Effect of adding ticagrelor to standard aspirin on saphenous vein graft patency in patients undergoing coronary artery bypass grafting (POPular CABG) a randomized, double-blind, placebo-controlled trial

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ORIGINAL RESEARCH ARTICLE

Effect of Adding Ticagrelor to Standard Aspirin on Saphenous Vein Graft Patency in Patients Undergoing Coronary Artery Bypass Grafting (POPular CABG)

A Randomized, Double-Blind, Placebo-Controlled Trial

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BACKGROUND: Approximately 15% of saphenous vein grafts (SVGs) occlude during the first year after coronary artery bypass graft surgery (CABG) despite aspirin use. The POPular CABG trial (The Effect of Ticagrelor on Saphenous Vein Graft Patency in Patients Undergoing Coronary Artery Bypass Grafting Surgery) investigated whether ticagrelor added to standard aspirin improves SVG patency at 1 year after CABG.

METHODS: In this investigator-initiated, randomized, double-blind, placebo-controlled, multicenter trial, patients with ≥1 SVGs were randomly assigned (1:1) after CABG to ticagrelor or placebo added to standard aspirin (80 or 100 mg). The primary outcome was SVG occlusion at 1 year, assessed with coronary computed tomography angiography, in all patients who had primary outcome imaging available. A generalized estimating equation model was used to perform the primary analysis per SVG. The secondary outcome was 1-year SVG failure, which was a composite of SVG occlusion, SVG revascularization, myocardial infarction in myocardial territory supplied by a SVG, or sudden death.

RESULTS: Among 499 randomized patients, the mean age was 67.9±8.3 years, 87.1% were male, the indication for CABG was acute coronary syndrome in 31.3%, and 95.2% of procedures used cardiopulmonary bypass. Primary outcome imaging was available in 219 patients in the ticagrelor group and 224 patients in the placebo group. The SVG occlusion rate in the ticagrelor group was 9.6% (44 of 457 SVGs) versus 10.1% in the placebo group (50 of 497 SVGs; odds ratio, 0.87 [95% CI, 0.49–1.55]; *P*=0.64). SVG failure occurred in 32 patients (12.9%) in the ticagrelor group versus 32 patients (13.0%) in the placebo group (hazard ratio, 1.04 [95% CI, 0.63–1.69]).

CONCLUSIONS: In this randomized, placebo-controlled trial, the addition of ticagrelor to standard aspirin did not reduce SVG occlusion at 1 year after CABG.

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Key Words: coronary artery bypass ■ saphenous vein ■ ticagrelor ■ vascular patency

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Clinical Perspective

What Is New?

- In this randomized, double-blind, placebo-controlled trial, the addition of ticagrelor to standard aspirin after coronary artery bypass grafting (CABG) did not reduce the rate of saphenous vein graft occlusions at 1 year.
- This conclusion differs from other studies that investigated this research question.

What Are the Clinical Implications?

- This trial provides no reason to routinely start ticagrelor in patients undergoing CABG.
- In patients undergoing CABG for acute coronary syndrome, ticagrelor is likely to provide antithrombotic and possibly pleiotropic benefits that have no relation to saphenous vein graft patency.
- Therefore, the POPular CABG trial (The Effect of Ticagrelor on Saphenous Vein Graft Patency in Patients Undergoing Coronary Artery Bypass Grafting Surgery) does not refute the advice of the guidelines to continue ticagrelor in patients undergoing CABG for acute coronary syndrome.

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
CABG	coronary artery bypass grafting
CCTA	coronary computed tomography angiography
COMPASS-CABG	Cardiovascular Outcomes for People Using Anticoagulation Strategies–CABG
DACAB	Compare the Efficacy of Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery
OR	odds ratio
PLATO	Platelet Inhibition and Patient Outcomes
POPular CABG	The Effect of Ticagrelor on Saphenous Vein Graft Patency in Patients Undergoing Coronary Artery Bypass Grafting Surgery
SVG	saphenous vein graft
TIMI	Thrombolysis in Myocardial Infarction

Revascularization by coronary artery bypass grafting (CABG) can provide significant benefit in survival and quality of life[1,2] and is favored over percutaneous coronary intervention in patients with diabetes, reduced left ventricular function, and extensive multivessel coronary artery disease.[3] Grafting of the left anterior descending artery with the left internal mammary artery has become the standard of care, and better patency has been suggested with a second arterial conduit.[4] Saphenous vein grafts (SVGs) continue to be widely used as second grafts, although 15% of SVGs occlude within the first year after surgery notwithstanding of the use of aspirin.[5–7] SVG occlusion is associated with adverse outcomes such as angina pectoris, myocardial infarction, and long-term mortality.[8–10] Although SVG occlusion is a complex, multifactorial process, platelets likely play an important role.[11,12] Stronger platelet inhibition could improve outcomes after CABG, and current guidelines advise continuing both aspirin and a $P2Y_{12}$ inhibitor in patients undergoing CABG for acute coronary syndrome (ACS).[13,14] Addition of a $P2Y_{12}$ inhibitor to aspirin may improve SVG patency, but prior studies in this area have provided conflicting results.[15–19] This may be partly attributable to the fact that the investigated $P2Y_{12}$ inhibitor was clopidogrel, to which 30% of treated patients have an inadequate inhibitory response and which is a less potent inhibitor than the currently recommended $P2Y_{12}$ inhibitors (ticagrelor and prasugrel) after ACS.[20] The $P2Y_{12}$ inhibitor ticagrelor is more potent and ensures more consistent response profiles.[21] We performed the randomized, double-blind, placebo-controlled POPular CABG trial (The Effect of Ticagrelor on Saphenous Vein Graft Patency in Patients Undergoing Coronary Artery Bypass Grafting Surgery) to investigate the effect of ticagrelor on SVG patency.

METHODS

These (deidentified) clinical trial data, methods used in the analysis, and materials used to conduct the research can be requested by qualified researchers who engage in independent scientific research and could be provided after review and approval of a research proposal. Data requests can be submitted at any time by contacting the corresponding author.

Study Design

The POPular CABG trial is an investigator-initiated, randomized, double-blind, placebo-controlled trial performed at 6 Dutch study sites. The study design has been published.[22] The full study protocol can be found in the Data Supplement.

The trial was approved by the medical ethics committee and by an institutional review board at each study site. The steering committee advised on all important changes during the course of the trial, and the trial was overviewed by a data safety monitoring board. An independent, external clinical research management company (Research Drive, Norg, the Netherlands) performed data monitoring.

Patients

Patients >21 years of age who underwent planned CABG with ≥1 SVGs were eligible for inclusion. Major exclusion criteria were, among others, use or expected use of oral anticoagulation after CABG or a definite indication for use of a $P2Y_{12}$ inhibitor or other antithrombotic agents other than aspirin after CABG. The inclusion and exclusion criteria are provided in

Table I in the Data Supplement. All patients provided written informed consent before or after CABG.

Randomization and Blinding

Patients were randomly assigned in a 1:1 ratio in a block size of 6 to ticagrelor or matching placebo (identical in appearance). Trial medication was issued by the hospital pharmacy in sequential order according to treatment assignments that were determined by a computer-generated random sequence stratified by center. The study remained blinded to all (patients, investigators, study personnel, outcome assessment teams, and those analyzing data) with the exception of the trial pharmacy until study completion.

Procedures

As soon as possible after successful CABG with SVG implantation, treatment with either ticagrelor 90 mg twice daily preceded by a loading dose if $P2Y_{12}$ naïve or placebo was started. The first dose of the study medication was given at the time of randomization. The trial medication was continued until 1 year after randomization. Trial regimen included cotreatment with aspirin in a dose of 80 to 100 mg daily. All patients were on maintenance dose of aspirin preoperatively and continued aspirin during the operation. The individual patient who was not on a maintenance dose of aspirin preoperatively started aspirin with a loading dose at least 1 day before surgery. Postoperative aspirin was administered according to local protocols and was given for life. Follow-up visits were scheduled at 6, 24, and 53 weeks. Coronary imaging by coronary computed tomography angiography (CCTA) was scheduled at 53 weeks for assessment of the primary outcome. Figure I in the Data Supplement depicts the study design. At each follow-up visit, patients were asked about interim clinical events and the use of cardiovascular medications. Documentation of clinical events was completed with case records from hospital admissions and from general practitioners. Unblinded data were accessible to the first 3 authors (L.M.W., P.W.A.J., and J.P.), the last author (J.M.t.B.), and the statistical analysis team (J.G.P.T. and J.C.K.) after completion of the trial. The first 3 authors and the last author (L.M.W., P.W.A.J., J.P., and J.M.t.B.) drafted the article. All authors have reviewed the article. L.M.W. and J.M.t.B. had final responsibility for the decision to submit for publication.

Outcomes

The primary outcome was 100% SVG occlusion. Single, sequential, and Y grafts were individually and, if applicable, per segment adjudicated on CCTA at 1 year. Figure II in the Data Supplement contains a detailed description of graft assessment. SVGs that were not adequately visualized on CCTA (eg, because of stairstep artifacts) were adjudicated as patent. In the case of missing CCTA, a coronary angiography could be used if performed between 35 and 53 weeks. The primary outcome was undefined in the absence of outcome imaging by CCTA or coronary angiography. An independent core laboratory whose 3 members were unaware of the trial medication assignment adjudicated the images from CCTA or coronary angiography.

The secondary outcome was SVG failure (a composite of SVG occlusion in any SVG as defined above, SVG revascularization, myocardial infarction in myocardial territory supplied by an SVG, or sudden death) at 1 year. Additional secondary outcomes were significant (≥70%) venous or arterial graft stenosis and any (venous or arterial) graft occlusion at 1 year. Safety outcomes were bleeding events, classified according to Bleeding Academic Research Consortium minor (type 2) and major (types 3–5), TIMI (Thrombolysis in Myocardial Infarction), and PLATO (Platelet Inhibition and Patient Outcomes) classifications, 30 days and 1 year after randomization. A clinical events committee blindly adjudicated these clinical events. The definitions are provided in Table II in the Data Supplement.

Statistical Analysis

As prespecified, the primary outcome was assessed with a mixed logistic effects model with random intercept for each patient. However, because of a lack of measurements per patient (≈2 SVGs per patient), this model resulted in an unstable odds ratio (OR) estimate and wide 95% CIs. Therefore, we used a generalized estimating equation model including terms for treatment to estimate between-group differences to analyze the primary outcome of SVG occlusion. The exchangeable covariance structure was used to model the correlation of SVG occlusion within a patient. The analysis included all SVGs with the defined primary outcome by randomized treatment assignment regardless of its implementation (intention to treat). Treatment effects of ticagrelor versus placebo were reported as ORs with 95% CIs and *P* values. In a first sensitivity analysis, we assumed that all SVGs that could not be visualized on the outcome images were analyzed as occluded. Second, we added all SVGs of patients who had died of cardiovascular causes as occluded to the data set. A third post hoc sensitivity analysis was performed in which we corrected the primary analysis per center. Fourth, we performed an analysis of the primary outcome on a per-protocol basis by excluding the SVGs of patients who had not received the trial medication in accordance with the study protocol. Last, we defined SVG occlusion on a per-patient basis if occlusion had occurred in at least 1 SVG. ORs with corresponding 95% CIs were calculated with conventional logistic regression analysis in patients with available outcome imaging. Prespecified subgroup analyses were performed for the primary outcome.

For the (time-to-event) secondary outcomes, hazard ratios and corresponding 95% CIs were determined with Cox proportional hazards regression analysis. Kaplan-Meier curves were used to depict the occurrence of secondary outcomes over time. Follow-up of event-free patients with incomplete clinical follow-up was censored at the last clinical contact. For all secondary outcomes, per-protocol (as defined earlier) analyses were performed as sensitivity analyses.

Continuous variables with normal distribution were expressed as mean with SD, and categorical variables were described as frequencies and percentages. A 2-sided value of $P<0.05$ was considered to be statistically significant. No adjustments for multiple comparisons were made for secondary outcomes, which therefore should be considered exploratory. Statistical analyses were performed with R software version 3.6.1 (R Foundation for Statistical Computing). This trial is registered at https//www.ClinicalTrials.gov (unique identifier: NCT02352402) and EudraCT (2014-002142-50).

Sample Size

The original design assumptions included a reduction of the SVG occlusion rate by ticagrelor from 15% to 10% (based on available literature at the time[5–7,15]), a Yules Y coefficient of 0.1715 per patient, and a mean of 2.4 SVGs per patient. From computer simulations, we estimated that inclusion of 575 patients with 1380 evaluable SVGs would provide the trial with 80% power.

Considering that 20% of patients would not have available primary outcome imaging, we estimated that 720 patients needed to be included. Because recruitment in the trial was slow, the sample size was revised, without knowledge of interim results, when the results of the DACAB trial[23] (Compare the Efficacy of Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery [SVG occlusion rates from 23.5% to 11.2%]) were published. We decided to continue the trial until inclusion of an equal number of evaluable SVGs to the DACAB trial. Corrected for the dropout rate as observed in the interim analysis, we estimated that with 1072 evaluable SVGs in 487 patients (ie, 2.2 SVGs per patient) the trial would have at least 80% power to statistically detect a reduction of the SVG occlusion rate from 15% to 9% at a 2-sided significance level of 0.05.

Retraction of Original Article

After publication of the original article, we found out that an incorrect randomization list for the patients of 1 participating site (the St Antonius Hospital) was used for the analysis after completion of the study. In all patients, including those in the St Antonius Hospital, randomization to the treatment groups was performed correctly; all patients received study medication according to their right assignment. However, a wrong second randomization list for the St. Antonius Hospital alone was used for the analysis, whereas the correct, first randomization list was used for the other 5 participating centers. This randomization list was erroneously generated 2 years after the start of the study, when randomization lists were generated for 3 new participating centers. Verification of the randomization lists and analyses of the other 5 centers demonstrated no errors. In consultation with *Circulation* editors, we decided to retract the original article and resubmit the article with the corrected analyses.

RESULTS

Trial Population

From March 27, 2015, through January 1, 2019, a total of 499 patients were included (Figure 1). Enrollment per study site is shown in Table III in the Data Supplement. After randomization, 3 patients were excluded from the analysis (3 patients withdrew full informed consent), so the study population consisted of 496 patients, of whom 2 patients were lost to follow-up at 12 months.

Baseline and procedural characteristics were comparable in both groups (Table 1). Mean age was 67.9±8.3 years; 87.1% were male. Indication for CABG was ACS in 31.3%, and cardiopulmonary bypass was used in 95.2% of procedures. At the 1-year follow-up, 216 of the patients (86.8%) in the ticagrelor group and 212 of the patients (85.8%) in the placebo group used aspirin. In the ticagrelor and placebo groups, 94 patients (37.8%) and 82 patients (33.2%), respectively, had permanently discontinued study medication, most frequently because of oral anticoagulation initiation after CABG (30 patients [12.1%] in the ticagrelor group and 27 patients [10.9%] in the placebo group). Over time, 14 patients (5.6%) in the ticagrelor group and 3 (1.2%) in the placebo group discontinued medication for bleeding. Table IV in the Data Supplement provides an overview of reasons for discontinuing study medication and data on medication use at 1 year.

Primary Outcome

A total of 443 patients (89.3%) with a total of 954 SVGs had primary outcome imaging available at 1 year after ran-

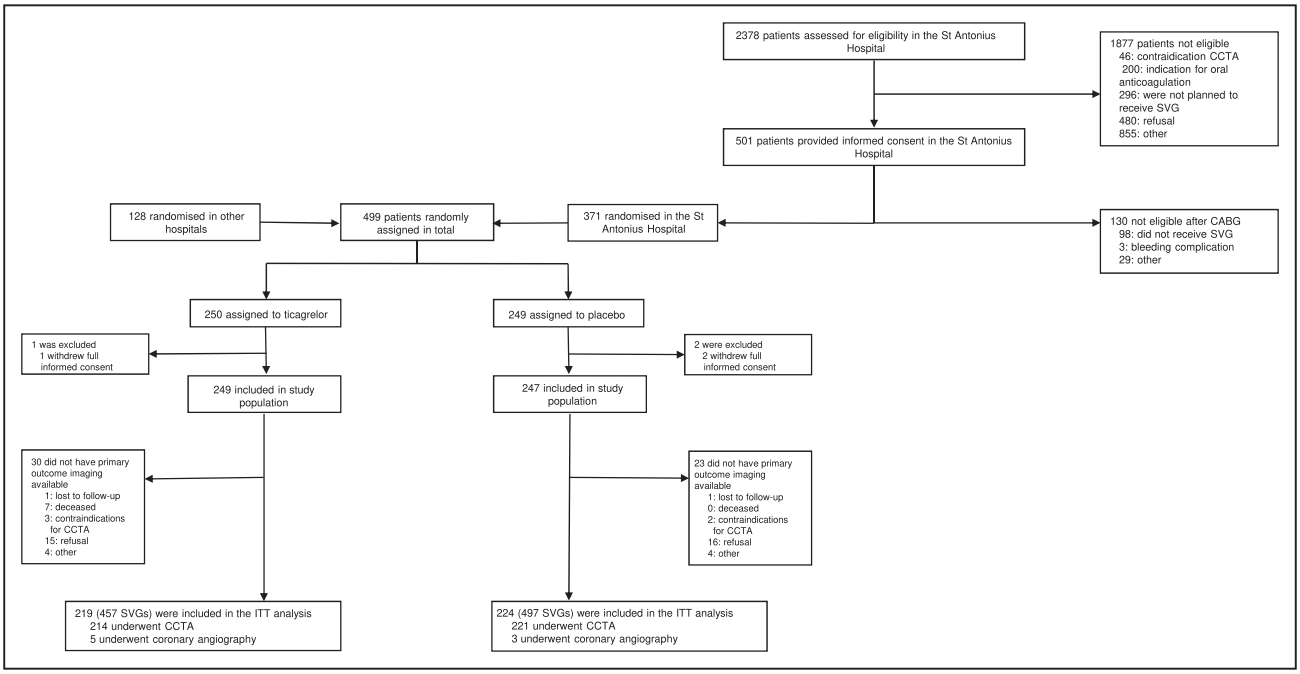

Figure 1. Randomization and follow-up.
CABG indicates coronary artery bypass grafting; CCTA, coronary computed tomography angiography; ITT, intention-to-treat; and SVG, saphenous vein graft.

Table 1. Characteristics of Included Patients and CABG Procedure at Baseline

Characteristics	Ticagrelor group (n=249)	Placebo group (n=247)
Age, y	68.1±8.4	67.7±8.2
Female sex, n (%)	29 (11.6)	35 (14.2)
Body mass index	27.7±4.1	28.0±4.2
Race, n (%)		
White	242 (97.2)	233 (94.3)
Other	4 (1.6)	9 (3.6)
Unknown	3 (1.2)	5 (2.0)
Creatinine clearance ≥60 mL·min^{-1}·1.73 m^{-2} at admission, n (%)†	202 (82.8)	201 (82.7)
Smoker,‡ n (%)	47 (18.9)	45 (18.2)
Diabetes, n (%)	60 (24.1)	68 (27.5)
Hypertension, n (%)	152 (61.0)	156 (63.2)
Hypercholesterolemia, n (%)§	248 (99.6)	244 (99.6)
Chronic obstructive pulmonary disease, n (%)	27 (10.8)	29 (11.7)
Peripheral artery disease, n (%)	25 (9.7)	25 (10.1)
Previous ACS, n (%)	36 (14.5)	44 (17.9)
Previous percutaneous coronary intervention, n (%)	36 (14.5)	42 (17.0)
Previous CABG, n (%)	1 (0.4)	2 (0.8)
Previous cerebrovascular accident, n (%)	2 (0.8)	5 (2.0)
Prior major bleeding, n (%)	12 (4.8)	6 (2.4)
Peptic ulcer in medical history, n (%)	15 (6.0)	10 (4.0)
Indication for CABG, n (%)		
Chronic coronary syndrome	157 (63.1)	162 (65.6)
ACS	81 (32.5)	74 (30.0)
Other	11 (4.4)	11 (4.5)
Left ventricular ejection fraction, n (%)		
>50%	196 (79.4)	190 (77.2)
30%–50%	46 (18.6)	48 (19.5)
<30%	3 (1.2)	8 (3.3)
Additive EuroSCORE‖	3.2±2.1	3.2±2.3
CABG+aortic valve replacement, n (%)	7 (2.8)	6 (2.4)
Use of cardiopulmonary bypass, n (%)	240 (96.4)	232 (93.9)
Graft type, n		
Left internal mammary artery	338	316
Right internal mammary artery	57	61
Radial artery	2	0
Saphenous vein	526	547
Mean total grafts/case, n	3.7±1.0	3.8±1.0
Mean total SVGs/case, n	2.1±0.9	2.2±1.0
Sequential grafting of SVG, n (%)		
Yes	181 (72.7)	182 (73.7)
No	67 (26.9)	64 (25.9)
Start study drug after CABG, n (%)		
<13 h	126 (50.6)	126 (51.0)
13–24 h	29 (11.6)	32 (13.0)
24–48 h	61 (24.5)	58 (23.5)
>48 h	33 (13.3)	31 (12.6)
Loading dose study medication administered, n (%)		
Yes	194 (79.5)	195 (79.6)
No	49 (20.1)	50 (20.4)

Plus-minus values are mean±SD. There were no significant differences between the 2 groups. Percentages may not total 100 because of rounding.

ACS indicates acute coronary syndrome; CABG, coronary artery bypass grafting; EuroSCORE, European System for Cardiac Operative Risk Evaluation; and SVG, saphenous vein graft.

*Body mass index is the weight in kilograms divided by the square of the height in meters.

†Calculated with the Chronic Kidney Disease Epidemiology Disease Collaboration formula.

‡Defined as current smoker or quit smoking for <6 mo.

§Defined as low-density lipoprotein >2.5 mmol/L at baseline or use or start of statin or other cholesterol-lowering medication at baseline.

‖The additive version of EuroSCORE is a method of calculating predicted operative mortality for patients undergoing cardiac surgery: 0 to 2 points, low risk; 3 to 5 points, intermediate risk; and ≥6 points, high risk.

domization: 219 patients (457 SVGs) in the ticagrelor group and 224 patients (497 SVGs) in the placebo group. Mean time of randomization after which CCTA was performed was 368±34 days in the ticagrelor group and 372±26 days in the placebo group. Ten SVGs (2.2%) in the ticagrelor group and 13 SVGs (2.6%) in the placebo group were not adequately visualized on CCTA. SVG occlusion occurred in 44 of 457 SVGs (9.6%) in the ticagrelor group and in 50 of 497 SVGs (10.1%) in the placebo group (OR, 0.87 [95% CI, 0.49–1.55]; *P*=0.64; Table 2). When analyzed on a per-patient basis in which subjects were defined as having at least 1 occluded SVG per patient, 26 of the 219 patients in the ticagrelor group had an occluded SVG (11.9%) versus 32 of the 224 patients (14.3%) in the placebo group (OR, 0.80 [95% CI, 0.46–1.41]; *P*=0.45). Results for the primary outcome were consistent among different subgroups, including patients whose indication for CABG was ACS (Figure 2).

Secondary Outcomes

The secondary outcomes of SVG failure occurred in 32 patients (12.9%) in the ticagrelor group and in 32 patients (13.0%) in the placebo group (OR, 1.04 [95% CI, 0.63–1.69]; *P*=0.89; Table 2). Individual components of the outcome SVG failure analyzed on a per-patient basis consisted of 26 SVG occlusions in the ticagrelor group versus 32 SVG occlusions in the placebo group, 4 SVG revascularizations in the ticagrelor group versus none in the placebo group, 3 cases of myocardial infarction in territory of a SVG in the ticagrelor group versus none in the placebo group, and 1 case of sudden death in the ticagrelor group versus none in the placebo group. Stenosis and occlusion rates in arterial grafts and all graft stenosis rates were low

Table 2. Primary Outcome, Secondary Outcomes, and Safety Outcomes by Intention-to-Treat Analyses

Outcomes	Ticagrelor group, n/total (%)	Placebo group, n/total (%)	OR (95% CI)	Hazard ratio (95% CI)	*P* value
Primary					
SVG occlusion (per SVG)	44/457 (9.6)	50/497 (10.1)	0.87 (0.49–1.55)		0.64
SVG occlusion (per patient)	26/219 (11.9)	32/224 (14.3)	0.80 (0.46–1.41)		0.45
Secondary					
SVG failure	32/249 (12.9)	32/247 (13.0)		1.04 (0.63–1.69)	0.89
30-d BARC 3–5 bleeding	5/249 (2.0)	5/247 (2.0)		1.00 (0.29–3.44)	>0.99
1-y BARC 3–5 bleeding	7/249 (2.8)	8/247 (3.2)		0.87 (0.32–2.40)	0.79
30-d BARC 2–5 bleeding	20/249 (8.0)	8/247 (3.2)		2.55 (1.12–5.79)	0.02
1-y BARC 2–5 bleeding	44/249 (17.7)	22/247 (8.9)		2.09 (1.25–3.49)	0.004

BARC indicates Bleeding Academic Research Consortium; OR, odds ratio; and SVG, saphenous vein graft.

An independent, blinded adjudication committee or core laboratory confirmed all outcomes. The 95% CIs were not adjusted for multiple comparisons, and no clinical inferences can be made from these analyses.

(significant stenosis and occlusion rates in arterial grafts: 9 of 359 arterial grafts [2.5%] in the ticagrelor group and 10 of 346 grafts [2.9%] in the placebo group; significant stenosis in all grafts: 2 of 816 grafts [0.2%] grafts in the ticagrelor group and 1 of 843 grafts [0.1%] in the placebo group). Incidence of Bleeding Academic Research Consortium major bleeding at 1 year was 7 (2.8%) in the ticagrelor group and 8 (3.2%) in the placebo group (hazard ratio, 0.87 [95% CI, 0.32–2.40]; *P*=0.79; Table 2 and Figure III in the Data Supplement). Incidence of Bleeding Academic Research Consortium minor bleeding at 1 year was 44 (17.7%) in the ticagrelor group and 22 (8.9%) in the placebo group (hazard ratio, 2.09 [95% CI, 1.25–3.49]; *P*=0.004; Table 2). Results of bleeding outcomes remained consistent when analyzed with TIMI and PLATO classifications. Clinical event rates were low in this study (Table 3).

The per-protocol analysis and sensitivity analyses rendered results consistent with those of the primary analyses. Results are depicted in Tables V and VI in the Data Supplement. Table VII in the Data Supplement provides reasons for exclusion from the intention-to-treat analysis.

DISCUSSION

In this investigator-initiated, randomized, double-blind, placebo-controlled, multicenter trial, we investigated the potential benefit of adding ticagrelor to standard therapy with aspirin in preventing SVG occlusion 1 year after CABG. The study displayed no effect of ticagrelor on the rate of SVG occlusions or on the composite of SVG occlusions with clinical events.

As mentioned, studies investigating the effect of the $P2Y_{12}$ inhibitor clopidogrel on SVG patency after CABG showed conflicting results.[15–19] A small, prematurely terminated study showed numerically lower SVG occlusion rates with aspirin and ticagrelor compared with aspirin alone.[24] However, the study evaluated graft patency early (at 3 months) after CABG and was not able to detect statistically significant differences because of the small sample size. The DACAB trial[23] randomly assigned 500 patients undergoing CABG to aspirin monotherapy, ticagrelor monotherapy, or aspirin and ticagrelor. SVG patency rates at 1 year were in favor of the aspirin and ticagrelor group (88.7%) and superior to the aspirin monotherapy group (76.5%; absolute risk difference, 12.2% [95% CI, 5.2%–19.2%]; *P*<0.001). Results from our POPular CABG trial are clearly not in line with the DACAB trial results. First, we found a 1-year SVG occlusion rate of 10.1% in the group of aspirin monotherapy, which was much lower than what was observed in the DACAB trial (23.5%). Second, we could not confirm the reduction in SVG occlusion rate with ticagrelor added to aspirin, as reported in the DACAB trial. We can only speculate on the reasons why the DACAB trial found a higher SVG occlusion rate and an effect on patency of adding ticagrelor. In the DACAB trial, the majority of patients underwent CABG without cardiopulmonary bypass (75.8%), which may have influenced patency,[25–28] and more patients underwent CABG for ACS (66.4%). The COMPASS-CABG (Cardiovascular Outcomes for People Using Anticoagulation Strategies–CABG)[29] compared the combination of rivaroxaban plus aspirin, rivaroxaban alone, and aspirin alone on bypass graft patency. They observed low SVG occlusion rates (≈10%) similar to those in our trial and concluded that the combination of rivaroxaban and aspirin (and rivaroxaban alone) did not reduce the graft occlusion rates compared with aspirin alone. Explanations for the fact that neither our trial nor COMPASS-CABG found a reduction of SVG occlusion rates with the use of additional antithrombotic therapy (either ticagrelor or rivaroxaban) remain hypothetical, but both studies suggest that SVG patency may be more dependent on mechanical factors (distal outflow) than thrombotic phenomena.[30,31] Notwithstanding, 2 recent meta-analyses[32,33] concluded that dual antiplatelet therapy with either ticagrelor or clopidogrel and aspirin provided superior SVG patency relative to aspirin alone, although it should be noted that only the 2 studies mentioned in this discussion were included in the analysis investigating dual antiplatelet therapy with aspirin and ticagrelor compared with aspirin.

In POPular CABG, no discernible effect of adding ticagrelor to aspirin on SVG patency could be found in the ACS subgroup, although the trial was not powered to detect differences in subgroups. Furthermore, it is possible that

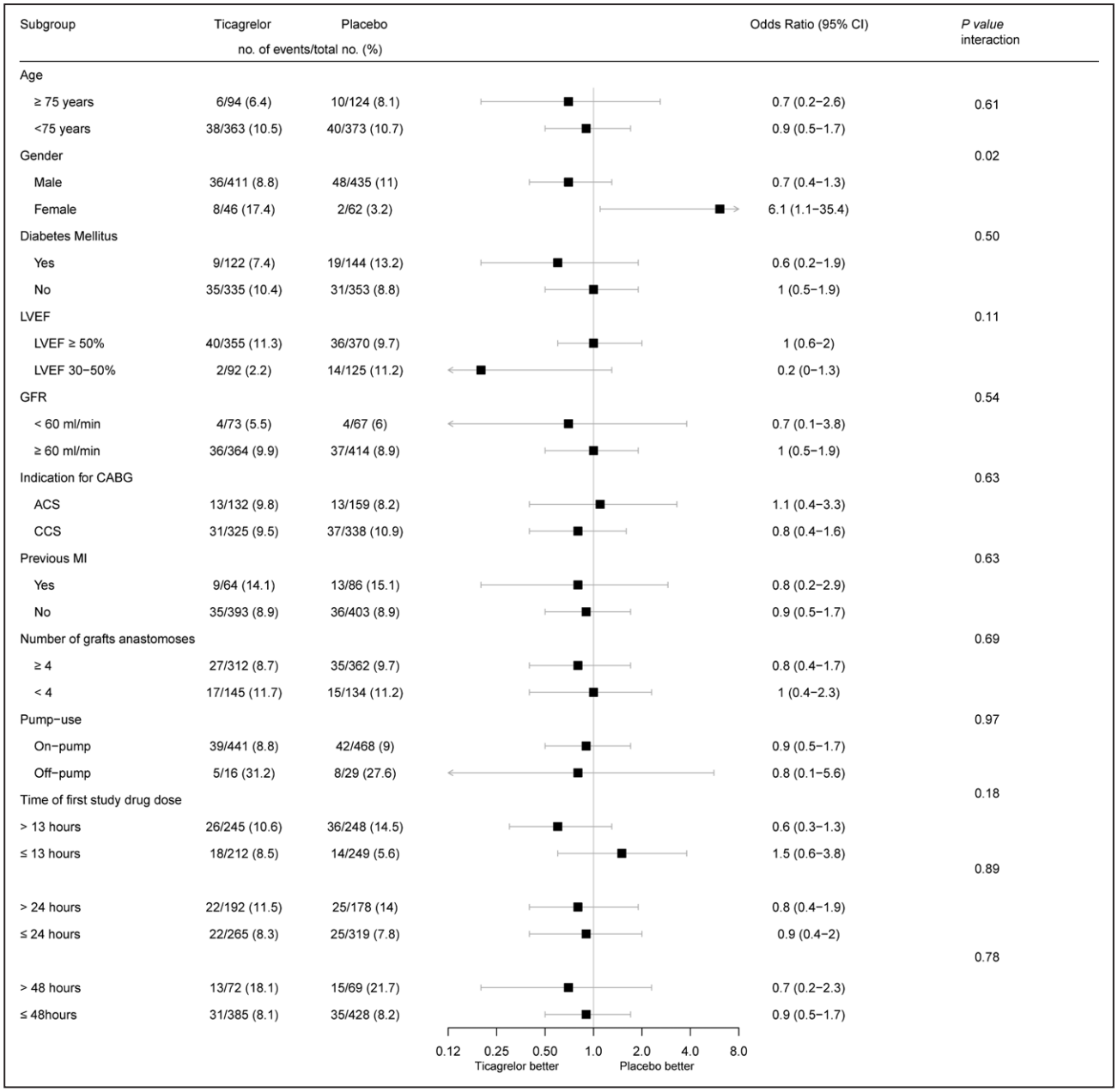

Figure 2. Subgroup analyses for the primary outcome.
Analyses of the primary outcome saphenous vein graft occlusion for the 12 prespecified subgroups. Estimates are unadjusted hazard ratios and 95% CIs at 1 year after randomization. ACS indicates acute coronary syndrome; CABG, coronary artery bypass grafting; CCS, chronic coronary syndrome; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; and MI, myocardial infarction.

ticagrelor has not only antithrombotic but also pleiotropic benefits[13] that have no relation to SVG patency. Additional research is needed to determine the most appropriate treatment after CABG, not only to optimize graft patency but also to improve clinical outcomes. Our trial does not refute the advice of the guidelines to continue ticagrelor in patients undergoing CABG for ACS. On the other hand, possible advantages of ticagrelor should be weighed against potential adverse effects such as dyspnea[34] and an increase in bleeding risk.[13] In our trial, more patients in the ticagrelor group discontinued the study medication for bleeding, and we can establish a significant increase in 30-day and 1-year minor, but not major, bleeding rates in the ticagrelor group. Bleeding rates in our trial were low. This was probably caused by the timing of randomization that was chosen, namely after CABG when the risk of bleeding was minimized.

A notable finding in our trial was the occurrence of more (cardiovascular) death in the ticagrelor group. Two deaths were attributable to cardiovascular causes; 1 death was caused by amyotrophic lateral sclerosis; 1 death was caused by oncological cause; and 3 deaths were caused by detrimental infections after CABG (2 mediastinitis and 1 pneumonia). On the basis of this verification, we think that the difference in mortality rate between the ticagrelor

Table 3. Clinical Event Rates at 1 Year After CABG

Event	Ticagrelor group (n = 249), n (%)	Placebo group (n = 247), n (%)	Hazard ratio (95% CI)
Death resulting from any cause	7 (2.8)	0 (0)	Not available
Cardiovascular death	2 (0.8)	0 (0)	Not available
Cerebrovascular accident/transient ischemic attack	6 (2.4)	8 (3.2)	0.74 (0.26–2.13)
ACS/myocardial infarction	6 (2.4)	3 (1.2)	2.01 (0.50–8.05)
Myocardial infarction in territory supplied by an SVG	3 (1.2)	0 (0)	Not available
Revascularization	11 (4.4)	4 (1.6)	2.77 (0.88–8.70)
SVG revascularization	4 (1.6)	0 (0)	Not available

ACS indicates acute coronary syndrome; CABG, coronary artery bypass grafting; and SVG, saphenous vein graft.
An independent, blinded adjudication committee confirmed all outcomes. The 95% CIs were not adjusted for multiple comparisons, and no clinical inferences can be made from these analyses.

group and the placebo group is attributable to chance. In addition, the outcome from the subgroup analysis that ticagrelor is disadvantageous in women is most probably a chance finding because of small sample size.

Our study has important limitations. First, the trial was powered for the surrogate outcome SVG occlusion, not for clinical events. Second, the study population consisted predominantly of White men. Third, we had a limited number of study sites only in the Netherlands, and most patients were enrolled at only 2 sites. Fourth, ≈75% of patients received sequential SVGs, which are less commonly used in contemporary practice. Fifth, although CCTA appears to be a good method to evaluate SVG occlusion, invasive angiography remains the gold standard. It may be difficult to assess SVG patency confidently with CCTA in some patients, especially those with sequential grafts.

CONCLUSIONS

In this randomized, placebo-controlled trial, adding ticagrelor to standard aspirin therapy did not reduce SVG occlusion rates 1 year after CABG.

ARTICLE INFORMATION

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Supplemental Materials

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