
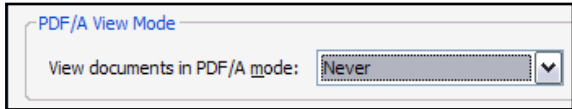
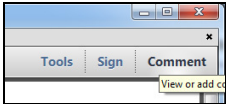
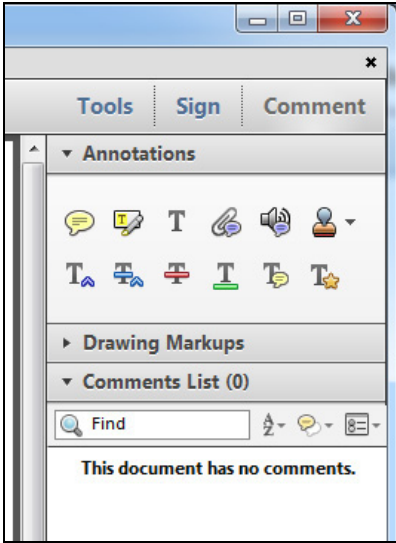
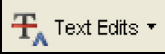


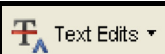

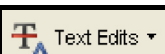





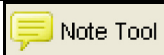




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# Contemporary Outcomes Following Coronary Artery Bypass Graft Surgery for Left Main Disease

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## ABSTRACT

**BACKGROUND** Although results of percutaneous coronary intervention (PCI) have been steadily improving, whether surgical outcomes have improved over time is not fully elucidated.

**OBJECTIVES** The authors sought to compare the current outcomes of patients undergoing coronary artery bypass grafting (CABG) with prior surgical results, in the context of randomized trials including the left main coronary artery (LM) stem.

**METHODS** The authors performed a propensity-matched analysis of patients randomized to CABG in the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) (enrollment period 2005 to 2007) and EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) (enrollment period 2010 to 2014) trials. All patients had LM disease with or without multivessel disease. Adjustment was based on 15 clinical and angiographic variables, including anatomic SYNTAX score, with a 2:1 ratio for the EXCEL and SYNTAX trials, collectively analyzing 909 subjects (n = 580 and n = 329, respectively). The primary endpoint was the composite of all-cause death, myocardial infarction (MI), stroke, or ischemia-driven revascularization at 3 years.

**RESULTS** Baseline characteristics, anatomic SYNTAX score, number and types of grafts, and duration of hospitalization for the procedures were similar in both groups. CABG procedures in the EXCEL compared with the SYNTAX trial were more often off-pump (29.6% vs. 15.4%; p < 0.001), and guideline-directed medical therapies were used more frequently in the EXCEL surgical cohort. The primary endpoint occurred in 14.0% and 20.9% (p = 0.008) of patients in the EXCEL and SYNTAX trials, respectively. With the exception of MI (4.1% vs. 3.7%), all nonhierarchical events tended to contribute to the improved outcomes in the more recent trial: all-cause death (5.5% vs. 8.5%), stroke (3.1% vs. 5.1%), and ischemia-driven revascularization (7.1% vs. 9.4%) in the EXCEL and SYNTAX trials, respectively.

**CONCLUSIONS** Over a 5- to 7-year period, significant improvement in event-free survival after surgical revascularization for LM disease at 3 years was noted between the SYNTAX and EXCEL trials, consistent with improving results with cardiac surgery over time. (Synergy Between PCI With Taxus and Cardiac Surgery [SYNTAX]; [NCT00114972](#); Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization [EXCEL]; [NCT01205776](#)) (J Am Coll Cardiol 2019;■:■-■) © 2019 by the American College of Cardiology Foundation.

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## ABBREVIATIONS AND ACRONYMS

**CABG** = coronary artery bypass graft

**CAD** = coronary artery disease

**GDMT** = guideline-directed medical therapy

**IDR** = ischemia-driven revascularization

**LM** = left main coronary artery

**LMCAD** = left main stem coronary artery disease

**MACCE** = major adverse cardiovascular or cerebrovascular events

**MI** = myocardial infarction

**PCI** = percutaneous coronary intervention

**SS** = SYNTAX score

Coronary artery bypass graft (CABG) surgery was introduced >50 years ago. In 1970, Favaloro et al. (1) reported the largest series of venous grafting, demonstrating its efficacy with low morbidity and mortality. Since then, CABG has been established as an effective treatment for coronary artery disease (CAD) not responding to pharmacological treatment, and is currently the preferred modality to treat complex CAD, with lower rates of death, myocardial infarction (MI), and repeat revascularization compared with percutaneous coronary intervention (PCI) (2-4).

In this half century of evolution, new procedural techniques have been implemented to improve CABG outcomes. Debates over the best techniques, including on-pump versus off-pump surgery, single versus

bilateral mammary artery grafts, radial artery versus right internal mammary versus carefully harvested saphenous vein grafts, continue (5-8). However, despite the evolution of CABG over the last decade, little is known about whether clinical outcomes after surgical revascularization have improved over time. By contrast, advancements in PCI devices and techniques have clearly been shown to result in enhanced event-free survival (9-12).

We therefore sought to determine whether clinical outcomes in patients undergoing CABG for the treatment of left main coronary artery (LM) stem CAD (LMCAD) have improved in the last decade by analyzing data from 2 major randomized clinical trials: The SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial and the EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial.

## METHODS

### STUDY POPULATION AND PROPENSITY MATCHING.

The present study is a post hoc, propensity-matched

analysis of patients randomized to CABG treatment of LMCAD in the SYNTAX and EXCEL trials. The EXCEL study methodology and main results have been previously published (13). Briefly, the EXCEL trial was an international, open-label, multicenter randomized trial that compared PCI with everolimus-eluting stents with CABG in patients with LMCAD. Recruitment occurred between 2010 to 2014, and the trial included 957 patients assigned to CABG. Patients were enrolled with a site-reported SYNTAX score (SS)  $\leq 32$  (low to intermediate anatomic complexity). Complete anatomic revascularization of all vessels 1.5 mm or larger in diameter in which the angiographic diameter stenosis was  $\geq 50\%$  was the treatment strategy; the use of arterial grafts was strongly recommended.

These outcomes were propensity matched to patients with LMCAD that were randomized to CABG in the SYNTAX trial. Details of the SYNTAX trial have been published elsewhere (2). In brief, the SYNTAX trial was a randomized, prospective trial comparing outcomes of patients with 3-vessel disease or LMCAD undergoing PCI with paclitaxel-eluting stents versus CABG. The trial randomized 1,800 total patients between 2005 and 2007 in Europe and United States. Of those, 897 patients were assigned for CABG, including 348 with LMCAD.

**ENDPOINTS AND DEFINITIONS.** The primary endpoint of interest was the composite of all-cause death, stroke, MI, or ischemia-driven revascularization (IDR) at 3 years, that is, major adverse cardiovascular or cerebrovascular events (MACCE). Secondary endpoints included the composite of all-cause death, stroke, or MI at 30 days and at 3 years. Each individual, nonhierarchical component of the primary outcome was also evaluated as secondary outcomes at 30 days and at 3 years. Definitions of the endpoints are described elsewhere (2,13). The definitions of death, stroke, IDR, and spontaneous MI were otherwise similar between the SYNTAX and EXCEL trials. However, the MI definitions were discordant

Dr. Puskas has been a consultant to Medtronic. Dr. Banning has received institutional sponsorship for a fellowship from Boston Scientific; and lecture fees from Boston Medtronic and Abbott Vascular. Dr. Kappetein is an employee of Medtronic. Dr. Sabik has been a consultant to Medtronic, Edwards Lifesciences, and Sorin; and has served on an advisory board for Medtronic Cardiac Surgery. Dr. Onuma is an employee of Cardialysis. Dr. Stone has been a consultant to Claret, Backbeat, Sirtex, Matrizyme, Miracor, Neovasc, V-wave, Shockwave, Valfix, TherOx, Reva, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, and Ancora; has received speaker honoraria from Amaranth and Terumo; holds equity in Ancora, Cagent, Qool Therapeutics, Aria, Caliber, Applied Therapeutics, SpectraWave, the MedFocus family of funds, and the BioStar family of funds; is director of SpectraWave; and his employer, Columbia University, receives royalties from sale of the MitraClip manufactured by Abbott Vascular. Prof. Serruys has been a consultant to Abbott, Biosensors, Medtronic, Micell Technologies, QualiMed, SINOMED, St. Jude Medical, Stentys, Svelte, Philips/Volcano, and Xeltis. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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between the 2 trials due to the requirement in the SYNTAX trial of the development of new Q waves to define a periprocedural MI, which was not applicable to the EXCEL trial. Thus, to properly match MI definitions, this definition was also applied for the EXCEL trial. All primary and secondary endpoints were adjudicated by an independent clinical events committee.

The anatomic SS was evaluated by specialized core laboratories (Cardialysis, Rotterdam, the Netherlands, for the SYNTAX trial, and the Cardiovascular Research Foundation, New York, New York, for the EXCEL trial). The SSII was calculated by the core laboratories using the patients' clinical characteristics added to the anatomic SS (14).

Trials protocols were approved by the ethics committee at each participating center, and all patients signed informed consent. Five-year follow-up has finished for the SYNTAX trial (15) and is ongoing for the EXCEL trial (for 5 years), with all patients having completed 3-year follow-up at the time of this report.

**STATISTICAL ANALYSIS.** All analyses were performed in the intention-to-treat population, which included all patients according to the arm to which they were randomly assigned, regardless of the received treatment. A propensity score model was developed to control for selection bias in the comparison between CABG patients in the SYNTAX and EXCEL trials. The propensity score for an individual is defined as the probability of being included in the SYNTAX (vs. EXCEL) trial conditional on the individual's baseline characteristics. The propensity score was estimated using a logistic regression model in which the study variable (SYNTAX vs. EXCEL trial) is the outcome and the baseline characteristics are the covariates. The following variables known to affect outcomes were included in the propensity score model as covariates: age, sex, body mass index, smoking status, presence of diabetes, heart failure, hyperlipidemia, hypertension, previous myocardial infarction, prior cerebrovascular accident, chronic obstructive pulmonary disease, peripheral vascular disease, pulmonary hypertension, creatinine >1.7 mg/dl, and SS as determined by the core laboratory. A greedy matching algorithm was used to match (1:2) SYNTAX patients with available control patients in the EXCEL trial, due to the higher sample size of LMCAD in the EXCEL trial with its exclusive inclusion of LMCAD. A caliper of 0.15 times the standard deviation of the propensity score was enforced to ensure closer matches (16).

**TABLE 1** Baseline Characteristics of the Propensity-Matched Groups Treated With CABG

	SYNTAX (n = 329)	EXCEL (n = 580)	p Value
Age, yrs	65.3 ± 10.1	65.5 ± 9.5	0.67
Male	76.0 (250/329)	75.3 (437/580)	0.83
Body mass index, kg/m <sup>2</sup>	27.8 ± 5.1	28.1 ± 4.7	0.35
Systolic blood pressure, mm hg	135.8 ± 21.4	131.9 ± 17.6	0.003
Diastolic blood pressure, mm hg	74.4 ± 12.4	73.2 ± 11.4	0.11
Smoking history			0.70
Current or former smoker	69.9 (230/329)	67.2 (390/580)	0.41
Current smoker	24.6 (81/329)	23.3 (135/580)	0.65
Former smoker	45.3 (149/329)	44.0 (255/580)	0.70
Diabetes mellitus	26.1 (86/329)	27.1 (157/580)	0.76
Exercise/diet alone	3.3 (11/329)	1.7 (10/580)	0.12
Medically treated	22.8 (75/329)	25.3 (147/580)	0.39
Insulin	10.3 (34/329)	7.1 (41/580)	0.09
Oral agents	16.4 (54/329)	21.2 (123/580)	0.08
Insulin and oral agents	4.0 (13/329)	2.9 (17/580)	0.41
Insulin alone	6.4 (21/329)	4.1 (24/580)	0.13
Oral agents alone	12.5 (41/329)	18.3 (106/580)	0.02
Congestive heart failure	4.9 (16/329)	5.3 (31/580)	0.75
Hyperlipidemia	75.1 (247/329)	77.4 (449/580)	0.42
Hypertension	75.7 (249/329)	75.3 (437/580)	0.91
Family history of CAD	29.5 (97/329)	62.9 (316/502)	<0.0001
Previous MI	23.4 (77/329)	21.7 (126/580)	0.56
Previous TIA or CVA	6.7 (22/329)	6.4 (37/580)	0.86
Previous TIA	3.3 (11/329)	3.5 (20/576)	0.92
Previous CVA	4.0 (13/329)	3.3 (19/580)	0.60
COPD	9.1 (30/329)	9.7 (56/580)	0.79
PVD	11.6 (38/329)	9.8 (57/580)	0.41
Carotid artery disease	8.8 (29/329)	7.9 (46/579)	0.65
Pulmonary hypertension	1.2 (4/329)	0.9 (5/580)	0.60
Creatinine >1.7 mg/dl	2.4 (8/329)	2.4 (14/580)	0.99
Dialysis	0.6 (2/329)	0.3 (2/580)	0.56
Previous cardiac surgery	0.3 (1/329)	0.0 (0/580)	0.18
Critical pre-procedural state	1.8 (6/329)	1.6 (9/580)	0.76
LVEF, %	58.8 ± 12.7	57.6 ± 8.9	0.14

Values are mean ± SD or % (n/N).

CABG = coronary artery bypass graft; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; EXCEL = Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PVD = peripheral vascular disease; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery; TIA = transient ischemic attack.

Continuous data are presented as mean ± SD of the mean or as median and interquartile range according to data distribution. Comparisons were performed using Student's *t*-test or Mann-Whitney *U* test as appropriate. Categorical data are presented as absolute number and percentages, and were compared with the chi-square test or Fisher's exact test. Event rates were based on Kaplan-Meier estimates in time-to-first-event analyses and compared with the log-rank test. A 2-sided *p* value of 0.05 was considered indicative of statistical significance. All statistical



**TABLE 2 Pre-Procedural, Anatomic, and Angiographic Characteristic of the Propensity-Matched Groups Treated With CABG**

	SYNTAX (n = 329)	EXCEL (n = 580)	p Value
Days from randomization to index procedure	15.1 ± 28.4	6.2 ± 8.9	<0.0001
Days of in-patient hospitalization	13.5 ± 9.6	12.3 ± 8.4	0.059
Critical pre-procedural state	1.8 (6/329)	1.6 (9/580)	0.76
Revascularization priority			<0.0001
Emergent	4.1 (13/320)	11.0 (62/565)	0.0004
Urgent	6.6 (21/320)	35.8 (202/565)	<0.0001
Elective	89.4 (286/320)	53.3 (301/565)	<0.0001
Diseased vessels			
Presence of LMCAD	100.0 (329/329)	100.0 (580/580)	-
Left main only	14.3 (47/329)	13.4 (78/580)	0.72
Left main + 1 vessel disease	20.1 (66/329)	31.3 (180/576)	0.0003
Left main + 2 vessel disease	31.3 (103/329)	37.8 (218/576)	0.05
Left main + 3 vessel disease	34.3 (113/329)	17.4 (100/576)	<0.0001
SYNTAX score, core lab	29.3 ± 11.9	28.3 ± 10.1	0.16
SYNTAX score tertiles, core lab			0.0003
Low, ≤22	31.0 (102/329)	28.8 (167/580)	0.48
Intermediate, 23–32	27.7 (91/329)	40.2 (233/580)	0.0002
High, ≥33	41.3 (136/329)	31.0 (180/580)	0.002
SYNTAX score II, CABG	31.5 ± 11.5	31.2 ± 10.2	0.62

Values are mean ± SD or % (n/N).  
Abbreviations as in Table 1.

analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, North Carolina).

## RESULTS

**POPULATION.** The propensity-matched study population comprised 909 patients from the SYNTAX (n = 329) and the EXCEL trials (n = 580). Except for an increased frequency of family history of CAD in the EXCEL group and a higher systolic blood pressure in the SYNTAX group, baseline characteristics and comorbidities were comparable between the 2 groups (Table 1). Patients in both groups also had similar SS and SSII (Table 2). As per inclusion in the analyses all patients had LMCAD, but SYNTAX subjects were more likely to have concomitant 3-vessel-disease with LMCAD (34.3% vs. 17.4%), whereas the EXCEL patients presented more 1-vessel disease with LMCAD (31.3% vs. 20.1%) when compared with their counterparts. The time from randomization to surgery was greater in the SYNTAX trial than the EXCEL trial (15 vs. 6 days). CABG procedures were more often elective in the SYNTAX trial compared with the EXCEL trial, whereas urgent and emergent CABG procedures were more commonly performed in EXCEL patients.

**CABG PROCEDURE.** The duration of bypass, cross clamping, and of the entire surgical procedure were similar between groups. Nor did the total number of

arterial and venous conduits differ. The CABG procedures in the EXCEL trial compared with the SYNTAX trial were more often off-pump (29.6% vs. 15.4%), with more blood cardioplegia (64.7% vs. 52%). Use of an in situ left internal mammary artery (98.7% vs. 94.4%; p = 0.002) and radial artery as a graft (10.3% vs. 5.7%; p = 0.01) were more common in the SYNTAX compared with the EXCEL trial, although there were no statistically significant differences between the groups in the total number of arterial or venous grafts, or the use of bilateral IMAs.

**MEDICATION USE.** Thirty-day and 3-year follow-up medication use is reported in Table 4. Guideline-directed medical therapy (GDMT) use was much more frequent in CABG patients at both time periods in the EXCEL surgical cohort compared with the SYNTAX surgical cohort, including more frequent use of antiplatelet agents, lipid-lowering drugs, beta-blockers, and agents affecting the renin-angiotensin axis.

**CLINICAL OUTCOMES.** The composite endpoint of MACCE at 3 years was higher in the SYNTAX group than the matched population from the EXCEL trial (20.9% vs. 14.0%; p = 0.008) (Central Illustration). The composite 3-year endpoint of death, stroke, or MI was also higher in the SYNTAX trial (14.0% vs. 9.6%; p = 0.05) (Table 5). At 30 days, there was no significant difference in MACCE between the groups (Table 5). With the exception of MI, all nonhierarchical components of the primary endpoint contributed to the better outcomes in the EXCEL trial compared with the SYNTAX trial: all-cause death (5.5% vs. 8.5%), any stroke (3.1% vs. 5.1%), and IDR (7.1% vs. 9.4%), respectively (Figure 1).

## DISCUSSION

The present study evaluated whether clinical outcomes of patients undergoing CABG for LMCAD have improved over the last decade. The major finding of the study is that 3-year rates of MACCE after surgical revascularization for LMCAD improved between the performance of the SYNTAX and EXCEL trials. Some differences in technique were also noted between the studies, most notably an increase in off-pump CABG and more extensive use of blood cardioplegia, although for the most part, measurable differences in surgical technique were not observed, including the use of single or multiple arterial grafts and procedural durations. Notably, the use of antiplatelet agents and other GDMT were substantially greater throughout the follow-up period in the EXCEL surgical group compared with the SYNTAX trial surgical group.

Major evolution of coronary revascularization technique with PCI has been easy to document, with shifts from balloon angioplasty to predominant use of bare-metal stents to first- and then second-generation drug-eluting stents. In addition, imaging and physiological guidance techniques have become increasingly used, and adjunct pharmacotherapy has improved (9,17,18). Along with these advances, PCI outcomes have steadily improved over the last 3 decades (11,12). However, whether clinical outcomes of patients undergoing CABG have improved over time has been more difficult to demonstrate (8), as exemplified by the 10-year follow-up of the ART (Arterial Revascularization Trial) demonstrating no significant long-term difference with use of a single vs. bilateral IMA grafts (19). The present study demonstrates that surgical outcomes have been improving over time, at least for LMCAD revascularization. The improvement in the 3-year rates of MACCE after CABG in the EXCEL trial compared with the SYNTAX trial underlie why the relative outcomes of CABG versus PCI for treatment of LMCAD have remained consistent over time despite use of clearly superior PCI devices and technique in the EXCEL trial compared with the SYNTAX trial (e.g., everolimus-eluting compared with paclitaxel-eluting stents, more frequent use of intra-vascular ultrasound guidance).

When comparing the 2 trials, the observed change in surgical approach is the increase in the use of off-pump surgery. Potential advantages of off-pump surgery include reduction of the risk of death, stroke, and MI in higher-risk patients (20). The outcomes of off-pump surgery are highly dependent on the expertise of the operator; incomplete revascularization and reduced graft patency may be more frequent when off-pump surgery is performed by less experienced surgeons (21-23). Many surgeons avoided off-pump surgery in the past in patients with LMCAD due to the hemodynamic disturbances that could occur with the displacement of the heart during the grafting process (24). Nonetheless, progression in equipment and techniques such as stabilizers and shunts have improved the reliability and outcomes of off-pump surgery (25,26). A recent large observational study demonstrated a reduction of mortality with off-pump compared with on-pump surgery, regardless of the number of grafts (20)—if performed by experienced surgeons. These findings could be perceived as if the higher use of off-pump CABG in the EXCEL trial compared with the SYNTAX trial played a role in the improvement in clinical outcomes after LMCAD CABG, in particular as regards the reduction of stroke, but also possibly mortality. However, debate over the benefits of the off-pump surgery persists, especially

**TABLE 3** Procedural Characteristics of the Propensity-Matched Groups Treated With CABG

	SYNTAX (N = 329)	EXCEL (N = 580)	p Value
Procedure duration, min*	202.0 ± 67.6	195.8 ± 64.5	0.18
Bypass duration, min	81.9 ± 37.4	85.8 ± 48.8	0.28
Cross clamp duration, min	51.2 ± 26.4	54.9 ± 26.5	0.09
Procedure-related factors			
Off-pump	15.4 (49/319)	29.6 (167/565)	<0.0001
Crystalloid cardioplegia	31.7 (101/319)	32.7 (130/397)	0.76
Blood cardioplegia	52.0 (166/319)	64.7 (257/397)	0.0006
Temperature of solution			0.02
Warm, >35°C	15.7 (42/268)	23.1 (89/385)	0.02
Cold, <35°C	84.3 (226/268)	76.9 (296/385)	0.02
Direction of cardioplegia perfusion			
Antegrade	81.9 (262/320)	87.4 (348/398)	0.04
Retrograde	14.4 (46/320)	22.9 (91/398)	0.004
Need for inotropic agents >48 h	10.3 (33/319)	11.7 (66/565)	0.55
Hemodynamic support device	3.4 (11/319)	2.8 (16/565)	0.61
Ventricular assist device	0.0 (0/319)	0.2 (1/565)	0.45
Intra-aortic balloon pump	3.4 (11/319)	2.7 (15/565)	0.50
Total arterial conduits	1.3 ± 0.6	1.4 ± 0.6	0.08
Total venous conduits	1.3 ± 0.9	1.3 ± 1.0	1.00
Any IMA used	96.9 (310/320)	98.6 (557/565)	0.08
LIMA	96.6 (309/320)	97.3 (550/565)	0.51
In-situ	98.7 (305/309)	94.4 (519/550)	0.002
Free	1.6 (5/309)	6.0 (33/550)	0.003
RIMA	23.8 (76/320)	25.3 (143/565)	0.61
In-situ	76.3 (58/76)	66.4 (95/143)	0.13
Free	23.7 (18/76)	33.6 (48/143)	0.13
Both IMAs used	23.4 (75/320)	25.3 (143/565)	0.53
Any radial artery used	10.3 (33/320)	5.7 (32/565)	0.01

Values are mean ± SD or % (n/N). \*From skin incision to closure.

IMA = internal mammary artery; LIMA = left internal mammary artery; RIMA = right internal mammary artery; other abbreviations as in Table 1.

given the long-term results from the CORONARY (Coronary Artery Bypass Surgery [CABG] Off or On Pump Revascularization Study) (similar 5-year rates of death, stroke, MI, renal failure, or repeat revascularization) (6), and the findings from a recent meta-analysis comprising 8,145 patients in which mortality at 4 years or longer was slightly higher (13.9% vs. 12.3%) with off-pump compared with on-pump surgery (27).

A major difference between the EXCEL and SYNTAX trials that may have contributed the most to the long-term improvement in surgical outcomes over time was the greater use of GDMT in the EXCEL trial, especially antiplatelet agents, statins, beta-blockers, and agents inhibiting the renin-angiotensin axis. The most recent guidelines of the American College of Cardiology/American Heart Association clearly state the benefits of the use of aspirin after CABG, or if the patient is intolerant, the use of an alternative antiplatelet (clopidogrel) (28). Both agents were used at

**TABLE 4** Discharge and 3-Year Follow-Up Medication Use of the Propensity-Matched Groups Treated With CABG

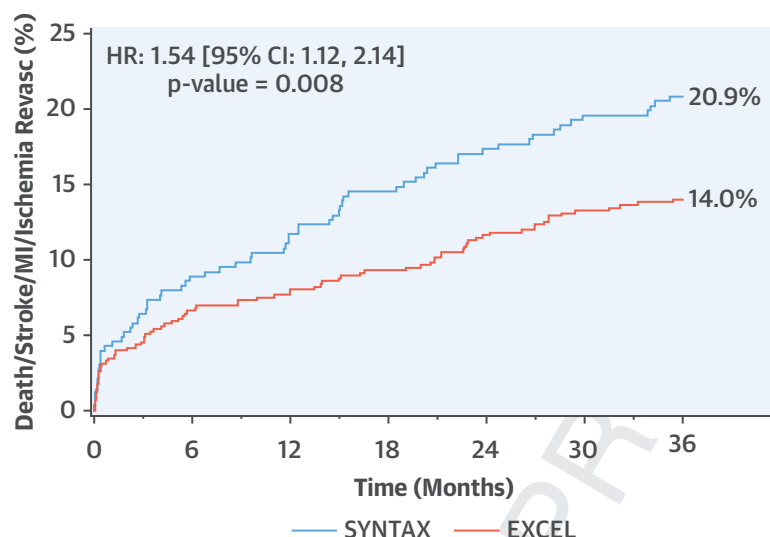
	SYNTAX (n = 329)	EXCEL (n = 580)		SYNTAX (n = 329)	EXCEL (n = 580)	
	Discharge		p Value	3 Years		p Value
Any lipid-lowering medication	77.2 (251/325)	91.9 (530/577)	<0.0001	82.6 (242/293)	96.1 (495/515)	<0.0001
Statin	75.1 (244/325)	92.3 (528/572)	<0.0001	81.2 (238/293)	96.1 (494/514)	<0.0001
Non-statin lipid-lowering agent	6.5 (21/325)	25.7 (147/572)	<0.0001	6.5 (19/293)	28.2 (144/510)	<0.0001
Aspirin or ADP antagonist	94.8 (308/325)	98.3 (567/577)	0.003	83.3 (244/293)	97.5 (502/515)	<0.0001
Aspirin	91.7 (298/325)	98.8 (563/570)	<0.0001	79.9 (234/293)	96.3 (493/512)	<0.0001
ADP antagonist	19.1 (62/325)	34.1 (197/577)	<0.0001	10.6 (31/293)	21.4 (110/515)	0.0001
Both, dual antiplatelet therapy	16.0 (52/325)	33.6 (194/577)	<0.0001	7.2 (21/293)	19.8 (102/515)	<0.0001
Anticoagulant, warfarin or DOAC	5.5 (18/325)	4.4 (25/572)	0.43	5.5 (16/293)	9.1 (46/508)	0.07
Beta-blocker	78.8 (256/325)	92.0 (526/572)	<0.0001	69.6 (204/293)	93.2 (480/515)	<0.0001
Calcium channel blocker	15.1 (49/325)	6.6 (38/572)	<0.0001	19.1 (56/293)	17.5 (89/508)	0.57
ACE inhibitor or ARB	49.8 (162/325)	40.4 (231/572)	0.006	66.9 (196/293)	53.6 (274/511)	0.0002
ACE inhibitor	43.1 (140/325)	39.0 (223/572)	0.23	49.1 (144/293)	47.8 (244/510)	0.72
ARB	7.1 (23/325)	2.1 (12/572)	0.0002	18.4 (54/293)	9.1 (46/507)	0.0001
Aldosterone antagonist	1.5 (5/325)	0.9 (5/572)	0.36	1.0 (3/293)	1.2 (6/506)	0.83
Nitrate	11.4 (37/325)	4.5 (26/572)	0.0001	10.2 (30/293)	8.3 (42/506)	0.36
Antianginal, other	1.5 (5/325)	0.9 (5/572)	0.36	3.8 (11/293)	3.4 (17/506)	0.77
Any antidiabetic medication	22.2 (72/325)	8.4 (48/572)	<0.0001	18.1 (53/293)	12.8 (65/506)	0.04
Any oral antidiabetic medication	14.2 (46/325)	4.9 (28/572)	<0.0001	14.3 (42/293)	9.9 (50/506)	0.057
Insulin	12.0 (39/325)	4.5 (26/572)	<0.0001	7.2 (21/293)	5.3 (27/506)	0.29
Diuretics	41.2 (134/325)	22.4 (128/572)	<0.0001	31.4 (92/293)	35.9 (182/507)	0.20
Antiarrhythmic agents	14.2 (46/325)	11.4 (65/572)	0.22	4.4 (13/293)	16.2 (82/507)	<0.0001
H2-receptor blockers	19.4 (63/325)	7.2 (41/572)	<0.0001	10.2 (30/293)	8.7 (44/508)	0.46

Values are % (n/N).  
ACE = angiotensin-converting enzyme; ADP = adenosine-diphosphate; ARB = angiotensin receptor blockers; DOAC = direct oral anticoagulant; other abbreviations as in Table 1.

30 days and 3 years more frequently alone and together in the EXCEL group than the SYNTAX group. Of note, a recent study reported higher graft patency with the use of DAPT compared with monotherapy (29). The survival benefit of and reduction in MI in patients with CAD treated with statins is well documented (30,31). In addition, although systolic blood pressure was found to be lower at recruitment in the EXCEL than in the SYNTAX trial, the use of beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers were greater in the EXCEL trial. A 20 mm Hg decrease in systolic blood pressure has been associated with up to 50% reduction in the risk of death due to ischemic heart disease and up to 62% reduction in death due to any stroke (32). These agents have also been associated with improved survival in patients with left ventricular dysfunction and chronic kidney disease (33–35). The possible key to the improvement in outcomes from the SYNTAX trial to the EXCEL trial may lie on the greater use of GDMT. This comes as an important message to cardiologists treating post-CABG patients, to never underestimate the power of optimized GDMT (36).

Another aspect of the present report supporting the improvement of CABG is that even with a significantly larger amount of patients undergoing either emergent or urgent procedures (thus with possibly worse prognosis) in the EXCEL trial compared with the SYNTAX trial, the primary outcome was still lower in the EXCEL trial.

**STUDY LIMITATIONS.** The present report is based on a post hoc analysis of propensity-matched populations from 2 major randomized trials, and thus has inherent limitations. The differences in technique and GDMT were not randomized, and propensity matching may not have accounted for unmeasured confounders. In addition, the multifactorial nature of all the changes that may have occurred, such as surgical technique, post-procedural and nursing care, and use of cardiac rehabilitation, cannot be accounted for. With the time difference between the trials and obvious difference in variables such as medication use (36), sites and operators, and differences in population characteristics, conclusion as to which particular variable might be responsible for the improvement observed cannot be made. The results of the present analysis should thus be considered

**CENTRAL ILLUSTRATION** Improvement in Outcomes After CABG for LM Disease**Number at risk:**

SYNTAX	329	294	282	272	261	252	248
EXCEL	580	530	519	506	492	476	461

Modolo, R. et al. J Am Coll Cardiol. 2019;■(■):■-■.

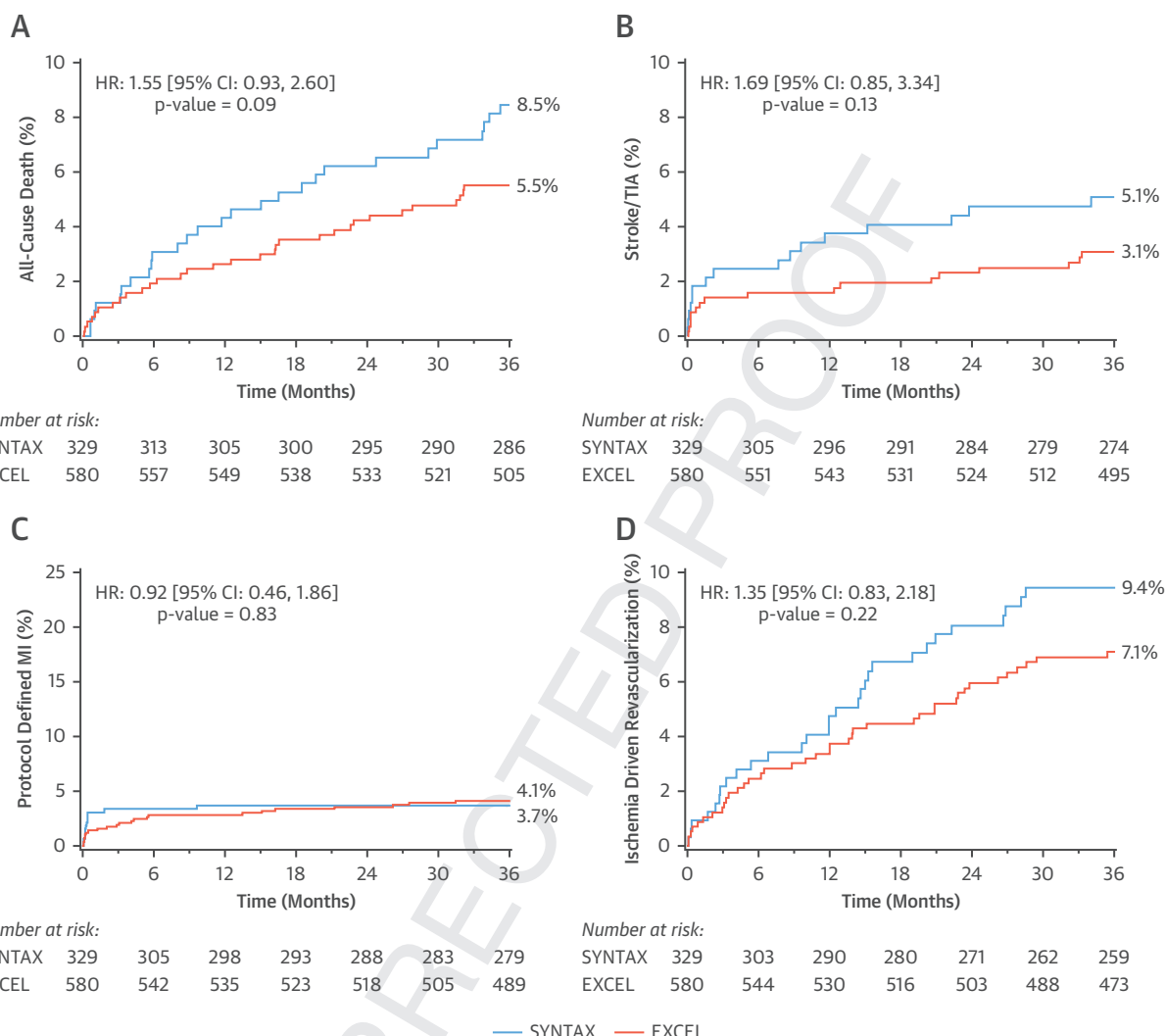
Time-to-first event curves for the primary composite endpoint of all-cause death, any stroke, myocardial infarction or ischemia driven revascularization in patients undergoing CABG for left main disease in the SYNTAX (blue line) and EXCEL (red line) trials. Median follow-up time for both population was 1,095 days (interquartile range: 1,095 days). CABG = coronary artery bypass grafting; LM = left main coronary artery.

**TABLE 5** Thirty-Day and 3-Year Clinical Outcomes of the Propensity-Matched Groups Treated With CABG

	SYNTAX (n = 329)		EXCEL (n = 580)			
	30-Day		p Value		3-Year	
					p Value	
Composite endpoints						
Death, MI, stroke, or IDR	4.3 (14)	3.5 (20)	0.54	20.9 (67)	14.0 (79)	0.008
Death, MI, or stroke	4.3 (14)	2.8 (16)	0.23	14.0 (45)	9.6 (54)	0.05
Death						
All-cause	0.9 (3)	0.7 (4)	0.72	8.5 (27)	5.5 (31)	0.09
Cardiovascular	0.9 (3)	0.7 (4)	0.72	5.4 (17)	3.2 (18)	0.12
Myocardial infarction						
Any	3.0 (10)	1.4 (8)	0.09	3.7 (12)	4.1 (23)	0.83
Periprocedural	2.7 (9)	1.2 (7)	0.09	3.1 (10)	1.2 (7)	0.052
Spontaneous	0.0 (0)	0.2 (1)	0.45	0.3 (1)	3.1 (17)	0.007
Cerebrovascular events						
Any	1.8 (6)	1.0 (6)	0.32	5.1 (16)	3.1 (17)	0.13
Stroke	1.2 (4)	1.0 (6)	0.81	4.2 (13)	2.2 (12)	0.09
Ischemic	0.9 (3)	0.9 (5)	0.94	3.5 (11)	1.8 (10)	0.11
Hemorrhagic	0.3 (1)	0.2 (1)	0.69	0.6 (2)	0.5 (3)	0.86
Transient ischemic attack	0.6 (2)	0.0 (0)	0.06	0.9 (3)	0.9 (5)	0.93
Revascularizations						
Any	2.1 (7)	0.9 (5)	0.11	11.6 (36)	7.3 (40)	0.03
Ischemia-driven	0.9 (3)	0.9 (5)	0.94	9.4 (29)	7.1 (39)	0.22
Graft occlusion	0.3 (1)	1.0 (6)	0.22	3.2 (10)	5.2 (29)	0.17

Values are % (n). The percentages of events correspond to Kaplan-Meier estimates.

IDR = ischemia driven revascularization; MI = myocardial infarction; other abbreviations as in Table 1.

**FIGURE 1** Time-to-First Event Curves for the Individual Components of the Primary Endpoint

Time-to-first event curves for the individual components of the primary endpoint in patients undergoing CABG for left main disease in the SYNTAX (blue line) and EXCEL (red line) trials. (A) All cause death, (B) myocardial infarction, (C) any stroke/TIA, (D) ischemia driven revascularization. CABG = coronary artery bypass grafting; TIA = transient ischemic attack.

hypothesis-generating, and describe associations, but not causality.

## CONCLUSIONS

These limitations notwithstanding, the present comparison of surgical outcomes from the older SYNTAX trial and the contemporary EXCEL trial in patients with LMCAD over a 5- to 7-year period demonstrated

improved event-free survival after CABG during 3-year follow-up, consistent with improving results over time with cardiac surgery.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** The incidence of major adverse cardiovascular and cerebrovascular events following coronary artery bypass surgery have decreased over a period of 5 to 7 years due to improvements in technology and technique.

**TRANSLATIONAL OUTLOOK:** Further studies are needed to determine whether improvement in clinical outcomes will be sustained over a longer period of time.

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**KEY WORDS** coronary artery bypass graft, drug-eluting stents, left main coronary artery disease



### Contemporary Outcomes Following Coronary Artery Bypass Graft Surgery for Left Main Disease

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The authors performed a propensity-matched analysis of patients randomized to coronary artery bypass grafting (CABG) for left main stem disease in the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) and EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) (contemporary) trials to identify whether clinical outcomes after the procedure have improved over time. We analyzed 909 patients (n = 580 in the EXCEL trial and n = 329 in the SYNTAX trial). CABG procedures in the EXCEL trial compared with the SYNTAX trial were more often off-pump, and medical therapies were used more frequently in the EXCEL surgical cohort. major adverse cardiovascular or cerebrovascular events occurred in 14.0% and 20.9% (p = 0.008) of patients in the EXCEL and SYNTAX trials, respectively. The authors observed that in randomized patients, clinical outcomes after CABG for left main disease have improved over time.

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