Comparing results of bypass surgery and percutaneous coronary intervention for left main disease by surgical revascularization pump strategy

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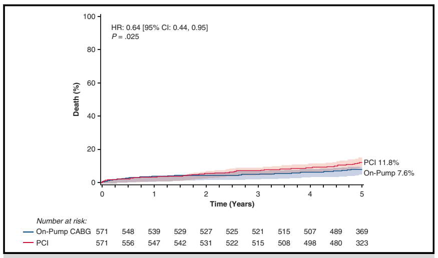
ABSTRACT

Objective: We performed a post hoc analysis of the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial to determine the effect an on-versus off-pump strategy had on outcomes when compared with percutaneous coronary intervention.

Methods: All randomized patients in EXCEL (n = 1905) were included. The outcomes of interest were the primary end point composite of death from any cause, stroke, or myocardial infarction; the composite study end point or ischemia-driven revascularization; and the rate of death from any cause at 5 years. Event rates were based on Kaplan–Meier estimates in time-to-first-event analyses.

Results: Propensity matching resulted in groups of 1142 patients (571 each) for on-pump coronary artery bypass grafting versus percutaneous coronary intervention and 472 patients (236 each) for off-pump coronary artery bypass grafting versus percutaneous coronary intervention. In the on-pump coronary artery bypass grafting versus percutaneous coronary intervention matched groups, the composite end point was similar (18.0% vs 22.1%, $P = .19$) and the composite end point or ischemia-driven revascularization (23.3% vs 31.0%, $P = .01$) was lower, and mortality (7.6% vs 11.8%, $P = .025$) was lower in the on-pump coronary artery bypass grafting group at 5 years. In the off-pump coronary artery bypass grafting versus percutaneous coronary intervention matched groups, the composite end point (19.4% vs 22.2%, $P = .47$), composite end point or ischemia-driven revascularization (25.9% vs 34.2%, $P = .07$), and mortality (12.5% vs 14.2%, $P = .59$) were similar at 5 years.

Conclusions: In the EXCEL trial, on-pump coronary artery bypass grafting was associated with a decreased 5-year rate of the composite outcome of death, stroke, myocardial infarction, or ischemia-driven revascularization, and decreased mortality when compared with percutaneous coronary intervention, whereas outcomes of off-pump coronary artery bypass grafting were similar to percutaneous coronary intervention. (JTCVS Open 2023;■:1-17)



Death at 5 years was lower in on-pump CABG versus matched PCI patients in the EXCEL trial.

CENTRAL MESSAGE

Composite end point (death, MI, stroke, or IDR) and death at 5 years were lower in on-pump CABG versus matched PCI patients in the EXCEL trial. Off-pump CABG and PCI patients had similar results.

PERSPECTIVE

In propensity-matched patients in the EXCEL trial, the composite end point (death, MI, stroke, or IDR) and death at 5 years were lower in on-pump CABG versus PCI patients, whereas off-pump CABG versus matched PCI patients had similar outcomes. These data suggest the outcomes of the EXCEL trial may have been different if all surgical revascularization was done on-pump.

See Discussion on page XXX.

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Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
EXCEL	= Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization
IDR	= ischemia-driven revascularization
LMCAD	= left main coronary artery disease
MI	= myocardial infarction
OR	= odds ratio
PCI	= percutaneous coronary intervention
SYNTAX	= Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery

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The cardiopulmonary bypass (CPB) strategy (on-pump vs off-pump) used in coronary artery bypass grafting (CABG) is a choice made by surgeons taking into account their experience and numerous patient factors. In the randomized Evaluation of XIENCE versus CABG for Effectiveness of Left Main Revascularization (EXCEL) trial, CABG was performed with (on-pump) or without (off-pump) CPB at the discretion of the surgeon.[1,2]

The impact that pump strategy has on CABG outcomes remains disputed despite extensive research and numerous well-designed trials.[3-6] Multiple studies have shown worse outcomes with off-pump CABG,[3,4] but the long-term effects of an off-pump strategy are still controversial. In a post hoc analysis of the EXCEL trial, off-pump surgery was associated with a significantly higher risk of death from any cause at 3 years when compared with on-pump surgery.[7] Given these findings, we asked, "Would the principal outcomes of the EXCEL trial be different if all surgical revascularization was done on-pump? Or off-pump?" The purpose of this study was to determine the effect pump strategy had on outcomes in the EXCEL trial.

MATERIALS AND METHODS

Patients and Procedures

This study is a retrospective, post hoc analysis of the EXCEL trial. The design and results of EXCEL have been reported previously.[1,2] Briefly, the EXCEL trial included 126 centers on 4 continents and randomized 1905 patients with left main coronary artery disease (LMCAD) and visually assessed SYNTAX scores 32 or less to either CABG (n = 957) or percutaneous coronary intervention (PCI) with contemporary everolimus-eluting stents (n = 948). Among the 957 patients assigned to CABG, 940 underwent revascularization, with CABG as the first procedure in 923 patients—this latter group comprised the study group for the present analysis (Figure E1). Likewise, among the 948 patients assigned to PCI, the 932 patients in whom PCI was performed as the first revascularization procedure comprised the present study group. CABG was performed with (on-pump) or without (off-pump) cardiopulmonary bypass at the discretion of the surgeon. The trial was approved by the ethics committee or an institutional review board at each participating center. All patients provided a written informed consent for publication of study data.

Eligibility

Potential patients were assessed for eligibility at each participating center by a heart team consisting of a surgeon and an interventional cardiologist. Inclusion criteria were (1) unprotected LMCAD with greater than 70% stenosis or 50% to 70% stenosis with either noninvasive evidence of left main ischemia or intravascular ultrasound with a minimum lumen area less than 6.0 mm^2 or fractional flow reserve 0.80 or less; (2) a visually assessed SYNTAX score 32 or less, which represents low or intermediate complexity;[8] and (3) clinical and anatomic eligibility for both PCI and CABG. Exclusion criteria for the EXCEL trial included (1) any history of prior CABG or left main PCI or prior non–left main PCI within 1 year; (2) need for cardiac surgery other than CABG; (3) inability to tolerate DAPT for 1 year; and (4) a creatine kinase-myocardial band greater than the upper limit of normal. The extent of disease and SYNTAX score were determined at an independent angiographic core laboratory.

Outcomes

The primary end points of this post hoc analysis were (1) the composite end point of death from any cause, stroke, or myocardial infarction (MI) (the primary end point of the EXCEL trial); (2) the primary composite or ischemia-driven revascularization (IDR) (a major secondary end point of the EXCEL trial); and (3) all-cause death. Per the EXCEL trial, MI was divided into periprocedural (MI within 72 hours of the index procedure) and spontaneous (MI after 72 hours). Additional secondary end points of interest were the individual components of the composite end point. Outcomes were assessed through 5 years, the longest follow-up duration in EXCEL. An independent central events committee reviewed and adjudicated all adverse events using original source documents.

Data Analysis

Propensity matching. Because EXCEL did not randomize surgical patients into on-pump CABG versus off-pump CABG, differences in patient and angiographic characteristics were present between these groups.[7] Therefore, we used propensity matching to afford matched comparisons of on-pump CABG versus PCI and off-pump CABG versus PCI.[9] We created 2 separate propensity models for on-pump CABG versus PCI and off-pump strategy versus PCI. To construct the propensity score, we used preoperative variables and multivariable logistic regression to identify factors associated with PCI versus on- and off-pump CABG. Patients in the PCI and CABG arms were matched using a 1-to-1 strategy with caliper set to 0.15 of the standard deviation of the logit of the propensity score (∼0.06) (Figure E2).

Comparisons. Event rates were based on Kaplan–Meier estimates in time-to-first-event analyses. In time-to-first-event analyses, hazard ratios with 95% CIs were determined, and event rates were compared with the use of the log-rank test. Categorical variables were compared with the use of the chi-square test or Fisher exact test. Continuous variables were compared with the use of Student *t* test or the Wilcoxon rank-sum test for non-normally distributed data. For propensity score–matched comparisons, paired tests were used given there were pairs of patients who shared a correlation in their baseline covariates.

Modeling. Given violation of nonproportional hazards over time in CABG versus PCI groups, logistic regression models were developed with log-time adjustment to calculate odds ratios (ORs) and CIs. Multilevel modeling was done to account for clustering by procedure site. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute, Inc).

RESULTS

Baseline characteristics of unmatched patients were similar (Table E1), except the mean SYNTAX score was slightly higher in PCI patients compared with on-pump CABG patients (26.9 ± 8.8 vs 25.9 ± 9.7, $P = .03$). Propensity matching yielded 571 PCI patients well matched to 571 on-pump CABG patients. A separate propensity matching yielded 236 PCI patients well matched to 236 off-pump CABG patients. After matching, the baseline characteristics of each group were similar to its matched group (Table 1). There were no significant differences between matched groups except the mean SYNTAX score was slightly higher in PCI patients compared with off-pump CABG patients (27.3 ± 8.6 vs 26.3 ± 10.0, $P = .03$).

Outcomes for unmatched groups at 5 years are shown in Table E2. Characteristics of revascularization in matched on-pump CABG and PCI patients, and matched off-pump CABG versus PCI patients are shown in Table E3.

TABLE 1. Baseline characteristics of propensity-matched groups for on-pump coronary artery bypass grafting versus percutaneous coronary intervention and off-pump coronary artery bypass grafting versus percutaneous coronary intervention

Characteristic	Statistic	On-pump N = 571	PCI N = 571	SMD	Off-pump N = 236	PCI N = 236	SMD
Age (y)	Mean ± SD (N)	66.0 ± 9.9	65.8 ± 10.0	0.02	65.3 ± 8.7	66.5 ± 8.9	−0.13
Male	n/N (%)	443/571 (77.6)	442/571 (77.4)	0.00	181/236 (76.7)	180/236 (76.3)	0.01
Prior MI	n/N (%)	98/571 (17.2)	94/571 (16.5)	0.02	36/236 (15.3)	42/236 (17.8)	−0.07
Prior PCI	n/N (%)	91/571 (15.9)	109/571 (19.1)	−0.08	36/236 (15.3)	42/236 (17.8)	−0.07
SYNTAX score (core lab)	Mean ± SD (N)	26.1 ± 9.8	26.8 ± 8.8	−0.08	26.3 ± 10.0	27.3 ± 8.6	−0.11
LM disease	n/N (%)	553/571 (96.8)	557/571 (97.5)	−0.04	229/236 (97.0)	231/236 (97.9)	−0.05
LM equivalent disease	n/N (%)	9/571 (1.6)	8/571 (1.4)	0.01	4/236 (1.7)	0/236 (0)	0.19
LM disease only	n/N (%)	104/571 (18.2)	88/571 (15.4)	0.07	35/236 (14.8)	28/236 (11.9)	0.09
LM + 1VD	n/N (%)	171/571 (29.9)	186/571 (32.6)	−0.06	80/236 (33.9)	74/236 (31.4)	0.05
LM + 2VD	n/N (%)	174/571 (30.5)	194/571 (34.0)	−0.08	75/236 (31.8)	89/236 (37.7)	−0.12
LM + 3VD	n/N (%)	113/571 (19.8)	97/571 (17.0)	0.07	43/236 (18.2)	40/236 (16.9)	0.03
Prior stroke or TIA	n/N (%)	39/571 (6.8)	24/571 (4.2)	0.12	18/236 (7.6)	11/236 (4.7)	0.12
Carotid artery disease	n/N (%)	42/571 (7.4)	37/571 (6.5)	0.03	21/236 (8.9)	26/236 (11.0)	−0.07
Peripheral vascular disease	n/N (%)	44/571 (7.7)	45/571 (7.9)	−0.01	22/236 (9.3)	31/236 (13.1)	−0.12
Congestive heart failure	n/N (%)	27/569 (4.7)	41/571 (7.2)	−0.10	17/236 (7.2)	17/235 (7.2)	0.00
Atrial fibrillation	n/N (%)	20/571 (3.5)	20/571 (3.5)	0.00	10/236 (4.2)	8/236 (3.4)	0.04
COPD	n/N (%)	43/571 (7.5)	36/571 (6.3)	0.05	21/236 (8.9)	19/236 (8.1)	0.03
Dialysis	n/N (%)	3/571 (0.5)	1/571 (0.2)	0.06	0/236 (0)	1/236 (0.4)	−0.09
Diabetes mellitus	n/N (%)	164/571 (28.7)	177/571 (31.0)	−0.05	61/236 (25.8)	67/236 (28.4)	−0.06
Anemia	n/N (%)	45/571 (7.9)	59/571 (10.3)	−0.09	23/236 (9.7)	20/236 (8.5)	0.04
Clinical presentation							
Recent MI (within 7 d)	n/N (%)	96/571 (16.8)	90/571 (15.8)	0.03	27/236 (11.4)	29/236 (12.3)	−0.03
Unstable angina	n/N (%)	153/571 (26.8)	148/571 (25.9)	0.02	52/236 (22.0)	43/236 (18.2)	0.10
BNP (pg/mL)	Mean ± SD (N)	233.3 ± 652.5 (275)	245.3 ± 572.5 (310)	−0.02	254.3 ± 608.0 (168)	150.9 ± 307.8 (127)	0.21
Serum creatinine (mg/dL)	Mean ± SD (N)	1.0 ± 0.4 (571)	1.0 ± 0.3 (571)	0.10	1.0 ± 0.3 (236)	1.0 ± 0.7 (236)	−0.09
Creatinine clearance (mL/min)	Mean ± SD (N)	88.6 ± 32.9 (571)	90.2 ± 33.4 (571)	−0.05	91.3 ± 29.1 (236)	91.8 ± 30.5 (236)	−0.02
LVEF (%)	Mean ± SD (N)	57.3 ± 8.8 (547)	57.0 ± 9.2 (546)	0.03	58.2 ± 9.4 (224)	57.2 ± 10.1 (216)	0.11

PCI, Percutaneous coronary intervention; *SMD*, standardized mean difference; *SD*, standard deviation; *MI*, myocardial infarction; *SYNTAX*, Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery; *LM*, left-main; *VD*, vessel disease; *TIA*, transient ischemic attack; *COPD*, chronic obstructive pulmonary disease; *BNP*, brain natriuretic peptide; *LVEF*, left ventricular ejection fraction.

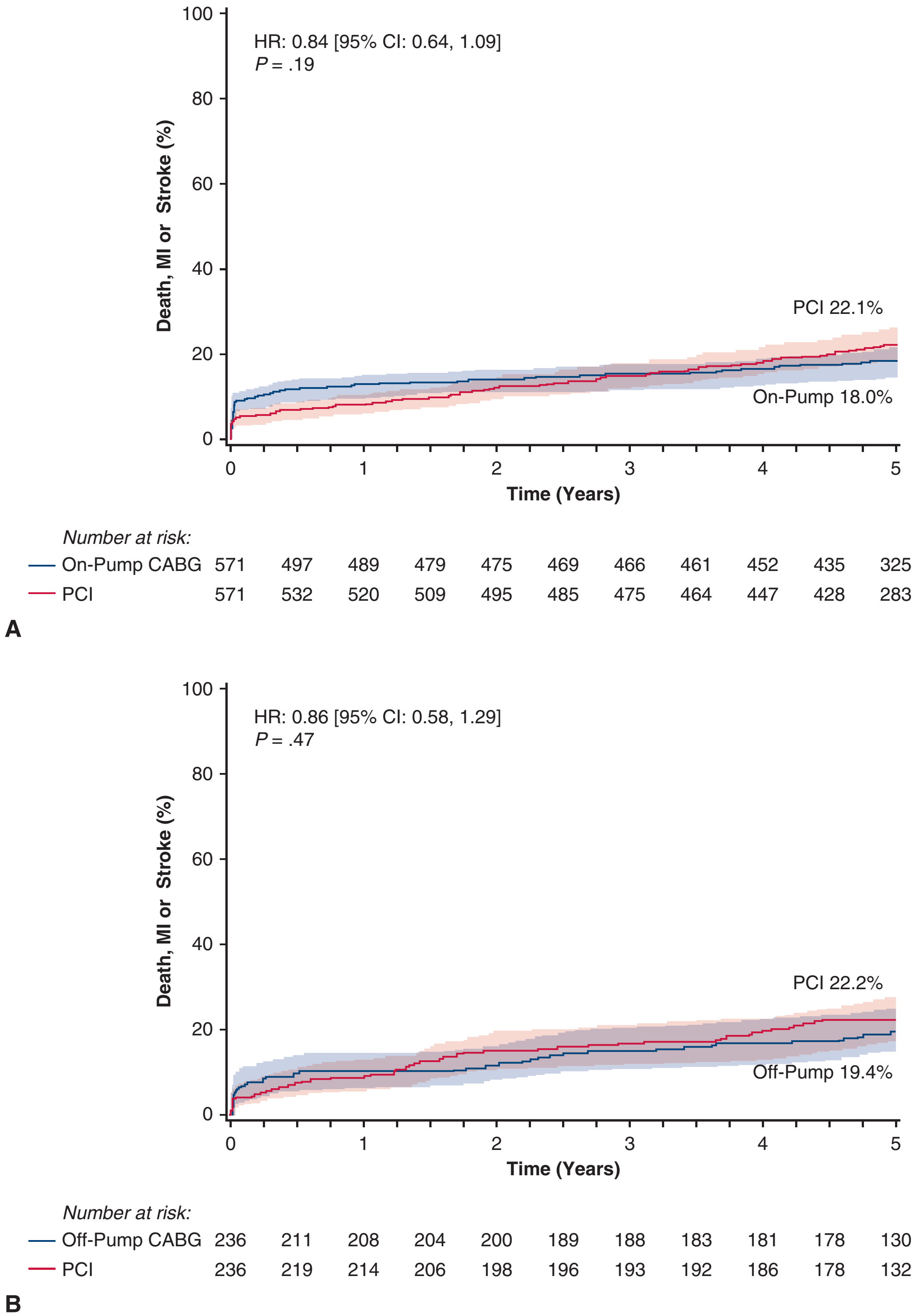


FIGURE 1. Time-to-event curves for the primary study composite end point (death, MI, or stroke) at 5 years in propensity-matched patients. A, On-pump CABG compared with PCI. B, Off-pump CABG compared with PCI. *Shading* represents 95% CIs. *HR*, Hazard ratio; *CI*, confidence interval; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting.

Medication management at 1-year and 5-year follow-up in matched on-pump CABG and PCI patients, and matched off-pump CABG and PCI patients are shown in Table E4.

As shown in Figure 1, the 5-year primary composite end point (all-cause death, all MI, or stroke) was similar in the matched on-pump CABG versus PCI groups (Figure 1, *A*,

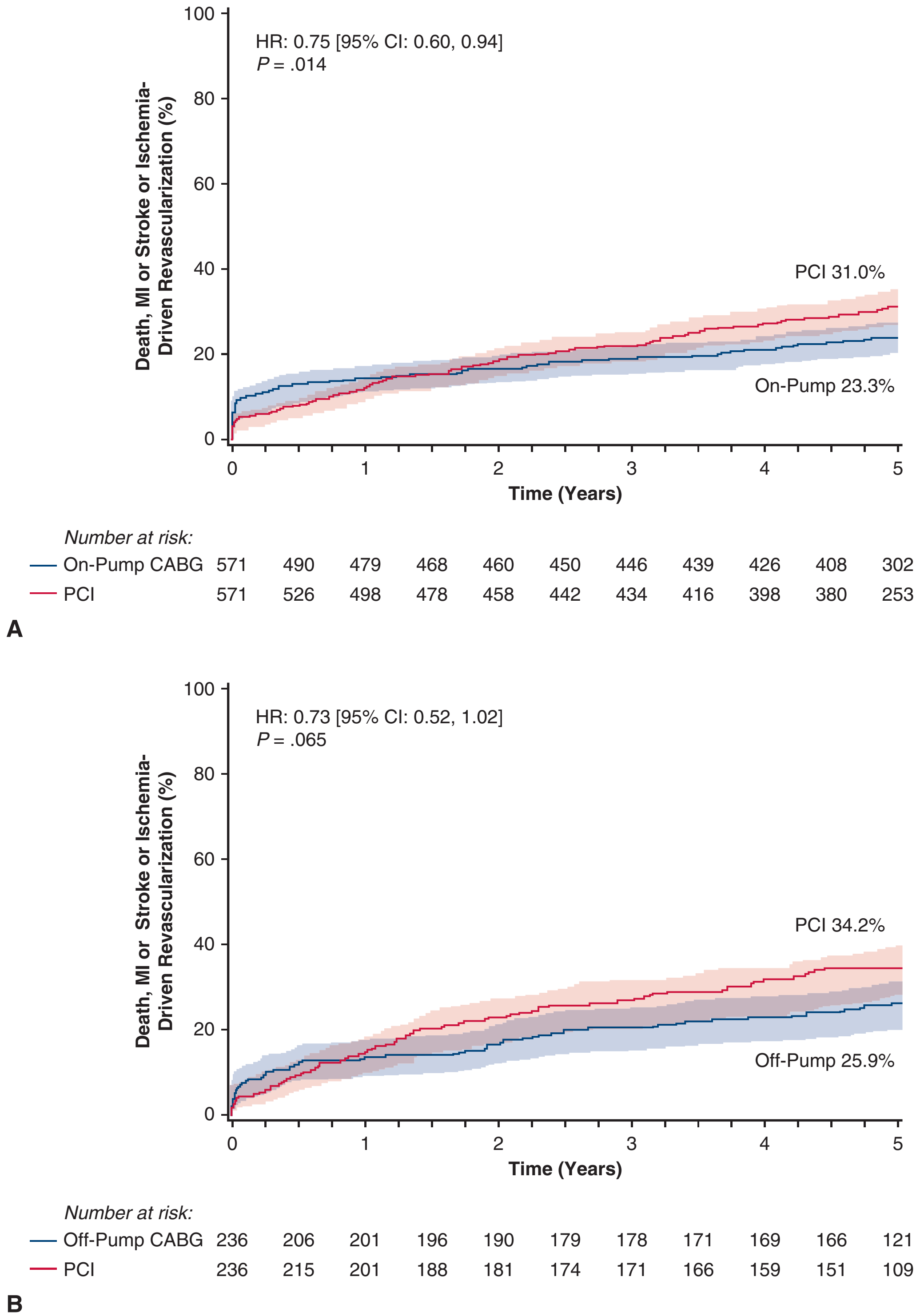
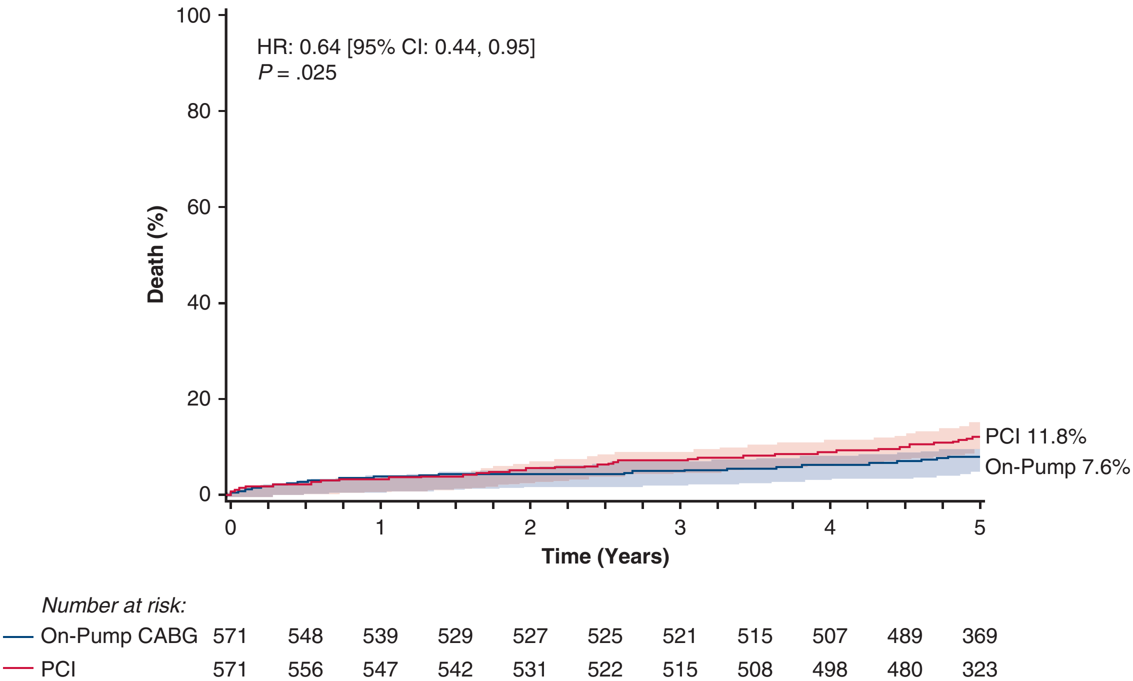


FIGURE 2. Time-to-event curves for death, MI, stroke, or IDR at 5 years in propensity-matched patients. A, On-pump CABG compared with PCI. B, Off-pump CABG compared with PCI. *Shading* represents 95% CIs. *HR*, Hazard ratio; *CI*, confidence interval; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting.

18.0% vs 22.1%, HR, 0.84 [95% CI, 0.64-1.09], *P* = .19) and the matched off-pump CABG versus PCI groups (Figure 1, *B*, 19.4% vs 22.2%, HR, 0.86 [95% CI, 0.58-1.29], *P* = .47). As shown in Figure 2 the 5-year composite end point or IDR was lower in the on-pump CABG group compared with the matched PCI group (Figure 2, *A*, 23.3%



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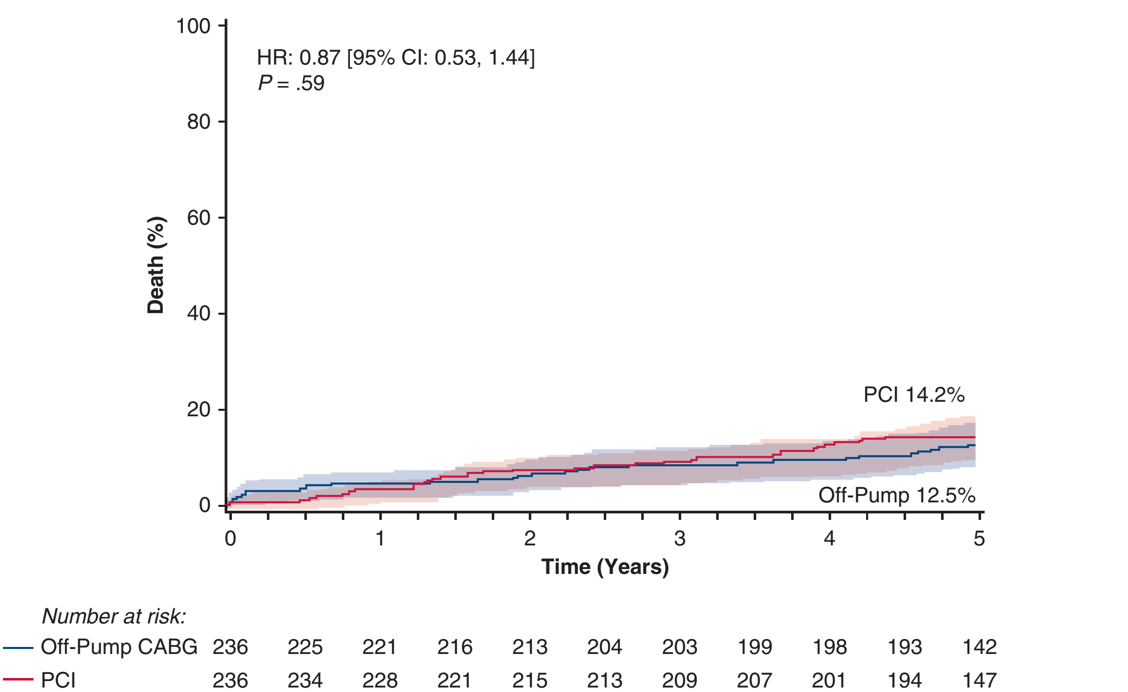
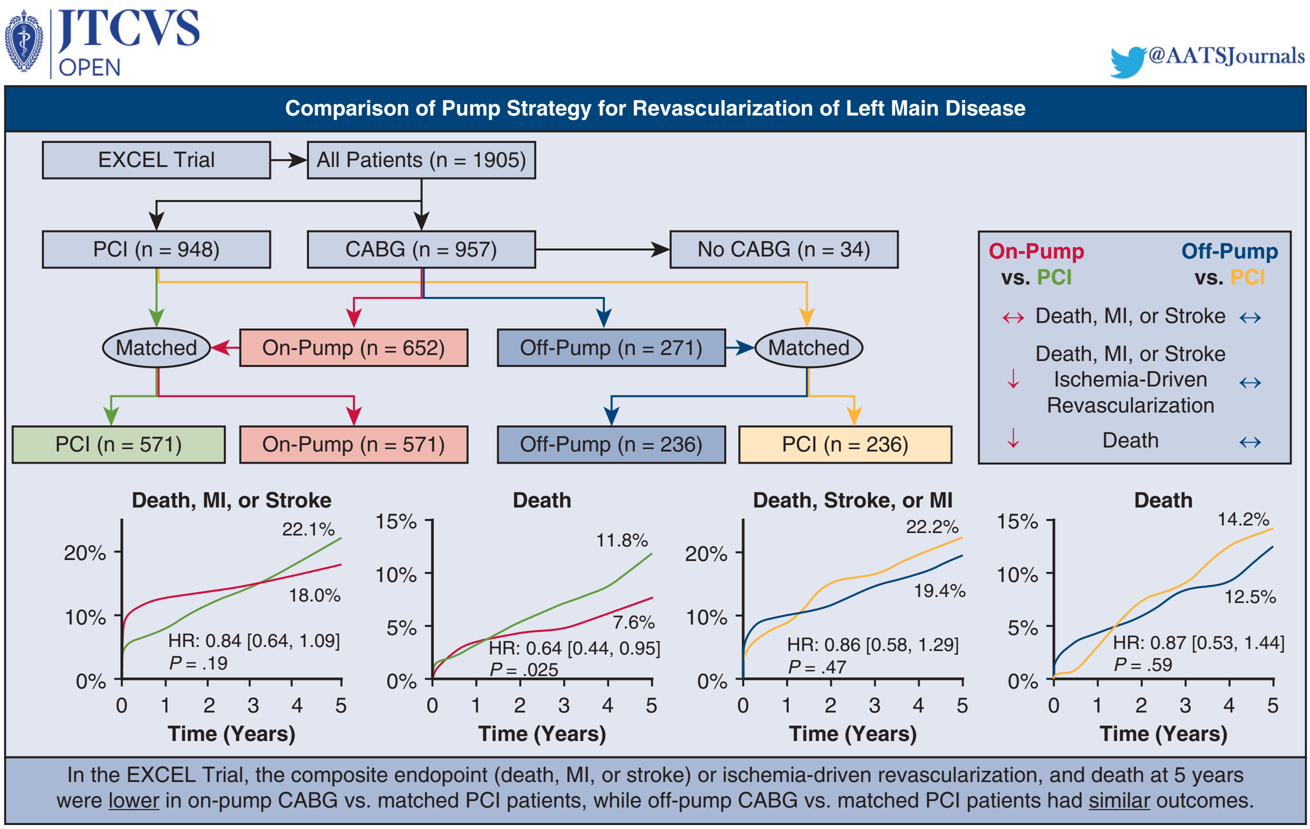


B

FIGURE 3. Time-to-event curves for all-cause death at 5 years in propensity-matched patients. A, On-pump CABG compared with PCI. B, Off-pump CABG compared with PCI. *Shading* represents 95% CIs. *HR*, Hazard ratio; *CI*, confidence interval; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting.



CABG = coronary artery bypass grafting; EXCEL = Evaluation of XIENCE versus Coronary Artery Bypass Sugery for Effectiveness of Left Main Revascularization; HR = hazard ratio; MI = myocardial infarction; and PCI = percutaneous coronary intervention.

FIGURE 4. In the EXCEL Trial, all-cause death at 5 years was lower in propensity-matched on-pump CABG versus PCI patients. *EXCEL*, Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting; *MI*, myocardial infarction; *HR*, hazard ratio.

vs 31.0%, HR, 0.75 [95% CI, 0.60-0.94], $P = .01$) and similar in the matched off-pump CABG and PCI groups (Figure 2, *B*, 25.9% vs 34.2%, HR, 0.73 [95% CI, 0.52-1.02], $P = .07$). As shown in Figure 3, all-cause death at 5 years was lower in the matched on-pump CABG versus PCI groups (Figure 3, 7.6% vs 11.8%, HR, 0.64 [95% CI, 0.44-0.95], $P = .025$) and similar in the matched off-pump CABG versus PCI groups (Figure 4, 12.5% vs 14.2%, HR, 0.87 [95% CI, 0.53-1.44], $P = .59$). Cardiovascular death was also lower at 5 years with on-pump CABG compared with PCI (4.2% vs 7.0%, $P = .05$), but higher with off-pump CABG compared with PCI (8.1% vs 5.8%, $P = .039$) (Table 2). Figure 4 summarizes these results.

In a post hoc analysis (Figure E3), the 5-year composite end point of all-cause death, spontaneous MI, or stroke was lower in the on-pump CABG group compared with the matched PCI group (13.0% vs 19.5%, HR, 0.66 [95% CI, 0.49, 0.89], $P = .007$) and similar in the matched off-pump CABG and PCI groups (16.0% vs 19.3%, HR, 0.82 [95% CI, 0.53-1.27], $P = .36$). In this analysis, there were no differences in all MI in either of the propensity-matched groups (Table 2). Periprocedural MI was higher in the on-pump CABG group (6.8%, Kaplan–Meier rate) when compared with the matched PCI group (3.3%, Kaplan–Meier rate) ($P = .009$). Conversely, there were fewer spontaneous MIs in the on-pump CABG group (3.5%, Kaplan–Meier rate) when compared with the matched PCI group (8.0%, Kaplan–Meier rate) ($P = .003$). All revascularizations and IDRs occurred more frequently in PCI patients compared with both on- and off-pump matched patients (Table 2).

By using multilevel modeling to account for clustering by procedure site, the 5-year primary composite end point (Table 3, OR, 0.71 [95% CI, 0.51-0.98], $P = .037$), all-cause death (OR, 0.51 [95% CI, 0.33-0.81], $P = .004$), and cardiovascular death (OR, 0.45 [95% CI, 0.25-0.82], $P = .009$) were lower in the matched on-pump CABG versus PCI groups. The 5-year primary composite end point (Table 3, OR, 1.03 [95% CI, 0.54-1.95], $P = .93$) and all-cause death (OR, 1.07 [95% CI, 0.49-2.32], $P = .86$) were similar in the matched off-pump CABG versus PCI groups, whereas cardiovascular death was higher in off-pump CABG (OR, 5.36 [95% CI, 1.15-25.02], $P = .033$).

TABLE 2. Primary and secondary outcomes for propensity-matched groups at 5 years

Outcome	Statistic	On-pump N = 571	PCI N = 571	P-value	Off-pump N = 236	PCI N = 236	P value
Death, MI, or stroke	% (n)	18.0 (101)	22.1 (123)	.10	19.4 (44)	22.2 (52)	.46
Death, MI, stroke, or IDR	% (n)	23.3 (130)	31.0 (173)	.004	25.9 (59)	34.2 (80)	.055
All death	% (n)	7.6 (42)	11.8 (65)	.001	12.5 (28)	14.2 (33)	.33
Cardiovascular	% (n)	4.2 (23)	7.0 (38)	.001	8.1 (18)	5.8 (13)	.039
Noncardiovascular	% (n)	3.6 (19)	5.2 (27)	.24	4.8 (10)	8.9 (20)	.009
All MI	% (n)	9.8 (55)	11.1 (60)	.76	7.1 (16)	10.1 (23)	.16
Periprocedural	% (n)	6.8 (39)	3.3 (19)	.001	4.3 (10)	4.3 (10)	.94
Spontaneous	% (n)	3.5 (19)	8.0 (42)	.0008	3.3 (7)	5.9 (13)	.10
Stroke or TIA	% (n)	5.0 (27)	3.9 (21)	.07	4.7 (10)	2.1 (5)	.20
All revascularizations	% (n)	9.6 (51)	16.7 (90)	.001	11.9 (26)	20.9 (47)	.017
PCI	% (n)	8.8 (47)	14.0 (75)	.022	10.7 (23)	16.9 (38)	.034
CABG	% (n)	0.7 (4)	3.9 (21)	.002	1.3 (3)	6.3 (14)	.011
IDR	% (n)	9.0 (48)	16.7 (90)	.0006	11.4 (25)	20.0 (45)	.020
PCI	% (n)	8.2 (44)	14.0 (75)	.010	10.2 (22)	15.9 (36)	.041
CABG	% (n)	0.7 (4)	3.9 (21)	.002	1.3 (3)	6.3 (14)	.011

Data presented as number of patients with events (Kaplan–Meier rate). *PCI*, Percutaneous coronary intervention; *MI*, myocardial infarction; *IDR*, ischemia-driven revascularization; *TIA*, transient ischemic attack; *CABG*, coronary artery bypass grafting.

DISCUSSION

The present analysis from the EXCEL trial, the largest prospective randomized trial of PCI versus CABG to date, provides direct comparisons of on-pump CABG to PCI, and off-pump CABG to PCI, specifically for the treatment of LMCAD. Overall, on-pump CABG was associated with better 5-year outcomes than PCI. On-pump CABG had a significantly lower rate of the primary study composite end point or IDR, lower mortality, and a lower rate of spontaneous MI than matched PCI patients at 5 years. Among matched off-pump CABG and PCI patients, outcomes were similar at 5 years except fewer revascularizations in the CABG group. These data suggest that long-term outcomes of on-pump CABG are superior to PCI, and most long-term outcomes of off-pump CABG are equivalent to PCI. In this analysis, it appears some of the long-term benefits of CABG over PCI are reduced with the off-pump technique.

Limited data are available on outcomes after off-pump CABG for LMCAD, but off-pump CABG has been associated with an increased risk of incomplete revascularization in non-LMCAD patients.[10] In the EXCEL trial, the deleterious impact of incomplete revascularization in patients with LMCAD may be even greater due to the large amount of myocardium at risk. This may account for the substantial difference in mortality between on-pump CABG versus PCI groups that was not present in the off-pump CABG versus PCI groups.

The impact that pump strategy has on outcomes remains disputed despite extensive research and numerous well-designed trials. In the Randomized On/Off Bypass (ROOBY) trial, 5-year survival and event-free survival were worse in patients who underwent off-pump CABG.[3] In the German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients (GOPCABE) trial, investigators reported that incomplete revascularization was associated with decreased survival at 5 years irrespective of an on-pump or off-pump strategy.[5] They also found that off-pump patients were more likely to have incomplete revascularization. However, the overall composite of death, MI, or repeat revascularization was similar between groups. In the CORONARY trial, no difference in the composite outcome of death, stroke, MI, renal failure, or repeat revascularization at 5 years was present between the on-pump

TABLE 3. Outcomes of propensity-matched groups at 5 years using logistic regression models with log-time adjustment and clustering effect by procedure site

Outcome	On-pump CABG vs PCI OR (95% CI)	On-pump CABG vs PCI P value	Off-pump CABG vs PCI OR (95% CI)	Off-pump CABG vs PCI P value
Death, MI, or stroke	0.71 (0.51-0.98)	.037	1.03 (0.54-1.95)	.93
All death	0.51 (0.33-0.81)	.004	1.07 (0.49-2.32)	.86
Cardiovascular	0.45 (0.25-0.82)	.009	5.36 (1.15-25.02)	.033

CABG, Coronary artery bypass grafting; *PCI*, percutaneous coronary intervention; *OR*, odds ratio; *CI*, confidence interval; *MI*, myocardial infarction.

and off-pump groups.[6] Of note, however, surgeons performing off-pump CABG in the GOPCABE and CORONARY trials were required to be experts, which was not a necessity in the ROOBY or EXCEL trials.

Data directly comparing on-pump versus off-pump CABG in the EXCEL trial at 3 years has been published.[7] In this analysis by Benedetto and colleagues,[7] inverse probability treatment weighting was used to estimate the average treatment effect of on-pump versus off-pump surgery. The authors found that off-pump surgery was associated with fewer grafts and vessels bypassed per patient, lower rates of revascularization of the left circumflex and right coronary arteries, and higher prevalence of a single graft to the left anterior descending. The authors concluded, “off-pump surgery was associated with a significant 2-fold increase in mortality at 3 years” when compared with on-pump surgery (8.8% vs 4.5%, HR, 1.94 [1.1-3.41], $P = .02$), and suggested the higher rate of incomplete revascularization may underlie the greater mortality risk in the off-pump surgery group. Our present analysis at 5 years comparing on-pump CABG versus PCI, and off-pump CABG versus PCI further supports the findings by Benedetto and colleagues.[7] We found an increase in mortality with PCI when compared with on-pump CABG and no significant difference in mortality between PCI and off-pump CABG.

The primary study end point of the EXCEL trial, the composite of death, stroke, or MI, was not significantly different with either on-pump or off-pump CABG versus PCI. However, had only spontaneous infarcts (MIs after 72 hours) been included in this end point, this rate would have been reduced with on-pump CABG but not with off-pump CABG compared with PCI. Periprocedural infarcts drove the initial steep rise in the composite end point of the on-pump CABG group (Figure 1). Irrespective of the controversy surrounding the definition of MI used, all-cause death at 5 years is less debatable. In our analysis, there was a clear mortality advantage of on-pump CABG over PCI, driven by a reduction in cardiovascular deaths.

Strengths and Limitations

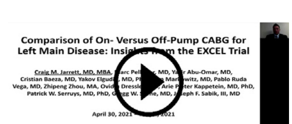
This analysis is the largest study to date comparing on-pump only CABG to PCI and off-pump CABG only to PCI. In addition, a large number of variables were collected prospectively, events were adjudicated by an independent committee using source documents, and a core laboratory reviewed the extent of disease and SYNTAX scores for all patients. Nonetheless, several limitations must be acknowledged. First, the EXCEL trial was not originally designed to compare on-pump CABG versus PCI and off-pump CABG versus PCI, and despite propensity matching the presence of unmeasured confounders cannot be excluded. Given matching was performed separately for each group, it is possible the PCI groups are different, which makes a direct comparison of on-pump CABG to off-pump CABG impossible. Moreover, propensity matching reduced the total number of patients included in the final analysis from 1855 to 1618, slightly reducing power to elicit differences between groups. In addition, patients enrolled in randomized trials are more homogenous (and tend to be lower risk) than those in observational studies given explicit inclusion and exclusion criteria. In this regard, the EXCEL trial was restricted to patients with LMCAD and a visually assessed SYNTAX score 32 or less, although 25% of the patients had a SYNTAX score 33 or greater by core laboratory analysis. Nonetheless, caution should be exercised when extrapolating these results to patients with complex coronary artery disease and non-LMCAD. Last, the present results apply to the skill levels and experience of the surgeons participating in EXCEL. Although not all surgeons who selected off-pump surgery were necessarily “expert” in this technique, their voluntary choice implies a comfort level with off-pump surgery in selected patients. Whether the present study results would have been different had only expert off-pump operators participated is unknown.

CONCLUSIONS

In the large, randomized multicenter EXCEL trial, had CABG been performed solely on-pump the surgical results may have been clearly superior to PCI, with lower 5-year rates of all-cause and cardiovascular death, spontaneous MI, and IDR. In contrast, off-pump CABG was not superior to PCI, other than a reduction in IDR. Given these findings and those from prior randomized trials, we believe these data collectively support the belief that optimal outcomes after revascularization for patients with LMCAD are achieved by on-pump CABG. Furthermore, we believe on-pump CABG should be considered the “gold standard” for surgical revascularization in future comparative studies between CABG and PCI, or at a minimum, expert off-pump surgeons should be mandated.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/21%20AM/Abstracts_Discussions/137.%20Comparison%20of%20On-%20versus%20off-Pump%20Revascularization%20for%20Left%20Main%20Disease_%20Insights%20from%20the%20Excel%20Trial.mp4.



Conflict of Interest Statement
A.P.K. is an employee of Medtronic, outside of the submitted work. P.W.S. reports receiving consulting fees from Abbott, Biosensors, Medtronic, Meril Life, Micell Technologies, Novartis, SINOMED, Philips/Volcano, Xeltis, and HeartFlow. G.W.S. reports speaker honoraria from Medtronic, Pulnovo, Infraredx; has served as a consultant to Valfix, TherOx, Robocath, HeartFlow, Ablative Solutions, Vectorious, Miracor, Neovasc, Abiomed, Ancora, Elucid Bio, Occlutech, CorFlow, Apollo Therapeutics, Impulse Dynamics, Vascular Dynamics, Shockwave, V-Wave, Cardiomech, Gore, Amgen; and has equity/options from Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, Valfix, Xenter; his daughter is an employee at Medtronic. Institutional disclosure: G.W.S.'s employer, Mount Sinai Hospital, receives research support from Abbott, Abiomed, Bioventrix, Cardiovascular Systems Inc, Phillips, Biosense-Webster, Shockwave, Vascular Dynamics and V-wave. J.F.S. reports receiving fees for serving on advisory boards from Medtronic and the Sorin Group, training fees from Medtronic, and research funding from Abbott and Edwards Lifesciences. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: CABG, EXCEL, off-pump, on-pump

Discussion

Presenter: Craig Jarrett

Unidentified Speaker 1. Dr Jarrett, thank you for that presentation. I'm going to ask David Taggart, who was the single largest enroller in the EXCEL trial, to comment.

Dr David Taggart *(Oxford, England)*. The ultrasound [inaudible] is the second largest part of why we contributed 100 patients. But yes, we were substantial contributors seeing to the trial from cardiologists and surgeons in Oxford. Umberto Benedetto and I published 3-year outcomes where we demonstrated that there did seem to be inferior outcomes with off-pump surgery at 3 years compared with on-pump surgery. However, we also demonstrated, and it comes back to really what Mario Gaudino talked about earlier today, is the experience of surgeons doing off-pump surgery. In our 3-year analysis, what we noted was a significantly lower rate of revascularization with off-pump surgery to both the lateral wall and to the inferior wall. So, the question comes back again, and I think we've had a superb presentation just now.

Dr Craig Jarrett *(Cleveland, Ohio)*.

Dr Taggart. It was absolutely excellent. I think we need to ask again—so what you have shown me today, I'm thoroughly convinced if done on-pump, you get better results than with PCI for left main. What I'd like to do is explore again in a bit more detail, was there a reason why the off-pump patients didn't do so well? Did they receive fewer graphs than the comparison on-pump group?

Dr Jarrett. Yes, the results we found were similar to your article with Benedetto. The caveat was we wanted to see how the EXCEL file would look if it was an on-pump-only strategy. This presentation in the article isn't really a true comparison of on versus off-pump, like the Benedetto article that was done. We do have the 5-year results that are subsequently filed from that Benedetto article, and it does show that that difference in all-cause deaths at 3 years persists. It actually increases. I think in the Benedetto article it was a low 4%. In the 5-year result, it's around 5%. I mean, not a huge bump, but it does persist. The study we were looking at was how would the EXCEL trial look if we did just do on-pump rather than a true comparison of on versus off. But to answer your question, yes, there were slightly fewer graphs in the off-pump group, similar to the present, similar to the results of the Benedetto article. That likely is part of the reason that we saw the results we did.

Unidentified Speaker 1. Terrific. Now, Dr Rosemary Kelly, our invited discussant for this article.

Dr Rosemary Kelly *(Minneapolis, Minn)*. The EXCEL trial has obviously undergone extensive analysis and reanalysis from many perspectives. What was great about the current presentation is that this really focuses on a uniquely surgical perspective of on-pump versus off-pump. I appreciate what the panel has discussed today is that revascularization is most successful when it's complete. I think that was the consideration that we just discussed. That was one of my concerns for the authors of this presentation. The other question I would have as we look at this going forward because these are striking findings, what would the authors consider in left main disease to be the most appropriate patient to consider for on-pump going forward from what they have found through their studies? Conversely, what would you identify as the appropriate candidate for off-pump strategies given what you've now analyzed?

Dr Jarrett. To answer your first question, what is the best candidate for patients with left main disease for on-pump surgery? I think the devil is in the details, and it probably goes to the experience of the surgeon. We haven't gotten to that point in the analysis as far as the experience of the surgeons. That is something we would like to finish if all that information is available. To some extent, it is. But I think that is probably the biggest factor. As far as patients who are good candidates for off-pump surgery, there were a fair number of patients in the EXCEL trials who had more right than just left main disease. Perhaps in patients with only left main disease we wouldn't have to worry about the lateral walls, which is what I think everyone on this panel is most concerned with, but also taking into account the experience of the surgeon.

Dr Kelly. Was there any evidence in your analysis, looking at the expertise of the institutions—and as to Dr Taggart's point, the high enrollers clearly had extensive off-pump experience. Was there any further analysis of the maybe lower enrollees who had any evidence of their expertise or lack of expertise in off-pump techniques?

Dr Jarrett. No. That is another factor we would like to consider. But given everyone's comments today, experience, and not only of the surgeon but also of the center, are super important questions we need to answer to finish up that project.

Dr Kelly. Okay. Thank you for your presentation.

Dr Mario Gaudino *(New York, NY)*. I want to raise a bit of caution about a propensity-matched study on such a small cohort of patients. The off-pump group is a small subgroup of the [inaudible] group. I think it's probably less than 50% on the [inaudible] group and then on the on-pump group. And it's even smaller when you propensity match. So, in those situations, the risk of type I and II errors is relatively high. If I look at the [inaudible] I have for your primary composite outcome, they are more or less parallel for on-pump and off-pump, but the fact that one reached statistical significance and the other doesn't with less than 200 matching the patient, it can very well be the type II error. On the other hand, I don't see a biological rationale why on-pump surgery should be better than PCI for stroke and off-pump should not. So, this is potentially a type I error. It's a great presentation, great hypothesis-generating data, but we just need to be cautious in interpreting them because of the small sample size.

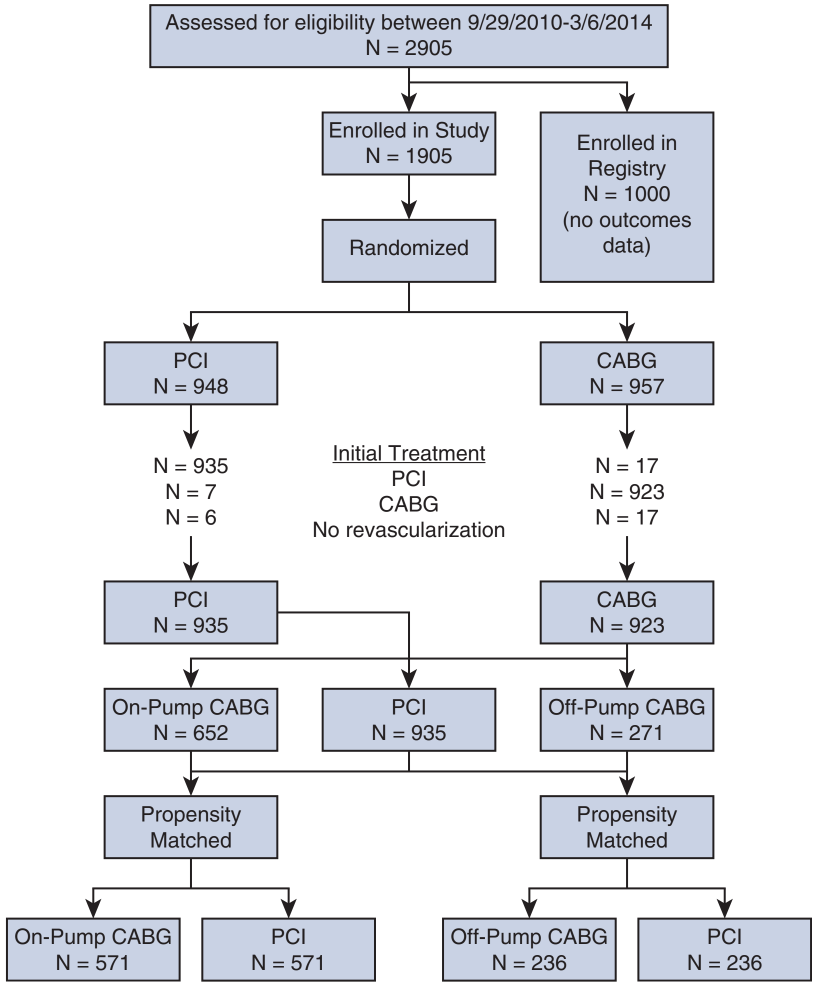

FIGURE E1. CONSORT diagram. *PCI*, Percutaneous coronary intervention; *CABG*, coronary artery bypass grafting.

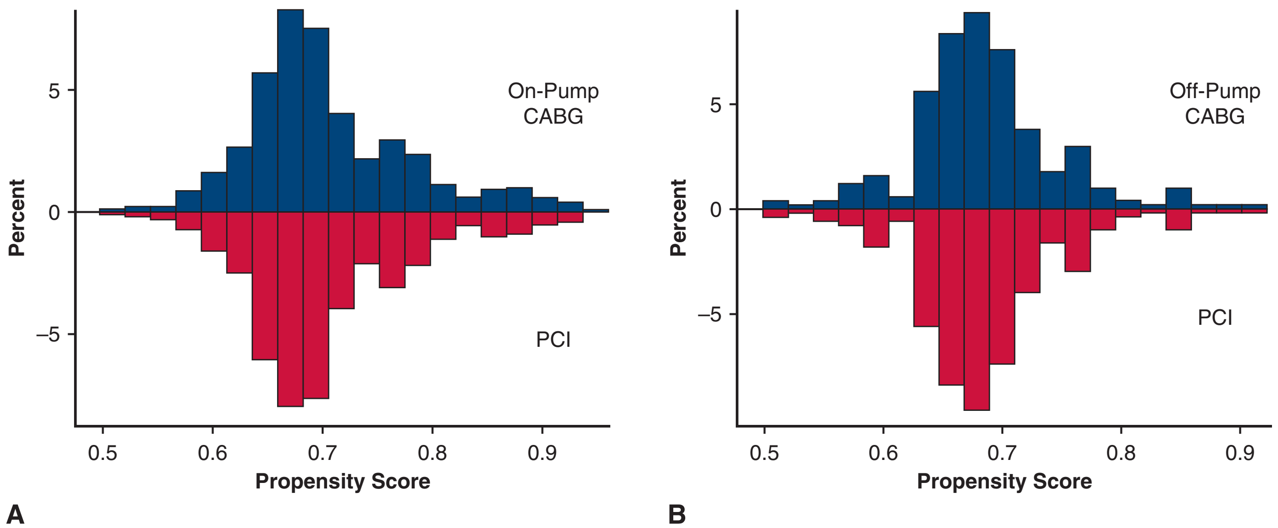

FIGURE E2. Mirrored histograms of the distribution of propensity scores. A, On-pump CABG compared with PCI. B, Off-pump CABG compared with PCI. *CABG*, Coronary artery bypass grafting; *PCI*, percutaneous coronary intervention.

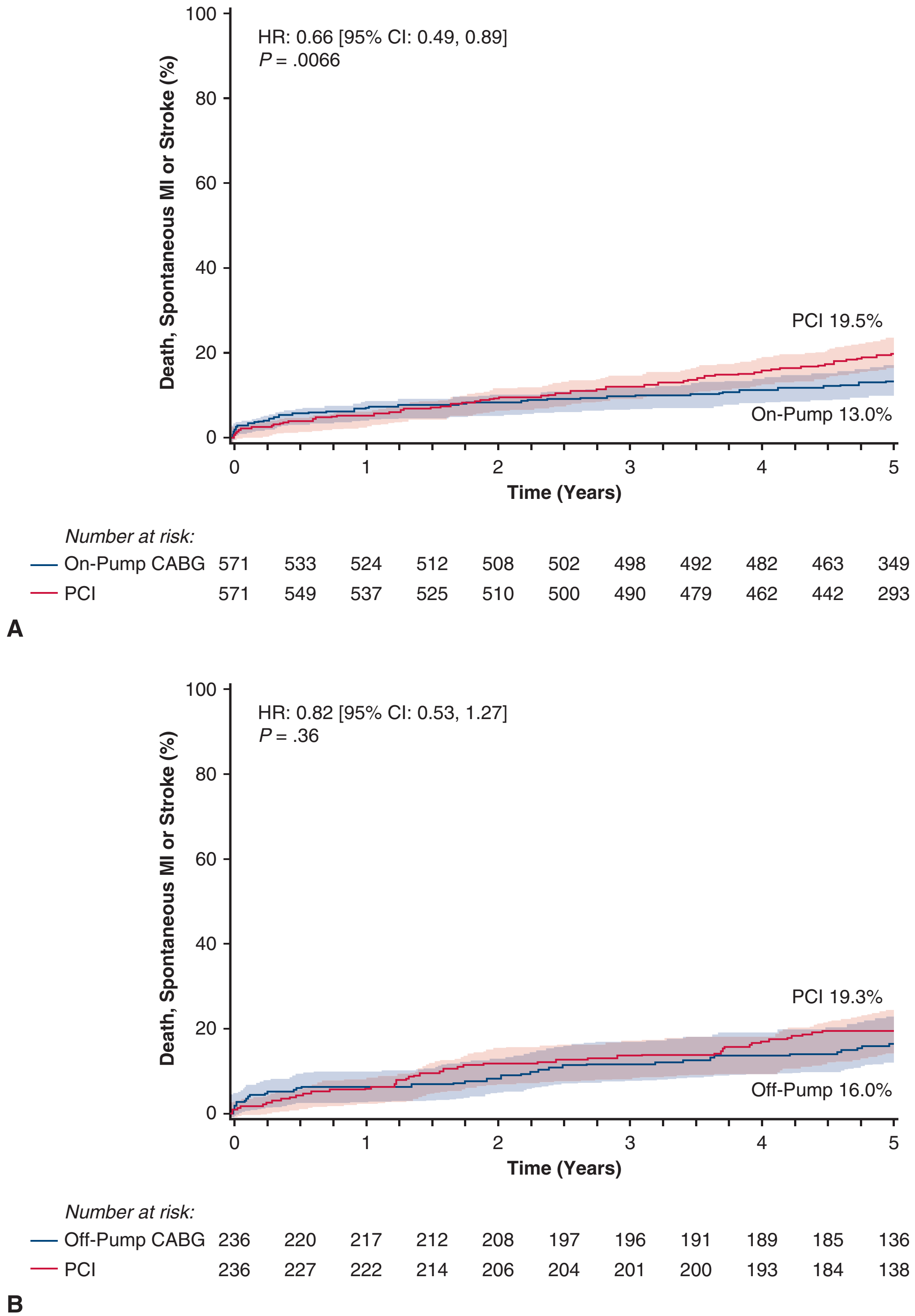

FIGURE E3. Time-to-event curves for death, spontaneous MI, or stroke at 5 years in propensity-matched patients. A, On-pump CABG compared with PCI. B, Off-pump CABG compared with PCI. Shading represents 95% CIs. *HR*, Hazard ratio; *CI*, confidence interval; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting.

TABLE E1. Baseline characteristics of unmatched on-pump coronary artery bypass grafting, off-pump coronary artery bypass grafting, and percutaneous coronary intervention patients

Characteristic	Statistic	On-pump N = 652	Off-pump N = 271	PCI N = 935	Overall *P* value	On-pump vs PCI *P* value	Off-pump vs PCI *P* value
Age (y)	Mean ± SD (N)	66.1 ± 9.7 (652)	65.2 ± 8.9 (271)	66.0 ± 9.6 (935)	.40	.77	.24
Male	n/N (%)	509/652 (78.1)	210/271 (77.5)	712/935 (76.1)	.66	.37	.65
Prior MI	n/N (%)	115/649 (17.7)	40/271 (14.8)	165/922 (17.9)	.47	.93	.23
Prior PCI	n/N (%)	107/652 (16.4)	40/271 (14.8)	170/933 (18.2)	.35	.35	.19
SYNTAX score	Mean ± SD (N)	25.9 ± 9.7 (631)	26.4 ± 10.0 (263)	26.9 ± 8.8 (905)	.10	.03	.38
LM Stenosis	n/N (%)	617/637 (96.9)	259/267 (97.0)	910/933 (97.5)	.71	.42	.63
LM Equivalent	n/N (%)	10/637 (1.6)	4/267 (1.5)	11/933 (1.2)	.79	.51	.68
LM Only	n/N (%)	120/637 (18.8)	40/267 (15.0)	160/933 (17.1)	.36	.39	.40
LM + 1VD	n/N (%)	192/637 (30.1)	91/267 (34.1)	289/933 (31.0)	.50	.72	.34
LM + 2VD	n/N (%)	192/637 (30.1)	86/267 (32.2)	314/933 (33.7)	.34	.14	.66
LM + 3VD	n/N (%)	123/637 (19.3)	46/267 (17.2)	158/933 (16.9)	.47	.23	.91
Prior stroke or TIA	n/N (%)	46/652 (7.1)	21/271 (7.7)	51/934 (5.5)	.26	.19	.16
Carotid artery disease	n/N (%)	54/650 (8.3)	24/269 (8.9)	74/931 (7.9)	.87	.80	.61
Peripheral vascular disease	n/N (%)	55/648 (8.5)	28/271 (10.3)	96/932 (10.3)	.45	.23	.99
Congestive heart failure	n/N (%)	34/649 (5.2)	22/271 (8.1)	66/933 (7.1)	.19	.14	.56
Atrial fibrillation	n/N (%)	25/652 (3.8)	11/271 (4.1)	32/935 (3.4)	.85	.66	.62
COPD	n/N (%)	52/651 (8.0)	25/270 (9.3)	64/934 (6.9)	.38	.39	.18
Dialysis	n/N (%)	3/652 (0.5)	0/271 (0)	2/935 (0.2)	.42	.39	.45
Diabetes mellitus	n/N (%)	186/652 (28.5)	70/271 (25.8)	282/935 (30.2)	.37	.48	.17
Anemia	n/N (%)	54/650 (8.3)	27/271 (10.0)	99/931 (10.6)	.30	.12	.75
Clinical presentation							
Recent MI (within 7 d)	n/N (%)	106/650 (16.3)	30/270 (11.1)	140/931 (15.0)	.13	.49	.10
Unstable angina	n/N (%)	167/650 (25.7)	62/270 (23.0)	225/931 (24.2)	.64	.49	.68
BNP (pg/mL)	Mean ± SD (N)	226.5 ± 633.7 (313)	269.3 ± 619.6 (196)	247.3 ± 554.4 (509)	.73	.63	.66
Serum creatinine (mg/dL)	Mean ± SD (N)	1.0 ± 0.4 (639)	1.0 ± 0.3 (269)	1.0 ± 0.4 (922)	.04	.08	.24
Creatinine clearance (mL/min)	Mean ± SD (N)	88.2 ± 33.0 (639)	91.2 ± 29.6 (269)	90.0 ± 32.6 (922)	.36	.26	.61
LVEF (%)	Mean ± SD (N)	57.2 ± 8.8 (625)	57.7 ± 9.4 (258)	57.0 ± 9.6 (881)	.54	.63	.27

PCI, Percutaneous coronary intervention; *MI*, myocardial infarction; *SYNTAX*, Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery; *LM*, left-main; *VD*, vessel disease; *TIA*, transient ischemic attack; *COPD*, chronic obstructive pulmonary disease; *BNP*, brain natriuretic peptide; *LVEF*, left ventricular ejection fraction.

TABLE E2. Primary and secondary outcomes for unmatched groups at 5 years

Outcome	Statistic	On-pump N = 652	Off-pump N = 271	PCI N = 935	Overall *P* value	On-pump vs PCI *P* value	Off-pump vs PCI *P* value
Death, MI, or stroke	% (n)	18.9 (121)	20.0 (52)	22.0 (201)	.51	.26	.58
Death, MI, stroke, or IDR	% (n)	24.3 (155)	26.1 (68)	31.5 (289)	.02	.007	.13
All death	% (n)	8.4 (53)	13.3 (34)	12.9 (117)	.02	.007	.84
Cardiovascular	% (n)	4.5 (28)	7.9 (20)	6.9 (61)	.09	.06	.54
Non-cardiovascular	% (n)	4.1 (25)	5.8 (14)	6.5 (56)	.16	.055	.72
All MI	% (n)	9.8 (63)	7.8 (20)	10.7 (95)	.45	.82	.22
Periprocedural	% (n)	6.9 (45)	4.5 (12)	4.0 (37)	.03	.01	.74
Spontaneous	% (n)	2.9 (18)	3.3 (8)	6.7 (58)	.004	.002	.04
Stroke or TIA	% (n)	5.0 (31)	5.6 (14)	3.3 (29)	.13	.09	.09
All revascularizations	% (n)	9.9 (60)	11.6 (29)	17.5 (154)	<.0001	<.0001	.03
PCI	% (n)	9.2 (56)	10.6 (26)	14.6 (129)	.004	.002	.11
CABG	% (n)	0.7 (4)	1.1 (3)	4.3 (38)	<.0001	<.0001	.02
IDR	% (n)	9.3 (57)	11.2 (28)	17.1 (151)	<.0001	<.0001	.03
PCI	% (n)	8.7 (53)	10.2 (25)	14.3 (126)	.003	.001	.10
CABG	% (n)	0.7 (4)	1.1 (3)	4.3 (38)	<.0001	<.0001	.02

Data presented as number of patients with events (Kaplan–Meier rate). *PCI*, Percutaneous coronary intervention; *MI*, myocardial infarction; *IDR*, ischemia-driven revascularization; *TIA*, transient ischemic attack; *CABG*, coronary artery bypass grafting.

TABLE E3. Characteristics of revascularization in on-pump coronary artery bypass grafting and matched percutaneous coronary intervention patients, and off-pump coronary artery bypass grafting versus matched percutaneous coronary intervention patients

Characteristic	Statistic	On-pump N = 571	PCI N = 571	Off-pump N = 236	PCI N = 236
Total vessels bypassed/stented	Mean ± SD	2.3 ± 0.5	1.7 ± 0.8	2.1 ± 0.6	1.7 ± 0.8
Total grafts per subject	Mean ± SD	2.7 ± 0.8	N/A	2.3 ± 0.7	N/A
Arterial	Mean ± SD	1.3 ± 0.6	N/A	1.4 ± 0.6	N/A
Venous	Mean ± SD	1.3 ± 1.0	N/A	0.9 ± 0.8	N/A
Site of distal anastomosis					
LAD	n/N (%)	558/568 (98.2)	N/A	234/235 (99.6)	N/A
LCX	n/N (%)	515/568 (90.7)	N/A	198/235 (84.3)	N/A
RCA	n/N (%)	229/568 (40.3)	N/A	73/235 (31.1)	N/A
LAD alone	n/N (%)	51/568 (9.0)	N/A	36/235 (15.3)	N/A
Total stents per subject	Mean ± SD	N/A	2.4 ± 1.5	N/A	2.5 ± 1.5
Total lesions stented per subject	Mean ± SD	N/A	1.9 ± 1.1	N/A	1.9 ± 1.1

PCI, Percutaneous coronary intervention; *SD*, standard deviation; *N/A*, not applicable; *LAD*, left anterior descending; *LCX*, left circumflex; *RCA*, right coronary artery; *CABG*, coronary artery bypass grafting.

TABLE E4. Medication management at 1-year and 5-year follow-up for on-pump coronary artery bypass grafting versus percutaneous coronary intervention and off-pump coronary artery bypass grafting versus percutaneous coronary intervention matched groups

Medication	On-pump N/571 (%)	PCI N/571 (%)	*P* value	Off-pump N/236 (%)	PCI N/236 (%)	*P* value
1-y follow-up						
Any lipid lowering	524/550 (95.3)	538/552 (97.5)	.052	213/225 (94.7)	221/229 (96.5)	.34
Aspirin	532/549 (96.9)	535/551 (97.1)	.85	215/225 (95.6)	221/229 (96.5)	.60
Any ADP antagonist	95/550 (17.3)	508/552 (92.0)	<.0001	92/225 (40.9)	204/229 (89.1)	<.0001
Both aspirin and any ADP antagonist	91/550 (16.5)	496/552 (89.9)	<.0001	87/225 (38.7)	198/229 (86.5)	<.0001
Warfarin or NOAC	55/535 (10.3)	20/544 (3.7)	<.0001	14/219 (6.4)	3/226 (1.3)	.005
Warfarin	49/535 (9.2)	20/544 (3.7)	.0002	12/219 (5.5)	3/226 (1.3)	.02
NOAC	6/533 (1.1)	0/544 (0)	.01	2/218 (0.9)	0/226 (0)	.24
5-y follow-up						
Any lipid lowering	467/485 (96.3)	463/474 (97.7)	.21	187/193 (96.9)	190/195 (97.4)	.75
Aspirin	450/484 (93.0)	440/473 (93.0)	.98	184/193 (95.3)	182/195 (93.3)	.39
Any ADP antagonist	70/485 (14.4)	302/474 (63.7)	<.0001	64/193 (33.2)	116/195 (59.5)	<.0001
Both aspirin and any ADP antagonist	58/485 (12.0)	286/474 (60.3)	<.0001	59/193 (30.6)	108/195 (55.4)	<.0001
Warfarin or NOAC	55/475 (11.6)	29/462 (6.3)	.005	13/184 (7.1)	5/188 (2.7)	.05
Warfarin	44/475 (9.3)	24/462 (5.2)	.02	10/183 (5.5)	3/188 (1.6)	.04
NOAC	11/473 (2.3)	5/461 (1.1)	.14	3/183 (1.6)	2/188 (1.1)	.68

PCI, Percutaneous coronary intervention; *ADP*, adenosine diphosphate; *NOAC*, novel oral anticoagulant.