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Outcomes After Coronary Stenting or Bypass Surgery for Men and Women With Unprotected Left Main Disease

The EXCEL Trial

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ABSTRACT

OBJECTIVES The aim of the present study was to assess outcomes after coronary artery bypass grafting surgery (CABG) and percutaneous coronary intervention (PCI) according to sex in a large randomized trial of patients with unprotected left main disease.

BACKGROUND In the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial, sex had a significant interaction effect with revascularization strategy, and women had an overall higher mortality when treated with PCI than CABG.

METHODS The EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial was a multinational randomized trial that compared PCI with everolimus-eluting stents and CABG in patients with unprotected left main disease. The primary endpoint was the composite of all-cause death, myocardial infarction, or stroke at 3 years.

RESULTS Of 1,905 patients randomized, 1,464 (76.9%) were men and 441 (23.1%) were women. Compared with men, women were older; had higher prevalence rates of hypertension, hyperlipidemia, and diabetes; and were less commonly smokers but had lower coronary anatomic burden and complexity (mean SYNTAX score 24.2 vs. 27.2, $p < 0.001$). By multivariate analysis, sex was not independently associated with either the primary endpoint (hazard ratio [HR]: 1.10; 95% confidence interval [CI]: 0.82 to 1.48; $p = 0.53$) or all-cause death (HR: 1.39; 95% CI: 0.92 to 2.10; $p = 0.12$) at 3 years. At 30 days, all-cause death, myocardial infarction, or stroke had occurred in 8.9% of woman treated with PCI, 6.2% of women treated with CABG, 3.6% of men treated with PCI, and 8.4% of men treated with CABG (p for interaction = 0.003). The 3-year rate of the composite primary endpoint was 19.7% in women treated with PCI, 14.6% in women treated with CABG, 13.8% in men treated with PCI, and 14.7% in men treated with CABG (p for interaction = 0.06). These differences were driven by higher periprocedural rates of myocardial infarction in women after PCI and in men after CABG.

CONCLUSIONS In patients with unprotected left main disease in the EXCEL trial, sex was not an independent predictor of adverse outcomes after revascularization. However, women undergoing PCI had a trend toward worse outcomes, a finding related to associated comorbidities and increased periprocedural complications. Further studies are required to determine the optimal revascularization modality in women with complex coronary artery disease. (J Am Coll Cardiol Intv 2018;11:1234–43) © 2018 by the American College of Cardiology Foundation.

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Coronary revascularization has long been the mainstay treatment for unprotected left main disease (UPLMD) (1,2). For several decades coronary artery bypass graft surgery (CABG) was considered standard of care for UPLMD. More recently percutaneous coronary intervention (PCI) has been increasingly used and has been demonstrated to be noninferior to surgery in selected patients with UPLMD (3,4). Previous studies have shown differences in outcomes between male and female subjects undergoing coronary revascularization (5,6). These differences were attributed mainly to different risk profiles between the sexes, as they disappeared after multivariate adjustment (7,8). In patients with multivessel disease and/or UPLMD, sex has been shown to be an important factor to be considered in the decision-making process of selecting the revascularization strategy (9). Specifically, in the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial, in which 1,800 patients with multivessel disease (including 705 patients with UPLMD) were randomized to PCI versus CABG, women undergoing PCI had a higher adjusted 4-year risk for mortality than men, whereas CABG outcomes were comparable between the sexes (5).

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This resulted in the inclusion of sex as a major determinant of the SYNTAX score II model that aims at selecting the best revascularization strategy on the basis of differences in predicted mortality (10). Conversely, poor outcomes of women undergoing PCI were not observed in a pooled analysis of the PRECOMBAT and BEST Korean trials (11). Sex differences have never been studied in a large dedicated randomized trial of patients with UPLMD. We therefore sought to describe the baseline and procedural characteristics and to assess outcomes in men and women with UPLMD treated with either CABG or PCI.

METHODS

STUDY POPULATION. The EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial was a multinational, open-label, randomized controlled trial that compared PCI with everolimus-eluting stents and CABG in patients with UPLMD. Its design has been previously described in detail elsewhere (12). For the present analysis we compared the baseline and procedural characteristics as well as 30-day and 3-year clinical outcomes of both treatment strategies in male and female patients.

ENDPOINTS AND DEFINITIONS. The primary endpoint was the composite of all-cause death, myocardial infarction (MI), or stroke at 3-year follow-up. Secondary endpoints included the composite of all-cause death, MI, or stroke at 30 days; the composite of all-cause death, MI, stroke, or ischemia-driven repeat revascularization at 30 days and 3 years; and each individual outcome at both time points. Detailed definitions of all trial endpoints are described elsewhere (12). Of note, periprocedural MI was defined as the occurrence within 72 h after PCI or CABG of either creatine kinase-MB >10 times the upper reference limit, creatine kinase-MB >5 times the upper reference limit plus new pathological Q waves in at least 2 contiguous leads, new persistent non-rate-related left bundle branch block, angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality. Stroke was defined as rapid onset of a new persistent neurological deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent nonvascular cause (e.g., trauma, tumor, infection). All events were adjudicated by an independent clinical events committee.

STATISTICAL ANALYSIS. Continuous data are presented as mean ± SD and were compared using the Student's *t*-test or Wilcoxon rank sum test as appropriate. Categorical data are presented as percentage (count) and were compared using chi-square tests. Clinical event rates are presented as Kaplan-Meier estimates in time-to-first-event analyses and were compared using the log-rank test. The independent predictors of the 3-year rates of the primary endpoint and all-cause mortality were determined using Cox proportional hazards regression, using the following candidate variables: PCI

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft surgery

CI = confidence interval

HR = hazard ratio

MI = myocardial infarction

PCI = percutaneous coronary intervention

UPLMD = unprotected left main disease

from Abbott Vascular, Boston Scientific, and Medtronic. Dr. Simonton is an employee of Abbott Vascular. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. *Drs. Serruys and Cavalcante contributed equally to this report.

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TABLE 1 Baseline Characteristics According to Sex and Randomization Arm

	Female PCI (n = 226)	Female CABG (n = 215)	Female Overall (n = 441)	Male PCI (n = 722)	Male CABG (n = 742)	Male Overall (n = 1,464)	p Value, Female vs. Male
Age (yrs)	66.8 ± 10.0	67.3 ± 10.4	67.1 ± 10.2	65.8 ± 95	65.5 ± 9.2	65.6 ± 9.4	0.002
Hyperlipidemia	73.5 (166)	74.9 (161)	74.1 (237)	70.2 (506)	67.5 (498)	68.8 (1,004)	0.03
Hypertension	81.0 (183)	76.3 (164)	78.7 (347)	72.2 (520)	72.7 (539)	72.4 (1,059)	0.008
Medically treated diabetes	32.7 (74)	28.8 (62)	30.8 (136)	28.7 (207)	27.4 (203)	25.2 (410)	0.02
Family history of premature CAD	54.9 (95)	54.3 (100)	54.6 (195)	70.4 (431)	68.4 (426)	69.4 (857)	<0.001
Never smoked	50.4 (114)	50.2 (107)	50.2 (221)	32.6 (234)	33.6 (247)	33.1 (481)	<0.001
Prior TIA or CVA	7.1 (16)	4.7 (10)	5.9 (26)	5.0 (36)	7.7 (57)	6.4 (93)	0.72
Peripheral vascular disease	10.6 (24)	7.5 (16)	9.1 (40)	10.2 (73)	9.2 (68)	9.7 (141)	0.72
COPD	8.8 (20)	10.7 (23)	9.8 (43)	6.2 (45)	8.1 (60)	7.2 (105)	0.08
Congestive heart failure	12.0 (27)	8.9 (19)	10.5 (46)	5.5 (40)	5.4 (40)	5.5 (80)	<0.001
Prior history of anemia	13.4 (30)	14.5 (31)	13.9 (61)	9.7 (70)	7.0 (52)	8.4 (122)	<0.001
Mitral (mild/moderate) regurgitation	34.1 (70)	36.3 (73)	35.2 (143)	27.6 (184)	27.8 (193)	27.7 (377)	0.004
Aortic (mild/moderate) regurgitation	16.2 (33)	9.5 (19)	12.9 (52)	9.7 (64)	11.0 (76)	10.3 (140)	0.72
Stable angina at presentation	52.9 (119)	53.0 (114)	53.0 (233)	53.1 (382)	53.1 (392)	53.1 (774)	0.94
Creatinine clearance (ml/min)	83.9 ± 34.7	80.6 ± 33.3	82.3 ± 34.0	91.7 ± 31.8	91.6 ± 31.4	91.6 ± 31.6	<0.001
Creatinine clearance <60 ml/min	28.1 (62)	26.3 (55)	27.2 (117)	14.3 (102)	12.3 (89)	13.3 (191)	<0.001
Left ventricular ejection fraction (%)	57.6 ± 10.9	58.7 ± 8.4	58.1 ± 9.8	56.8 ± 9.1	56.8 ± 9.2	56.8 ± 9.2	0.002

Values are mean ± SD or % (n).

CABG = coronary artery bypass graft; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

versus CABG, sex, age, creatinine clearance <60 ml/min, anatomic SYNTAX score, peripheral vascular disease, chronic obstructive pulmonary disease, left ventricular ejection fraction, and diabetes. Formal interaction testing was performed between sex and revascularization treatment on clinical outcomes at 30 days and 3 years. All analyses were performed in the intention-to-treat population. A 2-sided p value of 0.05 or less was considered to indicate statistical significance. All statistical analyses were performed with the use of SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

STUDY POPULATION AND BASELINE CHARACTERISTICS. From September 29, 2010, to March 6, 2014, 1,905 patients with UPLMD were recruited at 126 sites in 17

TABLE 2 Anatomical Characteristics by Core Laboratory Analysis

	Female PCI (n = 226)	Female CABG (n = 213)	Female Overall (n = 439)	Male PCI (n = 713)	Male CABG (n = 723)	Male Overall (n = 1,439)	p Value, Female vs. Male
Anatomic SYNTAX score	24.5 ± 8.6	24.0 ± 9.5	24.2 ± 9.0	27.7 ± 8.7	26.6 ± 9.8	27.2 ± 9.3	<0.001
≤22	46.1 (100)	46.2 (98)	46.2 (198)	27.8 (194)	37.3 (266)	32.6 (460)	<0.001
23-32	39.2 (85)	34.9 (74)	37.1 (159)	43.9 (306)	38.0 (271)	40.9 (577)	0.16
≥33	14.7 (32)	18.9 (40)	16.8 (72)	28.3 (197)	24.8 (177)	26.5 (374)	<0.001
Lesion location							
Ostial lesion	45.9 (102)	47.3 (98)	46.6 (200)	31.0 (216)	36.2 (254)	33.6 (470)	<0.001
Mid shaft	42.8 (95)	39.1 (81)	41.0 (176)	43.8 (305)	39.7 (278)	41.7 (583)	0.80
Distal lesion	73.0 (162)	69.1 (143)	71.1 (305)	81.8 (570)	76.7 (538)	79.3 (1,108)	0.0004
Any LM complex trifurcation or bifurcation	76.5 (173)	75.6 (161)	76.1 (334)	83.5 (598)	80.2 (580)	81.9 (1,178)	0.007
Number of diseased territories							
Isolated LM	25.7 (58)	27.2 (58)	26.4 (116)	14.7 (105)	14.9 (108)	14.8 (213)	<0.001
LM + 1-VD	32.7 (74)	33.3 (71)	33.0 (145)	30.2 (216)	30.2 (218)	30.2 (434)	0.25
LM + 2-VD	30.5 (69)	24.4 (52)	27.6 (121)	34.9 (250)	32.8 (237)	33.8 (487)	0.01
LM + 3-VD	10.2 (23)	14.6 (31)	12.3 (54)	18.9 (135)	20.3 (147)	19.6 (282)	<0.001

Values are mean ± SD or % (n).

LM = left main coronary artery; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; VD = vessel disease; other abbreviations as in Table 1.

countries, were randomly assigned to either CABG (n = 957) or PCI (n = 948), and were followed for a median of 3 years (interquartile range: 3.0 to 3.0 years). Of those, 1,464 (76.9%) were men and 441 (23.1%) were women. Compared with men, women were older; had higher prevalence rates of hypertension, hyperlipidemia, and diabetes; and were less commonly smokers. Women also more frequently had congestive heart failure, histories of anemia, and lower mean creatinine clearance (Table 1).

CORONARY ANATOMY CHARACTERIZATION. By angiographic core laboratory analysis, women compared with men had a lower mean angiographic SYNTAX score, with more women than men in the lower tercile (≤22) and fewer in the higher tercile (≥33). The left main lesion more frequently involved the ostium and less frequently the distal bifurcation or trifurcation in women compared with men. Additionally, women more frequently had isolated left main disease and less frequently had multivessel disease compared with men (Table 2).

PROCEDURAL FEATURES AND MEDICAL THERAPY. In PCI-treated patients, women had fewer vessels and lesions treated than men, with fewer stents implanted, resulting in a significantly lower mean total stent length (Table 3). Intravascular ultrasound use was more frequent in women than in men, with similar rates of fractional flow reserve use. A higher proportion of women achieved complete revascularization compared with men (Table 3). Despite the lower anatomic complexity and less extensive treatment, women had more ischemic and bleeding complications related to PCI, with more frequent need for hemodynamic support (Online Tables 1 and 2).

Among CABG-treated patients, women received fewer arterial grafts, including less frequent use of bilateral internal thoracic artery grafts. No differences between the sexes were observed in the number of vessels bypassed or in the use of off-pump surgery. As with PCI, women had a higher rate of CABG-related complications than men (Table 3).

As shown in Table 4, use of optimal medical therapy at hospital discharge and at 3-year follow-up was similar in women and men, although diuretic agent use in women was higher at both time points than in men.

CLINICAL OUTCOMES. The 3-year rate of the composite primary endpoint was 19.7% in women treated with PCI, 14.6% in women treated with CABG, 13.8% in men treated with PCI, and 14.7% in men treated with CABG (p = 0.14) (Figure 1). Major adverse cardiovascular and cerebral event (death, MI, stroke, or ischemia-driven revascularization) rates at 3 years were 27.4% in women treated with PCI, 20.1% in women treated with CABG, 21.4% in men treated with PCI, and 18.5% in men treated with CABG. Rates of all-cause death tended to be higher in women undergoing PCI (10.8% vs. 7.1% for men treated with PCI, 6.8% for women treated with CABG, and 5.5% for men treated with CABG; overall p = 0.06) (Figure 2). Acute results at 30 days were worse for women undergoing PCI, with rates of all-cause death, MI, or stroke of 8.9% in women treated with PCI, 6.2% in women treated with CABG, 3.6% in men treated with PCI, and 8.4% in men treated with CABG (p < 0.01) (Figure 3). The 30-day rates of major adverse cardiovascular and cerebral events were 8.9% in women treated with PCI, 6.6% in women treated with CABG, 3.6% in men treated with PCI, and 9.0% in men treated with CABG (p < 0.01). Rates of individual outcomes according to sex and randomization arm are presented in Table 5.

TABLE 3 PCI and CABG Procedural Characteristics According to Sex

	Female	Male	p Value
PCI	223	712	
Number of vessels treated	1.6 ± 0.8	1.7 ± 0.8	0.02
Number of lesions treated	1.8 ± 1.1	1.9 ± 1.1	0.01
Number of stents per patient	2.3 ± 1.6	2.5 ± 1.5	0.051
Left main	1.5 ± 0.8	1.5 ± 0.8	0.66
Non–left main	0.8 ± 1.1	0.9 ± 1.1	0.01
Total stent length (mm)	43.6 ± 34.3	50.8 ± 35.9	0.001
Post-dilatation done (per lesion)	72.8 (378/519)	72.9 (1,289/1,768)	0.95
IVUS use	83.9 (187)	75.1 (535)	0.007
FFR use	8.1 (18)	9.3 (66)	0.58
Contrast volume (ml)	245.1 ± 130.0	258.8 ± 126.3	0.06
Hemodynamic support during PCI	7.9 (19)	4.4 (34)	0.03
PCI complications*	14.9 (36)	8.9 (69)	0.007
Complete revascularization†	37.4 (82/219)	25.4 (177/698)	0.001
CABG	204	719	
Number of vessels bypassed	2.2 ± 0.6	2.3 ± 0.5	0.07
Off-pump CABG	29.9 (61)	29.2 (210)	0.85
Endoscopic venous graft harvesting	33.9 (64)	31.5 (206)	0.55
Procedures other than CABG‡	2.9 (6)	2.1 (15)	0.43
Total number of conduits	2.4 ± 0.8	2.6 ± 0.8	0.002
Number of arterial conduits	1.2 ± 0.5	1.4 ± 0.6	<0.001
Number of venous conduits	1.2 ± 0.9	1.2 ± 1.0	0.66
Complete arterial grafting	21.6 (44)	25.7 (185)	0.22
LIMA or RIMA use	97.5 (198)	99.2 (710)	0.07
BITA	20.7 (42)	31.1 (223)	0.004
CABG complications§	13.2 (27)	8.5 (61)	0.04

Values are mean ± SD, % (n), or n. *PCI complications included chest pain >10 min, electrocardiographic changes >10 min, slow flow/no reflow, distal embolization, side branch closure, acute vessel closure, coronary perforation, cardiac tamponade requiring pericardiocentesis, cardiac arrest requiring cardiopulmonary resuscitation, arrhythmias requiring defibrillation or cardioversion or temporary pacemaker, intubation, hypotension requiring vasopressors or hemodynamic support, coronary dissection, aortic dissection and procedural bleeding. †Defined as a residual SYNTAX score equal to zero by angiographic core laboratory assessment. ‡Procedures other than CABG included aortic, mitral, or tricuspid valve surgery; resynchronization pacer placement; and atrial appendage closure. §CABG complications included aortic dissection, arrhythmias (including atrial fibrillation), prolonged hypotension (>10 min or requiring support device), repeat sternotomy for bleeding, prolonged intubation (>24 h), stroke, injury to a cardiac structure, excessive bleeding, gastrointestinal bleeding, unplanned need for hemodynamic support, heart failure, cardiogenic shock, surgery redo, and cardiac arrest.

BITA = bilateral internal thoracic artery; FFR = fractional flow reserve; IVUS = intravascular ultrasound; LIMA = left internal thoracic artery; RIMA = right internal thoracic artery; other abbreviations as in Tables 1 and 2.

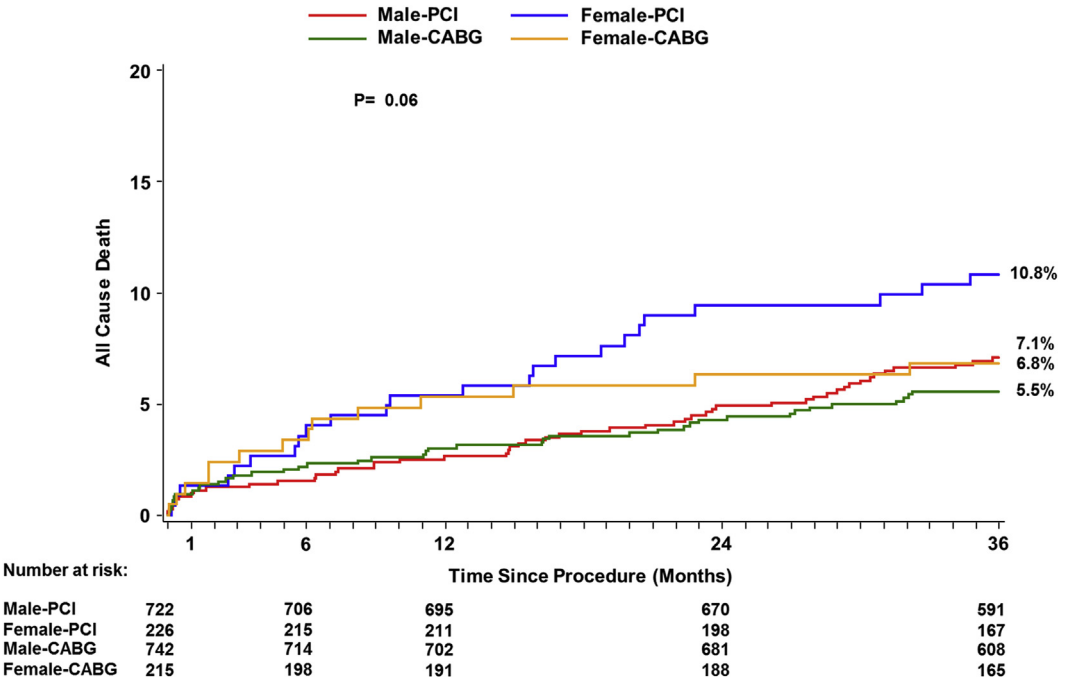
TABLE 4 Medical Treatment According to Sex and Randomization Arm

	Female PCI	Female CABG	Female Overall	Male PCI	Male CABG	Male Overall	p Value, Female vs. Male
At discharge	222	201	423	709	710	1,842	
Statins	95.9 (213)	91.0 (182)	93.6 (396)	96.6 (685)	93.0 (660)	94.8 (1,345)	0.27
Aspirin	98.2 (218)	99.0 (198)	98.6 (416)	99.3 (701)	98.9 (698)	99.1 (1,399)	0.41
$P2Y_{12}$ inhibitors	97.3 (216)	32.3 (65)	66.4 (281)	98.2 (696)	32.8 (233)	65.5 (929)	0.71
DAPT	95.9 (213)	31.3 (63)	65.2 (276)	97.3 (690)	32.3 (229)	64.8 (919)	0.85
Oral anticoagulant agents	2.3 (5)	3.5 (7)	2.8 (12)	1.0 (7)	4.5 (32)	4.3 (61)	0.92
Beta-blockers	80.2 (178)	91.0 (183)	85.3 (361)	84.2 (597)	93.0 (660)	88.6 (1,257)	0.07
Calcium-channel blockers	7.2 (16)	8.5 (17)	7.8 (33)	5.5 (39)	6.8 (48)	6.1 (87)	0.22
ACE inhibitors/ARBs	59.5 (132)	40.8 (82)	50.6 (214)	55.9 (407)	42.5 (302)	49.2 (698)	0.61
Nitrates	4.1 (9)	3.0 (6)	3.5 (15)	2.8 (20)	5.1 (36)	3.9 (56)	0.71
Diuretic agents	7.2 (16)	28.4 (57)	17.3 (73)	2.4 (17)	23.2 (165)	12.8 (182)	0.02
Antiarrhythmic agents	0.9 (2)	10.9 (22)	5.7 (24)	0.4 (3)	11.8 (84)	6.1 (87)	0.73
At 3 yrs	191	179	370	646	656	1,302	
Statins	95.3 (182)	95.0 (170)	95.1 (352)	97.4 (629)	96.2 (631)	96.8 (1,260)	0.16
Aspirin	93.7 (179)	96.1 (172)	94.9 (351)	94.7 (609)	95.1 (619)	94.9 (1,228)	0.98
$P2Y_{12}$ inhibitors	64.9 (124)	26.3 (47)	46.2 (171)	68.0 (439)	22.4 (147)	45.0 (586)	0.68
DAPT	60.2 (115)	24.0 (43)	42.7 (158)	64.2 (415)	20.4 (134)	42.2 (549)	0.85
Oral anticoagulant agents	5.4 (10)	9.9 (17)	7.5 (27)	4.1 (26)	9.4 (60)	6.8 (86)	0.61
Beta-blockers	83.7 (159)	95.6 (171)	89.4 (330)	86.8 (561)	93.7 (614)	90.3 (1,175)	0.62
Calcium-channel blockers	18.7 (35)	18 (31)	18.4 (66)	15.3 (97)	17.3 (110)	16.3 (207)	0.34
ACE inhibitors/ARBs	69.8 (132)	55.4 (98)	62.8 (230)	63.0 (404)	58.0 (373)	60.5 (777)	0.42
Nitrates	14.0 (26)	8.2 (14)	11.2 (40)	9.1 (58)	8.4 (53)	8.7 (111)	0.15
Diuretic agents	23.5 (44)	44.8 (77)	33.7 (121)	10.8 (69)	37.2 (237)	24.0 (306)	<0.001
Antiarrhythmic agents	5.9 (11)	15.7 (27)	10.6 (38)	1.6 (10)	17.3 (110)	9.4 (120)	0.50

Values are n or % (n).

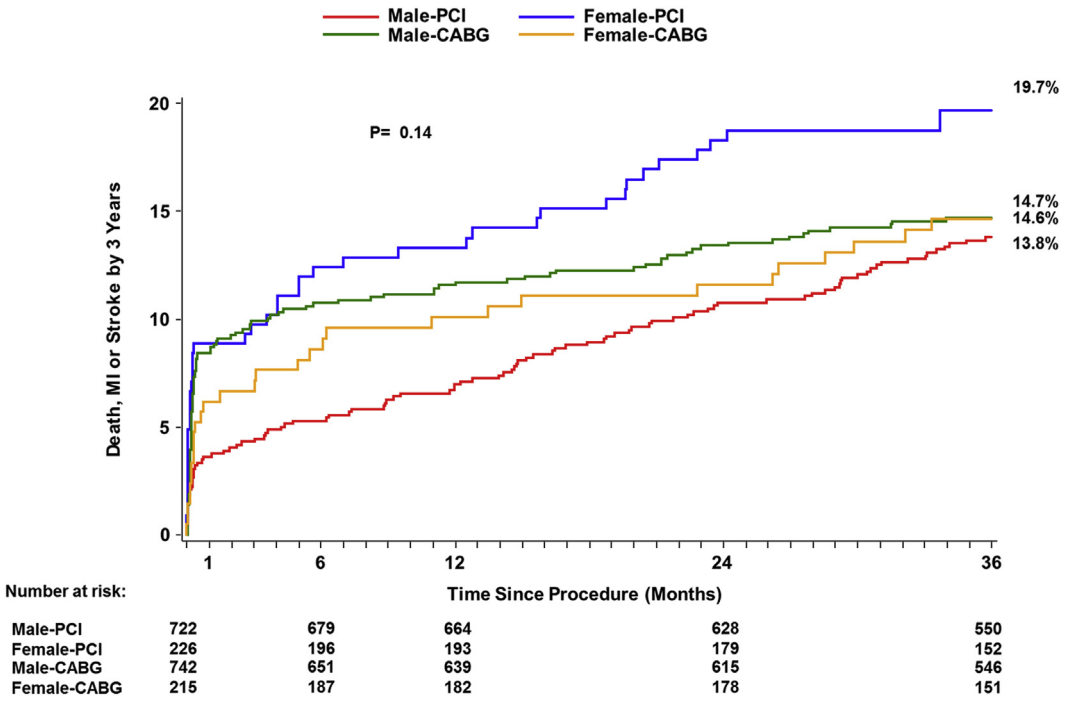
ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; DAPT = dual antiplatelet therapy; other abbreviations as in Table 1.

FIGURE 1 Time-to-First Event Curves for the Primary Endpoint of All-Cause Death, Myocardial Infarction, or Stroke at 3 Years Stratified by Sex and Revascularization Strategy



The p value is derived from a log-rank test. CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention.

FIGURE 2 Time-to-First Event Curves for All-Cause Death at 3 Years Stratified by Sex and Revascularization Strategy



The p value is derived from a log-rank test. MI = myocardial infarction; other abbreviations as in Figure 1.

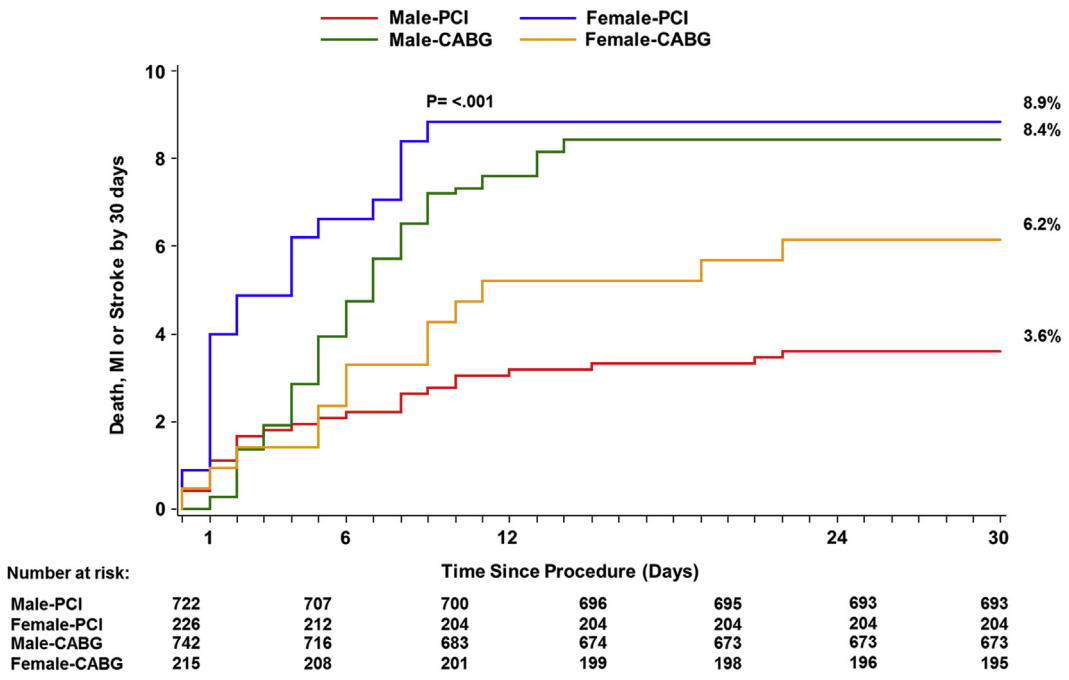
By formal interaction testing, a significant interaction was present between sex and treatment for the composite endpoint of death, stroke, or MI at 30 days (p for interaction = 0.003), but not at 3 years (p for interaction = 0.06) (Table 5). By multivariate analysis, sex was not independently associated with either the primary endpoint (hazard ratio: 1.10; 95% CI: 0.82 to 1.48; p = 0.53) or with all-cause death (hazard ratio: 1.39; 95% CI: 0.92 to 2.10; p = 0.12) at 3 years. Diabetes and chronic obstructive pulmonary disease were the only independent predictors of the primary endpoint. Age, chronic obstructive pulmonary disease, low ejection fraction, and diabetes were independently associated with all-cause mortality at 3 years (Table 6).

DISCUSSION

The findings of the present study can be summarized as follows: 1) in patients with UPLMD in the EXCEL trial, women had an overall worse baseline clinical risk profile than men; 2) conversely, women had overall less anatomic complexity than men, with lower SYNTAX scores, fewer left main bifurcation lesions, less concomitant multivessel disease, and greater likelihood of achieving complete revascularization after PCI; 3) nonetheless, women had more PCI-related ischemic and hemorrhagic complications than men; 4) a significant interaction between treatment and sex for the outcome of MI was present at 30 days and 3 years such that the relative risk for MI (in particular periprocedural MI) tended to be higher after PCI in women but tended to be higher after CABG in men; and 5) the highest unadjusted 3-year rates of the primary composite endpoint and major adverse cardiovascular and cerebral events occurred in women treated with PCI. Nonetheless, there were no significant interactions between sex and treatment for the 3-year primary or major secondary composite endpoints.

The main results of the EXCEL trial demonstrated that in patients with UPLMD and site-assessed low and intermediate SYNTAX scores, PCI and CABG are both acceptable alternatives for revascularization, with PCI resulting in improved outcomes within 30 days and CABG having better outcomes between 30 days and 3 years (4). The selection between the 2 alternatives should thus rely on assessment of the patient's comorbidities and anatomic characteristics, as

FIGURE 3 Time-to-First Event Curves for the Composite of All-Cause Death, Myocardial Infarction, or Stroke at 30 Days Stratified by Sex and Revascularization Strategy



The p value is derived from a log-rank test. Abbreviations as in Figures 1 and 2.

well as physician and patient preferences, through a comprehensive heart team discussion. Important subgroup analyses can provide useful information to help guide this decision-making process. The intrinsic differences between men and women in genetic and hormonal factors, as well as the prevalence and relative weighting of traditional clinical and anatomic risk factors make the assessment of the outcomes of

TABLE 5 Clinical Outcomes According to Sex and Randomization Arm

	Female PCI (n = 226)	Female CABG (n = 215)	p Value	Male PCI (n = 722)	Male CABG (n = 742)	p Value	p Value for Interaction
At 30 days							
All-cause death	1.3 (3)	1.4 (3)	0.94	0.8 (6)	1.0 (7)	0.81	0.95
MI	8.0 (18)	4.7 (10)	0.16	2.6 (19)	6.7 (49)	<0.001	0.001
Peri-procedural MI (within 48 h)	7.5 (17)	3.8 (8)	0.09	2.4 (17)	6.5 (48)	<0.001	<0.001
Stroke or TIA	1.3 (3)	1.0 (2)	0.71	0.4 (3)	1.4 (10)	0.06	0.17
ID revascularization	0.9 (2)	2.4 (5)	0.22	0.6 (4)	1.1 (8)	0.26	0.76
Death, MI, or stroke	8.9 (20)	6.2 (13)	0.26	3.6 (26)	8.4 (62)	<0.001	0.003
Death, MI, stroke, or ID revascularization	8.9 (20)	6.6 (14)	0.35	3.6 (26)	9.0 (66)	<0.001	0.003
At 3 yrs							
All-cause death	10.8 (24)	6.8 (26)	0.10	7.1 (50)	5.5 (40)	0.26	0.52
MI	11.7 (26)	6.8 (14)	0.08	6.9 (48)	8.8 (64)	0.12	0.02
Peri-procedural MI (within 48 h)	8.0 (18)	3.8 (8)	0.06	2.5 (18)	6.7 (49)	<0.001	<0.001
Stroke or TIA	4.7 (10)	5.2 (10)	0.88	2.0 (14)	3.8 (27)	0.04	0.26
ID revascularization	14.1 (30)	9.8 (19)	0.17	12.1 (84)	6.8 (48)	0.001	0.64
Death, MI, or stroke	19.7 (44)	14.6 (30)	0.10	13.8 (98)	14.7 (107)	0.46	0.06
Death, MI, stroke, or ID revascularization	27.4 (61)	20.1 (41)	0.06	21.4 (152)	18.5 (135)	0.35	0.18

Values are % (n). At 3 years, 1 woman undergoing CABG, 2 women undergoing PCI, 8 men undergoing CABG, and 1 man undergoing PCI were lost to follow-up.
ID = ischemia-driven; MI = myocardial infarction; TIA = transient ischemic attack; other abbreviations as in Table 1.

TABLE 6 Multivariable Analyses for the Primary Endpoint and All-Cause Death at 3 Years

	HR (95% CI)	p Value
Death, MI, or stroke at 3 yrs		
PCI (vs. CABG)	0.97 (0.75–1.25)	0.81
Women (vs. men)	1.10 (0.82–1.48)	0.53
Age (per year)	1.01 (0.99–1.02)	0.26
Creatinine clearance <60 ml/min	1.37 (0.97–1.94)	0.07
Anatomic SYNTAX score (per 1 U)	1.11 (0.94–1.31)	0.23
Peripheral vascular disease	0.84 (0.55–1.29)	0.42
Chronic obstructive pulmonary disease	2.34 (1.64–3.33)	<0.001
Left ventricular ejection fraction (per 1%)	1.00 (0.98–1.01)	0.66
Diabetes (vs. no diabetes)	1.53 (1.18–1.98)	0.002
All-cause death at 3 yrs		
PCI (vs. CABG)	1.14 (0.78–1.66)	0.50
Women (vs. men)	1.39 (0.92–2.10)	0.12
Age (per year)	1.03 (1.01–1.06)	0.007
Creatinine clearance <60 ml/min	1.58 (0.99–2.51)	0.06
Anatomic SYNTAX score (per 1 U)	1.10 (0.86–1.41)	0.43
Peripheral vascular disease	1.34 (0.80–2.26)	0.27
Chronic obstructive pulmonary disease	2.38 (1.46–3.89)	<0.001
Left ventricular ejection fraction (per 1%)	0.98 (0.96–1.00)	0.02
Diabetes (vs. no diabetes)	1.96 (1.34–2.86)	<0.001

CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

PCI and CABG within each sex group of paramount importance (13).

In the SYNTAX trial of patients with UPLMD and 3-vessel disease, sex was an important driver of the difference in mortality between the 2 revascularization modalities, with an adjusted HR for women of 1.70 (95% CI: 1.11 to 2.60) in the PCI arm and 0.59 (95% CI: 0.32 to 1.10) in the CABG arm at 4 years (14). This difference was reflected in a significant interaction effect (HR: 2.87; 95% CI: 1.35 to 6.07; p = 0.006) with a revascularization strategy, meaning that women had higher mortality when treated with PCI (9). The EXCEL trial also demonstrated significantly higher all-cause mortality in women undergoing PCI than in women undergoing CABG and men treated with either PCI or CABG. However, in EXCEL, sex was not independently related to mortality and did not have significant interaction effects with revascularization strategy for either mortality or the primary composite endpoint at 3 years. Although previous registry data have shown worse outcomes after PCI of UPLMD in women compared to men, these findings were related to baseline differences in which women had worse risk factor profile and higher anatomic complexity than men (7,8). Interestingly, in EXCEL, women also had a higher overall risk factor burden but conversely significantly lower coronary anatomic complexity with lower SYNTAX scores and fewer coronary lesions compared with men. The finding of less coronary anatomic burden and complexity in women compared with men corroborates a recent study that reported less overall plaque burden and slightly more favorable plaque composition characteristics in women. The reasons for this paradox of higher risk factor prevalence coupled with lower atherosclerotic burden and complexity are not yet elucidated (15). Regardless, the lesser extent of coronary artery disease in women compared with men contributed to complete revascularization as defined by a residual SYNTAX score of zero being achieved more frequently in women.

In the EXCEL trial, women undergoing PCI had higher rates of both periprocedural ischemic and bleeding complications compared with men, which contributed to the greater unadjusted rates of adverse outcomes observed in women. Specifically, periprocedural MI rates in women treated with PCI tended to be increased compared with women undergoing CABG, with a significant interaction effect between treatment and sex for periprocedural and all MI present at 30 days and 3 years. Consistent with our findings, prior studies have reported that women undergoing PCI are at increased risk for bleeding compared with men (16) and derive the greatest benefit of strategies aimed at reducing hemorrhagic complications (e.g., radial access, vascular closure devices, bivalirudin) (17). Furthermore, hemodynamic support devices were more frequently used during UPLMD PCI in women than men. In the majority of the cases (78.9%) the device was used prior to the PCI, which may in part reflect the operator's appreciation of greater procedural risk in women.

Data from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines?) registry suggested that women with acute coronary syndromes were less likely to receive optimal medical therapy at discharge than men (18). This could also influence overall outcomes and explain differences between the sexes. However, in EXCEL, no significant differences were observed in medical therapy between men and women with follow-up through 3 years. Overall, more than 90% of the patients of both sexes were receiving aspirin, statins, and beta-blockers at 3 years, which represents a high rate of optimal medical therapy that reflects the most contemporary treatment standards. Additional unmeasured risk factors in women such as more frequent microvascular disease, a higher prevalence

of diastolic dysfunction and heart failure with preserved ejection fraction, and hormonal differences may also underlie adverse outcomes in women (19).

STUDY LIMITATIONS. Although EXCEL is the largest UPLMD trial to date, the present study represents a subgroup analysis that is underpowered, and its results should be interpreted as hypothesis generating. To adequately power a study comparing clinical outcomes (death, MI, and stroke) between men and women undergoing revascularization for UPLMD, approximately 5,200 patients will be required with power of 80% at an alpha level of 5%. Women represented only 23% of the study population. It is possible that additional differences in outcomes between the sexes will emerge with longer term follow-up. Last, because the protocol restricted inclusion to patients with low and moderate anatomic complexity by SYNTAX score, our results are not representative of the entire spectrum of patients with UPLMD.

CONCLUSIONS

In selected patients with UPLMD and low and intermediate SYNTAX scores (as assessed by the local heart team physicians) undergoing revascularization in the EXCEL trial, women had a higher prevalence of clinical risk factors but less coronary anatomic burden and complexity than men. Women had more PCI-related complications than men and the highest rate of all-cause death, stroke, and MI at 30 days. However, after multivariate adjustment for baseline risk factors and SYNTAX score, sex was not an independent predictor of all-cause mortality or the primary composite measure of death, stroke, or MI at 3 years. Further studies are required to determine the optimal revascularization modality in women with complex coronary artery disease.

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PERSPECTIVES

WHAT IS KNOWN? Myocardial revascularization improves survival in patients with UPLMD. Previous studies have shown differences in outcomes between male and female patients undergoing revascularization; in the SYNTAX trial, women undergoing PCI had higher 4-year mortality compared to men, while CABG outcomes were comparable between sexes.

WHAT IS NEW? In the present study of patients with UPLMD undergoing contemporary PCI and CABG, women undergoing PCI had a trend toward worse outcomes at 3 years, a finding related to associated comorbidities and greater procedural complications. These findings confirm sex-specific outcomes in patients with UPLMD undergoing myocardial revascularization.

WHAT IS NEXT? Further studies are warranted to determine the optimal revascularization modality in women with complex coronary artery disease.

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KEY WORDS coronary artery bypass graft, female, male, percutaneous coronary intervention, sex, SYNTAX score

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