Long-Term Outcomes of Intravascular Ultrasound-Guided Stenting in Coronary Bifurcation Lesions

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Stenting for bifurcation lesions is still challenging, and the effect of intravascular ultrasound (IVUS) guidance on long-term outcomes has not been evaluated. We assessed the long-term outcomes of IVUS-guided stenting in bifurcation lesions. We evaluated 758 patients with de novo nonleft main coronary bifurcation lesions who underwent stent implantation from January 1998 to February 2006. We compared the adverse outcomes (i.e., death, stent thrombosis, and target lesion revascularization) within 4 years, after adjustment using a multivariate Cox proportional hazard model and propensity scoring. IVUS-guided stenting significantly reduced the long-term all-cause mortality (hazard ratio [HR] 0.31, 95% confidence interval [CI] 0.13 to 0.74, p = 0.008) in the total population and in the patients receiving drug-eluting stents (DESs) (HR 0.24, 95% CI 0.06 to 0.86, p = 0.03), but not in the patients receiving bare metal stents (HR 0.41, 95% CI 0.13 to 1.26, p = 0.12). IVUS-guided stenting had no effect on the rate of stent thrombosis (HR 0.48, 95% CI 0.16 to 1.43, p = 0.19) or target lesion revascularization (HR 1.47, 95% CI 0.79 to 2.71, p = 0.21). In patients receiving DESs, however, IVUS guidance reduced the development of very late stent thrombosis (0.4% vs 2.8%, p = 0.03, log-rank test). In conclusion, in patients receiving DESs, IVUS-guided stenting for treatment of bifurcation lesions significantly reduced the 4-year mortality compared to conventional angiographically guided stenting. In addition, IVUS guidance reduced the development of very late stent thrombosis in patients receiving DESs. **(Am J Cardiol 2010;106:612–618)**

Intravascular ultrasonography provides useful information on vessel anatomy and can result in optimal stent deployment. A large cohort study reported that intravascular ultrasound (IVUS) guidance during drug-eluting stent (DES) implantation significantly reduced the thrombosis rate and showed a favorable trend for repeat revascularization.[1] IVUS guidance might be even more useful in complex lesions such as bifurcation lesions. In addition, the long-term effect of IVUS guidance on bifurcation stenting has not been determined. Therefore, we evaluated the effect of IVUS-guided stenting on the long-term outcomes in patients with bifurcation lesions.

Methods

From January 3, 1998 to February 28, 2006, 7,221 patients underwent percutaneous coronary intervention with stenting at the Asan Medical Center (Seoul and Gangneung, Korea).[2] Of these, 758 consecutive patients underwent stenting for de novo nonleft main coronary bifurcation lesions with a side branch >2.0 mm in diameter, by visual estimation. The performance of IVUS-guided stenting was left to the physician's discretion. Patients were classified as having undergone IVUS-guided stenting if an IVUS examination was performed during any stenting procedure for the targeted lesions. Bare metal stents (BMSs) were the default treatment from January 1998 to January 2003, and DESs were the default choice beginning in February 2003. Qualitative and quantitative angiographic measurements were performed using standard techniques with automated edge-detection algorithms (CASS-5, Pie Medical, Maastricht, The Netherlands) in the angiographic analysis center of the Cardiovascular Research Foundation, Seoul, Korea. Any patient who received ≥1 DES in the treatment of targeted bifurcation lesions was assigned to the DES group. All patients were prescribed aspirin indefinitely, with additional clopidogrel at the physician's discretion.

The primary end point was death from any cause within the 4 years after index stenting. The secondary end points were stent thrombosis and target lesion revascularization during the same period. Stent thrombosis was assessed using the Academic Research Consortium definitions, including all levels of certainty, and by the timing of the event as early, late, or very late after the index coronary interven-

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Table 1
Baseline patient and procedural characteristics

Variable	IVUS Guidance (n = 473)	Angiographic Guidance (n = 285)	p Value
Clinical characteristics			
Age (years)	59 ± 10	60 ± 11	0.08
Men	344 (73%)	204 (72%)	0.73
Diabetes mellitus	95 (20%)	63 (22%)	0.51
Hypertension	205 (43%)	132 (46%)	0.43
Smoker	171 (36%)	102 (36%)	0.92
Hypercholesterolemia	134 (28%)	99 (35%)	0.06
Previous percutaneous coronary intervention	49 (10%)	21 (7%)	0.17
Previous coronary bypass	1 (0.2%)	1 (0.4%)	0.72
Acute coronary syndrome	248 (52%)	181 (64%)	0.003
Acute myocardial infarction	54 (11%)	42 (15%)	0.18
Primary percutaneous coronary intervention	24 (5%)	8 (3%)	0.13
Renal failure	5 (1.1%)	1 (0.4%)	0.29
Left ventricular ejection fraction (%)	60 ± 8	59 ± 10	0.61
Left ventricular dysfunction	36 (8%)	27 (10%)	0.28
Procedural characteristics			
Drug-eluting stent implantation	308 (65%)	112 (39%)	<0.001
Sirolimus-eluting stents	259 (84%)	94 (84%)	0.97
Paclitaxel-eluting stents	49 (16%)	18 (16%)	
One-stent strategy	386 (82%)	263 (92%)	<0.001
Multivessel percutaneous coronary intervention	137 (29%)	97 (34%)	0.14
Restenosis lesion	25 (5%)	11 (4%)	0.37
Ostial lesion	61 (13%)	9 (3%)	<0.001
Chronic total occlusion	12 (3%)	7 (3%)	0.95
Long lesion (≥30 mm)	279 (59%)	131 (46%)	<0.001
Use of glycoprotein IIb/IIIa inhibitor	18 (4%)	8 (3%)	0.46
Discontinuation of clopidogrel within 6 mo	29 (6%)	16 (6%)	0.77
Total stent length per lesion (mm)	34 ± 19	26 ± 14	<0.001
Stents used per lesion (n)	1.4 ± 0.7	1.2 ± 0.5	<0.001

Table 2
Quantitative angiographic measurements

Variable	IVUS Guidance (n = 473)	Angiographic Guidance (n = 285)	p Value
Reference diameter			
Before procedure			
Proximal (mm)	3.3 ± 0.5	3.1 ± 0.5	0.004
Distal (mm)	2.7 ± 0.5	2.6 ± 0.4	0.16
Mean (mm)	3.1 ± 0.5	3.0 ± 0.5	0.02
After procedure			
Proximal (mm)	3.4 ± 0.5	3.2 ± 0.5	0.001
Distal (mm)	2.6 ± 0.4	2.5 ± 0.4	0.06
At 4-year follow-up			
Proximal (mm)	3.1 ± 0.5	3.2 ± 0.4	0.49
Distal (mm)	2.6 ± 0.4	2.5 ± 0.3	0.80
Mean (mm)	2.8 ± 0.4	2.8 ± 0.5	0.57
Minimal luminal diameter			
Preprocedure (mm)	0.9 ± 0.5	0.8 ± 0.5	<0.001
Postprocedure (mm)	3.0 ± 0.5	2.8 ± 0.5	0.002
At follow-up (mm)	2.3 ± 0.8	2.1 ± 1.6	0.21
Acute gain (mm)	2.1 ± 0.6	2.1 ± 0.6	0.69
Late loss (mm)	0.7 ± 0.8	0.7 ± 1.7	0.78
Diameter stenosis (%)			
Preprocedure	70 ± 16%	74 ± 15%	0.003
Postprocedure	2 ± 12%	4 ± 12%	0.08
At follow-up	10 ± 27%	18 ± 49%	0.16
Lesion length (mm)	25 ± 14	21 ± 10	<0.001
Maximum balloon size	3.6 ± 0.4	3.4 ± 0.5	<0.001

tion.[3] Target lesion revascularization was defined as revascularization for a stenosis within the stent or within a region 5 mm adjacent to the stent. Target lesion revascularization was performed on the basis of clinical decision making, not angiographically, and was assessed after long-term follow-up, not dichotomously at 6 months. All clinical outcomes of interest were adjudicated by independent clinicians.

The baseline clinical and procedural characteristics were recorded in our institution's dedicated database by the clinical research nurses. Clinical follow-up was performed by office visit or telephone interview at 1, 6, and 12 months after the procedure and every 6 months thereafter. To reduce follow-up bias, the clinical outcomes were censored at 4 years in 2 sequential cohorts of patients with BMS or DES implantation. These data were used for the present study. The institutional review board at Asan Medical Center, Seoul and Gangneung, Korea, approved the present study, and all patients provided written informed consent for the use of the clinical and procedural data.

Categorical variables are presented as raw numbers and frequencies and were compared using the chi-square test to ensure equality of proportions. Continuous variables are presented as the mean ± SD and were compared using Student's *t* test. Kaplan-Meier analysis was used to determine the adverse event-free survival rate, and differences were analyzed using the log-rank test. We adjusted the results for significant differences in patient characteristics using Cox proportional hazards regression models that included all significant variables with $p < 0.2$ on univariate analysis. The covariates of the baseline demographic, clinical, angiographic, and procedural characteristics included all variables listed in Tables 1 and 2. The second multivariate Cox model, to identify the predictors of adverse outcomes, used backward elimination until only factors with $p < 0.1$ remained. Each propensity score was estimated from a logistic regression model for IVUS-guided versus angiographically guided stenting. The propensity scores were incorporated into the Cox proportional hazards regression model as covariates. The discrimination and calibration ability of the propensity score model was assessed by c-statistics and Hosmer-Lemeshow statistics. The c-statistic of the regression model for the propensity score was 0.72 (0.74 for DESs, 0.71 for BMSs). To evaluate the risk factors for very late stent thrombosis, the events were accessed beginning at the 1-year point. The patients who were event free at 1 year were assigned to a landmark analysis of 4 groups (by stent type and guidance method), and the effect of IVUS guidance for each stent type was separately analyzed. All analyses were performed on a per-patient basis. A p value < 0.05 was considered statistically significant. The Statistical Package for Social Sciences for Windows, version 12.0 (SPSS, Chicago, Illinois) was used for all analyses.

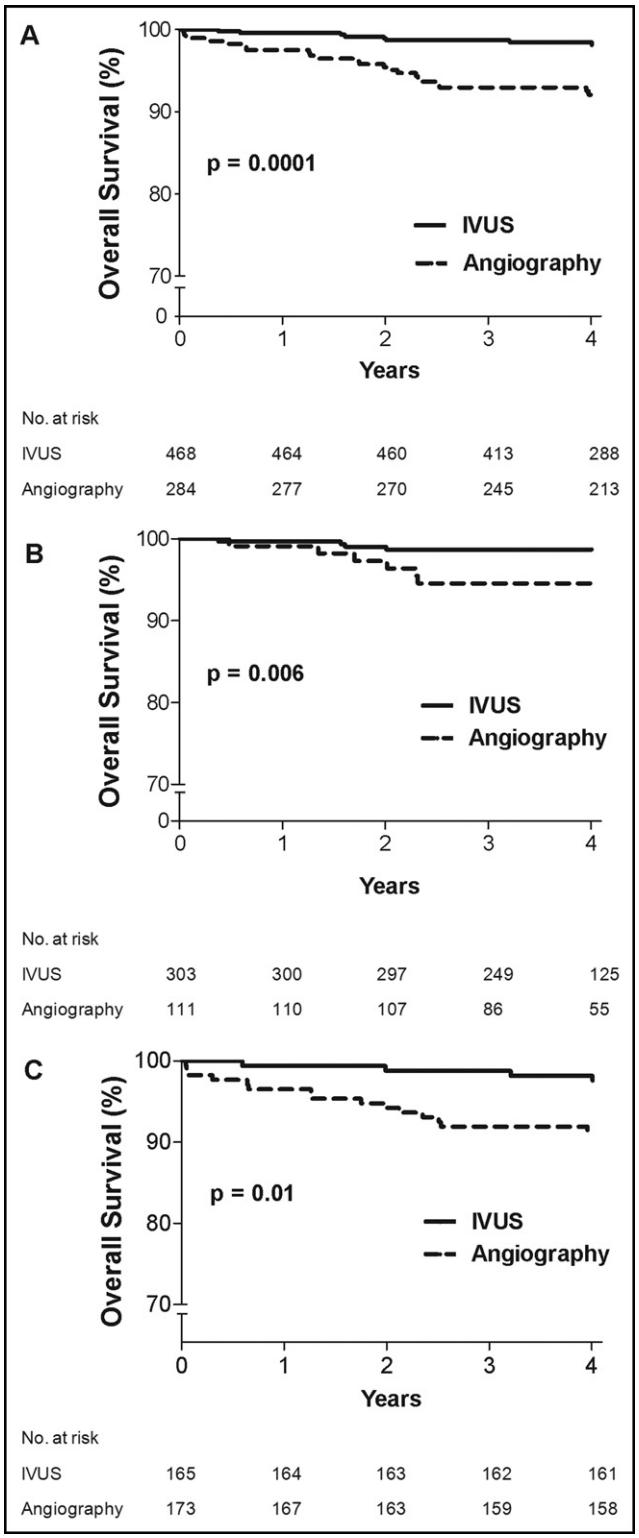

Figure 1. Unadjusted survival rates in *(A)* all patients overall, *(B)* patients implanted with DESs, *(C)* and patients implanted with BMSs. Numbers of patients at risk shown below each graph.

Results

A total of 758 patients were treated with stenting for nonleft main coronary bifurcation lesions. Of these, 473 underwent IVUS-guided and 285 underwent angiographically guided stenting. Patients who received IVUS-guided stenting were more likely to be implanted with DESs, to undergo complex stenting with 2 stents, to have ostial lesions, and to have longer lesions than the patients who underwent angiographically guided stenting (Table 1). Of the 420 patients implanted with DESs, 353 (84%) received sirolimus-eluting stents (Cypher, Cordis, Johnson & Johnson, New Brunswick, New Jersey) and 67 (16%) received paclitaxel-eluting stents (Taxus Express; Boston Scientific, Boston, Massachusetts). Although treatment with clopidogrel was at the physicians' discretion, only 4 patients who received DESs took clopidogrel for <3 months, with most patients (94%) prescribed clopidogrel for >6 months. Of the 420 patients receiving DESs, 62 (15%) were treated with cilostazol. Quantitative angiographic analysis showed that patients who underwent IVUS-guided stenting had longer lesions, larger reference diameters, larger postprocedural minimal luminal diameters, smaller preprocedure diameter stenosis, and maximum balloon sizes (Table 2). When the follow-up period was truncated at 4 years, the mean length of follow-up was 3.9 ± 0.6 years in the BMS group and 3.5 ± 0.7 years in the DES group. No significant difference was found in the follow-up duration between patients who underwent IVUS-guided and those who underwent angiographically guided stenting (3.7 ± 0.6 years vs 3.7 ± 0.8 years, $p = 0.90$).

During the 4 years of follow-up, 30 (4.0%) of the 758 patients died. On multivariate-adjusted Cox regression analysis, the IVUS-guided group had a significantly lower rate of all-cause mortality than did the angiographically guided group for the overall group, a difference observed in patients treated with DESs but not BMSs (Figure 1 and Table 3). In the second multivariate-adjusted Cox regression analysis, the independent risk factors for death were older age (hazard ratio [HR] 1.06, 95% confidence interval [CI] 1.02 to 1.10, $p = 0.001$), diabetes mellitus (HR 2.68, 95% CI 1.29 to 5.58, $p = 0.01$), and angiographically guided stenting (HR 3.92, 95% CI 1.74 to 8.84, $p = 0.001$). In the DES group, older age (HR 1.10, 95% CI 1.02 to 1.17, $p = 0.006$), discontinuation of clopidogrel within 6 months after the index procedure (HR 9.45, 95% CI 2.84 to 31.38, $p = 0.0002$), and angiographically guided stenting (HR 4.15, 95% CI 1.20 to 14.29, $p = 0.02$) were independent risk factors for death from any cause. In the BMS group, however, IVUS-guided stenting did not affect the all-cause mortality rate. In these patients, older age (HR 1.07, 95% CI 1.01 to 1.12, $p = 0.01$), diabetes mellitus (HR 2.73, 95% CI 1.10 to 6.83, $p = 0.03$), and presentation with acute coronary syndrome (HR 8.02, 95% CI 1.07 to 60.27, $p = 0.04$) were independent risk factors for death from any cause. When we assessed the causes of death, we found that 12 patients died from cardiovascular causes. IVUS-guided stenting significantly reduced the 4-year cardiovascular mortality rate compared to angiographically guided stenting (0.4% vs 3.6%, $p = 0.001$, using the log-rank method), an effect sustained after multivariate-adjusted analysis (HR 0.17, 95% CI 0.04 to 0.81). However, IVUS-guided stenting did not affect the noncardiovascular mortality rate (3.2% vs 5.4%, $p = 0.09$, log-rank method).

During the 4-year follow-up period, the incidence of stent thrombosis was somewhat lower in patients who un-

Table 3
Unadjusted and adjusted hazard ratios (HRs) of clinical outcomes after intravascular ultrasound (IVUS)-guided compared to angiographically guided stenting

Outcome	Overall Group		DES Group		BMS Group	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Unadjusted						
Death	0.22 (0.10–0.50)	<0.001	0.21 (0.06–0.72)	0.01	0.27 (0.09–0.81)	0.02
Stent thrombosis	0.45 (0.16–1.30)	0.14	0.27 (0.06–1.22)	0.09	0.78 (0.17–3.48)	0.74
Target lesion revascularization	1.36 (0.77–2.41)	0.29	0.94 (0.39–2.24)	0.88	2.13 (1.00–4.55)	0.05
Multivariate adjusted						
Death	0.31 (0.13–0.74)	0.008	0.24 (0.06–0.86)	0.03	0.41 (0.13–1.26)	0.12
Stent thrombosis	0.48 (0.16–1.43)	0.19	0.35 (0.08–1.64)	0.18	1.09 (0.22–5.34)	0.92
Target lesion revascularization	1.47 (0.79–2.71)	0.21	0.92 (0.38–2.25)	0.86	2.27 (0.99–5.25)	0.05
Propensity score adjusted						
Death	0.13 (0.03–0.66)	0.01	0.21 (0.06–0.73)	0.01	0.4 (0.1–1.2)	0.11
Stent thrombosis	0.30 (0.07–1.32)	0.11	0.28 (0.06–1.25)	0.10	1.0 (0.2–4.9)	0.98
Target lesion revascularization	0.63 (0.23–1.72)	0.36	0.90 (0.33–2.54)	0.84	1.67 (0.75–3.72)	0.21

derwent IVUS-guided than in those who underwent angiographically guided, stenting, but the difference was not significant (Figure 2 and Table 3). Of the 14 patients with stent thrombosis, 6 (43%) died from stent thrombosis, and all had undergone angiographically guided stenting. Of these 6 patients, 3 died within 1 year after the index procedure (18, 177, and 235 days) and 3 died after 1 year (620, 840, and 924 days). In subgroup analysis of stent type, no significant differences in the rate of the development of stent thrombosis were noted (Figure 2). However, the HRs for stent thrombosis showed a nonsignificant trend toward lower risk among patients who underwent IVUS-guided stenting and DES implantation (Table 3). The patients who underwent IVUS-guided stenting showed a tendency toward a lower rate of very late stent thrombosis, but the difference was not statistically significant (HR 0.12, 95% CI 0.01 to 1.01, $p = 0.05$). Within the DES group, IVUS-guided stenting significantly reduced the cumulative incidence of very late stent thrombosis (0.4% vs 2.8%, $p = 0.03$, log-rank test, Figure 3). In the second multivariate-adjusted Cox regression analysis, the discontinuation of clopidogrel within 6 months after stenting was the only independent risk factor for stent thrombosis in the DES group, and no significant risk factor was found in the BMS group. The overall incidence of definite stent thrombosis after 4 years was similar in patients who underwent IVUS-guided and angiographically guided stenting (0.8% vs 1.1%, $p = 0.77$, log-rank test); these similarities were observed in both the DES (0.7% vs 0.9%, $p = 0.79$, log-rank test) and BMS (1.2% vs 1.2%, $p = 0.97$, log-rank test) groups. In addition, the incidence of definite or probable stent thrombosis was similar in the patients who underwent IVUS- and angiographically guided stenting (overall, 1.1% vs 1.4%, $p = 0.67$; DES group, 0.7% vs 0.9%, $p = 0.79$; BMS group, 1.9% vs 1.7%, $p = 0.96$, respectively; log-rank test). According to target lesion revascularization, no significant difference was found between the patients treated with IVUS-guided and angiographically guided stenting in the DES or BMS groups (Figure 4). These trends were also sustained after adjustment (Table 3). When patients were stratified according to whether stenting was performed using a 2-stent strategy (stenting in the main branch and side branch, $n = 109$) or a 1-stent strategy (simple stenting in the main branch, $n = 649$), the crude incidence of death (3.7% vs 4.0%, $p = 0.96$, log-rank test), the incidence of stent thrombosis (1.9% vs 1.9%, $p = 0.99$, log-rank test) and target lesion revascularization (6.4% vs 7.4%, $p = 0.78$, log-rank test) was similar in the 2 groups. In addition, using the multivariate Cox model, the stenting technique was not significantly associated with the risk of death from any cause, stent thrombosis, or target lesion revascularization.

Discussion

We have shown in the present study that IVUS-guided stenting significantly reduced all-cause mortality in patients receiving DESs for the treatment of bifurcation lesions. In contrast, IVUS-guided stenting did not affect all-cause mortality in patients receiving BMSs, a finding compatible with previous reports on the treatment of de novo lesions. IVUS-guided stenting also showed a nonsignificant trend toward a lower rate of stent thrombosis, especially in patients receiving DESs. Furthermore, IVUS-guided stenting significantly reduced the development of very late stent thrombosis in the DES group, but it had no effect on the target lesion revascularization rate.

The results of several randomized trials of BMS implantation have found that routine IVUS guidance for all elective procedures has not generally been recommended.[4,5] Therefore, research investigating the effect of IVUS guidance has focused on complex lesions or patient subsets, such as those with bifurcation lesions. IVUS guidance provides very important information on the morphology of bifurcation lesions and the outcomes of stent optimization.[6] Furthermore, patients with bifurcation lesions are more vulnerable to stent thrombosis because of shear stress, low flow velocity, and multiple layers of stent struts.[7] Stenting for treatment of bifurcation lesions has shown a high incidence (3.6%) of cumulative stent thrombosis at 9 months, with bifurcation an independent risk factor for stent thrombosis.[8] More recently, a retrospective registry study reported that IVUS guidance for DES implantation might decrease the risk of long-term stent thrombosis and target lesion revascularization in propensity score-matched patients.[1] The

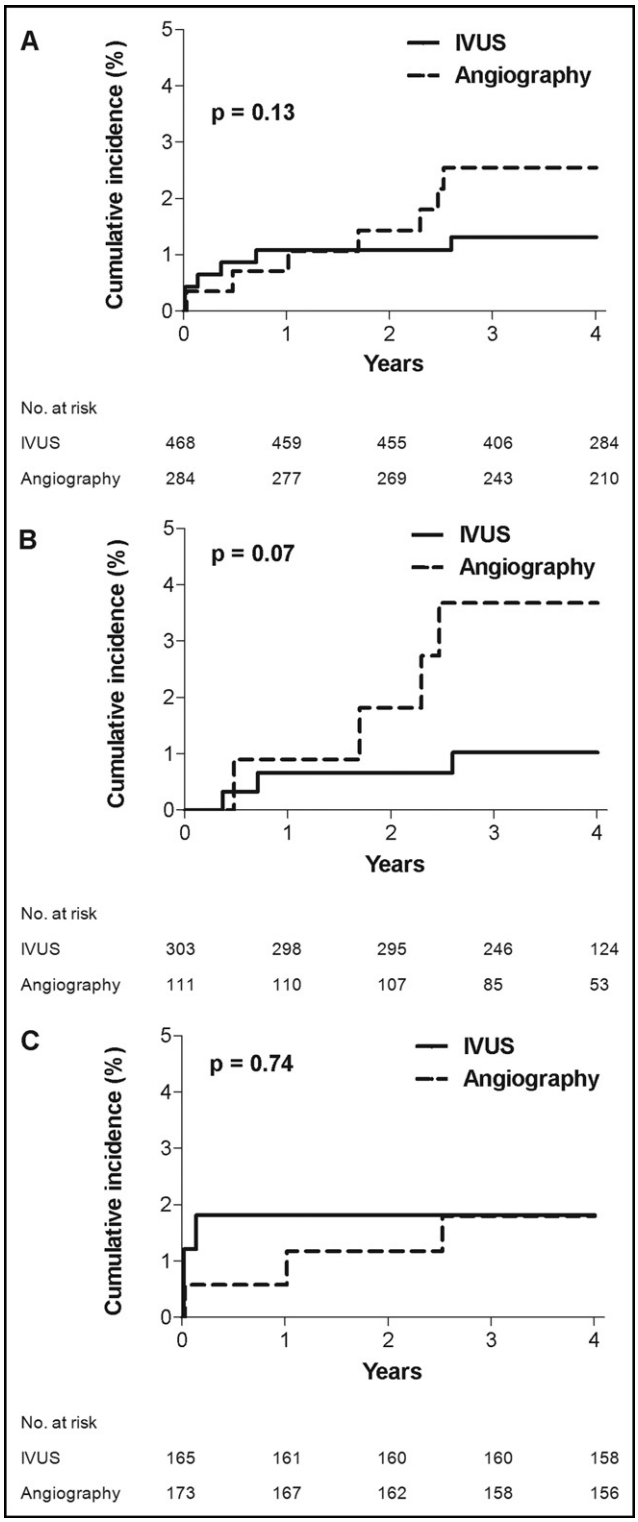

Figure 2. Unadjusted cumulative incidence of stent thrombosis in *(A)* all patients overall, *(B)* patients implanted with DESs, and *(C)* patients implanted with BMSs. Numbers of patients at risk shown below each graph.

cited study, however, was limited by a short follow-up period (1 year). Our study showed that IVUS guidance might decrease the risk of long-term mortality compared to angiography guidance, especially in patients implanted with DESs. Because IVUS-guided stenting reduced the cumula-

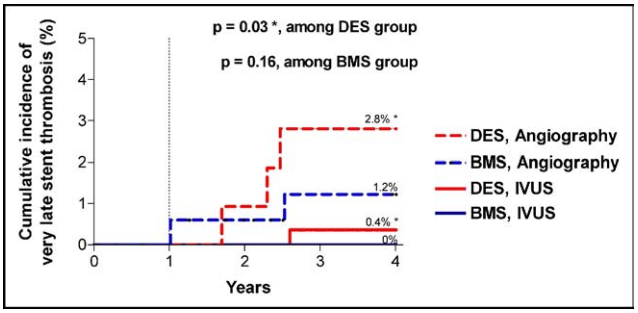

Figure 3. Unadjusted cumulative incidence of very late stent thrombosis in patients implanted with DESs under IVUS guidance and angiographic guidance.

tive incidence of very late stent thrombosis in the DES group, the long-term survival benefit of IVUS guidance in DES was mainly driven by a reduction in very late stent thrombosis. Underexpansion of stents and edge problems such as geographic miss, secondary lesions, and large plaque burden have been found to predict DES thrombosis.[9,10] Therefore, we would postulate that IVUS guidance might reduce the risk of long-term stent thrombosis by the greater mechanical benefit obtained by optimizing stent placement. Because late stent thrombosis is an important potential contributor to long-term mortality after DES treatment, our results have indicated that the difference in mortality between the 2 strategies might be driven by a diminished risk of late stent thrombosis after IVUS-guided stent placement. As in previous reports, discontinuation of clopidogrel within 6 months was also found to be a strong predictor of stent thrombosis and death in the DES group.[11] IVUS guidance did not provide a clear beneficial effect on the long-term occurrence of target lesion revascularization. The risk of target lesion revascularization was not associated with IVUS guidance, although a meta-analysis of patients who underwent stent implantation for nonselected lesions reported that IVUS guidance was associated with a lower rate of target vessel revascularization, not target lesion revascularization (odds ratio 0.62, 95% CI 0.49 to 0.78).[12] Most studies have shown no significant difference in binary restenosis in patients receiving BMSs.[4,5,13–15] Furthermore, the effect of IVUS guidance on target lesion revascularization using BMSs could not be confirmed, and the largest randomized study of IVUS-guided BMS implantation found that IVUS guidance was of no benefit for target vessel revascularization.[5] Unlike earlier reports, our data were derived from patients with only bifurcation lesions, not from those with all lesions, including nonbifurcation lesion. Furthermore, target lesion revascularization in our study was performed on the basis of clinical decision, not angiographically, and was assessed after long-term follow-up, not just dichotomously at 6 months. Our study included the largest specific population examined to date and the longest follow-up. Also, we included quantitative coronary analysis data, clarifying the stent thrombosis rate, and performed meticulous adjustment. A definite assessment of the relative merits of the guiding strategies should be reserved until a randomized study with a dedicated protocol has been performed.

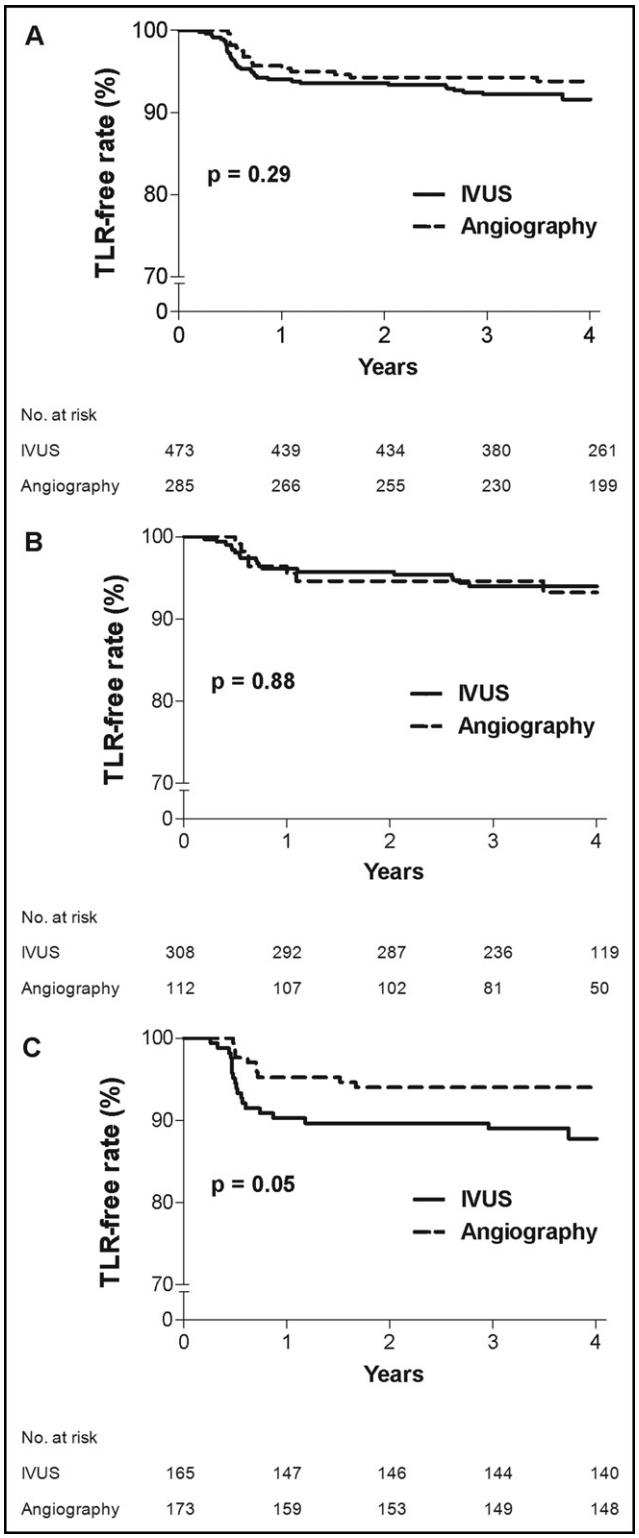

Figure 4. Unadjusted target lesion revascularization-free rates in *(A)* all patients overall, *(B)* patients implanted with DESs, and *(C)* patients implanted with BMs. Numbers of patients at risk shown below each graph.

Our study had several limitations. First, we used observational data from 2 central registries. The choice of guidance method was at the discretion of the treating physician, and optimal IVUS-determined procedural criteria were not prespecified. Therefore, although we adjusted our findings to avoid selection bias, the effect of confounders might not have been completely eliminated. Second, although our study population was the largest used to date to assess the outcomes of IVUS guidance, the population might still have been underpowered for the detection of a very low incidence of stent thrombosis. Third, we did not perform quantitative angiographic or IVUS measurements on the side branch, which might be essential to understanding the mechanisms of benefits offered by IVUS guidance. Although our study was exploratory, the results generated warrant the conduct of randomized trials to assess the usefulness of IVUS-guided stenting in patients with bifurcation lesions. Fourth, IVUS was performed more in patients undergoing DES implantation, who had received more antiplatelet therapy. These differences might have affected the outcomes.

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