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Mortality After Repeat Revascularization Following PCI or CABG for Left Main Disease

The EXCEL Trial

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ABSTRACT

OBJECTIVES The aim of this study was to investigate the incidence and impact on mortality of repeat revascularization after index percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) for left main coronary artery disease (LMCAD).

BACKGROUND The impact on mortality of the need of repeat revascularization following PCI or CABG in patients with unprotected LMCAD is unknown.

METHODS All patients with LMCAD and site-assessed low or intermediate SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) scores randomized to PCI ($n = 948$) or CABG ($n = 957$) in the EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial were included. Repeat revascularization events were adjudicated by an independent clinical events committee. The effect of repeat revascularization on mortality through 3-year follow-up was examined in time-varying Cox regression models.

RESULTS During 3-year follow-up, there were 346 repeat revascularization procedures among 185 patients. PCI was associated with higher rates of any repeat revascularization (12.9% vs. 7.6%; hazard ratio: 1.73; 95% confidence interval: 1.28 to 2.33; $p = 0.0003$). Need for repeat revascularization was independently associated with increased risk for 3-year all-cause mortality (adjusted hazard ratio: 2.05; 95% confidence interval: 1.13 to 3.70; $p = 0.02$) and cardiovascular mortality (adjusted hazard ratio: 4.22; 95% confidence interval: 2.10 to 8.48; $p < 0.0001$) consistently after both PCI and CABG ($p_{int} = 0.85$ for both endpoints). Although target vessel revascularization and target lesion revascularization were both associated with an increased risk for mortality, target vessel non–target lesion revascularization and non–target vessel revascularization were not.

CONCLUSIONS In the EXCEL trial, repeat revascularization during follow-up was performed less frequently after CABG than PCI and was associated with increased mortality after both procedures. Reducing the need for repeat revascularization may further improve long-term survival after percutaneous or surgical treatment of LMCAD. (EXCEL Clinical Trial; NCT01205776) (J Am Coll Cardiol Intv 2020;13:375–87) © 2020 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

CI = confidence interval

HR = hazard ratio

IQR = interquartile range

LM = left main coronary artery

LMCAD = left main coronary artery disease

MI = myocardial infarction

PCI = percutaneous coronary intervention

TLR = target lesion revascularization

TVR = target vessel revascularization

Iterations in coronary stent technologies, technique, and pharmacotherapies have enhanced the efficacy and safety of percutaneous coronary intervention (PCI), leading to lower rates of stent thrombosis, restenosis, and the need for repeat revascularization (1-6). Outcomes of coronary artery bypass grafting (CABG) have also improved with the use of multiple arterial grafts, minimally invasive techniques, and optimal medical therapy (4,7-11). The need for repeat revascularization is more common after PCI than CABG, although the differences between the techniques are diminishing over time (12-15). Although often considered a clinical endpoint of lesser importance compared with death, stroke, or myocardial infarction (MI), the need for repeat revascularization is associated with worse quality of life and exposes patients to new hospitalizations and procedural risks (13,16-18). In addition, the need for a repeat procedure after revascularization of the left main coronary artery (LM) may be associated with substantial morbidity and mortality given the large amount of subtended myocardium at risk (19). We therefore sought to characterize the incidence, predictors, and consequences of the need for repeat revascularization after the PCI or CABG for LM coronary artery disease (LMCAD) using contemporary devices and surgical techniques from the EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial.

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METHODS

STUDY DESIGN. The EXCEL trial was an international, open-label, multicenter, randomized trial that compared PCI using cobalt-chromium fluoropolymer-based everolimus-eluting stents (XIENCE, Abbott Vascular, Santa Clara, California) versus CABG in patients with LMCAD. The EXCEL trial design and principal results have been previously reported (19). In brief, inclusion criteria were LM diameter stenosis of ≥70% as estimated visually or stenosis of 50% to <70% if hemodynamically significant by noninvasive or invasive testing. All patients were required to have low or intermediate anatomic complexity of coronary artery disease, as defined by a site-determined SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score of ≤32. Consensus among the members of the heart team regarding the eligibility for revascularization with either PCI or CABG was required. Clinical follow-up was performed at 1 month, 6 months, and 1 year and then annually through 5 years. At the time of the present analysis, all patients had completed 3 years of follow-up. The primary endpoint of the EXCEL trial was the composite of death of any cause, stroke, or MI at a median follow-up time of 3 years. Major powered secondary endpoints included this composite endpoint at 30 days and the composite of death, stroke, MI, or ischemia-driven revascularization at 3 years.

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TABLE 1 Rates of Time to First Repeat Revascularization With Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting for Left Main Coronary Artery Disease During 3 Years of Follow-Up

	1 Year				3 Years			
	PCI (n = 948)	CABG (n = 957)	Hazard Ratio (95 CI)	p Value	PCI (n = 948)	CABG (n = 957)	Hazard Ratio (95 CI)	p Value
Any revascularization	6.9 (64)	4.6 (42)	1.51 (1.02–2.22)	0.04	12.9 (117)	7.6 (68)	1.73 (1.28–2.33)	0.0003
Revascularization with PCI	5.9 (54)	3.8 (35)	1.53 (1.00–2.33)	0.05	10.7 (97)	6.8 (61)	1.59 (1.16–2.19)	0.004
Revascularization with CABG	1.6 (15)	0.8 (7)	2.12 (0.86–5.20)	0.09	3.3 (30)	0.8 (7)	4.25 (1.87–9.68)	0.0002
Target vessel revascularization	6.3 (58)	4.2 (39)	1.47 (0.98–2.20)	0.06	11.0 (100)	7.1 (64)	1.56 (1.14–2.14)	0.005
Target lesion revascularization	5.4 (50)	4.0 (37)	1.33 (0.87–2.03)	0.19	9.4 (85)	6.8 (61)	1.38 (1.00–1.92)	0.052
Non-target lesion revascularization	1.8 (17)	0.2 (2)	8.45 (1.95–36.59	0.0006	3.3 (30)	0.7 (6)	5.00 (2.08–12.00)	<0.0001
Non-target vessel revascularization	0.9 (8)	0.4 (4)	1.98 (0.60–6.57)	0.26	2.7 (24)	0.8 (7)	3.40 (1.47–7.89)	0.002
Ischemia-driven revascularization	6.8 (63)	4.4 (40)	1.56 (1.05–2.31)	0.03	12.7 (115)	7.5 (67)	1.73 (1.28–2.33)	0.0003
Revascularization with PCI	6.8 (63)	4.4 (40)	1.56 (1.05–2.31)	0.03	10.5 (95)	6.7 (60)	1.59 (1.15–2.19)	0.005
Revascularization with CABG	1.6 (15)	0.8 (7)	2.12 (0.86–5.20)	0.09	3.3 (30)	0.8 (7)	4.25 (1.87–9.68)	0.0002
Target vessel revascularization	6.3 (58)	4.0 (37)	1.55 (1.03–2.34)	0.04	10.9 (99)	7.0 (63)	1.57 (1.15–2.16)	0.005
Target lesion revascularization	5.4 (50)	3.9 (36)	1.37 (0.89–2.10)	0.15	9.4 (85)	6.7 (60)	1.41 (1.01–1.96)	0.04
Non-target lesion revascularization	1.8 (17)	0.1 (1)	16.9 (2.25–126.86)	0.0002	3.2 (29)	0.6 (5)	5.80 (2.24–14.97)	<0.0001
Non-target vessel revascularization	0.8 (7)	0.4 (4)	1.73 (0.51–5.90)	0.38	2.5 (22)	0.8 (7)	3.11 (1.33–7.28)	0.006
Nonischemia-driven revascularization	0.5 (5)	0.2 (2)	2.47 (0.48–12.72)	0.26	1.0 (9)	0.3 (3)	2.96 (0.80–10.93)	0.09
Revascularization with PCI	0.4 (4)	0.2 (2)	1.98 (0.36–10.79)	0.42	0.8 (7)	0.3 (3)	2.30 (0.60–8.90)	0.21
Revascularization with CABG	0.1 (1)	0.0 (0)	–	0.32	0.2 (2)	0.0 (0)	–	0.16
Target vessel revascularization	0.4 (4)	0.2 (2)	1.97 (0.36–10.75)	0.43	0.8 (7)	0.3 (3)	2.29 (0.59–8.87)	0.22
Target lesion revascularization	0.4 (4)	0.1 (1)	3.94 (0.44–35.25)	0.19	0.8 (7)	0.3 (3)	2.30 (0.59–8.88)	0.22
Non-target lesion revascularization	0.0 (0)	0.1 (1)	–	0.31	0.0 (0)	0.1 (1)	–	0.31
Non-target vessel revascularization	0.1 (1)	0.0 (0)	–	0.32	0.2 (2)	0.0 (0)	–	0.16

Kaplan-Meier estimated rate (number of events).
CABG = coronary artery bypass grafting; CI = confidence interval; PCI = percutaneous coronary intervention.

Definitions of the primary and major secondary endpoints are reported elsewhere (19). Study monitors collected source documents of all primary and secondary endpoints for adjudication by an independent clinical events committee. The extent and complexity of coronary artery disease and the SYNTAX score at baseline were also assessed by an independent angiographic core laboratory. The investigation was approved by the ethics committee or Institutional Review Board at each center, and all patients provided informed consent.

The present study is a secondary analysis from the EXCEL trial investigating the incidence, risk factors, and prognostic impact of the performance of repeat revascularization procedures following PCI and CABG. The following type of adjudicated revascularization events were considered in this analysis: ischemia-driven revascularization, non-ischemia-driven revascularization, target lesion revascularization (TLR), target vessel revascularization (TVR), target-vessel non-TLR, non-TVR, repeat revascularization with PCI, and repeat revascularization with CABG. A complete list of definitions for the different types of repeat revascularization endpoints is reported in Online Table 1. We evaluated the effect of each type of repeat revascularization event on all-cause, cardiovascular, and noncardiovascular mortality at 3-year follow-up.

STATISTICAL ANALYSIS. All analyses were performed in the intention-to-treat population. Categorical variables were compared using the chi-square test or Fisher exact test. Continuous variables were compared using Student's *t*-test or the Wilcoxon rank sum test for skewed data. Event rates were on the basis of Kaplan-Meier estimates in time-to-first-event analyses and were compared using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) for PCI versus CABG were generated using Cox regression models. Predictors of repeat revascularization events were evaluated with multivariate Cox regression models separately for patients randomized to PCI or CABG, including clinical, angiographic, and procedural characteristics that were significantly associated with the outcome by univariate analysis or were deemed to be clinically important for each type of index procedure (full list of covariates for each model is included in the footnote of the respective table). The association of repeat revascularization with the risk for mortality at 3 years was evaluated using multivariate Cox regression models entering repeat revascularization, any MI, and any stroke as

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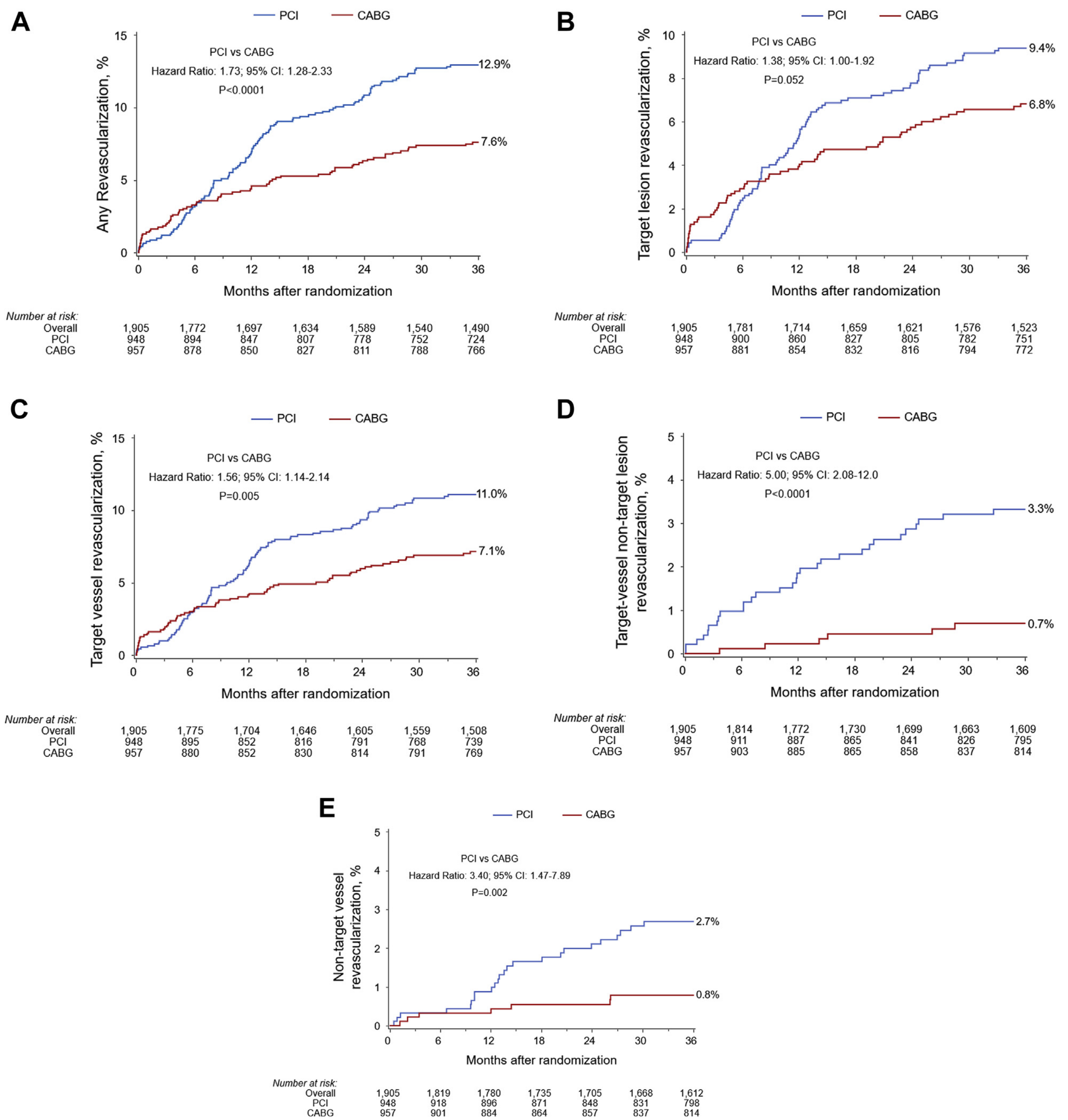
FIGURE 1 Kaplan-Meier Curves for Repeat Revascularization Within 3 Years After Percutaneous Coronary Intervention or Coronary Artery Bypass Grafting



(A) Any repeat revascularization. **(B)** Target lesion revascularization. **(C)** Target vessel revascularization. **(D)** Target vessel non-target lesion revascularization. **(E)** Non-target vessel revascularization. CABG = coronary artery bypass grafting; CI = confidence interval; PCI = percutaneous coronary intervention.

time-varying covariates alongside other baseline covariates, including age, sex, SYNTAX score, diabetes, chronic kidney disease, congestive heart failure, anemia, and ST-segment elevation MI or non-ST-segment elevation MI at presentation. Two-sided p values ≤0.05 were considered to indicate statistical significance. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

During a median follow-up time of 3 years (interquartile range [IQR]: 3 to 3 years), there were 346 repeat revascularization procedures among 185 patients (Online Table 2). Of these, 259 of 346 (74.9%) were PCI procedures and 87 of 346 (25.1%) were CABG procedures. Overall, 102 patients (55.1%) underwent 1 repeat revascularization procedure, 41 (22.2%) underwent 2 procedures, and 42 (22.7%) underwent >2 events. The median time to the first repeat revascularization procedure was 320 days (IQR: 141 to 616 days). Baseline clinical, angiographic, and procedural characteristics in patients with versus without any repeat revascularization procedures after the index PCI or CABG are reported in Online Tables 3 to 5. There were no significant differences in SYNTAX score between patients with versus without repeat revascularization at 3 years within both the PCI and the CABG groups (Online Table 4). Medication use over 3 years is reported in Online Table 6. Patients who required repeat revascularization were more likely to remain on dual-antiplatelet therapy through 3 years within both the PCI and the CABG groups. Patients who required repeat revascularization had higher rates of anginal symptoms at 3 years in both the PCI and CABG arms (Online Table 7).

RISK FOR REVASCULARIZATION BY PCI AND CABG. Median time to the first repeat revascularization was 347 days (IQR: 182 to 570 days) after PCI and 257 days (IQR: 83 to 628 days) after CABG ($p = 0.13$). Rates of time to first repeat revascularization over 3 years are reported in **Table 1 and Figures 1A to 1E**. Patients assigned to PCI had higher rates of any repeat revascularization at 3 years compared with those assigned to CABG (12.9% vs. 7.6%; HR: 1.73; 95% CI: 1.28 to 2.33; $p = 0.0003$). There were no significant differences between PCI and CABG in the rates of repeat revascularization at 6 months (3.1% vs. 3.2%; HR: 0.98; 95% CI: 0.59 to 1.63; $p = 0.93$). Most of the differences between the 2 strategies in the rates of repeat revascularization emerged beyond 6 months (Online Figures 1 and 2) (4.4% vs. 9.9%; HR: 2.33; 95% CI: 1.59 to 3.41; $p < 0.0001$). The cause of repeat revascularization was stent thrombosis in 8 of 117 patients (7.1%) after PCI and symptomatic graft occlusion in 42 of 68 patients (62.7%) after CABG ($p < 0.0001$). Most repeat revascularizations were performed with PCI in both the PCI and CABG groups. Overall, repeat revascularization with CABG during the 3-year follow-up was performed more frequently in patients randomized to initial PCI compared with CABG (3.3% vs. 0.8%; HR: 4.25; 95% CI: 1.87 to 9.68; $p = 0.0002$).

TABLE 2 Independent Predictors of Any Repeat Revascularization Within 3 Years After Percutaneous Coronary Intervention or Coronary Artery Bypass Grafting for Left Main Coronary Artery Disease

	Adjusted Hazard Ratio	95% CI	p Value
PCI group*			
Body mass index, per unit increase	1.04	1.00–1.07	0.04
Diabetes mellitus			
No diabetes mellitus	1.00 (reference)	–	–
Without insulin treatment	1.19	0.76–1.86	0.45
With insulin treatment	1.96	1.10–3.51	0.02
Hemodynamic support during the procedure	2.37	1.29–4.35	0.005
Use of statin at discharge	0.30	0.16–0.58	0.0003
CABG group†			
Age, per 10-yr increase	0.71	0.55–0.92	0.01
Female	1.64	0.94–2.86	0.08
Peripheral vascular disease	2.14	1.05–4.35	0.04

Adjusted hazard ratios and 95% CIs were generated using multivariate Cox regression analysis. Only the covariates significantly associated with the outcome are displayed. *This model included the following covariates: age, sex, body mass index, diabetes mellitus, left main distal segment or bifurcation lesions, use of intravascular ultrasound imaging, use of hemodynamic support during the procedure, core laboratory–assessed SYNTAX score, number of diseased non-left main vessels, and use of statin at discharge. †This model included the following covariates: age, sex, body mass index, diabetes mellitus, hyperlipidemia, peripheral vascular disease, clinical presentation with an acute coronary syndrome, core laboratory–assessed SYNTAX score, and number of arterial conduits used.

SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery; other abbreviations as in Table 1.

PREDICTORS OF REPEAT REVASCULARIZATION. Predictors of any repeat revascularization at 3 years

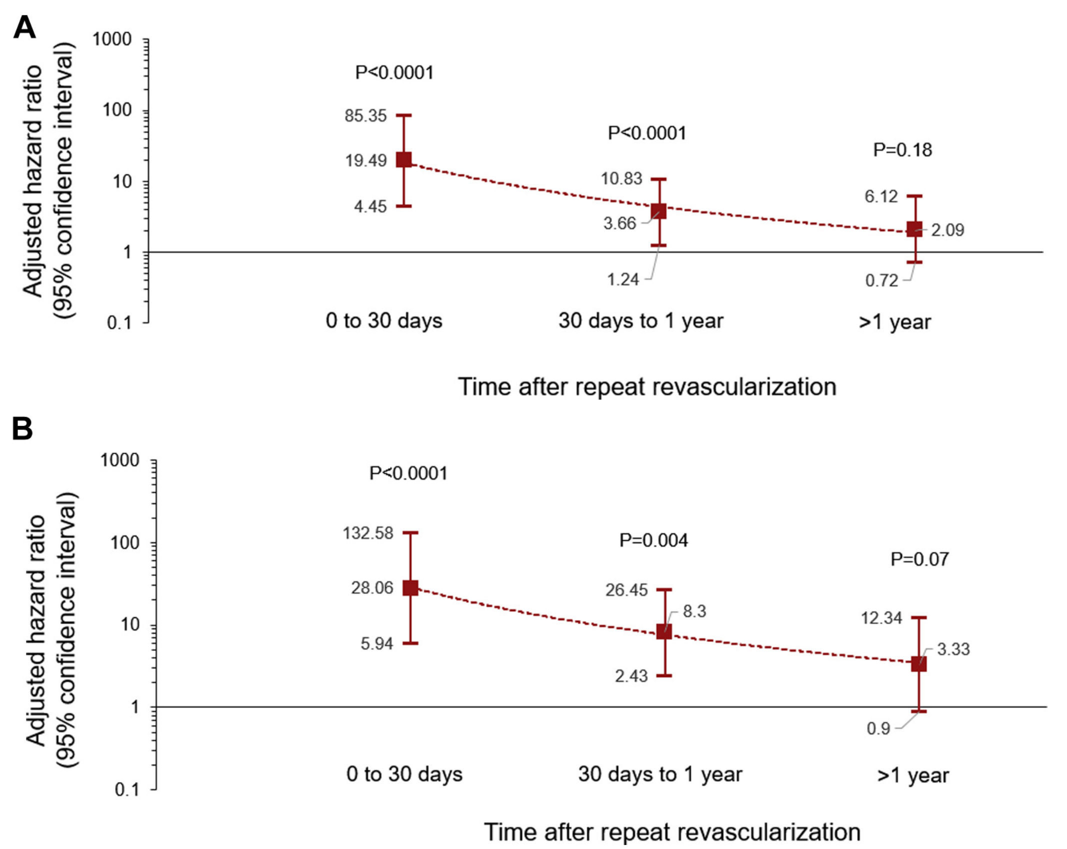
TABLE 3 Predictors of All-Cause and Cardiovascular Mortality at 3 Years After Percutaneous Coronary Intervention or Coronary Artery Bypass Grafting for Left Main Coronary Artery Disease

	Adjusted Hazard Ratio	95% Confidence Interval	p Value
All-cause mortality (128 events)			
Any repeat revascularization*	2.05	1.13–3.70	0.02
Any myocardial infarction*	4.03	2.43–6.67	<0.0001
Any stroke*	16.62	9.97–27.69	<0.0001
Age, per 10-yr increase	1.39	1.10–1.77	0.006
Diabetes mellitus	1.69	1.17–2.44	0.005
Anemia	2.15	1.45–3.18	0.0001
Cardiovascular mortality (74 events)			
Any repeat revascularization*	4.22	2.10–8.48	<0.0001
Any myocardial infarction*	5.30	2.86–9.83	<0.0001
Any stroke*	31.11	17.10–56.61	<0.0001
Age, per 10-yr increase	1.45	1.06–2.00	0.02
Congestive heart failure	2.04	1.04–4.00	0.002
Anemia	2.27	1.35–3.81	0.04
Diabetes mellitus	1.55	0.96–2.50	0.07

Adjusted hazard ratios and 95% confidence intervals were generated using multivariate Cox regression analysis. *Modeled as a time-varying covariate within the Cox regression model. The multivariate Cox regression model included the following covariates: any repeat revascularization, any myocardial infarction, any stroke, age, sex, diabetes, anemia, congestive heart failure, chronic kidney disease, ST-segment elevation myocardial infarction or non-ST-segment elevation myocardial infarction as clinical presentation, core laboratory–assessed SYNTAX score, and randomized assignment to PCI or CABG.

Abbreviations as in Tables 1 and 2.

FIGURE 2 Early and Late Risk for Mortality After Any Repeat Revascularization in the Overall Population

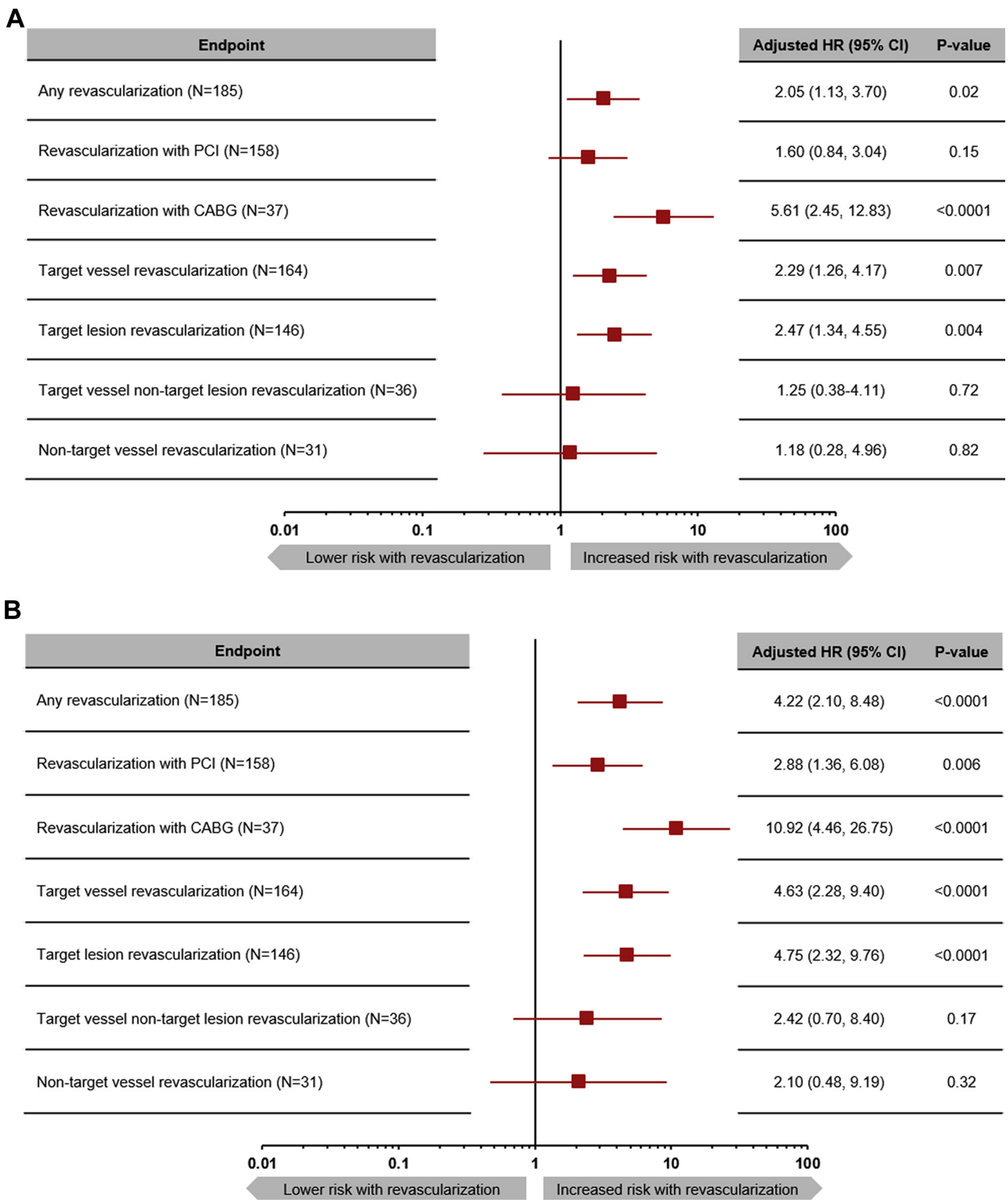


(A) All-cause mortality. **(B)** Cardiovascular mortality.

after PCI or CABG are reported in Table 2. Higher body mass index, insulin-treated diabetes, and hemodynamic support during the procedure were associated with a higher risk for repeat revascularization after PCI, while statin use at discharge was protective (adjusted HR: 0.30; 95% CI: 0.16 to 0.50; $p = 0.0003$). Younger age, female sex, and peripheral vascular disease were independent predictors of repeat revascularization after CABG.

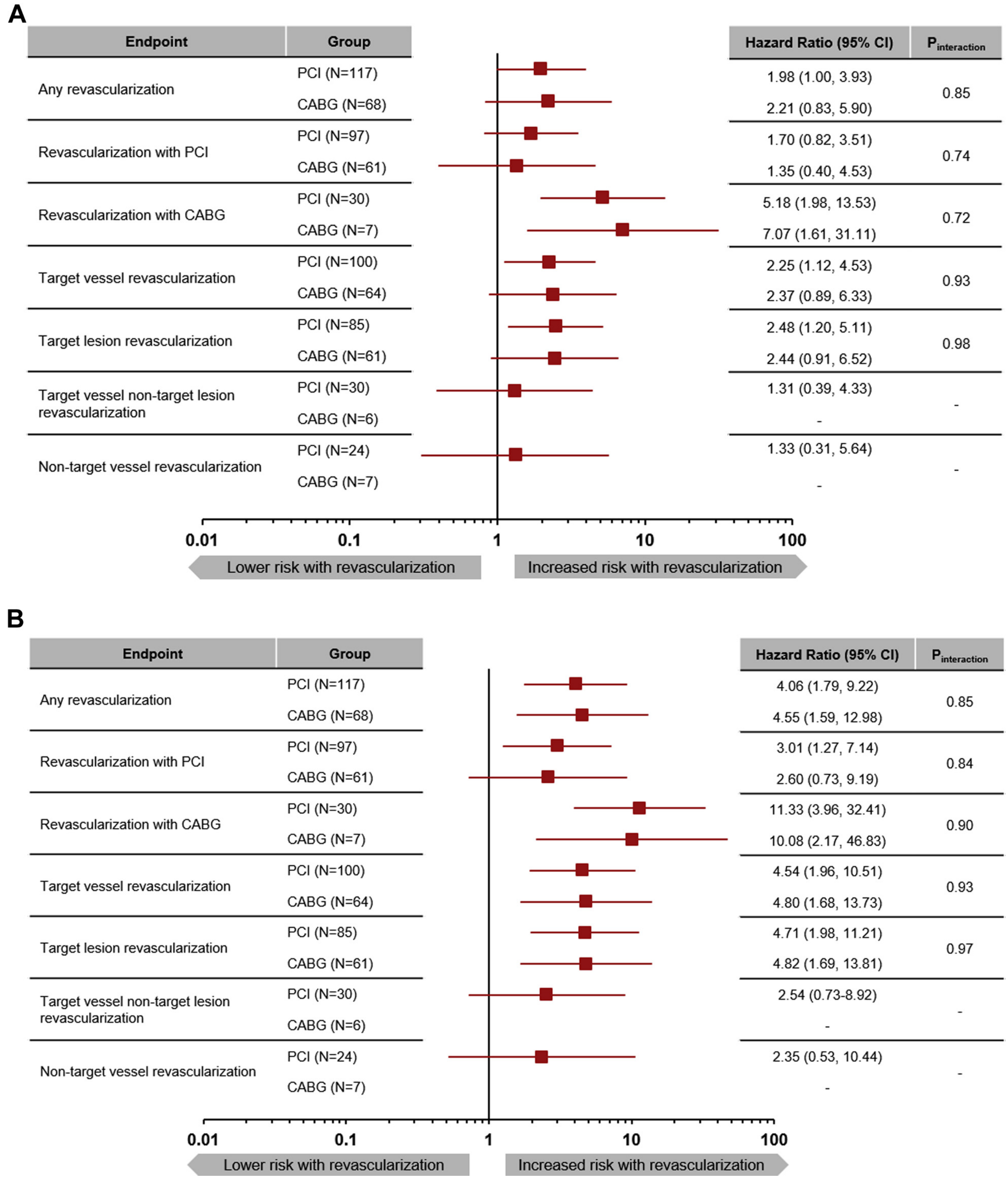
REPEAT REVASCULARIZATION AND MORTALITY. At 3 years, there were 128 all-cause deaths, including 74 cardiovascular deaths and 54 noncardiovascular deaths. Independent predictors of all-cause and cardiovascular mortality at 3 years in the overall population are reported in Table 3. The need for repeat revascularization was independently associated with increased risk for both all-cause mortality (adjusted HR: 2.05; 95% CI: 1.13 to 3.70; $p = 0.02$) and cardiovascular mortality (adjusted HR: 4.22; 95% CI: 2.10 to 8.48; $p < 0.0001$) but not noncardiovascular mortality (Online Tables 8 and 9). However, the magnitude of the association between repeat revascularization and all-cause mortality was smaller compared with that of MI (adjusted HR: 4.03; 95% CI: 2.43 to 6.67; $p < 0.0001$) or stroke (adjusted HR: 16.62; 95% CI: 9.97 to 27.69; $p < 0.0001$). Of note, the risk for mortality after repeat revascularization peaked within 30 days and then declined over time (Figure 2). The adjusted risk for 3-year all-cause and cardiovascular mortality according to the subtypes of repeat revascularization events is illustrated in Figure 3. TVR and TLR were both associated with increased all-cause and cardiovascular mortality. Conversely, both target-vessel non-TLR and non-TVR were not associated with increased all-cause and cardiovascular mortality. Of note, the need for repeat revascularization using CABG was strongly associated with increased all-cause mortality. The effect of repeat revascularization on mortality according to the

FIGURE 3 **Association Between Type of Repeat Revascularization and Mortality Within 3 Years in the Overall Population**



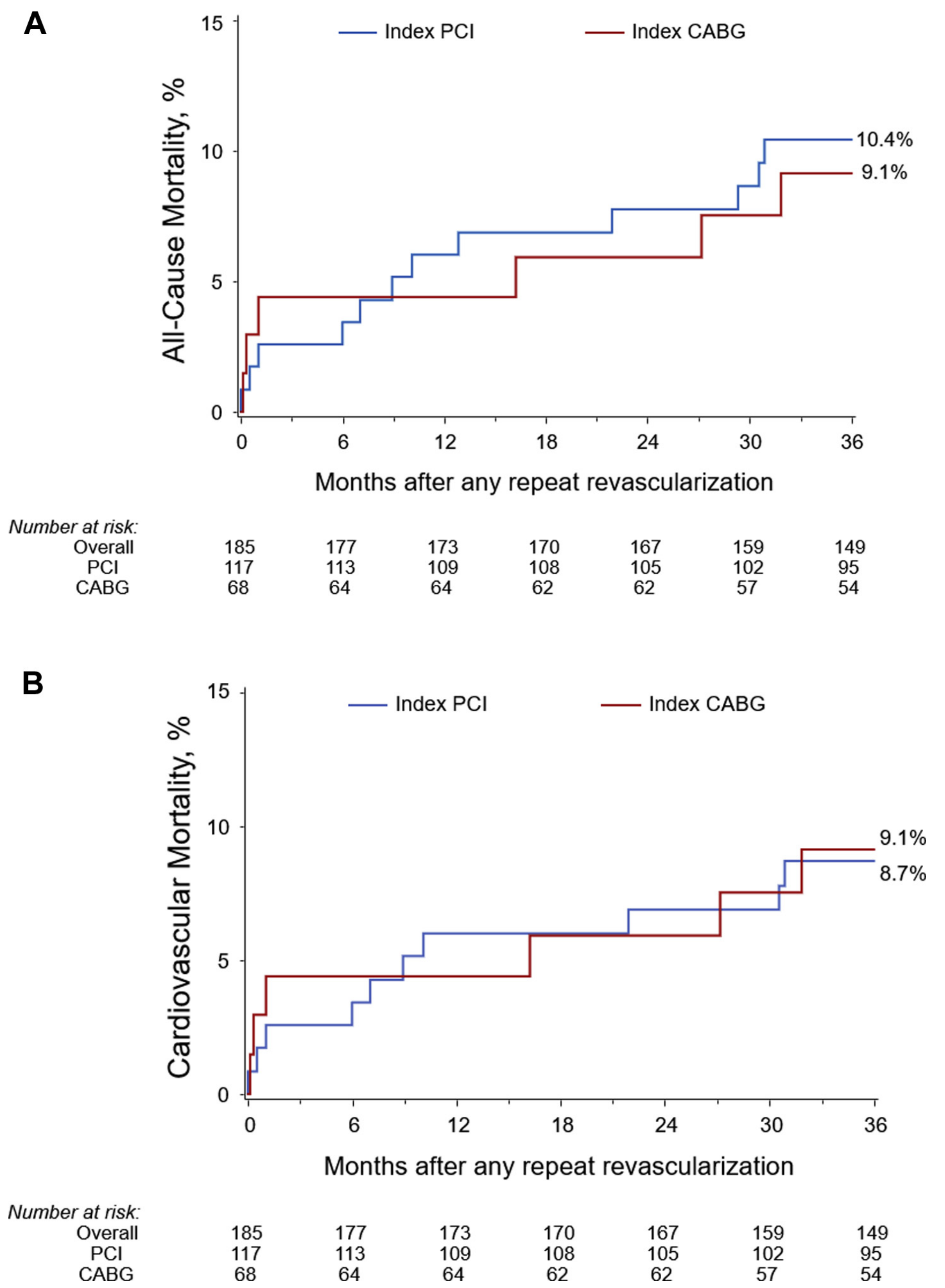
(A) All-cause mortality. **(B)** Cardiovascular mortality. CABG = coronary artery bypass grafting; CI = confidence interval; HR = hazard ratio; PCI = percutaneous coronary intervention.

FIGURE 4 **Association Between Type of Repeat Revascularization and Mortality Within 3 Years After Percutaneous Coronary Intervention or Coronary Artery Bypass Grafting**



(A) All-cause mortality. **(B)** Cardiovascular mortality. CABG = coronary artery bypass grafting; CI = confidence interval; PCI = percutaneous coronary intervention.

FIGURE 5 Kaplan-Meier Curves for All-Cause and Cardiovascular Mortality After Any Repeat Revascularization



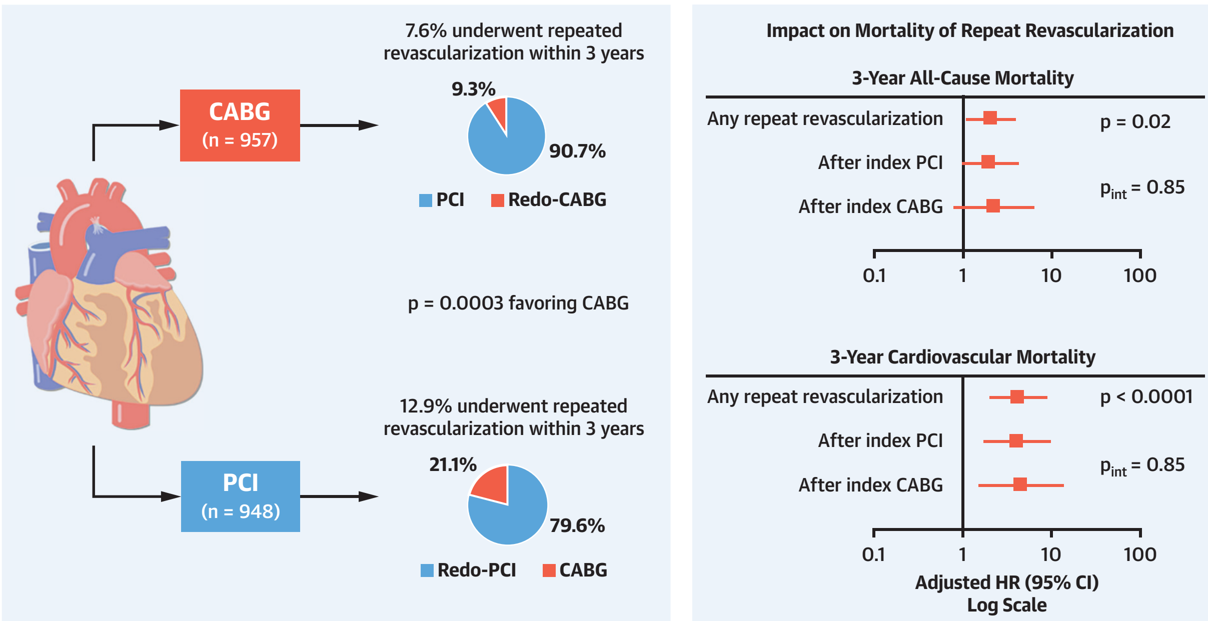
(A) All-cause mortality. **(B)** Cardiovascular mortality.

index revascularization strategy is illustrated in Figures 4 and 5. The effect of any repeat revascularization and its subtypes on both all-cause and cardiovascular mortality was consistent in patients undergoing initial PCI and CABG, without evidence of interaction.

DISCUSSION

The major findings of the present analysis from the EXCEL trial in which we evaluated the incidence, timing, and consequences of the need for repeat coronary revascularization following PCI or CABG for

CENTRAL ILLUSTRATION Repeat Revascularization and Mortality After Percutaneous Coronary Intervention or Coronary Artery Bypass Grafting for Left Main Coronary Artery Disease



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After percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) for left main coronary artery disease and low or intermediate anatomic complexity, the need for repeat revascularization was more common after PCI compared with CABG **(left)**. Of note, the need for repeat revascularization was independently associated with increased risk for both all-cause and cardiovascular mortality consistently after both PCI and CABG **(right)**. The lower rate of repeat revascularization after CABG compared with PCI may be one factor contributing to the long-term benefits of surgical revascularization. CI = confidence interval; HR = hazard ratio.

LMCAD are as follows (Central Illustration): 1) repeat revascularization procedures within 3 years were performed more commonly after PCI than CABG, mostly beyond the first 6 months after the index procedure (of note, the need for revascularization after PCI was infrequently due to stent thrombosis, while after CABG repeat revascularization was most often prompted by symptomatic graft occlusion); 2) the performance of any repeat revascularization procedure was an independent predictor of a subsequent increase in all-cause and cardiovascular mortality within 3 years after both PCI and CABG, a risk that peaked within 30 days after the repeat procedure and then declined over time (repeat revascularization was not associated with increased risk for noncardiac mortality); and 3) the magnitude and significance of the association between repeat revascularization and mortality depended upon its subtype, with TVR and TLR being strongly associated with increased risk for all-cause mortality, whereas target vessel non-TLR and non-TVR were not associated with increased all-cause mortality.

Although developments in technologies, technique, and pharmacotherapies have enhanced both the efficacy and safety of revascularization, the need for repeat revascularization remains a frequent adverse event after both PCI and CABG (1-5,20). Following PCI, stent-related complications or the development of new obstructive native coronary lesions remote from the stented vascular segment usually motivate most repeat revascularization procedures (1-5). After CABG, the need for repeat revascularization is generally driven by progression of native vessel disease distal to the site of anastomosis or by arterial or venous graft occlusion (1-5,20). Few studies have previously examined in detail the timing and impact on mortality of the need for repeat revascularization after an index revascularization with PCI or CABG. In the era of first-generation drug-eluting stents, this subject was examined in a report from the SYNTAX trial in which 1,800 patients with triple-vessel disease and/or LMCAD were randomized to CABG or PCI with paclitaxel-eluting stents (16). In this study, PCI was associated with higher risk for repeat revascularization at 5 years (13,17); repeat revascularization was an independent predictor of the composite of death, stroke, or MI after initial PCI but not after initial CABG, a finding driven mostly by an increased risk of MI (16).

In the present analysis from the EXCEL trial, we extend these prior observations to a larger LMCAD cohort with low or intermediate anatomic complexity treated with contemporary PCI devices and CABG techniques. Consistent with prior studies, the rates of repeat revascularization were lower after CABG than PCI, possibly related to the protective effect from progressive atherosclerosis developing proximally to the surgically anastomosed segment. Conversely, because PCI treats a only a focal target coronary lesion, the rate of subsequent repeat revascularization will be influenced by both the complexity of the actual lesion affecting stent-related events and from the development of new lesions upstream or downstream from the stented vascular segment (non-stent-related events) (21–23). However, it has also been shown that repeat revascularization procedures are performed for less severe anginal symptoms and health status deterioration after PCI compared with CABG, which may reflect differences in the threshold for or anatomic suitability of further revascularization after each procedure (13,17,24). This differential threshold may in part explain the more frequent use of repeat revascularization after PCI compared with CABG (13,17,24). Of note, the absolute differences in the rates of repeat revascularization between PCI and CABG in the EXCEL trial were smaller than from the SYNTAX trial, which may reflect the lower anatomic complexity of the EXCEL population as well as the greater safety and efficacy of contemporary everolimus-eluting stents compared with paclitaxel-eluting stents. Also, despite the slightly greater rates of revascularization in the PCI arm in EXCEL, the overall health status, quality of life, and freedom from angina at 3 years after PCI and CABG were not significantly different in this trial (25), in contrast to prior reports (26,27).

By time-varying multivariate analysis, repeat revascularization was associated with an increased risk for both all-cause and cardiovascular mortality through 3-year follow-up irrespective of the index revascularization strategy, although its impact was smaller than that of a stroke or an MI. However, the adjusted hazard of mortality after TLR following initial LMCAD revascularization in EXCEL (HR: 2.47; 95% CI: 1.34 to 4.55) was higher than that observed after PCI from a large drug-eluting stent database of non-LM PCI (HR: 1.22; 95% CI: 1.03 to 1.45), consistent with the larger amount of myocardium in jeopardy after failed LM revascularization (16). The effect on mortality following repeat revascularization in the present study was greater early after the event (within 30 days) and then attenuated over time, suggesting that the actual event of repeat revascularization per se was associated with increased risk.

The association between repeat revascularization and mortality is likely multifactorial and may be both causative and associative in nature. First, the need for repeat revascularization exposes patients to new hospitalizations with its integral risks. Second, every revascularization procedure carries risk; in this regard, mortality was significantly greater after repeat revascularization by CABG but not after PCI, reflecting inherent differences in the risks of these 2 strategies. This observation suggests that CABG should be reserved for repeat revascularization procedures that are not amenable to repeat PCI, irrespective of the initial revascularization approach. Third, prolonged dual-antiplatelet therapy after repeat revascularization is associated with increased bleeding and, in some reports, mortality (28,29). Finally, the need for repeat revascularization could represent a marker of more extensive coronary artery disease and comorbidity burden; however, the baseline SYNTAX score did not differ between patients who did and did not require repeat revascularization.

Of note, both TVR and TLR were significantly associated with an increased risk for all-cause and cardiovascular mortality, consistently after both PCI and CABG. Following LM PCI, repeat revascularization of a previously stented unprotected LM lesion secondary to drug-eluting stent failure (e.g., in-stent restenosis or stent thrombosis) is inherently associated with poor prognosis because of the large area of subtended myocardium at risk. Similarly, after CABG, after graft failure either repeat revascularization through PCI of a diseased graft or of the native occluded coronary artery may be associated with adverse events (30,31). Finally, non-TVR (which in this trial most commonly consisted of revascularization of the right coronary artery) and non-target lesion TVR (in this trial including lesions distal to the LM complex within the left anterior descending coronary artery and left circumflex coronary artery territories) were not associated with an increased risk for all-cause or cardiovascular mortality after either PCI or CABG. Considering the lower periprocedural morbidity of PCI compared with CABG, the present analysis suggests that new approaches to reduce the need for stent-related repeat revascularization may further improve the benefit/risk profile of PCI compared with CABG.

STUDY LIMITATIONS. First, because this was a secondary analysis from a randomized controlled trial, our findings should be considered hypothesis-generating. Second, detailed causes for repeat revascularization were not prospectively collected; however, most repeat revascularization events were adjudicated as ischemia-driven. Third, at the time of this analysis, only 3 years of follow-up were available; longer term follow-up (currently planned for 5 years) may demonstrate further differences between PCI and CABG in the rates of repeat revascularization and their prognostic significance. Fourth, bias from residual confounding in our multivariate models evaluating the association between repeat revascularization and mortality cannot be excluded.

CONCLUSIONS

Our findings in an unprotected LMCAD population suggest that the need for and performance of repeat revascularization procedures have prognostic implications, the magnitude of which depends on its indication and type of repeat revascularization. The lower rate of repeat revascularization after CABG compared with PCI may be one factor contributing to the favorable long-term prognosis of surgical revascularization seen in some prior trials. It is also plausible that measures to reduce repeat revascularization, including improved drug-eluting stents and implantation techniques, use of pan-arterial bypass grafting, and aggressive risk factor control with optimal medical therapy, may improve prognosis after both PCI and CABG.

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PERSPECTIVES

WHAT IS KNOWN? PCI is known to be associated with higher risk for repeat revascularization compared with CABG. However, its prognostic significance after revascularization of unprotected LMCAD remains unclear.

WHAT IS NEW? The need for repeat revascularization after both PCI and CABG for unprotected LMCAD was associated with increased mortality over 3 years, although with an associated risk that was smaller than that of MI or stroke. Of note, repeat revascularization of the index target coronary vessel (e.g., LM or proximal left anterior descending coronary artery) was associated with increased mortality, whereas repeat revascularization of the non-target vessel (e.g., right coronary artery) was not. Moreover, mortality was substantially greater after repeat revascularization by CABG than after PCI.

WHAT IS NEXT? Measures to reduce the need for repeat revascularization, including improved stent platforms and implantation technique, use of pan-arterial bypass grafting, and aggressive risk factor control with guideline-directed medical therapy, may improve prognosis after both PCI and CABG.

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KEY WORDS CABG, left main coronary artery, PCI, repeat revascularization

APPENDIX For supplemental tables and figures, please see the online version of this paper.