Generalizability of EXCEL and NOBLE results to a large registry population with unprotected left main coronary artery disease

Pil Hyung Lee[a], Se Hun Kang[a], Seungbong Han[b], Jung-Min Ahn[a], Jae Seok Bae[a], Cheol Hyun Lee[a], Soo-Jin Kang[a], Seung-Whan Lee[a], Young-Hak Kim[a], Cheol Whan Lee[a], Seong-Wook Park[a], Duk-Woo Park[a] and Seung-Jung Park[a]

Objective **The aim of this study was to determine how trial-based findings of EXCEL and NOBLE might be interpreted and generalizable in 'real-world' settings with comparison of data from the large-scaled, all-comer Interventional Research Incorporation Society – Left MAIN Revascularization (IRIS–MAIN) registry.**

Patients and methods **We compared baseline clinical and procedural characteristics and also determined how the relative treatment effect of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) was different in EXCEL and NOBLE, compared with those of the multicenter, IRIS–MAIN registry ($n = 2481$). The primary outcome for between-study comparison was a composite of death, myocardial infarction (MI), or stroke.**

Results **There were between-study differences in patient risk profiles (age, BMI, diabetes, and clinical presentation), lesion complexities, and procedural characteristics (stent type, the use of off-pump surgery, and radial artery); the proportion of diabetes and acute coronary syndrome was particularly lower in NOBLE than in other studies. Although there was interstudy heterogeneity for the protocol definition of MI, the risks for serious composite outcome of death, MI, or stroke were similar between PCI and CABG in EXCEL [hazard ratio (HR): 1.00; 95% confidence interval (CI): 0.79–1.26; $P = 0.98$] and in the matched cohort of IRIS–MAIN (HR: 1.08; 95%CI: 0.85–1.38; $P = 0.53$), whereas it was significantly higher after PCI than after CABG in NOBLE (HR: 1.47; 95%CI: 1.06–2.05; $P = 0.02$), which was driven by more common MI and stroke after PCI.**

Conclusion **In the comparison of a large-sized, all-comer registry, the EXCEL trial might represent better generalizability with respect to baseline characteristics and observed clinical outcomes compared with the NOBLE trial.** *Coron Artery Dis* **28:675–682**

Coronary Artery Disease 2017, **28**:675–682

Keywords: left main coronary artery disease, stent, surgery

[a]Department of Cardiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, and [b]Department of Applied Statistics, Gachon University, Seongnam, Korea

Correspondence to Duk-Woo Park, MD, PhD, Department of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: + 82 230 103 995; fax: + 82 2475 6898; e-mail: dwpark@amc.seoul.kr

Received 21 April 2017 **Revised** 19 June 2017 **Accepted** 5 July 2017

Introduction

Until recently, none of the randomized clinical trials comparing percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) for unprotected left main coronary artery (LMCA) disease were adequately powered and included contemporary PCI devices involving second generation drug-eluting stents (DES) [1]. The results of two important randomized trial, Evaluation of XIENCE Everolimus-Eluting Stent versus CABG for Effectiveness of Left Main Revascularization (EXCEL) and Nordic–Baltic–British Left Main Revascularization Study (NOBLE), have finally been released [2,3]. However, the two trials showed contradictory comparative results of PCI and CABG; EXCEL found PCI to be comparable to CABG, whereas NOBLE suggested CABG to be still better than PCI. This might intensify the confusion for clinical decision-making between PCI and CABG in patients with LMCA disease.

In addition, assessing the generalizability and the applicability of the findings from the EXCEL and NOBLE trials to the real-world population is likely to be of considerable interest, which could help the health care and scientific community understand the relevance and effect of clinical trial results. We, therefore, compared the baseline clinical and procedural characteristics of patients who were enrolled in EXCEL and NOBLE with those of patients who were enrolled in an unrestricted, 'all-comers' IRIS–MAIN (Interventional Research Incorporation Society–Left MAIN Revascularization) registry involving PCI and

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, *www.coronary-artery.com*.

DOI: 10.1097/MCA.0000000000000543

CABG for unprotected LMCA disease. We also compared the relative treatment effect of PCI and CABG in EXCEL and NOBLE with the results from our real-world registry.

Patients and methods

Study design and population

Details of the design and the organization of the EXCEL, NOBLE, and IRIS–MAIN study have been published elsewhere [1–3]. In brief, IRIS–MAIN is a nonrandomized, multinational, multicenter observational registry, and the study patients were recruited from 50 academic and community hospitals in Asia. The study had an 'all-comers' design, involving the consecutive enrollment of patients with unprotected LMCA disease who were treated with medical therapy, PCI, or CABG. The comparative key features of EXCEL, NOBLE, and IRIS–MAIN study are summarized in Table 1. From the IRIS–MAIN registry, a total of 2481 patients who were treated with second generation DES ($n = 1707$) and concurrent CABG ($n = 774$) between November 2006 and June 2014 were included and analyzed to compare with the results of the EXCEL and NOBLE trial. The current analysis was carried out as part of subanalyses of the IRIS–MAIN database and was approved by the institutional review board of the Asan Medical Center (Seoul, Korea), with a waiver of the requirement for written informed consent.

Outcome measures and definition

The primary outcome for between-study comparison was a serious composite endpoint of death from any cause, myocardial infarction (MI), or stroke. Additional secondary outcomes for comparison included the components of the primary outcome, as well as revascularization, and major adverse cardiac or cerebrovascular events (MACCE, defined as composite of death, MI, stroke, or revascularization). Detailed definitions of the study end points have been reported previously [1–3]. Overall, definitions for death, stroke, or revascularization were similar among studies. The protocol definition used for MI varied across studies. In IRIS–MAIN, MI was defined as follows: (a) if occurring within 48 h after the procedure, increase in the creatine kinase-myocardial band (CK-MB) more than five times the upper reference limit (URL) with at least one of the following: new pathologic Q waves or new bundle branch block, new graft or native coronary occlusion on angiography, and new regional wall motion abnormality or loss of viable myocardium on imaging studies; (b) if occurring after 48 h, increase in the CK-MB above URL with ischemic symptoms or signs; this MI definition was similar to the criteria used in our previous trials comparing

Table 1 Key features of each clinical study

Designs	EXCEL trial	NOBLE trial	IRIS–MAIN registry
Study type	Multicenter (126 sites in North/South America, Europe, Asia Pacific), prospective, open-label, randomized, noninferiority design trial comparing PCI and CABG	Multicenter (36 sites in northern Europe), prospective, open-label, randomized, noninferiority design trial comparing PCI and CABG	Multicenter (50 sites in Asia), prospective, nonrandomized observational registry including PCI, CABG, or medication alone
Main inclusion criteria	Unprotected LMCA disease with angiographic DS > 70%, as estimated visually, or 50% ≤ DS <70% with at least one of following: (a) noninvasive evidence of ischemia referable to LMCA lesion; (b) IVUS MLA ≤ 6.0 mm^2; or (c) FFR ≤ 0.80	Unprotected LMCA disease with angiographic DS > 50%, as estimated visually, or FFR <0.8	Unprotected LMCA disease with angiographic DS > 50%, as estimated visually
Key exclusion criteria	SYNTAX score ≥ 33, prior PCI at left main (any time) or any other coronary artery (within 1 year), prior CABG, concomitant valvular or aortic surgery, CK-MB more than normal or recent MI with CK-MB still elevated, left main reference vessel diameter <2.25 or > 4.25 mm	STEMI within 24 h, > 3 or complex additional coronary lesions (length > 25 mm, chronic total occlusion, two-stent bifurcation, calcified or tortuous vessel morphology), patient is too high risk for CABG or PCI, expected survival <1 year	Minimal exclusion criteria (prior CABG, concomitant valvular or aortic surgery)
Primary endpoint	Composite of all-cause death, MI, or stroke	Composite rate of all-cause death, nonprocedural MI, repeat revascularization, or stroke	Outcomes of interest were death, MI, stroke, repeat revascularization, and its composite outcome
Recruitment period	September 2010–March 2014	December 2008–January 2015	November 2006–December 2013
Follow-up period (median) (years)	3.0 (2.4–3.0)	3.1 (2.0–5.0)	3.0 (2.0–4.1)
Number of CABG patients	957	592	774
Number of PCI patients	948	592	1707
Stent type used for PCI	XIENCE cobalt–chromium everolimus-eluting stent	BioMatrix biolimus-eluting stent recommended since March 2010, but other CE-marked DES allowed	Any second generation DES available in each participating center

CABG, coronary artery bypass grafting; CK-MB, creatine kinase-myocardial band; DES, drug-eluting stent; DS, diameter stenosis; EXCEL, Evaluation of XIENCE Everolimus-Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; FFR, fractional flow reserve; IRIS—MAIN, Interventional Research Incorporation Society—Left MAIN Revascularization; IVUS, intravascular ultrasound; LMCA, left main coronary artery; MI, myocardial infarction; MLA, minimal lumen area; NOBLE, Nordic–Baltic–British Left Main Revascularization Study; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; SYNTAX, Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

PCI and CABG [4,5]. In EXCEL, periprocedural and spontaneous MI were separated at 72 h after the procedure and any elevation of CK-MB more than 10 times URL was also included as periprocedural MI. In NOBLE, only nonprocedural MI, which was defined as an increase in CK-MB or troponin more than one time the URL with ischemic symptoms or signs, was used.

Statistical analysis

The primary objective of this study was to assess how baseline features and procedures characteristics of randomized trials might be different compared with those of a real-world registry. Baseline characteristics including patient demographics, cardiovascular risk factors, clinical presentation, left ventricular function, the extent of coronary disease, and details of the procedures were compared between EXCEL, NOBLE, and the IRIS–MAIN study. Categorical variables are summarized as number (percentage) and continuous variables as mean ± SD or median (interquartile range).

A second objective of the study was to determine how the relative treatment effect of PCI and CABG in randomized trials differs from the findings in a real-world registry. Given the differences in the baseline characteristics between PCI and CABG enrolled in an observational study, propensity score matching was used to assemble a trial-like cohort of patients with similar baseline characteristics and who might be equivalently amenable to the two revascularization strategies. The propensity score is a conditional probability of having a particular exposure (PCI with first-generation or second generation DES versus concurrent CABG) given a set of baseline measured covariates [6]. The propensity score was estimated nonparametrically by fitting a logistic regression model using the variables outlined in Table 2. Matching was performed by a 1 : 1 matching protocol without replacement (greedy matching algorithm) with a caliper width equal to 0.2 of the SD of the logit of the propensity score. Standardized differences were estimated for all the baseline covariates before and after matching and values of less than 10.0% for a given covariate indicate a relatively small imbalance [7]. A Cox proportional hazards regression model with robust SEs that accounts for the clustering of the pairs was used to compare the risks of outcomes in the matched cohort. In addition, the characteristics and outcomes of unmatched patients in IRIS–MAIN, for whom clinical and anatomic equipoise for both PCI and CABG was not present, were assessed to characterize the features of a real-world population, who would not fulfill the eligibility criteria for clinical trials. All reported *P* values are two-sided and have not been adjusted for multiple testing. All the analyses were carried out using R software version 3.1.2.

Results

Patients and procedures characteristics

Baseline clinical and angiographic characteristics comparing randomized trials and real-world registry stratified by treatment strata are summarized in Table 2. Patients enrolled in EXCEL and NOBLE were slightly older than those in the IRIS–MAIN cohort. The mean BMI was lower in IRIS–MAIN than in EXCEL or NOBLE. Approximately one-third of patients in EXCEL and IRIS–MAIN had diabetes, but the proportion of diabetes was considerably lower in NOBLE. In addition, the proportion of acute coronary syndrome was substantially lower in NOBLE than in other studies. The mean or the median ejection fraction was more than 55% in all studies, which was comparable between PCI and CABG in randomized trials, but was significantly lower in CABG patients than in PCI patients of the registry. Compared with EXCEL (NOBLE data is not available), patients with more complex additional coronary disease (i.e. left main plus three-vessel disease) were more common in IRIS–MAIN (especially, in the CABG group). However, distal left main bifurcation involvement was more present in EXCEL and NOBLE than in IRIS–MAIN.

Procedural and surgical characteristics are shown in Table 3. In IRIS–MAIN, more than half of the patients were treated with an everolimus-eluting stent and one-third were treated with zotarolimus-eluting stents. Overall, the total number and the total length of stent per patient seem to be similar between randomized trials and registry. In EXCEL and NOBLE, more than 70% of the patients received PCI with intravascular ultrasound (IVUS) guidance, which was similar to IRIS–MAIN. In the CABG stratum, the proportion of patients who underwent off-pump surgery was considerably lower in EXCEL and NOBLE than in IRIS–MAIN. The number of total conduits was higher in IRIS–MAIN than in EXCEL and NOBLE. The internal mammary artery was used in more than 90% in both randomized trials and registry, whereas the radial artery was used in less than 10% in randomized trials, but more commonly used in the real-world registry.

Clinical outcomes

In IRIS–MAIN, after propensity score matching to assemble a cohort of patients with clinical equipoise for PCI and CABG at baseline, there were 670 matched pairs of patients with a median follow-up duration of 3.0 years (IQR: 2.0–4.1). Baseline characteristics and Kaplan–Meier curves for each clinical outcome in matched cohort of IRIS–MAIN are provided in Supplementary eTable 1 and Supplementary eFigure 1 (Supplemental digital content 1, *http://links.lww.com/MCA/A162*).

Comparative event rates and risks for relevant clinical outcomes between EXCEL, NOBLE, and the matched cohort of IRIS–MAIN are summarized in Table 4. All-cause mortality was similar between PCI and CABG in EXCEL,

Table 2 Comparison of baseline characteristics of the patients according to revascularization strata and clinical study

	PCI cohort			CABG cohort		
	EXCEL ($n=948$)	NOBLE ($n=592$)	IRIS–MAIN ($n=1707$)	EXCEL ($n=957$)	NOBLE ($n=592$)	IRIS–MAIN ($n=774$)
Age (years)	66.0±9.6	66.2±9.9	64.4±10.6	65.9±9.5	66.2±9.4	65.2±9.3
Male sex	722 (76.2)	476 (80.4)	1326 (77.7)	742 (77.5)	452 (76.4)	616 (79.6)
BMI	28.6±5.0	27.9±4.5	24.5±3.0	28.8±4.9	28.1±4.4	24.5±3.1
Diabetes	286 (30.2)	86 (14.5)	575 (33.7)	268 (28.0)	90 (15.2)	327 (42.2)
Hypertension	703 (74.5)	386 (65.2)	1089 (63.8)	701 (73.9)	389 (65.7)	516 (66.7)
Current smoker	222 (24.1)	108 (18.2)	406 (23.8)	193 (20.8)	127 (21.4)	206 (26.6)
Hyperlipidemia	668 (71.5)	482 (81.5)	836 (49.0)	652 (69.3)	464 (78.4)	406 (52.5)
Previous MI	169 (18.1)	NA	112 (6.6)	161 (16.9)	NA	89 (11.5)
Previous stroke	52 (5.5)	NA	148 (8.7)	67 (7.0)	NA	71 (9.2)
Previous PCI	174 (18.4)	116 (19.6)	263 (15.4)	152 (15.9)	118 (19.9)	100 (12.9)
Previous heart failure	67 (7.1)	NA	45 (2.6)	59 (6.2)	NA	24 (3.1)
Peripheral vascular disease	97 (10.3)	NA	76 (4.5)	84 (8.8)	NA	55 (7.1)
Chronic lung disease	65 (6.9)	NA	41 (2.4)	81 (8.5)	NA	26 (3.4)
Chronic renal insufficiency[a]	164 (17.6)	NA	75 (4.4)	144 (15.4)	NA	38 (4.9)
Clinical indication						
Stable angina or silent ischemia	573 (60.8)	486 (82.1)	697 (40.8)	575 (60.5)	491 (82.9)	337 (43.5)
ACS	369 (39.2)	106 (17.9)	1010 (59.2)	375 (39.5)	100 (16.9)	437 (56.5)
Ejection fraction (%)						
Mean	57.0±9.6	60 (IQR: 55–65)	59.0±10.2	57.3±9.0	60 (IQR: 52–64)	55.3±11.5
Disease extent						
LM only	163 (17.3)	NA	184 (10.8)	167 (17.8)	NA	21 (2.7)
LM plus 1VD	292 (31.0)	NA	440 (25.8)	292 (31.2)	NA	45 (5.8)
LM plus 2VD	325 (34.5)	NA	620 (36.3)	295 (31.5)	NA	155 (20.0)
LM plus 3VD	162 (17.2)	NA	463 (27.1)	182 (19.4)	NA	553 (71.4)
LM location						
Ostium or shaft	177 (18.2)	115 (19.4)	564 (33.0)	216 (20.8)	110 (18.6)	213 (27.5)
Distal bifurcation	771 (81.8)	477 (80.6)	1143 (67.0)	741 (79.2)	482 (81.4)	561 (72.5)
Right CAD	NA	NA	702 (41.1)	NA	NA	622 (80.4)
SYNTAX score[b]	20.6±6.2	22.5±7.5	NA	20.5±6.1	22.4±8.0	NA

Continuous variables are presented as mean±SD or median (IQR) and categorical variables are presented as number (percentage).
ACS, acute coronary syndrome; CAD, coronary artery disease; IQR, interquartile range; LM, left main; VD, vessel disease; other abbreviations as in Table 1.
[a]Chronic renal insufficiency was defined as creatinine clearance rate less than 60 ml/min in EXCEL and as serum creatinine more than or equal to 2.0 mg/dl in IRIS–MAIN.
[b]In the EXCLE trial, the SYNTAX score by core laboratory assessment was 26.9±8.8 in the PCI arm and 26.0±9.8 in the CABG arm.

NOBLE, and IRIS–MAIN (Fig. 1a). Although statistically insignificant, there was a trend toward a lower risk of stroke with PCI in EXCEL and IRIS–MAIN. By contrast, the risk of stroke was more than two times higher after PCI in NOBLE (Fig. 1b). Because of the different protocol definition of MI, the incidence and the relative treatment effect for MI was significantly different among studies. The risk of MI was similar between PCI and CABG in EXCEL (any periprocedural and spontaneous MI considered) and in IRIS–MAIN (periprocedural Q-wave MI and any spontaneous MI considered), but was higher in PCI patients in NOBLE (only spontaneous MI considered) (Fig. 2a). Accordingly, the risk for serious composite of death, MI, or stroke, which was defined as the primary comparative outcome between-study in the current analysis, was similar between PCI and CABG in EXCEL and the matched cohort of IRIS–MAIN. However, this composite outcome was significantly higher in the PCI group than in the CABG group in NOBLE (Fig. 2b). The rate of revascularization was consistently higher after PCI than after CABG, which was consistent in all three studies, but the relative risk was considerably higher in the registry. The risk of MACCE including revascularization was significantly higher in PCI patients in NOBLE and IRIS–MAIN, but tended to be nonsignificantly higher after PCI in EXCEL.

Unmatched cohort in the registry

To characterize the baseline features and outcomes in PCI and CABG patients without baseline clinical equipoise, who might be preferentially eligible for one of treatment, we also analyzed the unmatched cohort of IRIS–MAIN. As expected, unmatched CABG patients were at higher risk at baseline than matched CABG patients and vice versa for PCI patients (Supplementary eTable 2, Supplemental digital content 1, *http://links.lww.com/MCA/A162*). In the unmatched cohort, the risks of death, stroke, serious composite outcome, and MACCE were markedly higher in the CABG group than in the PCI group (Supplementary eTable 3 and Supplementary eFigure 2, Supplemental digital content 1, *http://links.lww.com/MCA/A162*). Despite this, the risk of revascularization was consistently higher in the PCI group.

Discussion

The aims of the current analysis are to describe the similarities and disparity between trial-based findings of EXCEL and NOBLE and those of a real-world registry as well as to explore their applicability and future implications in a real-world setting. The main findings of our study appear to suggest that the baseline characteristics and results are relatively similar in EXCEL and in

Table 3 Comparison of procedural and operative characteristics of the patients according to revascularization strata and clinical study

	PCI cohort			CABG cohort		
	EXCEL ($n=935$)	NOBLE ($n=580$)	IRIS–MAIN ($n=1707$)	EXCEL ($n=923$)	NOBLE ($n=567$)	IRIS–MAIN ($n=774$)
PCI procedures						
Stent technique				–	–	–
Left main stenting only or simple crossover	NA	395 (69.7)	1332 (78.0)	–	–	–
Two-stent technique	NA	181 (31.4)	375 (22.0)	–	–	–
Final kissing balloon	NA	277 (54.5)	507 (29.7)	–	–	–
Total stent number per patient	2.4 ± 1.5	2 (IQR: NA)	2.2 ± 1.2	–	–	–
Stent number in LMCA	NA	1 (IQR: 1–2)	1.7 ± 0.9	–	–	–
Total stent length per patient	49.1 ± 35.6	52 (IQR: NA)	52.3 ± 34.1	–	–	–
IVUS-guided PCI	722 (77.2)	430 (74.1)	1309 (76.7)	–	–	–
Use of hemodynamic support device	53 (5.2)	NA	85 (5.0)	–	–	–
DES type						
CoCr-EES	2251[a] (98.4)	–	626 (36.7)	–	–	–
BES	–	538 (89.1)	144 (8.4)	–	–	–
PtCr-EES	–	–	377 (22.1)	–	–	–
Re-ZES	–	–	459 (26.9)	–	–	–
PC-ZES	–	–	33 (1.9)	–	–	–
Other second DES	–	–	68 (4.0)	–	–	–
SES	–	42 (10.9)	–	–	–	–
CABG procedures						
Off-pump surgery	–	–	–	271 (29.4)	88 (15.6)	537 (69.4)
Number of conduits per patient	–	–	–	2.6 ± 0.8	2.5 ± 0.7	2.9 ± 0.9
Number of arterial grafts	–	–	–	1.4 ± 0.6	NA	1.6 ± 0.9
Number of vein grafts	–	–	–	1.2 ± 0.9	NA	1.3 ± 1.0
Use of internal mammary artery	–	–	–	908 (98.8)	524 (93.1)	729 (94.2)
Use of radial artery	–	–	–	55 (6.0)	26 (4.8)	283 (36.6)

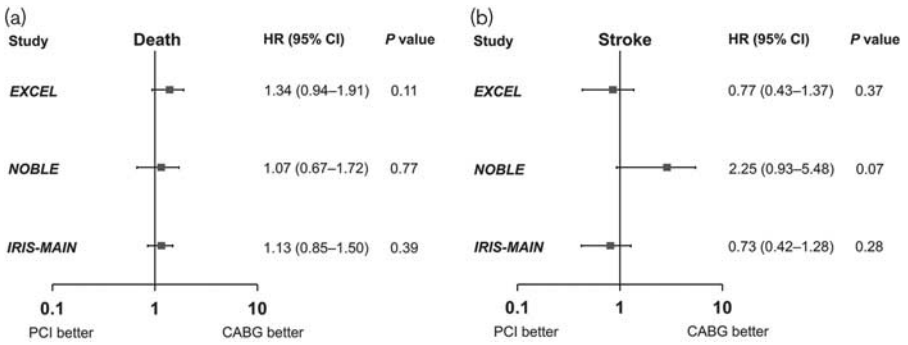
The patient numbers of EXCEL and NOBLE trials are based on per-protocol analyses.
Continuous variables are presented as mean ± SD or median (IQR) and categorical variables are presented as number (percentage).
BES, biolimus-eluting stent(s); CoCr-EES, cobalt–chromium everolimus-eluting stent(s); IMA, internal mammary artery; IQR, interquartile range; LMCA, left main coronary artery; PC-ZES, phosphorylcholine polymer-based zotarolimus-eluting stent(s); PtCr-EES, platinum chromium everolimus-eluting stent(s); Re-ZES, resolute zotarolimus-eluting stent(s); SES, sirolimus-eluting stent(s); other abbreviations as in Table 1.
[a]Stent number.

Table 4 Event rates and risk of clinical outcomes of percutaneous coronary intervention versus coronary artery bypass grafting in randomized trial of EXCEL and NOBLE and in the propensity-matched cohort of Interventional Research Incorporation Society–Left MAIN Revascularization registry

	EXCEL (PCI 948 vs. CABG 957)			NOBLE (PCI 592 vs. CABG 592)			IRIS–MAIN matched cohort ($n=670$)		
Outcomes	Event rate (at 3 years)	HR (95% CI)	*P* value	Event rate (at 5 years)	HR (95% CI)	*P* value	Event rate (at 3 years)	HR (95% CI)	*P* value
Death, MI, and stroke									
PCI	15.4	1.00 (0.79–1.26)	0.98	13	1.47 (1.06–2.05)	0.02	12.3	1.08 (0.85–1.38)	0.53
CABG	14.7	Reference		22	Reference		12.0	Reference	
Death									
PCI	8.2	1.34 (0.94–1.91)	0.11	11.6	1.07 (0.67–1.72)	0.77	9.7	1.13 (0.85–1.50)	0.39
CABG	5.9	Reference		9.5	Reference		9.3	Reference	
MI									
PCI	8.0	0.93 (0.67–1.28)	0.64	6.9	2.88 (1.40–5.90)	0.004	2.2	1.38 (0.72–2.64)	0.34
CABG	8.3	Reference		1.9	Reference		1.4	Reference	
Stroke									
PCI	2.3	0.77 (0.43–1.37)	0.37	4.9	2.25 (0.93–5.48)	0.07	1.7	0.73 (0.42–1.28)	0.28
CABG	2.9	Reference		1.7	Reference		2.5	Reference	
Revascularization									
PCI	12.9	1.72 (1.27–2.33)	< 0.001	16.2	1.50 (1.04–2.17)	0.03	10.6	4.67 (2.76–7.89)	< 0.001
CABG	7.6	Reference		10.4	Reference		2.1	Reference	
MACCE									
PCI	23.1	1.18 (0.97–1.45)	0.10	28.9	1.48 (1.11–1.96)	0.007	20.9	1.65 (1.33–2.05)	< 0.001
CABG	19.1	Reference		19.1	Reference		13.6	Reference	

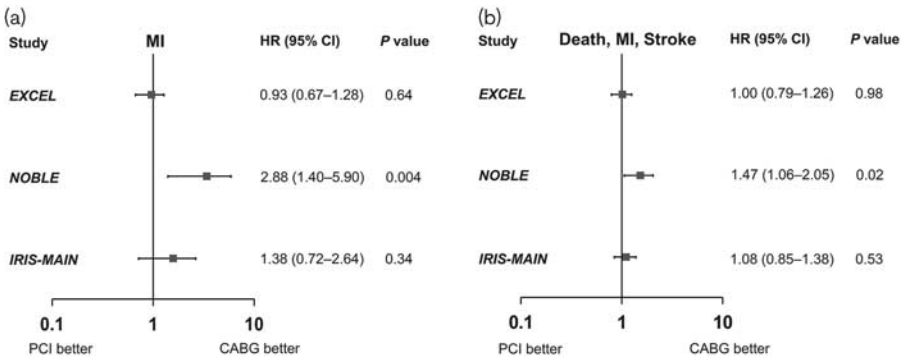
Event rates are shown as Kaplan–Meier estimates (percentage of events).
CI, confidence interval; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events; other abbreviations as in Table 1.

Fig. 1



Comparative hazard ratios for death and stroke according to clinical studies. Hazard ratios [PCI vs. CABG (reference)] are shown for death from any causes (Panel A) and stroke (Panel B). CABG, coronary artery bypass graft surgery; CI, confidence interval; EXCEL, HR, hazard ratio; IRIS–MAIN, Interventional Research Incorporation Society—Left MAIN Revascularization; NOBLE, Nordic–Baltic–British Left Main Revascularization Study; PCI, percutaneous coronary intervention.

Fig. 2



Comparative hazard ratios for MI and composite outcome according to clinical studies. Hazard ratios [PCI vs. CABG (reference)] are shown for MI (Panel A), and composite of death, MI, or stroke (Panel B). CABG, coronary artery bypass graft surgery; CI, confidence interval; EXCEL, Evaluation of XIENCE Everolimus-Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; HR, hazard ratio; IRIS–MAIN, Interventional Research Incorporation Society—Left MAIN Revascularization; NOBLE, Nordic–Baltic–British Left Main Revascularization Study; MI, myocardial infarction; PCI, percutaneous coronary intervention.

this large registry. With respect to serious composite outcome (death, MI, or stroke), the results of the EXCEL trial and the IRIS–MAIN registry suggest that PCI with contemporary DES is an acceptable alternative to CABG in patients with LMCA disease who have clinical equipoise for either strategy of revascularization; however, the results of the NOBLE trial suggest that CABG is still better than PCI.

Although a randomized trial is the gold standard to control for treatment selection bias, it cannot be easily feasible, with measurement of limited outcomes at a high cost per patient, and the results may not be generalizable because of a highly selected population. Instead, nonrandomized, observational data from large clinical databases can complement data from trials and may better reflect real-world practice. In the current analysis, we sought to determine the broader population to whom the findings of the EXCEL and NOBLE could be generalized and applicable. Our findings may contribute significantly toward clinical interpretation and understanding of the features and conflicting results of the EXCEL and NOBLE when applied in real-world practice.

There were considerable between-study differences in patient risk profiles (age, BMI, diabetes, and clinical presentation), lesion complexities (extent of coronary disease and involvement of distal bifurcation), and procedural characteristics (DES type, off-pump surgery, and use of the radial artery). Especially, the proportion of patients with diabetes and acute coronary syndromes was markedly lower in NOBLE, inconsistent with other studies. Over the last decade, changes in practice have occurred that would be expected to improve PCI and CABG outcomes [1]. This pattern was also observed in EXCEL and NOBLE. Second generation DESs, which

are associated with a low rate of stent thrombosis and revascularization [8], were almost exclusively used. Also, IVUS guidance was used in more than 70% of PCI patients in these trials, which was almost like the real-world practice. Considering the benefits of IVUS in defining disease distribution, informing stent sizing and technique, and enhancing stent optimization, the role of this tool in reducing left main restenosis, stent thrombosis, and related complications may be clinically meaningful [9,10]. However, in the CABG stratum, off-pump surgery and additional arterial revascularization using the radial artery were used less frequently in EXCEL and NOBLE than in the IRIS–MAIN registry; therefore, it is still argued that the operative practice in trials is probably less representative of real-world practice.

Until recently, several randomized or observational studies and meta-analyses suggest comparable outcomes between PCI and CABG for LMCA or multivessel disease, with similar rates of mortality and serious composite outcome of death, MI, or stroke, but more frequent stroke with CABG, and greater need for revascularization with PCI [4,5,11–13]. As a consequence, the risk of repeat revascularization of PCI needs to be balanced against the invasiveness and the risk of stroke of CABG. These findings were maintained in EXCEL and in matched cohort of IRIS–MAIN, but different findings were observed in NOBLE. All-cause mortality was similar after PCI or CABG, which was consistent among studies. However, there was interstudy heterogeneity for MI definition, which could lead to an imprecise estimate of the overall treatment effect. Irrespective of any symptom, sign, or ECG criteria, increase of CK-MB more than 10 times the URL was considered an MI event in EXCEL, but not in NOBLE and in IRIS–MAIN. When isolated CK-MB elevation more than 10 times was included in the MI definition of our registry, the incidence of periprocedural MI was significantly higher after CABG than after PCI (10.4 vs. 4.9%, $P < 0.001$). The protocol definition of MI was mostly different in recent landmark randomized trials comparing PCI with DES and CABG [4,5,11,14]. Whether only clinically driven MI should be considered or biomarker-driven MI without clinical symptoms or signs should also be included in trials comparing PCI and CABG is not yet clearly determined. As the hard composite endpoint (i.e. death, MI, or stroke) is very sensitive to the definition of periprocedural MI and trial results can vary widely for this, additional studies and efforts by trialists are warranted to improve standardization of the MI definition, which can be uniformly applied in several clinical trials. Unexpectedly, the 5-year risk of stroke was more than two times higher after PCI rather than after CABG in NOBLE, which was the in contrast to the results of EXCEL and IRIS–MAIN. Higher stroke after CABG was consistently observed in the SYNTAX and FREEDOM trial [11,14]. Several meta-analyses also showed similar findings [15,16]. The clear explanation for such a contradictory finding in NOBLE is still lacking and might be because of chance [17]. The risk of repeat revascularization after PCI relative to after CABG was considerably higher in IRIS–MAIN than in EXCEL and NOBLE, which might be explained by the fact that complete revascularization was intended in trials and there was no mandatory protocol for not permitting routine angiographic follow-up in registry.

Features of the unmatched cohort in our registry might indirectly reflect the patients who did not meet clinical and anatomic eligibility for both PCI and CABG in trial. As expected, unmatched CABG patients in our registry had too extensive or complex coronary disease or other clinical conditions, in which clinical equipoise was not present compared with PCI. By contrast, unmatched PCI patients were younger and had less complex clinical and anatomic characteristics than matched PCI patients. In the current practice pattern, these patients at lower risk might be preferentially treated by PCI rather than CABG, although clinical equipoise was present for either PCI or CABG. Also, the fact that more than 60% of patients might be eligible for PCI in the EXCEL screening registry suggests that the practical threshold for choosing PCI for LMCA treatment seems to be less stringent. Considering the lower invasiveness and the current practice pattern of PCI, further studies are required to better guide decision-making between PCI and CABG in patients with less complex disease (i.e. isolated left main disease, ostial or shaft lesion, or additional single-vessel disease).

Several limitations of the current study should be considered. First, our study is observational and therefore overall findings are explorative and hypotheses-generating only. Second, the choice of the treatment strategy in our registry was not randomized and thus is subject to selection bias. Despite rigorous statistical adjustments using propensity score matching, comparison of the relative treatment effects of PCI and CABG in our study with those from randomized trials might be limited because of unmeasured confounders. Third, as the IRIS–MAIN registry includes patients enrolled long before the development of the SYNTAX score, the systematic measurement of the SYNTAX score was not available. However, considerable differences in the SYNTAX score by site assessment and angiographic core laboratory assessment noted in EXCEL and a limited predictability of comparative outcomes by the SYNTAX score noted in NOBLE should be debated further. Such findings might represent a limitation of the SYNTAX score for optimal decision-making of revascularization strategies in patients with LMCA disease. Finally, assessment of complications and adjudication of end points tend to be less rigorous in registries and this also limits the value of the comparison.

Conclusion

We attempted to assess the generalizability and applicability of the findings from EXCEL and NOBLE to a real-world population compared with data from a large-scale, all-comer registry. Our explorative study suggests that EXCEL patients are less likely to be different in baseline characteristics and have similar outcomes (propensity adjusted for the registry), and therefore EXCEL is more generalizable than NOBLE in terms of inclusion and outcomes.

Acknowledgements

This work was supported by the CardioVascular Research Foundation, Seoul, Korea (2015-09).

Conflicts of interest

There are no conflicts of interest.

References

1 Lee PH, Ahn JM, Chang M, Baek S, Yoon SH, Kang SJ, *et al*. Left main coronary artery disease: secular trends in patient characteristics, treatments, and outcomes. *J Am Coll Cardiol* 2016; **68**:1233–1246.
2 Stone GW, Sabik JF, Serruys PW, Simonton CA, Genereux P, Puskas J, *et al*. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. *N Engl J Med* 2016; **375**:2223–2235.
3 Makikallio T, Holm NR, Lindsay M, Spence MS, Erglis A, Menown IB, *et al*. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. *Lancet* 2016; **388**:2743–2752.
4 Park SJ, Kim YH, Park DW, Yun SC, Ahn JM, Song HG, *et al*. Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Engl J Med* 2011; **364**:1718–1727.
5 Park SJ, Ahn JM, Kim YH, Park DW, Yun SC, Lee JY, *et al*. Trial of everolimus-eluting stents or bypass surgery for coronary disease. *N Engl J Med* 2015; **372**:1204–1212.
6 Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983; **70**:41–55.
7 Normand ST, Landrum MB, Guadagnoli E, Ayanian JZ, Ryan TJ, Cleary PD, *et al*. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. *J Clin Epidemiol* 2001; **54**:387–398.
8 Palmerini T, Benedetto U, Biondi-Zoccai G, Della Riva D, Bacchi-Reggiani L, Smits PC, *et al*. Long-term safety of drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol* 2015; **65**:2496–2507.
9 Park SJ, Kim YH, Park DW, Lee SW, Kim WJ, Suh J, *et al*. Impact of intravascular ultrasound guidance on long-term mortality in stenting for unprotected left main coronary artery stenosis. *Circ Cardiovasc Interv* 2009; **2**:167–177.
10 De la Torre Hernandez JM, Baz Alonso JA, Gomez Hospital JA, Alfonso Manterola F, Garcia Camarero T, Gimeno de Carlos F, *et al*. Clinical impact of intravascular ultrasound guidance in drug-eluting stent implantation for unprotected left main coronary disease: pooled analysis at the patient-level of 4 registries. *JACC Cardiovasc Interv* 2014; **7**:244–254.
11 Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, *et al*. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009; **360**:961–972.
12 Seung KB, Park DW, Kim YH, Lee SW, Lee CW, Hong MK, *et al*. Stents versus coronary-artery bypass grafting for left main coronary artery disease. *N Engl J Med* 2008; **358**:1781–1792.
13 Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, *et al*. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet* 2009; **373**:1190–1197.
14 Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, *et al*. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 2012; **367**:2375–2384.
15 Bravata DM, Gienger AL, McDonald KM, Sundaram V, Perez MV, Varghese R, *et al*. Systematic review: the comparative effectiveness of percutaneous coronary interventions and coronary artery bypass graft surgery. *Ann Intern Med* 2007; **147**:703–716.
16 Sipahi I, Akay MH, Dagdelen S, Blitz A, Alhan C. Coronary artery bypass grafting vs percutaneous coronary intervention and long-term mortality and morbidity in multivessel disease: meta-analysis of randomized clinical trials of the arterial grafting and stenting era. *JAMA Intern Med* 2014; **174**: 223–230.
17 Mack M, Holmes DR. Randomised trials in left main disease: a NOBLE effort. *Lancet* 2016; **388**:2715–2716.