Differential Event Rates and Independent Predictors of Long-Term Major Cardiovascular Events and Death in 5795 Patients With Unprotected Left Main Coronary Artery Disease Treated With Stents, Bypass Surgery, or Medication

Insights From a Large International Multicenter Registry

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Background—Identifying predictive factors for major cardiovascular events and death in patients with unprotected left main coronary artery disease is of great clinical value for risk stratification and possible guidance for tailored preventive strategies.

Methods and Results—The Interventional Research Incorporation Society-Left MAIN Revascularization registry included 5795 patients with unprotected left main coronary artery disease (percutaneous coronary intervention, n=2850; coronary-artery bypass grafting, n=2337; medication alone, n=608). We analyzed the incidence and independent predictors of major adverse cardiac and cerebrovascular events (MACCE; a composite of death, MI, stroke, or repeat revascularization) and all-cause mortality in each treatment stratum. During follow-up (median, 4.3 years), the rates of MACCE and death were substantially higher in the medical group than in the percutaneous coronary intervention and coronary-artery bypass grafting groups (P<0.001). In the percutaneous coronary intervention group, the 3 strongest predictors for MACCE were chronic renal failure, old age (≥65 years), and previous heart failure; those for all-cause mortality were chronic renal failure, old age, and low ejection fraction. In the coronary-artery bypass grafting group, old age, chronic renal failure, and low ejection fraction were the 3 strongest predictors of MACCE and death. In the medication group, old age, low ejection fraction, and diabetes mellitus were the 3 strongest predictors of MACCE and death.

Conclusions—Among patients with unprotected left main coronary artery disease, the key clinical predictors for MACCE and death were generally similar regardless of index treatment. This study provides effect estimates for clinically relevant predictors of long-term clinical outcomes in real-world left main coronary artery patients, providing possible guidance for tailored preventive strategies.

Clinical Trial Registration—URL: https://clinicaltrials.gov. Unique identifier: NCT01341327.

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Key Words: coronary disease ■ coronary artery bypass surgery ■ heart failure ■ percutaneous coronary intervention ■ stroke

Patients with unprotected left main coronary artery (ULMCA) disease are considered at highest-risk of adverse cardiovascular events and mortality within the broad range of risk for patients with obstructive coronary artery disease (CAD). On the basis of several clinical and anatomic characteristics and patient/physician preference, individual patients with ULMCA disease might be treated with percutaneous coronary intervention (PCI), coronary-artery bypass grafting (CABG), or medication alone.[1] Depending on the specific index treatment strategy, accurate knowledge of the key determinants of adverse cardiovascular events and mortality would be extremely useful for clinical and investigational purposes.

To date, several scoring systems have been developed for risk stratification and decision making of optimum revascularization strategy in patients with complex CAD with or without ULMCA disease.[2–5] However, easy application of these scoring systems in clinical practice might be hampered because of limited clinical performance and complexities. In particular,

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WHAT IS KNOWN

- Patients with unprotected left main coronary artery disease are considered at highest risk of adverse cardiovascular events and mortality. However, depending on the specific index treatment strategy, accurate knowledge of the key determinants of major cardiovascular events and mortality is still limited.

WHAT THE STUDY ADDS

- Our study identified the key predictive factors of cardiovascular events and all-cause mortality risks in large-sized, real-world population with unprotected left main coronary artery disease who were treated with percutaneous coronary intervention, coronary-artery bypass grafting, or medical treatment alone. Study findings would be useful for risk stratification, triaging more aggressive management, and improving long-term prognosis.

few investigations have evaluated the differential clinical determinants for predicting the risk of adverse cardiovascular events for each treatment stratum of PCI, CABG, or medication. The ability to rapidly identify the key predictive factors of cardiovascular events and all-cause mortality risks in patients with ULMCA disease would be useful for risk stratification, triaging more aggressive management, and improving long-term prognosis. Therefore, using the large multinational all-comers registry, including a real-world population with ULMCA disease, we sought to evaluate differential rates of major cardiovascular events and all-cause mortality and clinically relevant predictors of long-term outcomes according to the index treatment strategy.

Methods

Study Population and Database

The study population was a part of the IRIS-MAIN registry (Interventional Research Incorporation Society-Left MAIN Revascularization) that comprised patients with significant ULMCA stenosis between January 1995 and December 2013.[6] This was a nonrandomized, multinational, and multicenter observational study, and the study population was recruited from 50 academic and community hospitals in Asia (China, India, Indonesia, Japan, Malaysia, South Korea, Taiwan, and Thailand). The study was designed to evaluate the real-world outcomes of PCI, CABG, or medication alone among an unrestricted population with ULMCA disease. Therefore, the exclusion criteria were minimal; patients who presented with cardiogenic shock, those with prior CABG, and those who underwent concomitant valvular or aortic surgery were excluded. Diverse information on patient demographics, cardiovascular risk factors, clinical manifestations, hemodynamic status, left ventricular function, CAD extent, procedure/operation details, and outcomes during hospitalization and follow-up were collected from each participating center. Data were recorded in the prespecified, web-based, standardized case report form and periodically monitored by independent research personnel.

The registry was supported by the Cardiovascular Research Foundation, Seoul, Korea, and there was no industry involvement in the study design, conduct, or analysis. The study protocol was approved by the institutional review board of each center, and written informed consent was provided by all patients.

Treatment Modalities and Procedure

Selection of the particular type of treatments was at the discretion of the attending physician. Several clinical (age, comorbidity, frailty, comorbid conditions, clinical presentation, hemodynamic state, or patient/physician preference) and anatomic (lesion severity, disease extent, or procedural/surgical complexities) factors were considered as possible factors to have influenced treatment selection for the patient. Medication was administered in accordance with accepted guidelines and established standards of practice. PCI was performed according to standard guidelines.[7] The use of predilation, intravascular ultrasound, and intra-aortic balloon pumps, as well as the selection of a specific implanted stent type were at the discretion of the interventional cardiologists. Periprocedural anticoagulation was administered according to standard regimens. All patients undergoing PCI received a loading dose of aspirin and adenosine diphosphate receptor antagonists before or during the intervention. After the procedure, aspirin was continued indefinitely. Patients treated with bare-metal stents were prescribed clopidogrel or ticlopidine for at least 1 month, and patients treated with drug-eluting stents were prescribed clopidogrel for at least 12 months. Surgical revascularization was performed using standard bypass techniques. Graft selection and the choice of on- or off-pump surgery was made by the attending surgeon.

Outcomes and Definitions

Two primary outcomes were assessed for inclusion in the prediction analysis: major adverse cardiac and cerebrovascular events (MACCE) and death of any cause. MACCE was defined as a composite of death of any cause, myocardial infarction (MI), stroke, or repeat revascularization. Death was considered cardiac unless an unequivocal noncardiac cause could be established. The protocol definition of MI was as follows: (1) if occurring within 48 hours after the index treatment, an increase in the creatine kinase–myocardial band values >5× the upper reference limit with any of the 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 and (2) if occurring 48 hours after the index treatment, an increase in the creatine kinase–myocardial band values above the upper reference limit with ischemic symptoms or signs.[6] This MI definition was similar to criteria used in our previous trials comparing PCI and CABG.[8,9] Stroke, as indicated by neurological deficits, was confirmed by a neurologist on the basis of imaging modalities. Repeat revascularization included any percutaneous or surgical revascularization procedure, regardless of target or nontarget lesions or whether the procedure was clinically or angiographically driven.

Clinical follow-up was performed at 1 month, 6 months, and 1 year, and then annually thereafter via an office visit or telephone contact. All clinical events were based on clinical diagnoses assigned by the treating physician and centrally adjudicated according to the source documentation by an independent group of clinicians.

Statistical Analysis

Continuous variables are presented as mean±SD, whereas categorical variables are presented as counts or percentages. The prevalence of risk factors and patient characteristics among the 3 treatment groups (PCI, CABG, or medication) were compared using the Kruskal–Wallis test for continuous variables and the χ^2 test or Fisher exact test for categorical variables as appropriate. Cumulative event rates and incidence curves for clinical outcomes were generated using the Kaplan–Meier method and compared using the log-rank test.

In each treatment stratum of PCI, CABG, and medication, to identify independent predictors of MACCE and death, a Cox proportional hazards model with stepwise backward elimination methods (retention threshold; $P<0.05$) was used. Previously published candidate variables (demographics, coexisting clinical conditions, risk factors, and previous cardiovascular history, clinical presentations, left ventricular function, CAD extent, ULMCA lesion type, or right coronary involvement),[6] which are listed in Table 1, were introduced into a multivariable model. No method was used to impute missing values

Table 1. Baseline Clinical and Angiographic Characteristics by Index Treatment Strategy

Variable	PCI (n=2850)	CABG (n=2337)	Medication (n=608)	*P* Value
Age, y	62.7±11.0	63.5±9.4	66.7±10.6	<0.001
Old age (≥65 y), %	1303 (45.7)	1161 (49.7)	364 (59.9)	<0.001
Male sex, %	2128 (74.7)	1779 (76.1)	421 (69.2)	0.002
BMI, kg/m²*	24.5±3.0	24.5±2.9	24.4±3.2	0.650
High BMI (≥25 kg/m²), %	1190 (41.8)	976 (41.8)	248 (40.8)	0.900
Atrial fibrillation, %	71 (2.5)	57 (2.4)	24 (3.9)	0.100
Hypertension, %	1626 (57.1)	1337 (57.2)	390 (64.1)	0.004
Diabetes mellitus				
Any, %	922 (32.4)	879 (37.6)	223 (36.7)	<0.001
Requiring insulin, %	174 (6.1)	204 (8.7)	52 (8.6)	0.001
Current smoker, %	718 (25.2)	666 (28.5)	167 (27.5)	0.030
Hyperlipidemia, %	1199 (42.1)	910 (38.9)	258 (42.4)	0.050
Previous myocardial infarction, %	230 (8.1)	316 (13.5)	61 (10.0)	<0.001
Previous stroke, %	214 (7.5)	180 (7.7)	61 (10.0)	0.100
Previous heart failure, %	71 (2.5)	101 (4.3)	33 (5.4)	<0.001
Previous PCI, %	489 (17.2)	285 (12.2)	97 (16.0)	<0.001
Family history of CAD, %	244 (8.6)	261 (11.2)	37 (6.1)	<0.001
Chronic lung disease, %	67 (2.4)	70 (3.0)	23 (3.8)	0.100
Chronic renal failure, %	98 (3.4)	78 (3.3)	30 (4.9)	0.150
Peripheral vascular disease, %	92 (3.2)	216 (9.2)	48 (7.9)	<0.001
Clinical presentation				<0.001
Stable angina, %	1170 (41.1)	652 (27.9)	253 (41.6)	
Unstable angina, %	1288 (45.2)	1461 (62.5)	250 (41.1)	
NSTEMI, %	284 (10.0)	178 (7.6)	67 (11.0)	
STEMI, %	108 (3.8)	46 (2.0)	38 (6.2)	
Ejection fraction, %	59.7±9.8	56.7±11.3	55.4±11.6	<0.001
Low ejection fraction (<50%), %	317 (11.1)	479 (20.5)	129 (21.2)	<0.001
Disease extent				<0.001
Left main only, %	463 (16.2)	105 (4.5)	60 (9.9)	
Left main with 1 VD, %	695 (24.4)	209 (8.9)	89 (14.6)	
Left main with 2 VD, %	922 (32.4)	524 (22.4)	143 (23.5)	
Left main with 3 VD, %	770 (27.0)	1498 (64.1)	316 (52.0)	
Distal bifurcation involvement, %	1673 (58.7)	1579 (67.6)	335 (55.1)	<0.001
Right CAD involvement, %	1121 (39.3)	1737 (74.3)	406 (66.8)	<0.001

Values are mean±SD or n (%). BMI indicates body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; and VD, vessel disease.

*BMI is calculated as the weight in kilograms divided by the square of the height in meters.

or adjust the model for missing data. The proportional hazards assumption was confirmed by the examination of log (–log [survival]) curves and testing of partial (Schoenfeld) residuals,[10] and no relevant violations were found in the PCI, CABG, and medication strata. Statistical analyses were done with SPSS software, version 21.0 (SPSS, Inc, Chicago, IL). All *P* values were 2-sided, and those <0.05 were considered statistically significant.

Results

Baseline Characteristics

During the study period, a total of 5795 patients with ULMCA disease were included in the IRIS-MAIN registry. Among them, 2850 (49.2%) patients underwent PCI with stent implantation, 2337 (40.3%) received CABG, and 608 (10.5%) were treated with medication alone. Baseline clinical and angiographic characteristics of patients according to index treatment modality are shown in Table 1. Overall, compared with patients who underwent percutaneous or surgical revascularization, those who were treated with medication were significantly older, were more likely to be women, and had a higher prevalence of combined risk factors or comorbidities (ie, hypertension, previous stroke, previous heart failure, previous PCI, and lower ejection fraction [EF]). Among patients with coronary revascularization, compared with patients treated with PCI, patients treated with CABG were older; were more likely to have diabetes mellitus, previous MI, previous heart failure, and peripheral vascular disease; were less likely to have stable angina; had a significantly lower EF; and had a more severe extent of CAD, distal bifurcation involvement, and combined right CAD.

Outcomes

During the follow-up period (median, 4.3 years; interquartile interval, 2.7–7.3), 1073 patients died, 266 had a MI, 151 had a stroke, 547 had repeat revascularization, and 1633 had at least 1 MACCE. The rates of MACCE and all-cause mortality according to index treatment modality during the 5-year follow-up period are shown in Table 2 and Figure 1. The

Table 2. Five-Year Observed Outcomes by Index Treatment Strategy*

Outcomes	PCI (n=2850)	CABG (n=2337)	Medication (n=608)
MACCE	591 (25.7)	547 (19.9)	217 (42.5)
Death	246 (11.3)	306 (14.1)	161 (32.0)
Myocardial infarction	69 (3.2)	159 (7.1)	19 (4.5)
Periprocedural myocardial infarction	26 (0.9)	122 (5.2)	…
Spontaneous myocardial infarction	43 (2.3)	37 (1.9)	19 (4.5)
Repeat revascularization	340 (15.0)	90 (4.4)	53 (12.0)
Stroke	41 (2.0)	65 (3.3)	12 (2.9)

MACCE was defined as a composite of death, myocardial infarction, stroke, and repeat revascularization. CABG indicates coronary artery bypass grafting; MACCE, major adverse cardiac or cerebrovascular event; and PCI, percutaneous coronary intervention.

*Event rates were estimated with the use of Kaplan–Meier estimates, and *P* value was derived from the log-rank test.

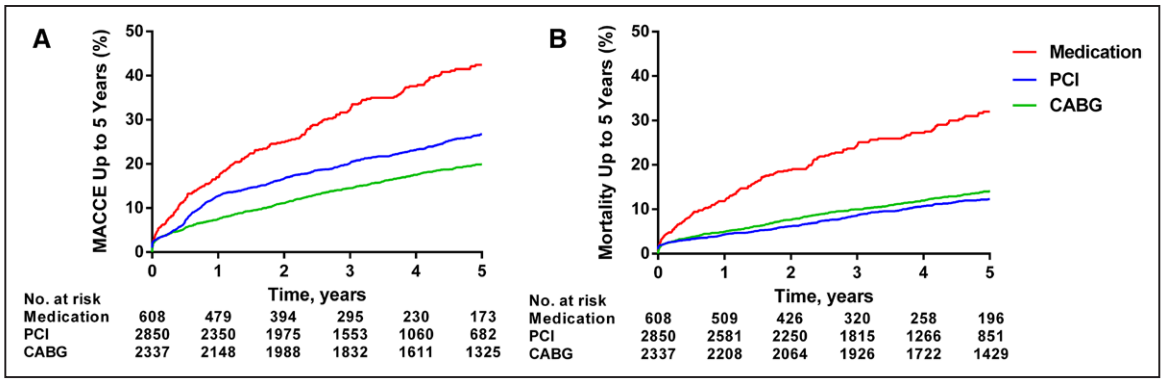

Figure 1. Kaplan–Meier curves for major adverse cardiac or cerebrovascular event and all-cause mortality stratified by treatment strategy. Major adverse cardiac or cerebrovascular event was defined as a composite of death, myocardial infarction, stroke, or repeat revascularization. *P* values were calculated using the log-rank test. CABG indicates coronary artery bypass graft surgery; MACCE, major adverse cardiac or cerebrovascular event; and PCI, percutaneous coronary intervention.

MACCE and overall death rates were substantially higher in the medication group than in the PCI and CABG groups (*P*<0.001); the MACCE rate was lowest in the CABG group, whereas the all-cause mortality was lowest in the PCI group. However, the rate of repeat revascularization was highest in patients with PCI and lowest in those with CABG. The MI and stroke rates were highest in patients treated with CABG and lowest in those treated with PCI.

Independent Predictors in Each Treatment Stratum

Independent predictors of MACCE and all-cause mortality in each treatment group after adjustment for baseline clinical characteristics are presented in Table 3 (PCI group), Table 4 (CABG group), and Table 5 (medication group). In patients who received PCI with stenting (Table 3), the 3 strongest predictors for occurrence of MACCE based on model Wald values were chronic renal failure (CRF), old age (≥65 years), and previous heart failure. CRF, old age (≥65 years), and low EF (<50%) were included the 3 strongest predictors of all-cause mortality in the PCI group. Differential 5-year MACCE and all-cause mortality rates stratified by the presence or absence of these clinically relevant predictors are shown in Figure 2A, showing good discriminatory capacity for predicting future events. In patients who received CABG, old age (≥65 years), CRF, and low EF (<50%) were the 3 strongest predictors of MACCE and all-cause mortality (Table 4), and differential event rates are illustrated in Figure 2B. For the highest-risk spectrum of medication alone group, old age (≥65 years), low EF (<50%), and diabetes mellitus were the 3 strongest predictors of MACCE and all-cause mortality (Table 5; Figure 2C).

In the revascularization group, independent predictors of MACCE and all-cause mortality are shown in Table I in the

Table 3. Independent Predictors of Major Adverse Cardiac or Cerebrovascular Event and Death in the Percutaneous Coronary Intervention Stratum

	MACCE*				Death			
Variable	Wald	HR	95% CI	*P* Value	Wald	HR	95% CI	*P* Value
Chronic renal failure	35.32	2.41	1.80–3.22	<0.001	92.60	4.92	3.55–6.80	<0.001
Old age (≥65 y)	23.59	1.48	1.27–1.74	<0.001	67.43	2.88	2.24–3.70	<0.001
Previous heart failure	14.58	1.95	1.38–2.74	<0.001	3.59	1.52	0.99–2.33	0.060
Diabetes mellitus	13.78	1.35	1.15–1.58	<0.001	9.39	1.43	1.14–1.79	0.002
Acute coronary syndrome	9.26	1.28	1.09–1.50	0.002	†	†	†	†
Low EF (<50%)	8.50	1.39	1.11–1.73	0.004	14.24	1.76	1.31–2.35	<0.001
Peripheral vascular disease	7.20	1.61	1.14–2.28	0.007	6.05	1.73	1.12–2.69	0.014
Atrial fibrillation	5.45	1.54	1.07–2.22	0.020	7.25	1.84	1.18–2.88	0.007
Hyperlipidemia	4.00	0.85	0.73–0.99	0.046	4.80	0.77	0.61–0.97	0.030
High BMI (≥25 kg/m^2)	†	†	†	†	5.27	0.76	0.59–0.96	0.020
Previous stroke	†	†	†	†	4.71	1.44	1.04–2.00	0.030
Chronic lung disease	†	†	†	†	3.90	1.65	1.004–2.67	0.048
Country variation (Korea vs rest of other country)	†	†	†	†	†	†	†	†

BMI indicates body mass index; CI, confidence interval; EF, ejection fraction; HR, hazard ratio; and MACCE, major adverse cardiac or cerebrovascular events.
*MACCE was defined as a composite of death, myocardial infarction, stroke, and repeat revascularization.
†Not in the final multivariate model.

Table 4. Independent Predictors of Major Adverse Cardiac or Cerebrovascular Event and Death in the Coronary-Artery Bypass Grafting Stratum

	MACCE*				Death			
Variables	Wald	HR	95% CI	*P* Value	Wald	HR	95% CI	*P* Value
Old age (≥65 y)	35.90	1.61	1.38–1.88	<0.001	75.82	2.25	1.88–2.70	<0.001
Chronic renal failure	41.22	2.71	2.00–3.67	<0.001	67.17	3.77	2.74–5.17	<0.001
Low EF (<50%)	31.59	1.62	1.37–1.91	<0.001	39.29	1.83	1.51–2.21	<0.001
Peripheral vascular disease	18.07	1.56	1.27–1.92	<0.001	7.11	1.38	1.09–1.75	0.008
Chronic lung disease	12.64	1.88	1.33–2.67	<0.001	16.69	2.19	1.50–3.18	<0.001
High BMI (≥25 kg/m^2)	9.17	0.78	0.67–0.92	0.002	5.72	0.80	0.67–0.96	0.020
Diabetes mellitus	8.76	1.26	1.08–1.48	0.003	5.92	1.24	1.04–1.48	0.020
Atrial fibrillation	5.80	1.62	1.09–2.41	0.020	11.75	2.03	1.35–3.04	0.001
Hyperlipidemia	4.01	0.85	0.73–0.99	0.045	6.54	0.79	0.66–0.95	0.010
Previous stroke	6.37	1.35	1.07–1.71	0.010	8.59	1.46	1.13–1.89	0.003
Sex, male	†	†	†	†	4.20	1.25	1.01–1.54	0.040
Country variation (Korea vs rest of other country)	†	†	†	†	†	†	†	†

BMI indicates body mass index; CI, confidence interval; EF, ejection fraction; HR, hazard ratio; and MACCE, major adverse cardiac or cerebrovascular events.

*MACCE was defined as a composite of death, myocardial infarction, stroke, and repeat revascularization.

†Not in the final multivariable model.

Data Supplement. Key predictors of MACCE and death were essentially similar. After risk adjustment, treatment with PCI (relative to CABG) was associated with an increased risk of MACCE. However, treatment modality was not retained as an independent predictor for mortality.

Discussion

The present study is, to the best of our knowledge, the largest cohort of patients with ULMCA disease to date to analyze the predictors of major cardiovascular events and death and to provide effect estimates for clinically relevant risk factors. Our major findings are that (1) significant differential outcomes were observed according to the index treatment modalities, and the rates of MACCE were highest in the medication group, intermediate in the PCI group, and lowest in the CABG group and (2) regardless of the index treatment strategy, the key clinical predictors for MACCE and all-cause mortality were generally uniform, whereas CRF, old age (≥65 years), previous heart failure, low EF (<50%), and diabetes mellitus were the strongest predictors for MACCE and death.

Previous several studies showed comparable clinical outcomes between PCI and CABG for ULMCA disease, with similar rates of mortality and serious composite outcome, a higher rate of stroke with CABG, and a higher rate of revascularization with PCI.[11–17] In most of these studies, patients treated with medication alone were excluded; therefore, the predictors and long-term prognosis of medically-treated patients with ULMCA disease were not adequately

Table 5. Independent Predictors of Major Adverse Cardiac or Cerebrovascular Event and Death in the Medication Stratum

	MACCE*				Death			
Variables	Wald	HR	95% CI	*P* Value	Wald	HR	95% CI	*P* Value
Old age (≥65 y)	30.18	2.16	1.64–2.84	<0.001	52.60	3.74	2.62–5.34	<0.001
Low EF (<50%)	14.60	1.73	1.31–2.29	<0.001	24.12	2.15	1.58–2.91	<0.001
Diabetes mellitus	11.54	1.57	1.21–2.04	0.001	10.32	1.64	1.21–2.22	0.001
Previous heart failure	5.76	1.70	1.10–2.62	0.020	8.69	1.95	1.25–3.05	0.003
Chronic renal failure	4.52	1.68	1.04–2.72	0.030	7.70	2.06	1.24–3.42	0.006
Previous PCI	†	†	†	†	5.71	0.58	0.37–0.91	0.020
Country variation (Korea vs rest of other country)	†	†	†	†	†	†	†	†

CI indicates confidence interval; EF, ejection fraction; HR, hazard ratio; MACCE, major adverse cardiac or cerebrovascular events; and PCI, percutaneous coronary intervention.

*MACCE was defined as a composite of death, myocardial infarction, stroke, and repeat revascularization.

†Not in the final multivariable model.

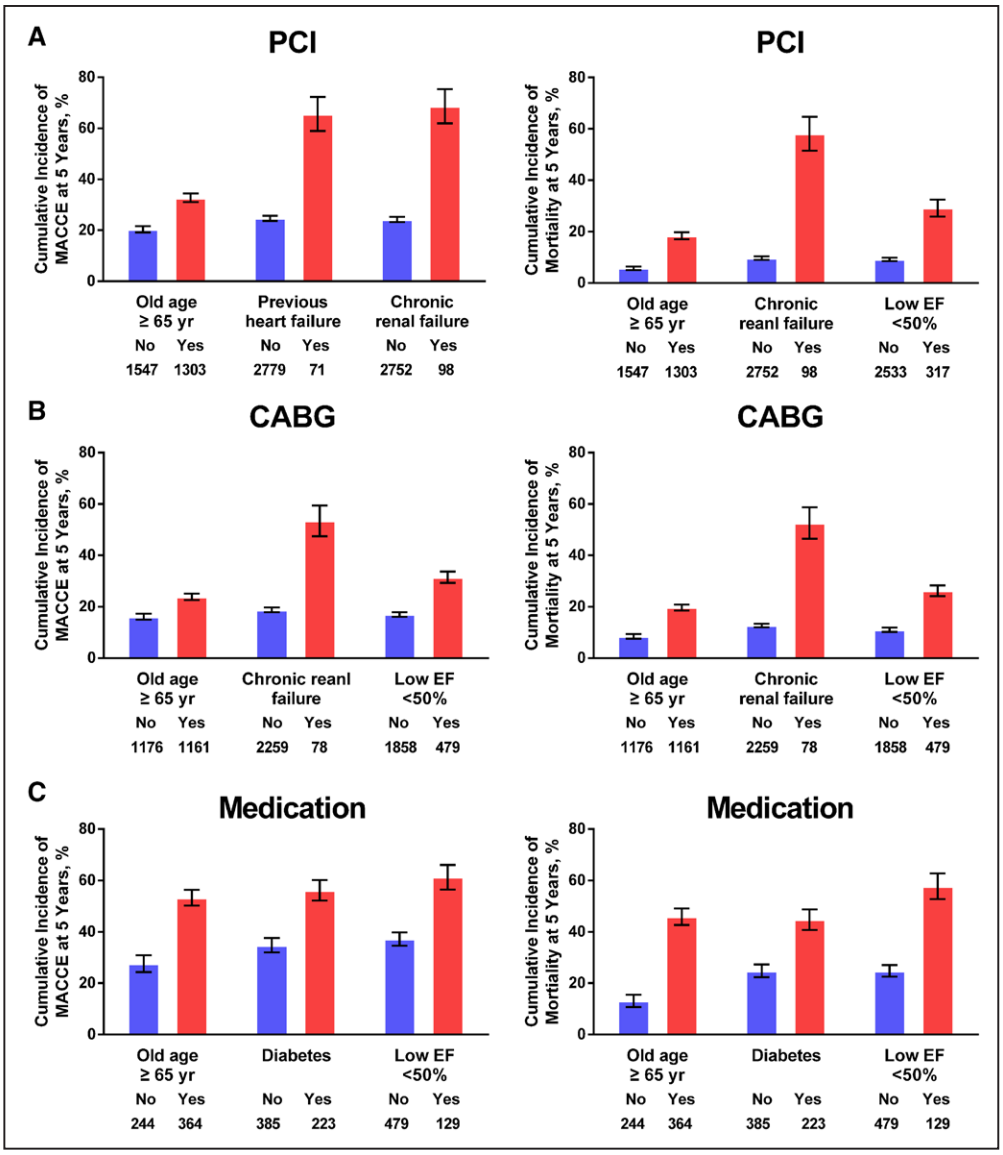

Figure 2. Five-year rates for major adverse cardiac or cerebrovascular events and all-cause mortality according to the 3 strongest predictors in each treatment group. Major adverse cardiac or cerebrovascular event was defined as a composite of death, myocardial infarction, stroke, and repeat revascularization. Cumulative incidences were estimated from the Kaplan–Meier curves at 5 y and are not simple tions. CABG indicates coronary artery bypass graft surgery; EF, ejection fraction; MACCE, major adverse cardiac or cerebrovascular event; and PCI, percutaneous coronary intervention.

evaluated. The current findings of the real-world registry showed that medication was associated with worst clinical outcomes rather than CABG or PCI. In our study, treatment choice was left to the physician or patient, and, thus, serious selection bias exists, particularly in the medication group. The short life expectancy or other severe comorbidities precluding revascularization procedures were strongly associated with increased risks of MACCE and mortality. Although baseline clinical covariates were substantially different according to the index treatment modalities, the key clinical predictors for MACCE and death were generally similar in each group of PCI, CABG, and medication alone; such findings suggest that, despite the distinct biological pathways of each risk factor, the prognostic impact of clinically relevant predictors were relatively uniform irrespective of treatment strategy.

Similar to previous reports involving multivessel CAD treated with PCI or CABG,[18–21] we found that renal insufficiency, low EF, age, and diabetes mellitus were the strongest predictors of MACCE and all-cause mortality in patients with ULMCA disease. In addition to these strongest predictors, other key predictors of major clinical events or death were peripheral vascular disease, atrial fibrillation, chronic lung disease, previous stroke, acute coronary syndrome, or high body mass index. In a clinical viewpoint, using these numerous clinically relevant variables that were considered potential predictors of MACCE and mortality in patients with ULMCA disease, an enhanced risk assessment would be feasible in the routine clinical practice, and also, this represents a first step to help us implement further preventive measures and tailored therapies (eg, use of specific devices or procedures, optimizing antithrombotic or concomitant medical therapy) in those patients at highest risk.

CRF was uniformly one of the strongest predictors of MACCE and all-cause mortality in patients with ULMCA who were treated either with PCI, CABG, or medication. Renal insufficiency was associated with low-grade inflammation and sympathetic nervous system or renin–angiotensin aldosterone system activation and was linked to cardiac disease with microvascular and metabolic abnormalities that might predispose an individual to ischemic or thrombotic vascular events.[22,23] Also, CRF was associated with an increased mortality, despite successful coronary revascularization.[24–26] Further studies are required to improve outcomes and guide decision making between CABG and PCI for patients with complex CAD and combined CRF.

Heart failure or low EF was also included in the strong predictors of cardiovascular events in patients with ULMCA disease regardless of treatment strategy. Optimal treatment for patients with CAD and left ventricular dysfunction remains controversial. In most clinical trials comparing PCI and CABG for the treatment of ULMCA disease, patients with severe left ventricular dysfunction were excluded,[11,12] and several registry studies and randomized trials showed conflicting clinical outcomes of PCI, CABG, or medication for patients with decreased systolic function.[27–29] Subsequent randomized trials will be critically important for the development of optimal treatment strategies for patients with CAD, heart failure, and severe left ventricular systolic dysfunction.

The presence of diabetes mellitus was also an important predictor of MACCE and all-cause mortality in patients with ULMCA disease and a more clinically important predictor of clinical events in the medication group in particular. Previous studies already showed that diabetes mellitus was associated with a diffuse form of atherosclerotic CAD and poor clinical outcomes in patients with complex CAD treated with either PCI or CABG.[30,31] Considering the high prevalence and prognostic impact of diabetes mellitus and the persistent lack of scientific evidence reflecting contemporary medical practice, further clinical trials beyond the FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) and the BARI 2D trials (Bypass Angioplasty Revascularization Investigation 2 Diabetes) are required to provide the evidence of the optimal medical treatment and revascularization approaches for patients with diabetes mellitus and advanced CAD in the real-world medical setting, with marked advancements in antidiabetic drugs, antithrombotic regimens, newer drug-eluting stents, and improved surgical procedures.

In our study, predictors of MACCE and death are essentially similar in the 3 treatment groups. This is in contrast with the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) and the SYNTAX II indicating that risk stratification can be used to select treatment modality. However, it is in line with the recent EXCEL (evaluation of XIENCE everolimus eluting stent versus coronary artery bypass surgery for effectiveness of left main revascularization) and NOBLE trial (Nordic-Baltic-British left main revascularization study) indication that the SYNTAX score (CAD extent) is not of major importance.[16,17] In addition, considerable differences of SYNTAX score by site assessment and angiographic core laboratory assessment noted in EXCEL and a limited predictability of comparative outcomes by SYNTAX score noted in NOBLE should be further debated. Such findings might represent a limitation of the SYNTAX score for optimal decision making of revascularization strategies in patients with left main coronary artery disease.

The primary results of 2 new trials of EXCEL and NOBLE showed conflicting results: EXCEL found that PCI is noninferior to CABG, whereas NOBLE shows that CABG is superior to PCI.[16,17] The conflicting results can be explained, in part, by substantial between-trial differences in patient assessment, risk profiles, study process, or device features, and a differential adoption of primary composite end point and definition of MI. For now, there might be no clear-cut answer on the optimal revascularization strategy in ULMCA disease. Nevertheless, the current analyses to identify the key predictive factors of major cardiovascular events and death in each treatment stratum would be clinically helpful for future risk stratification, more aggressive management in higher-risk subsets, and, thus, improving long-term outcomes.

Our study has some limitations. First, it was observational and has inherent methodological limitations; thus, its overall findings must be considered hypothetical and hypothesis generating only. Second, because the treatment choice was left to the physician or patient; thus, our findings are subject to selection bias. Third, varying treatment group sizes and follow-up durations represent a potential cause of group outcome differences that should be considered. Fourth, because the IRIS-MAIN registry contains patients enrolled long before the development of SYNTAX score, the systematic measurement of SYNTAX score was not available. Therefore, the detailed information of angiographic analysis cannot be incorporated for future risk-prediction modeling. Fifth, the protocol definition of MI was mostly different in recent clinical studies comparing PCI and CABG.[8,9,16,17,32,33] Because the composite end point of MACCE is sensitive to the definition of MI, study results can vary according to this discrepancy. Finally, because most of the patients in our registry were Asian, it remains uncertain whether these findings can be generalized to other ethnic or social groups with different patient and procedural characteristics.

In conclusion, using the largest multinational registry of patients with ULMCA disease treated with PCI, CABG, or medication, we found that several clinically relevant variables (CRF, old age, heart failure, low EF, and diabetes mellitus) were identified as the key determinants of major cardiovascular events and mortality. Our findings will help clinicians assess the risk of ULMCA disease and more aggressively manage patients with ULMCA disease who would be at higher risk of future events.

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Disclosures

None.

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Differential Event Rates and Independent Predictors of Long-Term Major Cardiovascular Events and Death in 5795 Patients With Unprotected Left Main Coronary Artery Disease Treated With Stents, Bypass Surgery, or Medication: Insights From a Large International Multicenter Registry

Se Hun Kang, Jung-Min Ahn, Cheol Hyun Lee, Pil Hyung Lee, Soo-Jin Kang, Seung-Whan Lee, Young-Hak Kim, Cheol Whan Lee, Seong-Wook Park, Duk-Woo Park and Seung-Jung Park

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