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Off-Pump Versus On-Pump Bypass Surgery for Left Main Coronary Artery Disease

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ABSTRACT

BACKGROUND Concerns remain for a greater risk of incomplete revascularization and reduced survival with off-pump coronary artery bypass grafting (CABG) surgery compared with on-pump surgery particularly in patients with left main disease and extensive underlying myocardial ischemia.

OBJECTIVES This study sought to compare outcomes following off-pump versus on-pump surgery for left main disease by performing a post hoc analysis from the multicenter, randomized EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial.

METHODS The EXCEL trial was designed to compare percutaneous coronary intervention with everolimus-eluting stents versus CABG in patients with left main disease. CABG was performed with or without cardiopulmonary bypass (on-pump vs. off-pump surgery) according to the discretion of the operator. The 3-year outcomes in the off-pump and on-pump groups were compared using inverse probability of treatment weighting (IPTW) for treatment effect estimation.

RESULTS Among 923 CABG patients, 652 and 271 patients underwent on-pump and off-pump surgery, respectively. Despite a similar extent of disease, off-pump surgery was associated with a lower rate of revascularization of the left circumflex coronary artery (84.1% vs. 90.0%; $p = 0.01$) and right coronary artery (31.1% vs. 40.6%; $p = 0.007$). After IPTW adjustment for baseline differences, off-pump surgery was associated with a significantly increased risk of 3-year all-cause death (8.8% vs. 4.5%; hazard ratio: 1.94; 95% confidence interval: 1.10 to 3.41; $p = 0.02$) and a nonsignificant difference in the risk for the composite endpoint of death, myocardial infarction, or stroke (11.8% vs. 9.2%; hazard ratio: 1.28; 95% confidence interval: 0.82 to 2.00; $p = 0.28$).

CONCLUSIONS Among patients with left main disease treated with CABG in the EXCEL trial, off-pump surgery was associated with a lower rate of revascularization of the coronary arteries supplying the inferolateral wall and an increased risk of 3-year all-cause death compared with on-pump surgery. (J Am Coll Cardiol 2019;74:729–40)

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

CI = confidence interval

HR = hazard ratio

IPTW = inverse probability of treatment weighting

MI = myocardial infarction

PCI = percutaneous coronary intervention

PS = propensity score

Coronary artery bypass grafting (CABG) surgery with cardiopulmonary bypass (on-pump surgery) is both safe and effective, but it is associated with substantial surgical morbidity. Performing CABG without cardiopulmonary bypass (off-pump surgery) has been proposed to reduce operative complications (1). During the past decade, with the introduction of better stabilizing systems and other technical improvements, there has been a revival of interest in off-pump surgery.

However, the long-term effects of off-pump surgery continue to be controversial (2–5). The increased technical complexity of the off-pump technique can result in lower rates of complete revascularization and reduced graft patency, particularly when off-pump surgery is performed by inexperienced surgeons (2,3), and this can potentially translate into reduced long-term survival (6,7). The impact of incomplete revascularization after off-pump surgery might be particularly relevant in patients with extensive myocardial ischemia such as those with left main disease. The EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial was a largescale multicenter randomized trial that compared percutaneous coronary intervention (PCI) with everolimus-eluting stents with CABG in patients with left main coronary artery disease (8,9). We sought to gain further insights into the use and outcomes of off-pump compared with on-pump surgery in patients with left main disease by analyzing the EXCEL CABG cohort.

SEE PAGE 741

METHODS

The present study is a post hoc retrospective analysis from the EXCEL trial. The study design (8) and main results (9) have been previously published. Briefly, among 1,905 patients who underwent randomization between 2010 and 2014, 948 were assigned to PCI and 957 to CABG. Among the 957 patients assigned to CABG, 940 underwent revascularization; CABG was the first procedure performed in 923 patients—this group constituted the study population for the present analysis. CABG was performed with or without cardiopulmonary bypass (on-pump vs. off-pump surgery) according to the discretion of the operator. The goal of CABG was complete anatomic revascularization of all vessels 1.5 mm or larger in diameter in which the angiographic diameter stenosis was 50% or more; the use of arterial grafts was strongly recommended. Epiaortic ultrasonography and transesophageal ultrasonography were recommended to assess the ascending aorta and ventricular and valvular function. Aspirin was administered during the perioperative period, and the use of clopidogrel during follow-up was allowed according to the local standard of care, but was not mandatory.

ELIGIBILITY. Patients were assessed for eligibility at each participating site by a heart team that consisted of an interventional cardiologist and a cardiac surgeon. Inclusion criteria were stenosis of the left main coronary artery of 70% or more as estimated visually, or stenosis of 50% to <70% if determined by means of noninvasive or invasive testing to be hemodynamically significant, and a consensus among the members of the heart team regarding eligibility for revascularization with either PCI or CABG. In addition, participants were required to have low-to-intermediate anatomic complexity of coronary artery disease, as defined by a site-determined SYNTAX score of 32 or lower (10). The extent of disease and SYNTAX score were assessed at an independent angiographic core laboratory.

STUDY ENDPOINTS. The major endpoints of interest for the present analysis were the composite of death from any cause, stroke, or myocardial infarction (MI) at 3 years, and the rate of death from any cause. Secondary endpoints included the individual components of the composite primary endpoint, repeat revascularization, symptomatic graft stenosis or occlusion, and in-hospital complications.

OUTCOME DEFINITIONS. Endpoint definitions in the EXCEL trial have been previously reported (8). Because off-pump surgery has been associated with a lower rate of early (<72 h) creatine kinase-MB release (11), in the present analysis for the MI definition, we included only events occurring after 72 h from the index operation (i.e., spontaneous MI). As a sensitivity analysis, we analyzed all MIs including periprocedural infarcts. Study monitors collected source documents of all primary and secondary endpoint events for adjudication by an independent events committee.

STATISTICAL ANALYSIS. Categorical variables were compared between the 2 groups with the use of the chi-square test or Fisher exact test. Continuous variables were compared with the use of Student's *t*-test or the Wilcoxon rank sum test for non-normally distributed data. Event rates were based on Kaplan-Meier estimates in time to first event and were compared using log-rank test and univariate proportional hazard model.

Because the 2 groups were not randomized, inverse probability of treatment weighting (IPTW) was used to estimate the average treatment effect in the treated population to draw inferences about the relative effectiveness of off-pump versus on-pump surgery (12). For this purpose, a generalized boosted model was implemented to estimate propensity scores (PS) adjusting for pre-treatment covariates, and the PS was assumed as the probability that an individual with pre-treatment characteristics X received off-pump surgery (twang package for R software [R Foundation for Statistical Computing, Vienna, Austria]). A total of 19 pre-treatment variables were included in the PS model: age, sex, body mass index, medically treated hyperlipidemia, medically treated hypertension, current smoking, transient ischemic attack and/or stroke, diabetes, pre-operative dialysis, peripheral vascular disease, chronic obstructive pulmonary disease, anemia, history of carotid artery disease, previous MI, recent MI (within 7 days), pre-operative atrial fibrillation, left ventricular ejection fraction, extent of coronary disease assessed by the core laboratory-determined SYNTAX score, and use of arterial grafts only. PS overlapping between the 2 groups was evaluated by graphical visualization of PS density distribution (Online Figure 1). Each treatment case was given a weight of 1, and each comparison case a weight $w_i = ps(x_i)/(1 - ps(x_i))$. The absolute standardized mean difference was used as a balance metric to summarize the difference between 2 univariate distributions of a single pre-treatment variable. A value ≥10% was considered as an indicator of imbalance (12). The effect of off-pump surgery on the primary endpoints was obtained by using weighted proportional hazard model including the treatment variable only and with doubly robust estimation that is a combination of IPTW and covariate adjustment correcting for residual imbalances after weighting. Both models were further adjusted for medication at discharge including beta-blockers, diuretic therapy, antilipidemic therapy, any adenosine diphosphate receptor inhibitors, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. Treatment effect was reported as hazard ratio (HR) and 95% confidence interval (CI). Subgroup analysis was performed in the weighted sample to test possible effect modifiers (interaction term), which included: age <70 years versus age ≥70 years; female versus male sex; SYNTAX score <23 versus ≥23; and revascularization using arterial grafts only versus with additional vein grafts. Finally, as a sensitivity analysis, treatment effect estimation was obtained using multivariable proportional hazard modeling including pre-treatment variables and further adjusting for medications at discharge and stratified for geographical regions. On-pump surgery was used as reference in all analyses.

All p values are 2-sided, and p values <0.05 were considered significant. Statistical analyses were performed using R version 3.5.1. The following packages were used: twang (twang: Toolkit for Weighting and Analysis of Nonequivalent Groups. R package version 1.5), prodlim (prodlim: Product-Limit Estimation for Censored Event History Analysis. R package version 2018.04.18), Publish (Publish: Format Output of Various Routines in a Suitable Way for Reports and Publication. R package version 2018.04.17), and ggplot2 (13).

RESULTS

PATIENTS AND PROCEDURES. The study population included 652 patients (70.6%) undergoing CABG with cardiopulmonary bypass (on-pump) and 271 patients (29.4%) treated with off-pump surgery. The prevalence of off-pump and on-pump surgery varied across recruiting geographies (Online Table 1). Baseline characteristics and angiographic data are presented in **Tables 1 and 2**. The 2 groups were comparable for most pre-treatment variables including the prevalence of bifurcation lesions, involvement of non-left main vessels, and SYNTAX score.

Operative data are summarized in Online Table 2. Patients undergoing off-pump surgery had significantly fewer vessels bypassed per patient (2.1 ± 0.6 vs. 2.3 ± 0.5; p = 0.0005) and fewer grafts per patient (2.3 ± 0.7 vs. 2.7 ± 0.8; p < 0.0001). Off-pump surgery was associated with a lower rate of revascularization of the left circumflex coronary artery (84.1% vs. 90.0%; p = 0.01) and right coronary artery (31.1% vs. 40.6%; p = 0.007), and a significantly higher prevalence of a single graft to the left anterior descending coronary artery (15.6% vs. 9.7%; p = 0.01). Off-pump surgery was associated with a higher prevalence of total arterial revascularization (35.4% vs. 20.4%; p < 0.001) due to a higher rate of bilateral internal mammary artery grafts (35.1% vs. 26.2%; p = 0.007), whereas use of the radial artery did not differ between the 2 groups (7.7% vs. 5.2%; p = 0.14). Medication use in patients treated with off-pump versus on-pump surgery appears in Online Tables 3 and 4.

CLINICAL OUTCOMES. In-hospital outcomes are reported in **Table 3**. Off-pump and on-pump surgery presented comparable incidence of major adverse events during index hospitalization (36.5% vs. 41.7%; p = 0.14). Stroke occurred and hospital mortality

JACC VOL. 74, NO. 6, 2019
AUGUST 13, 2019:729–40

TABLE 1 Baseline Characteristics According to Use of On-Pump Versus Off-Pump Surgery

	Off-Pump	On-Pump	p Value
Age, yrs	271	652	
	65.2 ± 8.9	66.1 ± 9.7	0.09
	65.0 (58.0–72.0)	67.0 (60.0–74.0)	
Sex			
Male	210/271 (77.5)	509/652 (78.1)	0.85
Female	61/271 (22.5)	143/652 (21.9)	0.85
Cigarette use			
Never used cigarettes	102/268 (38.1)	237/647 (36.6)	0.68
Former cigarette user, quit ≥1 month	106/268 (39.6)	283/647 (43.7)	0.24
Current cigarette user	60/268 (22.4)	127/647 (19.6)	0.35
Prior TIA or CVA	21/271 (7.7)	46/652 (7.1)	0.71
Prior TIA	8/268 (3.0)	26/650 (4.0)	0.46
Prior CVA	15/271 (5.5)	22/652 (3.4)	0.13
Congestive heart failure	22/271 (8.1)	34/649 (5.2)	0.10
NYHA functional class			
I	4/271 (1.5)	2/649 (0.3)	0.07
II	14/271 (5.2)	20/649 (3.1)	0.13
III	6/271 (2.2)	10/649 (1.5)	0.58
IV	0/271 (0.0)	2/649 (0.3)	1.00
Diabetes mellitus	70/271 (25.8)	186/652 (28.5)	0.40
Medically treated	63/271 (23.2)	174/652 (26.7)	0.28
Insulin (with or without oral agents)	9/271 (3.3)	61/652 (9.4)	0.002
Oral hypoglycemic agents (with or without insulin)	57/271 (21.0)	135/652 (20.7)	0.91
Insulin plus oral hypoglycemic agents	3/271 (1.1)	22/652 (3.4)	0.053
Insulin alone	6/271 (2.2)	39/652 (6.0)	0.02
Oral hypoglycemic agents alone	54/271 (19.9)	113/652 (17.3)	0.35
Exercise/diet without medication	7/271 (2.6)	12/652 (1.8)	0.47
Dialysis	0/271 (0.0)	3/652 (0.5)	0.56
PVD	28/271 (10.3)	55/648 (8.5)	0.37
COPD	25/270 (9.3)	52/651 (8.0)	0.53
History of anemia	27/271 (10.0)	54/650 (8.3)	0.42
History of carotid artery disease	24/269 (8.9)	54/650 (8.3)	0.76
Prior carotid stent	4/269 (1.5)	12/650 (1.8)	1.00
Prior endarterectomy	7/269 (2.6)	11/650 (1.7)	0.37
Known carotid stenosis	16/269 (5.9)	32/650 (4.9)	0.53
Other	0/269 (0.0)	3/650 (0.5)	0.56
Prior PCI	40/271 (14.8)	107/652 (16.4)	0.53
Prior CABG	0/271 (0.0)	0/652 (0.0)	N/A
Previous cardiac surgery	1/271 (0.4)	1/652 (0.2)	0.50
Previous valve surgery	0/271 (0.0)	1/652 (0.2)	1.00
Prior MI	40/271 (14.8)	115/649 (17.7)	0.27
Within 2 months	30/271 (11.1)	102/649 (15.7)	0.07
Clinical presentation			
Recent MI (within 7 days of randomization)	30/270 (11.1)	106/650 (16.3)	0.04
ST-segment elevation MI	6/270 (2.2)	8/647 (1.2)	0.37
Non–ST-segment elevation MI	24/270 (8.9)	94/647 (14.5)	0.02
Unstable angina w/o recent MI	62/270 (23.0)	167/650 (25.7)	0.38
Pre-operative atrial fibrillation	11/271 (4.1)	25/652 (3.8)	1.00
LVEF, %	258	625	
	57.7 ± 9.4	57.2 ± 8.8	0.29
	60.0 (55.0–65.0)	60.0 (50.0–62.0)	
Hemoglobin, g/dl	271	649	
Anemia			
Hemoglobin <12 g/dl and female	16/61 (26.2)	49/142 (34.5)	0.25
Hemoglobin <13 g/dl and male	33/210 (15.7)	114/507 (22.5)	0.04

Continued on the next page

TABLE 1 Continued

	Off-Pump	On-Pump	p Value
BNP, pg/ml	196	313	
	269.3 ± 619.6	226.5 ± 633.7	0.53
	77.2 (20.2–220.7)	69.0 (25.8–148.0)	
Serum creatinine, mg/dl, n	269	639	
	1.0 ± 0.3	1.0 ± 0.4	0.003
	0.9 (0.8–1.1)	1.0 (0.8–1.1)	
Creatinine clearance, ml/min, n	269	639	
	91.2 ± 29.6	88.2 ± 33.0	0.03
	88.3 (72.1–106.1)	82.8 (65.7–104.4)	
Creatinine clearance ≤ 60 ml/min	31/269 (11.5)	106/639 (16.6)	0.052

Values are n, mean ± SD, median (interquartile range), or n/N (%).

BNP = brain natriuretic peptide; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; LVEF = left ventricular ejection fraction; MI = myocardial infarction; N/A = not applicable; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; TIA = transient ischemic attack.

TABLE 2 Angiographic Core Laboratory Data According to Use of On-Pump Versus Off-Pump Surgery

	Off-Pump	On-Pump	p Value
LM DS%	261	628	
	65.8 ± 12.5	64.0 ± 12.3	0.05
	65.0 (54.5–75.5)	62.6 (54.4–72.5)	
LM stenosis (DS% ≥50%)	259/267 (97.0)	617/637 (96.9)	0.91
LM equivalent	4/267 (1.5)	10/637 (1.6)	1.00
LM			
Segment present	261/267 (97.8)	628/637 (98.6)	0.40
LM DS% ≥50%	259/261 (99.2)	617/628 (98.2)	0.37
Ostial	91/259 (35.1)	245/617 (39.7)	0.20
Shaft	82/259 (31.7)	262/617 (42.5)	0.003
Ostial/shaft only	126/259 (48.6)	368/617 (59.6)	0.003
Distal	200/259 (77.2)	457/617 (74.1)	0.33
Bifurcation	125/200 (62.5)	261/457 (57.1)	0.20
Trifurcation	75/200 (37.5)	196/457 (42.9)	0.20
Number of diseased non-LM coronary arteries			
0	40/267 (15.0)	121/637 (19.0)	0.15
1	92/267 (34.5)	194/637 (30.5)	0.24
2	88/267 (33.0)	196/637 (30.8)	0.52
3	47/267 (17.6)	126/637 (19.8)	0.45
SYNTAX score			
Baseline	263	631	
	26.4 ± 10.0	25.9 ± 9.7	0.80
	25.0 (19.0–31.0)	25.0 (19.0–32.0)	
<23	98/263 (37.3)	253/631 (40.1)	0.43
23–32	106/263 (40.3)	229/631 (36.3)	0.26
>32	59/263 (22.4)	149/631 (23.6)	0.70
Number of diseased vessels			
LAD	143/267 (53.6)	358/637 (56.2)	0.47
LCX	120/267 (44.9)	275/637 (43.2)	0.62
RCA	147/267 (55.1)	336/637 (52.7)	0.53

Values are n, mean ± SD, median (interquartile range), or n/N (%).

DS% = percent diameter stenosis; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LM = left main coronary artery; RCA = right coronary artery.

occurred in 1.1% versus 1.5% (p = 0.77) and 1.8% versus 1.1% (p = 0.35) of patients in the off-pump and on-pump groups, respectively. Significant differences were observed only for the incidence of any unplanned surgery or therapeutic radiological procedure (1.5% vs. 4.8%; p = 0.02) (Online Table 5) and post-operative atrial fibrillation/flutter (19.2% vs. 26.5%; p = 0.02), which were significantly lower in the off-pump group.

Three-year outcomes are presented in **Table 4**. The composite of death, spontaneous MI, or stroke occurred in 11.8% versus 9.1% (log-rank p = 0.23, HR: 1.30; 95% CI: 0.84 to 2.02) (Online Figure 2A) and

TABLE 3 In-Hospital Outcomes According to Use of On-Pump Versus Off-Pump Surgery

	Off-Pump (n = 271)	On-Pump (n = 652)	p Value
MAE	99 (36.5)	272 (41.7)	0.14
Death	5 (1.8)	7 (1.1)	0.35
MI	12 (4.4)	46 (7.1)	0.13
Periprocedural MI	12 (4.4)	44 (6.7)	
Spontaneous MI	0 (0.0)	2 (0.3)	
Stroke	3 (1.1)	10 (1.5)	0.77
Transfusion of ≥2 U blood	38 (14.0)	123 (18.9)	0.08
TIMI major or minor bleeding	25 (9.2)	62 (9.5)	0.89
Major arrhythmia	35 (12.9)	103 (15.8)	0.26
Unplanned coronary revascularization for ischemia	4 (1.5)	7 (1.1)	0.74
Any unplanned surgery or therapeutic radiologic procedure	4 (1.5)	31 (4.8)	0.02
Renal failure	4 (1.5)	19 (2.9)	0.2
Sternal wound dehiscence	3 (1.1)	6 (0.9)	0.73
Infection requiring antibiotics for treatment	20 (7.4)	63 (9.7)	0.27
Intubation for >48 h	6 (2.2)	22 (3.4)	0.35
Post-pericardiotomy syndrome	1 (0.4)	1 (0.2)	0.50
Post-operative atrial fibrillation/flutter	52 (19.2)	173 (26.5)	0.02

Values are n (%).

MAE = major adverse events; MI = myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

JACC VOL. 74, NO. 6, 2019
AUGUST 13, 2019:729–40

TABLE 4 **3-Year Outcomes According to Use of On-Pump Versus Off-Pump Surgery**

	Off-Pump (n = 271)	On-Pump (n = 652)	p Value
All-cause death, spontaneous MI, or stroke	31 (11.8)	58 (9.0)	0.20
All-cause death, all MI, or stroke	40 (15.0)	95 (14.7)	1.00
All-cause death	23 (8.8)	30 (4.7)	0.02
Cardiovascular death	15 (5.8)	19 (3.0)	0.053
Noncardiovascular death	8 (3.1)	11 (1.8)	0.21
All MI	17 (6.4)	9.3 (60)	0.15
Periprocedural MI	12 (4.5)	6.9 (45)	0.16
Spontaneous MI	6 (2.4)	17 (2.7)	0.74
Stroke or TIA	12 (4.7)	24 (3.8)	0.57
Stroke	9 (3.5)	19 (3.0)	0.72
Ischemic	7 (2.8)	17 (2.7)	0.99
Hemorrhagic	2 (0.8)	3 (0.5)	0.60
TIA	3 (1.2)	5 (0.8)	0.60
All revascularizations	19 (7.0)	43 (6.9)	0.37
PCI	19 (7.4)	40 (6.4)	0.59
CABG	3 (1.1)	3 (6.4)	0.26
Ischemia-driven revascularizations	21 (8.1)	43 (6.9)	0.51
PCI	18 (7.0)	40 (6.4)	0.74
CABG	3 (1.1)	3 (0.5)	0.26
Non-ischemia-driven revascularizations	1 (0.4)	2 (0.3)	0.87
PCI	1 (0.4)	2 (0.3)	0.87
CABG	0 (0.0)	0 (0.0)	-
Symptomatic graft stenosis or occlusion	19 (7.0)	31 (4.9)	0.32

Values are n (%) of Kaplan-Meier estimated rates.
Abbreviations as in Table 1.

all-cause death occurred in 8.8% versus 4.7% (log-rank $p = 0.02$; HR: 1.88; 95% CI: 1.09 to 3.24) (Online Figure 2B) of patients in the off-pump versus on-pump surgery groups, respectively. There were no significant differences between off-pump and on-pump surgery groups in the 3-year rates of revascularization or symptomatic graft stenosis or occlusion.

TREATMENT EFFECT ESTIMATION USING IPTW ANALYSIS. Imbalances (standardized mean difference ≥10%) were present in 5 of 19 pre-treatment variables selected for the PS model (Online Table 6). Patients receiving on-pump surgery were older, more frequently had recent MI, and were on dialysis, but were less likely to have hypertension and receive arterial grafts only. The IPTW analysis created weighted on-pump and off-pump surgical groups without residual imbalance (Online Table 6).

In the IPTW analysis, the 3-year cumulative incidence of death, spontaneous MI, or stroke in the off-pump and weighted on-pump groups were 11.8% versus 9.2%, respectively; HR: 1.28; 95% CI: 0.82 to 2.00; $p = 0.28$ (Figure 1A). The 3-year cumulative incidence of all-cause death in the off-pump and weighted on-pump groups were 8.8% versus 4.5%, respectively; HR: 1.94; 95% CI: 1.0 to 3.41; $p = 0.02$ (Figure 1B). These results were confirmed by doubly robust estimation (HR for death, MI, or stroke: 1.26; 95% CI: 0.79 to 2.01; $p = 0.34$; HR for all-cause death: 1.97; 95% CI: 1.08 to 3.60; $p = 0.03$). Similar results were noted when medications at discharge were entered in the doubly robust IPTW models (HR for death, MI/or stroke: 1.39; 95% CI: 0.84 to 2.30; $p = 0.19$; HR for all-cause death: 2.31; 95% CI: 1.20 to 4.46; $p = 0.01$). Sensitivity analysis using multivariable proportional hazard models (Online Tables 7 and 8) was consistent with the primary IPTW analysis. Treatment effect estimators in the different models are summarized in Online Table 9 and Figure 2.

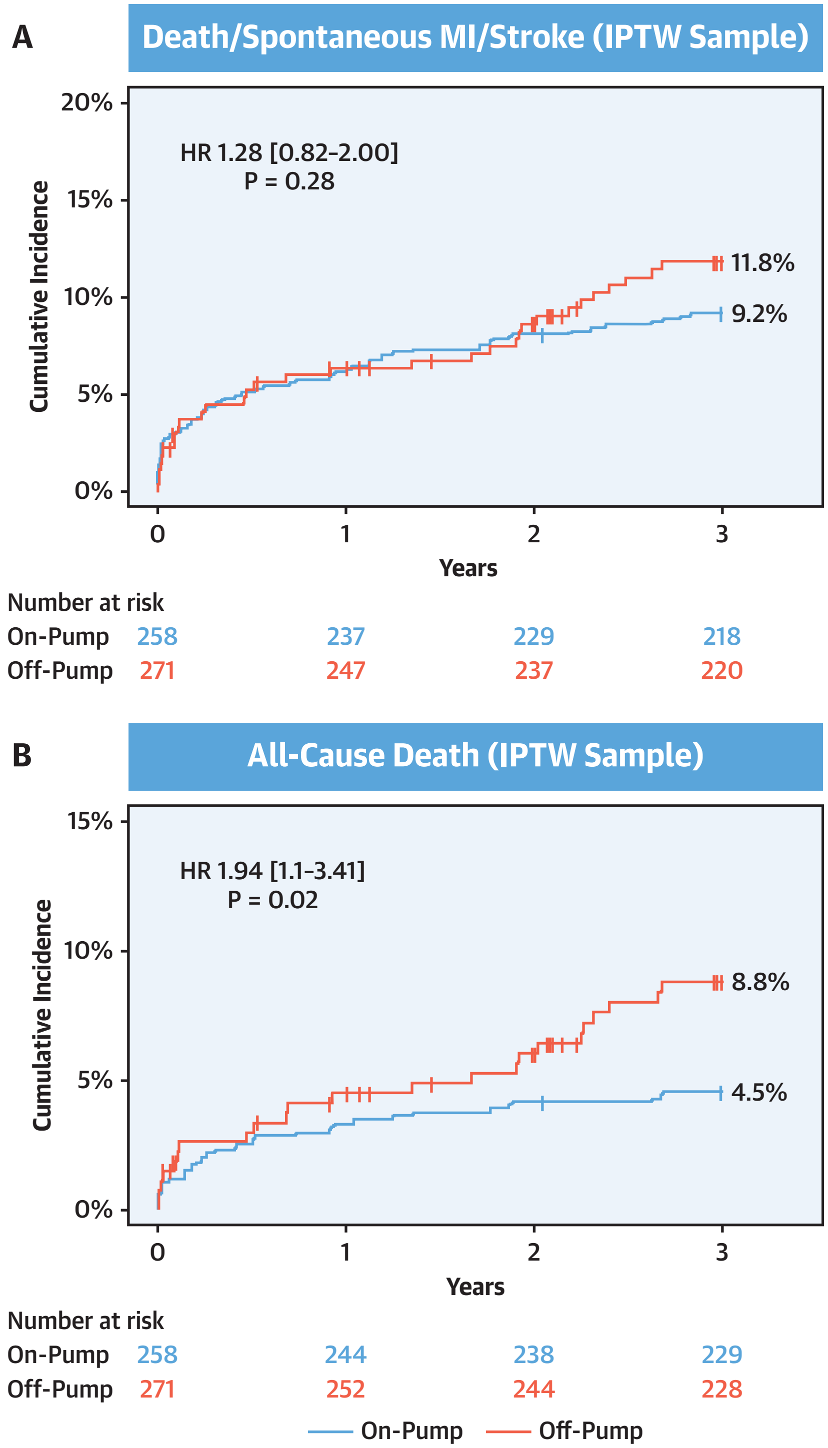
Subgroup analyses for the primary outcomes are presented in Figure 3. The SYNTAX score was the only significant modifier for the effect of off-pump versus on-pump surgery for the composite endpoint of death, MI, or stroke and all-cause mortality ($p_{interaction} = 0.035$ and $p = 0.02$, respectively). Specifically, off-pump compared with on-pump surgery was associated with a higher risk of death, MI, or stroke (HR: 1.72; 95% CI: 1.00 to 2.98) and all-cause death (HR: 3.01; 95% CI: 1.45 to 6.26) in patients with SYNTAX score ≥23, but not in those with SYNTAX score <23 (HR: 0.67; 95% CI: 0.29 to 1.56 and HR: 0.84; 95% CI: 0.30 to 2.33, respectively).

DISCUSSION

The present post hoc analysis from the EXCEL trial, the largest prospective randomized trial of left main revascularization to date, provides new insights into the effectiveness of off-pump surgery in this high-risk cohort. The off-pump and on-pump surgical groups were comparable for most baseline characteristics including the extent and complexity of coronary artery disease. Nonetheless, performance of off-pump compared with on-pump surgery was associated with use of fewer grafts, particularly to the left circumflex coronary artery and right coronary artery territories.

The 2 groups presented similar incidence of major adverse events during index hospitalization expect for a lower incidence of any unplanned surgery or therapeutic radiological procedure and post-operative atrial fibrillation/flutter (19.2% vs. 26.5%; $p = 0.02$), which were significantly lower in the off-pump group. At 3 years, off-pump surgery was associated with a significant 2-fold increase in mortality at 3 years (Central Illustration), an outcome that remained robust after adjustment for confounders in several different models. The higher rate of incomplete revascularization may underlie the increased greater mortality risk in the off-pump surgery group.

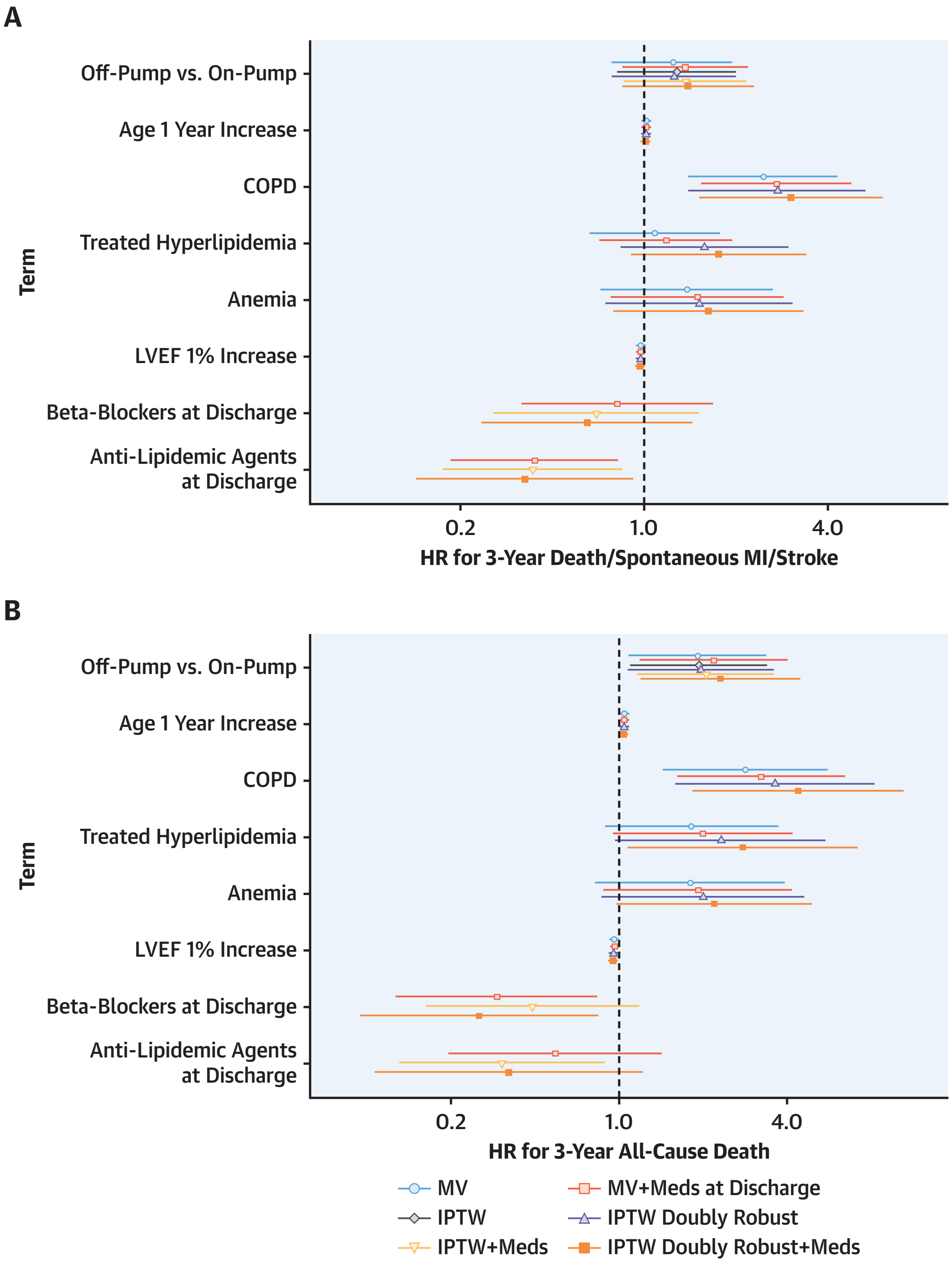
FIGURE 1 **Cumulative Incidence of the Composite of Death, Spontaneous MI, and/or Stroke and All-Cause Death in the Off-Pump and On-Pump Groups**



Cumulative incidence of the composite of death, spontaneous MI, and/or stroke **(A)** and all-cause death **(B)** in the off-pump and on-pump groups, respectively, is shown after inverse probability of treatment weighting (weighted sample) with relative treatment effect estimate. HR = hazard ratio; IPTW = inverse probability of treatment weighting; MI = myocardial infarction.

JACC VOL. 74, NO. 6, 2019
AUGUST 13, 2019:729-40

FIGURE 2 **Treatment Effect (Off-Pump vs. On-Pump) on the Composite of Death, Spontaneous MI, and/or Stroke and All-Cause Death Across Different Models**

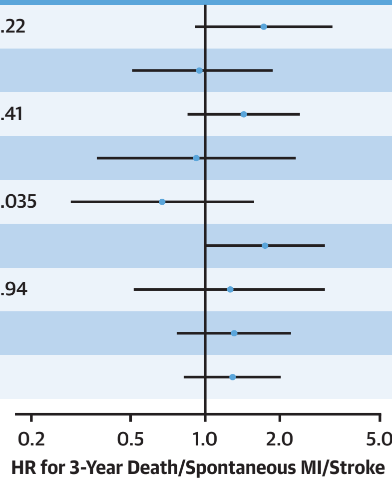


The Forest plot shows the treatment effect (off-pump vs. on-pump) on the composite of death, spontaneous MI, and/or stroke **(A)** and all-cause death **(B)** across different models implemented along with other relevant risk factors included in the models. COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; MV = multivariable proportional hazard model; other abbreviations as in Figure 1.

FIGURE 3 **Subgroup Analysis on the Composite of Death, Spontaneous MI, and/or Stroke and All-Cause Death in the Weighted Sample**

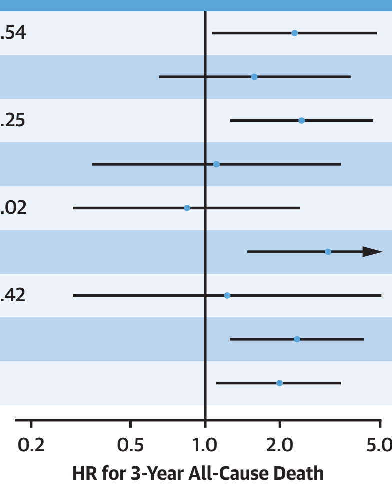
A

	Off-Pump n/N (%)	On-Pump n/N (%)	Interaction P	Estimate (95% CI)
Age ≥70	17/100 (17.0)	9/89 (10.3)	0.22	1.71 (0.91-3.20)
Age <70	14/171 (8.2)	14/169 (8.4)		0.97 (0.51-1.85)
Male	24/210 (11.4)	17/205 (8.2)	0.41	1.42 (0.85-2.37)
Female	7/61 (11.5)	7/53 (12.4)		0.92 (0.37-2.29)
Syntax Score <23	7/98 (7.1)	10/94 (10.3)	0.035	0.67 (0.29-1.56)
Syntax Score 23+	24/173 (13.9)	14/164 (8.3)		1.72 (1.00-2.98)
Arterial Grafts Only	10/96 (10.4)	7/81 (8.4)	0.94	1.25 (0.52-3.02)
With Vein Grafts	21/175 (12.0)	17/177 (9.4)		1.30 (0.77-2.19)
Overall	31/271 (11.4)	23/258 (9.1)		1.28 (0.82-2.00)



B

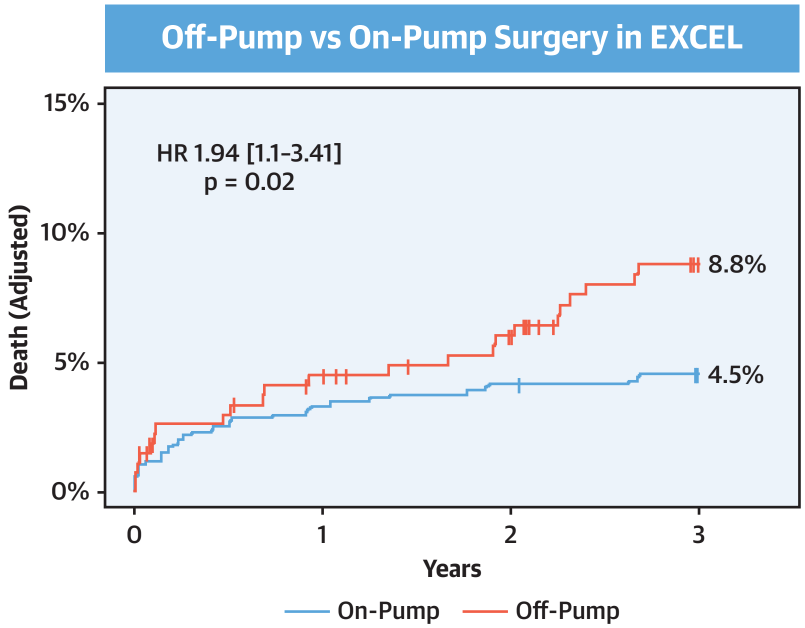
	Off-Pump n/N (%)	On-Pump n/N (%)	Interaction P	Estimate (95% CI)
Age ≥70	11/83 (13.3)	6/83 (6.4)	0.54	2.23 (1.06-4.67)
Age <70	12/188 (6.4)	6/175 (3.6)		1.55 (0.65-3.71)
Male	18/210 (8.6)	8/205 (3.7)	0.25	2.37 (1.24-4.55)
Female	5/61 (8.2)	4/53 (7.4)		1.10 (0.36-3.40)
Syntax Score <23	5/98 (5.1)	6/94 (6.0)	0.02	0.84 (0.30-2.33)
Syntax Score 23+	18/173 (10.4)	6/164 (3.6)		3.01 (1.45-6.26)
Arterial Grafts Only	4/96 (4.2)	3/81 (3.4)	0.42	1.21 (0.30-4.90)
With Vein Grafts	19/175 (10.9)	9/177 (4.9)		2.28 (1.25-4.16)
Overall	23/271 (8.5)	12/258 (4.5)		1.94 (1.10-3.41)



Subgroup analysis on the composite of death, spontaneous MI, and/or stroke **(A)** and all-cause death **(B)** in the weighted sample is shown. CI = confidence interval; other abbreviations as in Figure 1.

Limited data are available on the outcomes of off-pump surgery for the treatment of patients with left main disease. In the past, left main disease was considered a relative contraindication for off-pump surgery because of the hemodynamic fluctuations that could occur with changing the position of the heart during the process of grafting (14). However, advances in surgical technique (i.e., stabilizers and shunts) have enabled the performance of off-pump surgery in patients with left main disease. Another concern regards the degree of revascularization with off-pump surgery. An increased risk of incomplete revascularization associated with the off-pump technique has been described (15) that might have a larger deleterious impact in patients with left main disease given the extensive amount of myocardium at risk. Due to the unique technical challenges of off-pump surgery, clinical outcomes following this procedure are likely to be influenced by individual surgeon experience (16). In the EXCEL trial, information

CENTRAL ILLUSTRATION All-Cause Death After Off-Pump Versus On-Pump Surgery in Patients With Left Main Disease: Cumulative Incidence



Benedetto, U. et al. J Am Coll Cardiol. 2019;74(6):729–40.

The cumulative incidence (adjusted) of all-cause death after off-pump versus on-pump surgery in patients with left main disease undergoing surgical revascularization is shown. When compared with on-pump surgery, off-pump surgery was associated with a significantly higher incidence of death for any cause in patients with left main disease undergoing surgical revascularization in the EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial. Inverse probability of treatment weighting was used to compare the 2 groups. HR = hazard ratio.

regarding off-pump expertise for the participating surgeons was not available. However, the significantly higher rate of incomplete revascularization of the inferolateral wall in the off-pump group in the context of left main disease suggests suboptimal technique in some cases.

In previous randomized trials that included participating surgeons with limited off-pump CABG experience, off-pump surgery was associated with a significantly higher rate of incomplete revascularization and reduced survival and cardiac event-free survival (2,3). Conversely, in randomized trials where off-pump procedures were performed by experienced high-volume off-pump surgeons, the differences in the number of grafts and incidence of incomplete revascularization between off-pump and on-pump surgery were marginal, and long-term results were comparable (4,5).

The rate of conversion from off-pump to on-pump surgery is considered a proxy of surgical experience because particular skills are required to avoid hypotension and prolonged ischemia during off-pump surgery (17). Emergency conversion from off-pump to on-pump surgery due to hemodynamic instability is a major limitation of off-pump surgery and has consistently been associated with an increased risk of early and late adverse events (18). In randomized trials with participating experienced surgeons, emergent off- to on-pump conversion rates due to hypotension or ischemia were much lower than those observed in trials with participating surgeons with limited off-pump experience. In a recent post hoc analysis from the ART (Arterial Revascularization Trial) (19), performance of off-pump surgery by "sporadic" off-pump surgeons resulted in a high rate of conversion (12.9%) and use of fewer grafts and decreased survival compared with on-pump surgery. By contrast, the conversion rate was low (1%), and the number of grafts and 5-year mortality were comparable between the approaches when off-pump surgery was performed by high-volume off-pump surgeons. Of note, in the present analysis, data regarding off-pump to on-pump conversion were not available, and the surgical technique was classified on the basis of the treatment received. This limitation may have favored the off-pump group, further supporting the conclusion of increased risk with the off-pump approach.

In the present analysis, off-pump surgery was associated with a greater risk in patients with more complex coronary anatomy (SYNTAX score ≥23) in whom a significant 3-fold increased risk of death and 1.72-fold increased risk of the composite of death, MI, or stroke was observed. Conversely, the 2 techniques had comparable 3-year outcomes in patients with SYNTAX score <23. This interaction is supported by 2 previous smaller off-pump CABG studies in left main disease (20,21). In a study of 148 patients with left main disease, Birim et al. (20) observed that patients with a SYNTAX score ≥25 had an increased incidence of major adverse cardiac events. In a series of 331 patients undergoing off-pump surgery for left main disease, Carnero-Alcázar et al. (21) noted that the SYNTAX score was associated with late mortality and both early and follow-up major adverse cardiac and cerebrovascular events. Incomplete revascularization after off-pump CABG is likely to be more common in patients with extensive disease, underlying the poor prognosis in these patients. It has also been reported that off-pump surgery may increase the incidence of vein graft occlusion, but not affect arterial graft patency compared with on-pump surgery (22). In the present study, the excess rate of death with off-pump surgery was numerically more pronounced in patients who received vein grafts compared to arterial grafts only, although this difference did not reach statistical significance.

STUDY LIMITATIONS. The major limitation of the present analysis is its nonrandomized design. Multivariable and propensity adjustment can account for measured confounders, and the impact of unmeasured factors leading to choice of surgical technique cannot be excluded. However, the 2 original groups were comparable for most baseline characteristics, and patients enrolled in randomized trials are more homogeneous than those in observational studies. Finally, routine follow-up angiography was not performed in the EXCEL trial; subsequent angiography was driven by symptoms. The incidence of repeat revascularization and symptomatic graft stenosis and occlusion were numerically, but not significantly, higher in the off-pump group. The extent to which these differences (and undetected silent graft occlusions) may have contributed to the greater long-term mortality in the off-pump surgery group is unknown.

CONCLUSIONS

In the largescale, randomized multicenter EXCEL trial, despite a comparable extent of coronary disease between the 2 groups, performance of off-pump surgery was associated with a significantly lower rate of grafting of the left circumflex and right coronary arteries, and a 2-fold increase in all-cause mortality at 3 years compared with on-pump surgery.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The technical challenges of off-pump surgery may result in incomplete revascularization and suboptimal graft quality, which may have a greater adverse impact on patients with extensive myocardium at risk.

TRANSLATIONAL OUTLOOK: Further studies are needed to examine the outcomes of off-pump surgery performed by experienced surgeons in patients with left main coronary artery disease.

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KEY WORDS coronary artery bypass grafting, left main disease, off-pump

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