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Randomized Comparison of Clinical Outcomes Between Intravascular Ultrasound and Angiography-Guided Drug-Eluting Stent Implantation for Long Coronary Artery Stenoses

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Objectives This study sought to assess the impact of intravascular ultrasound (IVUS) guidance on clinical outcomes following drug-eluting stent implantation when treating long lesions.

Background The role of IVUS guidance when treating long lesions has been tested during bare-metal stent, but not during drug-eluting stent, implantation.

Methods A total of 543 patients treated with stents ≥28 mm in length were randomly assigned to IVUS guidance (n = 269) versus angiography guidance (n = 274). The primary endpoint was a composite of major adverse cardiac events (MACE), including cardiovascular death, myocardial infarction, target vessel revascularization, or stent thrombosis at 1 year following intervention.

Results In the intention-to-treat analysis, total stent length was 32.4 mm in the IVUS-guided arm versus 32.3 mm in angiography-guided arm (p = 0.84). Adjunct post-dilation was more frequently performed in the IVUS-guided arm (54.6% vs. 44.5%, p = 0.03); post-intervention minimal lumen diameters were similar (2.55 vs. 2.55 mm, respectively, p = 0.50); and MACE occurred in 12 (4.5%) patients in IVUS-guided arm and in 20 (7.3%) patients in the angiography-guided arm (p = 0.16). However, among the 269 patients assigned to IVUS guidance, IVUS was not used in 13 patients (4.8%); conversely, in 274 patients assigned to angiography alone, 41 patients (15.0%) were treated with IVUS guidance. Therefore, in a per-protocol analysis according to actual IVUS usage, minimum lumen diameter was larger (2.58 vs. 2.51 mm, p = 0.04), and MACE rates were lower: 4.0% in the IVUS-guided arm versus 8.1% in the angiography-guided arm (p = 0.048).

Conclusions A strategy of routine IVUS for drug-eluting stent implantation in long lesions did not improve the 1-year MACE rates. The IVUS use per operator decision was associated with improved results. (A New Strategy Regarding Discontinuation of Dual Antiplatelet; NCT01145079) (J Am Coll Cardiol Intv 2013;6:369–76) © 2013 by the American College of Cardiology Foundation

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Drug-eluting stents (DES) significantly improve clinical outcomes to reduce in-stent restenosis and repeat revascularization (1). However, even using DES, treating long lesions can be problematic (2), and the rate of stent thrombosis may be higher in this lesion subset (3). In the bare-metal stent era, the randomized TULIP (Thrombocyte Activity Evaluation and Effects of Ultrasound Guidance in Long Intracoronary Stent Placement) trial (4) has shown that intravascular ultrasound (IVUS) guidance when treating long lesions improves immediate and long-term angiographic and clinical outcomes. In the DES era, the clinical utility of IVUS has been reported for several subsets of complex lesions and has been shown to be beneficial when treating bifurcation and left main lesion subsets, whereas no benefit has been shown in patients with acute myocardial infarction (5–7). However, most data are retrospective and nonrandomized, and no clinical study has investigated the role of IVUS in long lesions treated with DES. Therefore, we have performed a multicenter, randomized study comparing IVUS-guided with angiography-guided DES implantation to assess the effect of IVUS guidance when treating patients with long lesions.

Abbreviations and Acronyms

CI = confidence intervals
DES = drug-eluting stent(s)
EES = everolimus-eluting stent(s)
E-ZES = Endeavor Sprint zotarolimus-eluting stent(s)
IQR = interquartile range
IVUS = intravascular ultrasound
MACE = major adverse cardiac event(s)
PCI = percutaneous coronary intervention
TVR = target vessel revascularization

Methods

Study population and design. The RESET (Real Safety and Efficacy of a 3-Month Dual Antiplatelet Therapy Following Zotarolimus-Eluting Stents Implantation) trial is a prospective, randomized, open-label, multicenter trial to demonstrate the noninferiority of 3-month duration of dual antiplatelet therapy following Endeavor Sprint zotarolimus-eluting stents (E-ZES) (Medtronic Inc., Santa Rosa, California) implantation compared with 12-month dual antiplatelet therapy after implantation with another DES (standard therapy) (8). In the pre-specified long lesion subset of this study, patients were randomly allocated to E-ZES versus everolimus-eluting stent (EES) (Xience V, Abbott Vascular, Santa Clara, California) and then randomly assigned to IVUS guidance or angiography guidance (2 × 2 design). Balanced, blocked randomization was conducted via a web-based randomization system. Patients were eligible if they were over 20 years of age and had a de novo lesion requiring a stent ≥28 mm in length in a vessel with a distal reference diameter ≥2.5 mm by visual angiographic estimation. Patients with a bleeding history within the prior 3 months; known hypersensitivity to heparin, aspirin, clopidogrel, or a limus-related drug; and cerebral vascular accident, peripheral artery occlusive diseases, thromboembolic disease, stent thrombosis, cardiogenic shock, left ventricular ejection fraction <40%, or acute ST-segment elevation myocardial infarction within 48 h after onset of symptoms were excluded. In addition, we did not include patients with left main disease requiring percutaneous coronary intervention (PCI), bifurcation lesions treated with a 2-stent technique, chronic total occlusions, and a history of PCI with DES. The study protocol was approved by the institutional review board at each participating institution, and written consent was obtained from all patients.

Stent implantation. DES implantation was performed according to standard techniques. E-ZES and EES were exclusively used in this study. If a lesion could not be covered with a single stent, overlapping stents were used. In the angiography-guided group, stent size and length were chosen by visual estimation, and adjunct high-pressure dilation was performed if an optimal result was not achieved, which was defined as angiographic residual diameter stenosis <30% and absence of angiographically detected dissection. In the IVUS-guided group, stent size and length were selected by online IVUS measurements, and adjunct high-pressure dilation was performed according to the discretion of operators based on the IVUS findings. One of 2 commercially available IVUS systems, Atlantis S or I-Lab (Boston Scientific Corp./SCIMED, Minneapolis, Minnesota) or Eagle Eye (Volcano Therapeutics, Rancho Cordova, California), was used. If a patient had more than 1 lesion treated, all lesions were treated according to the randomization scheme: either all lesions were treated with IVUS guidance or all lesions were treated with angiographic guidance.

Angiographic analysis. Quantitative coronary angiography analysis was performed using an off-line quantitative coronary angiographic system (CASS system, Pie Medical Instruments, Maastricht, the Netherlands) before and after stent implantation by individuals who were blinded to treatment assignment (DES type or IVUS vs. angiographic guidance) in an independent core laboratory at Cardiovascular Research Center, Seoul, Korea. Using the guiding catheter for magnification calibration, the diameters of the reference vessel (the average of the proximal and distal reference lumen diameters), the minimal luminal diameter, and the percentage diameter stenosis were measured before and after stenting from diastolic frames in a single, matched view showing the smallest minimal luminal diameter.

IVUS analysis. Each ultrasound study was analyzed at a core laboratory (Cardiovascular Research Center, Seoul, Korea) by analysts who were blinded to patient and procedural information. Standardized planimetry of lumen, stent, and vessel area was performed using planimetry software (Echoplaque version 3.0, INDEC Systems, Santa Clara,

California) in accordance with IVUS guidelines from the American College of Cardiology (9).

Study endpoints. Post-procedure clinical assessment was performed in-hospital and after 1, 3, 6, and 12 months either by clinic visitor or telephone interview. The primary endpoint was the occurrence of major adverse cardiac events (MACE), including cardiovascular death, myocardial infarction, stent thrombosis, or target vessel revascularization (TVR) at 1 year after procedure. The patients were not scheduled for routine angiographic follow-up.

Clinical events were defined according to the Academic Research Consortium (10). All deaths were considered cardiovascular deaths unless a definite noncardiovascular cause was established. Myocardial infarction was defined as the presence of clinical symptoms, electrocardiographic changes, or abnormal imaging findings of myocardial infarction combined with an increase in creatine kinase myocardial band fraction to greater than 3× the upper limit of the normal range or an increase in troponin T/troponin I to more than the 99th percentile of the upper normal limit, unrelated to an interventional procedure (10,11). Definite, probable, and possible stent thrombosis was defined according to the recommendations of the Academic Research Consortium (10,12). The timing of stent thrombosis was classified as acute (within 24 h), subacute (1 day to 1 month), and late (from day 31 to 365) post-index procedure. TVR was defined as a repeat PCI or bypass surgery of the target vessel with either: 1) ischemic symptoms or a positive stress test and angiographic diameter stenosis ≥50% by quantitative coronary angiographic analysis; or 2) angiographic diameter stenosis ≥70% by quantitative coronary angiographic analysis without ischemic symptoms or a positive stress test.

Adjunct pharmacology. Pre-PCI, all patients received at least 100 mg of aspirin. A loading dose of 300 mg of clopidogrel was administered at least 12 h before PCI. However, if the loading dose of clopidogrel was not administered 12 h in advance, the patient received a 600-mg loading dose of clopidogrel in the catheterization laboratory before PCI. Unfractionated heparin was administered to maintain the activated clotting time >250 s. The use of the glycoprotein IIb/IIIa inhibitors was left to the operator's discretion. After stent implantation, 100 mg of aspirin daily was prescribed indefinitely; and the duration of clopidogrel (at a dose of 75 mg daily) depended on the randomization assignment: 3-month duration following E-ZES implantation versus 12-month duration following EES implantation. The use of cilostazol was not allowed.

Sample size calculation and statistical analysis. Calculation of the sample size was based on a 2-sample and 2-sided test. From previous studies, the incidence of the composite events of cardiac death, myocardial infarction, stent thrombosis, or TVR was assumed to be 13.5% in the angiography-guided arm (13,14). The composite event rate in the IVUS-guided arm was assumed to be 6.0%, based on a 55% reduction in IVUS guidance compared with angiography guidance in the bare-metal stent TULIP study that compared IVUS versus angiographic guidance in a similar lesion cohort (5). Using a 2-sided alpha level of 0.05 and statistical power of 80%, 244 patients in the upstream arm and 244 patients in the provisional arm were needed. Considering a 10% follow-up loss, 544 patients were enrolled.

Both intention-to-treat and per-protocol analyses were performed. Statistical analysis was performed using the Statistical Analysis System software (SPSS version 19.0,

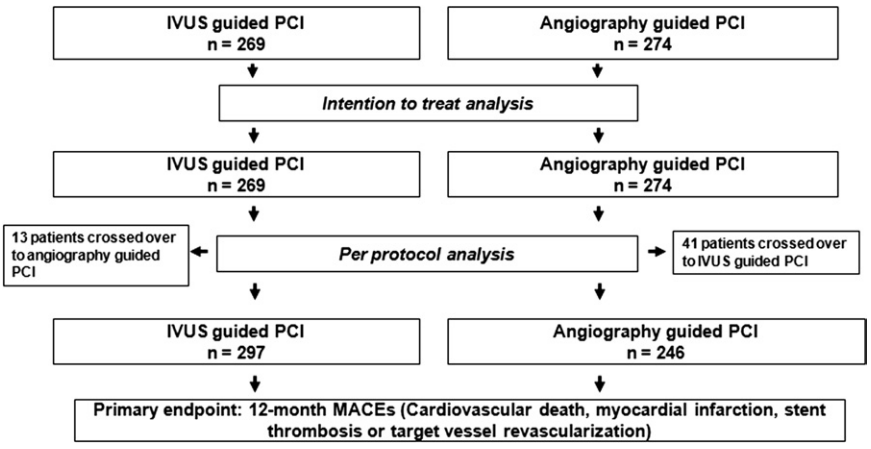

Figure 1. Study Flow Diagram

Clinical follow-up for 1 year was completed in all patients. IVUS = intravascular ultrasound; MACE = major adverse cardiac event(s); PCI = percutaneous coronary intervention.

Table 1. Baseline Clinical and Angiographic Characteristics According to the Intention-to-Treat Analysis

	IVUS Guidance	Angiography Guidance	p Value
Patients, n	269	274	
Age, yrs	62.8 ± 9.3	64.3 ± 8.7	0.06
Men	177 (65.8)	150 (54.7)	0.01
Hypertension	165 (61.3)	178 (65.8)	0.38
Diabetes mellitus	85 (31.6)	82 (29.9)	0.67
Dyslipidemia	165 (61.3)	165 (61.7)	0.94
Current smoking	58 (21.6)	47 (17.2)	0.19
Prior myocardial infarction	3 (1.1)	8 (2.9)	0.14
Left ventricular ejection fraction, %	55.3 ± 23.9	54.0 ± 25.0	0.51
Clinical presentation			0.90
Stable angina	143 (53.2)	141 (51.5)	
Unstable angina	102 (37.9)	106 (38.7)	
Acute myocardial infarction	24 (8.9)	27 (9.9)	
Duration of dual antiplatelet therapy, days	355 (95–365)	350 (92–365)	0.33
Multivessel disease	109 (40.5)	103 (37.6)	0.48
Treated vessels/patient, n	1.43 ± 0.56	1.37 ± 0.62	0.19
Target long lesions, n	269	274	
Coronary arteries			0.41
Left anterior descending artery	167 (62.1)	185 (67.5)	
Left circumflex artery	41 (15.2)	35 (12.8)	
Right coronary artery	61 (22.7)	54 (19.7)	
Type of stents			0.90
Zotarolimus-eluting stent	135 (50.2)	136 (49.6)	
Everolimus-eluting stent	134 (49.8)	138 (50.4)	
Lesion length, mm	29.6 (23.2–42.8)	30.6 (24.2–40.9)	0.52
Total stent length, mm	32.4 (28.0–45.9)	32.3 (28.0–44.6)	0.84
Adjunct post-dilation	147 (54.6)	122 (44.5)	0.03
Final balloon size, mm	3.1 ± 0.4	3.1 ± 0.4	0.87
Maximal inflation pressure, atm	13.5 ± 3.3	13.5 ± 3.1	0.87
Kissing balloon	3 (1.1)	4 (1.5)	1.00
Reference diameter, mm	2.82 (2.58–3.16)	2.80 (2.56–3.15)	0.37
Minimal lumen diameter, mm			
Pre-intervention	0.95 (0.73–1.23)	0.93 (0.70–1.22)	0.55
Post-intervention	2.55 (2.35–2.80)	2.55 (2.29–2.81)	0.50
Acute gain, mm	1.55 (1.30–1.88)	1.55 (1.30–1.91)	0.94

Continued in the next column

Table 1. Continued

	IVUS Guidance	Angiography Guidance	p Value
All lesions, n	406	381	
Coronary arteries			0.10
Left anterior descending artery	203 (50.0)	219 (57.5)	
Left circumflex artery	84 (20.7)	70 (18.4)	
Right coronary artery	119 (29.3)	92 (24.1)	
Type of stents			0.63
Zotarolimus-eluting stent	201 (49.5)	182 (47.8)	
Everolimus-eluting stent	205 (50.5)	199 (52.2)	
Lesion length, mm	25.2 (19.0–36.2)	26.1 (21.1–37.9)	0.14
Total stent length, mm	30.0 (28.0–42.2)	30.0 (28.0–43.0)	0.13
Adjunct post-dilation	193 (47.5)	165 (43.3)	0.23
Maximal inflation pressure, atm	13.4 ± 3.3	13.5 ± 3.0	0.72
Reference diameter, mm	2.88 (2.60–3.23)	2.82 (2.57–3.15)	0.12
Minimal lumen diameter, mm			
Pre-intervention	0.97 (0.74–1.30)	0.96 (0.72–1.28)	0.54
Post-intervention	2.60 (2.37–2.88)	2.57 (2.29–2.84)	0.15
Acute gain, mm	1.59 (1.32–1.90)	1.52 (1.31–1.89)	0.29

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

IBM, Chicago, Illinois). Data were expressed as mean ± SD, median (interquartile), or number and frequency. Comparisons of categorical variables were made using chi-square statistics and Fisher exact test. Student *t* test was used to compare continuous, normally distributed variables; otherwise, the Mann-Whitney *U* test was used. Relative risks with 95% confidence intervals (CI) were calculated to compare proportions of clinical events. Event-free survivals were generated by Kaplan-Meier survival curves and compared with log rank test. A p value of <0.05 was considered statistically significant.

Results

A total of 543 patients were randomly assigned to IVUS-guided (n = 269) or angiography-guided (n = 274) long (≥28-mm length) DES implantation. Among the 269 patients randomly assigned to IVUS guidance, IVUS was not used in 13 patients (4.8%) during stent implantation; reasons were patient refusal in 5, technical failure to deliver the IVUS catheter in 3, and physician decision due to unfavorable coronary anatomy (i.e., severe tortuosity) in 5 patients. Conversely, in 274 patients assigned to the angiography-guidance arm, 41 patients (15.0%) were treated with IVUS guidance; reasons were angiographically ambiguous anatomy in 20, and operator preference in complex lesions in 21 patients. Finally, IVUS-guided stent implantation was performed in 297 patients, and angiography guidance was used in 246 patients (Fig. 1).

=In the intention-to-treat analysis (Table 1), baseline characteristics of the study population were similar between the 2 groups except for a higher prevalence of male patients in the IVUS-guidance arm. The E-ZES and EES assignments were distributed evenly in the 2 arms. Median length of the target lesions was 30.3 mm, and one-half of target lesions were treated with overlapping stents. Adjunct post-stent balloon dilation was more frequently performed in the IVUS-guidance arm (54.6%) than in the angiography-guidance arm (44.5%,

Table 2. Baseline Clinical and Angiographic Characteristics According to Actual IVUS Use (Per-Protocol Analysis)

	IVUS Guidance	Angiography Guidance	p Value
Patients, n	297	246	
Age, yrs	62.8 ± 9.2	64.5 ± 8.6	0.04
Men	197 (66.3)	130 (52.8)	0.001
Hypertension	187 (63.0)	156 (63.4)	0.91
Diabetes mellitus	90 (30.3)	77 (31.3)	0.80
Dyslipidemia	190 (64.0)	144 (58.5)	0.20
Current smoking	67 (22.6)	38 (15.4)	0.04
Prior myocardial infarction	3 (1.0)	8 (3.3)	0.07
Left ventricular ejection fraction	55.2 ± 23.9	53.9 ± 25.1	0.54
Clinical presentation			0.70
Stable angina	151 (50.8)	133 (54.1)	
Unstable angina	116 (39.1)	92 (37.4)	
Acute myocardial infarction	30 (10.1)	21 (8.5)	
Duration of dual antiplatelet therapy, days	355 (94–365)	350 (93–365)	0.61
Multivessel disease	112 (37.7)	100 (40.7)	0.49
Treated vessels/patient, n	1.40 ± 0.60	1.39 ± 0.57	0.79
Target long lesions, n	297	246	
Coronary arteries			0.91
Left anterior descending artery	191 (64.3)	161 (65.4)	
Left circumflex artery	41 (13.8)	35 (14.2)	
Right coronary artery	65 (21.9)	50 (20.3)	
Type of stents			0.89
Zotarolimus-eluting stent	149 (50.2)	122 (49.6)	
Everolimus-eluting stent	148 (49.8)	124 (50.4)	
Lesion length, mm	29.8 (23.1–42.6)	30.5 (24.2–40.7)	0.47
Total stent length, mm	33 (29.2–45.7)	31 (30–44.7)	0.99
Adjunct post-dilation	162 (54.6)	112 (45.5)	0.05
Final balloon size, mm	3.2 ± 0.4	3.1 ± 0.3	0.03
Maximal inflation pressure, atm	13.4 ± 3.3	13.6 ± 3.0	0.67
Kissing balloon	4 (1.3)	3 (1.2)	1.00
Reference diameter, mm	2.82 (2.58–3.17)	2.79 (2.56–3.14)	0.09
Minimal lumen diameter, mm			
Pre-intervention	0.97 (0.73–1.28)	0.90 (0.69–1.18)	0.16
Post-intervention	2.58 (2.37–2.84)	2.51 (2.28–2.80)	0.04
Acute gain, mm	1.55 (1.29–1.89)	1.56 (1.30–1.90)	0.94
All lesions, n	435	352	
Coronary arteries			0.38
Left anterior descending artery	229 (52.6)	193 (54.8)	
Left circumflex artery	81 (18.6)	73 (20.7)	
Right coronary artery	125 (28.7)	86 (24.4)	
Type of stents			0.45
Zotarolimus-eluting stent	217 (49.9)	166 (47.2)	
Everolimus-eluting stent	218 (50.1)	186 (52.8)	
Lesion length, mm	25.5 (19.2–37.8)	25.8 (21.0–37.2)	0.46
Total stent length mm	30.0 (28.0–42.3)	30.0 (28.0–42.2)	0.44
Adjunct post-dilation	211 (48.5)	147 (41.8)	0.06
Maximal inflation pressure, atm	13.3 ± 3.3	13.7 ± 3.0	0.13
Reference diameter, mm	2.88 (2.60–3.23)	2.82 (2.57–3.15)	0.03
Minimal lumen diameter, mm			
Pre-intervention	0.99 (0.74–1.31)	0.95 (0.72–1.25)	0.26
Post-intervention	2.60 (2.37–2.88)	2.55 (2.29–2.84)	0.03
Acute gain, mm	1.58 (1.32–1.91)	1.53 (1.31–1.89)	0.29

Values are mean ± SD, n (%), or median (IQR).
Abbreviations as in Table 1.

p = 0.03). On quantitative coronary angiography analysis, post-intervention minimal lumen diameters were not different between the 2 arms (median: 2.55 [interquartile range (IQR): 2.35 to 2.80] mm in IVUS guidance vs. median: 2.55 [IQR: 2.29 to 2.81] mm in angiography guidance; p = 0.50].

In the per-protocol analysis (Table 2), the post-intervention minimal lumen diameters were greater in the IVUS-guidance arm: median: 2.58 (IQR: 2.37 to 2.84) mm after IVUS guidance versus median: 2.51 (IQR: 2.28 to 2.80) mm after angiography guidance (p = 0.04).

IVUS-measured post-intervention minimal lumen area was 5.0 mm^2 in the intention-to-treat analysis and 5.1 mm^2 in the per-protocol analysis (Table 3).

Clinical outcomes. Clinical follow-up was completed for 543 patients (100%) at 1 year after the index procedure. In the intention-to-treat analysis, the 1-year incidence of MACE, including cardiovascular death, myocardial infarction, stent thrombosis, or TVR was lower in the IVUS-guided arm (4.5%, n = 12) than in the angiography-guided arm (7.3%, n = 20), but the difference did not reach statistical significance (relative risk: 0.59, 95% CI: 0.28 to 1.24; p = 0.16) (Table 4, Fig. 2A).

Table 3. Post-Intervention IVUS Analysis

	Intention-to-Treat Analysis	Per-Protocol Analysis
Target lesions, n	256	297
Proximal reference external elastic membrane area, mm^2	16.0 (13.5–18.9)	16.1 (13.6–19.4)
Proximal reference lumen area, mm^2	8.2 (6.7–10.1)	8.3 (6.6–10.3)
Proximal reference plaque area, mm^2	8.2 (6.1–9.3)	7.7 (6.2–9.6)
Minimal lumen area, mm^2	5.0 (4.3–6.3)	5.1 (4.4–6.5)
Distal reference external elastic membrane area, mm^2	9.0 (6.8–12.0)	9.2 (6.9–12.2)
Distal reference lumen area, mm^2	5.8 (4.5–8.9)	5.8 (4.6–7.1)
Distal reference plaque area, mm^2	3.2 (2.0–5.1)	3.3 (2.0–5.1)

Values are median (IQR).
Abbreviations as in Table 1.

Table 4. Analysis of 1-Year Clinical Outcomes

Intention-to-Treat Analysis	IVUS Guidance (n = 269)	Angiography Guidance (n = 274)	Relative Risk (95% CI)	p Value
Death				
Any cause	3 (1.1)	2 (0.7)	1.53 (0.25–9.25)	0.64
Cardiovascular cause	0 (0.0)	1 (0.4)	—	1.00
Myocardial infarction	0 (0.0)	2 (0.7)	—	0.50
TVR	12 (4.5)	18 (6.6)	0.66 (0.31–1.41)	0.28
Stent thrombosis	1 (0.4)	1 (0.4)	—	1.00
Cardiovascular death or myocardial infarction	0 (0.0)	3 (1.1)	—	0.25
MACE (death from cardiovascular death, myocardial infarction, stent thrombosis, or TVR)	12 (4.5)	20 (7.3)	0.59 (0.28–1.24)	0.16
Per-Protocol Analysis	**IVUS Guidance (n = 297)**	**Angiography Guidance (n = 246)**	**Relative Risk (95% CI)**	**p Value**
Death				
Any cause	3 (1.0)	2 (0.8)	1.24 (0.21–7.51)	0.81
Cardiovascular cause	0 (0.0)	1 (0.4)	—	0.99
Myocardial infarction	0 (0.0)	2 (0.8)	—	0.99
TVR	12 (4.0)	18 (7.3)	0.53 (0.25–1.13)	0.10
Stent thrombosis	1 (0.3)	1 (0.4)	—	1.00
Cardiovascular death or myocardial infarction	0 (0.0)	3 (1.2)	—	0.99
MACE (death from cardiovascular death, myocardial infarction, stent thrombosis, or TVR)	12 (4.0)	20 (8.1)	0.48 (0.23–0.99)	0.048

Values are n (%).
CI = confidence interval(s); IVUS = intravascular ultrasound; MACE = major adverse cardiac events; TVR = target vessel revascularization.

However, because the goal of this study was to assess the impact of actual IVUS guidance on the clinical outcomes of DES implantation and because 13 patients in the IVUS arm were treated with angiographic guidance alone, whereas 41 patients in the angiography arm were treated with IVUS guidance, a per-protocol analysis according to actual use of IVUS was performed. According to actual use of IVUS guidance, the 1-year MACE rate was significantly lower in the IVUS-guided arm than in the angiography-guided arm (4.0% vs. 8.1%, relative risk: 0.48, 95% CI: 0.23 to 0.99; p = 0.048) (Table 4, Fig. 2B). MACE was not observed in 41 patients who crossed over from the angiography-guided to the IVUS-guided arm.

Discussion

This randomized IVUS-guided versus angiography-guided DES implantation trial in long lesions demonstrated that a strategy of routine IVUS did not improve the MACE at 1 year following intervention. The IVUS use per operator decision was associated with improved results. Although there was only a trend toward a reduction in the primary endpoint (1-year MACE) when patients were analyzed according to the intention-to-treat principle, 15.0% of the patients in the angiography arm were actually treated with IVUS guidance whereas IVUS was not performed in 4.8% of the patients assigned to IVUS guidance. Therefore, when patients were analyzed according to how they were actually treated, IVUS guidance resulted in a statistically significant decrease in MACE from 8.1% to 4.0% (p = 0.048).

Although IVUS has been useful for evaluating lesion morphology and optimizing PCI procedures, especially in complex lesions, the beneficial role of IVUS guidance in routine clinical practice has been controversial. In the bare-metal stent era, 2 meta-analyses, the first, including both registries and randomized trials and the second, including only the 7 randomized IVUS-guidance versus angiographic-guidance trials, showed that IVUS guidance reduced restenosis and repeat revascularization and MACE, but not death or myocardial infarction (15,16). In particular, the randomized TULIP study, which enrolled a lesion subset similar to the current study, showed that IVUS-guided bare-metal stent implantation was superior to angiography guidance in terms of a reduction in restenosis (23% vs. 43%, p = 0.008), target lesion revascularization (10% vs. 23%, p = 0.018), and overall clinical events, including death, myocardial infarction, or target lesion revascularization (12% vs. 27%, p = 0.026) despite the use of more stents (1.4 vs. 1.1, p < 0.001) and longer stents (42 vs. 35 mm, p = 0.001) (4).

The data in the DES era has been less compelling, mostly because of the lack of randomized trials. Nevertheless, several registries have reported the clinical utility of IVUS in patients who were treated with DES (6,7,17,18). Conversely, 3 other studies, including 1 randomized trial and 1

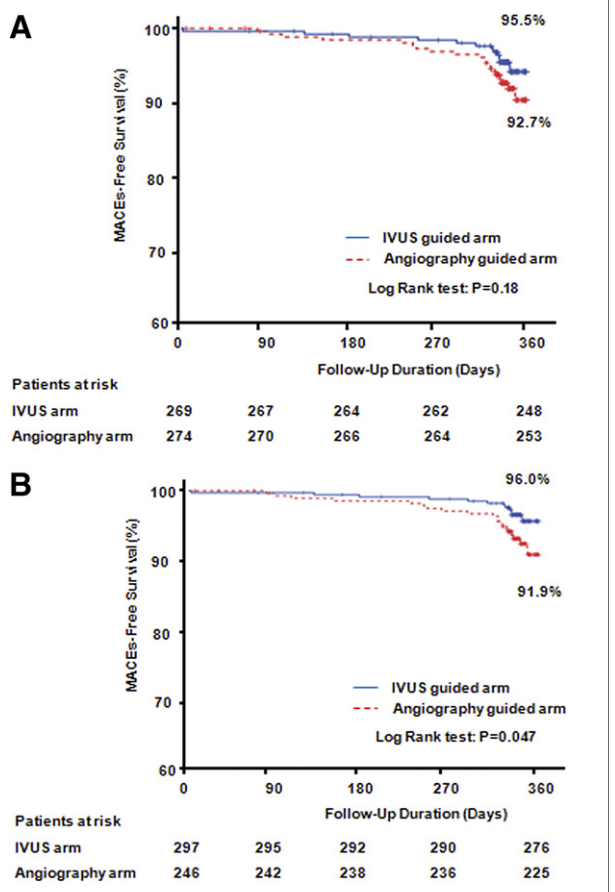

Figure 2. Kaplan-Meier 1-Year MACE-Free Survival After Index Procedure

Intention-to-treat analysis **(A)** and per-protocol analysis **(B).** Abbreviations as in Figure 1.

study in patients with ST-segment elevation myocardial infarction, failed to show any beneficial effects of IVUS guidance compared with angiography guidance (5,19,20). The current study differs from the 1 randomized trial in the DES era in that it focused on long lesions. One previous study showed that DES use blunts, but does not eliminate the impact of stent length on long-term outcomes, including restenosis and thrombosis (21). As indicated in the current study, IVUS provides useful information regarding stent status that can lead to optimal stent expansion to overcome the potential deleterious effects of longer DES.

This study is the first randomized trial to test the effect of IVUS guidance in long lesions in the DES era. In the intention-to-treat analysis, IVUS guidance led to more adjunct balloon inflations, but no difference in stent length or final minimal lumen diameter, and only a trend toward a lower 1-year MACE rate. However, these results were affected by the finding that 4.8% of patients in the IVUS-guided arm did not have IVUS guidance during the PCI procedure, and 15.0% of patients in the angiography-guided arm did, in violation of the protocol, have IVUS guidance of the DES implantation procedure. This considerable crossover rate diluted the power to document the clinical benefit of IVUS guidance. However, even though it may be prone to bias, we performed a secondary per-protocol analysis that did show a beneficial clinical impact of IVUS guidance. The quantitative coronary angiographic analysis in the current study may partially explain the difference between the per-protocol and intention-to-treat analyses; the post-intervention minimal lumen diameter was significantly greater in IVUS-guided versus the angiography-guided group in the per-protocol analysis, but not in the intention-to-treat analysis. This was similar to the randomized TULIP trial in which the post-intervention minimal lumen diameter was significantly greater in the IVUS-guided versus the angiography-guided group to explain the finding that IVUS guidance was associated with more favorable clinical outcomes (4).

Optical coherence tomography is another intravascular imaging modality and was recently introduced in clinical practice. Higher resolution of optical coherence tomography could be useful to evaluate the surface vascular changes and stent strut coverage. However, optical coherence tomography has a limitation to evaluate true vessel size and large vessel in the proximal part of major epicardial arteries due to narrow scan area and shallow penetration depth. Additionally, the role of optical coherence tomography–guided stent implantation is not sufficiently established and should be tested comparing angiography or IVUS (22,23).

Study limitations. First, the sample size was insufficient to evaluate the usefulness of IVUS because: 1) the event rate was lower than predicted in the angiographic-guided group; 2) the relative reduction of MACE was around 40%; and 3) it failed to take into account procedural crossover. Most investigators had extensive experience with IVUS guidance, and it has been speculated that experienced IVUS users approach PCI differently than IVUS nonusers do. Second, the follow-up duration was only 12 months, and the beneficial effect of IVUS guidance may increase over time (6,7,24). Third, because specific IVUS criteria for optimal stent expansion to improve clinical outcomes were not suggested, adjunct balloon dilation was at the discretion of the operating physicians. There might be the possibility that IVUS information could be underutilized. Fourth, 2 types of DES, rather than a single type of DES, were used. Fifth, because the lesions with chronic total occlusion and bifurcation lesions requiring 2-stent implantation were not included, the generalized application of these results to the entire long lesions cohort demands careful attention. Finally, pre-intervention IVUS was performed in 53% of the IVUS-guided arm because only post-stent IVUS was mandated in this study.

Conclusions

A strategy of routine IVUS did not improve the MACE at 1 year following intervention in this population. The IVUS use per operator decision was associated with improved results. These findings should be validated in other randomized clinical trials with larger populations.

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REFERENCES

1. Stone GW, Ellis SG, Cox DA, et al., for the TAXUS-IV Investigators. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221–31.
2. Kastrati A, Dibra A, Mehilli J, et al. Predictive factors of restenosis after coronary implantation of sirolimus- or paclitaxel-eluting stents. Circulation 2006;113:2293–300.
3. Kimura T, Morimoto T, Nakagawa Y, et al., for the j-Cypher Registry Investigators. Very late stent thrombosis and late target lesion revascularization after sirolimus-eluting stent implantation: five-year outcome of the j-Cypher Registry. Circulation 2012;125:584–91.
4. Oemrawsingh PV, Mintz GS, Schalij MJ, et al., for the TULIP Study Investigators. Intravascular ultrasound guidance improves angiographic and clinical outcome of stent implantation for long coronary artery stenoses: final results of a randomized comparison with angiographic guidance (TULIP Study). Circulation 2003;107:62–7.
5. Ahmed K, Jeong MH, Chakraborty R, et al., for the Other Korea Acute Myocardial Infarction Registry Investigators. Role of intravascular ultrasound in patients with acute myocardial infarction undergoing percutaneous coronary intervention. Am J Cardiol 2011;108:8–14.
6. Park SJ, Kim YH, Park DW, et al., for the MAIN-COMPARE Investigators. Impact of intravascular ultrasound guidance on long-term mortality in stenting for unprotected left main coronary artery stenosis. Circ Cardiovasc Interv 2009;2:167–77.
7. Kim JS, Hong MK, Ko YG, et al. Impact of intravascular ultrasound guidance on long-term clinical outcomes in patients treated with drug-eluting stent for bifurcation lesions: data from a Korean multicenter bifurcation registry. Am Heart J 2011;161:180–7.
8. Kim BK, Hong MK, Shin DH, et al., for the RESET Investigators. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (Real Safety and Efficacy of 3-Month Dual Antiplatelet Therapy Following Endeavor Zotarolimus-Eluting Stent Implantation). J Am Coll Cardiol 2012;60:1340–8.
9. Mintz GS, Nissen SE, Anderson WD, et al. American College of Cardiology clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound studies (IVUS): a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2001;37:1478–92.
10. Cutlip DE, Windecker S, Mehran R, et al., for the Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
11. Vranckx P, Cutlip DE, Mehran R, et al. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity: addendum to the historical MI definitions used in stent studies. EuroIntervention 2010;5:871–4.
12. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med 2007;356:1020–9.
13. Park DW, Kim YH, Song HG, et al. Comparison of everolimus- and sirolimus-eluting stents in patients with long coronary artery lesions: a randomized LONG-DES-III (Percutaneous Treatment of LONG Native Coronary Lesions With Drug-Eluting Stent-III) trial. J Am Coll Cardiol Intv 2011;4:1096–103.
14. Lee SW, Park SW, Kim YH, et al., for the DECLARE-LONG II Study Investigators. A randomized, double-blind, multicenter comparison study of triple antiplatelet therapy with dual antiplatelet therapy to reduce restenosis after drug-eluting stent implantation in long coronary lesions: results from the DECLARE-LONG II (Drug-Eluting Stenting Followed by Cilostazol Treatment Reduces Late Restenosis in Patients With Long Coronary Lesions) trial. J Am Coll Cardiol 2011;57:1264–70.
15. Casella G, Klauss V, Ottani F, Siebert U, Sangiorgio P, Bracchetti D. Impact of intravascular ultrasound-guided stenting on long-term clinical outcome: a meta-analysis of available studies comparing intravascular ultrasound-guided and angiographically guided stenting. Catheter Cardiovasc Interv 2003;59:314–21.
16. Parise H, Maehara A, Stone GW, Leon MB, Mintz GS. Meta-analysis of randomized studies comparing intravascular ultrasound versus angiographic guidance of percutaneous coronary intervention in pre-drug-eluting stent era. Am J Cardiol 2011;107:374–82.
17. Roy P, Steinberg DH, Sushinsky SJ, et al. The potential clinical utility of intravascular ultrasound guidance in patients undergoing percutaneous coronary intervention with drug-eluting stents. Eur Heart J 2008;29:1851–7.
18. Claessen BE, Smits PC, Kereiakes DJ, et al. Impact of lesion length and vessel size on clinical outcomes after percutaneous coronary intervention with everolimus- versus paclitaxel-eluting stents pooled analysis from the SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) and COMPARE (Second-Generation Everolimus-Eluting and Paclitaxel-Eluting Stents in Real-Life Practice) randomized trials. J Am Coll Cardiol Intv 2011;4:1209–15.
19. Jakabcin J, Spacek R, Bystron M, et al. Long-term health outcome and mortality evaluation after invasive coronary treatment using drug eluting stents with or without the IVUS guidance: randomized control trial: HOME DES IVUS. Catheter Cardiovasc Interv 2010;75:578–83.
20. Park KW, Kang SH, Yang HM, et al. Impact of intravascular ultrasound guidance in routine percutaneous coronary intervention for conventional lesions: data from the EXCELLENT trial. Int J Cardiol 2012 Apr 3 [E-pub ahead of print].
21. Mauri L, O'Malley AJ, Popma JJ, et al. Comparison of thrombosis and restenosis risk from stent length of sirolimus-eluting stents versus bare metal stents. Am J Cardiol 2005;95:1140–5.
22. Finn AV, Chandrashekhar Y, Narula J. IVUS or OCT: either or survivor . . . . J Am Coll Cardiol Img 2011;4:1047–9.
23. Huisman J, Hartmann M, von Birgelen C. Ultrasound and light: friend or foe? On the role of intravascular ultrasound in the era of optical coherence tomography. Int J Cardiovasc Imaging 2011;27:209–14.
24. Hur SH, Kang SJ, Kim YH, et al. Impact of intravascular ultrasound-guided percutaneous coronary intervention on long-term clinical outcomes in a real world population. Catheter Cardiovasc Interv 2013;81:407–16.

Key Words: coronary artery disease ■ drug-eluting stent ■ intravascular ultrasound.