Effect of Age and Sex on Outcomes After Stenting or Bypass Surgery in Left Main Coronary Artery Disease

Hanbit Park, MD[1], Jung-Min Ahn, MD[1], Yong-Hoon Yoon, MD, Osung Kwon, MD, Kyusup Lee, MD, Do-Yoon Kang, MD, Pil Hyung Lee, MD, Seung-Whan Lee, MD, Seong-Wook Park, MD, Duk-Woo Park, MD*, and Seung-Jung Park, MD, for the IRIS-MAIN Registry Investigators

Age and sex contribute to determining coronary revascularization strategies for patients with left main coronary artery (LMCA) disease. We examined age- and sex-related differences in comparative outcomes after percutaneous coronary intervention (PCI) or coronary-artery bypass grafting (CABG) for LMCA disease. A total of 4,001 patients with LMCA disease (men, n = 3,100, women, n = 901) who underwent PCI (n = 2,615) or CABG (n = 1,386) from the Interventional Research Incorporation Society-Left MAIN Revascularization registry were analyzed. Patients were stratified into subgroups according to the tertiles of age (<60 years, 60 to 69 years, and ≥70 years) and sex. The primary outcome was the composite of death from any cause, myocardial infarction, or stroke. During the median 6.3 years of follow-up, the adjusted risks for primary outcome after PCI relative to CABG were similar in patients aged <60 years (hazard ratio [HR]: 0.64, 95% confidence interval [CI]: 0.35 to 1.16), 60 to 69 years (HR: 1.21; 95% CI: 0.82 to 1.80), and ≥70 years (HR: 0.90; 95% CI: 0.66 to 1.22) with no significant age-related interactions ($P_{interaction}$ = 0.57). The primary outcome risks following PCI versus CABG were similar between male (HR: 0.92; 95% CI: 0.72 to 1.17) and female (HR: 0.89; 95% CI: 0.52 to 1.50) ($P_{interaction}$ = 0.65). Significant interactions were absent for age or sex and revascularization type for all-cause mortality ($P_{interaction}$ = 0.34 for age and $P_{interaction}$ = 0.99 for sex), repeat revascularization ($P_{interaction}$ = 0.10 for age and $P_{interaction}$ = 0.65 for sex), and major adverse cardiac or cerebrovascular events ($P_{interaction}$ = 0.29 for age and $P_{interaction}$ = 0.30 for sex). *In conclusion,* there were no significant age- or sex-related differences in comparative outcomes after PCI or CABG for LMCA disease. **(Am J Cardiol 2019;124:678−687)**

Left main coronary artery (LMCA) disease is one of the most complex anatomical lesion subsets and is associated with poorer clinical outcomes compared with non-LMCA disease.[1] With adoption of drug-eluting stents (DES), percutaneous coronary intervention (PCI) for complex LMCA disease has become technically feasible and several studies have shown comparable PCI outcomes to coronary-artery bypass grafting (CABG).[2−7] Recent randomized controlled trials and a patient-level meta-analysis demonstrated that PCI and CABG had comparable safety profiles in patients with LMCA stenosis and low-to-intermediate anatomic complexity.[8-10] The demographic factors age and sex are important considerations choosing PCI or CABG in daily clinical practice. Several studies showed conflicting results with regard to the impact of age and sex on clinical outcomes in patients with multivessel coronary artery disease (CAD).[11-13] However, it is still unknown whether there are age- or sex-related differences in the relative outcomes after PCI and CABG for LMCA disease. We therefore evaluated whether an interaction exists between age/sex factors and treatment with PCI compared with CABG for long-term outcomes in "real-world" patients with significant LMCA disease.

Methods

The study population was a part of the Interventional Research Incorporation Society-Left MAIN Revascularization (IRIS-MAIN) registry. Details on study design and enrollment characteristics have been published previously.[14,15] In brief, the IRIS-MAIN registry is physician-initiated, noncompany-sponsored, multinational, multicenter observational study enrolling consecutive patients with unprotected LMCA disease who were treated with PCI, CABG, or medical therapy alone between January 1995 and December 2015. Of a total of 4,501 patients enrolled in the registry, the present study consisted of 4,001 patients (3,100 men and 901 women) with significant LMCA disease who were treated with PCI or CABG (PCI, n = 2,615; CABG, n = 1,386; Figure 1 and Figure 2). The institutional review boards at participating centers approved the research protocol and written informed consents were obtained from all patients.

Selection of treatment strategy was at the discretion of the attending physician. Several clinical and angiographic factors and patients' preference were considered as possible

Department of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea. Manuscript received March 16, 2019; revised manuscript received and accepted May 16, 2019.

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[1]The first two authors (Drs. H. Park and J.M. Ahn) contributed equally to this article.

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*Corresponding author: Tel: +82-2-3010-3995; fax: +82-2-487-5918.

E-mail address: dwpark@amc.seoul.kr (D.-W. Park).

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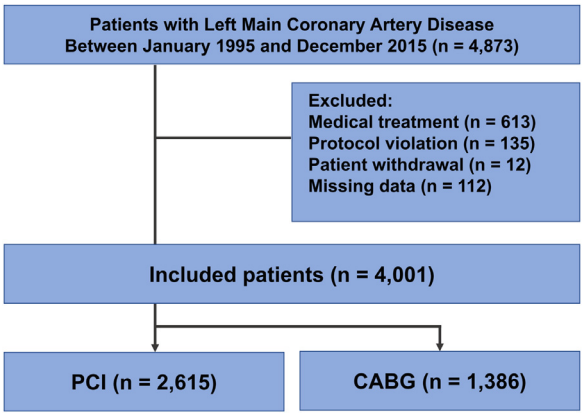

Figure 1. Flow chart.
Flow chart on the selection process. Patients with left main coronary artery disease included between January 1995 and December 2015.
CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

factors influencing treatment selection.[14] PCI was performed according to the local standard protocols. PCI was performed using bare metal stents for 1995 to 2002, first-generation DES for 2003 to 2006, and second-generation DES for 2007 to 2015. Dual antiplatelet therapy was initiated before PCI and was continued for a minimum of 1 month (for bare-metal stents) or 1 year (for DES) thereafter. CABG was performed with or without cardiopulmonary bypass at the discretion of the operator.[14] The internal mammary artery was preferentially utilized for revascularization of the left anterior descending artery.

Information on patient demographics, cardiovascular risk factors, clinical manifestations, hemodynamic status, left ventricular function, coronary angiographic results, procedural characteristics, and in-hospital and follow-up outcomes were collected from hospital charts or databases in each center according to the prespecified definitions. Follow-up data were obtained from hospital charts or by contacting patients or referring physicians. Data were recorded in a prespecified, web-based, standardized case report form and periodically monitored by independent research personnel.

The primary study outcome was a composite of all-cause death, myocardial infarction (MI), or stroke at 5 years. Various secondary outcomes were also assessed, including all-cause mortality, repeat revascularization, and major adverse cardiac and cerebrovascular events (MACCE) (defined as a composite of all-cause death, MI, stroke, or repeat revascularization).

The definition of MI was as follows: (1) if occurring within 48 hours after the procedure, presenting an increase in the creatine kinase-myocardial band (CK-MB) values >5 times the upper reference limit (URL) with any of following: new pathological Q waves or new bundle branch block, new graft or new native coronary occlusion documented on angiography, and new regional wall motion abnormality or loss of viable myocardium on imaging studies; (2) if occurring after 48 hours, an increase in the CK-MB values above the URL with ischemic symptoms or signs.[14,15] Stroke, as indicated by neurological deficits, was confirmed by a neurologist based on imaging modalities. Repeat revascularization included any percutaneous or surgical revascularization procedure, regardless of target or nontarget lesions. All clinical events were centrally adjudicated according to the source documentation by an independent group of clinicians who were blinded to the treatment type.

Categorical variables were expressed as frequencies with percentages and were compared using the Chi-square test, unless the expected number of values in any cell of the 2×2 contingency table was <5, in which case Fisher's exact test was used. Continuous variables were expressed as mean $\pm$ SD and were compared using the Student t test or 1-way ANOVA. Cumulative event rates were determined from time-to-event data, for which patients were censored at the time of withdrawal from the study or at last follow-up, were displayed using of Kaplan-Meier plots, and compared using the log-rank test.

To assess the treatment effect of PCI relative to CABG for clinical outcomes, we constructed Cox proportional hazard models for the entire cohort and for each age and sex category. Multivariable Cox regression analyses was performed to adjust for potential confounders identified by the investigators using a literature search and based on data available across all relevant studies. These covariates included age, sex, body-mass index, diabetes mellitus, prior history of MI, prior history of stroke, chronic kidney

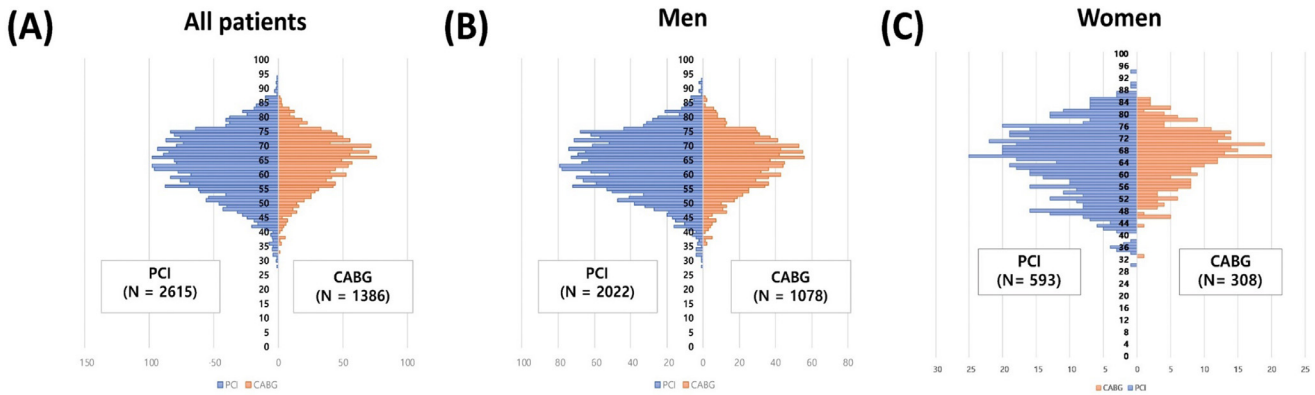

Figure 2. Histogram showing age distribution in PCI and CABG.
The figure shows the age distribution of all patients **(A)**, men **(B)**, and women **(C)**.
CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

disease, low left ventricular ejection fraction (<40%), acute coronary syndrome at presentation, disease extent of CAD, LMCA lesion location, and the year of the index procedure (to account for differences in treatment, study population, and changes in standards of care over time). To assess the interaction of the age tertiles and sex with the treatment effects of PCI relative to CABG, formal interaction testing was performed, in which the interaction variables were subsequently added to the model for the entire cohort in which age tertiles and sex were included as risk-adjusting covariates. In the model for each age tertile, age was included in the model as a continuous variable to adjust for intratertile differences of age between the PCI and CABG groups.

All reported p values are 2-sided and have not been adjusted for multiple testing. A p value less than 0.05 was considered statistically significant. Statistical analyses were performed using the statistical software SPSS version 20.0 (IBM Corp., Armonk, New York).

Results

A total of 4,001 patients were included in the current analysis. All patients that had received PCI versus CABG were stratified according to tertiles of age at the index procedures and stratified according to sex (Figure 2). The mean age was significantly higher in the CABG group than in the PCI group (Table 1). Overall, when compared with the PCI group, the CABG group had a higher prevalence of cardiovascular risk factors (i.e., diabetes, history of heart failure, valvular heart disease, MI, or peripheral vascular disease, lower ejection fraction, and acute coronary syndrome). In addition, CABG patients had a higher anatomic complexity (i.e., more extensive CAD and distal left main involvement).

Baseline characteristics of patients in the PCI and CABG groups stratified by sex are shown in Table 2. Compared with men, women were older and more often had higher body-mass index, hypertension, and acute coronary syndromes, but less often were current smokers, had prior MI, or peripheral vascular disease. With regard to anatomic features, women had less severe CAD and less involvement of distal bifurcation. Medication use except statins was similar between women and men. Procedural characteristics of PCI and CABG according to age and sex categories are summarized in Table I and II in the Data Supplement.

The median follow-up period was 6.3 years (interquartile range, 4.0 to 9.4). Unadjusted 5-year rates of primary and secondary outcomes after PCI and CABG stratified by age and sex categories are shown in Table 3. The 5-year rate of primary composite outcome of all-cause death, MI, or stroke was significantly higher in the CABG group compared with the PCI group (Figure I in the Data Supplement). This trend was consistent for all age categories, but was statistically significant for age <60 years and showed a nonsignificant trend for the age tertiles of 60 to 69 years and age ≥70 years. PCI compared with CABG was also associated with a significantly lower risk of all-cause death but had a significantly higher risk of repeat revascularization and a similar risk of MACCE. The 5-year rate of primary composite outcome was higher in the CABG group compared with the PCI group in both men and women (although not statistically significant for women) (Figure II in the Data Supplement). In general, the observed differences in clinical outcomes after PCI and CABG did not differ between men and women.

The adjusted hazard ratios for the relative effect of CABG and PCI stratified by age and sex categories are summarized in Table 4 and Figure 3. After adjustment of a wide range of clinical covariates, the risk of primary composite outcome was similar between CABG- and PCI-treated patients. The relative treatment effects of PCI and CABG were not significantly modified according to the age category ($P_{interaction} = 0.57$) and the sex category ($P_{interaction} = 0.65$) (Figure 3). The adjusted risk of all-cause death was also similar between PCI and CABG and was not significantly modified by the age ($P_{interaction} = 0.34$) and sex ($P_{interaction} = 0.99$) (Figure 3). The risks of repeat revascularization and MACCE consistently favored the CABG group over the PCI group without significant interaction modified by the age or sex category (Figure 3 and Figure 3).

Discussion

The major findings of the present analysis, the largest study to date evaluating the relative treatment effect of PCI and CABG for LMCA disease stratified by age and sex categories are (1) that PCI compared with CABG is associated a similar 5-year risk of primary composite outcome of all-cause death, MI, or stroke; (2) that significant interaction was absent between age or sex and treatment with PCI and CABG regarding the relative risk of primary composite outcome; and (3) PCI compared with CABG showed a similar risk for all-cause death but higher risk of repeat revascularization and MACCE; in addition, there were no significant age- or sex-related differences in the long-term risks for all-cause death, repeat revascularization, or MACCE.

A previous meta-analysis suggested that patient age modified the treatment effect of PCI and CABG on mortality, whereas a mortality benefit on CABG over PCI was found in patients aged 65 years or older with multivessel CAD.[11,16] A recent observational study showed similar findings;[13] a significant mortality benefit of CABG relative to PCI was evident in patients aged ≥70 years but a neutral risk was found in younger patients. The interaction of age with an assigned treatment might be mediated by more favorable clinical characteristics in younger patients. In addition, older age might be a marker for more severe comorbidity and frailty, which were commonly unmeasured. Contrary to previous findings of patients with multivessel CAD, we found that there was no significant age-related difference in the adjusted risk of primary composite outcome and mortality in patients with LMCA disease. For all age categories, PCI compared with CABG showed a similar risk for serious composite outcome and mortality. Our findings were similar with the most recent clinical trials EXCEL and NOBLE, in which the relative treatment effect of PCI and CABG was not significantly modified by the age category.[8,9] In addition, a more recent meta-analysis of 11 randomized trials involving multivessel or LMCA disease showed that there was no significant treatment

Table 1
Baseline characteristics of patients according to age category

	Entire cohort (N = 4,001)			Age < 60 years (N = 1,305)			Age 60−69 years (N = 1,420)			Age ≥ 70 years (N = 1,276)			p Value for Age Group
	PCI (N = 2,615)	CABG (N = 1,386)	p Value	PCI (N = 914)	CABG (N = 391)	p Value	PCI (N = 866)	CABG (N = 554)	p Value	PCI (N = 835)	CABG (N = 441)	p Value	
Variable													
Age (year)	63.7 ± 10.8	64.6 ± 9.1	0.007	51.8 ± 6.0	53.1 ± 5.1	<0.001	64.6 ± 2,8	64.8 ± 2.8	0.22	75.7 ± 4.6	74.4 ± 3.7	<0.001	<0.001
Men	2022 (77.3%)	1078 (77.8%)	0.77	724 (79.2%)	326 (83.4%)	0.10	682 (78.8%)	433 (78.2%)	0.84	616 (73.8%)	319 (72.3%)	0.63	<0.001
BMI (kg/m^2)	24.5 ± 3.0	24.6 ± 3.1	0.28	25.1 ± 2.9	25.0 ± 3.1	0.66	24.5 ± 2.8	24.7 ± 2.9	0.15	23.9 ± 3.1	24.1 ± 3.1	0.17	<0.001
Hypertension	1619 (61.9%)	884 (63.8%)	0.26	468 (51.2%)	211 (54.0%)	0.39	541 (62.5%)	356 (64.3%)	0.53	610 (73.1%)	317 (71.9%)	0.70	<0.001
Diabetes mellitus	884 (33.8%)	581 (41.9%)	<0.001	255 (27.9%)	159 (40.7%)	<0.001	336 (38.8%)	243 (43.9%)	0.07	293 (35.1%)	179 (40.6%)	0.06	<0.001
Insulin-requiring	133 (5.1%)	111 (8.0%)	<0.001	36 (3.9%)	30 (7.7%)	0.007	41 (4.7%)	56 (10.1%)	<0.001	56 (6.7%)	25 (5.7%)	0.55	0.14
Current smoker	642 (24.6%)	373 (26.9%)	0.11	294 (32.2%)	152 (38.9%)	0.02	209 (24.1%)	142 (25.6%)	0.57	139 (16.6%)	79 (17.9%)	0.62	<0.001
Prior Heart failure	59 (2.3%)	50 (3.6%)	0.02	6 (0.7%)	15 (3.8%)	<0.001	16 (1.8%)	21 (3.8%)	0.04	37 (4.4%)	14 (3.2%)	0.35	0.001
Dyslipidemia*	1654 (63.3%)	742 (53.5%)	<0.001	575 (62.9%)	218 (55.8%)	0.02	545 (62.9%)	298 (53.8%)	0.001	534 (64.0%)	226 (51.2%)	<0.001	0.73
Valvular heart disease	14 (0.5%)	44 (3.2%)	<0.001	3 (0.3%)	10 (2.6%)	0.001	3 (0.3%)	20 (3.6%)	<0.001	8 (1.0%)	14 (3.2%)	0.008	0.24
Prior MI	193 (7.4%)	184 (13.3%)	<0.001	57 (6.2%)	66 (16.9%)	<0.001	69 (8.0%)	70 (12.6%)	0.005	67 (8.0%)	48 (10.9%)	0.11	0.79
Prior stroke	212 (8.1%)	118 (8.5%)	0.70	44 (4.8%)	27 (6.9%)	0.16	72 (8.3%)	42 (7.6%)	0.69	96 (11.5%)	49 (11.1%)	0.91	<0.001
Peripheral vascular disease	105 (4.0%)	112 (8.1%)	<0.001	16 (1.8%)	18 (4.6%)	0.006	35 (4.0%)	54 (9.7%)	<0.001	54 (6.5%)	40 (9.1%)	0.11	<0.001
Chronic lung disease	64 (2.4%)	52 (3.8%)	0.03	6 (0.7%)	10 (2.6%)	0.01	15 (1.7%)	20 (3.6%)	0.04	43 (5.1%)	22 (5.0%)	>0.99	<0.001
Chronic kidney disease	107 (4.1%)	67 (4.8%)	0.31	16 (1.8%)	17 (4.3%)	0.01	29 (3.3%)	25 (4.5%)	0.33	62 (7.4%)	25 (5.7%)	0.29	<0.001
Ejection fraction (%)	59.1 ± 8.9	55.2 ± 11.4	<0.001	59.8 ± 7.9	55.6 ± 11.5	<0.001	59.6 ± 8.7	55.8 ± 10.9	<0.001	57.9 ± 10.1	54.2 ± 12.0	<0.001	<0.001
Ejection fraction ≤ 40%	127 (4.9%)	188 (13.6%)	<0.001	34 (3.7%)	51 (13.0%)	<0.001	35 (4.0%)	67 (12.1%)	<0.001	58 (6.9%)	70 (15.9%)	<0.001	0.002
Acute coronary syndrome	1463 (55.9%)	933 (67.3%)	<0.001	532 (58.2%)	260 (66.5%)	0.006	453 (52.3%)	369 (66.6%)	<0.001	478 (57.2%)	304 (68.9%)	<0.001	0.15
Emergent procedure	88 (3.4%)	40 (2.9%)	0.47	30 (3.3%)	14 (3.6%)	0.92	27 (3.1%)	16 (2.9%)	0.93	31 (3.7%)	10 (2.3%)	0.221	0.88
Extent of CAD			<0.001			<0.001			<0.001			<0.001	<0.001
Only	278 (10.6%)	31 (2.2%)		155 (17.0%)	15 (3.8%)		74 (8.5%)	12 (2.2%)		49 (5.9%)	4 (0.9%)		
1-VD	648 (24.8%)	79 (5.7%)		245 (26.8%)	30 (7.7%)		212 (24.5%)	30 (5.4%)		191 (22.9%)	19 (4.3%)		
2-VD	950 (36.3%)	268 (19.3%)		308 (33.7%)	90 (23.0%)		327 (37.8%)	112 (20.2%)		315 (37.7%)	66 (15.0%)		
3-VD	739 (28.3%)	1008 (72.7%)		206 (22.5%)	256 (65.5%)		253 (29.2%)	400 (72.2%)		280 (33.5%)	352 (79.8%)		
Number of total lesions	2.4 ± 1.3	3.9 ± 1.6	<0.001	2.1 ± 1.2	3.7 ± 1.7	<0.001	2.4 ± 1.3	3.9 ± 1.6	<0.001	2.7 ± 1.4	4.1 ± 1.6	<0.001	<0.001
Left main lesion location													
Ostial or Shaft	1289 (49.3%)	565 (40.8%)	<0.001	467 (51.1%)	165 (42.2%)	0.004	414 (47.8%)	224 (40.4%)	0.008	408 (48.9%)	176 (39.9%)	0.003	0.17
Distal Bifurcation	1549 (59.2%)	903 (65.2%)	<0.001	518 (56.7%)	249 (63.7%)	0.02	534 (61.7%)	360 (65.0%)	0.23	497 (59.5%)	294 (66.7%)	0.02	0.07
Medication at discharge													
Aspirin	2557 (97.8%)	1330 (96.0%)	0.001	899 (98.4%)	374 (95.7%)	0.007	843 (97.3%)	532 (96.0%)	0.22	815 (97.6%)	424 (96.1%)	0.19	0.53
P2Y12 inhibitors	2517 (96.3%)	1175 (84.8%)	<0.001	878 (96.1%)	344 (88.0%)	<0.001	829 (95.7%)	466 (84.1%)	<0.001	810 (97.0%)	365 (82.8%)	<0.001	0.06
Beta blockers	1703 (65.1%)	682 (49.2%)	<0.001	608 (66.5%)	192 (49.1%)	<0.001	553 (63.9%)	283 (51.1%)	<0.001	542 (64.9%)	207 (46.9%)	<0.001	0.32
Calcium Channel blockers	1375 (52.6%)	905 (65.3%)	<0.001	485 (53.1%)	267 (68.3%)	<0.001	481 (55.5%)	370 (66.8%)	<0.001	409 (49.0%)	268 (60.8%)	<0.001	0.001
ACE inhibitor or ARBs	995 (38.0%)	323 (23.3%)	<0.001	292 (31.9%)	89 (22.8%)	0.001	342 (39.5%)	117 (21.1%)	<0.001	361 (43.2%)	117 (26.5%)	<0.001	<0.001
Statins	2011 (76.9%)	762 (55.0%)	<0.001	694 (75.9%)	210 (53.7%)	<0.001	655 (75.6%)	296 (53.4%)	<0.001	662 (79.3%)	256 (58.0%)	<0.001	0.02

Data are shown as mean with standard deviation or numbers.

* Dyslipidemia was defined as elevated fasting total cholesterol level above 200 mg/dL or treated with statins.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; VD = vessel disease.

Table 2
Baseline characteristics of patients according to sex category

	Men (N = 3,100)				Women (N = 901)				p Value for sex
	Total (N = 3,100)	PCI (N = 2,022)	CABG (N = 1,078)	p Value	Total (N = 901)	PCI (N = 593)	CABG (N = 308)	p Value	
Variable									
Age (year)	63.7 ± 10.1	63.5 ± 10.5	64.0 ± 9.10	0.13	65.1 ± 10.9	64.5 ± 11.9	66.4 ± 8.7	0.005	<0.001
BMI (kg/m^2)	24.5 ± 2.9	24.4 ± 2.8	24.5 ± 3.1	0.22	24.8 ± 3.4	24.8 ± 3.5	24.8 ± 3.0	0.98	0.014
Hypertension	1881 (60.7%)	1213 (60.0%)	668 (62.0%)	0.30	622 (69.0%)	406 (68.5%)	216 (70.1%)	0.66	<0.001
Diabetes mellitus	1132 (36.5%)	684 (33.8%)	448 (41.6%)	<0.001	333 (37.0%)	200 (33.7%)	133 (43.2%)	0.007	0.84
Insulin-requiring	178 (5.7%)	94 (4.6%)	84 (7.8%)	<0.001	66 (7.3%)	39 (6.6%)	27 (8.8%)	0.29	0.10
Current smoker	970 (31.3%)	614 (30.4%)	356 (33.0%)	0.14	45 (5.0%)	28 (4.7%)	17 (5.5%)	0.72	<0.001
Prior heart failure	79 (2.5%)	44 (2.2%)	35 (3.2%)	0.09	30 (3.3%)	15 (2.5%)	15 (4.9%)	0.10	0.25
Dyslipidemia*	1847 (59.6%)	1268 (62.7%)	579 (53.7%)	<0.001	549 (60.9%)	386 (65.1%)	163 (52.9%)	0.001	0.49
Valvular heart disease	40 (1.3%)	8 (0.4%)	32 (3.0%)	<0.001	18 (2.0%)	6 (1.0%)	12 (3.9%)	0.007	0.16
Prior MI	322 (10.4%)	160 (7.9%)	162 (15.0%)	<0.001	55 (6.1%)	33 (5.6%)	22 (7.1%)	0.43	<0.001
Prior stroke	256 (8.3%)	166 (8.2%)	90 (8.3%)	0.95	74 (8.2%)	46 (7.8%)	28 (9.1%)	0.57	>0.99
Peripheral vascular disease	187 (6.0%)	93 (4.6%)	94 (8.7%)	<0.001	30 (3.3%)	12 (2.0%)	18 (5.8%)	0.005	0.002
Chronic lung disease	99 (3.2%)	59 (2.9%)	40 (3.7%)	0.28	17 (1.9%)	5 (0.8%)	12 (3.9%)	0.003	0.05
Chronic kidney disease	131 (4.2%)	81 (4.0%)	50 (4.6%)	0.46	43 (4.8%)	26 (4.4%)	17 (5.5%)	0.55	0.54
Ejection fraction (%)		58.8 ± 9.0	54.8 ± 11.4	<0.001		60.4 ± 8.6	56.7 ± 11.6	<0.001	<0.001
Ejection fraction ≤40%	255 (8.2%)	103 (5.1%)	152 (14.1%)	<0.001	60 (6.7%)	24 (4.0%)	36 (11.7%)	<0.001	0.14
Acute coronary syndrome	1810 (58.4%)	1104 (54.6%)	706 (65.5%)	<0.001	586 (65.0%)	359 (60.5%)	227 (73.7%)	<0.001	<0.001
Emergent procedure	103 (3.3%)	68 (3.4%)	35 (3.2%)	0.95	25 (2.8%)	20 (3.4%)	5 (1.6%)	0.193	0.48
Extent of CAD				<0.001				<0.001	<0.001
Only	201 (6.5%)	179 (8.9%)	22 (2.0%)		108 (12.0%)	99 (16.7%)	9 (2.9%)		
1-VD	584 (18.8%)	517 (25.6%)	67 (6.2%)		143 (15.9%)	131 (22.1%)	12 (3.9%)		
2-VD	938 (30.3%)	734 (36.3%)	204 (18.9%)		280 (31.1%)	216 (36.4%)	64 (20.8%)		
3-VD	1377 (44.4%)	592 (29.3%)	785 (72.8%)		370 (41.1%)	147 (24.8%)	223 (72.4%)		
Number of total lesions	3.0 ± 1.6	2.4 ± 1.3	3.9 ± 1.6	<0.001	2.8 ± 1.7	2.3 ± 1.3	3.9 ± 1.7	<0.001	0.01
Left main lesion location									
Ostial or Shaft	1379 (44.5%)	948 (46.9%)	431 (40.0%)	<0.001	475 (52.7%)	341 (57.5%)	134 (43.5%)	<0.001	<0.001
Distal Bifurcation	1935 (62.4%)	1233 (61.0%)	702 (65.1%)	0.03	517 (57.4%)	316 (53.3%)	201 (65.3%)	0.001	0.007
Medication at discharge									
Aspirin	3009 (97.1%)	1973 (97.6%)	1036 (96.1%)	0.03	878 (97.4%)	584 (98.5%)	294 (95.5%)	0.01	0.62
P2Y12 inhibitors	2856 (92.1%)	1939 (95.9%)	917 (85.1%)	<0.001	836 (92.8%)	578 (97.5%)	258 (83.8%)	<0.001	0.56
Beta blockers	1851 (59.7%)	1326 (65.6%)	525 (48.7%)	<0.001	534 (59.3%)	377 (63.6%)	157 (51.0%)	<0.001	0.84
Calcium Channel blockers	1723 (55.6%)	1034 (51.1%)	689 (63.9%)	<0.001	557 (61.8%)	341 (57.5%)	216 (70.1%)	<0.001	0.001
ACE inhibitors or ARBs	1031 (33.3%)	783 (38.7%)	248 (23.0%)	<0.001	287 (31.9%)	212 (35.8%)	75 (24.4%)	0.001	0.45
Statins	2188 (70.6%)	1576 (77.9%)	612 (56.8%)	<0.001	585 (64.9%)	435 (73.4%)	150 (48.7%)	<0.001	0.001

Data are shown as mean with standard deviation or numbers.

* Dyslipidemia was defined as elevated fasting total cholesterol level above 200 mg/dL or treated with statins.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; VD = vessel disease.

Table 3
Observed 5-year outcomes after PCI and CABG stratified by age group and sex

		Entire cohort (N = 4001)			Age <60 years (N = 1305)			Age 60–69 years (N = 1420)			Age ≥70 years (N = 1276)		
		PCI	CABG	p	PCI	CABG	p	PCI	CABG	p	PCI	CABG	p Value
Primary endpoint: Composite of all-cause death, MI, or stroke	All	263 (10.8%)	194 (14.5%)	0.001	35 (4.0%)	29 (7.7%)	0.009	79 (9.6%)	67 (12.4%)	0.10	149 (19.9%)	98 (23.1%)	0.13
	Men	207 (11.0%)	155 (15.0%)	0.002	27 (3.9%)	25 (8.0%)	0.009	59 (9.1%)	56 (13.4%)	0.03	121 (22.1%)	74 (24.3%)	0.35
	Women	56 (10.1%)	39 (12.8%)	0.17	8 (4.4%)	4 (6.2%)	0.54	20 (11.6%)	11 (9.2%)	0.57	28 (13.8%)	24 (20.1%)	0.12
Secondary outcomes													
All-cause death	All	229 (9.4%)	182 (13.6%)	<0.001	26 (3.0%)	24 (6.4%)	0.006	67 (8.2%)	63 (11.7%)	0.03	136 (18.0%)	95 (22.4%)	0.05
	Men	182 (9.7%)	144 (13.9%)	0.001	19 (2.7%)	20 (6.4%)	0.007	51 (7.9%)	51 (12.2%)	0.02	112 (20.4%)	73 (24.0%)	0.17
	Women	47 (8.4%)	38 (12.5%)	0.04	7 (3.9%)	4 (6.2%)	0.41	16 (9.4%)	12 (10.0%)	0.78	24 (11.4%)	22 (18.5%)	0.08
Repeat revascularization	All	255 (10.1%)	43 (3.2%)	<0.001	96 (10.8%)	19 (5.0%)	0.001	95 (11.4%)	13 (2.4%)	<0.001	64 (8.1%)	11 (2.5%)	<0.001
	Men	184 (9.5%)	32 (3.1%)	<0.001	75 (10.8%)	13 (4.1%)	<0.001	68 (10.5%)	11 (2.6%)	<0.001	41 (7.0%)	8 (2.6%)	0.006
	Women	71 (12.3%)	11 (3.6%)	<0.001	21 (11.2%)	6 (9.3%)	0.64	27 (14.9%)	2 (1.7%)	<0.001	23 (11.1%)	3 (2.6%)	0.006
MACCE	All	479 (19.3%)	229 (17.1%)	0.062	123 (13.9%)	46 (12.2%)	0.30	161 (19.4%)	78 (14.5%)	0.02	195 (25.5%)	105 (24.7%)	0.79
	Men	364 (19.1%)	179 (17.3%)	0.16	95 (13.6%)	36 (11.5%)	0.26	121 (18.6%)	65 (15.5%)	0.18	148 (26.6%)	78 (25.5%)	0.77
	Women	115 (20.1%)	50 (16.4%)	0.19	28 (15.0%)	10 (15.5%)	0.93	40 (22.5%)	13 (10.8%)	0.01	47 (22.6%)	27 (22.6%)	>0.99

Data are shown as event numbers. Cumulative rates of events are based on Kaplan–Meier estimates. P-values are derived by use of log-rank test.
CABG = coronary artery bypass grafting; MACCE = a composite of death from any cause, myocardial infarction, stroke, or repeat revascularization; PCI = percutaneous coronary intervention.

interaction according to age ($P_{interaction}$=0.98). Although we are unable to provide a precise explanation for the temporal change in age effect on the relative benefit of PCI and CABG, remarkable technical advancements in coronary stents, procedure techniques, and introduction of adjuvant antithrombotic drugs might reduce the gap of the treatment effect of CABG and PCI and diminish the age-related effect on outcomes.

Sex-specific differences have been recognized with respect to prevalence, pathogenesis, and prognosis of CAD and have also been associated with differential outcomes after coronary revascularization.[17–20] In addition, some studies have suggested that treating physicians are less likely to pursue an aggressive approach for CAD treatment in women than in men in the "real-world" practice.[21–23] Our previous report showed that women had different clinical and lesion characteristics but similar long-term clinical outcomes after PCI with DES for LMCA disease.[24] However, female is conventionally considered as a risk factor for open heart surgery and has been included as a poor prognostic factor in multiple cardiac operative risk scores (i.e., EuroScore II, the Society of Thoracic Surgeons score, the modified Parsonnet score).[25–27] Nevertheless, recent reports suggested that there were no sex-related differences in clinical outcomes after CABG in diverse spectrum of patients with multivessel CAD who underwent PCI and CABG.[10,16,28,29] Similarly, in our study, there were no significant sex-related differences with respect to 5-year risks of primary composite outcome, all-cause death, repeat revascularization, and MACCE after PCI or CABG for LMCA disease. Although the mechanisms responsible for these observations are speculative, our findings carry significant implications for clinical practice and suggest that the sex of the patient should not influence treatment decisions for PCI or CABG.

Some limitations of our analysis should be considered. This was a nonrandomized, observational study and hence was subject to potential selection and ascertainment bias despite adjustment using a wide range of clinical covariates. In particular, we could not deny the presence of an unadjusted clinical profile and propensity scores for PCI or CABG in elderly patients for whom PCI was more preferentially selected because of their comorbidities and patient preference. Thus, the overall findings are to be considered hypothetical and hypotheses-generating only. Second, there was a possibility that our analyses did not have sufficient statistical power to detect clinically meaningful differences in the subgroup analysis using age and sex categories. Third, an analysis stratified according to Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score could not be performed, owing to insufficient data to calculate the score. Finally, it is uncertain whether the overall findings from our study can be applied to other ethnic or society groups differing in terms of patient and/or procedural characteristics and specific clinical practices. In conclusion, in this large observational cohort of patients with LMCA narrowing, there was no significant age- and sex-related difference in the long-term risks of primary composite outcome, all-cause mortality, repeat revascularization, and MACCE of PCI relative to CABG.

Table 4
Adjusted hazard ratios for clinical outcomes after PCI and CABG stratified by age group and sex

		Entire cohort		Age <60 years		Age 60−69 years		Age ≥70 years		$P_{interaction}$ with age
		Adjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	
Primary endpoint: Composite of death, MI, or stroke	All	0.94 (0.75−1.16)	0.55	0.64 (0.35−1.16)	0.14	1.21 (0.82−1.80)	0.34	0.90 (0.66−1.22)	0.49	0.57
	Men	0.92 (0.72−1.17)	0.47	0.54 (0.28−1.02)	0.06	1.05 (0.68−1.63)	0.83	0.97 (0.70−1.36)	0.88	0.76
	Women	0.89 (0.52−1.50)	0.65	1.97 (0.36−10.77)	0.44	2.02(0.82−4.98)	0.13	0.48 (0.23−0.99)	0.05	0.46
	$P_{interaction}$ with sex		0.65		0.34		0.17		0.30	
Secondary outcomes										
All death	All	0.89 (0.71−1.12)	0.33	0.63 (0.32−1.24)	0.18	1.16 (0.76−1.76)	0.49	0.85 (0.62−1.16)	0.30	0.34
	Men	0.89 (0.69−1.15)	0.38	0.55 (0.26−1.15)	0.11	1.08 (0.68−1.73)	0.74	0.91 (0.65−1.29)	0.61	0.42
	Women	0.76 (0.44−1.31)	0.32	1.31 (0.22−7.77)	0.77	1.34 (0.53−3.37)	0.54	0.45 (0.21−0.99)	0.047	0.54
	$P_{interaction}$ with sex		0.99		0.43		0.45		0.30	
Repeat revascularization	All	5.42 (3.81−7.71)	<0.001	3.62 (2.11−6.23)	<0.001	8.29 (4.43−15.50)		5.35 (2.64−10.86)	<0.001	0.10
	Men	5.14 (3.42−7.72)	<0.001	4.01 (2.12−7.57)	<0.001	6.68 (3.33−13.37)	<0.001	4.70 (2.05−10.80)	<0.001	0.14
	Women	5.92 (2.93−11.95)	<0.001	2.08 (0.64−6.69)	0.22	9.61 (2.28−40.41)	0.002	6.06 (1.58−23.29)	0.009	0.32
	$P_{interaction}$ with sex		0.64		0.39		0.32		0.46	
MACCE	All	1.73 (1.44−2.08)	<0.001	1.81 (1.22−2.68)	0.003	2.36 (1.72−3.24)	<0.001	1.28 (0.97−1.70)	0.08	0.29
	Men	1.67 (1.36−2.05)	<0.001	1.74 (1.13−2.69)	0.009	2.05 (1.44−2.92)	<0.001	1.33 (0.97−1.84)	0.08	0.53
	Women	1.89 (1.26−2.84)	0.002	1.75 (0.66−4.67)	0.26	4.12 (1.96−8.68)	<0.001	1.00 (0.55−1.83)	0.99	0.44
	$P_{interaction}$ with sex		0.30		0.84		0.12		0.77	

Adjusted hazard ratios (PCI group reference to CABG group) and associated 95% confidence intervals are calculated from Cox regression models adjusted for age, sex, body-mass index, diabetes mellitus, prior history of MI, prior history of stroke, chronic kidney disease, low left ventricular ejection fraction (<40%), acute coronary syndrome at presentation, extent of coronary artery disease (left main only, 1-vessel disease, 2-vessel disease, or 3-vessel disease), left main lesion location (ostial/shaft or distal bifurcation) and the year of the index procedure.

CABG = coronary artery bypass grafting; CI = confidence interval; HR = hazard ratio; MACCE = a composite of death from any cause, myocardial infarction, stroke, or repeat revascularization; PCI = percutaneous coronary intervention.

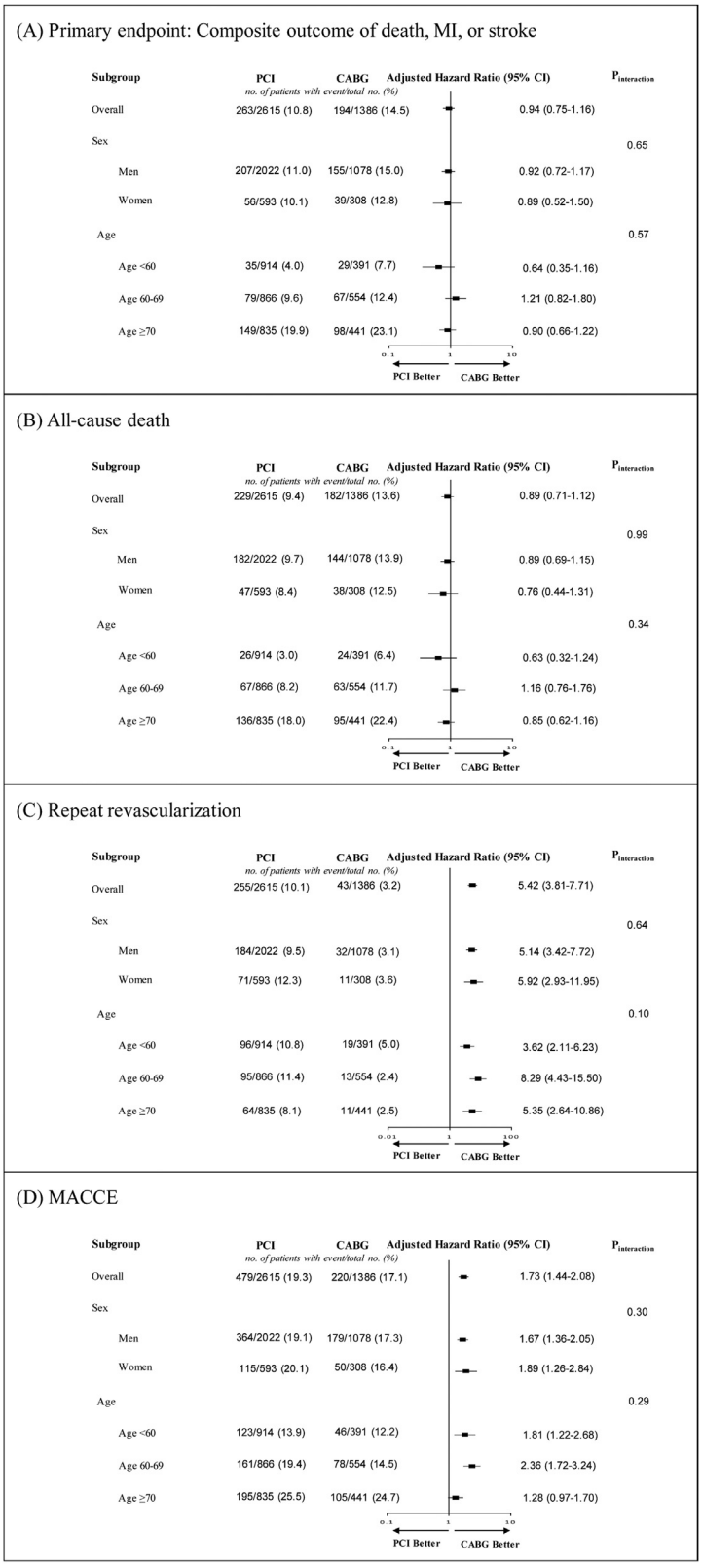

Figure 3. Adjusted hazard ratio for clinical outcomes after PCI and CABG, according to sex and age categories.
Adjusted hazard ratios (PCI reference to CABG) are shown for primary composite outcome of all-cause death, MI, or stroke (**A**), all-cause death (**B**), repeat revascularization (**C**), and MACCE (**D**).
CABG = coronary artery bypass grafting; CI = confidence interval; MACCE = major adverse cardiac and cerebrovascular events; MI = myocardial infarction; PCI = percutaneous coronary intervention; MACCE was defined as a composite of all-cause death, MI, stroke, or repeat revascularization.

Role of the Sponsors

The sponsors played no role in this study. There was no industry involvement in the design or conduct of the study; the collection, management, analysis, and interpretation of the data, and approval of the manuscript; or the decision to submit the manuscript for publication.

Disclosures

None.

Supplementary materials

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