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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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

Editorial, see p 1808

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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 mg or 100 mg). The primary outcome was SVG occlusion at 1 year, assessed with coronary computed tomography angiography, in all patients that 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 randomly assigned 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 220 patients in the ticagrelor group and 223 patients in the placebo group. The SVG occlusion rate in the ticagrelor group was 10.5% (51 of 484 SVGs) versus 9.1% in the placebo group (43 of 470 SVGs), odds ratio, 1.29 [95% CI, 0.73–2.30]; *P*=0.38. SVG failure occurred in 35 (14.2%) patients in the ticagrelor group versus 29 (11.6%) patients in the placebo group (odds ratio, 1.22 [95% CI, 0.72–2.05]).

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

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02352402.

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The full author list is available on page 1806.

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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 with 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.

Revascularization by coronary artery bypass grafting (CABG) can provide significant benefit in survival and quality of life,[1,2] and is favored above 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, even though 15% of SVGs occlude within the first year after surgery notwithstanding 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 to continue 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 previous 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. All important changes during the course of the trial were advised on by the steering committee and the trial was overviewed by a data safety monitoring board. Data monitoring was performed by an independent, external clinical research management company (Research Drive, Norg, The Netherlands).

Patients

Patients >21 years 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 commenced. 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 a 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 administration 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 manuscript was drafted by the first 3 authors and the last author (L.M.W., P.W.A.J., J.P., and J.M.t.B.). All authors have reviewed the manuscript. 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 stair-step 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 Bleeding Academic Research Consortium major (type 3,4,5), Thrombolysis in Myocardial Infarction, and Platelet Inhibition and Patient Outcomes classifications, 30 days and 1 year after randomization. These clinical events were blindly adjudicated by a clinical events committee. The definitions are provided in Table II in the Data Supplement.

Statistical Analysis

As prespecified, the primary outcome was assessed using a mixed logistic effects model with random intercept for each patient. However, because of the 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 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% CI 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 a cardiovascular cause 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 SVGs of patients that 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 standard deviation and categorical variables were described as frequencies and percentages. A 2-sided *P* value <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 have nonavailable 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.

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 presented 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 acute coronary syndrome in 31.3%, and cardiopulmonary bypass was used in 95.2% of procedures. At 1 year follow-up, 217 (87.9%) of the patients in the ticagrelor group and 212 (85.1%) of the patients in the placebo group used aspirin. In the ticagrelor group, 89 patients (36.0%) and, in the placebo group, 87 patients (34.9%) had permanently discontinued study medication, most frequently because of oral anticoagulation initiation after CABG (28 patients [11.3%] in the ticagrelor group and 29 [11.7%] patients in the placebo group). Over time, 11 patients (4.5%) in the ticagrelor group and 6 (2.4%) 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 regarding 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 randomization: 220 patients (484 SVGs) in the ticagrelor group and 223 patients (470 SVGs) in the placebo group. Mean days of randomization after which CCTA was performed was 370 days (±35) in the ticagrelor group and 371 days (±23) in the placebo group. In the ticagrelor group, 18 SVGs (3.7%) and, in the placebo group, 5 SVGs (1.1%) were not adequately visualized on CCTA. SVG occlusion occurred in 51 of 484 SVGs in the ticagrelor group (10.5%) and in 43 of 470 SVGs (9.1%) in the placebo group (OR, 1.29 [95% CI, 0.73–2.30]; *P*=0.38; Table 2). When analyzed on a per patient basis, in which subjects were defined as having at least one occluded SVG per patient, 31 patients of the 220 patients in the ticagrelor group had an occluded SVG (14.1%) versus 27 patients of the 223 patients (12.1%) in the placebo group (OR, 1.19 [95% CI, 0.69–2.08]; *P*=0.54). 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 35 (14.2%) patients in the ticagrelor group and in 29 (11.6%) patients in the placebo group (OR, 1.22 [95% CI, 0.72–2.05]; *P*=0.37; Table 2). Individual components of the outcome SVG failure analyzed on a per patient basis consisted of 31 SVG occlusions in the ticagrelor group versus 27 SVG occlusions in the placebo group,

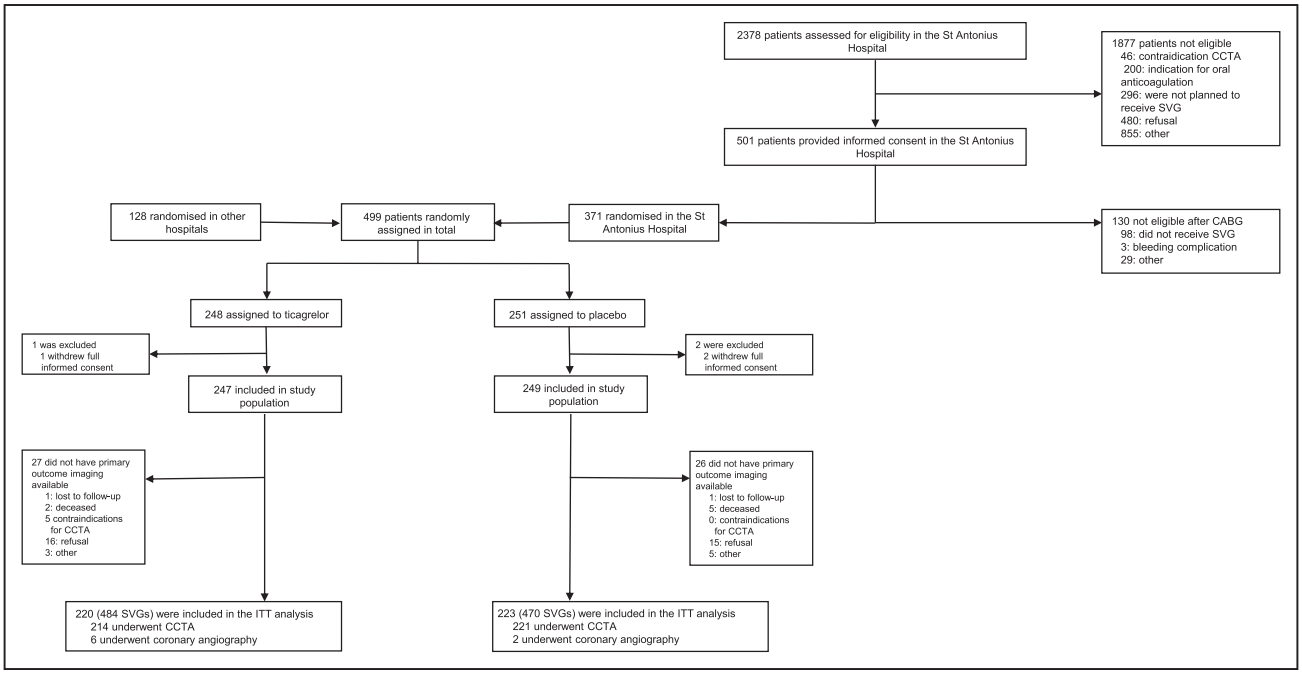

Figure 1. Randomization and follow-up.
CABG indicates coronary artery bypass grafting; CCTA, coronary computed tomography angiography; ITT, intention-to-treat; and SVG, saphenous vein graft.

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

Characteristics	Ticagrelor group (n=247)	Placebo group (n=249)
Age, y	68.0±8.2	67.8±8.5
Female sex, n (%)	35 (14.2)	29 (11.6)
Body mass index*	28.0±4.2	27.8±4.0
Race, n (%)		
White	240 (97.2)	235 (94.4)
Other	3 (1.2)	10 (4.0)
Unknown	4 (1.6)	4 (1.6)
Creatinine clearance ≥60 mL·min^{-1}·1.73 m^{-2} at admission,† n (%)	203 (82.2)	200 (80.3)
Smoker,‡ n (%)	44 (17.8)	48 (19.3)
Diabetes, n (%)	61 (24.7)	67 (26.9)
Hypertension, n (%)	154 (62.3)	154 (61.8)
Hypercholesterolemia, n (%)§	247 (100.0)	245 (98.4)
Chronic obstructive pulmonary disease, n (%)	30 (12.1)	26 (10.4)
Peripheral artery disease, n (%)	26 (10.5)	24 (9.6)
Previous acute coronary syndrome, n (%)	82 (33.2)	73 (29.3)
Previous percutaneous coronary intervention, n (%)	38 (15.4)	40 (16.1)
Previous CABG, n (%)	1 (0.4)	2 (0.8)
Previous cerebrovascular accident, n (%)	3 (1.2)	4 (1.6)
Prior major bleeding, n (%)	10 (4.0)	8 (3.2)
Peptic ulcer in medical history, n (%)	15 (6.1)	10 (4.0)
Indication for CABG, n (%)		
Chronic coronary syndrome	159 (64.4)	160 (64.3)
Acute coronary syndrome	82 (33.2)	73 (29.3)
Other	6 (2.4)	16 (6.4)
Left ventricular ejection fraction, n (%)		
>50%	199 (80.6)	187 (75.1)
30%–50%	38 (15.4)	56 (22.5)
<30%	6 (2.4)	5 (2.0)
Additive EuroSCOREǁ	3.3±2.20	3.09±2.2
CABG+aortic valve replacement, n (%)	7 (2.8)	6 (2.4)
Use of cardiopumonary bypass, n (%)	238 (96.4)	234 (94.0)
Graft type, n		
Left internal mammary artery	318	336
Right internal mammary artery	56	62
Radial artery	2	0
Saphenous vein	544	529
Mean total grafts/case	3.7±1.0	3.7±1.0
Mean total saphenous vein grafts/case	2.2±1.0	2.1±0.9
Sequential grafting of SVG, n (%)		
Yes	185 (75.2)	178 (71.5)
No	61 (24.8)	70 (28.1)
Start study drug after CABG, n (%)		
<13 h	117 (47.4)	135 (54.2)
13-24 h	36 (14.6)	25 (10.0)
24-48 h	57 (23.1)	62 (24.9)
>48 h	37 (15.0)	27 (10.8)
Loading dose study medication administered, n (%)		
Yes	191 (78.9)	198 (80.2)
No	50 (20.7)	49 (19.8)

Plus-minus values are means±SD. There were no significant differences between the 2 groups. Percentages may not total 100 because of rounding. CABG indicates coronary artery bypass grafting; and SVG, saphenous vein graft.

*The 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 quitted smoking <6 months.

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

ǁThe additive version of European System for Cardiac Operative Risk Evaluation (EuroSCORE) is a method of calculating predicted operative mortality for patients undergoing cardiac surgery: 0–2 points, low risk; 3–5 points, intermediate risk; and ≥6 points, high risk.

4 SVG revascularizations in the ticagrelor group versus none in the placebo group, 2 cases of myocardial infarction in the territory of a SVG in the ticagrelor group versus 1 case in the placebo group, and no sudden death in the ticagrelor group versus 1 case in the placebo group. Stenosis and occlusion rates in arterial grafts and all graft stenosis rates were low (significant stenosis and occlusion rates in arterial grafts: 8 of 337 (2.4%) arterial grafts in the ticagrelor group and 11 of 368 (3.0%) grafts in the placebo group; significant stenosis in all grafts: 3 of 821 (0.4%) grafts in the ticagrelor group and 0 of 838 grafts (0%) in the placebo group). Incidence of Bleeding Academic Research Consortium major bleeding at 1 year was 9 (3.6%) in the ticagrelor group and 6 (2.4%) in the placebo group (hazard ratio, 1.52 [95% CI, 0.54–4.28]; *P*=0.42; Table 2, Figure III in the Data Supplement). Incidence of Bleeding Academic Research Consortium minor bleeding at 1 year was 35 (14.2%) in the ticagrelor group and 31 (12.4%) in the placebo group (hazard ratio, 1.15 [95% CI, 0.71–1.86]; *P*=0.57; Table 2). Results of bleeding outcomes remained consistent when analyzed with Thrombolysis in Myocardial Infarction and Platelet Inhibition and Patient Outcomes 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

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

Outcomes	Ticagrelor group n/ total (%)	Placebo group n/ total (%)	Odds Ratio (95% CI)	Hazard ratio (95% CI)	*P* value
Primary					
SVG occlusion (per SVG)	51/484 (10.5)	43/470 (9.1)	1.29 (0.73–2.30)		0.38
SVG occlusion (per patient)	31/220 (14.1)	27/223 (12.1)	1.19 (0.69–2.08)		0.54
Secondary					
SVG failure	35/247 (14.2)	29/249 (11.6)	1.22 (0.72–2.05)		0.37
30-day BARC 3–5 bleeding	6/247 (2.4)	4/249 (1.6)		1.53 (0.43–5.41)	0.51
1-year BARC 3–5 bleeding	9/247 (3.6)	6/249 (2.4)		1.52 (0.54–4.28)	0.42
30-day BARC 2–5 bleeding	15/247 (6.1)	13/249 (5.2)		1.18 (0.56–2.47)	0.67
1-y BARC 2–5 bleeding	35/247 (14.2)	31/249 (12.5)		1.15 (0.71–1.86)	0.57

All outcomes were confirmed by an independent, blinded adjudication committee or core laboratory. The 95% CIs were not adjusted for multiple comparisons, and no clinical inferences can be made from these analyses. BARC indicates Bleeding Academic Research Consortium; and SVG denotes saphenous vein graft.

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 previously mentioned, results from 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 in comparison 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 either 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 9.1% 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 adding ticagrelor 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 trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies–CABG)[29] compared the combination of rivaroxaban plus aspirin, rivaroxaban alone, or aspirin alone on bypass graft patency. They observed similar low SVG occlusion rates (≈10%) as in our trial and concluded that the combination of rivaroxaban and aspirin (and rivaroxaban alone) did not reduce the graft occlusion rates in comparison 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 in comparison 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 ticagrelor has not only antithrombotic but also pleiotropic benefits[13] that have no relation to SVG patency. Our trial does not refute the advice of the guidelines to continue ticagrelor in patients undergoing CABG for ACS. However, possible advantages of ticagrelor should be weighed against potential adverse effects, such as dyspnea[34] and an increase in bleeding risk.[13] Therefore, further research is needed to determine the most appropriate treatment after CABG, not only to optimize graft patency but also to improve clinical outcomes. Bleeding

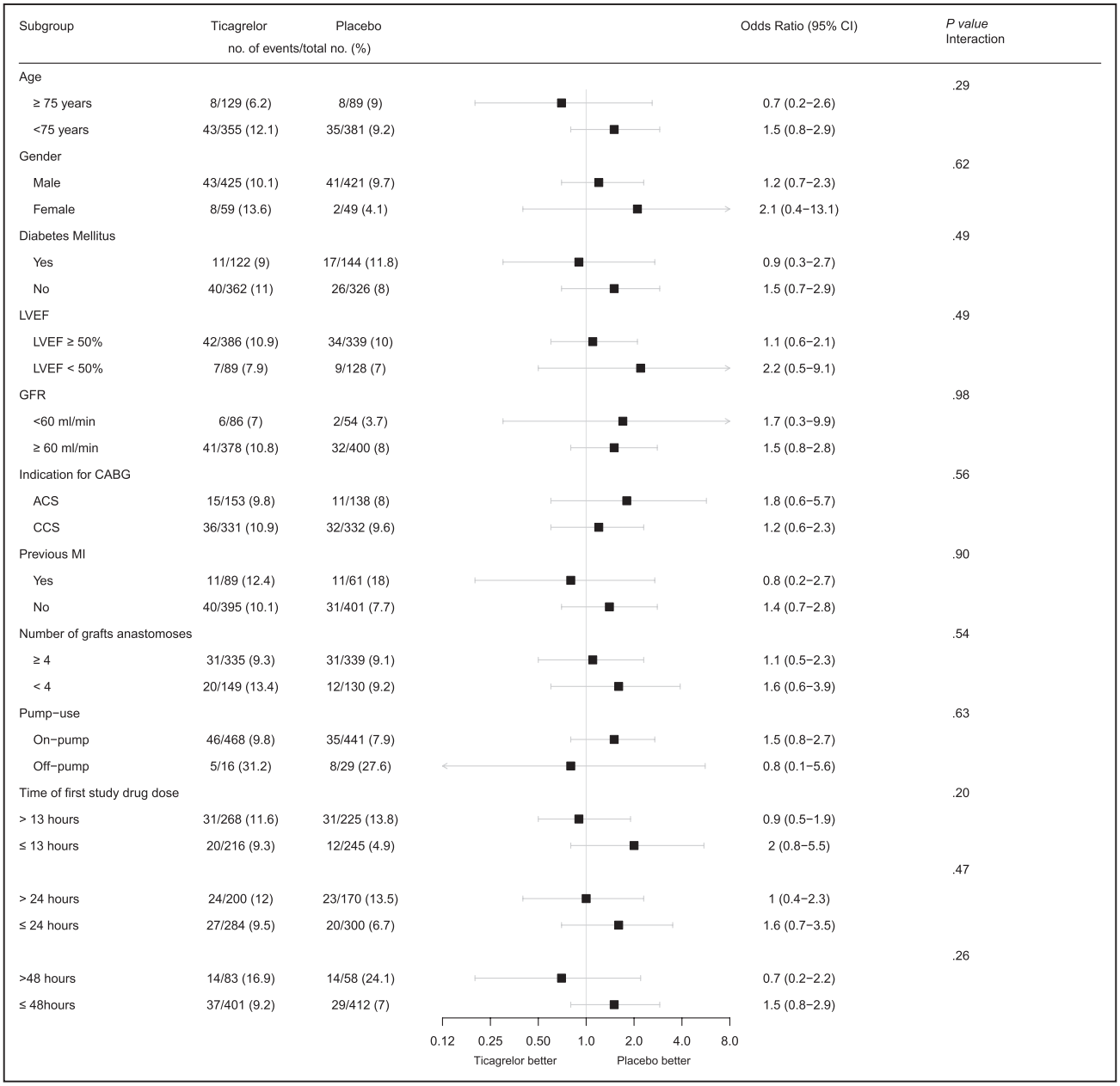

Figure 2. Subgroup analyses for the primary outcome.
Analyses of the primary outcome SVG occlusion for the 12 prespecified subgroups. Estimates are unadjusted hazard ratios and 95% CIs at 1 year after randomization. ACS indicates acute coronary syndrome; CABG, coronary artery bypass grafting; CCS, chronic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

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. Another notable finding in our trial was the occurrence of more (SVG) revascularizations in the ticagrelor group. We speculate that this could have been prompted by more complaints of dyspnea in the ticagrelor group, leading to more coronary angiographies and subsequent revascularizations, whereas ischemia detection had not been performed. The finding that 5 of 9 elective revascularizations were performed without ischemia detection supports this hypothesis.

Our study has important limitations. First, the trial was powered for the surrogate outcome SVG occlusion, and 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, 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 confidently assess SVG patency with CCTA in some patients, and especially with sequential grafts.

Table 3. Clinical Event Rates at 1 Year After Coronary Artery Bypass Grafting

Event	Ticagrelor group (n=247) n (%)	Placebo group (n = 249) n (%)	Hazard ratio (95% CI)
Death from any cause	2 (0.8)	5 (2.0)	0.40 (0.08–2.06)
Cardiovascular death	1 (0.4)	2 (0.8)	0.51 (0.05–5.58)
Cerebrovascular accident/transient ischemic attack	6 (2.4)	8 (3.2)	0.76 (0.26–2.18)
Acute coronary syndrome/myocardial infarction	6 (2.4)	3 (1.2)	2.03 (0.51–8.13)
Myocardial infarction in territory supplied by a saphenous vein graft	2 (0.8)	1 (0.4)	2.02 (0.18–22.24)
Revascularization	13 (5.3)	2 (0.8)	6.68 (1.51–29.59)
Saphenous vein graftrevascularization	4 (1.6)	0 (0)	Not available

All outcomes were confirmed by an independent, blinded adjudication committee. The 95% CIs were not adjusted for multiple comparisons, and no clinical inferences can be made from these analyses.

In conclusion, 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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