

New-Onset Atrial Fibrillation After PCI or CABG for Left Main Disease

The EXCEL Trial

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CME/MOC Objective for This Article: Upon completion of this activity, the learner should be able to: 1) describe the incidence and predictors of new-onset atrial fibrillation following PCI and CABG; 2) define the impact of post-operative new-onset atrial fibrillation on the long-term risk of death

and stroke following revascularization for left main disease; and 3) consider the impact that strategies to prevent, monitor for and treat new-onset atrial fibrillation may have on improving the prognosis of patients undergoing surgical revascularization for left main disease.

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ABSTRACT

BACKGROUND There is limited information on the incidence and prognostic impact of new-onset atrial fibrillation (NOAF) following percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) for left main coronary artery disease (LMCAD).

OBJECTIVES This study sought to determine the incidence of NOAF following PCI and CABG for LMCAD and its effect on 3-year cardiovascular outcomes.

METHODS In the EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial, 1,905 patients with LMCAD and low or intermediate SYNTAX scores were randomized to PCI with everolimus-eluting stents versus CABG. Outcomes were analyzed according to the development of NOAF during the initial hospitalization following revascularization.

RESULTS Among 1,812 patients without atrial fibrillation on presentation, NOAF developed at a mean of 2.7 ± 2.5 days after revascularization in 162 patients (8.9%), including 161 of 893 (18.0%) CABG-treated patients and 1 of 919 (0.1%) PCI-treated patients ($p < 0.0001$). Older age, greater body mass index, and reduced left ventricular ejection fraction were independent predictors of NOAF in patients undergoing CABG. Patients with versus without NOAF had a significantly longer duration of hospitalization, were more likely to be discharged on anticoagulant therapy, and had an increased 30-day rate of Thrombolysis In Myocardial Infarction major or minor bleeding (14.2% vs. 5.5%; $p < 0.0001$). By multivariable analysis, NOAF after CABG was an independent predictor of 3-year stroke (6.6% vs. 2.4%; adjusted hazard ratio [HR]: 4.19; 95% confidence interval [CI]: 1.74 to 10.11; $p = 0.001$), death (11.4% vs. 4.3%; adjusted HR: 3.02; 95% CI: 1.60 to 5.70; $p = 0.0006$), and the primary composite endpoint of death, MI, or stroke (22.6% vs. 12.8%; adjusted HR: 2.13; 95% CI: 1.39 to 3.25; $p = 0.0004$).

CONCLUSIONS In patients with LMCAD undergoing revascularization in the EXCEL trial, NOAF was common after CABG but extremely rare after PCI. The development of NOAF was strongly associated with subsequent death and stroke in CABG-treated patients. Further studies are warranted to determine whether prophylactic strategies to prevent or treat atrial fibrillation may improve prognosis in patients with LMCAD who are undergoing CABG. (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization [EXCEL]; [NCT01205776](https://clinicaltrials.gov/ct2/show/study/NCT01205776)) (J Am Coll Cardiol 2018;71:739-48) © 2018 by the American College of Cardiology Foundation.

Recent randomized trials have suggested that percutaneous coronary intervention (PCI) with contemporary drug-eluting stents is an acceptable alternative to coronary artery bypass graft surgery (CABG) for selected patients with left main coronary artery disease (LMCAD) (1,2). As such, identification of pre-procedural and post-procedural factors that affect outcomes after both revascularization modalities may affect the choice between PCI and CABG. New-onset atrial fibrillation (NOAF) is a common post-operative complication of CABG, and in earlier studies (mostly in patients with multivessel disease), NOAF was associated with prolonged hospitalization, increased rates of adverse events, and greater health care costs (3,4). A recent analysis from the MAIN-COMPARE registry (Revascularization for Unprotected Left MAIN Coronary Artery Stenosis: COMparison of Percutaneous Coronary Angioplasty versus Surgical REvascularization From Multi-Center Registry) in Asia reported that pre-operative atrial fibrillation (AF) was a predictor of long-term morbidity and mortality after CABG in patients with LMCAD (5); however, the incidence and prognostic impact of NOAF following contemporary PCI and CABG in patients with LMCAD in sinus rhythm are largely unknown. In the present study, we sought to determine the incidence, predictors, and outcomes of NOAF in patients with LMCAD who underwent percutaneous or surgical revascularization in the randomized EXCEL trial (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization).

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METHODS

STUDY DESIGN AND ENDPOINTS. The design of the EXCEL trial has been reported previously (1,6). In brief, EXCEL was an international, multicenter, randomized trial that compared everolimus-eluting stents with CABG in patients with LMCAD and low or intermediate SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) scores (≤ 32) in whom equipoise for revascularization with both techniques was present after heart team review. Randomization was performed with the use of an interactive voice-based or Internet-based system in block sizes of 16, 24, or 32, with stratification according to diabetes (present vs. absent), SYNTAX score (≤ 22 vs. ≥ 23), and study center. The goal of PCI was complete revascularization of all ischemic territories with fluoropolymer-based cobalt-chromium everolimus-eluting stents

(Xience, Abbott Vascular, Santa Clara, California). CABG was performed with or without cardiopulmonary bypass according to the discretion of the operator, with the goal of complete anatomic revascularization of all vessels ≥ 1.5 mm in diameter with $\geq 50\%$ diameter stenosis; the use of multiple arterial grafts was strongly recommended. Beta-blockers (or amiodarone for patients with contraindications to beta-blocker use) were recommended for pre-operative prophylaxis of post-operative AF in the surgical arm of the trial. All CABG-treated patients were to receive beta-blockers post-procedure unless contraindicated. Amiodarone use for 5 days post-CABG was also allowed in all patients for rhythm control according to the local standard of care. Use of other medications in the PCI and CABG arms of the trial has been described previously (1,6).

The primary endpoint was a composite of death from any cause, stroke, or myocardial infarction (MI) at 3 years. Major powered secondary endpoints included the primary composite endpoint at 30 days and the composite of death, stroke, MI, or ischemia-driven revascularization at 3 years. Additional secondary endpoints included the components of the primary and secondary endpoints at 30 days and 3 years, stent thrombosis and symptomatic graft stenosis or occlusion at 30 days and 3 years, and periprocedural major adverse events occurring within 30 days, all as previously defined (1,6). NOAF was defined as the occurrence of any episode of AF or flutter (collectively termed AF for this analysis) following the index procedure through the time of discharge that lasted at least 30 s and was captured on a standard 12-lead electrocardiogram or cardiac telemetry, or that required medical treatment.

The investigation was approved by the Institutional Review Board or Ethics Committee at each participating center, and all patients signed written informed consent forms. Major endpoints were adjudicated by an independent clinical events committee (Cardiovascular Research Foundation, New York, New York). Angiographic analyses were performed at an angiographic core laboratory (Cardiovascular Research Foundation). Follow-up is currently complete for all patients through 3 years. Median follow-up for clinical outcomes was 3 years.

STATISTICAL METHODS. For the purpose of this study, arrhythmic events during the hospitalization following the index CABG or PCI procedure were analyzed. All analyses were performed in the

ABBREVIATIONS AND ACRONYMS

AF	= atrial fibrillation or flutter
BMI	= body mass index
CABG	= coronary artery bypass grafting
CI	= confidence interval
HR	= hazard ratio
LMCAD	= left main coronary artery disease
LVEF	= left ventricular ejection fraction
MI	= myocardial infarction
NOAF	= new-onset atrial fibrillation or flutter
PCI	= percutaneous coronary intervention

TABLE 1 Baseline Characteristics According to the Development of In-Hospital New-Onset Atrial Fibrillation

	NOAF (n = 162)	No NOAF (n = 1,650)	p Value
Age, yrs	69.0 ± 8.1	65.4 ± 9.6	<0.0001
Female	33/162 (20.4)	383/1,650 (23.2)	0.41
Hyperlipidemia	122/162 (75.3)	1,143/1,647 (69.4)	0.12
Hypertension	119/162 (73.5)	1,211/1,650 (73.4)	0.99
Prior stroke or transient ischemic attack	9/162 (5.6)	102/1,649 (6.2)	0.75
Congestive heart failure	6/162 (3.7)	107/1,645 (6.5)	0.16
Diabetes mellitus, medically treated	38/162 (23.5)	441/1,650 (26.7)	0.37
Chronic obstructive pulmonary disease	18/162 (11.1)	117/1,647 (7.1)	0.06
History of anemia	23/161 (14.3)	152/1,646 (9.2)	0.04
History of carotid artery disease	9/160 (5.6)	140/1,644 (8.5)	0.20
Peripheral vascular disease	20/160 (12.5)	157/1,646 (9.5)	0.23
Critical pre-operative state	4/162 (2.5)	24/1,649 (1.5)	0.31
Valve disease (moderate or less)			
Aortic stenosis	5/150 (3.3)	36/1,536 (2.3)	0.40
Mitral stenosis	2/149 (1.3)	9/1,529 (0.6)	0.25
Aortic regurgitation	21/150 (14.0)	162/1,527 (10.6)	0.20
Mitral regurgitation	53/150 (35.3)	435/1,531 (28.4)	0.07
Tricuspid regurgitation	37/148 (25.0)	383/1,517 (25.2)	0.95
Prior percutaneous coronary intervention	34/162 (21.0)	272/1,648 (16.5)	0.15
Previous cardiac surgery	0/162 (0.0)	8/1,650 (0.5)	1.00
Prior myocardial infarction	36/161 (22.4)	276/1,637 (16.9)	0.08
Clinical presentation			
Recent MI (within 7 days)	29/162 (17.9)	242/1,643 (14.7)	0.28
ST-segment elevation MI	2/162 (1.2)	24/1,637 (1.5)	1.00
Non-ST-segment elevation MI	27/162 (16.7)	210/1,637 (12.8)	0.17
Unstable angina	35/162 (21.6)	411/1,643 (25.0)	0.34
Body mass index, kg/m ²	29.3 ± 5.4	28.5 ± 4.9	0.14
Left ventricular ejection fraction, %	56.1 ± 9.1	57.4 ± 9.2	0.05
SYNTAX score (core laboratory assessed)	26.5 ± 9.6	26.6 ± 9.4	0.90
Baseline laboratory values			
Creatinine clearance, ml/min	87.1 ± 32.8	90.1 ± 32.2	0.16
Hemoglobin, g/dl	13.5 ± 1.6	13.6 ± 1.6	0.74
Brain natriuretic peptide, units	241.6 ± 427.3	224.7 ± 557.2	0.04
CHADS ₂ score	1.7 ± 1.3	1.6 ± 1.3	0.45
CHA ₂ DS ₂ -VASC score	3.3 ± 1.4	3.2 ± 1.4	0.29

Values are mean ± SD or n/N (%).

CHADS₂ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and stroke, transient ischemic attack, or thromboembolism; CHA₂DS₂-VASC = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and stroke, transient ischemic attack, or thromboembolism; vascular disease, age 65 to 74 years, and female sex; MI = myocardial infarction; NOAF = new-onset atrial fibrillation or flutter; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

as-treated population, excluding patients with in-hospital AF before the index procedure and those who did not undergo revascularization procedures. Continuous variables are reported as mean ± standard deviation and were compared using the Student's *t*-test. Categorical variables are expressed as counts and percentages and were compared with the chi-square or Fisher exact test, as appropriate. Predictors of NOAF in patients undergoing CABG were determined in a Cox proportional hazards model including the following clinical and angiographic

variables: age, sex, history of medically treated diabetes, history of hypertension, history of congestive heart failure, recent MI (<7 days), body mass index (BMI), baseline hemoglobin, baseline renal insufficiency (creatinine clearance <60 ml/min), left ventricular ejection fraction (LVEF), angiographic core laboratory-assessed SYNTAX score, off-pump versus on-pump CABG, number of bypass conduits, and bypass of the left circumflex artery. The same model was tested in patients who underwent off-pump surgery. A second Cox proportional hazards model was constructed in patients who underwent on-pump surgery including the foregoing covariates (except off-pump vs. on-pump surgery) in addition to bypass duration, cross-clamp duration, use of crystalloid cardioplegia, and retrograde cardioplegia.

Event rates at 30 days and 3 years were estimated using the Kaplan-Meier method, with comparisons made using the log-rank test. Multivariable Cox proportional hazard analyses were used to determine whether NOAF was an independent predictor of all-cause death, cardiovascular death, stroke, and the primary composite outcome measure of death, MI, or stroke at 3 years. The following covariates were included in the model: NOAF, age, sex, medically treated diabetes, history of hypertension, history of congestive heart failure, recent MI (<7 days), BMI, baseline renal insufficiency, LVEF, left main distal bifurcation lesion, and core laboratory SYNTAX score. Multivariable analyses were also performed in the CABG cohort alone with the same variables, in addition to on-pump versus off-pump surgery. A 2-sided *p* value <0.05 was considered to be statistically significant for all tests. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

BASILINE AND PROCEDURAL CHARACTERISTICS. Among the 1,905 patients randomized in EXCEL, 70 had in-hospital AF before revascularization, and 23 did not undergo PCI or CABG. Thus 1,812 randomized patients with LMCAD without AF on presentation were included in the analysis, including 893 and 919 patients treated with CABG and PCI, respectively. NOAF developed at a mean of 2.7 ± 2.5 days after revascularization in 162 patients (8.9%), including 161 of 893 (18.0%) CABG-treated patients and 1 of 919 (0.1%) PCI-treated patients (*p* < 0.0001). All NOAF episodes consisted of AF; 1 patient had both AF and atrial flutter. Baseline characteristics of patients with and without NOAF are shown in [Table 1](#). Patients with NOAF were older and were more likely to have a

history of anemia and MI and lower LVEF. Pre-procedure laboratory values were similar between groups except for a slightly higher brain natriuretic peptide level in patients with versus without NOAF. Procedural characteristics were also similar in patients with versus without NOAF except for more frequent blood cardioplegia, retrograde cardioplegia, and grafting of the left circumflex artery during the index CABG (Table 2). Pre-operative amiodarone in the CABG group was administered to 3 of 160 (1.9%) patients and 12 of 727 (1.7%) patients, respectively, who had or did not have in-hospital post-CABG NOAF (p = 0.11).

By multivariable analysis, the independent predictors of NOAF in patients undergoing CABG were older age, greater BMI, and reduced LVEF (Table 3). The C-statistics for the relationships among age, BMI, LVEF, and the subsequent development of NOAF were 0.62, 0.53, and 0.55, respectively. In patients undergoing off-pump CABG, age (hazard ratio [HR]: 1.05; 95% confidence interval [CI]: 1.03 to 1.08; p < 0.0001), BMI (HR: 1.06; 95% CI: 1.01 to 1.09; p = 0.03), and LVEF (HR: 0.98; 95% CI: 0.96 to 0.99; p = 0.03) were confirmed as important predictors of NOAF. In patients undergoing on-pump surgery, age and retrograde cardioplegia independently predicted NOAF (Online Table 1).

By the time of hospital discharge, NOAF had resolved in 139 of 162 patients (85.8%), including 20 patients who underwent cardioversion. The duration of hospitalization was significantly longer in patients with versus without NOAF (14.3 ± 10.9 days vs. 8.3 ± 7.5 days; p < 0.0001). Discharge medications varied substantially according to the occurrence of NOAF (Table 4). Patients with NOAF were more frequently discharged with anticoagulant therapy with either warfarin or a novel oral anticoagulant agent, whereas dual antiplatelet therapy was more commonly prescribed to patients without NOAF. Aspirin was equally prescribed in both groups. Antiarrhythmic medications and diuretics were also more frequently used in patients with NOAF.

CLINICAL OUTCOMES. The development of in-hospital NOAF was associated with increased unadjusted 30-day rates of major and minor bleeding, but not with adverse cardiovascular events; after multivariable adjustment adjusted for differences in baseline characteristics, the 30-day risk for the composite outcome of death, MI, or stroke was higher in patients with NOAF compared with patients without NOAF (Online Table 2). At 3 years, in addition to major and minor bleeding, NOAF was associated with increased rates of all-cause death, cardiovascular death, stroke,

TABLE 2 Procedural Characteristics According to the Development of In-Hospital New-Onset Atrial Fibrillation

	NOAF (n = 162)	No NOAF (n = 1,650)	p Value
PCI group (including staged procedures)			
Hemodynamic support device used	0/2 (0.0)	54/999 (5.4)	1.00
PCI of the distal left main bifurcation	1/1 (100.0)	516/908 (56.8)	1.00
Procedure duration, min	103.0 ± 4.2	80.6 ± 42.4	0.24
CABG group			
Revascularization priority			
Emergent	15/161 (9.3)	86/732 (11.7)	0.38
Urgent	55/161 (34.2)	235/732 (32.1)	0.61
Elective	91/161 (56.5)	411/732 (56.1)	0.93
Off-pump coronary artery bypass grafting	43/161 (26.7)	217/732 (29.6)	0.46
Intermittent cross-clamp	36/118 (30.5)	153/515 (29.7)	0.86
Crystalloid cardioplegia	25/118 (21.2)	158/513 (30.8)	0.04
Blood cardioplegia	89/118 (75.4)	332/513 (64.7)	0.03
Direction of cardioplegia			
Antegrade	106/118 (89.8)	450/515 (87.4)	0.46
Retrograde	40/118 (33.9)	112/515 (21.7)	0.005
Other surgical procedures performed	106/118 (89.8)	450/515 (87.4)	0.46
Number of conduits per patient	2.6 ± 0.8	2.6 ± 0.8	0.71
Internal mammary artery used	157/161 (97.5)	721/728 (99.0)	0.12
Pan-arterial revascularization	41/161 (25.5)	180/732 (24.6)	0.82
Vessels bypassed per subject	2.3 ± 0.5	2.2 ± 0.6	1.00
Coronary artery bypassed			
Left anterior descending	158/160 (98.8)	720/728 (98.9)	0.70
Left circumflex	149/160 (93.1)	636/728 (87.4)	0.04
Right	54/160 (33.8)	279/728 (38.3)	0.28
CABG duration, min	252.6 ± 78.9	240.9 ± 67.7	0.11
Bypass duration, min	86.3 ± 45.4	82.7 ± 44.7	0.23
Cross-clamp duration, min	56.9 ± 28.5	54.7 ± 27.2	0.66

Values are mean ± SD or n/N (%).
 CABG = coronary artery bypass grafting; NOAF = new-onset atrial fibrillation or flutter; PCI = percutaneous coronary intervention.

TABLE 3 Independent Predictors of In-Hospital New-Onset Atrial Fibrillation in Patients Undergoing Coronary Artery Bypass Grafting

	Adjusted Hazard Ratio (95% Confidence Interval)	p Value
Age, per yr	1.05 (1.03-1.07)	<0.0001
Male	1.31 (0.82-2.11)	0.26
Body mass index, per kg/m ²	1.05 (1.01-1.09)	0.009
Diabetes mellitus, medically treated	0.71 (0.47-1.08)	0.11
Hypertension, medically treated	0.92 (0.61-1.39)	0.68
Congestive heart failure	0.58 (0.24-1.39)	0.20
SYNTAX score, per unit	1.01 (0.99-1.03)	0.30
Creatinine clearance <60 ml/min	1.09 (0.64-1.87)	0.74
Baseline hemoglobin, per g/dl	1.00 (0.88-1.14)	0.50
Recent myocardial infarction	1.12 (0.70-1.79)	0.63
Left ventricular ejection fraction, %	0.97 (0.96-0.99)	0.02
On-pump surgery	0.80 (0.54-1.20)	0.29
Total number of bypass conduits	0.89 (0.70-1.14)	0.36
Bypass of the left circumflex artery	1.67 (0.86-3.21)	0.13

Abbreviation as in Table 1.

TABLE 4 Medications at Discharge According to the Development of In-Hospital New-Onset Atrial Fibrillation

	NOAF (n = 162)	No NOAF (n = 1,650)	p Value
Aspirin	155/157 (98.7)	1,597/1,612 (99.1)	0.66
CABG group	154/156 (98.7)	711/717 (99.2)	0.59
PCI group	1/1 (100.0)	886/895 (99.0)	0.91
ADP antagonist	54/158 (34.2)	1,120/1,617 (69.3)	<0.0001
CABG group	53/157 (33.8)	241/719 (33.5)	0.95
PCI group	1/1 (100.0)	879/898 (97.9)	0.16
Both aspirin and ADP antagonist	53/158 (33.5)	1,107/1,617 (68.5)	<0.0001
CABG group	52/157 (33.1)	237/719 (33.0)	0.97
PCI group	1/1 (100.0)	870/898 (96.9)	0.16
Warfarin	16/158 (10.1)	19/1,617 (1.2)	<0.0001
Novel oral anticoagulant agent	0/158 (0.0)	2/1,617 (0.1)	1.00
Warfarin or novel oral anticoagulant agent	16/158 (10.1)	21/1,617 (1.3)	<0.0001
CABG group	16/157 (10.2)	15/719 (2.1)	<0.0001
PCI group	0/1 (0.0)	6/898 (0.7)	0.74
Low-molecular-weight heparin	3/158 (1.9)	10/1,617 (0.6)	0.10
CABG group	3/157 (1.9)	5/719 (0.7)	0.15
PCI group	0/1 (0.0)	5/898 (0.6)	0.94
Antiarrhythmic agent	72/158 (45.6)	34/1,617 (2.1)	<0.0001
CABG group	72/157 (45.9)	30/719 (4.2)	<0.0001
PCI group	0/1 (0.0)	4/898 (0.4)	0.95
Beta-blocker	144/158 (91.1)	1,412/1,617 (87.3)	0.16
CABG group	143/157 (91.1)	667/719 (92.8)	0.47
PCI group	1/1 (100.0)	745/898 (83.0)	0.65
Calcium channel blocker	16/158 (10.1)	99/1,617 (6.1)	0.051
CABG group	16/157 (10.2)	45/719 (6.3)	0.08
PCI group	0/1 (0.0)	54/898 (6.0)	0.80
ACE inhibitor or ARB	69/158 (43.7)	809/1,617 (50.0)	0.13
CABG group	69/157 (43.9)	300/719 (41.7)	0.61
PCI group	0/1 (0.0)	509/898 (56.7)	0.25
Statin	145/158 (91.8)	1,532/1,617 (94.7)	0.12
CABG group	144/157 (91.7)	666/719 (92.6)	0.70
PCI group	1/1 (100.0)	866/898 (96.4)	0.84
Diuretic	48/158 (30.4)	196/1,617 (12.1)	<0.0001
CABG group	48/157 (30.6)	165/719 (22.9)	0.04
PCI group	0/1 (0.0)	31/898 (3.5)	0.85

Values are n/N (%).
ACE = angiotensin-converting enzyme; ADP = adenosine diphosphate receptor; ARB = angiotensin receptor blocker; other abbreviations as in Table 2.

and the primary composite endpoint of death, MI, or stroke (Table 5). By multivariable analysis, NOAF was an independent predictor of all-cause death, cardiovascular death, stroke, and the primary composite outcome of all-cause death, MI, or stroke at 3 years in the overall population and in the CABG-treated group (Table 6).

The increased 3-year rate of cardiovascular death in patients with versus without NOAF was driven by deaths adjudicated as stroke related and heart failure related (2.6% vs. 0.6%; p = 0.005; and 1.9% vs. 0.4%; p = 0.009, respectively). Among the 10 patients with in-hospital NOAF who had a stroke during follow-up, 5 (50%) were not taking warfarin or a novel oral

anticoagulant agent at the time of the event. As shown in the Central Illustration, the rate of the 3-year composite primary endpoint of death, MI, or stroke was reduced in patients treated with PCI compared with patients treated with CABG who had NOAF development. In contrast, PCI and CABG had nonsignificantly different rates of the 3-year primary endpoint if NOAF did not occur.

DISCUSSION

The major findings from the present analysis from the EXCEL trial, in which the incidence, predictors, and prognostic impact of in-hospital NOAF in patients with LMCAD undergoing PCI or CABG were examined, are as follows: 1) NOAF was frequent after CABG but extremely rare after PCI; 2) older age, greater BMI, and reduced LVEF were independent predictors of NOAF after CABG; 3) NOAF was associated with prolonged hospitalization and increased 30-day rates of bleeding; and 4) NOAF was a strong independent predictor of the 3-year rates of all-cause and cardiovascular death, stroke, and the primary composite endpoint of death, MI, or stroke after CABG.

Among patients with LMCAD and sinus rhythm who were enrolled in the EXCEL trial, in-hospital NOAF was much more likely to develop after CABG than after PCI. The 18% rate of NOAF after CABG for LMCAD in the present study is consistent with prior reports in which post-CABG AF developed in 11% to 40% of patients (7-10). The range of post-operative NOAF between studies likely reflects differences in patient populations (e.g., operative urgency, critical state, and hemodynamic stability), the use of pre-operative prophylactic therapies (e.g., beta-blockers and amiodarone), and variability in the rigor and duration of detection. Patients enrolled in EXCEL were relatively stable and not high risk, with equipoise for revascularization by either PCI or surgery. Nonetheless, in-hospital NOAF occurred in only 1 patient after PCI, markedly less than after CABG, a finding reflecting in part the fact that relatively few patients in EXCEL presented with acute MI, a cohort more commonly affected by post-PCI AF (11-13).

NOAF was a powerful predictor of adverse outcomes during 3-year follow-up after CABG, in particular stroke, cardiovascular death, and all-cause death. Notably, NOAF was a stronger multivariable predictor of death after CABG than either diabetes or reduced LVEF. As shown in the Central Illustration, PCI had superior 3-year event-free survival compared with CABG if NOAF after surgery occurred. PCI may thus be preferred in selected patients who have a very high risk of NOAF after surgery. In this regard,

TABLE 5 Clinical Outcomes at 3 Years According to the Development of In-Hospital New-Onset Atrial Fibrillation

	All Patients			CABG-Treated Patients		
	NOAF (n = 162)	No NOAF (n = 1,650)	p Value	NOAF (n = 161)	No NOAF (n = 893)	p Value
Death, MI, or stroke	19.3 (36)	12.8 (208)	0.02	22.6 (36)	12.8 (93)	0.002
All-cause death	11.3 (18)	6.1 (99)	0.01	11.4 (18)	4.3 (31)	0.0005
Cardiovascular	8.9 (14)	3.4 (55)	0.0007	9.0 (14)	2.4 (17)	<0.0001
Noncardiovascular	2.6 (4)	2.8 (44)	0.94	2.6 (4)	2.0 (14)	0.61
MI	11.4 (18)	8.0 (130)	0.14	11.4 (18)	8.0 (58)	0.19
Stroke or TIA	7.9 (12)	2.8 (44)	0.0007	7.9 (12)	3.0 (21)	0.005
Stroke	6.5 (10)	2.3 (37)	0.002	6.6 (10)	2.4 (17)	0.009
Ischemic	5.3 (8)	1.8 (28)	0.004	5.4 (8)	2.1 (15)	0.03
Hemorrhagic	1.3 (2)	0.7 (11)	0.40	1.3 (2)	0.4 (3)	0.20
TIA	1.4 (2)	0.4 (7)	0.14	1.4 (2)	0.6 (4)	0.31
Bleeding						
TIMI major/minor	16.8 (27)	6.7 (109)	<0.0001	16.9 (27)	8.6 (63)	0.002
TIMI major	6.8 (11)	2.8 (46)	0.005	6.9 (11)	4.0 (29)	0.11
TIMI minor	10.6 (17)	3.9 (64)	<0.0001	10.7 (17)	4.7 (34)	0.004
BARC scale, any	18.6 (30)	12.9 (210)	0.03	18.8 (30)	15.4 (112)	0.29
Type 1	0.0 (0)	2.4 (39)	0.05	0.0 (0)	2.1 (15)	0.07
Type 2	6.9 (11)	5.5 (89)	0.44	6.9 (11)	5.0 (36)	0.32
Type 3	8.7 (14)	4.1 (67)	0.007	8.8 (14)	5.2 (38)	0.09
Type 4	7.5 (12)	2.9 (47)	0.002	4.4 (7)	3.3 (24)	0.49
Type 5	4.3 (7)	1.5 (25)	0.009	0.0 (0)	0.1 (1)	0.64

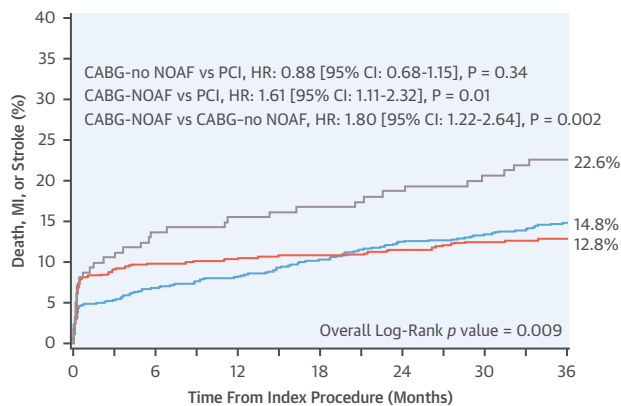
Values are Kaplan-Meier estimates, presented as % (n).

BARC = Bleeding Academic Research Consortium; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; TIA = transient ischemic attack, TIMI = Thrombolysis in Myocardial Infarction; other abbreviations as in [Tables 1 and 2](#).

TABLE 6 Independent Predictors of 3-Year Clinical Outcomes*

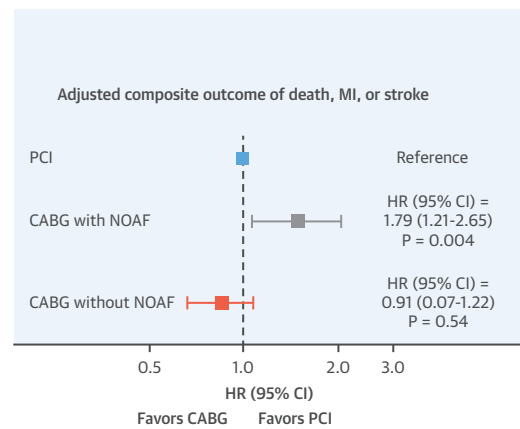
	All Patients (n = 1,812)		CABG Group (n = 893)	
	Hazard Ratio (95% Confidence Interval)	p Value	Hazard Ratio (95% Confidence Interval)	p Value
All-cause death				
NOAF	2.06 (1.21-3.50)	0.008	3.02 (1.60-5.7)	0.0006
Age	1.03 (1.01-1.06)	0.02	—	—
Left ventricular ejection fraction, %	0.97 (0.96-0.99)	0.008	0.97 (0.93-0.99)	0.03
Diabetes mellitus	1.77 (1.16-2.69)	0.008	—	—
Congestive heart failure	—	—	2.48 (1.00-6.12)	0.049
Cardiovascular death				
NOAF	3.25 (1.76-5.98)	0.0002	4.86 (2.27-10.44)	<0.0001
Diabetes mellitus	1.92 (1.12-3.31)	0.02	—	—
Left ventricular ejection fraction, %	0.97 (0.95-1.00)	0.048	—	—
Stroke				
NOAF	4.08 (1.89-8.78)	0.0003	4.19 (1.74-10.11)	0.001
Renal insufficiency	2.29 (1.02-5.13)	0.045	—	—
Diabetes mellitus	2.52 (1.29-4.93)	0.007	3.22 (1.32-7.87)	0.01
Male	0.47 (0.24-0.92)	0.03	—	—
Body mass index	0.91 (0.85-0.98)	0.01	—	—
Composite death, MI, or stroke				
NOAF	1.84 (1.26-2.68)	0.002	2.13 (1.39-3.25)	0.0004
Diabetes mellitus	1.55 (1.17-2.07)	0.003	1.63 (1.08-2.44)	0.02
Hypertension	—	—	1.68 (1.00-2.82)	0.048
Renal insufficiency	1.51 (1.04-2.19)	0.03	—	—

*The full list of covariates tested appears in the Methods section. Covariates not appearing in the table were not statistically significant in the final models. Abbreviations as in [Tables 1 and 2](#).

CENTRAL ILLUSTRATION Atrial Fibrillation After Left Main Revascularization

Number at risk	0	6	12	18	24	30	36
All PCI	919	855	837	811	789	773	696
CABG, no NOAF	732	652	641	632	627	609	553
CABG, NOAF	161	139	136	130	127	122	111

— All PCI — CABG, no NOAF — CABG, NOAF



Kosmidou, I. et al. *J Am Coll Cardiol.* 2018;71(7):739-48.

Time-to-event curves and adjusted hazard ratios (HR) for the 3-year primary composite endpoint of death, myocardial infarction (MI), or stroke in patients with left main coronary artery disease without pre-procedural atrial fibrillation who underwent revascularization by percutaneous coronary intervention (PCI) (n = 919) versus coronary artery bypass grafting (CABG) with the subsequent development of new-onset atrial fibrillation (NOAF) before hospital discharge (n = 161) versus coronary artery bypass grafting without new-onset atrial fibrillation before hospital discharge (n = 732). The 3-year adverse event rates were highest in coronary artery bypass grafting-treated patients with new-onset atrial fibrillation and similar in coronary artery bypass grafting-treated patients without new-onset atrial fibrillation and in percutaneous coronary intervention-treated patients. CI = confidence interval.

advanced age, increased BMI, and reduced LVEF were independent clinical predictors of NOAF after CABG for LMCAD, consistent with previous reports (7,14,15). However, although these associations were statistically significant, the C-statistics for the correlations between these risk factors and NOAF were modest, and many patients who may benefit from CABG have these characteristics (16). Thus, although the increased periprocedural risk of NOAF should be recognized in patients with advanced age, increased BMI, and/or reduced LVEF, rather than avoiding CABG in these patients, effective pre-operative and perioperative measures (prophylactic beta-blockers or amiodarone) (17,18) should be considered to prevent the post-surgical occurrence of NOAF. Consistent with previous reports (19,20), the strategy of surgical revascularization (on-pump vs. off-pump) in EXCEL was not a predictor of NOAF.

In patients undergoing on-pump CABG, the use of retrograde cardioplegia was a strong predictor of NOAF. Potential adverse effects of retrograde cardioplegia have been previously reported (21), and they may in part be related to the delay in cardiac arrest and subsequent myocardial protection with retrograde compared with antegrade cardioplegia.

However, total bypass duration and cross-clamp duration were not associated with an increased risk for AF, a finding suggesting that alternate mechanisms may underlie the increased rate of NOAF with retrograde cardioplegia.

The higher periprocedural rates of stroke with CABG compared with PCI that has been noted in most prior trials (22,23) may in part be explained by the greater rate of NOAF after surgical revascularization (24). Although a recent large registry-based analysis suggested that post-operative AF was a predictor only of early stroke (25), in the present study the increased rate of stroke with in-hospital NOAF emerged not within 30 days, but during long-term follow-up. A low proportion (10.2%) of patients with NOAF after CABG in EXCEL was discharged with long-term oral anti-coagulant therapy (reflecting the high in-hospital rate of conversion to sinus rhythm), and although the 3-year post-CABG rate of stroke was relatively low compared with prior studies, 50% of the post-CABG NOAF patients who developed a stroke during follow-up were not being treated with anticoagulant therapy at the time. Future studies are warranted to determine the extent to which recurrent AF during long-term follow-up contributed to the late stroke

risk (26,27). Alternatively, in-hospital NOAF that resolves may be a marker of high-risk patients' characteristics, systemic inflammation, and diffuse vascular atherosclerosis (28), thus predisposing patients with NOAF to thrombotic or atheroembolic events (29), with or without recurrent AF. Continuous monitoring may elucidate whether recurrent AF episodes precede cerebrovascular events in this patient population.

In addition to affecting long-term prognosis, NOAF was strongly associated with prolonged hospitalization, likely attributable to its management (rate control and attempted pharmacological or electrical cardioversion, diuresis, and initiation of anticoagulation in some patients), and with bleeding complications (in part from anticoagulation) that may have contributed to the poor prognosis of patients with NOAF (30,31). The ongoing formal EXCEL cost substudy will assess the extent to which NOAF increased costs in CABG-treated patients.

STUDY STRENGTHS AND LIMITATIONS. As a large randomized trial of patients with LMCAD who were undergoing revascularization, EXCEL provides clinically relevant insights regarding the relative frequency of NOAF after PCI and CABG and of its association with long-term cardiovascular outcomes. However, several limitations should be considered. First, the present analysis was post hoc, and it should thus be considered hypothesis generating. Second, the absolute number of events (NOAF, stroke, and death) was modest, and not all confounders in their described relationships may have been identified. Third, although we excluded patients with in-hospital AF before revascularization from the present analysis, a history of prior AF was not captured in the case report form and systematic screening for pre-operative AF was not done; as such, pre-procedure episodes of AF may have been missed. Fourth, pre-CABG use of amiodarone was uncommon, and data on the rate of perioperative beta-blocker use were not collected. We thus cannot speak to the efficacy of these measures in preventing NOAF or

influencing prognosis. Finally, data on arrhythmias during follow-up (including AF recurrence) were not systematically collected in the present study.

CONCLUSIONS

In the randomized EXCEL trial comparing PCI and CABG for the treatment of LMCAD in patients with low and intermediate SYNTAX scores, NOAF occurred almost exclusively following CABG and was a powerful predictor of all-cause death, cardiovascular death, stroke, and the composite endpoint of death, MI, or stroke at 3 years. Further studies are needed to identify patients at high risk for NOAF after CABG to guide prophylactic measures, to examine the potential role of implantable monitors to detect AF recurrence in patients with NOAF who convert to sinus rhythm before hospital discharge, and to determine whether the routine use of long-term oral anticoagulation in patients with in-hospital NOAF improves long-term prognosis after CABG for LMCAD.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL

SKILLS: AF occurs much more commonly after CABG surgery than after PCI. Patients developing AF after CABG for LMCAD face elevated risks of stroke, cardiovascular mortality, and all-cause mortality during the subsequent 3 years than do patients without AF.

TRANSLATIONAL OUTLOOK: Additional studies are needed to determine whether long-term monitoring for detection of AF after CABG and oral anticoagulant therapy could improve the prognosis of patients undergoing CABG for LMCAD.

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KEY WORDS atrial fibrillation, coronary artery bypass grafting, left main disease, mortality, percutaneous coronary intervention, prognosis, stroke

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



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