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ORIGINAL RESEARCH

Sex Differences in Outcomes After Percutaneous Coronary Intervention or Coronary Artery Bypass Graft for Left Main Disease: From the DELTA Registries

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BACKGROUND: Controversy exists over whether sex has significant interaction with revascularization strategy for unprotected left main coronary artery disease. Higher mortality has been reported among women treated with percutaneous coronary intervention compared with coronary artery bypass grafting.

METHODS AND RESULTS: The DELTA (Drug-Eluting Stents for Left Main Coronary Artery Disease) and DELTA-2 registries are international, multicentric registries evaluating the outcomes of subjects undergoing coronary revascularization for unprotected left main coronary artery disease. The primary outcome was a composite of death, myocardial infarction, or cerebrovascular accidents. The population consisted of 6253 patients, including 1689 (27%) women. Women were older and more likely to have diabetes and chronic kidney disease than men ($P<0.05$). At a median follow-up of 29 months (interquartile range 12–49), a significant interaction between sex and revascularization strategy was observed for the primary end point ($p_{int}=0.012$) and all-cause death ($p_{int}=0.037$). Among women, compared with percutaneous coronary intervention, coronary artery bypass grafting was associated with lower risk of the primary end point (event rate 9.5% versus 15.3%; adjusted hazard ratio [AHR], 0.53; 95% CI, 0.35–0.79, $P<0.001$) and all-cause death (event rate 5.6% versus 11.7% AHR, 0.50; 95% CI, 0.30–0.82) and no significant differences were observed in men.

CONCLUSIONS: In women undergoing coronary revascularization for unprotected left main coronary artery disease, coronary artery bypass grafting was associated with lower risk of death, myocardial infarction, or cerebrovascular accidents whereas no significant differences between coronary artery bypass grafting and percutaneous coronary intervention were observed in men. Further dedicated studies are needed to determine the optimal revascularization strategy in women with unprotected left main coronary artery disease.

Key Words: cardiovascular disease in women ■ coronary revascularization ■ unprotected left main coronary artery disease

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CLINICAL PERSPECTIVE

What Is New?

- Coronary artery bypass graft appears to provide a selective prognostic advantage over percutaneous coronary intervention for unprotected left main coronary artery disease among women.

What Are the Clinical Implications?

- When discussing the optimal revascularization strategy for unprotected left main coronary artery, sex may be taken into account to gauge the decision between coronary artery bypass graft and percutaneous coronary intervention.

Nonstandard Abbreviations and Acronyms

DELTA	drug-eluting stents for left main coronary artery disease
EXCEL	Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization
MACCE	major adverse cardio-cerebrovascular events
PRECOMBAT	Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease
SYNTAX	Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery
ULMCA	unprotected left main coronary artery

Coronary revascularization is the mainstay treatment for unprotected left main coronary artery (ULMCA) disease, because of its prognostic advantage compared with medical therapy.[1,2] Traditionally, coronary artery bypass graft (CABG) surgery has been considered the standard of care for ULMCA disease, but recent evidence supports the noninferiority of percutaneous coronary intervention (PCI) in selected patients.[3,4] Female sex is considered to be a risk factor for adverse outcomes following coronary revascularization and initial reports on CABG surgery showed a trend toward poorer postoperative and long-term prognosis in women.[5,6] Similarly, worse outcomes in women have been reported in the PCI setting.[7–9] Although these differences have been consistently highlighted, they have been mainly attributed to different risk factor profiles between sexes as they are attenuated or disappear in multivariable analysis adjusting for baseline confounders.[10,11] However, in patients with multivessel disease or ULMCA disease the evidence is still conflicting. In the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial, which enrolled 1800 subjects with multivessel disease, including 705 with ULMCA disease, women undergoing PCI had a higher adjusted 4-year mortality rates when compared with men, whereas CABG outcomes did not differ between sexes.[12] Conversely, poorer outcomes in women undergoing PCI was not observed in post hoc analysis of the PRECOMBAT (Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) trial.[13] More recently, sex was not found to be an independent predictor of adverse outcomes at 3-year follow-up in women undergoing PCI for ULMCA in the EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial.[14] Evidence regarding the impact of sex on ULMCA disease thus appears to be conflicting. We therefore sought to evaluate outcomes women as compared with men with ULMCA disease undergoing either PCI or CABG using data from the large DELTA (Drug-Eluting Stents for Left Main Coronary Artery Disease) and DELTA 2 real-world registries.[15,16]

METHODS

Study Population

The study population consisted of the pooled DELTA and DELTA 2 registries. The DELTA registry included all-comer patients with ULMCA disease treated in 14 centers with either PCI with first-generation drug-eluting stents (DES) or CABG between April 2002 and April 2006.[15] The DELTA 2 registry included all-comer patients with ULMCA disease treated with PCI with new-generation DES in 19 centers in 7 countries between April 2006 and December 2015.[16] All data related to hospital admissions, procedures, and outcomes were collected at each center. Information on clinical status at the latest clinical follow-up was obtained by clinical visits, telephone interviews, and referring physicians. Dual-antiplatelet therapy was administered according to hospital and physician practice. Angiographic follow-up was scheduled according to hospital practice or if a noninvasive evaluation or clinical presentation suggested myocardial ischemia. The present study was conducted in compliance with the Declaration of Helsinki and was approved by local Ethics Committee at each participant center. All patients provided written informed consent to take part in the study. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Definitions

Study definitions of the DELTA and DELTA 2 registries were homogeneous and published previously.[15] The following events were cumulatively analyzed at last available clinical follow-up: all-cause and cardiac death, nonfatal myocardial infarction (MI), cerebrovascular accident (CVA), target lesion revascularization (TLR), and target vessel revascularization (TVR). Major adverse cardio-cerebrovascular events (MACCE) were defined as the composite end point of all-cause death, MI, CVA, and TVR. TLR was defined as any repeat intervention of the target lesion or other complication of the target lesion. The target lesion was defined as the treated segment 5 mm proximally to the stent and 5 mm distally to the stent.[15] TVR was defined as any repeat intervention of any segment of the target vessel, defined as the entire major coronary vessel proximal and distal to the target lesion, including upstream and downstream branches and the target lesion itself. Cerebrovascular accidents were defined as stroke, transient ischemic attacks, and reversible ischemic neurological deficits adjudicated by a neurologist and confirmed by brain imaging. In-hospital non–Q-wave MI was defined as the elevation of the serum creatine kinase isoenzyme myocardial band that was 3x the upper limit of normal in the PCI group and 5x the upper limit of normal in the CABG group, in the absence of new pathological Q waves. In this analysis were included as cumulative MI (1) all Q-wave MI that occurred during hospital stay and follow-up; and (2) all spontaneous MI occurring after hospital discharge. Q-wave MI was defined as the development of new pathological Q waves in 2 or more contiguous leads with or without creatine kinase or creatine kinase-myocardial band levels elevated above normal. Spontaneous MI was defined as the occurrence after hospital discharge of any value of troponin and/or creatine kinase-myocardial band greater than the upper limit of normal if associated with clinical and/or electrocardiogram change.[15]

Study End Points

Consistently with DELTA and DELTA 2, the primary study objective was the composite of all-cause death, MI, and CVA at long-term follow-up. Secondary objectives were all-cause death, the composite of all-cause death, and MI, MACCE, TVR, and TLR at long-term follow-up.[15]

Statistical Analysis

Individual patient data were pooled in a single prespecified data set and analyzed. Baseline characteristics are reported as number (percentage), mean±SD, or median (interquartile range). Continuous variables were compared using Student's *t* test or Wilcoxon rank sum test as appropriate. Categorical variables were compared using chi-square test. Missing data were imputed using multiple imputation with fully conditional specification. Event rates with 95% CIs and absolute rate differences at follow-up were estimated using the Kaplan-Meier method as time to first event. Predictors for in-hospital events were estimated using

Table 1. Baseline Characteristics According to Sex and Treatment

	Total (6253)	Women (1689)		Men (4564)		*P* value, women vs men	Missing data N (%)
		PCI (1365)	CABG (324)	PCI (4002)	CABG (562)		
Age, y	68±11	70±12	68±10	67±11	65±10	<0.001	105 (1.7)
Family history of coronary artery disease	1803 (29)	403 (29)	86 (27)	1173 (28)	141 (25)	0.153	367 (5.9)
Hypertension	4547 (73)	1090 (80)	236 (73)	2858 (71)	363 (64)	<0.001	0 (0.0)
Dyslipidemia	4244 (68)	968 (68)	228 (70)	2703 (68)	346 (62)	0.003	1 (0.0)
Never smoker	3765 (60)	1062 (78)	269 (83)	2196 (55)	238 (42)	<0.001	0 (0.0)
Diabetes	1916 (31)	474 (35)	100 (31)	1143 (29)	199 (35)	0.001	0 (0.0)
Chronic kidney disease	1246 (20)	360 (26)	9 (3)	850 (21)	27 (5)	0.024	134 (2.1)
Clinical presentation						<0.001	0 (0.0)
Stable angina	5147 (82)	896 (66)	289 (89)	2921 (73)	496 (88)		
Acute coronary syndrome	1106 (18)	469 (34)	35 (11)	1081 (27)	66 (12)		
ST-segment–elevation myocardial infarction	286 (26)	71 (5)	2 (1)	208 (5)	5 (1)	0.562	
Previous revascularization	2341 (37)	481 (35)	52 (16)	1725 (43)	83 (15)	<0.001	35 (0.5)
Previous PCI	2040 (32)	411 (30)	48 (15)	1507 (38)	74 (13)	<0.001	
Previous CABG	512 (8)	100 (7)	13 (4)	389 (10)	10 (2)	0.008	
Left ventricular ejection fraction	53±12	53±11	54±11	53±12	53±11	<0.001	1210 (19.3)

Values are expressed as n (%) or mean±SD as appropriate. *P* values refer to female vs male comparison. CABG indicates coronary artery bypass surgery; and PCI, percutaneous coronary intervention.

Table 2. Coronary Anatomy and Procedural Characteristics

	Total (6253)	Women (1689)		Men (4564)		*P* value, women vs men	Missing values N (%)
		PCI (1365)	CABG (324)	PCI (4002)	CABG (562)		
LMCA bifurcation	4597 (74)	969 (71)	190 (59)	3117 (78)	387 (69)	<0.001	86 (1.4)
Multivessel disease	4952 (79)	1011 (74)	305 (94)	3107 (78)	529 (94)	0.130	0 (0.0)
Right coronary artery disease	3046 (48)	525 (39)	235 (73)	1863 (47)	423 (76)	<0.001	92 (1.4)
Elective procedure	4655 (75)	912 (67)	243 (75)	3010 (75)	490 (87)	<0.001	0 (0.0)
Number of treated vessels	2.0±1.2	1.6±0.8	3.0±1.6	1.8±1.1	2.8±1.4	<0.001	1039 (15.9)
Intravascular ultrasound	1984 (38)	505 (39)	…	1479 (38)	…	0.710	197 (3.7)
Mean LMCA stent diameter, mm*	3.6±0.4	3.5±0.3	…	3.6±0.4	…	0.010	
Total stent length, mm*	26±19	26±20	…	23±17	…	<0.001	
Max balloon diameter, mm*	3.9±0.5	3.8±0.5	…	3.9±0.5	…	<0.001	

Values are expressed as n (%) or mean±SD as appropriate. *P* values refer to female vs male comparison. CABG indicates coronary artery bypass surgery; LMCA, left main coronary artery; and PCI, percutaneous coronary intervention.

*Reported only in the DELTA 2 registry.

multivariate binary regression analysis including all variables with *P* values <0.05 in univariate analysis and using a rule of 1:10 covariates per number of events to avoid overfitting. Predictors for end point events were estimated using multivariate Cox regression analysis including all variables with *P* values <0.05 in univariate analysis and using a rule of 1:10 covariates per number of events to avoid overfitting. Proportionality assumptions for the variables included in the Cox models was tested by evaluating each variable interaction with time. Interaction testing was performed between sex and revascularization strategy for in-hospital and long-term outcomes. Multivariate interaction testing was performed adjusting for the same variables included in the multivariate Cox regression model for each end point (a full list of the covariates used in each multivariable model is provided in the footnote of figure legends and in Data S1). A 30-day landmark analysis using a multivariate Cox regression model and multivariate interaction was performed as sensitivity analysis, in order to control for relevant in-hospital events; all patients alive at 30 days were included in the analysis. A 2-sided *P* value of 0.05 or less was considered to indicate statistical significance. All analyses were performed using IBM SPSS Statistics 20 (IBM, Armonk, NY) or R v3.1.2.

Table 3. Clinical Outcomes According to Sex and Treatment

	Women			Men			
	PCI (1365)	CABG (324)	*P* value	PCI (4002)	CABG (562)	*P* value	P_{int}
In hospital							
Death/MI/CVA	108 (7.9)	70 (21.6)	<0.001	224 (5.6)	163 (29)	<0.001	<0.001
Death	33 (2.4)	7 (2.2)	0.110	58 (1.4)	9 (1.6)	0.084	0.250
MACCE	109 (8)	73 (22.6)	<0.001	228 (5.7)	187 (33.3)	<0.001	<0.001
MI	72 (5.3)	60 (18.5)	<0.001	164 (4.1)	154 (27.4)	<0.001	<0.001
CVA	7 (0.5)	5 (1.5)	0.044	4 (0.1)	7 (1.2)	<0.001	0.005
Long-term							
Death/MI/CVA	209 (15.3)	31 (9.5)	0.023	500 (12.5)	98 (17.5)	0.120	0.010
Death MI	192 (14.1)	22 (6.8)	0.003	484 (12.1)	84 (14.9)	0.989	0.007
Death	160 (11.7)	18 (5.6)	0.010	408 (10.2)	65 (11.6)	0.494	0.039
MACCE	371 (27.2)	42 (13)	<0.001	1002 (25)	113 (20.1)	<0.001	0.107
Target lesion revascularization	132 (9.7)	11 (3.4)	<0.001	362 (9)	22 (3.9)	<0.001	0.898
Target vessel revascularization	201 (14.7)	15 (4.6)	<0.001	589 (14.7)	25 (4.4)	<0.001	0.532

Results are presented as absolute number (percentage). Reported *P* are *P* for adjusted odds ratio (in hospital outcomes) or adjusted hazard ratio (long term outcomes). The last column reports the *P* for the interaction term.

CABG indicates coronary artery bypass graft; CVA, cerebrovascular accident; MACCE, major adverse cardio-cerebrovascular event; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

RESULTS

Study Population

The total, pooled population of the DELTA and DELTA 2 registries consisted of 6253 subjects undergoing coronary revascularization for ULMCA disease. Among these, 5367 (86%) were treated by PCI and 886 (14%) underwent CABG surgery. Women were 1689, representing 27% of the total population. Overall, women were older than men and had a higher prevalence of hypertension, dyslipidemia, diabetes, and chronic kidney disease. Women were also more likely to present with acute coronary syndromes and to receive more surgical revascularization than men. Table 1 summarizes baseline clinical characteristics of the population, and Table 2 procedural characteristics.

In-Hospital Outcomes

In hospital combined end point of death, periprocedural MI, and CVA occurred in 6.1% of patients in the PCI group and 26.3% of patients in the CABG group (adjusted odds ratio [AOR] 4.33; 95% CI, 3.95–4.71; *P*<0.001). In-hospital combined end point of death, MI, and CVA occurred in 5.6% of men undergoing PCI, 29% of men treated with CABG (AOR, 5.49; 95% CI, 4.93–6.10; *P*<0.001), 7.9% of women undergoing PCI, and 21.6% of women treated with CABG (AOR, 2.67; 95% CI, 2.03–3.11; *P*<0.001, *P* for interaction=0.001). In-hospital death occurred in 1.8% of patients in the CABG group and in 1.7% of the PCI group (AOR, 1.57; 95% CI, 0.68–2.16; *P*=0.52). The risk of in-hospital mortality was consistent across sexes (*P* for interaction=0.25). In-hospital MI occurred in 4.4% of patients undergoing PCI and 24.2% of patients undergoing CABG (AOR, 5.00; 95% CI, 3.99–6.25; *P*<0.001). Periprocedural MI occurred in 4.1% of men undergoing PCI, 27.4% of men undergoing CABG (AOR, 6.29; 95% CI, 5.61–7.04; *P*<0.001), 5.3% of women treated with PCI, and 18.5% of women treated with CABG (AOR, 3.05; 95% CI, 2.58–3.60; *P*<0.001, *P* for interaction<0.001). In-hospital CVA in 0.4% of men undergoing PCI, 1.5% of men undergoing CABG (AOR, 2.54; 95% CI, 1.56–4.16; *P*<0.001), 0.1% of women treated with PCI, and 1.2% of women treated with CABG (AOR, 3.67; 95% CI, 2.08–6.46; *P*<0.001, *P* for interaction=0.005). Patients undergoing CABG had higher rates of in-hospital MACCE (29.4% versus 6.3%; AOR, 5.16; 95% CI, 4.73–5.63; *P*<0.001). In-hospital MACCE occurred in 5.7% of men undergoing PCI, 33.3% of

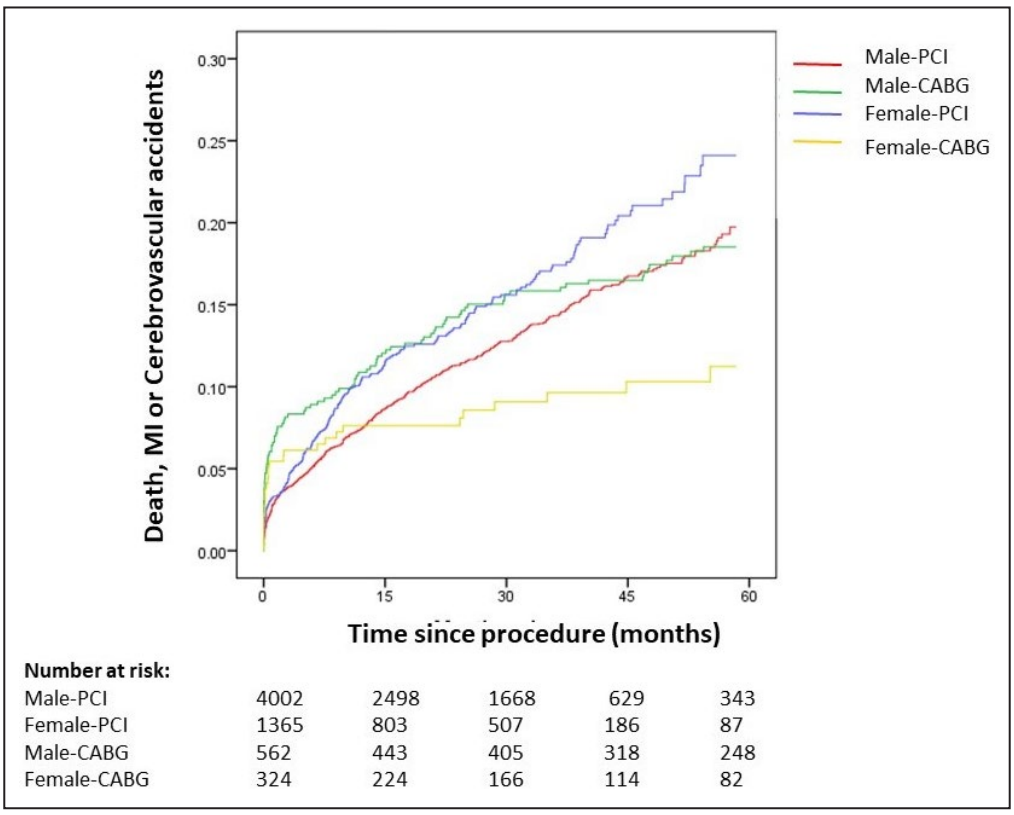


Figure 1. Time to first event curves for the primary composite outcome of death, myocardial infarction, or cerebrovascular accident according to sex and revascularization strategy.
CABG indicates coronary artery bypass grafting surgery; CVA, cerebrovascular accident; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

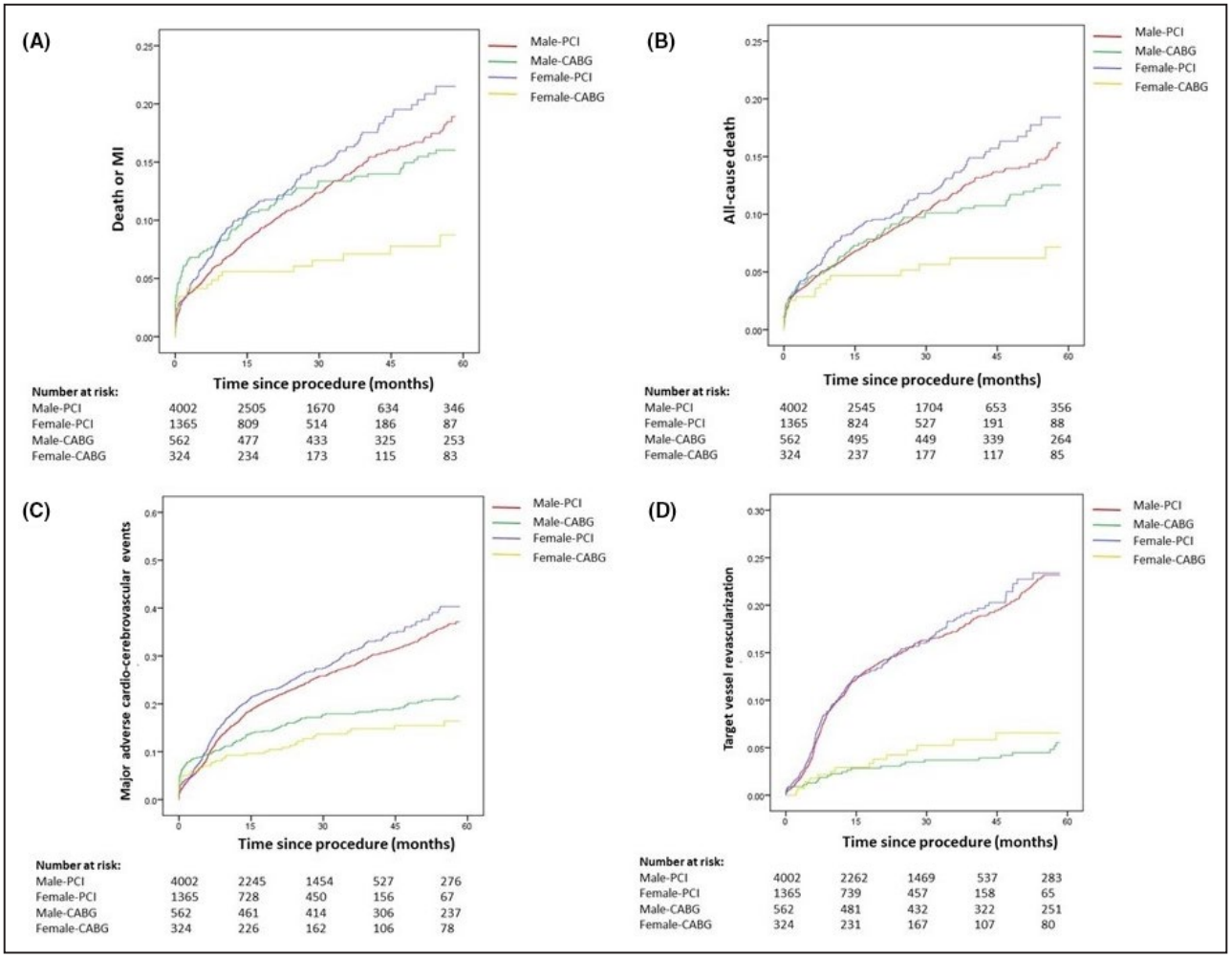


Figure 2. Time to first event curves for the composite of death and myocardial infarction (A), all-cause death (B), major adverse cardio-cerebrovascular events (C), and target vessel revascularization (D) according to sex and revascularization strategy.

CABG indicates coronary artery bypass grafting surgery; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

men treated with CABG (AOR, 6.77; 95% CI, 6.11–7.50), 8% of women treated with PCI, and 22.6% of women treated with CABG (AOR, 2.91; 95% CI, 2.51–3.37, *P* for interaction <0.001). Table 3 summarizes these results.

Long-Term Outcomes

At a median follow-up time of 29 months (interquartile range 12–49 months), the primary composite outcome of all-cause death, MI, or CVA occurred in 14.4% of patients in the CABG group versus 13.3% of patients in the PCI group (adjusted hazard ratio [AHR], 0.96; 95% CI, 0.78–1.18; *P*=0.74). The risk of all-cause death, MI, or CVA at follow-up among women was lower with CABG than with PCI (AHR, 0.66; 95% CI, 0.45–0.98; *P*=0.042), whereas in men the risk was comparable across different revascularization strategies (AHR, 1.18; 95% CI, 0.94–1.49; *P*=0.161, *P* for interaction 0.012). CABG was associated with lower risk of death or MI compared with PCI among women (6.8% versus 14.1%; AHR, 0.53; 95% CI, 0.34–0.83; *P*=0.005) whereas there were no significant differences between CABG and PCI among men (14.9% versus 12.1%; AHR, 1.07; 95% CI, 0.90–1.27; *P*=0.841; *P* for interaction 0.008).

Overall, the rates of all-cause death were 9.4% in the CABG group and 10.6% in the PCI group (AHR, 0.76; 95% CI, 0.59–0.97; *P*=0.028). Death occurred in 5.6% of women who underwent CABG versus 11.7% of women who underwent PCI (AHR, 0.55; 95% CI, 0.33–0.90; *P*=0.018) compared with 11.6% of men treated with CABG versus 10.2% of men treated with PCI (AHR, 1.05; 95% CI, 0.87–1.27; *P*=0.611; *P* for interaction 0.037). CABG was overall associated with lower risk of TVR (4.5% versus 14.7%; AHR, 0.24; 95% CI, 0.17–0.33; *P*<0.001) and TLR (3.7% versus 9.2%; AHR, 0.37; 95% CI, 0.26–0.53; *P*<0.001). The risk of both TVR and TLR was lower with CABG compared with PCI, consistently among men and women (*P* for

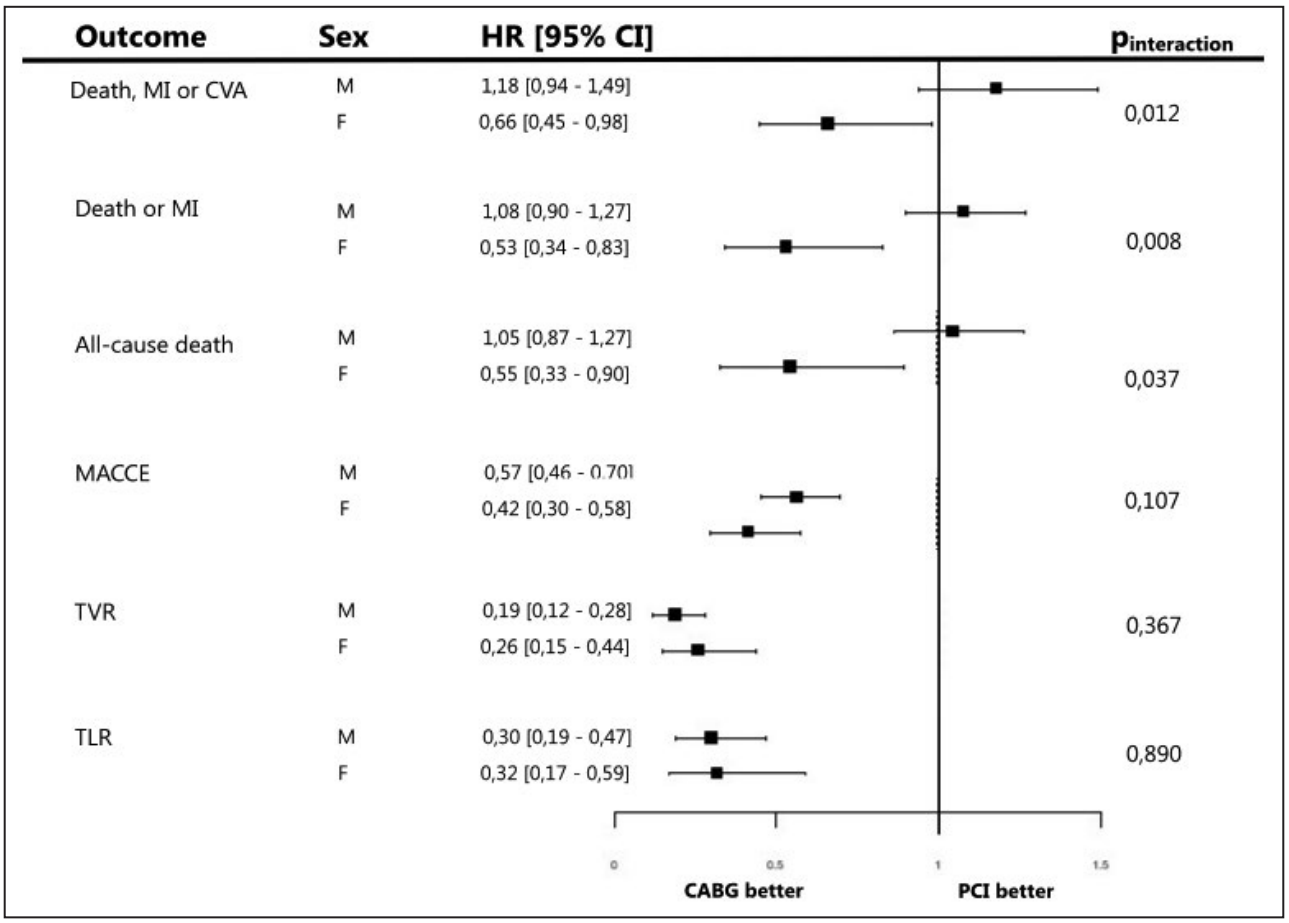


Figure 3. Adjusted hazard ratio forest plots displaying the interaction between sex and revascularization strategy in the entire DELTA registries population.

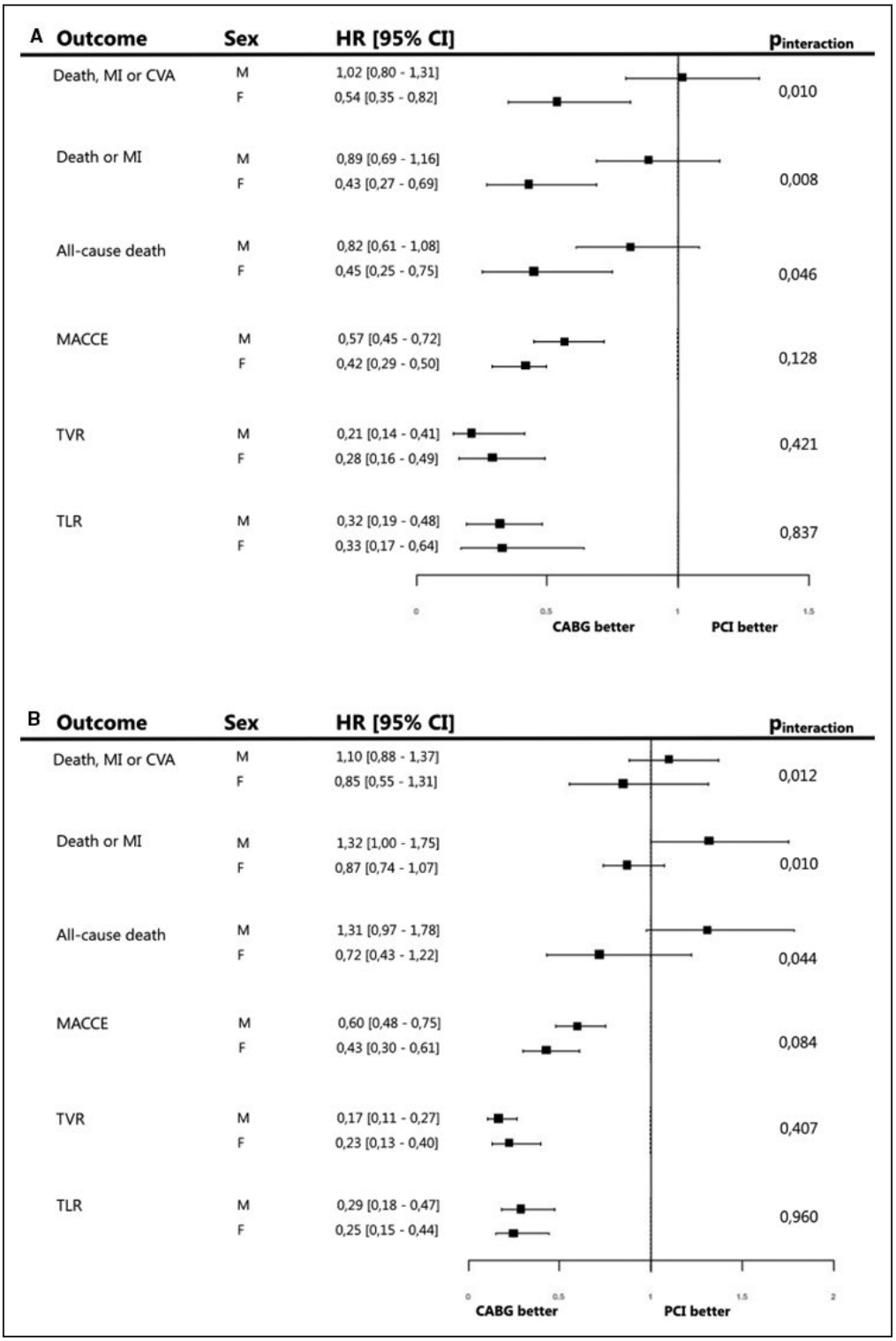
Variables included in the model for primary end point were age, hypertension, dyslipidemia, diabetes, chronic kidney disease, acute coronary syndromes, LVEF, elective procedure, sex, and CABG. For the composite of death and MI: age, dyslipidemia, diabetes, chronic kidney disease, acute coronary syndromes, previous revascularization, LVEF, elective procedure, CABG, and sex. For all-cause death: age, diabetes, chronic kidney disease, acute coronary syndrome, elective procedure, LVEF, CABG, and sex. For MACCE: age, hypertension, smoking status, diabetes, chronic kidney disease, acute coronary syndromes, LVEF, LMCA bifurcation, multivessel disease, elective procedure, number of treated vessels, CABG, and sex. For TVR: hypertension, dyslipidemia, diabetes, chronic kidney disease, previous revascularization, LMCA bifurcation, multivessel disease, number of treated vessels, CABG, and sex. For TLR: hypertension, diabetes, chronic kidney disease, previous revascularization, LMCA bifurcation, multivessel disease, LVEF, CABG, and sex. CABG indicates coronary artery bypass grafting surgery; CVA, cerebrovascular accident; DELTA, Drug-Eluting Stents for Left Main Coronary Artery Disease; F, female sex; HR, hazard ratio; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction; M, male sex; MACCE, major adverse cardio-cerebrovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; TLR, target lesion revascularization; and TVR, target vessel revascularization.

interaction 0.375 for TVR and 0.890 for TLR, respectively). Figures 1–3 and Table 3 summarize these findings.

A sensitivity analysis including the registries as covariates was run to take into account for the internal variability of the data set as well as for different DES generations, which yielded consistent results (Table S1). These results were also consistent in the subgroup of patients treated with first-generation DES (Table S2 and Figure 4A). When the analysis was restricted to patients receiving new-generation DES in the PCI arm, no significant differences in terms of primary end point, death, or MI and all-cause death could be identified between PCI and CABG in both women and men, in the face of a significant interaction between sex and revascularization strategy (Table S3 and Figure 4B).

A sensitivity analysis excluding patients who had a history of prior CABG was also performed, and the results were in line with the main analysis comprising the entire population (Table S4).

The prespecified 30-day landmark analysis confirmed the association between CABG and lower risk of all-cause death, MI, or CVA (AHR, 0.65; 95% CI, 0.51–0.85; *P*=0.001); all-cause death or MI (AHR, 0.77; 95% CI, 0.61–0.97; *P*=0.039); and all-cause death



(AHR, 0.72; 95% CI, 0.55–0.98; *P*=0.019). Significant interaction with sex was evident for all 3 outcomes, with women having a larger benefit from CABG when compared with men (*P* for interaction 0.003, 0.015, and 0.010, respectively). CABG was also associated with lower rates of MACCE, TVR, and TLR at the prespecified 30-day landmark analysis, and the effect was consistent between men and women (*P* for interaction 0.138, 0.181, and 0.534 respectively). Table S5 and Figures S1 and S2 report the landmark analysis.

Figure 4. Adjusted hazard ratio forest plots displaying the interaction between sex and revascularization strategy.
(**A**) Shows the HR of surgical vs percutaneous revascularization including only subjects who received a first-generation drug eluting stent (DES) in the percutaneous coronary intervention (PCI) arm. On the other hand (**B**) shows HR including only new-generation DES in the PCI arm. For what concerns first-generation DES, variables included in the multivariate model were as follows. Variables included in the model for primary end point were age, chronic kidney disease, acute coronary syndromes, LVEF, elective procedure, sex, and CABG. For the composite of death and MI: age, chronic kidney disease, acute coronary syndromes, previous revascularization, LVEF, elective procedure, CABG, and sex. For all-cause death: age, chronic kidney disease, acute coronary syndrome, elective procedure, LVEF, CABG, and sex. For MACCE: age, chronic kidney disease, acute coronary syndromes, LVEF, LMCA bifurcation, elective procedure, CABG, and sex. For TVR and TLR: LMCA bifurcation, multivessel disease, CABG, and sex. For new-generation DES on the other hand: Variables included in the model for primary end point were age, hypertension, dyslipidemia, diabetes, chronic kidney disease, acute coronary syndromes, previous revascularization, LVEF, elective procedure, number of treated vessels, sex, and CABG. For the composite of death and MI: age, hypertension, dyslipidemia, diabetes, chronic kidney disease, acute coronary syndromes, previous revascularization, LVEF, elective procedure, sex, and CABG. For all-cause death: age, hypertension, dyslipidemia, diabetes, chronic kidney disease, acute coronary syndrome, previous revascularization, elective procedure, LVEF, CABG, and sex. For MACCE: age, hypertension, smoking status, diabetes, chronic kidney disease, acute coronary syndromes, previous revascularization, LVEF, LMCA bifurcation, multivessel disease, number of treated vessels, elective procedure, CABG, and sex. For TVR: hypertension, smoking status, diabetes, chronic kidney disease, acute coronary syndromes, previous revascularization, LMCA bifurcation, multivessel disease, number of treated vessels, CABG, and sex; TLR: hypertension, smoking status, diabetes, chronic kidney disease, LMCA bifurcation, number of treated vessels, CABG, and sex. CVA indicates cerebrovascular accident; HR, hazard ratio; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction; MACCE, major adverse cardio-cerebrovascular event; MI, myocardial infarction; TLS, target lesion revascularization; and TVR, target vessel revascularization.

DISCUSSION

The main findings of our study are as follows: (1) women with ULMCA lesions undergoing revascularization tend to be older and to have a greater prevalence of comorbidities compared with men; (2) although overall there were no significant differences in outcomes between CABG and PCI at long-term follow-up, CABG appeared to be associated with significantly lower rates of death, MI, or CVA among women but not among men; (3) CABG was associated with significantly lower rates of TVR and TLR compared with PCI, irrespective of sex; and (4) new-generation DES appear to have comparable results as CABG in both women and man.

Recent evidence has shown that in selected patients with ULMCA and low to intermediate anatomical complexity PCI and CABG have comparable midterm results.[3,4] The clinical decision-making between the 2 revascularization strategies therefore relies on the individual assessment of each patient comorbidity profile, anatomical complexity, and a shared discussion among a multidisciplinary heart team.[17] Sex-specific differences in outcomes have been extensively described among patients with cardiovascular disease. However, whether sex should play a role in informing clinical decision-making between revascularization strategies in patients with ULMCA lesions is unknown. In the landmark SYNTAX trial, 1800 subjects with multivessel disease, including approximately one third with ULMCA involvement, were randomized to receive either CABG or PCI.[12] Women were shown to have a higher mortality risk at 4 years when compared with men in the PCI arm (HR, 1.70; 95% CI, 1.11–2.70) but not in the CABG arm (HR, 0.59; 95% CI, 0.32–1.10), with a significant interaction effect between sex and revascularization strategy.[18] Subsequently reported 10-year data, however, showed a nonsignificant trend for better outcomes in both men and women treated with CABG, and significant interaction between sex and revascularization strategy could no longer be detected.[19] In light of such results, sex has been eliminated as a component of the SYNTAX II score, a risk score meant to aid in the decision between CABG and PCI for coronary revascularization.[20] A subanalysis of the PRECOMBAT trial, 600 subjects with 141 women, did not show a significant interaction between revascularization strategies (P_{int}=0.469).[13] Noteworthy, the trial was conducted in Asia, and therefore a different sex interaction effect in Asian population has been postulated.[13] Finally, in the EXCEL trial 1800 patients, 23% women, were randomized to receive either PCI or CABG for ULMCA disease.[14] Women had a higher overall risk factor burden and suffered from more periprocedural bleeding and ischemic complication in the PCI arm, which led to higher unadjusted rates of adverse events as compared with men.[14] Although sex was not significantly associated with the primary composite end point of death, MI, or stroke, a significant interaction between sex and revascularization strategy was detected at 30 days but not at 3 years.[14]

In the DELTA registries, compared with CABG, PCI was associated with both worse in-hospital and long-term outcomes among women, whereas no significant differences between PCI and CABG were observed among men. Consistently with the EXCEL trial, women displayed a higher risk profile and greater comorbidity burden. In the present study, however, the protective effect of surgical revascularization remained significant even on multivariate analysis. The interaction between sex and revascularization strategy remained consistent across the DES-generation subgroup, suggesting a persistent advantage of CABG over PCI irrespective of the DES generation

used. However, the effect of CABG versus PCI in the subgroup of patients who received a new-generation DES appeared to be attenuated in women. It is possible that the reduction of power inherent in the subgroup analysis may have increased the probability of type 2 error, therefore the chance of missing a beneficial effect of CABG over PCI in women treated with new-generation DES. However, the benefits of using new-generation DES has been established in both women and men[21] and different stent technology may account, at least partially, for the different results observed in the SYNTAX and EXCEL trials and potentially for the difference in terms of results between the DELTA registries and the EXCEL trial.

Limitations

The DELTA registries include a large, international population of all-comers patients treated for ULMCA disease over a wide time span. Intrinsically to their registry design, a significant risk of bias cannot be eliminated. Indeed, women were more likely to be treated with CABG, indicating operator bias, which could have introduced an imbalance in baseline characteristics leading to a difference with respect to previous trials. In addition, the overall number of women undergoing CABG was somewhat exiguous with respect to the full population, comprising only 324 subjects, which could have introduced further bias. Furthermore, CABG and PCI groups may not be fully comparable: younger subjects with a lower burden of comorbidities could potentially be more likely to undergo CABG. This fact could in part explain CABG better outcomes. Moreover, there are relevant data that could not be retrieved from the overall databases. Patients' overall operative risk may not have been adequately assessed given the lack of data on validated risk scores, including the EuroSCORE or the Society of Thoracic Surgeons Score. Among these, most notably detailed information about preprocedural and postprocedural SYNTAX scores. Indeed, in the SYNTAX trials complete revascularization was achieved in similar proportions in men and women, whereas in the EXCEL trial women were more likely than men to undergo complete revascularization, which may account in part for the difference in results between these trials.[13,14] Finally, there was a substantial lack of data on optimal medical treatment at follow-up. Given the fact that it has been shown that women are less likely to receive guideline-directed optimal medical therapy, an imbalance in terms of treatment cannot be excluded as a factor influencing the observed higher rates of adverse events in women.[22] Furthermore, it should be acknowledged that post-PCI treatment, including optimization of dual antiplatelet regimens, has been subject to intense investigation and improved antiplatelet management may account for improved outcomes in the EXCEL Trial.[14]

CONCLUSIONS

In this large, all-comers international multicenter registry of patients undergoing coronary revascularization for ULMCA disease, women had a higher risk profile and comorbidity burden compared with men. PCI had worse outcomes compared with CABG among women but not among men, with a significant interaction between sex and revascularization strategy. Further studies addressing sex-specific differences in the risks and benefits of each revascularization strategies are warranted.

APPENDIX

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Supplemental Material

Data S1
Tables S1–S5
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Data S1. Supplementary Statistical Appendix

Covariates included in the multivariate binary logistic regression models to identify predictors for in hospital events:

1. **In-hospital composite of death, myocardial infarction and cerebrovascular events:** sex, hypertension, dyslipidemia, smoking status, diabetes, chronic kidney disease (CKD), previous revascularization, left ventricular ejection fraction (LVEF), left main coronary artery (LMCA) bifurcation, multivessel disease, elective vs urgent procedure, number of vessels treated.

	OR (95% CI)	p value
Age	0.99 (0.99-1.00)	0.249
Sex (F)	1.27 (1.18-1.37)	<0.001
Hypertension	0.84 (0.77-0.91)	<0.001
Dyslipidemia	0.76 (0.72-0.83)	<0.001
Smokers	1.22 (1.14-1.31)	<0.001
Diabetes	1.09 (1.01-1.18)	<0.001
Chronic kidney disease	0.69 (0.63-0.76)	<0.001
Acute coronary syndromes	0.91 (0.83-1.1)	0.061
Previous revascularization	0.55 (0.51-0.59)	<0.001
LVEF	0.99 (0.98-0.99)	<0.001
LMCA bifurcation	0.90 (0.83-0.98)	0.011
Multivessel disease	2.18 (1.95-2.46)	<0.001
Elective procedure	0.78 (0.72-0.84)	<0.001
Number of treated vessel	1.64 (1.57-1.72)	<0.001
CABG	5.43 (5.03-5.87)	<0.001

2. **In-hospital all-cause death:** age, sex, hypertension, dyslipidemia, smoking status, CKD, acute coronary syndrome (ACS) on presentation, previous revascularization, LVEF, elective vs urgent procedure.

	OR (95% CI)	p value
Age	1.05 (1.04-1.06)	<0.001
Sex (F)	1.63 (1.39-1.91)	<0.001
Hypertension	1.30 (1.08-1.57)	0.005
Dyslipidemia	0.53 (0.45-0.62)	<0.001
Smokers	0.83 (0.71-0,97)	0.026
Diabetes	1.10 (0.93-1.39)	0.248
Chronic kidney disease	1.86 (1.57-2.20)	<0.001
Acute coronary syndromes	6.22 (5.31-7.29)	<0.001
Previous revascularization	0.60 (0.51-0.72)	<0.001
LVEF	0.93 (0.92-0.94)	<0.001
LMCA bifurcation	0.90 (0.76-1.07)	0.259
Multivessel disease	1.14 (0.94-1.39)	0.183
Elective procedure	0.15 (0.13-0.18)	<0.001

Number of treated vessel	1.06 (0.95-1.17)	0.291
CABG	1.07 (0.86-1.33)	0.566

3. **In-hospital myocardial infarction:** age, sex, hypertension, dyslipidemia, smoking status, diabetes, CKD, ACS on presentation, previous revascularization, LVEF, multivessel disease, elective procedure, number of vessels treated

	OR (95% CI)	p value
Age	0.99 (0.98-0.99)	<0.001
Sex (F)	1.12 (1.03-1.23)	0.008
Hypertension	0.80 (0.74-0.88)	<0.001
Dyslipidemia	0.87 (0.81-0.95)	0.002
Smokers	1.35 (1.25-1.47)	<0.001
Diabetes	1.14 (1.04-1.23)	0.003
Chronic kidney disease	0.53 (0.47-0.59)	<0.001
Acute coronary syndromes	0.42 (0.36-0.48)	<0.001
Previous revascularization	0.60 (0.55-0.65)	<0.001
LVEF	1.01 (1.00-1.01)	0.007
LMCA bifurcation	0.95 (0.86-1.03)	0.228
Multivessel disease	2.86 (2.59-3.27)	<0.001
Elective procedure	1.21 (1.10-1.33)	<0.001
Number of treated vessel	1.75 (1.66-1.84)	<0.001
CABG	6.86 (6.32-7.45)	<0.001

4. **In-hospital cerebrovascular event:** sex, hypertension, diabetes, CKD, previous revascularization, left main coronary artery (LMCA) bifurcation treatment, elective procedure.

	OR (95% CI)	p value
Age	1.01 (0.99-1.23)	0.212
Sex (F)	2.48 (1.77-3.47)	<0.001
Hypertension	7.98 (3.52-18.10)	<0.001
Dyslipidemia	0.88 (0.62-1.25)	0.469
Smokers	0.81 (0.57-1.51)	0.240
Diabetes	2.05 (1.46-2.86)	<0.001
Chronic kidney disease	1.71 (1.19-2.46)	0.004
Acute coronary syndromes	0.98 (0.63-1.52)	0.927
Previous revascularization	0.44 (0.29-0.67)	<0.001
LVEF	0.99 (0.98-1.01)	0.854
LMCA bifurcation	0.36 (0.26-0.51)	<0.001
Multivessel disease	1.75 (1.06-2.87)	0.028
Elective procedure	0.45 (0.32-0.63)	<0.001
Number of treated vessel	1.45 (1.17-1.79)	0.001
CABG	6.43 (4.59-8.99)	<0.001

5. **In-hospital major adverse cardio- cerebro-vascular events (MACCE):** sex, hypertension, diabetes, CKD, LVEF, multivessel disease, elective procedure, previous revascularization, LVEF, number of treated vessels.

	OR (95% CI)	p value
Age	0.99 (0.99-1.00)	0.572
Sex (F)	1.21 (1.12-1.30)	<0.001
Hypertension	0.85 (0.78-0.91)	<0.001
Dyslipidemia	0.88 (0.62-1.25)	0.469
Smokers	0.81 (0.57-1.51)	0.240
Diabetes	0.74 (0.69-0.79)	<0.001
Chronic kidney disease	0.65 (0.59-0.71)	<0.001
Acute coronary syndromes	0.94 (0.86-1.04)	0.249
Previous revascularization	0.54 (0.49-0.58)	<0.001
LVEF	0.99 (0.98-0.99)	<0.001
LMCA bifurcation	0.95 (0.87-1.02)	0.158
Multivessel disease	2.01 (1.81-2.23)	<0.001
Elective procedure	0.83 (0.76-0.91)	<0.001
Number of treated vessel	1.66 (1.58-1.73)	<0.001
CABG	6.18 (5.73-6.65)	<0.001

Covariates included in the multivariate Cox regression models to identify predictors for events on follow up:

1. **Composite of all-cause death, myocardial infarction and cerebrovascular accidents:** age, hypertension, dyslipidemia, diabetes, CKD, ACS on presentation, LVEF, previous revascularization, elective vs urgent procedure, sex.

Univariate analysis for primary endpoint

Variable	HR (95% CI)	p value
Age	1.04 (1.03-1.05)	<0.001
Sex (F)	1.13 (0.97-1.32)	0.106
Hypertension	1.18 (1.01-1.38)	0.032
Dyslipidemia	0.86 (0.75-0.99)	0.037
Smokers	0.92 (0.81-1.06)	0.264
Diabetes	1.42 (1.24-1.63)	<0.001
Chronic kidney disease	2.09 (1.80-2.43)	<0.001
Acute coronary syndromes	2.46 (2.13-2.86)	<0.001
Previous revascularization	0.86 (0.74-0.98)	0.034
LVEF	0.96 (0.95-0.96)	<0.001
LMT bifurcation	0.99 (0.85-1.16)	0.897

Multivessel disease	1.12 (0.94-1.33)	0.225
Elective procedure	0.48 (0.41-0.55)	<0.001
Number of treated vessel	1.05 (0.96-1.15)	0.280
CABG	0.86 (0.71-1.04)	0.125

Time-variable interaction (testing proportional hazard assumption)

Variable	p-value
Age	0.126
Sex	0.661
Hypertension	0.409
Dyslipidemia	0.083
Diabetes	0.607
CKD	0.825
ACS	0.052
LVEF	0.118
Previous revascularization	0.150
Elective procedure	0.063
CABG	0.932

2. **Composite of all-cause death and myocardial infarction:** age, dyslipidemia, diabetes, CKD, ACS on presentation, previous revascularization, LVEF, elective vs urgent procedure, sex.

Univariate for death or MI

Variable	HR (95% CI)	p value
Age	1.04 (1.03-1.05)	<0.001
Sex (F)	1.07 (0.92-1.25)	0.386
Hypertension	1.12 (0.96-1.32)	0.148
Dyslipidemia	0.85 (0.73-0.98)	0.027
Smokers	0.95 (0.82-1.09)	0.487
Diabetes	1.44 (1.25-1.66)	<0.001
Chronic kidney disease	2.15 (1.84-2.51)	<0.001
Acute coronary syndromes	2.55 (2.19-2.96)	<0.001
Previous revascularization	0.85 (0.73-0.99)	0.036
LVEF	0.95 (0.95-0.96)	<0.001
LMT bifurcation	1.05 (0.89-1.24)	0.545
Multivessel disease	1.08 (0.91-1.29)	0.385
Elective procedure	0.47 (0.40-0.54)	<0.001
Number of treated vessel	1.04 (0.95-1.14)	0.413
CABG	0.75 (0.61-0.92)	0.006

Time-variable interaction (testing proportional hazard assumption)

Variable	p-value
Age	0.111
Sex	0.569

Dyslipidemia	0.103
Diabetes	0.460
CKD	0.897
ACS	0.054
LVEF	0.111
Previous revascularization	0.097
Elective procedure	0.068
CABG	0.934

3. **All-cause death:** age, diabetes, CKD, ACS on presentation, elective vs urgent procedure, LVEF, sex.

Univariate analysis for all cause death

Variable	HR (95% CI)	p value
Age	1.05 (1.04-1.06)	<0.001
Sex (F)	1.07 (0.90-1.27)	0.438
Hypertension	1.12 (0.94-1.33)	0.191
Dyslipidemia	0.81 (0.69-0.95)	0.008
Smokers	0.95 (0.81-1.11)	0.514
Diabetes	1.39 (1.19-1.64)	<0.001
Chronic kidney disease	2.45 (2.07-2.89)	<0.001
Acute coronary syndromes	2.44 (2.08-2.85)	<0.001
Previous revascularization	0.79 (0.67-0.94)	0.007
LVEF	0.95 (0.94-0.96)	<0.001
LMT bifurcation	1.04 (0.87-1.25)	0.631
Multivessel disease	1.11 (0.91-1.35)	0.324
Elective procedure	0.47 (0.40-0.55)	<0.001
Number of treated vessel	1.04 (0.95-1.14)	0.413
CABG	0.68 (0.54-0.86)	0.001

Time-variable interaction (testing proportional hazard assumption)

Variable	p-value
Age	0.093
Sex	0.541
Diabetes	0.888
CKD	0.608
ACS	0.051
LVEF	0.060
Elective procedure	0.067
CABG	0.240

4. **MACCE:** age, hypertension, smoking status, diabetes, CKD, ACS on presentation, LVEF, LMCA bifurcation, multivessel disease, elective vs urgent procedure, number of treated vessels, sex.

Univariate HR for MACCE

Variable	HR (95% CI)	p value
Age	1.02 (1.01-1.02)	<0.001
Sex (F)	1.05 (0.94-1.18)	0.367
Hypertension	1.21 (1.08-1.35)	0.001
Dyslipidemia	1.01 (0.91-1.13)	0.803
Smokers	0.89 (0.80-1.00)	0.032
Diabetes	1.45 (1.31-1.61)	<0.001
Chronic kidney disease	1.71 (1.52-1.92)	<0.001
Acute coronary syndromes	1.38 (1.22-1.57)	<0.001
Previous revascularization	1.09 (0.99-1.21)	0.092
LVEF	0.98 (0.97-0.98)	<0.001
LMT bifurcation	1.32 (1.17-1.49)	<0.001
Multivessel disease	1.28 (1.12-1.46)	<0.001
Elective procedure	0.67 (0.60-0.75)	<0.001
Number of treated vessel	1.13 (1.06-1.21)	0.001

Time-variable interaction (testing proportional hazard assumption)

Variable	p-value
Age	0.106
Sex	0.695
Hypertension	0.658
Smoking status	0.445
Diabetes	0.098
CKD	0.138
ACS	0.071
LVEF	0.330
LMCA bifurcation	0.543
Multivessel disease	0.058
Number of treated vessels	0.099
Elective procedure	0.061
CABG	0.055

5. **Target vessel revascularization:** hypertension, dyslipidemia, diabetes, CKD, previous revascularization, LMCA bifurcation, multivessel disease, number of treated vessels, sex.

Univariate analysis for TVR

Variable	HR (95% CI)	p value
Age	1.00 (0.99-1.01)	0.298
Sex (F)	0.99 (0.85.1.17)	0.989
Hypertension	1.23 (1.05-1.44)	0.009
Dyslipidemia	1.18 (1.02-1.37)	0.030
Smokers	0.88 (0.76-1.01)	0.070
Diabetes	1.51 (1.32-1.74)	<0.001
Chronic kidney disease	1.46 (1.24-1.73)	<0.001

Acute coronary syndromes	1.09 (0.93-1.28)	0.284
Previous revascularization	1.43 (1.24-1.64)	<0.001
LVEF	0.99 (0.98-1.00)	0.227
LMT bifurcation	1.83 (1.53-2.19)	<0.001
Multivessel disease	1.38 (1.14-1.66)	0.001
Elective procedure	0.99 (0.84-1.16)	0.866
Number of treated vessel	1.22 (1.12-1.33)	<0.001
CABG	0.22 (0.16.0.31)	<0.001

Time-variable interaction (testing proportional hazard assumption)

Variable	p-value
Sex	0.912
Hypertension	0.737
Dyslipidemia	0.545
Diabetes	0.073
CKD	0.127
Previous Revascularization	0.119
LMCA bifurcation	0.602
Multivessel disease	0.136
Number of treated vessels	0.064
CABG	0.849

6. **Target lesion revascularization:** hypertension, diabetes, CKD, previous revascularization, LMCA bifurcation, multivessel disease, number of treated vessels, sex.

Univariate analysis for TLR

Variable	HR (95% CI)	p value
Age	0.99 (0.98-1.00)	0.305
Sex (F)	1.06 (0.88-1.29)	0.548
Hypertension	1.32 (1.08-1.61)	0.007
Dyslipidemia	1.16 (0.96-1.39)	0.124
Smokers	0.89 (0.75-1.07)	0.209
Diabetes	1.55 (1.30-1.84)	<0.001
Chronic kidney disease	1.57 (1.28-1.93)	<0.001
Acute coronary syndromes	1.17 (0.96-1.43)	0.109
Previous revascularization	1.33 (1.12-1.58)	0.001
LVEF	0.99 (0.98-1.02)	0.093
LMT bifurcation	2.06 (1.63-2.60)	<0.001
Multivessel disease	1.26 (1.01-1.59)	0.044
Elective procedure	0.94 (0.77-1.15)	0.569
Number of treated vessel	1.23 (1.10-1.38)	<0.001
CABG	0.32 (0.22-0.45)	<0.001

Time-variable interaction (testing proportional hazard assumption)

Variable	p-value
Sex	0.714
Hypertension	0.278
Diabetes	0.151
CKD	0.077
Previous Revascularization	0.741
LMCA bifurcation	0.618
Multivessel disease	0.304
Number of treated vessels	0.186
CABG	0.678

Table S1. Sensitivity analysis including registry (DELTA vs DELTA 2) as covariates. Variables included each model conform to those reported in the Statistical Appendix. CVA, cerebrovascular accident; MACCE, major adverse cardio-cerebrovascular event; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

	Sex	**HR (95% CI)**	**p value**	**p int**
Death MI CVA	M	0.99 (0.78-1.26)	0.972	0.010
	F	0.55 (0.37-0.83)	0.004	
Death MI	M	0.87 (0.68-1.13)	0.305	0.007
	F	0.44 (0.28-0.69)	<0.001	
All-cause death	M	0.90 (0.76-1.30)	0.967	0.037
	F	0.55 (0.32-0.90)	0.018	
MACCE	M	0.54 (0.44-0.67)	<0.001	0.118
	F	0.40 (0.29-0.55)	<0.001	
TVR	M	0.23 (0.15-0.36)	<0.001	0.348
	F	0.29 (0.16-0.47)	<0.001	
TLR	M	0.29 (0.18-0.46)	<0.001	0.885
	F	0.31 (0.16-0.58)	<0.001	

Table S2. Adjusted Hazard ratios and interaction analysis of the primary and secondary outcomes, including only patients in whom first-generation drug-eluting stents were used in the percutaneous coronary intervention arm. Variables included each model conform to those reported in the Statistical Appendix. CVA, cerebrovascular accident; MACCE, major adverse cardio-cerebrovascular event; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

	Sex	HR (95% CI)	p value	p int
Death MI CVA	M	1.02 (0.80-1.31)	0.849	0.010
	F	0.54 (0.35-0.82)	0.004	
Death MI	M	0.89 (0.69-1.16)	0.418	0.008
	F	0.43 (0.27-0.69)	0.001	
All-cause death	M	0.82 (0.61-1.08)	0.178	0.046
	F	0.45 (0.25-0.75)	0.003	
MACCE	M	0.57 (0.45-0.72)	<0.001	0.128
	F	0.42 (0.29-0.59)	<0.001	
TVR	M	0.21 (0.14-0.41)	<0.001	0.421
	F	0.28 (0.16-0.49)	<0.001	
TLR	M	0.32 (0.19-0.48)	<0.001	0.837
	F	0.33 (0.17-0.64)	0.001	

Table S3. Adjusted multivariate Hazard ratios and interaction analysis of the primary and secondary outcomes, including only patients in whom new generation drug-eluting stents were used in the percutaneous coronary intervention arm. Variables included each model conform to those reported in the Statistical Appendix. CVA, cerebrovascular accident; MACCE, major adverse

cardio-cerebrovascular event; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

	Sex	HR (95% CI)	p value	p int
Death MI CVA	M	1.10 (0.88-1.37)	0.397	0.012
	F	0.85 (0.55-1.31)	0.465	
Death MI	M	1.32 (1.00-1.75)	0.048	0.010
	F	0.87 (0.74-1.07)	0.097	
All-cause death	M	1.31 (0.97-1.78)	0.077	0.044
	F	0.72 (0.43-1.22)	0.229	
MACCE	M	0.60 (0.48-0.75)	<0.001	0.084
	F	0.43 (0.30-0.61)	<0.001	
TVR	M	0.17 (0.11-0.27)	<0.001	0.407
	F	0.23 (0.13-0.40)	<0.001	
TLR	M	0.29 (0.18-0.47)	<0.001	0.960
	F	0.25 (0.15-0.44)	<0.001	

Table S4. Sensitivity analysis excluding patients with a history of previous coronary artery bypass surgery. Variables included each model conform to those reported in the Statistical Appendix. CVA, cerebrovascular accident; MACCE, major adverse cardio-cerebrovascular event; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

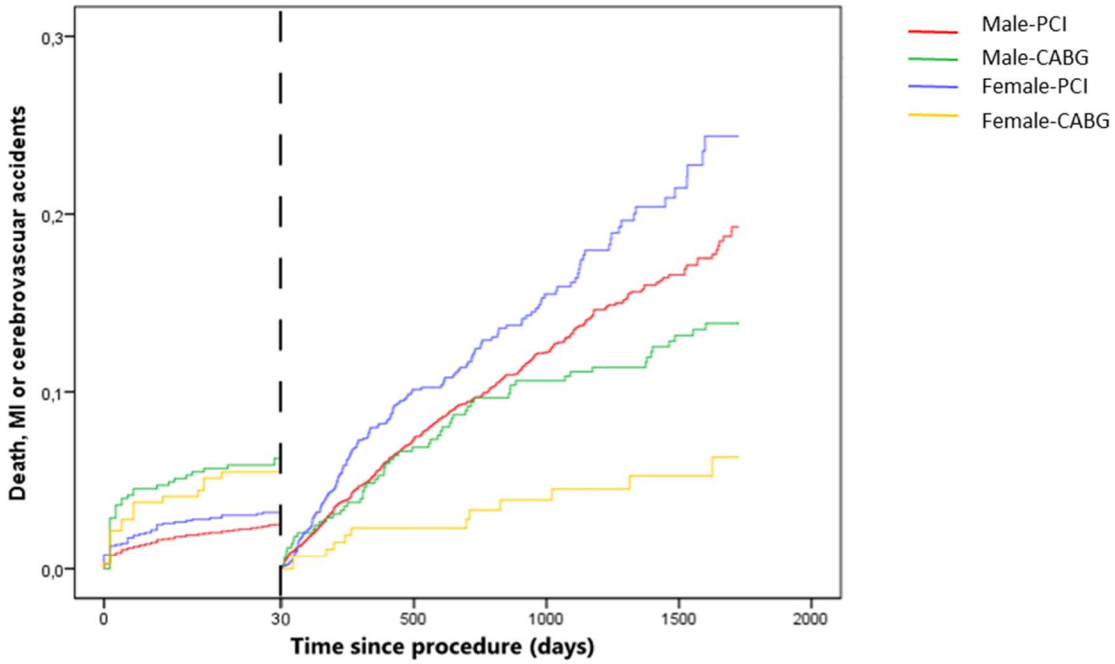
	Sex	HR (95% CI)	p value	p int
Death MI CVA	M	1.15 (0.90-1.45)	0.266	0.023
	F	0.67 (0.45-1.00)	0.054	
Death MI	M	1.00 (0.78-1.28)	0.994	0.015
	F	0.53 (0.33-0.84)	0.007	
All-cause death	M	0.94 (0.71-1.24)	0.670	0.055
	F	0.54 (0.32-0.89)	0.017	
MACCE	M	0.56 (0.46-0.69)	<0.001	0.078
	F	0.39 (0.28-0.55)	<0.001	
TVR	M	0.19 (0.13-0.29)	<0.001	0.657
	F	0.23 (0.13-0.40)	<0.001	
TLR	M	0.29 (0.18-0.49)	<0.001	0.671
	F	0.26 (0.13-0.52)	<0.001	

Table S5. Adjusted Hazard ratios and interaction analysis of the primary and secondary outcomes on 30-day landmark analysis. Variables included each model conform to those reported in the Statistical Appendix. CVA, cerebrovascular accident; MACCE, major adverse cardio-cerebrovascular event; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

	Sex	HR (95% CI)	p value	p int

Death MI CVA	M	0.83 (0.63-1.11)	0.215	0.003
	F	0.31 (0.17-0.56)	<0.001	
Death MI	M	0.93 (0.71-1.22)	0.613	0.015
	F	0.47 (0.29-0.76)	0.002	
All-cause death	M	0.89 (0.66-1.21)	0.465	0.010
	F	0.35 (0.18-0.68)	0.002	
MACCE	M	0.39 (0.31-0.51)	0.009	0.138
	F	0.28 (0.19-0.42)	<0.001	
TVR	M	0.19 (0.12-0.29)	<0.001	0.181
	F	0.30 (0.18-0.52)	<0.001	
TLR	M	0.43 (0.25-0.76)	0.004	0.534
	F	0.29 (0.17-0.48)	<0.001	

Figure S1. Time to first event curves for the landmark analysis for the primary endpoint, composite of all-cause death, myocardial infarction and cerebrovascular accidents. MI = myocardial infarction; CVA = cerebrovascular accident; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting surgery.



Number at risk:

Male-PCI	4002	3860	2498	1668	629	343
Female-PCI	1365	1307	803	507	186	87
Male-CABG	562	489	443	405	318	248
Female-CABG	324	280	224	166	114	82

Figure S2. Time to first event curves for the landmark analysis for the composite of death and myocardial infarction (Panel A), all-cause death (Panel B), major adverse cardio-cerebrovascular events (Panel C) and target vessel revascularization (Panel D) according to sex and revascularization strategy. MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting surgery.