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Impact of Intravascular Ultrasound Guidance on Long-Term Mortality in Stenting for Unprotected Left Main Coronary Artery Stenosis

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Background—Although intravascular ultrasound (IVUS) guidance has been useful in stenting for unprotected left main coronary artery stenosis, its impact on long-term mortality is still unclear.

Methods and Results—In the MAIN-COMPARE registry, patients with unprotected left main coronary artery stenosis in a hemodynamically stable condition underwent elective stenting under the guidance of IVUS (756 patients) or conventional angiography (219 patients). Patients with acute myocardial infarction were excluded. The 3-year outcomes between the 2 groups were primarily compared using propensity-score matching in the entire and separate populations according to stent type. In 201 matched pairs of the overall population, there was a tendency of lower risk of 3-year morality with IVUS guidance compared with angiography guidance (6.0% versus 13.6%, log-rank $P=0.063$; hazard ratio, 0.54; 95% CI, 0.28 to 1.03; Cox-model $P=0.061$). In particular, in 145 matched pairs of patients receiving drug-eluting stent, the 3-year incidence of mortality was lower with IVUS guidance as compared with angiography guidance (4.7% versus 16.0%, log-rank $P=0.048$; hazard ratio, 0.39; 95% CI, 0.15 to 1.02; Cox model $P=0.055$). In contrast, the use of IVUS guidance did not reduce the risk of mortality in 47 matched pairs of patients receiving bare-metal stent (8.6% versus 10.8%, log-rank $P=0.35$; hazard ratio, 0.59; 95% CI, 0.18 to 1.91; Cox model $P=0.38$). The risk of myocardial infarction or target vessel revascularization was not associated with the use of IVUS guidance.

Conclusions—Elective stenting with IVUS guidance, especially in the placement of drug-eluting stent, may reduce the long-term mortality rate for unprotected left main coronary artery stenosis when compared with conventional angiography guidance. **(*Circ Cardiovasc Intervent*. 2009;2:167-177.)**

Key Words: coronary disease ■ ultrasonics ■ imaging ■ stents ■ left main coronary artery

After the introduction of coronary stents, the feasibility of the percutaneous interventional approach for unprotected left main coronary artery (LMCA) stenosis, in which no graft to the left anterior descending artery and left circumflex artery is patent, was demonstrated.[1] More recently, drug-eluting stent (DES), in conjunction with advances in equipment and pharmacological therapy, has improved outcomes of percutaneous coronary intervention (PCI) for these complex coronary lesions.[2–16] In particular, the application of intravascular ultrasound (IVUS) has been useful in determining anatomic configuration, selecting treatment strategy, and defining optimal stenting outcomes in PCI.[17–20] Indeed, angiography has limitations in assessing lesion morphology and the true luminal size of LMCA because of aortic cusp opacification, streaming of contrast agent, short vessel length, and lack of a normal reference segment.[20] Therefore, IVUS assessment before the procedure cannot only detect significant stenosis but can also select the appropriate diameter and length of the stent.[17] In addition, IVUS can be very helpful in optimally expanding the stent, with or without poststent balloon dilatation, to avoid under- or overstretch of the stent diameter.[18]

Despite this applicability, the impact of IVUS on long-term clinical outcomes in unprotected LMCA stenting is still unclear. Therefore, using the large, multicenter registry of the MAIN-COMPARE (revascularization for unprotected left MAIN coronary artery stenosis: COMparison of Percutaneous coronary Angioplasty versus surgical REvascularization) study, which was designed to assess the real-world outcomes

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of revascularization therapy for unprotected LMCA stenosis,[16] we compared long-term outcomes of IVUS-guided stenting and conventional angiography-guided stenting. In addition, the outcomes were further stratified according to stent type to assess the differential effectiveness of IVUS in the placement of DES and bare-metal stent (BMS).

Methods

Patients

The protocol of MAIN-COMPARE study was described previously.[16] Briefly, patients with unprotected LMCA stenosis who underwent either coronary artery bypass graft surgery or PCI as the index procedure were enrolled at 12 major cardiac centers in Korea between January 2000 and June 2006. In this analysis, patients who underwent elective stenting at the unprotected LMCA were divided into those undergoing stent implantation under IVUS guidance and those undergoing stent placement under conventional angiography guidance. The procedure was considered IVUS guided when IVUS examination was performed during the procedure for guidance of optimal stenting. Patients who had prior bypass surgery, underwent concomitant valvular or aortic surgery, or presented with cardiogenic shock or myocardial infarction (MI) were excluded. This study was approved by the local ethnics committee at each hospital. The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Procedures

Before March 2003, when DES became available in Korea, BMS was used as the default stent. Beginning in March 2003, however, DES was used for most patients, with the choice of sirolimus-eluting (Cypher, Cordis Corp, Johnson & Johnson, Miami Lakes, Fla) or paclitaxel-eluting (Taxus, Boston Scientific, Natick, Mass) stents at the operator's discretion. All procedures were performed with standard interventional techniques. Use of IVUS was determined by the operator, and IVUS images were obtained using a manual or automatic pullback system with commercially available imaging systems (40 MHz IVUS catheter, Boston Scientific: 20 MHz IVUS catheter, Volcano, Rancho Cordova, Calif). The use of predilation or intra-aortic balloon pump was at the discretion of the operator. Stent overexpansion with high-pressure inflation was performed in selected patients with suboptimal expansion or stent inapposition, as shown by angiography or IVUS. Debulking devices, including cutting balloon angioplasty, rotablator, or debulking coronary atherectomy, were used in selected patients with severe calcified or fibrous plaques at the discretion of the operator.

Antiplatelet therapy and periprocedural anticoagulation followed the standard regimen. Before or during the procedure, patients were administered loading doses of aspirin (200 mg) and clopidogrel (300 or 600 mg) or ticlopidine (500 mg), unless they had previously received antiplatelet medications. After the procedure, patients were maintained on aspirin (100 to 200 mg once daily) and clopidogrel (75 mg once daily) or ticlopidine (250 mg twice daily) for at least 6 months after DES and for at least 1 month after BMS placement, with longer treatment with clopidogrel at the operator's discretion. Patients with high-risk clinical profiles or who underwent complicated procedures were also administered cilostazol (100 mg twice daily) for 1 month at the discretion of the operator.

Primary Outcomes and Definitions

The primary end point of the study was mortality. All other comparisons with regard to MI, target vessel revascularization (TVR), or composite of events were considered secondary end points of the study.

All deaths were considered of cardiac origin unless a noncardiac origin was established clinically or at autopsy. MI was defined as creatine kinase-MB levels >3 times the upper limit of the normal value, with or without electrocardiographic changes. TVR was defined as any repeat revascularization in any left anterior descending artery or left circumflex artery, as well as in the target segment. For systemic risk stratification before the procedure, standard Euro SCORE was measured, with a score ≥6 defined as a high-risk score and an estimated operative mortality ≥10%.[21]

Statistical Analysis

Differences between groups of patients undergoing IVUS and angiography guidances in baseline clinical, angiographic, and procedural characteristics were compared using the *t* test or Wilcoxon rank sum test for continuous variables, and the χ^2 test or Fisher exact test for categorical variables, as appropriate.

To reduce the impact of treatment-selection bias and potential confounding in an observational study, we performed rigorous adjustment for significant differences in characteristics of patients by the use of the propensity-score matching.[22,23] The propensity scores were estimated using multiple logistic-regression analysis. All prespecified covariates were included in the full nonparsimonious models for treatment with IVUS guidance versus angiography guidance (Table 1). A propensity score, indicating the predicted probability of receiving a specific treatment conditional on the observed covariates, was then calculated from the logistic equation for each patient. The discrimination and calibration ability of each propensity-score model was assessed by means of the c-statistic and the Hosmer-Lemeshow statistic. New propensity scores were incorporated to assess the efficacy of IVUS guidance in either BMS or DES implantations. For development of a propensity score-matched pairs without replacement (a 1:1 match), Greedy 5→1 digit match algorithm was used as shown previously.[15] Patients who did not have close pairs were not included in the final matched population.

After the propensity score-matched sample has been formed, we assessed the balance in baseline covariates between the 2 groups in the propensity score-matched cohort. Continuous variables were compared with the paired *t* test or the Wilcoxon signed rank test, as appropriate, and categorical variables were compared with the McNemar's or marginal homogeneity test, as appropriate. The effect of treatment on the outcomes and its statistical significance was estimated by using appropriate statistical methods for matched data. In the propensity score-matched cohort, the reduction in the risk of outcome was compared by the use of a Cox regression model with robust SEs that accounted for the clustering of matched pairs.[24] The proportional hazard assumptions of the model were assessed by plotting the scaled Schoenfeld residuals. In addition, to compensate the limitation of analysis for matched population, multivariable Cox models were further created in all patients, and DES and BMS subgroups, using covariates listed in Table 1 and propensity score. Cumulative incidence rates of individual clinical outcomes and composite outcomes were estimated by the Kaplan–Meier method and compared by the log-rank test. To avoid bias due to different follow-up, the outcome was censored at a fixed point of 3 years (1080 days) in the 2 groups.

All reported *P* values are 2-sided, and $P<0.05$ were considered to indicate statistical significance. SAS software, version 9.1 (SAS Institute, Cary, NC) and the R programming language were used for statistical analysis.

Results

Patient Characteristics

Overall Patients

A total of 975 patients were included in this analysis: 756 (77.5%) underwent IVUS-guided stenting and 219 (22.5%) underwent angiography-guided stenting. Baseline clinical, angiographic, and procedural characteristics of the 2 groups are listed in Table 1. Patients undergoing IVUS guidance were younger, had a lower prevalence of prior coronary angioplasty, heart failure, peripheral disease, renal failure, and 3-vessel disease, and had higher left ventricular ejection fraction and lower Euro SCORE. The prevalence of bifurcation LMCA involvement was similar in the 2 groups.

Table 1. Baseline Clinical, Angiographic, and Procedural Characteristics

Variable	IVUS Guidance (n=756)	Angiography Guidance (n=219)	*P*
Patients	756	219	
Demographic characteristics			
Age, y	59.7±11.5	65.4±11.1	<0.001
Male gender	522 (69.0)	159 (72.6)	0.31
Coexisting conditions			
Diabetes			
Any type	204 (27.0)	72 (32.9)	0.09
Insulin treated	39 (5.2)	21 (9.6)	0.02
Hypertension	360 (47.6)	120 (54.8)	0.06
Hyperlipidemia	229 (30.3)	59 (26.9)	0.34
Current smoker	191 (25.3)	49 (22.4)	0.38
Family history of coronary artery disease	58 (7.7)	11 (5.0)	0.18
Previous myocardial infarction	56 (7.4)	16 (7.3)	0.96
Previous coronary angioplasty	130 (17.2)	52 (23.7)	0.03
Previous congestive heart failure	6 (0.8)	7 (3.2)	0.006
Cerebrovascular disease	50 (6.6)	22 (10.0)	0.09
Peripheral vascular disease	9 (1.2)	7 (3.2)	0.04
Chronic lung disease	15 (2.0)	4 (1.8)	0.88
Chronic renal failure	14 (1.9)	9 (4.1)	0.05
Atrial fibrillation	9 (1.2)	6 (2.7)	0.10
Acute coronary syndrome	466 (61.6)	133 (60.7)	0.81
Left ventricular ejection fraction, %	62.7±8.5	59.4±12.2	0.001
Euro SCORE			
Mean	3.4±2.2	4.4±2.4	<0.001
High score≥6	124 (16.4)	71 (32.4)	<0.001
Angiographic characteristics			
Lesion location			
Ostium or shaft	392 (51.9)	104 (47.5)	0.26
Bifurcation	364 (48.1)	115 (52.5)	
Extent of diseased vessel			
Left main only	227 (30.0)	31 (14.2)	<0.001
Left main plus single-vessel disease	184 (24.3)	47 (21.5)	
Left main plus 2-vessel disease	187 (24.7)	67 (30.6)	
Left main plus 3-vessel disease	158 (20.9)	74 (33.7)	
Right coronary artery disease	239 (31.6)	101 (46.1)	<0.001
De novo lesions	732 (96.8)	214 (97.7)	0.49
Procedural characteristics			
Use of glycoprotein IIb/IIIa inhibitors	47 (6.2)	9 (4.1)	0.24
Use of intra-aortic balloon pump	28 (3.7)	4 (1.8)	0.17
Direct stenting	155 (20.5)	36 (16.4)	0.18
No. stents implanted at left main	1.2±0.4	1.2±0.5	0.66
Total stent length at left main	27.3±20.9	30.1±20.7	0.08
Average stent diameter at left main	3.6±0.5	3.4±0.4	0.002
Bifurcation treatment			
Single stenting	226 (62.1)	71 (61.7)	0.95
Complex stenting (≥2 stents)	138 (37.9)	44 (38.3)	

Data are mean±SD or N (%).

Table 2. Baseline Characteristics of the Propensity-Matched Patients

	All			Drug-Eluting Stent			Bare-Metal Stent		
	IVUS Guidance	Angiography Guidance	*P*	IVUS Guidance	Angiography Guidance	*P*	IVUS Guidance	Angiography Guidance	*P*
Patients	201	201		145	145		47	47	
Age, y	65.28±10.50	64.31±10.66	0.26	64.21±10.77	64.99±10.14	0.47	61.94±11.71	60.09±10.92	0.39
Male gender	139 (69.2)	146 (72.6)	0.52	102 (70.3)	102 (70.3)	1.00	39 (83.0)	37 (78.7)	0.82
Diabetes									
Any type	70 (34.8)	63 (31.3)	0.52	49 (33.8)	49 (33.8)	1.00	9 (19.2)	11 (23.4)	0.79
Insulin treated	18 (9.0)	17 (8.5)	1.00	15 (10.3)	16 (11.0)	1.00	4 (8.51)	2 (4.26)	0.69
Hypertension	116 (57.7)	104 (51.7)	0.26	86 (59.3)	85 (58.6)	1.00	20 (42.6)	16 (34.0)	0.57
Hyperlipidemia	62 (30.9)	53 (26.4)	0.38	42 (29.0)	44 (30.3)	0.90	9 (19.2)	10 (21.3)	1.00
Current smoker	44 (21.9)	46 (22.9)	0.90	28 (19.3)	30 (20.7)	0.88	13 (27.7)	15 (31.9)	0.83
Family history of CAD	10 (5.0)	9 (4.5)	1.00	8 (5.5)	7 (4.8)	1.00	2 (4.3)	3 (6.4)	1.00
Previous myocardial infarction	18 (9.0)	16 (8.0)	0.85	10 (6.9)	11 (7.6)	1.00	3 (6.4)	4 (8.5)	1.00
Previous coronary angioplasty	43 (21.4)	46 (22.9)	0.80	38 (26.2)	38 (26.2)	1.00	6 (12.8)	6 (12.8)	1.00
Previous congestive heart failure	3 (1.5)	3 (1.5)	1.00	2 (1.4)	3 (2.1)	1.00	1 (2.1)	0	1.00
Cerebrovascular disease	17 (8.5)	16 (8.0)	1.00	17 (11.7)	15 (10.3)	0.85	1 (2.1)	1 (2.1)	1.00
Peripheral vascular disease	5 (2.5)	5 (2.5)	1.00	4 (2.8)	5 (3.5)	1.00	0	0	1.00
Chronic lung disease	3 (1.5)	3 (1.5)	1.00	4 (2.8)	3 (2.1)	1.00	0	0	1.00
Chronic renal failure	7 (3.5)	5 (2.5)	0.77	7 (4.8)	6 (4.1)	1.00	0	0	1.00
Atrial fibrillation	6 (3.0)	5 (2.5)	1.00	3 (2.1)	3 (2.1)	1.00	0	0	1.00
Acute coronary syndrome	122 (60.7)	124 (61.7)	0.92	91 (62.8)	89 (61.4)	0.90	25 (53.2)	28 (59.6)	0.66
LVEF, %	61.47±10.62	61.38±10.20	0.23	60.18±10.35	61.17±10.99	0.48	63.27±6.15	62.44±8.93	0.93
LM location									
Ostium or shaft	93 (46.3)	96 (47.8)	0.83	61 (42.1)	62 (42.8)	1.00	28 (59.6)	29 (61.7)	1.00
Bifurcation	108 (53.7)	105 (52.2)		84 (57.9)	83 (57.2)		19 (40.4)	18 (38.3)	
Extent of diseased vessel									
LM only	28 (13.9)	29 (14.4)	0.36	6 (4.1)	8 (5.5)	0.61	22 (46.8)	21 (44.7)	0.87
LM plus single-vessel disease	53 (26.4)	45 (22.4)		35 (24.1)	32 (22.1)		10 (21.3)	10 (21.3)	
LM plus 2-vessel disease	59 (29.4)	62 (30.9)		48 (33.1)	48 (33.1)		10 (21.3)	12 (25.5)	
LM plus 3-vessel disease	61 (30.4)	65 (32.3)		56 (38.6)	57 (39.3)		5 (10.6)	4 (8.5)	
RCA disease	76 (37.8)	93 (64.3)	0.082	75 (51.7)	80 (55.2)	0.63	11 (23.4)	9 (19.2)	0.82
De novo lesions	196 (97.5)	196 (97.5)	1.00	141 (97.2)	142 (97.9)	1.00	46 (97.9)	45 (95.7)	1.00
No. stents implanted at LM	1.18±0.46	1.20±0.50	0.62	1.23±0.51	1.24±0.57	0.83	1.09±0.28	1.13±0.34	0.53
Total stent length at LM	29.09±20.81	30.41±21.03	0.54	35.16±23.81	35.63±22.65	0.85	16.66±8.46	16.85±7.36	0.91
Complex stenting	45 (22.4)	45 (22.4)	1.00	39 (26.9)	42 (29.0)	0.77	1 (2.1)	2 (4.3)	1.00

Data are mean±SD or N (%). CAD indicates coronary artery disease; LVEF, left ventricular ejection fraction; LM, left main coronary artery; RCA, right coronary artery.

DES at the LMCA was similarly used in 529 patients (70.0%) undergoing IVUS guidance and 153 (69.9%) undergoing angiography guidance ($P=0.98$).

Propensity-Matched Patients

After performing propensity score matching in the entire population, a total of 201 matched pairs of patients were created (Table 2). The patients with use of IVUS or angiography guidances were well matched with regard to baseline clinical, angiographic, and procedural characteristics. The c-statistic of the regression model for the propensity score was 0.70, and the Hosmer-Lemeshow Goodness-of-Fit was 0.31. In addition, there was no significant difference in clinical characteristics between IVUS-guided versus angiography-guided groups among 145 pairs of patients receiving DES and 47 pairs of patients receiving BMS. The c-statistic was 0.72 and 0.82, and the Hosmer-Lemeshow Goodness-of-Fit was 0.57 and 0.27 in DES and BMS lesions, respectively.

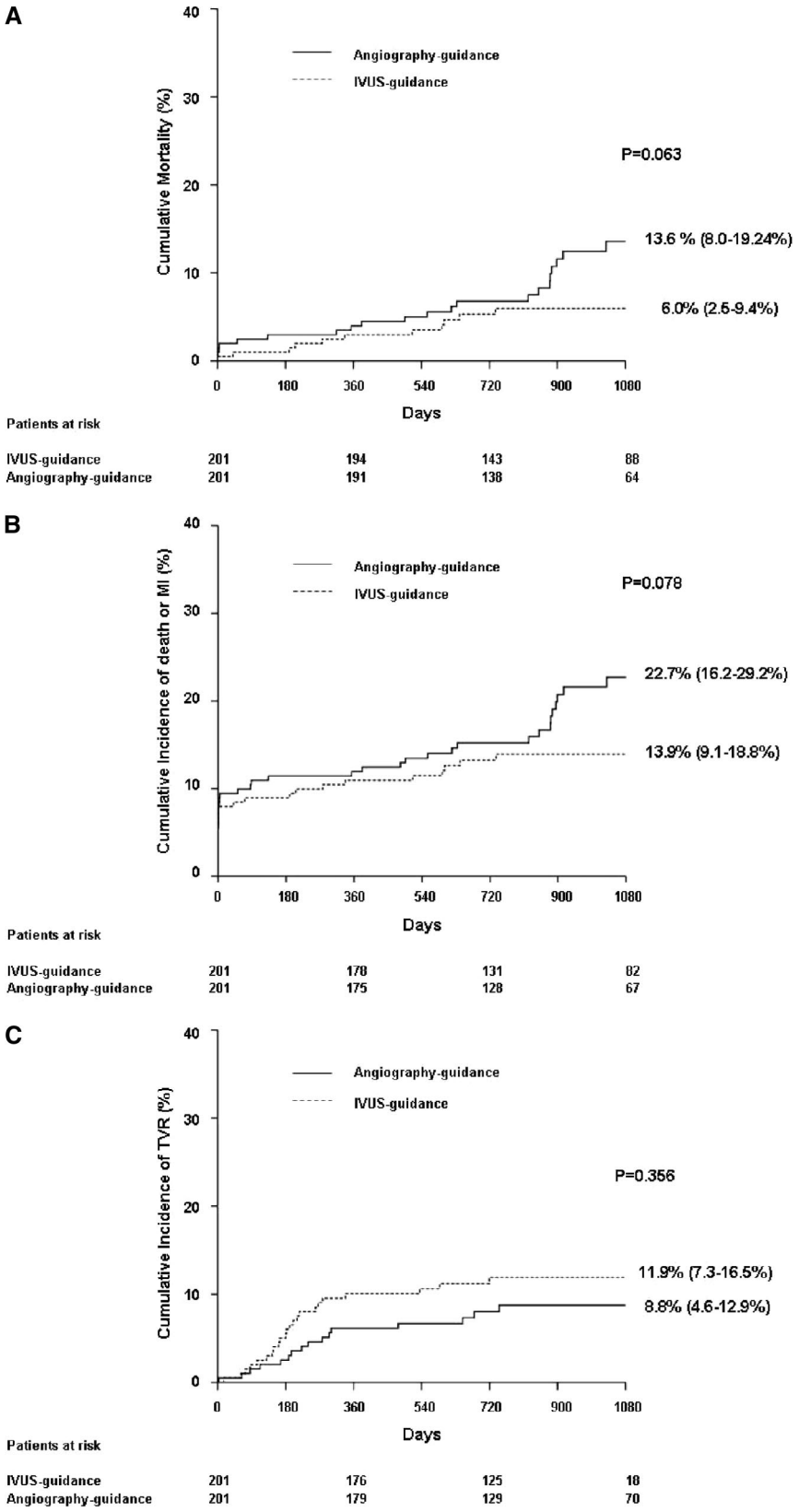


Figure 1. Kaplan–Meier incidence curves of outcomes following IVUS and angiography guidances in 201 propensity-matched pairs of the overall population. Three-year incidences in the 2 groups were presented as percent (95% CI) and were statistically compared with a log-rank test. A, Three-year incidences of death. B, Three-year incidence of death or MI. C, Three-year incidence of death, MI, or TVR.

Outcomes

Overall Patients

During follow-up, 34 deaths (15 in BMS and 19 in DES), 56 MIs, and 86 TVRs occurred in patients undergoing IVUS guidance, and 29 deaths (11 in BMS and 18 in DES), 24 MIs, and 19 TVRs in those undergoing angiography guidance during the follow-up. There were 23 cardiac deaths in the IVUS-guided group and 21 in the angiography-guided group.

Table 3. Hazard Ratios for Clinical Outcomes With Use of IVUS Guidance as Compared With Angiography Guidance Among Propensity-Matched Patients

	All			Drug-Eluting Stent			Bare-Metal Stent		
Outcome	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Death	0.54	0.28 to 1.03	0.061	0.39	0.15 to 1.02	0.055	0.59	0.18 to 1.91	0.38
MI	0.76	0.41 to 1.40	0.38	0.83	0.43 to 1.57	0.56	0.97	0.23 to 4.16	0.97
Death or MI	0.66	0.42 to 1.04	0.071	0.61	0.35 to 1.07	0.082	0.70	0.27 to 1.8	0.46
TVR	1.33	0.72 to 2.48	0.37	0.80	0.35 to 1.86	0.62	2.31	0.68 to 7.9	0.18
Death, MI, or TVR	0.80	0.54 to 1.19	0.28	0.64	0.39 to 1.04	0.074	1.12	0.52 to 2.41	0.78

Therefore, in the entire population of 975 patients, IVUS guidance was significantly associated with death (hazard ratio [HR], 0.31 [95% CI, 0.19 to 0.51] in overall; HR, 0.27 [95% CI, 0.14 to 0.52] in DES; HR, 0.36 [95% CI, 0.16 to 0.78] in BMS) and death or MI (HR, 0.470 [95% CI, 0.33 to 0.67] in overall; HR, 0.43 [95% CI, 0.28 to 0.67] in DES; HR, 0.55 [95% CI, 0.30 to 1.02] in BMS) as compared with angiography guidance. However, the risk of TVR (HR, 1.28 [95% CI, 0.78 to 2.10] in overall; HR, 0.96 [95% CI, 0.51 to 1.83] in DES; HR, 1.82 [95% CI, 0.82 to 4.04] in BMS) was not decreased by IVUS guidance. Angiographic stent thrombosis occurred in 3 patients undergoing IVUS guidance and 1 in those undergoing angiography guidance. Among them, late stent thrombosis beyond 1 year occurred in 1 patient undergoing IVUS guidance.

Propensity-Matched Patients

Figure 1 depicts the 3-year incidence of adverse outcomes in 201 matched pairs of overall patients with 14 deaths in IVUS guidance and 24 deaths in angiography guidance. The propensity-matched patients did not violate the proportional hazard assumption against time with respect to the death, TVR, and composite of death, death or MI, or death, MI, or TVR. At 3 years, 102 patients (51%) undergoing IVUS guidance and 116 patients (58%) undergoing angiography guidance were lost to follow-up. The incidence of 3-year morality tended to be lower in IVUS-guided group than in angiography-guided group, but this difference was not statistically significant. Accordingly, there was a nonsignificant tendency of lower risk of mortality with use of IVUS guidance compared with angiography guidance as indicated in Table 3. However, the risk of MI, TVR, or composite outcomes did not differ between the 2 groups.

In Figure 2, the incidence of 3-year mortality with 6 deaths in IVUS guidance and 14 deaths in angiography guidance significantly differed between IVUS-guided versus angiography-guided groups among 145 matched pairs of patients receiving DES by long-rank test. Therefore, in such a cohort, IVUS guidance was likely to reduce the risk of 3-year mortality (Table 3). In contrast, as indicated in Figure 3 and Table 3, IVUS guidance was not associated with a reduction of mortality in 47 matched pairs of patients receiving BMS, in whom 5 and 8 deaths occurred in IVUS and angiography guidances, respectively. No association was found between IVUS guidance and the risk of MI or TVR in patients receiving either DES or BMS.

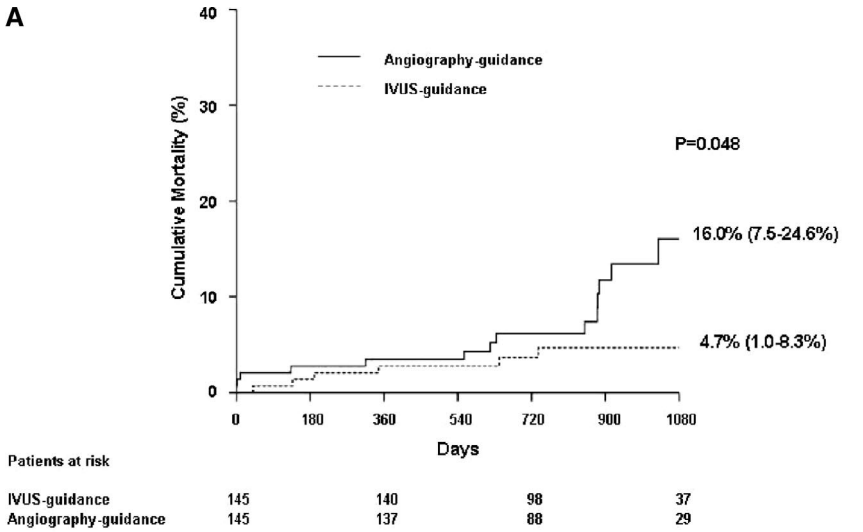
In the other multivariable Cox models using covariates with propensity score and variables listed in Table 1, IVUS guidance was significantly associated with death in overall patients (HR, 0.46; 95% CI, 0.24 to 0.87, $P=0.016$) and those receiving BMS (HR, 0.34; 95% CI, 0.13 to 0.89, $P=0.029$), but not in those receiving DES (HR, 0.64; 95% CI, 0.24 to 1.75, $P=0.39$).

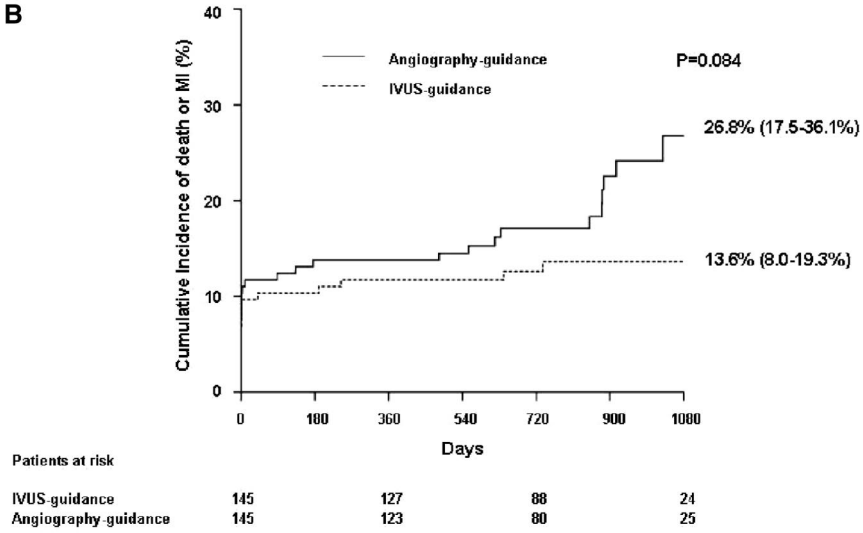
Discussion

We showed that IVUS-guided stenting may have a marginal benefit in reducing long-term mortality rate compared with conventional angiography-guided stenting for unprotected LMCA stenosis. In contrast to marginal improvements in survival, the risk of repeat revascularization was not modified by the use of IVUS.

Although IVUS may play a fundamental role in the treatment of complex coronary artery disease,[17–20] there is little information about the long-term clinical benefits of IVUS-guided PCI for unprotected LMCA stenosis. In a small study comparing the outcomes in 24 patients undergoing IVUS-guided PCI and 34 patients undergoing angiography-guided PCI with DES for unprotected LMCA stenosis, there was no difference in the incidence of adverse events comprising death, MI, or TVR.[25] This study, however, was limited by its small sample size, performance in a single center, and limited follow-up. In contrast, our study is more powered to evaluate the impact of IVUS guidance on long-term clinical benefits, because it involves a large registry of patients who underwent elective PCI for unprotected LMCA stenosis in multiple centers with long-term clinical observation.

The most important finding of this study was that the use of IVUS guidance, as compared with angiography guidance, in stenting for unprotected LMCA stenosis might reduce the incidence of long-term mortality. The rate of all-cause mortality, which was the primary end point of this study, is the most pertinent outcome to evaluate treatment effectiveness, because other clinical outcomes, such as cause-specific death or MI, can be confounded by several factors in reporting or adjudicating the events.[26] In this study, when the outcomes were rigorously adjusted by the propensity score, we found that the risk of 3-year mortality for IVUS guidance was ≈60% lower than that for angiography-guidance in the matched population. To our knowledge, this study is the first to demonstrate the possible benefit of IVUS guidance in reducing long-term mortality of during PCI for unprotected LMCA disease.





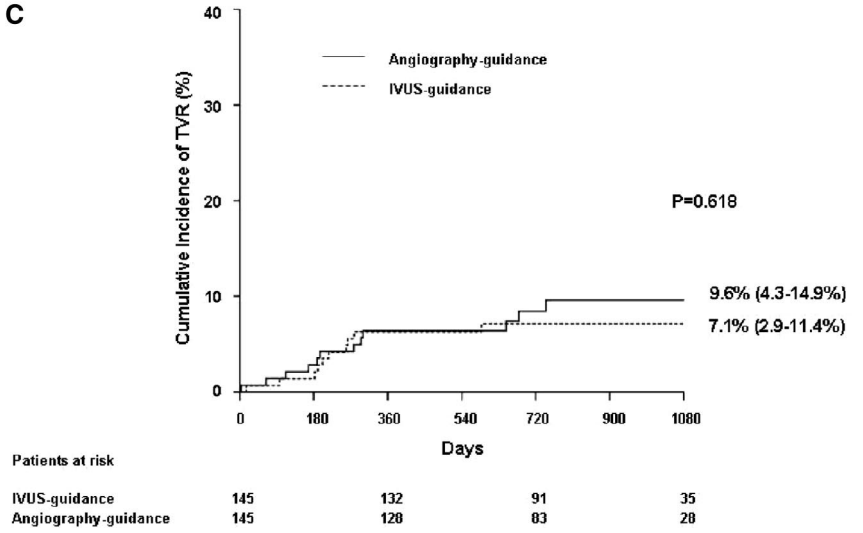


Figure 2. Kaplan–Meier incidence curves of outcomes following IVUS and angiography guidances in 145 propensity-matched pairs of patients receiving drug-eluting stent. Three-year incidences in the 2 groups were presented as percent (95% CI) and were statistically compared with a log-rank test. A, Three-year incidences of death. B, Three-year incidence of death or MI. C, Three-year incidence of death, MI, or TVR.

The mechanism of late mortality benefit by using IVUS guidance is not certain. However, based on the clear difference of mortality incidence beyond 1 year in propensity-matched patients receiving DES, not in matched-patients receiving BMS, may provide a potential mechanism why IVUS guidance had a long-term survival benefit as compared with conventional angiography guidance. Recent studies have suggested that the risk of stent thrombosis, in particular late

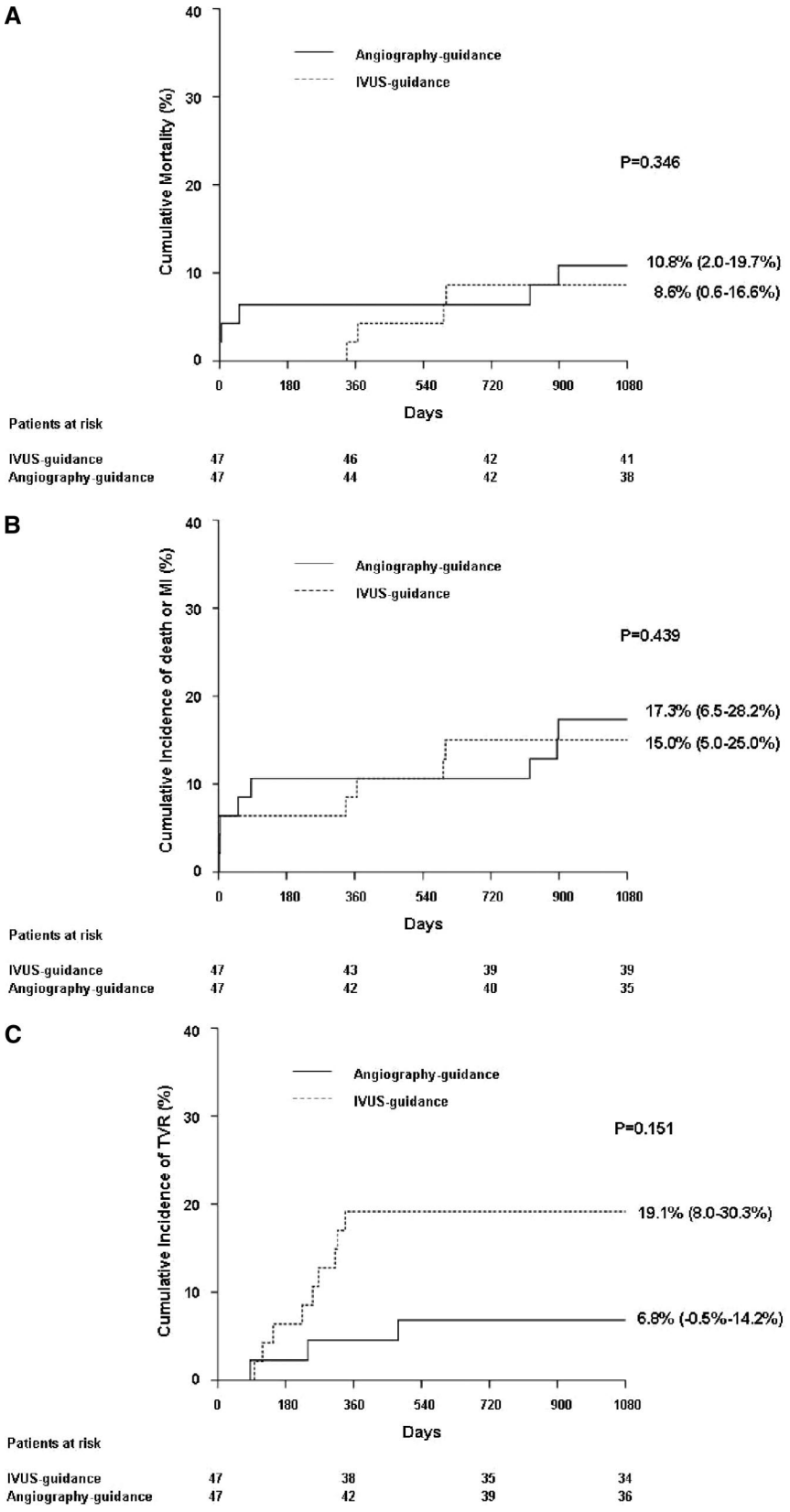


Figure 3. Kaplan–Meier incidence curves of outcomes following IVUS and angiography guidances in 47 propensity-matched pairs of patients receiving bare-metal stent. Three-year incidences in the 2 groups were presented as percent (95% CI) and were statistically compared with a log-rank test. A, Three-year incidences of death. B, Three-year incidence of death or MI. C, Three-year incidence of death, MI, or TVR.

thrombosis, may be higher with DES than BMS.[27–29] In a large registry study, DES stent thrombosis was found to occur even after 3 years, whereas BMS stent thrombosis was clustered in the early phase after placement.[30] Considering that stent thrombosis at unprotected LMCA is apt to present with sudden death,[27] a reduction of stent thrombosis with IVUS guidance may reinforce the benefits in clinical outcomes for patients receiving DES compared with those

receiving BMS. A temporal pattern of survival difference in the DES group supports our hypothesis, in that the survival curves between IVUS and angiography guidance started to separate and progressively diverged after 1 year, when very late stent thrombosis might occur. These findings, together with those of previous studies, indicate that use of IVUS may improve long-term survival by reducing the risk of stent thrombosis in DES treatment.

Several previous studies proposed a possibility that IVUS guidance during PCI may reduce stent thrombosis of DES. Compared with angiography, IVUS has a unique ability to assess suboptimal results of LMCA stenting, which may be associated with the occurrence of stent thrombosis. IVUS evaluations of stent underexpansion, incomplete lesion coverage, small stent area, large residual plaque, and inapposition have been found to predict stent thrombosis after DES placement.[31–35] Alternatively, the appropriate selection of stenting strategy by IVUS guidance may play a role in improving outcomes. Systemic use of a 2-stent strategy, compared with a single-stent strategy, may increase the risk of stent thrombosis as well as repeat revascularization in bifurcation LMCA lesions.[7,9,35–37] A better insight into plaque configuration with IVUS can diminish the unnecessary use of 2-stent procedures by distinguishing true stenosis versus pseudostenosis caused by various artifacts, including the device, coronary spasm, or calcification at the side branch.[17] However, the superior benefit of IVUS guidance in DES treatment was not consistently observed in the other Cox model using propensity score as a covariate for all patients. Therefore, further researches with a careful follow-up protocol should be performed to provide more confirmative information.

Our finding, regarding the influence of IVUS on repeat revascularization rate, conflicts with those of previous studies showing the benefit of IVUS guidance in reducing restenosis of BMS.[38,39] We found that IVUS guidance did not reduce the incidence of repeat revascularization following either BMS or DES treatments. Although the mechanism is not clear, it may be partly due to the low incidence of repeat revascularization observed in our study. We found that the 3-year cumulative rate of TVR after DES implantation was within a single digit, ranging from 7.1% to 9.1% with angiography- or IVUS-guidances in the matched population. Alternatively, an inherent limitation of a nonrandomized study design may have contributed to the outcomes. Because the use of IVUS or angiography was at the discretion of the operator, IVUS guidance might be selected for lesions with more complex coronary anatomy, in which ultrasound examination seemed to be necessary. Moreover, this study did not have any prespecified target of optimal stenting for IVUS guidance. Thus, sufficient luminal gain enough to reduce restenosis may not have been achieved with IVUS guidance compared with angiography guidance.

Study Limitations

Our study had several limitations, including its use of a nonrandomized registry. Therefore, despite rigorous statistical adjustment, unmeasured confounders may have influenced the outcomes. Although patients presenting with cardiogenic shock or acute MI were retrieved for fair comparison, IVUS-guided stenting may be preferred for patients in stable hemodynamic condition. In addition, comparisons in the propensity-matched subgroups of DES and BMS patients might be seriously impaired by underpowered study population and low incidence of events to clearly detect the differential risk of death, MI, or revascularization. In fact, none of the 15 Cox models reported in Table 3 produced a $P<0.05$. Second, using a significance threshold of 0.05 may lead to high type I error rate among multiple comparisons. Third, participating centers were high-volume tertiary institutions and adopted IVUS as a routine ancillary practice in patients undergoing LMCA stenting. Therefore, the outcomes observed in this study may not be applicable to institutions with a restricted indication for the use of IVUS. In fact, studies in such centers may underestimate the role of IVUS. Fourth, this study may be underpowered to compare the effectiveness of IVUS versus angiography after propensity-score matching. Finally, quantitative IVUS or angiographic assessment was not performed. Therefore, the relationship between the quantitative results of imaging parameters and clinical outcomes could not be assessed. Given the aforementioned limitations, our study is truly exploratory to provide the clinical insight and warrants future randomized studies having enough sample size and prespecified protocol to assess the efficacy of IVUS-guided PCI in DES placement for LMCA lesions.

Conclusions

Using a large registry, we found that long-term mortality after unprotected LMCA stenting was reduced by IVUS guidance as compared with conventional angiography guidance. This result indicates that the routine use of IVUS is generally recommended while performing elective PCI for unprotected LMCA stenosis.

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Disclosures

None.

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