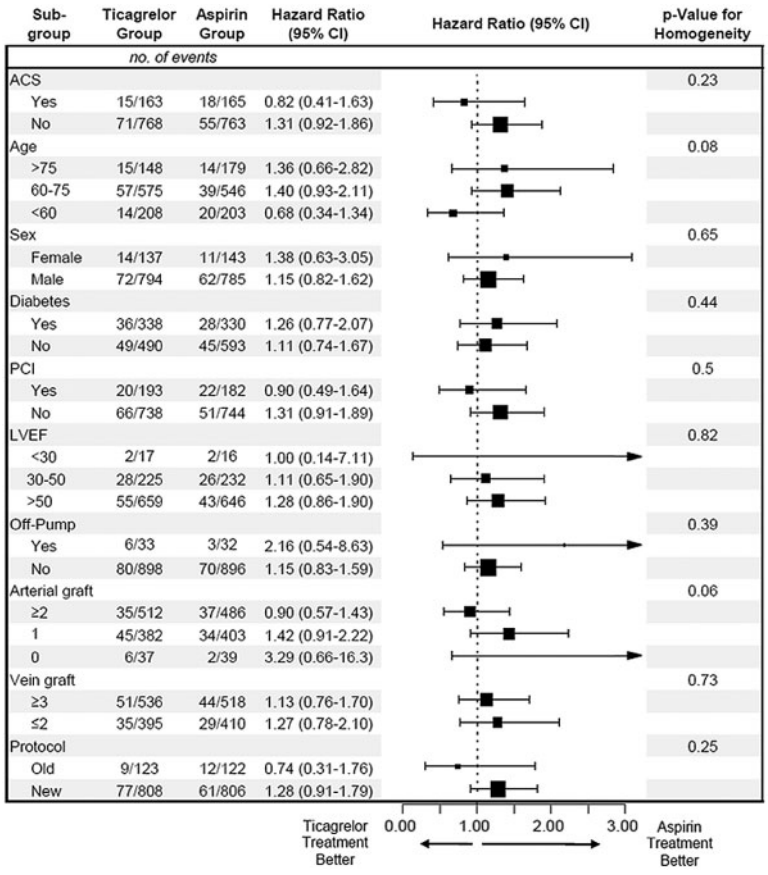
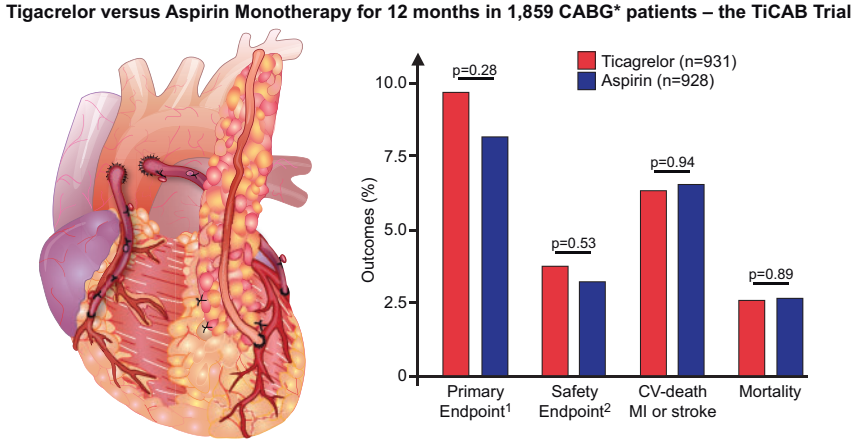


Figure 3 Hazard ratios are shown for all subgroups with 95% confidence interval and *P*-value for interaction at 12 months. Patients could have had more than one type of endpoint. ACS, acute coronary syndrome; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention, and old protocol describes patients who received study medication also on days -5 to -3 prior to CABG; new protocol implies that patients have received study medication after CAGB.



Take home figure The TiCAB trial. A randomized controlled trial comparing ticagrelor vs. aspirin monotherapy for 12 months in patients after coronary artery bypass grafting (CABG). *) CABG - coronary artery bypass grafting; 1) The primary endpoint combines cardiovascular (CV) death, MI, stroke or revascularization; 2) The safety endpoint is defined as bleeding grade 3, 4 or 5 of the Bleeding Academic Research Consortium (BARC). Outcomes show no significant differences between ticagrelor and aspirin monotherapy.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: Dr H.S. reports grants and personal fees from Astra Zeneca, during the conduct of the study; personal fees from MSD SHARP & DOHME, personal fees from AMGEN, personal fees from Bayer Vital GmbH, personal fees from Boehringer Ingelheim, personal fees from Daiichi Sankyo, personal fees from Novartis, personal fees from Servier, personal fees from Brahms GmbH, personal fees from Bristol-Myers Squibb, personal fees from Medtronic, personal fees from Sanofi Aventis, personal fees from Synlab, outside the submitted work. Dr M.O. reports personal fees from Smith/Nephew, personal fees from Baxter, outside the submitted work. Dr U.Z. reports grants and personal fees from Astra Zeneca, during the conduct of the study; grants and personal fees from Bayer, personal fees from Boehringer Ingelheim, grants and personal fees from BMS, personal fees from Novartis, personal fees from MSD, personal fees from Sanofi, grants and personal fees from Pfizer, personal fees from Trommsdorff, outside the submitted work. Dr C.H. reports personal fees from AstraZeneca, during the conduct of the study. Dr G.L. reports other from Astra Zeneca, during the conduct of the study; personal fees from Edwards, outside the submitted work. All other authors have nothing to disclose.

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