Outcomes of left main revascularization in patients with acute coronary syndromes and stable ischemic heart disease: Analysis from the EXCEL trial

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Background Prompt revascularization is often required in acute coronary syndromes (ACS), whereas stable ischemic heart disease (SIHD) may allow for more measured procedural planning. Whether the acuity of presentation preferentially affects outcomes after coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI) in patients with left main coronary artery disease (LMCAD) is unknown. We investigated whether the acuity of presentation discriminated patients who derived a differential benefit from PCI versus CABG in the randomized Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial.

Methods We used multivariable Cox models to assess the interaction between the acuity of presentation, type of revascularization and outcomes in patients with low or intermediate SYNTAX scores enrolled in EXCEL.

Results At baseline, 1151 patients (60.7%) presented with SIHD and 746 patients (39.3%) presented with an ACS. The acuity of presentation was not associated with the primary endpoint of all-cause death, MI, or stroke at 3 years (multivariable adjusted hazard ratio [HR] 0.94; 95% CI 0.70–1.26, P = .64). The primary endpoint rate was similar in patients assigned to PCI versus CABG whether they presented with SIHD (adjusted HR 1.04; 95% CI 0.73–1.48]) or with ACS (HR 0.82; 95% CI 0.54–1.26) ($P_{interaction}$ = .34).

Conclusions The acuity of presentation did not predict outcomes in patients with LMCAD undergoing revascularization, nor did it discriminate patients who derive greater event-free survival from PCI versus CABG. (Am Heart J 2019;214:9-17.)

Patients who present with left main coronary artery disease (LMCAD) have varying risks of adverse outcomes depending on their baseline characteristics. The acuity of presentation is a key determinant in the timing and the choice of revascularization strategy in patients with CAD.[1] Historically, coronary artery bypass grafting (CABG) has been regarded as the gold standard therapy for LMCAD whereas percutaneous coronary intervention (PCI) is the gold standard treatment of acute myocardial infarction (MI). In practice, an early invasive strategy with prompt revascularization (most commonly with PCI) is often preferred in higher risk patients with acute coronary syndromes (ACS), whereas a more measured "heart team" discussion and risk stratification are considered appropriate for lower risk patients with stable ischemic heart disease (SIHD).[2]

There have been no dedicated clinical trials comparing CABG versus PCI in patients with ACS, let alone in patients presenting with ACS and LMCAD. Recent post-hoc analyses have suggested that CABG may be superior to PCI with drug-eluting stents (DES) in patients with ACS and complex (multivessel or LM) CAD.[3,4] Whether outcomes of CABG compared with PCI in patients with

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LMCAD and ACS differ from those with SIHD is unknown. As such, compelling evidence to inform how the acuity of presentation should guide decisions about revascularization is lacking.[5] Accordingly, we conducted a prespecified analysis from the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial to address whether the acuity of presentation identifies patients who may experience a greater clinical benefit from revascularization by PCI versus CABG.

Methods

Study population

The rationale and design of the EXCEL trial have been published previously.[6] EXCEL was a prospective, international, randomized trial that recruited patients with unprotected LMCAD and site-assessed low to intermediate SYNTAX scores between September 2010 and March 2014.[7] EXCEL assessed whether PCI with everolimus-eluting stents was non-inferior to CABG for the composite first occurrence of all-cause death, stroke, or MI at 3 years (primary endpoint). The trial was approved by the investigational review board or ethics committee at each participating center. All patients provided written informed consent. The trial was sponsored and funded by Abbott Vascular (Santa Clara, CA), which participated in the design of the protocol and in the selection and management of sites but was not involved in the writing of the drafts of the manuscript or in the management or analysis of the data, although it had the right to a nonbinding review. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Study outcomes

Components of the primary endpoints were centrally adjudicated by a blinded clinical events committee using pre-specified criteria. MI was defined in the post-procedure interval (72 hours after either PCI or CABG) as any rise in CK-MB >10× upper reference limit or any rise in CK-MB >5× upper reference limit associated with: i) new pathological Q waves, or ii) angiographically documented graft or native coronary artery occlusion, or iii) imaging evidence of new loss of viable myocardium. Spontaneous MI was defined as any rise in CK-MB or troponin >1× upper reference limit associated with any of the above-mentioned EKG or imaging criteria, or ECG changes indicative of new ischemia (ST-segment elevation or depression). The definition for stroke has been reported elsewhere.[7] The extent of CAD and SYNTAX score were assessed at an independent angiographic core laboratory. Ischemia-driven revascularization was defined as any repeated CABG or PCI for a lesion with a diameter stenosis ≥50% by quantitative coronary analysis combined with either a corresponding positive functional study, ECG changes, typical ischemic symptoms, or abnormal IVUS (≤4 mm^2 for non-LM lesions, ≤6 mm^2 for LM lesions), or fractional flow reserve ≤0.80.

Statistical analysis

Outcomes were analyzed according to whether the patient presented with ACS (unstable angina, non–ST-segment elevation MI [NSTEMI], or ST-segment elevation MI >48 hours) versus SIHD (including angina, anginal equivalent symptoms or silent ischemia). Continuous variables are presented using the mean (standard deviation) or median (interquartile range) and were compared using t-test or Wilcoxon rank-sum tests for non-normally distributed data, as appropriate. Discrete variables are presented as counts (percentages), and were compared using either Pearson's χ^2 or the Fisher exact test, as appropriate. Time-to-event analyses are displayed using Kaplan–Meier estimates and were compared by the log-rank test. Statistical significance was set at a 2-sided $\alpha = 0.05$. No adjustments were made for multiple comparisons.

Multivariable Cox proportional hazards models were developed to adjust for known or potential confounding factors and for acuity of presentation (ACS versus SIHD) and to test for interaction. Multivariable Cox proportional hazards models were developed to adjust for known or potential confounding factors. In addition to acuity of presentation (ACS versus SIHD), the candidate independent predictors included demographics (age, sex, country of randomization), prior medical history (diabetes mellitus, hypertension, heart failure, peripheral arterial disease, chronic obstructive pulmonary disease, significant valvular heart disease, previous PCI), baseline characteristics (body mass index, systolic blood pressure, heart rate, hemoglobin, creatinine, left ventricular ejection fraction, atrial fibrillation or flutter, New York Heart Association functional class, Canadian Cardiovascular Society angina class), and core laboratory-assessed angiographic features (SYNTAX score, LM lesion location [ostial or mid-shaft versus distal lesion], number of non-LM diseased vessels). The proportionality assumption was assessed by adding an interaction term between the interested variable and survival time as a time-dependent variable to the model (see Supplemental Figures 1 to 3). If none of the time dependent covariates were significant then those predictors were proportional. Only patients with complete information were included in the models and no data imputation was performed.

The robustness of the association between the acuity of presentation, the type of revascularization and outcomes was tested in a series of sensitivity analyses. To ascertain the possible confounding effect of patients with no revascularization and crossovers from assigned CABG to PCI and inversely on outcomes, we repeated the analyses in the per-protocol population (perfect adherence to eligibility criteria, treatment assignment and assessment) and

Table I. Baseline characteristics by acuity of presentation

Characteristics	SIHD (n = 1151)	ACS (n = 746)	*P*
Randomized assignment			.52
Percutaneous coronary intervention	575 (50.0%)	369 (49.4%)	
Coronary artery bypass grafting	576 (50.0%)	377 (50.6%)	
Acuity of presentation			
Acute coronary syndromes			
ST-segment elevation myocardial infarction	—	27 (3.6%)	—
Non–ST-segment elevation myocardial infarction	—	255 (34.2%)	—
Unstable angina	—	464 (62.2%)	—
Stable coronary artery disease, CCS Class			
I	146 (12.7%)	—	—
II	484 (42.1%)	—	—
III	312 (27.1%)	—	—
IV	65 (5.6%)	—	—
Silent ischemia/other	144 (12.5%)	—	—
Demographics			
Age, years	67.0 (60.0, 73.0)	66.0 (59.0, 73.0)	.25
Male	892 (77.6%)	564 (75.6%)	.32
Body mass index, kg/m^2	28.0 (25.4, 31.6)	27.8 (25.2, 31.2)	.63
Site location			
North America	423 (36.8%)	328 (44.0%)	.002
Europe	671 (58.3%)	397 (53.2%)	.03
Asia, Australia, or South America	57 (5.0%)	21 (2.8%)	.11
Medical history			
Diabetes mellitus	320 (27.8%)	232 (31.1%)	.12
Hypertension	889 (77.2%)	513 (68.8%)	<.0001
Hyperlipidemia	861/1150 (74.9%)	466/744 (62.6%)	<.0001
Current cigarette use	212/1142 (18.6%)	200/742 (27.0%)	<.0001
Previous myocardial infarction	147/1140 (12.9%)	179/741 (24.2%)	<.0001
Previous percutaneous coronary intervention	215/1150 (18.7%)	111 (14.9%)	.03
Previous cerebrovascular accident	43/1150 (3.7%)	25 (3.4%)	.66
Heart failure	81/1149 (7.0%)	45/742 (6.1%)	.40
Chronic renal insufficiency*	187/1124 (16.6%)	118/733 (16.1%)	.76
Chronic obstructive pulmonary disease	80/1149 (7.0%)	68/745 (9.1%)	.09
Peripheral vascular disease	112/1148 (9.8%)	68/741 (9.2%)	.68

Continuous data are expressed as median (25%, 75%). *Calculated creatinine clearance <60 ml/min. ACS, acute coronary syndromes; CCS, Canadian Cardiovascular Society; SIHD, stable ischemic heart disease.

the as-treated population (treatment received, regardless of assignment). All statistical analyses were performed with SAS software version 9.4 (SAS Institute, Cary, NC).

Results

Study population

Of 1905 patients randomized in EXCEL, 1897 with known acuity presentation at baseline were included in the analysis, 1151 (60.7%) and 746 (39.3%) of whom presented with SIHD and ACS respectively. Patients with SIHD most commonly had Canadian Cardiovascular Society class II or III symptoms (69.2%), whereas patients presenting with ACS predominantly had unstable angina (62.2%) or NSTEMI (34.2%). In each group, the proportion of patients treated with PCI versus CABG was similar (Table I). Three-year follow-up was complete in 1800 patients (94.5%), with a median follow-up of 36 months.

Baseline and procedural characteristics

The baseline and presenting characteristics of patients with SIHD and ACS varied (Tables I and II). Patients enrolled in North America were more likely to present with an ACS compared with European, Asian and South American patients. Patients who presented with an ACS were more likely to have experienced a previous MI but were less likely to have undergone a prior PCI. Patients with SIHD were more frequently hypertensive, dyslipidemic, and had a higher mean left ventricular ejection fraction. There was no significant difference in the SYNTAX score baseline between groups. The median time to revascularization was shorter among patients presenting with an ACS. Most patients in both groups were treated with guideline-directed medical therapy at discharge. There were modest differences in procedural characteristics between patients with ACS and SIHD (Table III). CABG was less likely to be performed on an elective basis in patients with ACS.

Table II. Clinical and angiographic characteristics by acuity of presentation

Characteristics	SIHD (n = 1151)	ACS (n = 746)	*P*
Presenting characteristics			
Systolic blood pressure, mm Hg	132.0 (120.0, 146.0)	130.0 (119.0, 142.0)	.0001
Heart rate, beats per minute	67.0 (60.0, 76.0)	68.0 (60.0, 76.0)	.41
Hemoglobin, g/L	13.8 (12.8, 14.7)	13.6 (12.5, 14.7)	.003
Creatinine clearance, mL/min	84.7 (67.4, 105.1)	87.9 (67.1, 109.3)	.22
Platelet count, 10^9/L	218.0 (185.0, 260.0)	218.0 (182.0, 259.0)	.50
Left ventricular ejection fraction	60.0 (55.0, 64.0)	57.0 (50.0, 60.0)	<.0001
Atrial flutter/fibrillation	50 (4.3%)	21 (2.8%)	.09
Valvular heart disease, non-severe*			
Aortic stenosis	31/1061 (2.9%)	13/700 (1.9%)	.16
Aortic regurgitation	132/1061 (12.4%)	59/694 (8.5%)	.01
Mitral stenosis	5/1054 (0.5%)	6/698 (0.9%)	.36
Mitral regurgitation	328/1065 (30.8%)	190/695 (27.3%)	.12
Tricuspid regurgitation	283/1056 (26.8%)	167/687 (24.3%)	.25
Angiographic findings (core lab)			
SYNTAX score, median (interquartile range)	26.0 [20.0, 32.0]	26.0 [20.0, 32.0]	.75
Left main lesion			
Ostial	384/1104 (34.8%)	283/716 (39.5%)	.04
Mid shaft	454/1104 (41.1%)	302/716 (42.2%)	.66
Distal lesion	857/1104 (77.6%)	552/716 (77.1%)	.79
Number of non-left main diseased vessels			
1	352/1132 (31.1%)	230/738 (31.2%)	.97
2	369/1132 (32.6%)	251/738 (34.0%)	.53
3	202/1132 (17.8%)	138/738 (18.7%)	.64
Time from randomization to first revascularization, days	3 (1, 7)	2 (1, 5)	<.0001
In PCI-assigned patients	2 (1, 5)	1 (1, 3)	<.0001
In CABG-assigned patients	5 (2, 8)	4 (2, 6)	.001
Discharge medications			
Aspirin	1101/1106 (99.5%)	707/721 (98.1%)	.002
P2Y12 inhibitors, any	738/1113 (66.3%)	468/722 (64.8%)	.51
Clopidogrel	595/1113 (53.5%)	363/722 (50.3%)	.18
Prasugrel	108/1113 (9.7%)	72/722 (10.0%)	.85
Ticagrelor	35/1113 (3.1%)	33/722 (4.6%)	.11
Any warfarin/new oral anticoagulant	32/1113 (2.9%)	19/722 (2.6%)	.76
Statin	1041/1113 (93.5%)	692/722 (95.8%)	.03
Beta-blockers	976/1113 (87.7%)	635/722 (88.0%)	.87
ACEI or ARB	532/1113 (47.8%)	375/722 (51.9%)	.08
Long-acting nitrates	39/1113 (3.5%)	32/722 (4.4%)	.31

Continuous data are expressed as median (25%, 75%). *Patients with severe concomitant valvular heart disease were excluded from randomization. *ACS*, Acute coronary syndrome; *IQR*, interquartile range; *NYHA*, New York Heart Association; *SIHD*, stable ischemic heart disease; *ACEI*, Angiotensin converting enzyme inhibitor; *ARB*, angiotensin II receptor antagonist.

Acuity of presentation and outcomes after LM revascularization

The acuity of presentation was not associated with the primary composite endpoint of all-cause death, stroke, or MI or at 3 years (adjusted HR 0.94; 95% CI 0.70–1.26; P = .64). By multivariable analysis, chronic obstructive pulmonary disease, diabetes mellitus and the presence of non-severe valvular heart disease were independent predictors of the primary endpoint at 3 years (Supplemental Table I). Even though the KM curves crossed, none of the time-dependent interaction terms for the Cox model are significant, which indicated the proportional hazard assumptions are satisfied.

As shown in Table IV, among patients with SIHD, the primary endpoint was not significantly different in patients assigned to PCI versus CABG (Kaplan–Meier [KM] estimates: 15.7% versus 13.5% respectively; adjusted HR 1.04; 95% CI 0.73–1.48) (Figure 1).

Similarly, among patients presenting with ACS, the 3-year rates of death, stroke or MI were similar between PCI and CABG (KM: 14.1% versus 16.5% respectively; adjusted HR 0.82; 95% CI: 0.54–1.26). The interaction between the acuity of presentation and the effect of PCI versus CABG on outcomes was not significant (P = .34). Of note, among patients with ACS randomized to PCI versus CABG, the 3-year rates of death, stroke or MI were similar and consistent in those with unstable angina (13.7% versus 17.7% respectively, HR 0.74; 95% CI 0.46–1.18) and NSTEMI (14.9% versus 14.7% respectively, HR 0.97; 95% CI 0.53–1.80) ($P_{interaction}$ = .48).There were also no significant

Table III. Procedural revascularization details

Characteristics	SIHD	ACS	*P*
Patients assigned to PCI	n = 575	n = 369	
Number of vessels undergoing PCI*	1.7 ± 0.8	1.8 ± 0.8	.02
PCI performed in non-LM lesion	287/566 (50.7%)	211/365 (57.8%)	.03
Number of treated non-LM lesions	0.9 ± 1.1	1.0 ± 1.1	.06
Non LM vessels treated			
Left anterior descending coronary artery	151/566 (26.7%)	114/365 (31.2%)	.13
Left circumflex	87/566 (15.4%)	66/365 (18.1%)	.28
Right	146/566 (25.8%)	102/365 (27.9%)	.47
Number of lesion undergoing PCI	1.9 ± 1.1	2.0 ± 1.1	.045
Number of stents implanted	2.4 ± 1.5	2.6 ± 1.6	.046
Total stent length, mm	48.4 ± 35.5	50.1 ± 36.0	.42
PCI duration†, min	62.0 [41.0, 93.0]	61.0 [40.0, 94.0]	.92
Total contrast used, cc	254 ± 126	258 ± 130	.65
Total fluoroscopy time, min	20.0 [13.0, 31.0]	20.0 [13.0, 31.0]	.94
Patients assigned to CABG	n = 576	n = 377	
Number of vessels bypassed	2.2 ± 0.5	2.3 ± 0.6	.10
Total number of conduits	2.6 ± 0.8	2.6 ± 0.8	.55
No. of arterial conduits	1.4 ± 0.6	1.4 ± 0.6	.77
Left anterior mammary artery	539/552 (97.6%)	354/364 (97.3%)	.71
Right anterior mammary artery	137/552 (24.8%)	88/364 (24.2%)	.82
≥2 arterial conduits	172/554 (31.0%)	117/365 (32.1%)	.75
Arterial grafts only	142/555 (25.6%)	85/365 (23.3%)	.43
Cross clamp duration, min	50.0 [37.5, 67.0]	48.0 [37.0, 65.0]	.37

Continuous data expressed as mean ± standard deviation. *LM plus non LM arteries; †Defined from first guidewire introduced to last guidewire removed. *ACS*, Acute coronary syndrome; *LM*, left main coronary artery; *PCI*, percutaneous coronary intervention; *SIHD*, stable ischemic heart disease.

Table IV. Outcomes for PCI Versus CABG according to the acuity of presentation

Events at 3 years	PCI (n = 944)	CABG (n = 953)	Adjusted HR [95% CI]	*P*
Stable ischemic heart disease (n = 1151)	(n = 575)	(n = 576)		
All-cause death, stroke, or MI			1.04 [0.73, 1.48]	.34
Number of events, crude event rate (%)	89 (15.4%)	76 (13.2%)		
Kaplan–Meier estimated event rate	15.7%	13.5%		
All-cause death, stroke, MI, or IDR			1.32 [0.98, 1.78]	.22
Number of events, crude event rate (%)	138 (24.0%)	102 (17.7%)		
Kaplan–Meier estimated event rate	24.3%	18.2%		
Acute coronary syndrome (n = 746)	(n = 369)	(n = 377)		
All-cause death, stroke, or MI			0.82 [0.54, 1.26]	.34
Number of events, crude event rate (%)	52 (14.1%)	61 (16.2%)		
Kaplan–Meier estimated event rate	14.4%	16.5%		
All-cause death, stroke, MI, or IDR			0.97 [0.67, 1.41]	.22
Number of events, crude event rate (%)	74 (20.1%)	73 (19.4%)		
Kaplan–Meier estimated event rate	20.4%	19.8%		

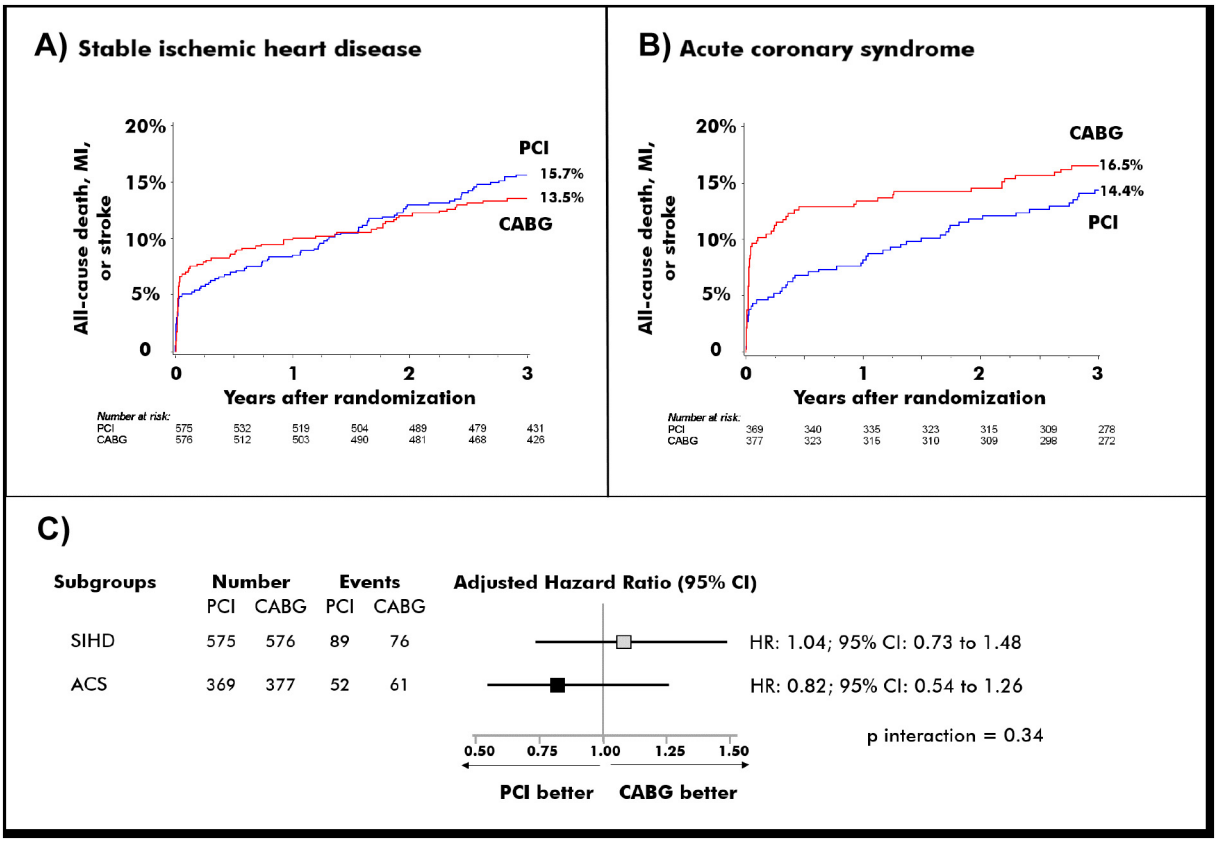
$P_{interaction}$ for acuity of presentation and revascularization strategy = 0.34 for the primary endpoint of death, stroke or MI, and $P_{interaction}$ = 0.22 for the secondary endpoint of death, stroke, MI, or IDR. *CABG*, coronary artery bypass graft; *CI*, confidence interval; *IDR*, ischemia-driven revascularization; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention.

interactions between clinical syndrome acuity at presentation, revascularization assignment and the 3-year rates of the major secondary endpoint of death, stroke, MI or ischemia-driven revascularization (Table IV), or the individual components of these endpoints (Table V). The results were similar in sensitivity analyses performed in the per protocol and as treated populations (Supplemental Tables II and III).

Discussion

The present analysis from the EXCEL trial is the first to investigate the impact of the acuity of presentation on outcomes of PCI versus CABG in patients with LMCAD from a carefully conducted, large-scale randomized trial using contemporary DES. We found that among patients with significant LMCAD and low to intermediate SYNTAX scores, those presenting with ACS derived similar event-free survival

Figure 1



Adjusted Cox proportional hazards estimates of the cumulative 3-year risk of all-cause death, stroke, or myocardial infarction according to the acuity of presentation and treatment assignment. The acuity of presentation did not identify patients with left main disease who were more or less likely to benefit from revascularization by percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG). In an analysis unadjusted for differences in baseline characteristics, the effect of PCI or CABG was similar whether the patient presented with stable ischemic heart disease (SIHD) (hazard ratio [HR] 1.04; 95% confidence interval [CI] 0.73–1.48) or as an acute coronary syndrome (ACS) (HR 0.68; 95% CI 0.50–0.94) (A and B) ($P_{interaction}$ = 0.34). (C) Multivariable adjusted analyses (see methods). The adjusted $P_{interaction}$ was also 0.34. MI = myocardial infarction.

Table V. Three-year outcomes for PCI versus CABG according to the acuity of presentation

	Stable ischemic heart disease			Acute coronary syndromes			
	PCI	CABG	HR (95% CI)*	PCI	CABG	HR (95% CI)*	$P_{interaction}$*
All-cause death	8.5% (48)	6.3% (35)	1.35 [0.87–2.08]	6.9% (25)	5.2% (19)	1.33 [0.73–2.42]	.88
Myocardial infarction	7.7% (43)	6.6% (37)	1.15 [0.74–1.78]	8.4% (30)	11.1% (41)	0.73 [0.45–1.16]	.21
Stroke	2.7% (15)	4.2% (23)	0.64 [0.33–1.22]	2.3% (8)	3.9% (14)	0.57 [0.24–1.36]	.43
Ischemia-driven revascularization	13.5% (75)	7.0% (38)	1.99 [1.39–2.94]	11.7% (41)	8.1% (29)	1.44 [0.89–2.31]	.23
ST/GO†	0.6% (3)	4.5% (24)	0.12 [0.04–0.39]	1.1% (4)	6.6% (23)	0.17 [0.06–0.48]	.67

Event rates displayed as KM estimates at 3 years (number of events). *Unadjusted analyses. †ST – stent thromboses (definite or probable) were recorded in patients assigned to PCI, whereas GO – graft occlusions (symptomatic) were recorded in patients assigned to CABG.
CABG, coronary artery bypass graft; CI, confidence interval; GO, graft occlusion; HR, hazard ratio; IDR, ischemia-driven revascularization; MI, myocardial infarction; PCI, percutaneous coronary intervention; ST, definite stent thrombosis.

after revascularization as those with SIHD. Moreover, the acuity of presentation did not identify those who had a greater relative benefit from PCI or surgical revascularization (despite the more frequent need for urgent surgical revascularization in ACS). When protocol compliance and crossovers were considered, the observed effects remained similar.

The present results have clinical relevance given the paucity of prior data to guide decision-making in patients with ACS and LMCAD. In the MILESTONE registry, 929 ACS patients presenting with complex CAD and treated by PCI were compared with 929 propensity-matched patients treated by CABG.[8] In a subgroup of 100 patients with LMCAD, CABG resulted in a numerically superior but non-significantly different rate of 3-year survival compared with stenting (HR 0.69; 95% CI 0.30–1.58; $P = .39$). Of interest, stenting was associated with improved outcomes in older patients (>65 years), women, and those with higher operative EuroSCORE (>5). Of note, DES were used in only 5% of patients enrolled in the MILESTONE registry. In the CUSTOMIZE registry of 583 patients with LMCAD and ACS (222 and 361 patients treated with PCI and CABG respectively), the adjusted 1-year rate of MACE was significantly higher in patients treated with PCI (HR 2.7; 95% CI 1.2–5.9; $P = .01$). This effect was mainly driven by an increased rate of target lesion revascularization in PCI patients (8.1% versus 1.7%, $P = .001$).[9] Of note, all PCI patients enrolled in this registry were treated with DES.

Other post hoc and subgroup analyses from randomized trials have contributed insights to the impact of the acuity of presentation in patients with complex CAD (though not necessarily with LMCAD). In a patient-level pooled analysis from the BEST, PRECOMBAT, and SYNTAX trials, CABG was associated with a reduction of all-cause death, stroke or MI in patients with complex CAD over a median follow-up of 60 months (HR 1.35; 95% CI 1.02–1.79; $P = .04$).[3] The difference was mainly driven by an increased rate of MI with PCI. However, first-generation DES were used in most of the patients in these trials, which have a substantially increased rate of stent thrombosis and MI in complex patients compared with contemporary DES.[10] Previous studies have been confounded by the use of different types and generations of stents (bare metal and early generation DES), varying extent of revascularization in PCI patients with multivessel CAD, and inconsistent use of guideline-directed medical therapy following revascularization. In the present large-scale trial in which PCI with cobalt chromium everolimus-eluting stents was compared with CABG in patients with LMCAD, both revascularization modalities were observed to yield comparable efficacy in patients with ACS and SIHD, including the hazard of MI.

Finally, no prior studies have examined whether there was an interaction between clinical syndrome acuity (ACS versus SIHD) at presentation and outcomes with PCI versus CABG in complex CAD. The results of the present study suggest that this variable need not be a major reason to favor PCI or CABG either in ACS or SIHD, at least in patients with LMCAD and low or intermediate SYNTAX scores. Thus, notwithstanding the impetus for an accelerated revascularization decision in critically ill patients (such as those with ACS and LMCAD), our results suggest that the interventional cardiologist and cardiac surgeon should discuss together the best type of revascularization for a given patient, balancing the ischemic and bleeding risks of PCI versus CABG and other differences between the two procedures in early morbidity versus late durability. The likelihood of safely achieving complete revascularization should weigh heavily in these decisions, rather than the speed to revascularization.[11,12]

The present findings from EXCEL may also inform updated guidelines. Current US societal recommendations favor CABG over PCI in LMCAD to improve survival,[13-15] unless PCI can be performed more rapidly and safely than CABG in the patient with ACS and LMCAD.[13,16] In contrast, current European Society of Cardiology guidelines do not directly address the question of acuity of presentation in LMCAD,[16] rather emphasizing the joint decision of the heart team based on the coronary anatomy and preoperative risk.

Limitations

Randomization in EXCEL was not stratified by clinical syndrome acuity, and thus despite multivariable analysis we cannot rule out possible effects from unmeasured confounders. Some LMCAD patients with ACS requiring urgent PCI or surgical revascularization may not have been randomized. There was an important amount of unclarified selection biases that went into determining the subject who were enrolled and randomized in this study, such as the patients characteristics and operator's preference. Per design, EXCEL restricted enrollment to patients with site-assessed low and intermediate SYNTAX scores. Our results should not be extrapolated to patients with extensive CAD burden (site-assessed SYNTAX score $\geq$33), in whom CABG has been shown to outperform PCI.[17] ACS patients were excluded from randomization in EXCEL if their biomarker levels were elevated at baseline; our results thus don't apply to patients with NSTEMI in whom PCI is required prior to biomarker normalization for clinical instability. In this regard, the median time to revascularization was 2 days in patients with ACS (versus 3 days in patients with SIHD). The results of our study also do not apply to patients who present with ST-segment elevation MI due to LM occlusion, for whom emergency PCI is advised in most instances.[5] Moreover, in patients with ACS it can be difficult to determine whether the LM lesion was the culprit, versus a non-LM lesion being the culprit with severe LM disease as a bystander. Finally, follow-up is complete in EXCEL only through 3 years. Longer-term outcomes are required to examine whether PCI versus CABG outcomes vary meaningfully over-time as a function of clinical syndrome presentation.

Conclusions

The present study suggests that in patients with LMCAD and low or intermediate SYNTAX scores, CABG and PCI confer a similar 3-year similar prognosis, with consistent outcomes in those with ACS and SIHD. These findings

may influence clinical practice by diminishing the primacy for immediate revascularization in patients with ACS who can be medically stabilized, and by strengthening the role of the heart team in reaching optimal revascularization decisions independent of clinical syndrome acuity.

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Disclosures

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Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.04.016.

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