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ORIGINAL ARTICLE

Long-Term Clinical Impact of Intravascular Ultrasound Guidance in Stenting for Left Main Coronary Artery Disease

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BACKGROUND: Compared with angiographic guidance, intravascular ultrasound (IVUS)-guided percutaneous coronary intervention (PCI) is associated with better clinical outcomes. However, its very long-term clinical effect is still unclear in patients undergoing PCI for unprotected left main coronary artery disease.

METHODS: To compare 10-year outcomes of IVUS-guided versus angiography-guided PCI for left main coronary artery disease, we evaluated 975 patients who underwent unprotected left main coronary artery PCI between January 2000 and June 2006 from the MAIN-COMPARE (The Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry. The 10-year rates of clinical outcomes (death; the composite of death, Q-wave myocardial infarction [MI], or stroke; and target-vessel revascularization) were compared between IVUS guidance and angiography guidance. Adjusted analyses were performed with the use of inverse-probability-treatment-weighting and propensity score matching.

RESULTS: Among the 975 patients, 756 (77.5%) had IVUS guidance. The observed 10-year incidence rate of death (16.4% versus 31.0%, $P<0.001$) and composite of death, Q-wave MI, or stroke (19.2% versus 32.9%, $P<0.001$) was significantly lower in the IVUS-guided than in the angiography-guided group. The 10-year incidence rate of target-vessel revascularization was similar between the 2 groups (21.8% versus 18.3%, $P=0.41$). After adjusting for potential confounders with inverse-probability-treatment-weighting, IVUS was associated with lower incidence of mortality (hazard ratio, 0.75 [95% CI, 0.55–1.03]; $P=0.07$) and composite of death, Q-wave MI, or stroke (hazard ratio, 0.79 [95% CI, 0.59–1.06]; $P=0.11$). In 208 propensity score–matched pairs, IVUS was also associated with lower incidence of death (hazard ratio, 0.73 [95% CI, 0.53–1.02]; $P=0.07$) and composite outcome of death, Q-wave MI, or stroke (hazard ratio, 0.71 [95% CI, 0.52–0.97]; $P=0.03$). The benefit of IVUS-guided PCI was consistent in the various subsets of clinical and anatomic characteristics.

CONCLUSIONS: In patients undergoing PCI for unprotected left main coronary artery disease, IVUS-guided PCI compared with angiography-guided PCI was associated with lower long-term (10-year) risks of morality and composite of death, Q-wave MI, or stroke.

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GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: coronary disease ■ myocardial infarction ■ percutaneous coronary intervention ■ stents

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WHAT IS KNOWN

- Left main coronary artery disease is a high-risk subset of obstructive coronary artery disease. Previous studies reported that the use of intravascular ultrasound–guided percutaneous coronary intervention for left main coronary artery disease was associated with better clinical outcomes. However, its long-term impact on outcomes is still unclear.

WHAT THE STUDY ADDS

- In patients undergoing percutaneous coronary intervention for left main coronary artery disease, intravascular ultrasound–guided percutaneous coronary intervention was associated with lower rates of 10-year mortality and serious composite outcome of death, Q-wave myocardial infarction, or stroke, as compared with angiography-guided percutaneous coronary intervention.
- Our study confirmed again that the early benefit of intravascular ultrasound was consistent during very long-term clinical follow-up.

Nonstandard Abbreviations and Acronyms

EXCEL	Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization
HR	hazard ratio
INFINITE	Intravascular Ultrasound- Versus Angiography-Guided Percutaneous Coronary Intervention for Patients With Left Main Bifurcation Lesion
IVUS	intravascular ultrasound
LMCA	left main coronary artery
MAIN-COMPARE	Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization
MI	myocardial infarction
NOBLE	Nordic–Baltic–British Left Main Revascularisation
OPTIMAL	Optimization of Left Main Percutaneous Coronary Intervention With Intravascular Ultrasound
PCI	percutaneous coronary intervention
TVR	target-vessel revascularization
ULTIMATE	Intravascular Ultrasound-Guided Drug-Eluting Stents Implantation in "All-Comers" Coronary Lesions

Left main coronary artery (LMCA) disease is a high-risk subset of obstructive coronary artery disease owing to the large area of involvement of myocardium and therefore coronary artery bypass grafting has been recommended as the choice of revascularization.[1,2] Despite this, percutaneous coronary intervention (PCI) for such complex lesion has substantially evolved. The remarkable advancements in stent technology, technical improvement, and adjunctive drug therapy have not only widened the indication of PCI for LMCA disease but also improved procedural- and long-term clinical outcomes.[3–5]

Although LMCA PCI has expanded rapidly in the real-world clinical practice on the basis of compelling evidence,[6–8] intervention for this high-risk anatomic lesion remains a challenging procedure and many unresolved technical issues still remain. In particular, accurate pre-PCI anatomic assessment (eg, the vessel size, lesion morphology, and delineation of the carina) and post-PCI evaluation (eg, adequate stent expansion/apposition, side branch and carina assessment, and edge dissections) may be crucial for optimizing procedural outcomes and ensuring long-term durability of LMCA PCI; thus, the utilization of intracoronary imaging as one of the adjunctive PCI tools has increased.[9] A prior clinical trial showed that compared with angiographic guidance, intravascular ultrasound (IVUS)-guided stenting was associated with better clinical outcomes in patients with complex coronary artery disease as well as in the all-comer setting.[10–13] In this context, the benefit of IVUS may be more conspicuous for complex LMCA PCI with regard to preinterventional lesion assessment and postinterventional stent optimization rather than for simple lesions.[14] Several studies suggested that IVUS-guided intervention was associated with reduced risks of mortality and major cardiovascular events in LMCA PCI, compared with angiography-guided intervention.[15–17] However, data are still limited with regard to very long-term clinical effect of IVUS guidance in patients undergoing LMCA stenting.

Recently, we reported the 10-year clinical outcomes after myocardial revascularization for LMCA disease in the MAIN-COMPARE (The Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry, which showed similar rates of death and a composite outcome of death, Q-wave myocardial infarction (MI), or stroke after PCI and coronary artery bypass grafting.[18] In the present study, we evaluated the impact of IVUS guidance on 10-year mortality and major adverse events in patients undergoing PCI using data from the extended follow-up of the MAIN-COMPARE study.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Table 1. Baseline Characteristics of the Patients*

Characteristics	Unadjusted data			Data adjusted with the inverse probability weighting			After propensity score matching		
	IVUS guidance (n=756)	Angiography guidance (n=219)	*P* value	IVUS guidance (n=756)	Angiography guidance (n=219)	*P* value	IVUS guidance (n=208)	Angiography guidance (n=208)	*P* value
Age, y	59.7±11.5	65.4±11.1	<0.001	60.9±11.6	61.3±11.4	0.63	64.6±11.2	64.5±10.6	0.96
Male sex	522 (69.0)	159 (72.6)	0.31	69.8%	69.4%	0.99	156 (75.0)	152 (73.1)	0.66
Diabetes									
Any diabetes	204 (27.0)	72(32.9)	0.09	28.5%	30.2%	0.61	70 (33.7)	69 (33.2)	0.92
Requiring insulin	39 (5.2)	21 (9.6)	0.02	6.2%	6.3%	0.94	19 (9.1)	20 (9.6)	0.87
Hypertension	360 (47.6)	120 (54.8)	0.06	48.8%	49.0%	0.95	107 (51.4)	109 (52.4)	0.84
Hyperlipidemia	229 (30.3)	57 (26.0)	0.22	30.9%	23.1%	0.03	69 (33.2)	55 (26.4)	0.13
Current smoker	191 (25.3)	49 (22.4)	0.38	24.6%	23.7%	0.79	54 (26.0)	48 (23.1)	0.49
Previous PCI	130 (17.2)	52 (23.7)	0.03	18.7%	18.9%	0.97	52 (25.0)	49 (23.6)	0.73
Previous MI	56 (7.4)	16 (7.3)	0.96	7.7%	8.4%	0.73	16 (7.7)	16 (7.7)	>0.99
Previous CHF	6 (0.8)	7 (3.2)	0.006	1.1%	1.1%	0.97	4 (1.9)	3 (1.4)	0.70†
Cerebrovascular disease	50 (6.6)	22 (10.0)	0.09	7.1%	6.3%	0.67	11 (5.3)	18 (8.7)	0.18
Peripheral arterial disease	9 (1.2)	7 (3.2)	0.04	1.4%	1.5%	0.92	6 (2.9)	5 (2.4)	0.76
Chronic renal failure	14 (1.9)	9 (4.1)	0.05	2.2%	2.2%	0.99	6(2.9)	6(2.9)	>0.99
Atrial fibrillation	9 (1.2)	6 (2.7)	0.12	1.5%	3.1%	0.93	5 (2.4)	5 (2.4)	>0.99
Acute coronary syndrome	466 (61.6)	133 (60.7)	0.81	61.6%	62.9%	0.73	123 (59.1)	126 (60.6)	0.76
Ejection fraction, %	62.7±8.5	59.4±12.2	0.001	62.3±9.0	62.3±10.6	>0.99	61.4±10.5	60.6±11.1	0.47
LM disease location			0.26			0.99			0.62
Ostium or shaft	392 (51.9)	104 (47.5)		51.3%	51.2%		96 (46.2)	101 (48.6)	
Distal bifurcation	364 (48.1)	115 (52.5)		48.7%	48.8%		112 (53.8)	107 (51.4)	
Extent of diseased vessel			<0.001			0.93			0.65
LM only	227 (30.0)	31 (14.2)		26.5%	24.6%		24 (11.5)	30 (14.4)	
LM plus 1-vessel disease	184 (24.3)	47 (21.5)		23.7%	25.0%		50 (24.0)	47 (22.6)	
LM plus 2-vessel disease	158 (20.9)	67 (30.6)		26.2%	25.7%		72 (34.6)	63 (30.3)	
LM plus 3-vessel disease	158 (20.9)	74 (33.7)		23.6%	24.8%		62 (29.8)	68 (32.7)	
RCA disease	239 (31.6)	101 (46.1)	<0.001	34.8%	35.1%	0.93	96 (46.2)	95 (45.7)	0.92
Restenotic lesions	24 (3.2)	5 (2.3)	0.49	3.0%	3.2%	0.89	10 (4.8)	5 (2.4)	0.19
Stent type			0.97			0.94			0.74
Drug-eluting stent	529 (70.0)	153 (69.9)		70.0%	70.3%		150 (72.1)	147 (70.7)	
Bare-metal stent	227 (30.0)	66 (30.1)		30.0%	29.7%		58 (27.9)	61 (29.3)	
Crossover technique	613 (81.1)	171 (78.1)	0.32	80.4%	78.9%	0.62	165 (79.3)	163 (78.4)	0.81
Post-dilation	453 (59.9)	124 (56.6)	0.38	59.3%	61.0%	0.64	124 (59.6)	118 (56.7)	0.55
Final kissing balloon	248 (32.8)	75 (34.3)	0.69	33.0%	32.7%	0.93	70 (33.7)	71 (34.1)	0.92

CHF indicates congestive heart failure; IVUS, intravascular ultrasound; LM, left main; MI, myocardial infarction; PCI, percutaneous coronary intervention; and RCA, right coronary artery.

*Values are mean±SD or number (percentage).

†Fisher exact test was used.

Study Population and Procedure

The design of the MAIN-COMPARE study was described previously.[4,19] Briefly, the MAIN-COMPARE study included consecutive patients with unprotected LMCA disease (diameter stenosis of >50%) who underwent PCI or coronary artery bypass grafting in 12 major cardiac centers in Korea between January 2000 and June 2006. Patients with prior coronary artery bypass grafting, concomitant valvular or aortic surgery, ST-elevation MI, or

cardiogenic shock at presentation were excluded. This study was approved by the local ethics committee of each hospital, and all the patients provided written informed consent. All the authors assumed responsibility for the accuracy and completeness of the data, reported analyses, and data interpretation.

All the PCI procedures were performed with standard interventional techniques. For the purpose of the present study, patients who underwent elective stenting for unprotected LMCA disease were categorized into 2 groups as follows: patients who underwent PCI with IVUS guidance and those who underwent PCI with angiographic guidance. The use of IVUS was determined by the treating operator. The procedure was considered IVUS-guided PCI when an IVUS examination was performed during the procedure. The timing of the IVUS (before stenting, after stenting, or both) evaluation was also left to the operator's discretion. The IVUS images were obtained using a manual or automatic pullback system with commercially available systems (Boston Scientific Corporation, San Jose, CA; or Volcano Corporation, Rancho Cordova, CA). Our registry had no specific IVUS criteria for device sizing, or identification and treatment of malapposition and/or underexpansion. The final decision for additional procedures taken after the IVUS examination was left to the operator.

The standard regimens were followed in the antiplatelet therapy and periprocedural anticoagulation. Before or during the procedure, the patients were received loading doses of aspirin (200 mg) and clopidogrel (300 or 600 mg), unless they had previously received antiplatelet medications. After the procedure, the patients were maintained on aspirin indefinitely and clopidogrel for at least 6 months, with longer duration at the physician's discretion. During follow-up, patient management including medical treatment was performed in accordance with accepted guidelines and established standards of care.

Clinical Outcomes and Follow-Up

The main outcomes of this study were death from any cause; the composite of all-cause death, Q-wave MI, or stroke; and target-vessel revascularization (TVR).[18,19] In the current study, all-cause mortality was assessed, which was the most unbiased method to report deaths in a clinical trial or observational study. Q-wave MI was defined as the documentation of a new pathological Q-wave after the index PCI. Stroke, as detected by neurological deficits, was confirmed by a neurologist and on imaging modalities. TVR was defined as repeat revascularization of the target vessel, including any segment of the left anterior descending or left circumflex artery, as well as in the target segment. All clinical events were confirmed by source documentation collected at each hospital and were centrally adjudicated by independent clinicians who were unaware of the revascularization strategy.

Clinical follow-up was recommended at 1 month, 6 months, 1 year, and annually thereafter. In the 10-year MAIN-COMPARE study, the follow-up period was extended through December 31, 2016 to ensure that all patients had the opportunity to be followed up for at least 10 years. The medical records review and telephone contact were used to complete the follow-up data to beyond 10 years. Complete information on vital status and date of death were obtained through December 31, 2016, from the National Population Registry of the Korea National Statistical Office on the basis of the unique 13-digit personal identification number that all Korean citizens have. The detailed methods for data acquisition and management during extended follow-up have been reported elsewhere.[18]

Statistical Analysis

Summary statistics are presented as percentages in the case of categorical variables and as means with SDs in the case of continuous variables. Differences in baseline clinical, angiographic, and procedural characteristics between the IVUS- and angiography-guided stenting groups were compared using the Student *t* test for continuous variables and the χ^2 test for categorical variables. In case of a categorical variable with expected count <5, Fisher exact test was used. Event rates were based on Kaplan-Meier estimates in time-to-first-event analyses and were compared using log-rank test. All available follow-up data were used for the long-term outcome analyses without censoring clinical events beyond 10 years.

To reduce the influence of selection bias and the potential confounders, we performed propensity score–adjusted analyses for rigorous adjustment for differences in baseline characteristics between the IVUS- and angiography-guided group. First, we performed analyses using inverse-probability-treatment-weighting based on propensity scores.[20] Propensity scores were estimated without regard to outcomes using nonparsimonious multiple logistic-regression analysis, which included all variables outlined in Table 1. The cumulative event curves were estimated using a weighted Kaplan-Meier method and inverse-probability-treatment-weighting.[21] Subsequently, we also conducted analyses using propensity score matching. Propensity score matching was conducted with a 1:1 matching

Table 2. Observed 10-Year Event Rates and Crude HRs for Clinical Outcomes Between IVUS and Angiography Guidance

	Event rates at 10 y, n (%)*		Unadjusted risk†	
	IVUS guidance (n=756)	Angiography guidance (n=219)	HR (95% CI)	*P* value
Death	125 (16.4%)	67 (31.0%)	0.54 (0.41–0.70)	<0.001
Composite outcome (death, Q-wave MI, or stroke)	146 (19.2%)	72 (32.9%)	0.57 (0.44–0.73)	<0.001
Q-wave MI	18 (2.4%)	6 (2.7%)	0.74 (0.29-1.87)	0.53
Stroke	21 (2.8%)	7 (3.2%)	0.74 (0.31-1.74)	0.49
TVR	159 (21.8%)	195 (18.3%)	1.16 (0.83–1.63)	0.41

HR indicates hazard ratio; IVUS, intravascular ultrasound; MI, myocardial infarction; and TVR, target-vessel revascularization.
*Event rates (%) were derived from the Kaplan-Meier estimates.
†HRs are for the IVUS guidance group, as compared with the angiography guidance group.

protocol without replacement (a nearest-neighbor matching algorithm with a "greedy" heuristic), with a caliper width equal to 0.15 of the SD of the logit of the propensity score.[22] In the matched cohort, event curves were constructed with the Kaplan-Meier estimates and compared using Cox proportional hazard regression models. Finally, we assessed whether the relative benefit of IVUS-guided PCI over angiography-guided PCI is consistent in major subgroups of clinical, anatomic, and procedural characteristics.

All reported *P* are 2-sided, and any value <0.05 was considered statistically significant. Statistical analyses were performed with the SAS version 9.3 software (SAS Institute, Cary, NC) and the R programming language (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Population and Baseline Characteristics

Between January 2000 and June 2006, a total of 2240 patients with unprotected LMCA disease were enrolled in the MAIN-COMPARE registry. Among 1102 patients who underwent PCI with stent implantation, 975 had detailed information on the PCI guidance strategy, of whom 756 (77.5%) underwent IVUS-guided stent implantation and 219 (22.5%) underwent angiography-guided stent implantation. The baseline clinical, angiographic, and procedural characteristics of the IVUS- and the angiography-guided group are shown in Table 1. Compared with the patients in the angiography-guided group, those in the IVUS-guided group were younger and more likely to have a lower prevalence of insulin-dependent diabetes, prior PCI, prior heart failure, peripheral disease, and renal failure, and higher ejection fraction. With regard to anatomic characteristics, the locations of the LMCA disease were similar between the 2 groups, but the angiography-guided group had higher number of diseased coronary vessels. The type of stent and procedural characteristics were similar between the groups. The size of the LMCA stent was significantly larger in the IVUS-guided group (3.56±0.46 versus 3.44±0.42 mm, *P*=0.002), while the length was similar between the groups (27.3±20.9 versus 30.1±20.7 mm, *P*=0.08).

After adjustment with inverse-probability-treatment-weighting, all the clinical covariates, except for dyslipidemia, were well balanced (Table 1). After propensity score matching, 208 pairs of patients with similar baseline characteristics were assembled and most baseline characteristics were also well balanced between the 2 groups (Table I in the Data Supplement).

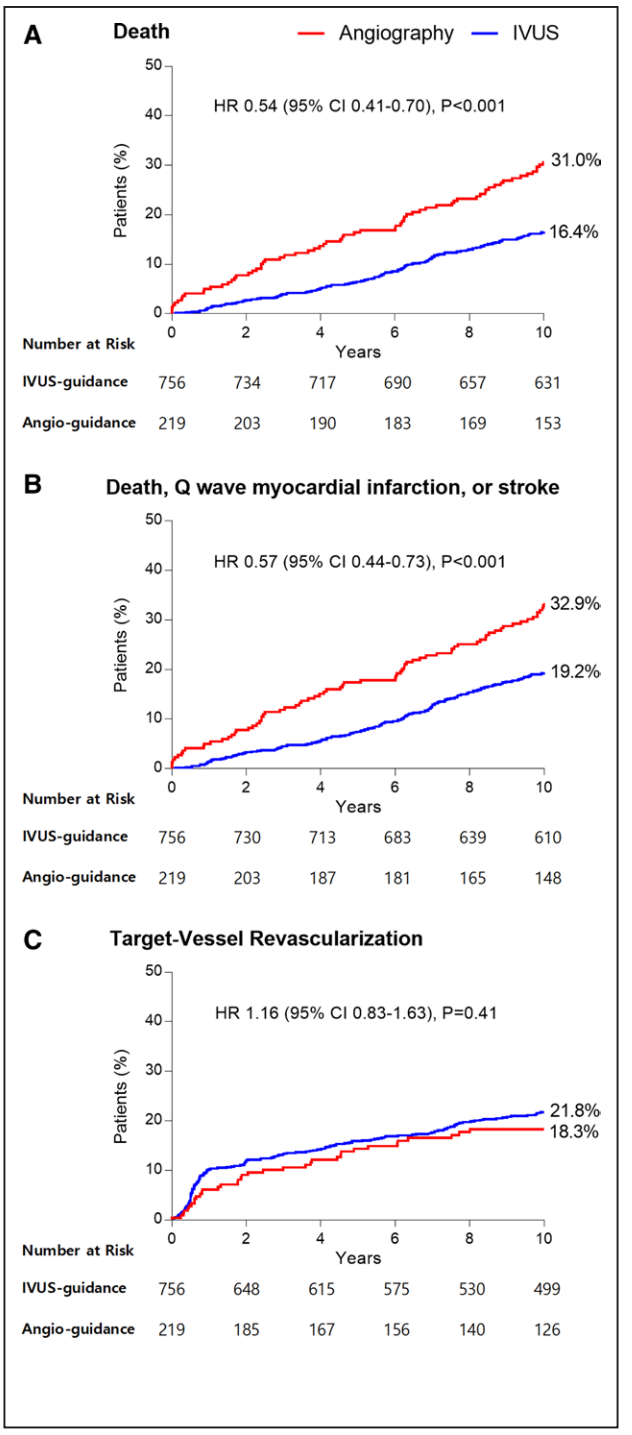

Figure 1. Unadjusted Kaplan-Meier event curves of 10-y clinical outcomes.
P are calculated from the log-rank test. The HRs (hazard ratios) are for the intravascular ultrasound (IVUS)-guided group in comparison with the angiography-guided group.

Ten-Year Clinical Outcomes

The overall median follow-up duration was 11.9 years (interquartile range, 10.7–13.4 years), and the maximum follow-up was 17.0 years. In the overall period, 251 deaths (25.7%; 171 in the IVUS-guided group and 80 in the angiography-guided group); 284 composite outcomes (29.1%; 197 in the IVUS-guided group and 87 in the angiography-guided group), and 216 TVRs (22.2%; 175 in the IVUS-guided group and 41 in the angiography-guided group) were reported.

The observed (unadjusted) 10-year rates of clinical outcomes between the IVUS- and angiography-guided groups are shown in Table 2, Figure 1, and Figure I in the Data Supplement. As compared with angiography-guided PCI, IVUS-guided PCI was significantly associated with a lower 10-year mortality (31.0% versus 16.4%, *P*<0.001) and composite of death, Q-wave MI, or stroke (32.9% versus 19.2%, *P*<0.001). The 10-year incidence rate of TVR was similar between IVUS- and angiography-guided groups (21.8% versus 18.3%, *P*=0.40).

The propensity score–adjusted (inverse-probability-treatment-weighting-weighted and propensity-matching) event rates and curves for clinical outcomes are shown in Table 3, Figure 2, and Figure II in the Data Supplement. IVUS-guided PCI tended to be associated with lower 10-year risk of death (hazard ratio [HR], 0.75 [95% CI, 0.55–1.03]; *P*=0.07) and composite of death, Q-wave MI, or stroke (HR, 0.79 [95% CI, 0.59–1.06]; *P*=0.11), as compared with angiography-guided PCI. The 10-year adjusted risk of TVR was similar between the 2 groups (HR, 1.20 [95% CI, 0.82–1.74]; *P*=0.36). After propensity score matching, the use of IVUS was associated with lower risk of 10-year mortality (HR, 0.73 [95% CI, 0.53–1.02]; *P*=0.07) and composite outcome (HR, 0.71 [95% CI, 0.52–0.97]; *P*=0.03). A similar risk of TVR remained in the propensity-matched cohort. Throughout the follow-up period, 13 (1.3%) patients had a definite or probable stent thrombosis (1.2% in the IVUS-guided group and 1.8% in the angiography-guided group).

In the subgroup analysis, the benefit of IVUS guidance over angiography guidance was consistent in various subsets of clinical and anatomic characteristics with respect to the 10-year risks of mortality and composite of death, Q-wave MI, or stroke (Figure 3).

DISCUSSION

In this large-scale, longest-term, multicenter cohort of patients who underwent PCI with stent implantation for unprotected LMCA disease, as compared with angiography guidance, IVUS-guided stent implantation was associated with lower 10-year adjusted risks of death and the composite of death, Q-wave MI, or stroke. The adjusted risk of TVR was similar between the 2 groups. The benefit of IVUS guidance was consistent regardless of clinical, lesion, or procedural characteristics. This is the first report that presented the very long-term and sustained clinical effect of IVUS guidance over 10 years in patients who underwent LMCA PCI.

Compared with the conventional angiography, which reveals the 2-dimensional luminal shadowing of the coronary anatomy, IVUS provides accurate tomographic measurement for the assessment of the coronary lumen and vessel characteristics and thus helps in the decision on the stent implantation technique, selection of optimal stent size and landing zones, and optimization of the final stenting result.[23] Prior trials and meta-analysis demonstrated that compared with angiographic guidance, IVUS-guided stent implantation was associated with favorable outcomes in terms of target-lesion revascularization, MI, stent thrombosis, or major adverse cardiac events at 1 year in patients with complex lesions such as long lesions or chronic total occlusions.[10–12,24,25] A recent single-center report also showed that IVUS-guided PCI was associated with the lower long-term (median, 5 years) risk of mortality and major adverse cardiac events compared with angiography-guided PCI in patients with complex coronary artery lesion.[26] In the Intravascular ULTIMATE trial (Ultrasound-Guided Drug-Eluting Stents Implantation in "All-Comers" Coronary Lesions), the clinical effect of IVUS guidance in comparison with that of angiography guidance was determined in all-comer patients and the primary end point of target-vessel failure at 1 year was significantly lower in the IVUS guidance group than in the angiography guidance group.[13]

In this respect, the beneficial effect of IVUS on clinical outcomes may be remarkable in patients undergoing PCI for the complex anatomic features of LMCA disease. The use of IVUS for LMCA PCI has increased in routine clinical practice,[27] and IVUS-guided PCI was performed in >70% of patients enrolled in the recent EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) and NOBLE (Nordic–Baltic–British Left Main Revascularization) clinical trials.[6,7] Data are still limited with regard to the impact of the IVUS guidance on the clinical outcome

Table 3. Adjusted HRs for 10-Year Clinical Outcomes Between IVUS and Angiography Guidance

	Adjusted risk with the inverse probability weighting		Adjusted Risk with the propensity score matching	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Death	0.75 (0.55–1.03)	0.07	0.73 (0.53–1.02)	0.07
Composite outcome (death, Q-wave MI, or stroke)	0.79 (0.59–1.06)	0.11	0.71 (0.52–0.97)	0.03
Q-wave MI	0.76 (0.20–1.98)	0.58	0.60 (0.17–2.14)	0.44
Stroke	1.44 (0.55–3.72)	0.46	1.02 (0.37–2.83)	0.98
TVR	1.20 (0.82–1.74)	0.36	1.17 (0.75–1.81)	0.50

HRs are for the IVUS guidance group, as compared with the angiography guidance group. HR indicates hazard ratio; IVUS, intravascular ultrasound; MI, myocardial infarction; and TVR, target-vessel revascularization.

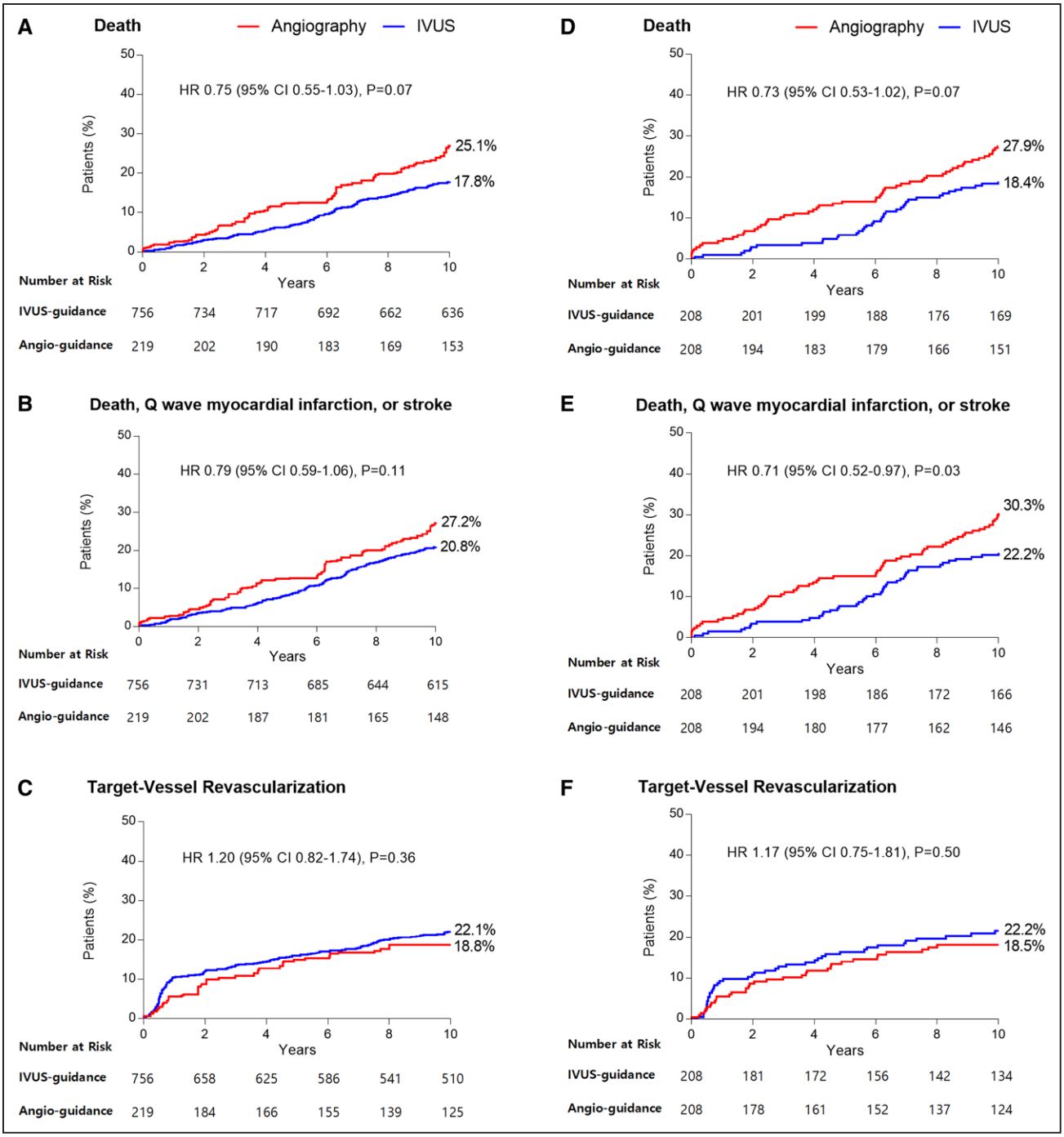

Figure 2. Adjusted event curves for 10-y clinical outcomes.
A–**C**, Adjusted curves with the inverse-probability-treatment-weighting, and (**D**–**F**) adjusted curves with the propensity score matching. HR indicates hazard ratio; and IVUS intravascular ultrasound.

after LMCA PCI, which has been only investigated in observational studies.[15–17] All studies uniformly indicated that IVUS guidance play a role in improving clinical outcomes and mortality. Consistent with previous findings, our study also showed the clear benefit of IVUS guidance on very long-term mortality and incidence of serious composite outcome.

Despite this, these observational findings should be interpreted with caution.[28] In most previous studies and in our study, IVUS was more frequently employed in younger lower-risk individuals. Therefore, a possible healthy candidate bias for IVUS use could have influenced the study results. A remarkable reduction in mortality and hard clinical end point cannot be fully supported by the true clinical effect of IVUS guidance. In addition, residual confounding and, in particular, unknown confounders may have biased the results favoring IVUS-guided PCI. Second, IVUS guidance was

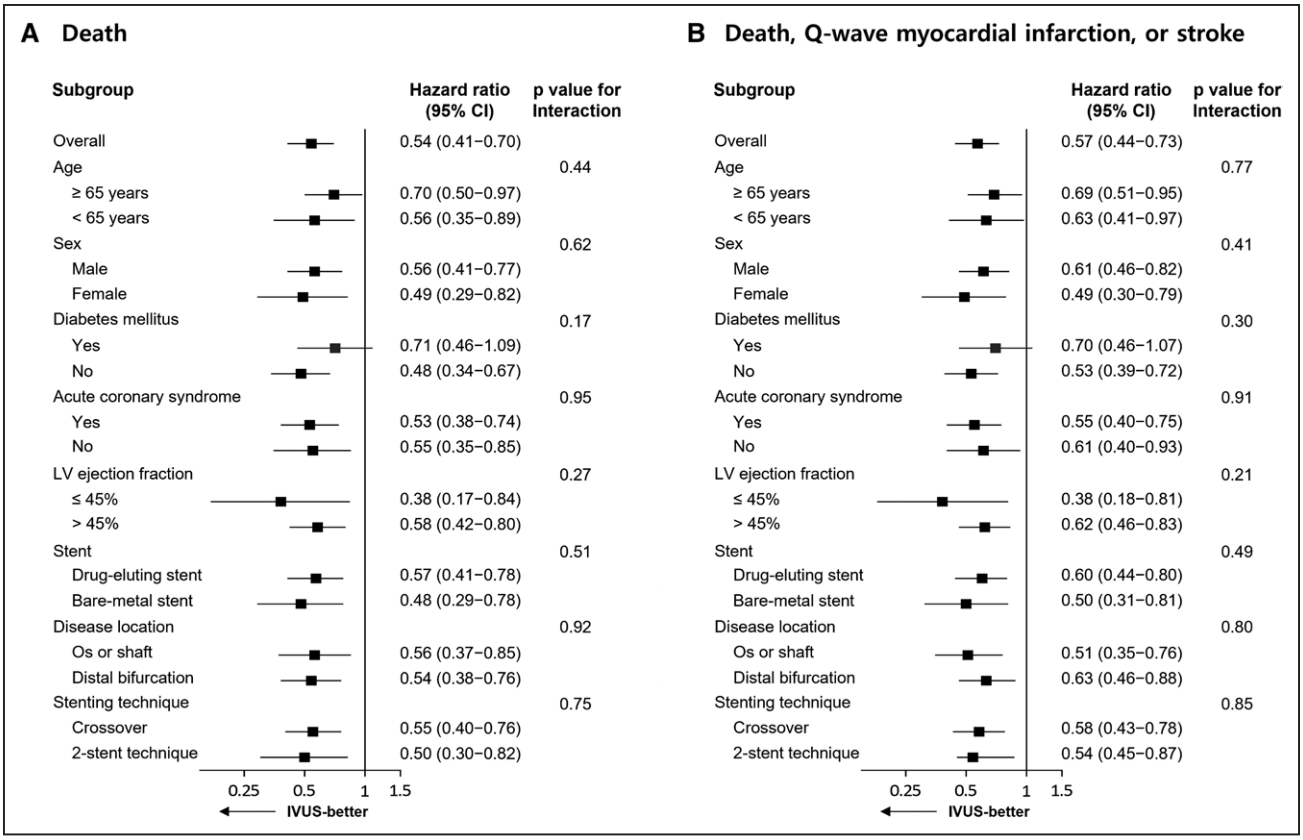

Figure 3. Major subgroup analyses according to clinical, anatomic, and procedural characteristics.
The subgroup analyses were performed with respect to (**A**) 10-y mortality, and (**B**) incidence of composite outcome of death, Q-wave myocardial infarction, or stroke. IVUS indicates intravascular ultrasound; and LV, left ventricle.

predominantly common in elective PCI situations. As acute clinical presentation (ie, unstable clinical settings or MI) is more catastrophic in LMCA disease than in non-LMCA disease, angiography-directed PCI without time-consuming imaging support in urgent or emergent situations may penalize the angiography-only group. To minimize this bias, patients who underwent PCI in emergent settings were excluded in our study. Considering these inherent limitations of observational studies, a randomized controlled trial is required to determine the true clinical effect of IVUS guidance in patients undergoing LMCA PCI and therefore ongoing RCTs (ie, OPTIMAL [Optimization of Left Main Percutaneous Coronary Intervention With Intravascular Ultrasound; NCT04111770] and INFINITE [Intravascular Ultrasound- Versus Angiography-Guided Percutaneous Coronary Intervention for Patients With Left Main Bifurcation Lesion; NCT04072003]) will provide more compelling evidence for IVUS-guided LMCA PCI.

The exact mechanism of IVUS guidance for LMCA PCI with a relevant clinical benefit is still unclear and only hypothetical. IVUS can provide a more detailed information than angiography on lesion characteristics about lumen size, plaque characterization, and plaque distribution in the LMCA and its branches, thereby guiding optimal stent sizing, length, and positioning.[29,30] This would contribute to the bigger stent size of the IVUS-guided group, which is associated with decreased rate of stent restenosis.[14] In particular, IVUS may be helpful to decide the optimal stenting strategy (ie, provisional or complex dual stenting) for distal complex LMCA bifurcation lesions. Last, post-PCI IVUS examination can ensure optimal stent strut apposition and expansion with subsequent post-dilatation and achieve larger stent diameters. Although theoretical and practical advantages may be evident with IVUS guidance for LMCA PCI, the direct linkage of mechanistic PCI optimization with relevant clinical benefit is still a hypothetical judgment. In addition, the selective or routine application of IVUS for LMCA intervention in the real-world PCI setting is associated with the particulars of clinical practice and experience, as well as the specific expertise of the interventional cardiologists. Last, it should be further determined how contemporary state-of-the-art PCI with combined use of imaging guidance (whether by IVUS or optical coherent tomography) and invasive functional testing (ie, fractional flow reserve) can improve outcomes of complex PCI including LMCA interventions.[30,31]

This study had several limitations. First, it was observational and had inherent methodological limitations;

thus, its overall findings must be considered hypothetical and hypothesis generating only. Second, the choice of IVUS- or angiography-guided PCI was left to the physician's discretion; thus, our findings might be venerable to selection bias. Although the propensity score analyses were performed to adjust for this selection bias, the possibility of other unmeasured confounders having affected the results cannot be excluded. Third, quantitative IVUS or angiographic analyses were not performed in this registry. Therefore, the relationship of quantitative imaging parameters and clinical outcomes could not be assessed. Fourth, our study was not sufficiently powered to detect the hard clinical end points such as stent thrombosis, death, or individual component of the serious composite outcome. Fifth, we only considered objective Q-wave MI without including enzyme-based periprocedural MI owing to nonuniform definitions and controversial prognostic impact. Finally, our study evaluated first-generation drug-eluting stents and bare-metal stents for the treatment of LMCA disease. Thus, the present findings should be confirmed through an extended follow-up of the EXCEL trial and NOBLE trial by using the contemporary drug-eluting stents.

CONCLUSIONS

In this longest-term study of LMCA PCI, IVUS-guided stent implantation was associated with lower adjusted risks of mortality and serious composite outcome of death, Q-wave MI, or stroke, as compared with angiography-guided stent implantation. IVUS may be a valuable adjunctive tool for PCI for preinterventional lesion assessment and postinterventional stent optimization for LMCA PCI. However, the true clinical effect of IVUS guidance for LMCA PCI can only be confirmed or refuted through large-scale RCTs.

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Disclosures

None.

Supplemental Materials

Online Table I
Online Figures I and II

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