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Effect of Intravascular Ultrasound–Guided Drug-Eluting Stent Implantation

5-Year Follow-Up of the IVUS-XPL Randomized Trial

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ABSTRACT

OBJECTIVES The goal of this study was to evaluate whether the beneficial effect of use of intravascular ultrasound (IVUS) is sustained for long-term follow-up.

BACKGROUND The use of IVUS promoted favorable 1-year clinical outcome in the IVUS-XPL (Impact of Intravascular Ultrasound Guidance on the Outcomes of Xience Prime Stents in Long Lesions) trial. It is not known, however, whether this effect is sustained for long-term follow-up.

METHODS The IVUS-XPL trial randomized 1,400 patients with long coronary lesions (implanted stent length ≥28 mm) to receive IVUS-guided (n = 700) or angiography-guided (n = 700) everolimus-eluting stent implantation. Five-year clinical outcomes were investigated in patients who completed the original trial. The primary outcome was the composite of major adverse cardiac events, including cardiac death, target lesion–related myocardial infarction, or ischemia-driven target lesion revascularization at 5 years, analyzed by intention-to-treat.

RESULTS Five-year follow-up was completed in 1,183 patients (85%). Major adverse cardiac events at 5 years occurred in 36 patients (5.6%) receiving IVUS guidance and in 70 patients (10.7%) receiving angiographic guidance (hazard ratio: 0.50; 95% confidence interval: 0.34 to 0.75; p = 0.001). The difference was driven mainly by a lower risk for target lesion revascularization (31 [4.8%] vs. 55 [8.4%]; hazard ratio: 0.54; 95% confidence interval: 0.33 to 0.89; p = 0.007). By landmark analysis, major adverse cardiac events between 1 and 5 years occurred in 17 patients (2.8%) receiving IVUS guidance and in 31 patients (5.2%) receiving angiographic guidance (hazard ratio: 0.53; 95% confidence interval: 0.29 to 0.95; p = 0.031).

CONCLUSIONS Compared with angiography-guided stent implantation, IVUS-guided stent implantation resulted in a significantly lower rate of major adverse cardiac events up to 5 years. Sustained 5-year clinical benefits resulted from both within 1 year and from 1 to 5 years post-implantation. (Impact of Intravascular Ultrasound Guidance on the Outcomes of Xience Prime Stents in Long Lesions [IVUS-XPL Study]: Retrospective and Prospective Follow-Up Study; NCT03866486) (J Am Coll Cardiol Intv 2020;13:62–71) © 2020 by the American College of Cardiology Foundation.

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The IVUS-XPL (Impact of Intravascular Ultrasound Guidance on the Outcomes of Xience Prime Stents in Long Lesions) randomized trial demonstrated that the use of intravascular ultrasound (IVUS)-guided drug-eluting stent (DES) implantation, compared with angiography-guided DES implantation, resulted in a significantly lower rate of 1-year major adverse cardiac events, mainly because of a lower rate of the need of target lesion revascularization (TLR) (1). However, these data were limited because of relatively short-term follow-up of 1 year, while TLR or target vessel revascularization has been reported to continue without attenuation beyond 1 year even in the era of new-generation DES (2-7). Also, among 7 previously reported randomized trials comparing IVUS guidance versus angiographic guidance for DES implantation, 3 studies reported only 1-year clinical outcomes (8-10), while 4 studies reported 2-year clinical outcomes (11-14). Therefore, there is no randomized trial evidence evaluating the long-term effect of IVUS guidance during DES implantation beyond 2 years, and it is not known whether the 1-year benefit of IVUS guidance is sustained for longer-term follow-up.

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We report the 5-year clinical outcomes of the randomized IVUS-XPL trial to determine whether the beneficial 1-year effect of IVUS guidance is sustained up to 5 years when patients are treated with contemporary DES.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

DES = drug-eluting stent(s)

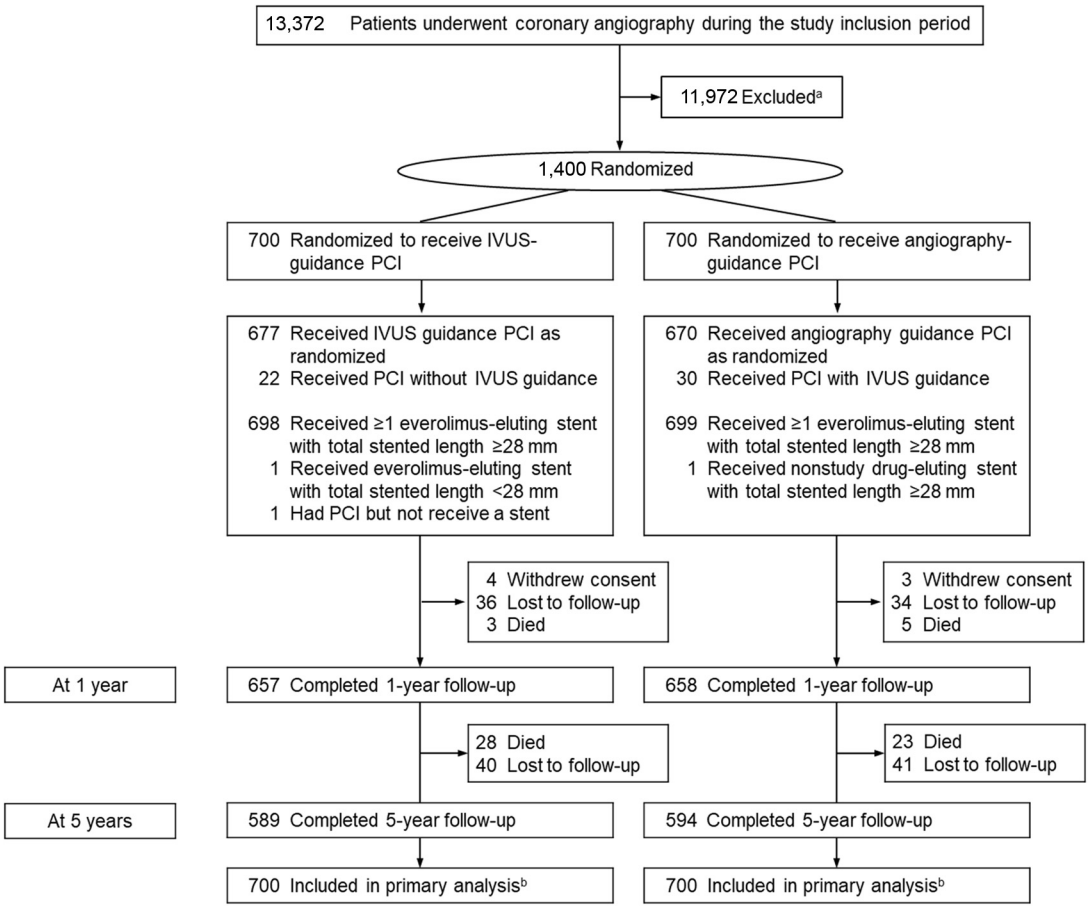
HR = hazard ratio

IVUS = intravascular ultrasound

PCI = percutaneous coronary intervention

TLR = target lesion revascularization

FIGURE 1 Study Design



[a]Data were not collected regarding specific reasons for ineligibility. [b]All patients were included in the primary time-to-event analysis for the duration of their follow-up, including patients who withdrew consent or were lost to follow-up. IVUS = intravascular ultrasound; PCI = percutaneous coronary intervention.

TABLE 1 Baseline Clinical Characteristics

	End of Trial at 1 Year			End of Trial at 5 Years		
	IVUS Guidance (n = 657)	Angiographic Guidance (n = 658)	p Value	IVUS Guidance (n = 589)	Angiographic Guidance (n = 594)	p Value
Age, yrs	63 ± 9	64 ± 9	0.413	63 ± 9	63 ± 9	0.340
Male	452 (69)	455 (69)	0.890	408 (69)	409 (69)	0.877
Body mass index, kg/m^2	24.6 ± 2.9	24.7 ± 3.1	0.537	24.7 ± 2.9	24.8 ± 3.0	0.664
Hypertension	425 (65)	419 (64)	0.702	382 (65)	373 (63)	0.461
Diabetes mellitus	211 (32)	235 (36)	0.168	178 (30)	206 (35)	0.101
Insulin-requiring diabetes	16 (2)	17 (3)	0.864	11 (2)	17 (3)	0.261
Dyslipidemia	445 (68)	434 (66)	0.494	396 (67)	393 (66)	0.696
Current smoker	144 (22)	168 (26)	0.123	134 (23)	153 (26)	0.228
Prior myocardial infarction	33 (5)	29 (4)	0.599	30 (5)	27 (5)	0.660
Prior percutaneous coronary intervention	73 (11)	68 (10)	0.649	66 (11)	60 (10)	0.538
Prior coronary artery bypass graft	18 (3)	16 (2)	0.725	16 (3)	16 (3)	0.981
Left ventricular ejection fraction, %	63.0 ± 9.8	62.3 ± 10.2	0.244	62.8 ± 9.8	62.3 ± 10.2	0.396
Clinical presentation			0.252			0.321
Stable angina	335 (51)	340 (52)		291 (49)	307 (52)	
Unstable angina	231 (35)	209 (32)		211 (36)	189 (32)	
Acute myocardial infarction	91 (14)	109 (17)		87 (15)	98 (17)	
Number of diseased vessels			0.163			0.101
1	227 (35)	197 (30)		214 (36)	181 (31)	
2	236 (36)	243 (37)		203 (35)	222 (37)	
3	194 (30)	218 (33)		172 (29)	191 (32)	
Number of treated lesions per patients	1.31 ± 0.55	1.36 ± 0.56	0.128	1.31 ± 0.55	1.35 ± 0.57	0.246
Duration of dual-antiplatelet treatment, days	365 (180–365)	365 (180–365)	0.864	365 (180–424)	365 (180–448)	0.484
Medications at discharge						
Statins	629 (96)	629 (96)	0.897	564 (96)	568 (96)	0.911
Beta-blockers	466 (71)	457 (70)	0.559	421 (72)	411 (69)	0.390
Angiotensin-converting enzyme inhibitors	172 (26)	194 (30)	0.181	156 (27)	176 (30)	0.229
Angiotensin II receptor blockers	221 (34)	217 (33)	0.800	200 (34)	196 (33)	0.727
Calcium-channel blockers	220 (34)	229 (35)	0.520	188 (32)	209 (36)	0.181

Values are mean ± SD, n (%), or median (interquartile range).
IVUS = intravascular ultrasound.

METHODS

STUDY DESIGN AND POPULATION. The IVUS-XPL trial was an investigator-initiated, randomized, multicenter study conducted at 20 centers in Korea that enrolled patients who received everolimus-eluting stents (Xience Prime, Abbott Vascular, Santa Clara, California) to treat long coronary lesions (1). The detailed design and the 1-year results have been previously described (1). Briefly, patients with typical chest pain or evidence of myocardial ischemia were eligible for enrollment if implantation of an everolimus-eluting stent for a long coronary lesion (implanted stent ≥28 mm in length) was indicated on the basis of angiographic lesion length estimation (1). Study participants were randomly assigned in a 1:1 ratio (**Figure 1**) to undergo either IVUS-guided or angiography-guided stent implantation immediately after coronary angiography but before percutaneous coronary intervention (PCI). Everolimus-eluting stent implantation was performed according to standard techniques. In the angiography-guided stent implantation group, stent size and length were chosen by visual estimation, and adjunct high-pressure post-dilation was performed if an optimal result was not achieved (1). In the IVUS-guided stent implantation group, stent size and length were selected by online IVUS measurements, and adjunct high-pressure dilation was performed according to the discretion of the physicians, on the basis of the IVUS findings. Use of IVUS was allowed at any step of PCI (before, during, or after PCI). IVUS examination before and during PCI was not mandatory, but IVUS examination was mandatory after PCI (1). In the IVUS-XPL trial, IVUS criteria for stent optimization after PCI were defined as a minimal luminal cross-sectional area greater than

TABLE 2 Angiographic and Procedural Characteristics for Target Lesions

	End of Trial at 1 Year			End of Trial at 5 Years		
	IVUS Guidance (n = 657)	Angiographic Guidance (n = 658)	p Value	IVUS Guidance (n = 589)	Angiographic Guidance (n = 594)	p Value
Coronary artery			0.109			0.070
Left anterior descending coronary artery	431 (66)	395 (60)		393 (67)	358 (60)	
Left circumflex coronary artery	85 (13)	102 (16)		77 (13)	92 (16)	
Right coronary artery	141 (22)	161 (25)		119 (20)	144 (24)	
Baseline quantitative coronary angiographic data						
Reference vessel diameter, mm	2.89 ± 0.46	2.84 ± 0.45	0.105	2.89 ± 0.44	2.85 ± 0.45	0.128
Minimum luminal diameter, mm	0.83 ± 0.43	0.82 ± 0.43	0.563	0.83 ± 0.43	0.81 ± 0.43	0.619
Diameter stenosis, %	71.2 ± 14.4	71.4 ± 14.4	0.859	71.5 ± 14.4	71.5 ± 14.3	0.921
Lesion length, mm	34.9 ± 10.8	35.2 ± 10.5	0.562	35.1 ± 10.8	35.3 ± 10.7	0.706
Adjunct post-dilatation	498 (76)	375 (57)	<0.001	441 (75)	334 (56)	<0.001
Final balloon size, mm	3.15 ± 0.43	3.05 ± 0.42	<0.001	3.16 ± 0.44	3.05 ± 0.42	<0.001
Overlapping stent	141 (22)	129 (20)	0.405	130 (22)	120 (20)	0.431
Number of stents per lesion	1.3 ± 0.5	1.2 ± 0.5	0.492	1.3 ± 0.5	1.3 ± 0.5	0.541
Stent edge dissections	12 (2)	13 (2)	0.843	12 (2)	13 (2)	0.857
Coronary perforation	0	0	1.000	0	0	1.000
Maximal inflation pressure, atm	16.5 ± 4.1	15.9 ± 4.1	0.048	16.5 ± 4.1	15.9 ± 4.1	0.089
Post-intervention quantitative coronary angiographic data						
Total stented length, mm	39.3 ± 10.8	35.2 ± 10.5	0.738	39.4 ± 12.7	39.2 ± 12.5	0.779
Reference vessel diameter, mm	3.04 ± 0.44	2.97 ± 0.44	0.003	3.05 ± 0.44	2.97 ± 0.43	0.004
Minimum luminal diameter, mm	2.64 ± 0.42	2.56 ± 0.40	0.001	2.65 ± 0.42	2.56 ± 0.39	<0.001
Diameter stenosis, %	12.9 ± 8.6	13.5 ± 8.1	0.216	12.9 ± 8.5	13.5 ± 8.0	0.202

Values are n (%) or mean ± SD.
IVUS = intravascular ultrasound.

the luminal cross-sectional area at the distal reference segments (1).

Institutional Review Board approval was obtained at each site, and written consent was obtained from all patients for their participation in IVUS-XPL. However, the requirement to obtain written informed consent from patients for this current analysis was waived because this extended follow-up study was regarded as a historical observational study without interventions.

EVALUATION OF STUDY ENDPOINT DURING 5 YEARS. The primary endpoint was a composite of major adverse cardiac events, including cardiac death, target lesion-related myocardial infarction, or ischemia-driven TLR at 5 years. Clinical assessment, including the evaluation of cardiac symptoms and compliance with medications, was performed at the physician office visit every 3 to 6 months during the 5-year follow-up period. Follow-up data were collected from medical records by the dedicated clinical research coordinators from each of the participating centers and entered into a computer database by a specialist from a clinical data management center (Cardiovascular Research Center, Seoul, Korea). A blinded independent clinical events committee adjudicated all nonprocedural components of the primary endpoint on the basis of the original source documents.

Clinical events were defined according to the Academic Research Consortium and were previously described (1,15). All deaths were considered cardiac deaths unless a definite noncardiac cause could be established. Target lesion-related myocardial infarction during the 5-year follow-up period after hospital discharge was defined as the presence of clinical symptoms, electrocardiographic changes, or abnormal imaging findings of myocardial infarction, combined with an increase in the creatine kinase-MB fraction above the upper normal limits or an increase in troponin T or troponin I to a level greater than the 99th percentile of the upper normal limit (1) with the territory of the myocardial infarction supplied by the coronary artery containing the index procedure stented lesion (1,15,16). Definite, probable, and possible stent thrombosis were defined according to the recommendations of the Academic Research Consortium (1,16). Ischemia-driven TLR was defined as repeat PCI or bypass surgery of the target lesion with either of the following: 1) symptoms of ischemia

TABLE 3 Clinical Outcomes

	Patients				
	IVUS Guidance (n = 700)	Angiographic Guidance (n = 700)	Hazard Ratio (95% CI)	p Value	p Value for Interaction
At 5 yrs					
Major adverse cardiac event	36 (5.6)	70 (10.7)	0.50 (0.34–0.75)	0.001	
Cardiac death	6 (0.9)	14 (2.2)	0.43 (0.17–1.12)	0.074	
Target lesion–related MI	4 (0.6)	6 (0.9)	0.67 (0.19–2.36)	0.525	
Ischemia-driven TLR	31 (4.8)	55 (8.4)	0.54 (0.33–0.89)	0.007	
Definite or probable stent thrombosis	2 (0.3)	2 (0.3)	1.00 (0.14–7.10)	1.000	
Acute	1 (0.1)	1 (0.1)			
Subacute	1 (0.1)	0 (0.0)			
Late	0 (0.0)	1 (0.1)			
Landmark analyses					
Major adverse cardiac event					0.817
≤1 yr	19 (2.9)	39 (5.8)	0.48 (0.28–0.83)	0.007	
1–5 yrs	17 (2.8)	31 (5.2)	0.53 (0.29–0.95)	0.031	
Cardiac death					0.550
≤1 yr	3 (0.4)	5 (0.7)	0.60 (0.14–2.52)	0.480	
1–5 yrs	3 (0.5)	9 (1.4)	0.33 (0.90–1.23)	0.083	
Target lesion–related MI					–
≤1 yr	0 (0.0)	1 (0.1)	–	0.320	
1–5 yrs	4 (0.6)	5 (0.8)	0.80 (0.21–2.97)	0.736	
Ischemia-driven TLR					0.675
≤1 yr	17 (2.5)	33 (5.0)	0.51 (0.28–0.91)	0.020	
1–5 yrs	14 (2.3)	22 (3.7)	0.61 (0.31–1.20)	0.150	
Definite or probable stent thrombosis					–
<1 yr	2 (0.3)	2 (0.3)	1.00 (0.14–7.10)	1.000	
1–5 yrs	0 (0.0)	0 (0.0)	–	–	

Values are n (%). Event rates are cumulative Kaplan-Meier event rates. The p values were calculated using the log-rank test, and p values for interaction were derived from time-dependent Cox regression for the interaction between treatment and time. Major adverse cardiac events from cardiac death, target lesion–related MI, or ischemia-driven TLR.

CI = confidence interval; IVUS = intravascular ultrasound; MI = myocardial infarction; TLR = target lesion revascularization.

or positive stress test results and angiographic diameter stenosis of 50% or greater by quantitative coronary angiographic analysis; or 2) angiographic diameter stenosis of 70% or greater by quantitative coronary angiographic analysis without symptoms of ischemia or positive stress test results (1).

STATISTICAL ANALYSIS. Categorical variables are reported as numbers and percentages and were compared using the chi-square test or Fisher exact test. Continuous variables are reported as mean ± SD or median (interquartile range) as appropriate, and these variables were compared using Student's *t*-test or the Mann-Whitney *U* test.

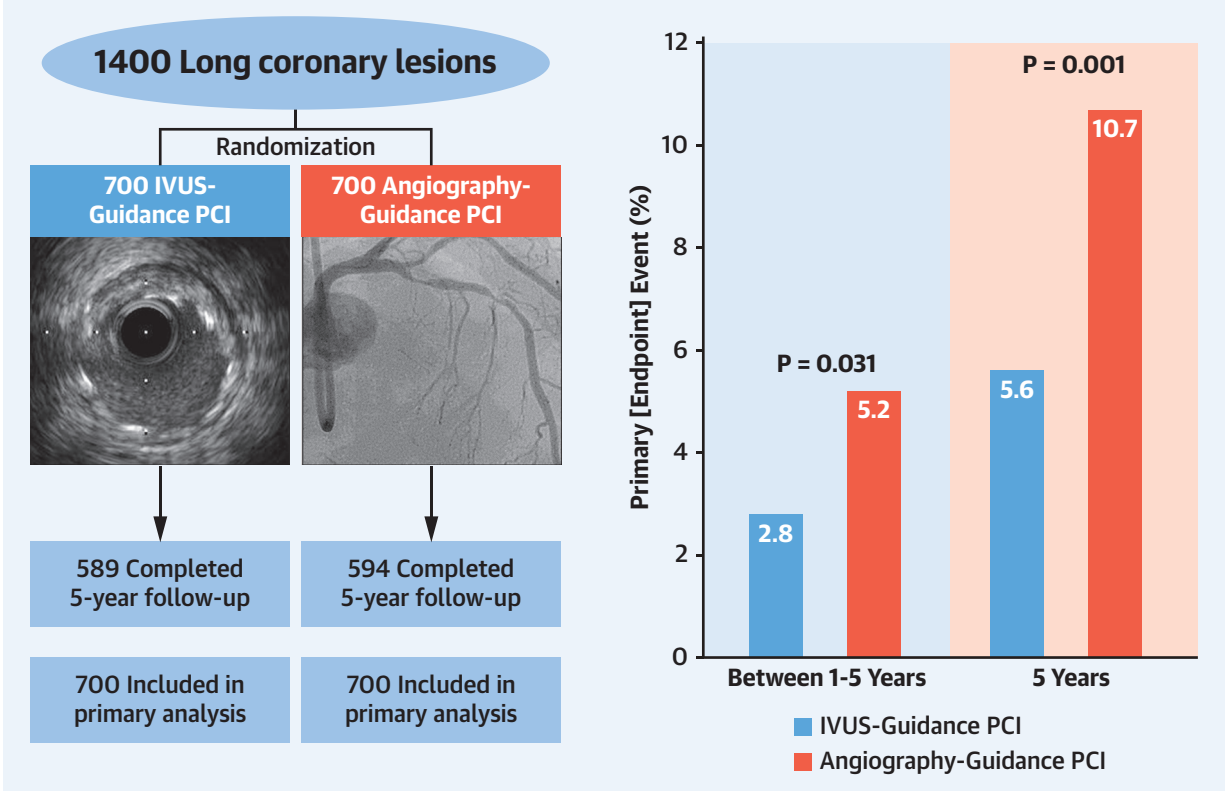
The primary analysis was performed on an intention-to-treat basis to compare whether IVUS-guided stent implantation would be superior to angiography-guided stent implantation with respect to the first occurrence of the primary endpoint event. Cumulative incidences of major adverse cardiac events at 5 years, which was the primary endpoint of the present analysis, were calculated using the Kaplan-Meier estimates and compared using the log-rank test. Information on patients who were lost to follow-up or who died was used as censored data in the survival analysis. Although patients could experience more than 1 component of the primary endpoint, each patient was assessed until the occurrence of their first event and only once during the analysis. Hazard ratios (HRs) were calculated separately for events that occurred within 1 year and those that occurred between 1 and 5 years. Also, we performed a test for the interaction between treatment and time using time-dependent Cox regression. Subgroup analysis was performed, and heterogeneity of the effects in subgroups was assessed using interaction terms in the Cox proportional hazards model.

All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, North Carolina). All tests were 2 sided, and p values of <0.05 were considered to indicate statistical significance.

RESULTS

A total of 1,315 patients (94%) completed 1-year follow-up, and 1,183 patients (85%) completed 5-year follow-up. Median follow-up duration was 5 years (interquartile range: 5 to 5 years). Baseline

CENTRAL ILLUSTRATION **5-Year Follow-Up of the IVUS-XPL Randomized Trial**



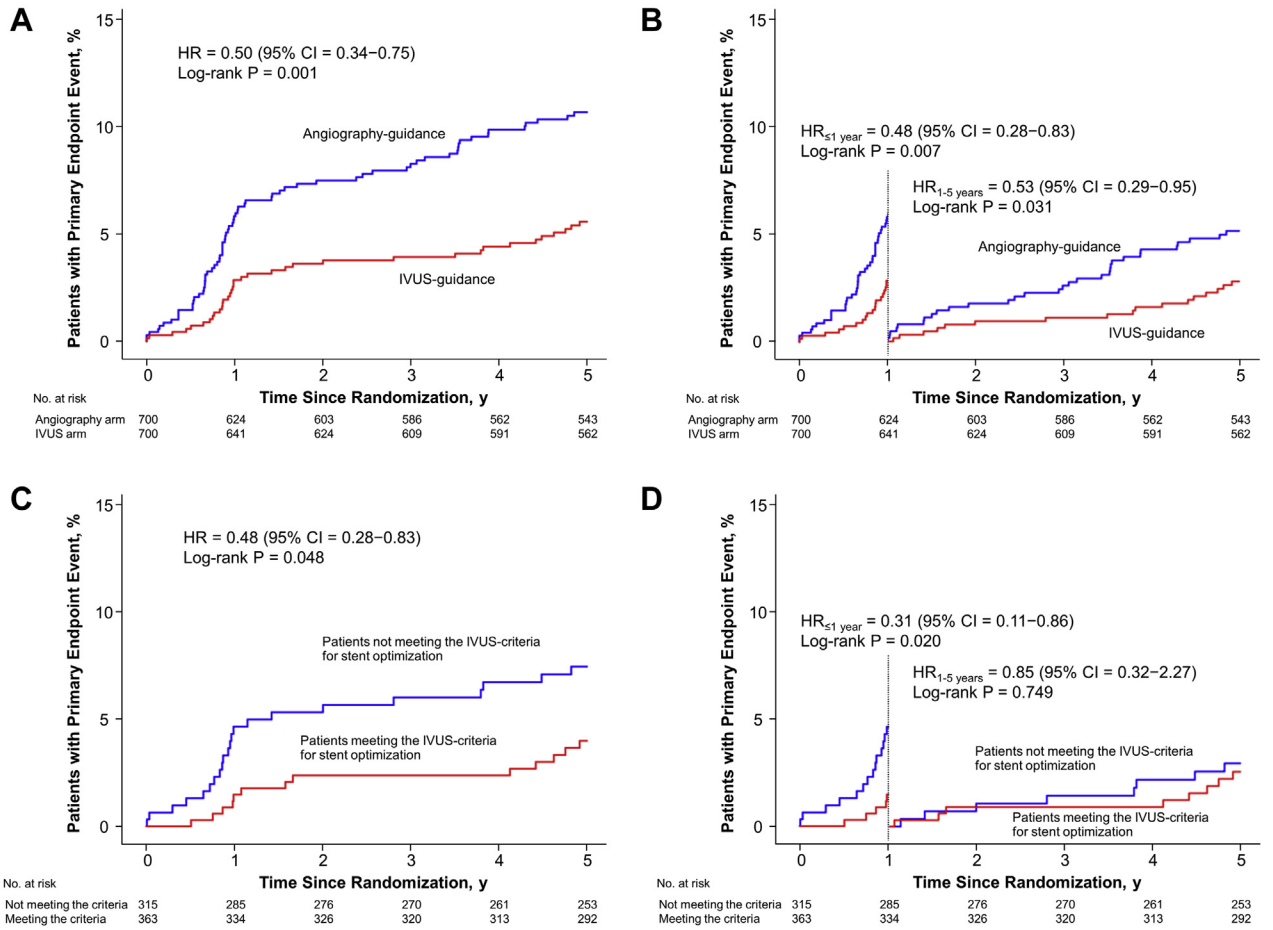
Hong, S.-J. et al. J Am Coll Cardiol Intv. 2020;13(1):62-71.

Intravascular ultrasound (IVUS) guidance was associated with a substantial reduction in the risk for major adverse cardiac events at 5 years compared with angiographic guidance. Between 1 and 5 years, the outcome differences diverged. PCI = percutaneous coronary intervention.

clinical, angiographic, and procedural characteristics of patients who completed 1- and 5-year follow-up are presented in Tables 1 and 2. Total duration of dual-antiplatelet therapy was not different between the IVUS-guided and angiography-guided arms (median 12 months [interquartile range: 6 to 14 months] vs. 12 months [interquartile range: 6 to 15 months], respectively; p = 0.484).

Clinical outcomes are shown in Table 3. At 5 years, the primary endpoint of major adverse cardiac events occurred in 36 patients (5.6%) receiving IVUS guidance and in 70 patients (10.7%) receiving angiographic guidance (HR: 0.50; 95% confidence interval [CI]: 0.34 to 0.75; p = 0.001) (Table 3, Central Illustration, Figure 2A). For cardiac death alone, there were 6 patients (0.9%) in the IVUS-guided stent group and 14 patients (2.2%) in the angiography-guided stent group (HR: 0.43; 95% CI: 0.17 to 1.12; p = 0.074). Target lesion-related myocardial infarction occurred in 4 patients (0.6%) in the IVUS-guided stent group and in 6 patients (0.9%) in angiography-guided stent group (HR: 0.67; 95% CI: 0.19 to 2.36; p = 0.525). Ischemia-driven TLR was performed in 31 patients (4.8%; 28 patients with ischemic symptoms or positive stress test results and angiographic diameter stenosis ≥50% by quantitative coronary angiographic analysis and 3 patients with angiographic diameter stenosis ≥70% by quantitative coronary angiographic analysis without ischemic symptoms or positive stress test results) in the IVUS-guided group and in 55 patients (8.4%; 50 and 5 patients, respectively) in the angiography-guided group (HR: 0.54; 95% CI: 0.33 to 0.89; p = 0.007). Patients within the IVUS-guided stent group who did not meet IVUS criteria for stent optimization had a significantly higher incidence of the primary endpoint at 5 years compared with those who met IVUS criteria for stent optimization

FIGURE 2 Kaplan-Meier Estimates of Occurrence of Primary Endpoint for All Patients and for Patients Who Underwent Intravascular Ultrasound-Guided Stent Implantation



(A) All patients. **(B)** Landmark analyses for all patients. **(C)** Patients in intravascular ultrasound (IVUS)–guided percutaneous coronary intervention (PCI) group who underwent IVUS-guided stent implantation. **(D)** Landmark analyses for the patients in IVUS-guided PCI group who underwent IVUS-guided stent implantation. Cumulative incidence curves for the primary endpoint of cardiac death, target lesion–related myocardial infarction, and target lesion revascularization. CI = confidence interval; HR = hazard ratio.

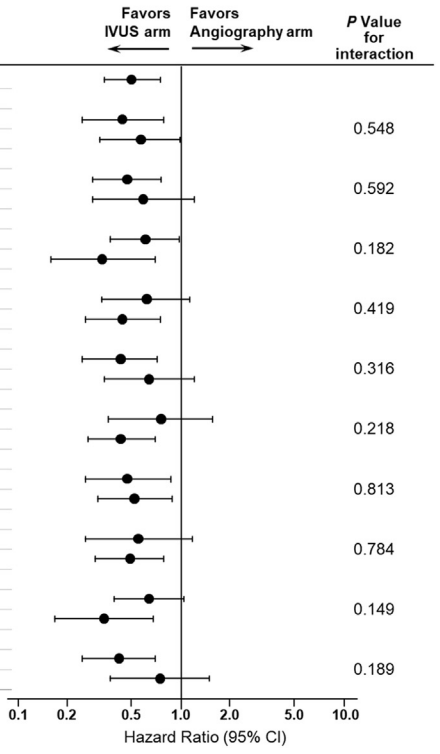
(7.4% vs. 4.0%, respectively; HR: 0.48; 95% CI: 0.28 to 0.83; p = 0.048) (Figure 2C).

One-year landmark analysis for major adverse cardiac events is presented in Table 3. Between 1 and 5 years, the primary endpoint of major adverse cardiac events occurred in 17 patients (2.8%) receiving IVUS guidance and in 31 patients (5.2%) receiving angiographic guidance (HR: 0.53; 95% CI: 0.29 to 0.95; p = 0.031) (Figure 2B). A test for interaction between treatment effect and time was not significant for major adverse cardiac events (p for interaction = 0.817). There were no statistically significant differences between year 1 and year 5 in the landmark analysis between patients who did not meet IVUS criteria and those who met IVUS criteria for stent optimization (HR: 0.85; 95% CI: 0.32 to 2.27; p = 0.749) (Figure 2D). Also, a test for interaction between treatment effect and time was not significant among the patients in the IVUS-guided PCI group who underwent IVUS-guided stent implantation (p for interaction = 0.159).

The per-protocol-based comparison for the primary endpoint of major adverse cardiac events was consistent with the intention-to-treat comparison. At 5 years, major adverse cardiac events occurred in 5.8% of patients who underwent IVUS-guided stent

FIGURE 3 Subgroup Analyses of the 5-Year Rates of Major Adverse Cardiac Events Among Patients Randomized to Receive Either Angiographic Guidance or Intravascular Ultrasound Guidance

Subgroup	IVUS-guidance No. of events	IVUS-guidance No. of patients	Angiography-guidance No. of events	Angiography-guidance No. of patients	Hazard Ratio (95% CI)	*P* Value for interaction
All patients	36	700	70	700	0.50 (0.34–0.75)	
Age, y						
<65	17	350	36	345	0.44 (0.25–0.79)	0.548
≥65	19	350	34	355	0.57 (0.32–0.99)	
Sex						
Male	24	483	50	481	0.47 (0.29–0.76)	0.592
Female	12	217	20	219	0.59 (0.29–1.21)	
Hypertension						
Yes	27	454	43	444	0.37 (0.37–0.98)	0.182
No	9	246	27	256	0.33 (0.16–0.70)	
Diabetes mellitus						
Yes	16	250	28	256	0.62 (0.33–1.14)	0.419
No	20	450	72	444	0.44 (0.26–0.75)	
Dyslipidemia						
Yes	20	471	45	458	0.43 (0.25–0.72)	0.316
No	16	229	25	242	0.64 (0.34–1.21)	
Current smoker						
Yes	12	155	18	181	0.76 (0.36–1.57)	0.218
No	24	545	52	519	0.43 (0.27–0.70)	
Clinical presentation						
Stable angina	15	358	32	356	0.47 (0.26–0.87)	0.813
Acute coronary syndrome	21	342	38	344	0.52 (0.31–0.89)	
No. of diseased vessels						
One	11	230	17	210	0.55 (0.26–1.18)	0.784
Two or three	25	470	53	490	0.49 (0.30–0.79)	
Coronary arteries						
LAD	26	455	37	419	0.64 (0.39–1.05)	0.149
LCX or RCA	10	245	33	281	0.34 (0.17–0.68)	
Reference vessel diameter, mm						
<3.00	21	417	53	451	0.42 (0.25–0.70)	0.189
≥3.00	15	283	17	249	0.75 (0.37–1.50)	



CI = confidence interval; IVUS = intravascular ultrasound; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; RCA = right coronary artery.

implantation (n = 708) and 10.5% of those who underwent angiography-guided stent implantation (n = 692) (HR: 0.53; 95% CI: 0.36 to 0.79; p = 0.002).

In subgroup analyses, the lower 5-year rate of major adverse cardiac events in the IVUS guidance arm was consistent across numerous subgroups (**Figure 3**).

DISCUSSION

In this extended 5-year follow-up study of the IVUS-XPL randomized clinical trial in which patients with long coronary lesions were randomized to IVUS- versus angiography-guided everolimus-eluting stent implantation, the use of IVUS guidance was associated with a significant 50% relative reduction in the risk for major adverse cardiac events at 5 years compared with conventional angiographic guidance. Furthermore, these differences diverged between 1 and 5 years. Accordingly, our findings suggested sustained 5-year better clinical outcomes for major adverse cardiac events with IVUS-guided stent implantation compared with angiography-guided stent implantation, even in the current DES implantation era.

Several recent randomized trials and meta-analyses have shown that IVUS-guided DES implantation was superior to angiography-guided DES implantation. However, all previously published randomized trials, including reports from IVUS-XPL, reported outcomes within 2 years (1,8–14). In our study, patients in IVUS-XPL were followed for up to 5 years. We found that the 1-year beneficial effect of IVUS guidance was not only sustained up to 5 years but increased between 1 and 5 years. Besides the randomized trials, the ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) registry reported 2-year follow-up outcomes (17). Similar to our findings, the early improvement of event-free survival after DES implantation with IVUS guidance was further increased with longer term follow-up to 2 years compared with angiographic

guidance. Choi et al. (18) reported clinical outcomes (median follow-up of 64 months) among patients with complex coronary artery lesions, and IVUS-guided PCI was associated with a lower long-term risk for cardiac death and adverse cardiac events compared with angiography-guided PCI. Andell et al. (19) also reported favorable clinical outcomes (composite endpoint of all-cause mortality, restenosis, or definite stent thrombosis) during more than 5 years of follow-up for patients undergoing IVUS-guided unprotected left main coronary artery stenting compared with those undergoing angiography-guided unprotected left main coronary artery stenting.

Another important finding is that the IVUS guidance patients who did not meet IVUS criteria for stent optimization had a significantly higher incidence of the primary endpoint at 5 years compared with those who met IVUS criteria for stent optimization. Therefore, although meeting the optimization criteria even the use of IVUS can be technically difficult, the achievement of the sufficient minimal stent area by adjunctive post-dilation with the appropriate size of noncompliant balloon can lead to 5-year sustained benefit of IVUS guidance.

In our study and unlike previous reports of the long-term benefits of IVUS guidance, only the second-generation everolimus-eluting stent was used. Everolimus-eluting stents have improved stent performance with better vascular healing and reendothelialization properties suggesting a reduced need for intravascular imaging guidance (20,21). For example, one optical coherence tomographic study revealed that the everolimus-eluting stent had more favorable strut coverage than the first-generation DES (21). A meta-analysis revealed that among different DES types, the lowest stent thrombosis rate was observed when the everolimus-eluting stent was used (22). Also, according to the recent 5-year results of the SORT OUT IV (Scandinavian Organization for Randomized Trials With Clinical Outcome) trial, the major adverse cardiac event rate was significantly lower in patients treated with everolimus-eluting stents than in those treated with first-generation sirolimus-eluting stents, largely because of a lower risk for very late definite stent thrombosis (2). Very late definite or probable stent thrombosis occurred in 0.2% of patients treated with everolimus-eluting stents and in 1.4% of those treated with sirolimus-eluting stents (HR: 0.16; 95% CI: 0.05 to 0.53; $p = 0.003$). However, as shown in the present study, the clinical benefit of use of IVUS, although perhaps attenuated, is still important in contemporary clinical practice. In the SORT OUT IV trial, ischemia-driven TLR still continued to occur beyond 1 year, even after the use of everolimus-eluting stents (2–4).

STUDY LIMITATIONS. First, we evaluated randomized patients, and our patients completed 5-year follow-up after stent implantation. Second, we used a single type of DES. Third, only long lesions were included. Fourth, the observed overall event rate was relatively low. Our results should thus be interpreted cautiously, especially concerning differences in low-frequency clinical endpoints and subgroups. Finally, a 15% rate of loss to follow-up at 5 years cannot be considered low. However, baseline clinical, angiographic, and procedural characteristics among patients who completed 5-year follow-up were not different between the 2 groups.

CONCLUSIONS

Among patients with lesions requiring long stents, the use of IVUS-guided everolimus-eluting stent implantation, compared with angiography-guided stent implantation, resulted in a significantly lower rate of major adverse cardiac events up to 5 years. This sustained 5-year benefit resulted from both within 1-year advantage from IVUS guidance and an increasing benefit from 1 to 5 years.

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PERSPECTIVES

WHAT IS KNOWN? The use of IVUS promoted favorable 1-year clinical outcomes in the randomized trial.

WHAT IS NEW? Compared with angiography-guided stent implantation, IVUS-guided stent implantation resulted in a significantly lower rate of major adverse cardiac events up to 5 years.

WHAT IS NEXT? Further studies with patients with more complex lesions in randomized trial are required to evaluate long-term clinical benefit of IVUS.

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