

Long-Term Outcome of Consecutive Patients With Previous Coronary Bypass Surgery, Treated With Newer-Generation Drug-Eluting Stents

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Background—Percutaneous coronary intervention (PCI) in patients with previous coronary artery bypass grafting (CABG) is associated with adverse clinical events. Although newer generation drug-eluting stents showed favorable short-term safety profiles, there is a lack of long-term outcome data. We evaluated the impact of previous CABG on 5-year clinical outcomes of patients treated with PCI using newer-generation drug-eluting stents.

Methods and Results—In this patient-level pooled analysis of the prospective TWENTE (The Real-World Endeavor Resolute versus Xience V Drug-Eluting Stent Study in Twente) trial and nonenrolled TWENTE registry, we assessed a consecutive series of patients who underwent PCI with newer-generation drug-eluting stents for non-ST-segment-elevation acute coronary syndromes or stable angina. Of all 1709 patients, 202 (11.8%) had a history of CABG. Patients with previous CABG had significantly higher 5-year rates of cardiac death (10.4% versus 4.3%; $P < 0.001$) and target vessel revascularization (25.0% versus 8.1%; $P < 0.001$). These differences remained statistically significant after adjustment for differences in baseline characteristics. Landmark analysis revealed that from 1- to 5-year follow-up, the rates of cardiac death (8.1% versus 3.2%; $P < 0.001$) and target vessel revascularization (17.1% versus 5.9%; $P < 0.001$) were significantly higher in patients with previous CABG. Among patients with a history of CABG, PCI of an obstructed vein graft was associated with a higher rate of 5-year target vessel revascularization ($P = 0.003$).

Conclusions—At 5-year follow-up after PCI with newer-generation drug-eluting stents, the risk of cardiac death and target vessel revascularization was significantly higher in patients with previous CABG. The target vessel revascularization rate was highest in patients who underwent PCI of obstructed vein grafts. (*J Am Heart Assoc.* 2018;7:e007212. DOI: 10.1161/JAHA.117.007212.)

Key Words: coronary artery bypass graft • drug-eluting stent • percutaneous coronary intervention • Resolute • Xience V

Patients with a history of coronary artery bypass grafting (CABG) are often older, have more comorbidities, and require treatment of more complex target lesions.^{1–3} Gradual failure of a bypass graft, lesion recurrence, and disease progression in native coronary vessels are the main causes of repeat revascularization in patients with a history of CABG.^{4–7} Current guidelines recommend percutaneous coronary intervention (PCI) as the first choice for treating late (>1 month)

graft failure, because of an increased mortality risk associated with redo CABG.^{8,9}

PCI in patients with previous bypass surgery is often complex and more often associated with adverse clinical outcomes.^{10–12} Several studies have shown significantly higher rates of repeat target vessel revascularization,^{7,13} particularly if PCI was performed in degenerated saphenous vein grafts (SVGs), which also bear an increased risk for

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Accompanying Tables S1 and S2 are available at <http://jaha.ahajournals.org/content/7/3/e007212/DC1/embed/inline-supplementary-material-1.pdf>

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Clinical Perspective

What Is New?

- This first analysis of 5-year follow-up after percutaneous coronary intervention with newer-generation drug-eluting stents in patients with versus without previous coronary artery bypass grafting demonstrated that percutaneous coronary intervention with newer-generation drug-eluting stents in patients with previous coronary artery bypass grafting is safe, but the risk of repeat revascularization remains high.

What Are the Clinical Implications?

- Knowledge of the safety but increased risk of repeat revascularization following percutaneous coronary intervention in patients with previous bypass surgery, particularly if a diseased vein graft requires treatment, will be relevant to cardiologists and other physicians involved in heart team discussions and informed consent.

embolizing friable debris and atherothrombotic material.^{2,14–18} The introduction of the early drug-eluting stents (DESs) improved clinical outcomes of PCI in bypass grafts, compared with bare metal stents.^{19–21} Newer-generation DESs showed even more favorable short-term safety profiles.¹⁴ However, there is a lack of long-term data on outcomes after PCI with newer-generation DESs in patients with versus without previous CABG.^{15,16}

In this study, we investigated the 5-year clinical outcomes of a consecutive series of patients treated with PCI with newer-generation DESs for stable angina or non–ST-segment–elevation acute coronary syndromes²² and evaluated the impact of previous CABG on long-term outcomes. In addition, among patients with a history of CABG, we compared the long-term clinical results following PCI in native coronary arteries versus bypasses.

Methods

The data that support the findings of this study are available to other researchers on request.

Study Design and Patient Population

This analysis was performed using the patient-level pooled data (n=1709) from the prospective TWENTE (Real-World Endeavor Resolute vs Xience V Drug-Eluting Stent Study in Twente) trial and the nonenrolled TWENTE registry²²; details of these studies have been reported previously.^{23,24} In brief, the TWENTE trial (ClinicalTrials.gov identifier NCT01066650) is an investigator-initiated, patient-blinded, randomized, comparative DES trial with limited exclusion criteria.²³ A total of

1391 patients were enrolled between June 18, 2008, and August 26, 2010, at Thoraxcentrum Twente, Enschede, the Netherlands, and were 1:1 randomized to treatment with Resolute zotarolimus-eluting stents (Medtronic Vascular) or Xience V everolimus-eluting stents (Abbott Vascular).²³ During the course of the randomized trial, 318 eligible but nonenrolled patients were treated at the operator's discretion with one of the DESs that were examined in the randomized trial, using the same routine clinical and procedural strategies.²⁴ Both studies complied with the Declaration of Helsinki for investigation in human beings and were approved by the Medical Ethical Committee Twente and the institutional review board (Medisch Spectrum Twente (Thoraxcentrum Twente)). All participants in the randomized trial provided written informed consent. For the registry, patients were not required to change behavior or take action other than following their regular treatment; therefore, according to Dutch law, and as approved by the Medical Ethical Committee Twente, written informed consent from patients in this registry was not required.

Pooling data from both studies permitted the assessment of a consecutive series of 1709 patients who were treated at a high-volume tertiary center for cardiac intervention (Thoraxcentrum Twente, Enschede, the Netherlands) by PCI with a second-generation DES for non–ST-segment–elevation acute coronary syndromes or stable angina. The current study evaluated the impact of previous CABG on 5-year outcomes. Baseline characteristics and 1-year clinical outcomes of patients with versus without previous CABG have been reported.¹⁴

Clinical Procedures

Patients from the TWENTE trial and the nonenrolled TWENTE registry were treated by the same operators. Interventional procedures were performed according to standard techniques, routine clinical procedures, and current medical guidelines. Details of the intervention, medical treatment, ECG assessment, and laboratory tests have been described^{23,24} and did not differ between studies.

Definitions of Clinical End Points

End point definitions, which did not differ between the randomized trial and registry,^{23,24} were based on suggestions from the Academic Research Consortium,²⁵ including the addendum on the definition of myocardial infarction (MI).²⁶ In brief, death was considered cardiac unless an evident noncardiac cause could be established. MI was defined by any creatine kinase concentration of more than double the upper limit of normal with elevated values of confirmatory cardiac biomarkers. Target vessel MI was related to the target vessel or could not be related to another vessel. Target vessel

revascularization was defined as any repeat coronary revascularization of the target vessel by repeat PCI or surgery.

Acquisition and Analysis of Clinical Follow-up Data

Clinical follow-up data were obtained at visits to outpatient clinics or, if not feasible, by telephone or medical questionnaire. Monitoring was performed by an independent, external clinical research organization (Diagram, Zwolle, the Netherlands). Independent contract research organizations (Cardialysis, Rotterdam, the Netherlands; Diagram, Zwolle, the Netherlands) performed the adjudication of adverse clinical events for both randomized trial participants and nonenrolled eligible patients.

Statistical Analyses

Data were reported as frequencies and percentages for dichotomous and categorical variables and as mean±SD for continuous normally distributed variables. The chi-square test and Fisher exact test were used as appropriate. Differences in continuous variables between groups were assessed with the Student *t* test. The time to clinical end points was assessed according to Kaplan–Meier methods, and the log-rank test was applied for between-group comparisons. Hazard ratios were computed using Cox proportional hazards regression analysis. Propensity score analysis was used for adjustment of potential confounders. All variables that were plausible potential confounders were used for the propensity score: age, sex, diabetes mellitus, previous PCI, previous MI, current smoker status, clinical syndrome at presentation, chronic renal failure, left anterior descending artery treatment, left main artery treatment, peripheral arterial disease, multivessel treatment, treatment of at least 1 bifurcation lesion, and treatment of at least 1 chronic total occlusion. This propensity score was estimated using multiple logistic regression analysis. The propensity score coefficients are shown in Table S1. A multivariate Cox regression model, including the propensity score as an independent variable, was then used to adjust for the propensity score. In addition to multivariate analysis with use of propensity score adjustment, a sensitivity analysis was performed including all covariates separately in a multiple regression analysis (Table S2). A 2-sided *P* value <0.05 was considered significant. Data analysis was performed with SPSS (version 22.0; IBM Corp).

Results

Baseline Characteristics

Of all 1709 patients, 202 (11.8%) had a history of CABG, which had been performed 11.2 ± 8.5 years before the index

PCI. Sole use of arterial grafts was present in only 18% of the patients, whereas 63% were treated with a combination of arterial grafts and SVGs. Obstructed bypass grafts were present in 141 patients (69.8%) with previous CABG (arterial graft: 22.7%; SVG: 77.3%). In 111 of these patients, the obstructed graft was the culprit lesion (ie, lesion causing complaints), but only 65 patients (58.6%) underwent graft PCI; the other 46 patients (41.4%) were treated in native coronary vessels. Differences in baseline characteristics are shown in Table 1.

Clinical Event Rates at 5-Year Follow-up

Patients with previous CABG had a significantly higher 5-year rate of target vessel revascularization than patients without previous CABG (25.0% versus 8.1%; *P*<0.001; Table 2), whereas the rate of definite stent thrombosis was low and similar for both groups (0.6% versus 0.8%). Cardiac death occurred more often in patients with previous CABG (10.4% versus 4.3%; *P*<0.001). There was no between-group difference in the incidence of non-target vessel-related revascularization (7.9% versus 7.5%). The time-to-event curves of several outcome parameters are displayed in Figures 1 and 2.

Multivariate analysis with propensity score adjustment demonstrated, after adjustment for all available known potential confounders, that the 5-year rates of target vessel revascularization (adjusted hazard ratio: 3.00; 95% confidence interval, 2.01–4.46) and cardiac death (adjusted hazard ratio: 1.87; 95% confidence interval, 1.03–3.39) were significantly higher in patients with previous CABG (Table 2).

Landmark analysis between 1- and 5-year follow-up showed significantly higher cardiac mortality in patients with previous CABG (8.1% versus 3.2%; *P*<0.001; Figure 3), whereas there was no significant between-group difference in cardiac death during the first 12 months (2.5% versus 1.1%; *P*=0.11). In addition, target vessel revascularization occurred more often in patients with previous CABG during both the first 12 months and from 1- to 5-year follow-up (0–1 year: 9.5% versus 2.4%, *P*<0.001; 1–5 years: 17.1% versus 5.9%, *P*<0.001; Figure 3). Stent thrombosis rates were similar during the first 12 months and from 1- to 5-year follow-up (Figure 4).

Subgroup Analysis Among Patients With Previous CABG

The outcome of patients with a history of CABG was assessed according to the actually treated vessel. PCI of a diseased bypass graft was associated with a worse 5-year clinical outcome (Table 3). Target vessel revascularization

Table 1. Baseline Characteristics

Patient Characteristics	All Patients (n=1709)		P Value
	Previous CABG (n=202)	No Previous CABG (n=1507)	
Age, y, mean±SD	68.5±9.4	64.1±10.7	<0.001
Women	41 (20.3)	435 (28.9)	0.011
Diabetes mellitus	58 (28.7)	315 (20.9)	0.012
Hypertension	113 (55.9)	845 (56.1)	0.972
Hypercholesterolemia	143/199 (71.9)	853/1476 (57.8)	<0.001
Current smoker	22 (10.9)	388 (25.7)	<0.001
Family history of CAD	108/181 (59.7)	734/1403 (52.3)	0.062
Previous MI	82 (40.6)	505 (33.5)	0.046
Previous PCI	81 (40.1)	299 (19.8)	<0.001
Clinical syndrome at presentation			0.023
NSTEMI	40 (19.8)	435 (28.9)	
Unstable angina	51 (25.2)	358 (23.8)	
Stable angina	111 (55.0)	714 (47.4)	
Chronic renal failure	13 (6.4)	46 (3.1)	0.013
LVEF <30%	10/144 (6.9)	35/1106 (3.2)	0.022
Peripheral arterial disease	26 (14.0)	122 (9.0)	0.032
Multivessel treatment	52 (25.7)	345 (22.9)	0.368
Total number of lesions treated per patient			0.381
1	133 (65.8)	927 (61.5)	
2	49 (24.3)	436 (28.9)	
≥3	20 (9.9)	144 (9.6)	
At least one chronic total occlusion treated	12 (5.9)	111 (7.4)	0.462

Values are n (%) unless otherwise stated. CABG indicates coronary artery bypass grafting; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment-elevation myocardial infarction; PCI, percutaneous coronary intervention.

rates were higher in patients with graft lesions who underwent PCI of the bypass graft than in patients (with or without graft lesions) who were treated exclusively in native coronary arteries (39.6% versus 18.5% and 18.1%; $P=0.003$; Figure 5).

Discussion

Main Findings

We assessed the 5-year outcomes of a consecutive series of 1709 patients treated with PCI with second-generation DESs for non-ST-segment-elevation acute coronary syndromes or stable angina, and then compared the long-term outcomes of 202 patients with previous CABG versus 1507 patients who had no history of bypass surgery. This study is the first to assess the impact of previous CABG on 5-year outcomes after PCI with newer-generation DESs. Patients with previous CABG had significantly higher 5-year rates of target vessel

revascularization (25.0% versus 8.1%) and cardiac death (10.4% versus 4.3%) than patients who had no history of CABG. These differences remained statistically significant after adjustment for between-group differences in baseline characteristics. When the analysis was confined to events that occurred within the second to fifth years of follow-up, patients with versus without previous CABG still showed significant differences in the aforementioned clinical end points. Among patients with a history of CABG, PCI of an obstructed bypass graft was associated with a higher rate of 5-year target vessel revascularization.

Previous CABG and Cardiovascular Event Risk

Previous studies reported conflicting mortality data following PCI in patients with versus without a history of CABG.^{7,10–13,15,17} In patients presenting with ST-segment-elevation MI, there was no baseline-adjusted difference in 1-year outcome between patients with versus without previous

Table 2. Five-Year Clinical Event Rates in Patients With Previous CABG Versus Patients Without a History of Bypass Surgery

Patient Characteristics	All Patients (n=1709)		Unadjusted HR (95% CI)	P Value	Adjusted HR (95% CI)	P Value
	Previous CABG (n=202)	No Previous CABG (n=1507)				
Any death	35 (17.4)	150 (10.1)	1.81 (1.25–2.61)	0.001	1.36 (0.88–2.10)	0.16
Cardiac death	20 (10.4)	63 (4.3)	2.46 (1.49–4.06)	<0.001	1.87 (1.03–3.39)	0.04
Any myocardial infarction	22 (11.5)	107 (7.3)	1.58 (1.00–2.50)	0.05	1.60 (0.95–2.70)	0.08
Target vessel MI	19 (9.9)	94 (6.4)	1.55 (0.94–2.53)	0.08	1.67 (0.96–2.93)	0.07
Target vessel revascularization	47 (25.0)	116 (8.1)	3.41 (2.43–4.79)	<0.001	3.00 (2.01–4.46)	<0.001
Target lesion revascularization	38 (20.3)	85 (5.9)	3.71 (2.53–5.44)	<0.001	3.43 (2.19–5.36)	<0.001
Non-target vessel revascularization	15 (7.9)	107 (7.5)	1.08 (0.63–1.86)	0.78	0.87 (0.47–1.61)	0.65
Target vessel failure	73 (37.6)	231 (15.7)	2.66 (2.04–3.46)	<0.001	2.69 (1.99–3.65)	<0.001
Definite stent thrombosis	1 (0.6)	11 (0.8)	0.69 (0.09–5.36)	0.72	0.66 (0.07–6.20)	0.72

Values are n (%). Data were analyzed using the Kaplan-Meier method, which implies that patients who could not be followed up for the entire 5 years because of death, consent withdrawal, or loss to follow-up were censored at the exact moment of dropout. Therefore, the percentages provided in the table may differ slightly from the results of straightforward calculations of nominator divided by denominator. CABG indicates coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

CABG.^{7,13} In other studies, among patients treated for various types of acute coronary syndromes, 1-year mortality was significantly higher in patients with a history of CABG.^{10,12} In

addition, among patients with various types of acute coronary syndromes, the long-term baseline-adjusted risk of all-cause and cardiac mortality following treatment with or without PCI

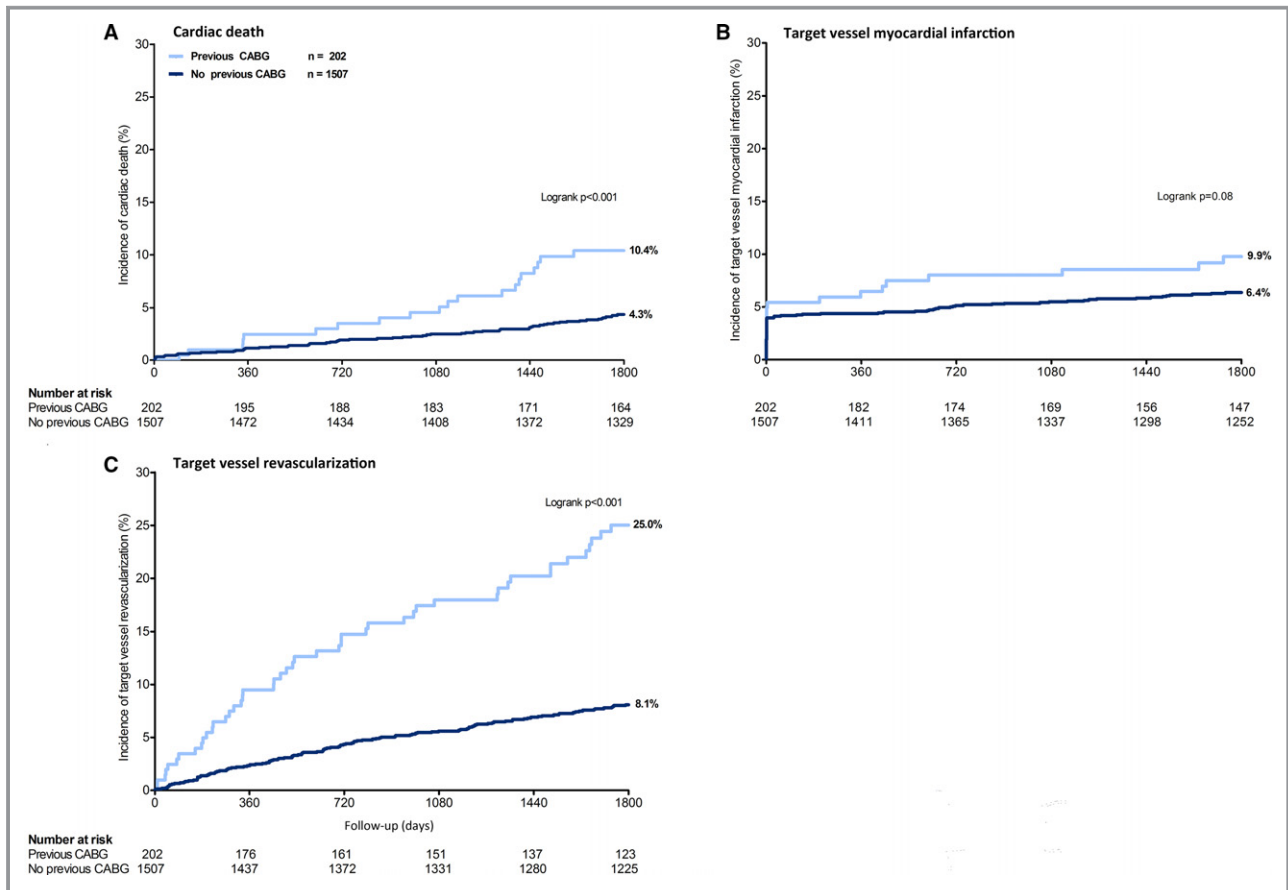


Figure 1. Five-year time-to-event curves of several clinical outcome parameters. Kaplan-Meier cumulative incidence curves at 5 years for patients with versus without previous coronary artery bypass grafting (CABG) for (A) cardiac death, (B) target vessel myocardial infarction, and (C) target vessel revascularization.

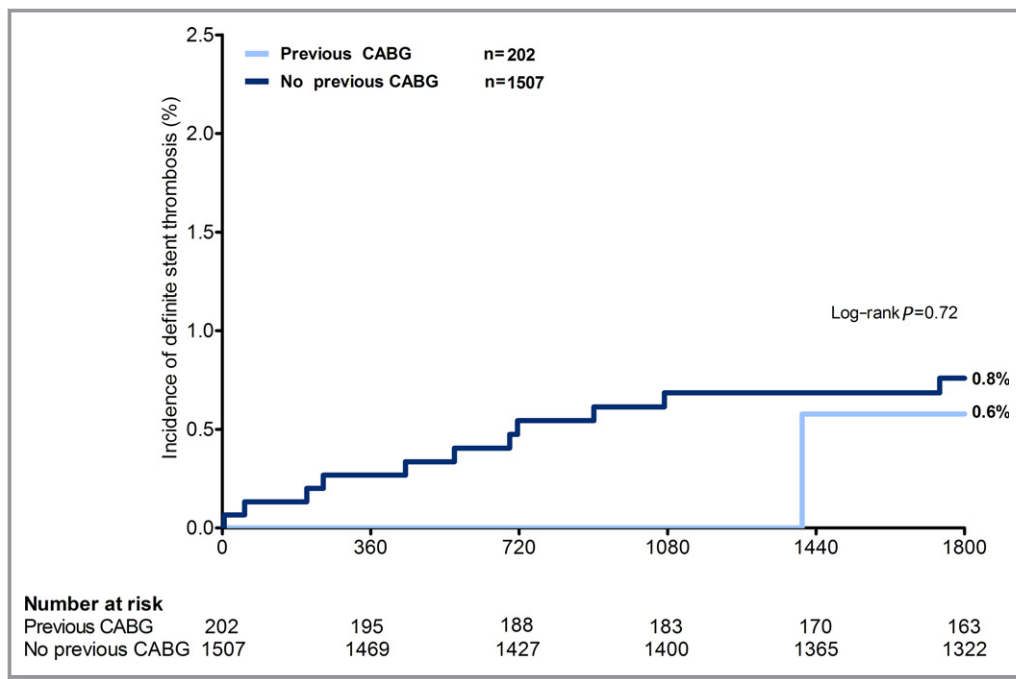


Figure 2. Five-year time-to-event curves of definite stent thrombosis. Kaplan–Meier cumulative incidence curve at 5 years for patients with versus without previous coronary artery bypass grafting (CABG) for definite stent thrombosis.

was not significantly increased in patients who had a history of CABG.^{11,15,17}

In the present study, following adjustment for potential confounders, 5-year cardiac mortality risk was significantly higher in all-comer patients who previously had undergone CABG (adjusted hazard ratio: 1.87). This difference was mainly based on a significantly higher rate of cardiac death during the second to fifth years of follow-up (8.1% versus 3.2%). This difference in cardiac mortality from the aforementioned studies may be largely explained by differences in study population and treatment. In the current study, we assessed a consecutive series of patients who were treated with newer-generation DESs for all clinical syndromes except ST-segment–elevation MI,^{14,22} whereas other studies with long-term follow-up exclusively examined patients with ST-segment–elevation MI or patients with acute coronary syndromes.^{10,11,17} Furthermore, these patients had been treated with or without PCI—before the introduction of the newer-generation DES.^{11,17}

In our study, patients with a history of CABG who were treated with PCI with newer-generation DESs had a 3.1-times higher baseline-adjusted risk of repeat target vessel revascularization during the 5-year follow-up compared with patients who had no history of CABG. In the era of early generation DESs, the risk of repeat target vessel revascularization was also higher in patients with previous CABG.^{10,11,15,17}

Venous and Arterial Bypass Grafts

We observed that the risk of repeat revascularization was highest in patients who had undergone a stent implantation in a diseased SVG, which corroborates previous studies.^{15–17,27,28} In addition, we found that patients with a stenosis in a bypass graft who were treated in the native vessel had a target vessel revascularization rate that was similar to that of patients with nonobstructed (ie, patent) bypass grafts who were treated for native vessel lesions (18.5% versus 18.1%). Both subgroups of patients had relatively high rates of target vessel revascularization compared with patients without a history of CABG; this finding may be due to high lesion complexity, comorbidities, and aggressive atherosclerosis and disease progression in native coronary vessels in patients with a history of CABG.

In patients who were treated with a second-generation DES in a bypass graft, the incidence of target vessel revascularization during the first year was similar to what had been seen 2 decades ago after the treatment of native coronary vessels with bare metal stents. But unlike the restenosis process in bare metal stents, which generally is confined to the first 6 to 8 months, bypass degeneration is a steady process that leads to a target vessel revascularization rate as high as 40% after no more than 5 years from PCI with contemporary DESs.

A known disadvantage of using saphenous veins as bypass material is the accelerated progression of atherosclerosis in

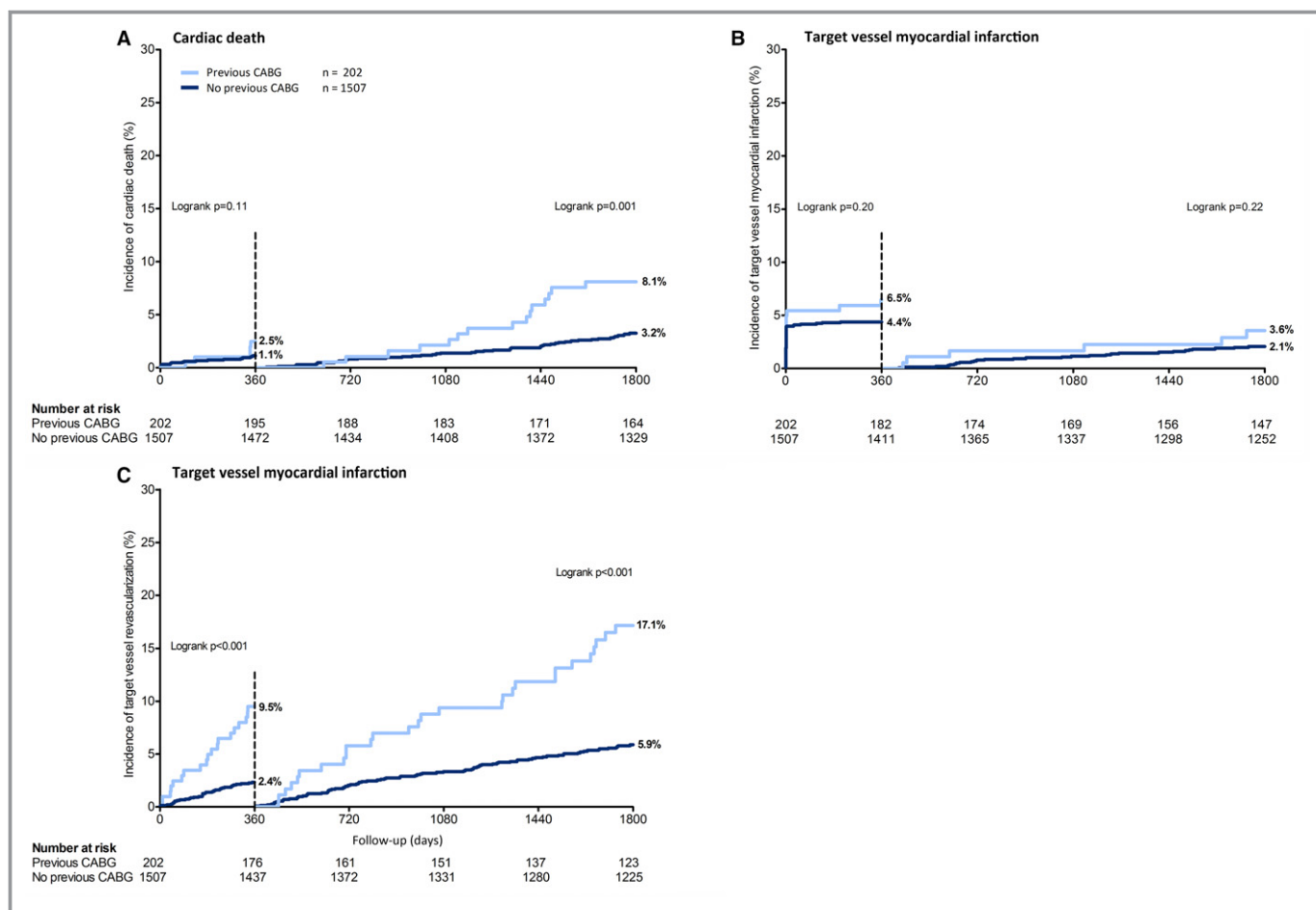


Figure 3. Five-year time-to-event curves of several clinical outcome parameters with landmark analysis at 1 year. Landmark analysis at 1-year follow-up for patients with versus without previous coronary artery bypass grafting (CABG) for (A) cardiac death, (B) target vessel myocardial infarction, and (C) target vessel revascularization.

SVGs, which leads to friable plaques with a high risk of embolization and thrombosis and, ultimately, high rates of graft stenosis and bypass occlusion.^{1–3} Ten years after CABG, $\approx 75\%$ of SVGs are severely diseased or occluded.^{29,30} Attrition in SVGs and the development of new native vessel stenosis (distal to the bypass anastomosis) related to progression of coronary atherosclerosis are typical causes of late graft failure.² Consequently, PCI in SVGs is associated with a higher risk of atheroma embolization, resulting in the no-reflow phenomenon, graft perforation, and restenosis, compared with PCI in native coronary vessels.¹⁸

In contrast to SVGs, arterial bypass grafts are significantly less susceptible to attrition and accelerated atherosclerosis; therefore, they are more likely to remain patent than SVGs.⁴ The most frequent causes of arterial graft dysfunction are neointimal hyperplasia secondary to a vascular trauma during surgical preparation of the graft or anastomosis and general disease progression in the native coronary vasculature.³¹ A greater patency of arterial grafts was also observed in the present study population. Patients

with previous CABG required treatment of the left descending artery less often than patients without previous CABG (17.3% versus 55.4%) because of (generally) proper functioning of the left internal mammary artery to left descending artery bypass grafts.

Long-Term Outcome of PCI With Newer-Generation DESs After Previous CABG

Most CABG-related studies examined patients treated with bare metal stents or first-generation DESs.^{12,13,15,16} The use of first-generation DESs in graft vessel lesions was associated with improved long-term clinical outcomes compared with bare metal stent use.^{19–21} Little is known about the use of second-generation DESs in patients with previous CABG.^{14,32,33} Long-term follow-up data are scarce but of particular interest, as a previous study suggested the presence of a late “catch-up” in target vessel revascularization after PCI with first-generation DESs in SVGs.³⁴

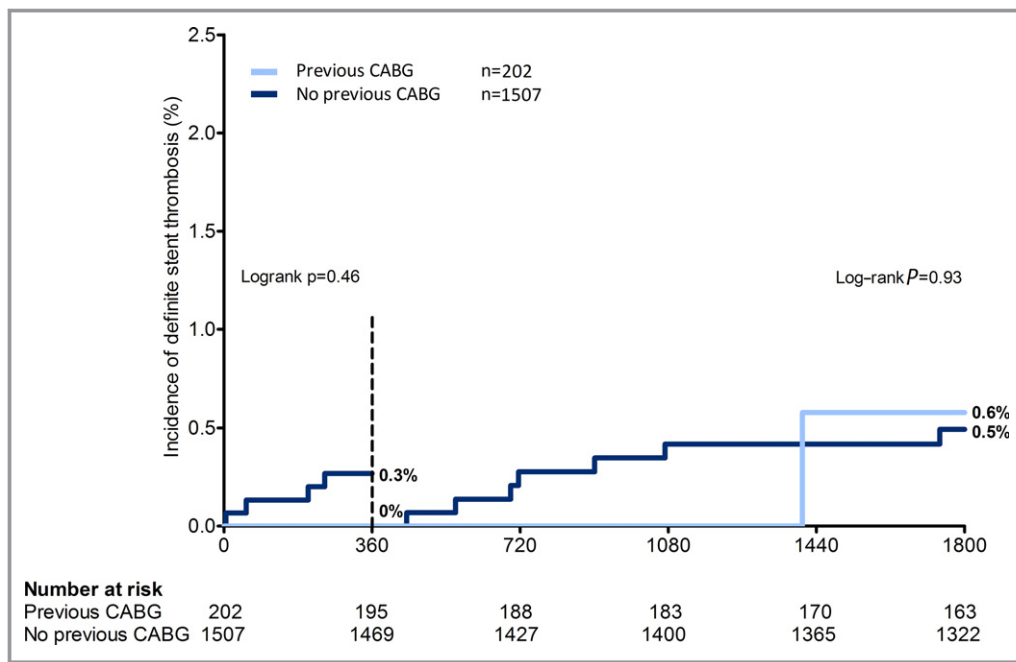


Figure 4. Five-year time-to-event curves of definite stent thrombosis with landmark analysis at 1 year. Landmark analysis at 1-year follow-up for patients with versus without previous coronary artery bypass grafting (CABG) for definite stent thrombosis.

A relatively small, retrospective, observational study that included patients during a period of 9 years (with inevitable changes in PCI technique, devices, and medications) found significantly lower 1- and 2-year rates of a composite end point of safety and efficacy in patients treated with newer-generation DESs. Another retrospective analysis used a historical control group to show, at 1-year follow-up, no significant differences in target vessel revascularization between early versus newer-generation DESs (10.2% versus 10.7%).³³ Our group previously reported a target vessel revascularization rate of 9.4% in patients with a history of CABG at 1-year follow-up.¹⁴ The difference in event rate from the above-mentioned study may be best explained by dissimilarities in study population.

Implications of the Study

This first analysis of 5-year follow-up after PCI with newer-generation DESs in patients with versus without previous CABG demonstrated a persistently low risk of MI and stent thrombosis despite a history of CABG. PCI with newer-generation DESs in patients with previous CABG is safe, but the high long-term rate of target vessel revascularization shows that after treatment with newer-generation DESs, the risk of repeat revascularizations remains high. In times of increasingly low adverse event rates of randomized all-comer trials,³⁵ it will be of paramount importance to keep enrolling patients with a history of CABG to ensure adequate statistical power. In clinical practice, knowledge of the safety but

Table 3. Subgroup Analysis in Patients With Previous CABG, Based on Culprit and Target Vessels: 5-Year Outcomes

Patient Characteristics	Patients With Previous CABG (n=202)			P Value
	Culprit Vessel Is Native Vessel That Was Stented (n=91)	Culprit Vessel Is Bypass Graft, But Native Vessel Was Stented (n=46)	Culprit Vessel Is Bypass Graft That Was Stented (n=65)	
Cardiac death	9 (10.6)	7 (15.3)	4 (6.5)	0.33
Target vessel MI	6 (6.9)	4 (9.1)	9 (14.7)	0.30
Target vessel revascularization	15 (18.1)	8 (18.5)	24 (39.6)	0.003

Values are n (%). Data were analyzed using the Kaplan-Meier method, which implies that patients who could not be followed up for the entire 5 years because of death, consent withdrawal, or loss to follow-up were censored at the exact moment of dropout. Therefore, the percentages provided in the table may differ slightly from the results of straightforward calculations of nominator divided by denominator. CABG indicates coronary artery bypass grafting; MI, myocardial infarction.

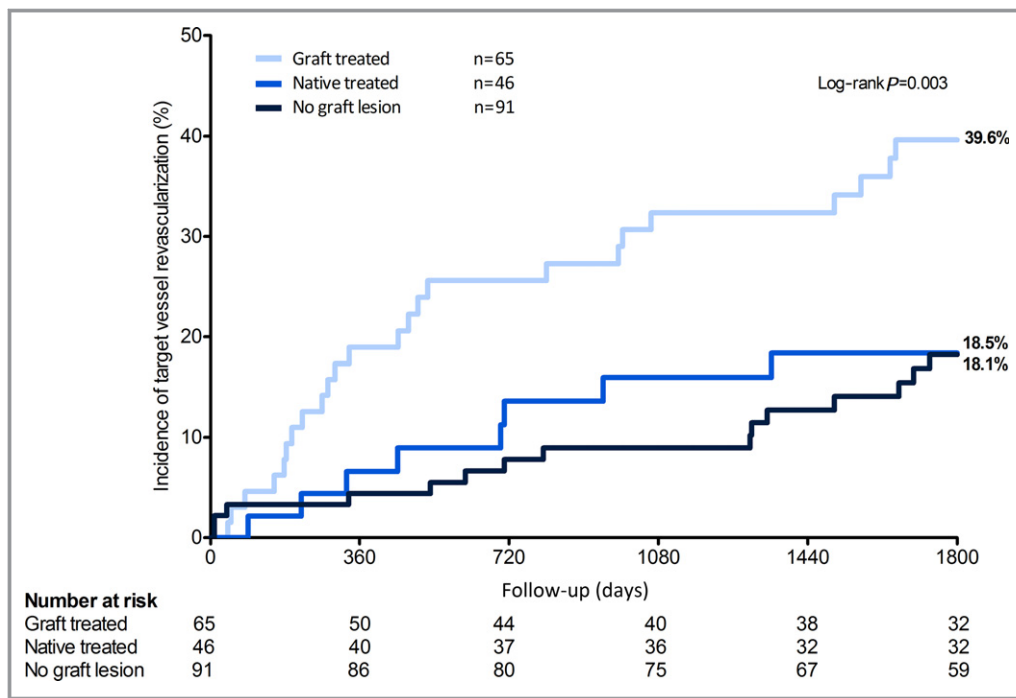


Figure 5. Five-year time-to-event curves of target vessel revascularization in subgroups of patients with previous coronary artery bypass grafting (CABG). Kaplan–Meier cumulative incidence curves for target vessel revascularization for subgroups of patients with a history of CABG.

increased risk of repeat target vessel revascularization following PCI in patients with previous coronary bypass surgery—particularly if a diseased SVG requires treatment—will be relevant to cardiologists and other physicians involved in heart team discussions and informed consent.

Limitations

The sample size of the CABG group (n=202) limits the power of the study to show statistically significant differences in outcomes, especially in subgroup analyses. The results of this post hoc analysis are hypothesis generating, and the findings should not be transferred to the setting of primary PCI, as patients with acute ST-segment–elevation MI were not assessed. The choice of treating native vessels or bypass grafts was left to the operator’s discretion; because a native vessel PCI is generally the preferred approach,⁹ patients with the most complex native vessel disease may have undergone bypass treatment because a native vessel PCI was no longer an option. However, in the present study, the high target vessel revascularization rate in patients treated in SVGs supports the “native vessel first” strategy.

Conclusions

At 5-year follow-up after PCI with newer-generation DES, the risk of cardiac death and target vessel revascularization was

significantly higher in patients with previous CABG. The target vessel revascularization rate was highest in patients who underwent PCI of obstructed vein grafts.

Sources of Funding

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Disclosures

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References

- Tejada JG, Velazquez M, Hernandez F, Albarran A, Gomez I, Rodriguez S, Andreu J, Tascon J. Percutaneous revascularization in patients with previous coronary artery bypass graft surgery. Immediate and 1-year clinical outcomes. *Int J Cardiol*. 2009;134:201–206.
- Scarsini R, Zivelonghi C, Pesarini G, Vassanelli C, Ribichini FL. Repeat revascularization: percutaneous coronary intervention after coronary bypass graft surgery. *Cardiovasc Revasc Med*. 2016;17:272–278.
- Ribichini F, Pugno F, Ferrero V, Wijns W, Vacca G, Vassanelli C, Virmani R. Long-term histological and immunohistochemical findings in human venous aorto-coronary bypass grafts. *Clin Sci (Lond)*. 2008;114:211–220.
- Sabik JF, Blackstone EH, Gillinov AM, Smedira NG, Lytle BW. Occurrence and risk factors for reintervention after coronary artery bypass grafting. *Circulation*. 2006;114(1 Suppl):I454–I460.

5. Tatoulis J, Buxton BF, Fuller JA. Patency of 2127 arterial to coronary conduits over 15 years. *Ann Thorac Surg*. 2004;77:93–101.
6. Escaned J. Secondary revascularization after CABG surgery. *Nat Rev Cardiol*. 2012;9:540–549.
7. Garg P, Kamaruddin H, Iqbal J, Wheeldon N. Outcomes of primary percutaneous coronary intervention for patients with previous coronary artery bypass grafting presenting with ST-segment elevation myocardial infarction. *Open Cardiovasc Med J*. 2015;9:99–104.
8. Morrison DA, Sethi G, Sacks J, Henderson WG, Grover F, Sedlis S, Esposito R. Percutaneous coronary intervention versus repeat bypass surgery for patients with medically refractory myocardial ischemia: AWESOME randomized trial and registry experience with post-CABG patients. *J Am Coll Cardiol*. 2002;40:1951–1954.
9. Windecker S, Kohli P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Juni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2014;35:2541–2619.
10. Nikolsky E, McLaurin BT, Cox DA, Manoukian SV, Xu K, Mehran R, Stone GW. Outcomes of patients with prior coronary artery bypass grafting and acute coronary syndromes: analysis from the ACUITY (acute catheterization and urgent intervention triage strategy) trial. *J Am Coll Cardiol Interv*. 2012;5:919–926.
11. Berry C, Pieper KS, White HD, Solomon SD, van de Werf F, Velazquez EJ, Maggioni AP, Califf RM, Pfeffer MA, McMurray JJ. Patients with prior coronary artery bypass grafting have a poor outcome after myocardial infarction: an analysis of the valsartan in acute myocardial infarction trial (VALIANT). *Eur Heart J*. 2009;30:1450–1456.
12. Teixeira R, Vieira MJ, Ribeiro MA, Goncalves L, Gersh BJ. Prognosis following acute coronary syndromes according to prior coronary artery bypass grafting: meta-analysis. *Eur Heart J Acute Cardiovasc Care*. 2015;4:518–527.
13. Iqbal J, Kwok CS, Kontopantelis E, de Belder MA, Ludman PF, Glannoudi M, Gunning M, Zaman A, Mamas MA. Outcomes following primary percutaneous coronary intervention in patients with previous coronary artery bypass surgery. *Circ Cardiovasc Interv*. 2016;9:e003151.
14. Sen H, Lam MK, Tandjung K, Löwik MM, van Houwelingen KG, Stael MG, Louwerenburg HW, de Man FFAH, Linssen GCM, Grandjean JG, Doggen CJM, van Birgelen C. Impact of previous coronary artery bypass surgery on clinical outcome after percutaneous interventions with second generation drug-eluting stents in TWENTE trial and Non-Enrolled TWENTE registry. *Int J Cardiol*. 2014;176:885–890.
15. Yamaji K, Kimura T, Morimoto T, Nakagawa Y, Inoue K, Nobuyoshi M, Mitsudo K. Percutaneous coronary intervention in patients with previous coronary artery bypass grafting (from the J-Cypher Registry). *Am J Cardiol*. 2013;112:1110–1119.
16. Xanthopoulos I, Davlourou P, Tsigkas G, Panagiotou A, Hahalís G, Alexopoulos D. Long-term clinical outcome after percutaneous coronary intervention in graft vs native vessels in patients with previous coronary artery bypass grafting. *Can J Cardiol*. 2011;27:716–724.
17. Nikolsky E, Mehran R, Yu J, Witzensbichler B, Brodie BR, Kornowski R, Brener S, Xu K, Dangas GD, Stone GW. Comparison of outcomes of patients with ST-segment elevation myocardial infarction with versus without previous coronary artery bypass grafting (from the harmonizing outcomes with revascularization and stents in acute myocardial infarction [HORIZONS-AMI] trial). *Am J Cardiol*. 2013;111:1377–1386.
18. Brilakis ES, Saeed B, Banerjee S. Drug-eluting stents in saphenous vein grafts interventions: a systematic review. *EuroIntervention*. 2010;5:722–730.
19. Mehilli J, Pache J, Abdel-Wahab M, Schulz S, Byrne RA, Tiroch K, Hausleiter J, Seyfarth M, Ott I, Ibrahim T, Fhsaro M, Laugwitz KL, Massberg S, Nuemann FJ, Richardt G, Schömig A, Kastrati A. Drug-eluting versus bare-metal stents in saphenous vein graft lesions (ISAR-CABG): a randomised controlled superiority trial. *Lancet*. 2011;378:1071–1078.
20. Brilakis ES, Lichtenwalter C, Abdel-Karim AR, de Lemos JA, Obel O, Addo T, Roesle M, Haagen D, Rangan BV, Saeed B, Bissett JK, Sachdeva R, Voudris VV, Karyofilis P, Kar B, Rossen J, Fasseas P, Berger P, Banerjee S. Continued benefit from paclitaxel-eluting compared with bare-metal stent implantation in saphenous vein graft lesions during long-term follow-up of the SOS (stenting of saphenous vein grafts) trial. *J Am Coll Cardiol Interv*. 2011;4:176–182.
21. Agostoni P, Vermeersch P, Semeraro O, Verheye S, van Langenhove G, van den Heuvel P, Convens C, van den Branden F, Bruining N. Intravascular ultrasound comparison of sirolimus-eluting stent versus bare metal stent implantation in diseased saphenous vein grafts (from the RRISC [reduction of restenosis in saphenous vein grafts with Cypher sirolimus-eluting stent] trial). *Am J Cardiol*. 2007;100:52–58.
22. von Birgelen C, van der Heijden LC, Basalus MW, Kok MM, Sen H, Louwerenburg HW, van Houwelingen KG, Stael MG, de Man FFAH, Linssen GCM, Tandjung K, Doggen CJM, van der Palen J, Löwik MM. Five-year outcome after implantation of zotarolimus- and everolimus-eluting stents in randomized participants and nonenrolled eligible patients: a secondary analysis of a randomized trial. *JAMA Cardiol*. 2017;2:268–276.
23. von Birgelen C, Basalus MWZ, Tandjung K, van Houwelingen KG, Stael MG, Louwerenburg JH, Linssen GCM, Said SA, Kleijne MA, Sen H, Löwik MM, van der Palen J, Verhorst PMJ, de Man FFAH. A randomized controlled trial in second-generation zotarolimus-eluting Resolute stents versus everolimus-eluting Xience V stents in real-world patients: the TWENTE trial. *J Am Coll Cardiol*. 2012;59:1350–1361.
24. Sen H, Tandjung K, Basalus MWZ, Löwik MM, van Houwelingen KG, Stael MG, Louwerenburg HW, de Man FFAH, Linssen GCM, Nijhuis R, Nienhuis MB, Verhorst PMJ, van der Palen J, von Birgelen C. Comparison of eligible non-enrolled patients and the randomized TWENTE trial population treated with Resolute and XIENCE V drug-eluting stents. *EuroIntervention*. 2012;8:664–671.
25. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical endpoints in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344–2351.
26. Vranckx P, Cutlip DE, Mehran R, Kint PP, Silber S, Winecker S, Serruys PW. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. *EuroIntervention*. 2010;5:871–874.
27. Lopes RD, Mehta RH, Hafley GE, Williams JB, Mack MJ, Peterson ED, Allen KB, Harrington RA, Gibson CM, Califf RM, Kouchoukos NT, Ferguson TB, Alexander JH. Relationship between vein graft failure and subsequent clinical outcomes after coronary artery bypass surgery. *Circulation*. 2012;125:746–756.
28. Brilakis ES, Rao SV, Banerjee S, Goldman S, Shunk KA, Holmes DR, Honeycutt E, Roe MT. Percutaneous coronary intervention in native arteries versus bypass grafts in prior coronary artery bypass grafting patients: a report from the National Cardiovascular Data Registry. *J Am Coll Cardiol Interv*. 2011;4:844–850.
29. FitzGibbon GM, Leach AJ, Kafka HP, Keon WJ. Coronary bypass graft fate: long-term angiographic study. *J Am Coll Cardiol*. 1991;17:1075–1080.
30. Campeu L, Enjalbert M, Lesperance J, Vaisilic C, Grondin CM, Bourassa MG. Atherosclerosis and late closure of aortocoronary saphenous vein grafts: sequential angiographic studies at 2 weeks, 1 year, 5 to 7 years, and 10 to 12 years after surgery. *Circulation*. 1983;68:111–117.
31. Hwang MH, Meadows WR, Palac RT, Piao ZE, Pfiarre R, Loeb HS, Gunnar RM. Progression of native coronary artery disease at 10 years: insights from a randomized study of medical versus surgical therapy for angina. *J Am Coll Cardiol*. 1990;16:1066–1070.
32. Kitabata H, Loh JP, Pendyala LK, Badr S, Dvir D, Barbash IM, Minha S, Torguson R, Chen F, Sattler LF, Suddath WO, Kent KM, Pichard AD, Waksman R. Two-year follow-up of outcomes of second-generation everolimus-eluting stents versus first-generation drug-eluting stents for stenosis of saphenous vein grafts used as aortocoronary conduits. *Am J Cardiol*. 2013;112:61–67.
33. Costopoulos C, Latib A, Naganuma T, Sticchi A, Chieffo A, Fignini F, Carlino M, Montorfano M, Naim C, Kawauchi M, Giannini F, Colombo A. Comparison of first- and second-generation drug-eluting stents in saphenous vein grafts used as aorto-coronary conduits. *Am J Cardiol*. 2013;112:318–322.
34. Yang TH, Kim DJ, Jin HY, Cho YW, Chung SR, Kim DK, Kim YB, Jang JS, Kim U, Seol SH, Kim DK, Kim DS. Angiographic late catch-up phenomenon after sirolimus-eluting stent implantation. *Int J Cardiol*. 2012;160:48–52.
35. von Birgelen C, Kok MM, van der Heijden LC, Danse PW, Scholte M, Gin RMTJ, Sömi S, van Houwelingen KG, Stael MG, de Man FFAH, Louwerenburg JHW, Hartmann M, Zocca P, Linssen GCM, van der Palen J, Doggen CJM, Löwik MM. Very thin strut biodegradable polymer everolimus-eluting and sirolimus-eluting stents versus durable polymer zotarolimus-eluting stents in allcomers with coronary artery disease (BIO-RESORT): a three-arm, randomised, non-inferiority trial. *Lancet*. 2016;388:2607–2617.

SUPPLEMENTAL MATERIAL

Table S1. Propensity score coefficients of the logistic regression model for having a history of CABG or not having a history of CABG.

	Beta	Standard error
Age (yrs)	-0.040	0.009
Women	0.714	0.208
Diabetes mellitus	-2.10	0.190
Previous PCI	-0.794	0.186
Previous MI	-0.177	0.184
Current smoker	0.903	0.267
Clinical syndrome at presentation		
Non-ST-elevation MI (versus stable angina)	0.501	0.221
Instable angina (versus stable angina)	-0.062	0.205
Chronic renal failure	-0.351	0.381
LAD treated	1.794	0.219
Left main treated	-2.313	0.334
Peripheral arterial disease	0.232	0.262
Multivessel treatment	-0.327	0.230
At least one bifurcation lesion treated	-0.201	0.346
At least one chronic total occlusion treated	0.458	0.247

Table S2. Sensitivity analysis of adjusting in the Cox regression hazard model for the propensity score for all variables separately.

	Propensity score adjustment		Adjusting for each variable separately	
	Adjusted hazard ratio (95%-CI)	p-value	Adjusted hazard ratio (95%-CI)	p-value
Any death	1.36 (0.88-2.10)	0.16	1.32 (0.87-1.98)	0.19
Cardiac death	1.87 (1.03-3.39)	0.04	1.74 (0.99-3.06)	0.05
Any myocardial infarction	1.60 (0.95-2.70)	0.08	1.54 (0.91-2.61)	0.11
Target vessel myocardial infarction	1.67 (0.96-2.93)	0.07	1.65 (0.94-2.90)	0.08
Target vessel revascularization	3.00 (2.01-4.46)	<0.001	2.97 (2.00-4.41)	<0.001
Target lesion revascularization	3.43 (2.19-5.36)	<0.001	3.45 (2.20-5.42)	<0.001
Non-target vessel revascularization	0.87 (0.47-1.61)	0.65	0.92 (0.51-1.65)	0.78
Target vessel failure	2.69 (1.99-3.65)	<0.001	2.50 (1.85-3.39)	<0.001
Definite stent thrombosis	0.66 (0.07-6.20)	0.72	0.52 (0.05-5.44)	0.59

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