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Intravascular Ultrasound Versus Angiography-Guided Drug-Eluting Stent Implantation

The ULTIMATE Trial

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ABSTRACT

BACKGROUND Intravascular ultrasound (IVUS)-guided drug-eluting stent (DES) implantation is associated with fewer major adverse cardiovascular events compared with angiography guidance for patients with individual lesion subset. However, the beneficial effect on major adverse cardiovascular event outcome of IVUS guidance over angiography guidance in all-comers who undergo DES implantation still remains understudied.

OBJECTIVES This study aimed to determine the benefits of IVUS guidance over angiography guidance during DES implantation in all-comer patients.

METHODS A total of 1,448 all-comer patients who required DES implantation were randomly assigned (1:1 ratio) to either an IVUS guidance or angiography guidance group. The primary endpoint was target-vessel failure (TVF) at 12 months, including cardiac death, target-vessel myocardial infarction, and clinically driven target-vessel revascularization (TVR). The procedure was defined as a success if all IVUS-defined optimal criteria were met.

RESULTS At 12 months follow-up, 60 TVFs (4.2%) occurred, with 21 (2.9%) in the IVUS group and 39 (5.4%) in the angiography group (hazard ratio [HR]: 0.530; 95% confidence interval [CI]: 0.312 to 0.901; p = 0.019). In the IVUS group, TVF was recorded in 1.6% of patients with successful procedures, compared with 4.4% in patients who failed to achieve all optimal criteria (HR: 0.349; 95% CI: 0.135 to 0.898; p = 0.029). The significant reduction of clinically driven target-lesion revascularization or definite stent thrombosis (HR: 0.407; 95% CI: 0.188 to 0.880; p = 0.018) based on lesion-level analysis by IVUS guidance was not achieved when the patient-level analysis was performed.

CONCLUSIONS The present study demonstrates that IVUS-guided DES implantation significantly improved clinical outcome in all-comers, particularly for patients who had an IVUS-defined optimal procedure, compared with angiography guidance. (Intravascular Ultrasound Guided Drug Eluting Stents Implantation in "All-Comers" Coronary Lesions [ULTIMATE]; NCT02215915) (J Am Coll Cardiol 2018;72:3126–37) © 2018 by the American College of Cardiology Foundation.

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Percutaneous implantation of a drug-eluting stent (DES) has dramatically reduced the incidence of in-stent restenosis (ISR) and the requirement of revascularization when compared with bare-metal stents (1-3). However, stent thrombosis (ST) and target-vessel revascularization (TVR) after implantation of a first-generation DES still remain major concerns especially in patients who are at high risk and have complex lesions, which lead to increased mortality (4,5).

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Intravascular ultrasound (IVUS) provides anatomic information in detail about reference vessel dimensions and lesion characteristics including severity of diameter stenosis, lesion length, and morphology (vulnerable plaque), which are poorly detected by coronary angiography. Early studies (6-8) have demonstrated the reduction of ISR and ST if DES implantation is guided by IVUS. Thereafter, both randomized and observational studies have reported the clinical benefits of IVUS guidance for patients with chronic total occlusion (CTO) (9,10), long lesions (11,12), and acute coronary syndrome (ACS) with complex bifurcation lesions (13), which is in line with the improvement of long-term health outcomes (14). More recently, meta-analyses have pointed out that the reduction of major adverse cardiac events (MACE) after DES implantation for complex lesions by IVUS guidance was primarily driven by less need of target-lesion revascularization (TLR) (15,16); however, controversy exists. It also seems that the beneficial effect of IVUS guidance for simple lesions is unclear. Moreover, whether the benefit of IVUS guidance is still present in the modern DES era still remains unknown. Accordingly, this prospective, multicenter, randomized trial (ULTIMATE [Intravascular Ultrasound Guided Drug Eluting Stents Implantation in "All-Comers" Coronary Lesions] trial) was designed to compare the efficacy and safety between IVUS-guided and angiography-guided second-generation DES implantation in all-comer patients with coronary artery disease.

METHODS

STUDY DESIGN. The ULTIMATE trial was a multicenter, prospective, randomized study to evaluate the benefits by IVUS-guided compared with angiography-guided DES implantation in all-comer patients. This study was registered at clinicaltrials.gov (NCT02215915) and was in accordance with the Declaration of Helsinki and International Conference on Harmonization of Good Clinical Practices. The study was conducted at 8 centers, and the study protocol was approved by the institutional review board at each participating center. Written informed consent for participation in the trial was obtained from all patients. The funding sources did not participate in the design or conduct of the study, analysis or interpretation of the data, or the decision to submit the manuscript for publication. The authors had access to the complete database, vouch for the accuracy and integrity of the data and all analyses, prepared the manuscript, and controlled the decision to publish.

STUDY CRITERIA. Inclusion criteria included patients who had silent ischemia, stable or unstable angina, or myocardial infarction (MI) (including both ST-segment elevation and non-ST-segment elevation MI) >24 h from the onset of chest pain to admission, and a de novo coronary lesion eligible for DES implantation. Patients would be excluded if they had: 1) comorbidity with a life expectancy <12 months; 2) intolerant of antithrombotic therapy; 3) significant anemia, thrombocytopenia, or leucopenia; 4) history of major hemorrhage (intracranial, gastrointestinal, and so on); 5) chronic total occlusion lesion in either the left anterior descending coronary artery, or left circumflex artery or right coronary artery not recanalized; and 6) severe calcification needing rotational atherectomy. Operators who had yearly percutaneous coronary intervention (PCI) cases <200 were also blocked from participating in this study.

THE SEALED ENVELOPE SYSTEM. Eligible patients were randomized in a 1:1 ratio to receive either IVUS or angiography guidance by random envelope method before PCI. A matched block method stratified by clinician was used to generate the random sequence of envelope allocations. Allocation was assigned to each block using simple randomization, with the block sequence being repeated, swapping the order of the 2 treatments, giving an equal number of patients in the 2 groups over to the matched block. To ensure that the random sequence could not be anticipated, the block size was selected randomly to be 5, 10, or 15. A random number generator within the statistical analysis package SPSS was then used to generate the random sequence for these blocks, which was treated as the seed calculated by multiplying the seconds and minutes portion of the

ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology
ACS = acute coronary syndrome
AHA = American Heart Association
CD = cardiac death
CI = confidence interval
CK-MB = creatine kinase-MB
CSA = cross-sectional area
CTO = chronic total occlusion
DES = drug-eluting stent(s)
EEM = external elastic membrane
HR = hazard ratio
ISR = in-stent restenosis
IVUS = intravascular ultrasound
MACE = major adverse cardiac events
MI = myocardial infarction
MLA = minimal lumen area
MSA = minimal stent area
PCI = percutaneous coronary intervention
ST = stent thrombosis
TLR = target-lesion revascularization
TVF = target-vessel failure
TVMI = target-vessel myocardial infarction
TVR = target-vessel revascularization
URL = upper reference limit

computer's internal clock. This process would then generate a pseudorandom distribution in the range 0 to 1. Values <0.5 were allocated to the angiography guidance group, and those ≥0.5 to the IVUS guidance group. These allocations were printed onto cards that were folded and put into small black envelopes, and then each small envelope with a card was sealed in sequentially numbered opaque black envelopes to make sure that the allocations could not be seen through transillumination. These envelopes were kept in the research office in the cath labs where all documents were left in the custody of an independent technician and an independent nurse. This process was performed for each clinician on joining the collaborative trial group. When a patient was considered to be eligible for enrollment and informal consent was obtained, the independent technician and nurse were the only 2 qualified persons to open the envelope. To open the envelop in advance was not allowed through the randomization. The envelope number and patient identifying details were recorded on a form and sent to the trial administration center to confirm recruitment.

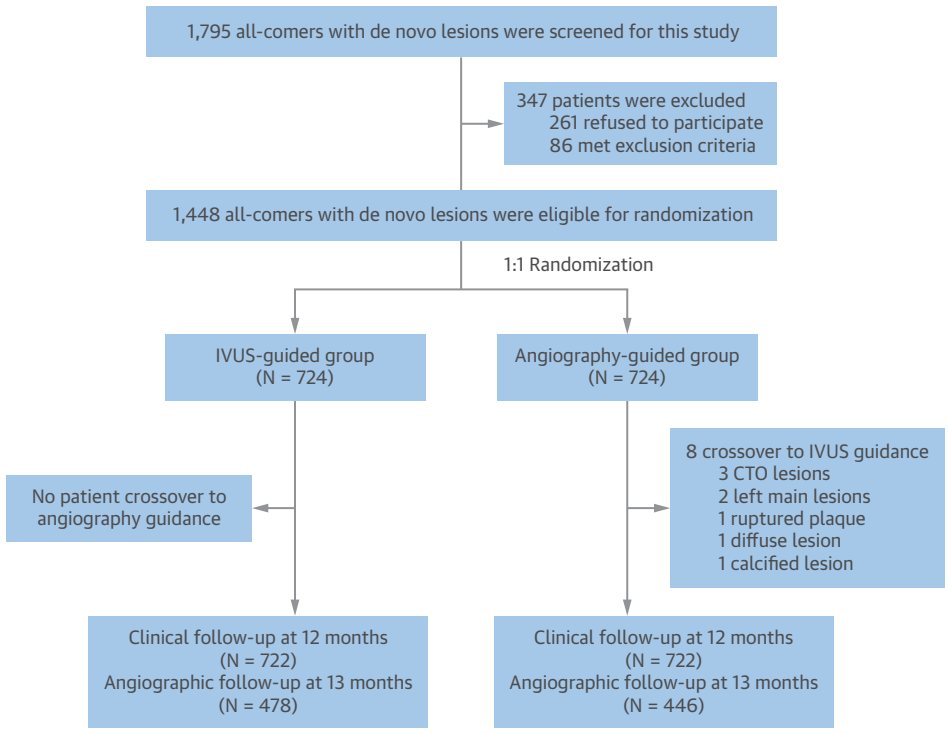
DEFINITIONS OF LESIONS SPECIFICITIES, ANGIOGRAPHY GUIDANCE, AND IVUS GUIDANCE. All lesions were classified as Type A, Type B1, Type B2, or Type C according to American College of Cardiology (ACC)/American Heart Association (AHA) classification (17).

In the angiography-guided group, stent diameter and length were selected by visual estimation with the ratio of stent/vessel diameter of 1.1:1.0. Post-dilation with a noncompliant balloon (balloon/stent diameter = 1.0:1.0) inflated at >18 atm was performed for all lesions. Angiographic success was defined as Thrombolysis In Myocardial Infarction (TIMI) flow grade 3, residual stenosis <20%, and the absence of ≥type B dissection.

In the IVUS-guided group, IVUS catheter was advanced at least 10 mm distal to the lesion or stent edge after intracoronary administration of nitroglycerin (100 to 200 μg). IVUS images were obtained with automated pullback (0.5 mm/s) using a commercially available imaging system with a 40-MHz mechanical transducer (Boston Scientific, Natick, Massachusetts) for onsite measurements. All IVUS images were stored onto a DVD thereafter for off-line measurements. Minimal lumen diameter, minimal lumen area (MLA), reference lumen area, and plaque burden were measured onsite by IVUS. The cross-sectional area (CSA) of the lumen was defined as the integrated area central to the intimal leading-edge echo. Plaque burden was calculated as: (EEM CSA − lumen CSA)/EEM CSA, where EEM is the external elastic membrane. The MLA site was defined as the slice with the smallest lumen area. The lesion length was defined as the distance between the distal and proximal reference segments. The definition of reference segment was a cross-sectional image adjacent to the lesion that has <40% plaque burden. IVUS dissection was defined as a longitudinal tear parallel to the vessel wall (18). Stent diameter was calculated according to the lumen diameter of the distal reference (ratio of 0.8 to media diameter or 1:1 to lumen diameter). The proximal and distal landing zones for stent implantation were defined as the sites where the plaque burden was <50% according to IVUS measurement. Pre-dilation was left at the physician's discretion. Similarly, post-dilation using a noncompliant balloon (balloon/stent diameter = 1.0:1.0) inflated at >18 atm was performed for all lesions. The IVUS-defined criteria for the optimal stent deployment included: 1) the MLA in the stented segment is >5.0 mm^2, or 90% of the MLA at the distal reference segments; 2) plaque burden 5-mm proximal or distal to the stent edge is <50%; and 3) no edge dissection involves media with a length >3 mm. For edge dissection induced by the stent, study protocol recommended balloon dilatation using a relative smaller balloon at a lower pressure. In order to achieve criterion 1, a larger balloon (up to 80% EEM diameter or 110% stent diameter) was repeat inflated at a higher pressure. An additional stent was not recommended unless there was stent strut fracture confirmed by IVUS. For >50% residual plaque burden, repeat ballooning was recommend using a smaller balloon (<80% EEM diameter). IVUS-defined optimal PCI was determined only if these 3 criteria were simultaneously achieved. Otherwise, the PCI procedure was defined as suboptimal if any of those 3 criteria was not met.

PCI AND MEDICATIONS. All procedures were performed according to the current PCI guidelines. Unfractionated heparin was used during the procedure to maintain an activated clotting time >250 s. An additional 3,000 IU of heparin was added if the procedure was longer than 1 h. A loading dose of aspirin (300 mg) and clopidogrel (600 mg, or ticagrelor with 180 mg) was recommended for all patients if not used before admission, at least 2 h before PCI procedure. Selection of DES types, procedural technique, and use of glycoprotein IIb/IIIa inhibitor were at the discretion of the operators. After PCI, all patients were prescribed aspirin 100 mg daily indefinitely and clopidogrel 75 mg daily (ticagrelor 90 mg twice a day) for at least 12 months.

FIGURE 1 Study Flowchart



A total of 1,448 all-comers patients were randomly assigned to either the IVUS guidance or angiography guidance group. CTO = chronic total occlusion; IVUS = intravascular ultrasound; PCI = percutaneous coronary intervention.

STUDY ENDPOINTS. The primary endpoint was the occurrence of target-vessel failure (TVF) at 12 months after indexed procedure, defined as the composite of cardiac death (CD), target-vessel myocardial infarction (TVMI), and clinically driven TVR. Death from cardiac causes was defined as any death without a clear noncardiac cause. Protocol-defined periprocedural MI (within 72 h) was defined as creatine kinase-MB (CK-MB) >10 times the upper reference limit (URL) of the assay, or >5 times the URL plus either: 1) new pathological Q waves in >2 contiguous leads or new left bundle branch block; or 2) angiographically documented graft or coronary artery occlusion, or new severe stenosis with thrombosis; or 3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Periprocedural MI for patients with an evolving MI was defined as CK-MB >20% increase (within 72 h) after implantation of a DES. Spontaneous MI (after 72 h) was defined as a clinical syndrome consistent with MI with CK-MB or troponin >1 time the URL and new ST-segment elevation or depression, or other findings as mentioned earlier in the text. All MIs were considered to be TVMI unless there was clear evidence that they were attributable to a nontarget vessel (19). Clinically driven TVR was defined as angina or ischemia referable to the target vessel requiring repeat PCI or CABG. The major secondary endpoints included all-cause death, MI, TLR, ISR, stroke, and each individual component of the primary endpoint. The safety endpoint was ST, according to the definition by the Academic Research Consortium (19). Contrast-induced nephropathy was defined as an increase in serum creatinine by >25% or 44.1 μmol/l within 3 days after the procedure. An independent events committee who was blinded to study design and randomization results (excluded from the original medical documents) assessed all clinical events.

FOLLOW-UP. After hospital discharge, clinical follow-up was performed with visits (preferred) or telephone contact at 1, 6, and 12 months. Follow-up would be continued annually to 5 years after the index procedure. Angiographic follow-up was performed at 13 months after the index procedure unless clinically indicated earlier in order to avoid the visual stenosis reflex. A 13-month angiographic follow-up as well as a 5-year clinical follow-up is ongoing and will be presented in another paper.

TABLE 1 Baseline Clinical Characteristics

	IVUS Guidance (n = 724)	Angiography Guidance (n = 724)	p Value
Age, yrs	65.2 ± 10.9	65.9 ± 9.8	0.19
Male	535 (73.9)	530 (73.2)	0.77
BMI, kg/m^2	25.3 ± 18.0	25.4 ± 19.3	0.90
Hypertension	512 (70.7)	521 (72.0)	0.60
Hyperlipidemia	389 (53.7)	400 (55.2)	0.56
Diabetes	217 (30.0)	226 (31.2)	0.61
Current smoker	253 (34.9)	228 (31.5)	0.16
Clinical presentation			
Silent ischemia	60 (8.3)	61 (8.4)	0.92
Stable angina	95 (13.1)	96 (13.3)	0.94
Unstable angina	488 (67.4)	466 (64.4)	0.22
Acute myocardial infarction	81 (11.2)	101 (14.0)	0.11
Prior stroke	85 (11.7)	85 (11.7)	NS
Prior MI	67 (9.3)	86 (11.9)	0.10
Prior PCI	126 (17.4)	144 (19.9)	0.23
Prior CABG	10 (1.4)	8 (1.1)	0.64
LVEF, %	60.9 ± 7.9	60.3 ± 9.3	0.19
Symptomatic HF	99 (13.7)	115 (15.9)	0.24
Laboratory			
Hemoglobin, g/l	134.0 ± 15.8	133.5 ± 15.7	0.49
Creatinine, μmol/l	82.0 ± 52.1	79.8 ± 33.7	0.34
eGFR <60 ml/min/1.73 m^2	180 (24.9)	169 (23.5)	0.53
eGFR <45 ml/min/1.73 m^2	61 (8.4)	63 (8.8)	0.83
LDL-C, mmol/l	2.3 ± 0.9	2.4 ± 0.9	0.09
Medications at discharge			
DAPT	720 (99.4)	717 (99.0)	0.36
OAC plus antiplatelet therapy	2 (0.3)	3 (0.4)	1.00
Statin	719 (99.3)	722 (99.7)	0.26
Medications at 1-yr follow-up			
DAPT	697 (96.3)	705 (97.4)	0.23
OAC plus antiplatelet therapy	2 (0.3)	4 (0.6)	0.41
Statin	692 (95.6)	699 (96.5)	0.34

Values are mean ± SD or n (%).

BMI = body mass index; CABG = coronary artery bypass grafting; DAPT = dual antiplatelet therapy with aspirin and $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor); eGFR = estimated glomerular filtration rate; HF = heart failure; IVUS = intravascular ultrasound; LDL-C = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; MI = myocardial infarction; OAC = oral anticoagulation therapy; PCI = percutaneous coronary intervention.

STATISTICAL ANALYSIS. We hypothesized that the rate of a 1-year TVF would be 2.9% in the IVUS guidance group and 6.1% in the angiography guidance group on the basis of previous studies (9,12-14). Accordingly, a total of 1,316 patients were needed to detect a power of 0.8 (type II error = 0.20, α = 0.05, 2-tailed). Because of the considerable uncertainty of patients lost to follow-up, the enrollment was extended to 1,448 patients (10% increment).

All principal analyses were performed on the basis of the intention-to-treat principle on the patient level. Patients were also stratified by lesion classifications based on ACC/AHA definition (17). All treated lesions were grouped into optimal (met all 3 criteria) or suboptimal (at least 1 criterion was not achieved) by IVUS definition. The distribution of continuous variables was assessed by the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± SD for normal distribution and compared using Student's *t*-test or expressed as median for non-normal distribution and compared using the Mann-Whitney *U* test. Categorical variables were expressed as frequencies or percentages and compared by chi-square statistics or Fisher exact test. Survival curves with time-to-event data generated by the Kaplan-Meier method were compared using the log-rank test. Difference in the primary endpoint between the 2 groups was compared using the Cox proportional hazard model, with report of the hazard ratio (HR), 95% confidence interval (CI), and p value. A p value <0.05 was considered statistically significant. All analyses were performed with the use of the statistical program SPSS 24.0 (SPSS Institute, Chicago, Illinois).

RESULTS

BASELINE CLINICAL CHARACTERISTICS. From August 2014 to May 2017, a total of 1,448 patients (9.5%) of 15,281 patients who underwent PCI from 8 Chinese centers were randomized to either IVUS guidance (n = 724) or angiography guidance (n = 724) group (**Figure 1**, Online Figure 1). The most common reasons for not enrolling were inconvenience (including PCI at a bad time, insufficient technicians to perform onsite measurements, no sufficient time because of too many cases daily), unreimbursed by Medicare, and a 40-MHz mechanical transducer (Boston Scientific, Natick, Massachusetts) unavailable. Baseline clinical characteristics were well matched between the 2 groups (**Table 1**). The majority of patients (78.5%) presented with ACS. Eight patients in the angiography guidance arm finally were crossed over to the IVUS guidance group due to angiographically complex lesions, at the discretion of the operators.

LESIONS AND PROCEDURAL CHARACTERISTICS. Multivessel disease was seen in 54.9% of patients. Mean lesion length was 34.5 mm, and 66.9% of lesions were classified as Type B2/C lesion (**Table 2**). A transradial approach was dominantly used. Larger and longer stents were used in the IVUS guidance group, with more frequent requirement of post-dilation with larger noncompliant balloons inflated at higher pressures (**Table 2**), which resulted in a larger minimal lumen diameter post-DES implantation (Online Table 1). IVUS guidance was associated with longer procedural times and increased contrast volumes, which did not increase the

occurrence of contrast-induced nephropathy (Table 2). Rotablation atherectomy was undertaken for 9 patients in the IVUS guidance group according to IVUS findings. One patient needed an additional stent to cover the dissection caused by post-dilation. Thirty-three patients still did not achieve optimal IVUS criteria even after post-dilation.

IVUS ASSESSMENT AFTER DES IMPLANTATION. Immediately after DES implantation, 471 lesions from 404 patients did not meet all 3 IVUS-defined criteria for optimal procedures. After multiple post-dilations, finally, a total of 384 patients (53%) (578 lesions) met those 3 criteria (Online Table 2, Online Figure 2). A lower rate of optimal PCI was largely caused by the difficulty of achieving criterion 2 (plaque burden at 5 mm proximal or distal to the stent edge <50%). Seven dissections at the distal edge occurred because of aggressive post-dilation to meet the optimal criteria. Plaque protrusion was found in a total of 21 lesions (2.2%) in the IVUS guidance group, of them, only 2 plaque protrusion localized at the site of the MLA, leading to nonsignificant differences between MLA and the minimal stent area (MSA).

PRIMARY ENDPOINT BASED ON PATIENT-LEVEL COMPARISON. Twelve-month clinical follow-up was available in 1,444 patients (99.7%; n = 4 [0.27%] were lost to follow-up, 2 in each group). At 30-day follow-up, primary and secondary endpoints were comparable between the 2 groups (Table 3).

By 12 months after the PCI procedure, 60 TVFs occurred, with 21 (2.9%) in the IVUS guidance group and 39 (5.4%) in the angiography guidance group (HR: 0.530; 95% CI: 0.312 to 0.901; p = 0.019) (Table 3, Figure 2). Differences in clinically driven TVR, TVMI, and CD were insignificant between the 2 groups. There were 6 definite/probable ST (Table 3, Online Table 3), with 1 probable ST (0.1%) in the IVUS group and 5 (0.7%) in the angiography guidance group (2 definite and 3 probable; p = 0.10). However, there was no significant difference in the composite of clinically driven TLR and definite ST between groups (Figure 2E, Table 3). Pre-specified subgroup analysis showed a tendency for patients with ACS or multivessel disease to possibly benefit from IVUS guidance (Online Figure 3). Patients who met the optimal criteria had a lower rate of TVF at 12 months (1.6%), compared with that in patients who had a suboptimal PCI procedure (4.4%; HR: 0.349; 95% CI: 0.135 to 0.898; p = 0.029) (Central Illustration). Non-target-lesion revascularization was performed in 5 (0.7%) in the IVUS group and 3 (0.4%) in the angiography guidance group (p = 0.726).

TABLE 2 Angiographic and Procedural Characteristics of Treated Lesions

	IVUS Guidance	Angiography Guidance	p Value
Total number of lesions treated	962	1,016	
Mean lesion length, mm	35.06 ± 21.68	34.05 ± 20.70	0.29
Lesion specificities			0.51
Left main trunk	95 (9.9)	87 (8.6)	
Left anterior descending artery	457 (47.5)	474 (46.7)	
Left circumflex artery	166 (17.3)	171 (16.8)	
Right coronary artery	244 (25.4)	284 (28.0)	
Multi-vessel disease*	381 (52.6)*	414 (57.2)*	0.08
AHA/ACC lesion type B2/C	636 (66.1)	688 (67.7)	0.45
Bifurcation lesion	226 (23.5)	269 (26.5)	0.13
2-stent technique	84 (8.7)	98 (9.6)	0.48
Chronic total occlusion	85 (8.8)	91 (9.0)	0.93
Moderate to several calcification lesions	243 (25.3)	246 (24.2)	0.59
Radial access*	686 (94.8)	701 (96.8)	0.07
Post-dilation performed	928 (96.6)	956 (94.9)	0.11
Per patient*			
Stent number	2.40 ± 1.55	2.47 ± 1.56	0.39
Mean stent diameter, mm	3.15 ± 0.42	2.99 ± 0.38	<0.001
Mean stent length, mm	66.42 ± 46.17	66.49 ± 44.36	0.98
Maximum balloon diameter, mm	3.84 ± 0.52	3.62 ± 0.51	<0.001
Maximum post-dilation pressure, atm	19.8 ± 3.7	19.2 ± 3.6	0.003
Per lesion			
Stent number	1.81 ± 0.80	1.76 ± 0.77	0.16
Mean stent diameter, mm	3.14 ± 0.51	2.97 ± 0.48	<0.001
Mean stent length, mm	49.99 ± 25.10	47.38 ± 22.42	0.02
Maximum balloon diameter, mm	3.73 ± 0.56	3.51 ± 0.53	<0.001
Maximum post-dilation pressure, atm	19.7 ± 3.7	19.0 ± 3.7	<0.001
Total stent numbers	1,738	1,788	0.10
Everolimus-eluting stent	235 (13.5)	257 (14.4)	
Zotarolimus-eluting stent	593 (34.1)	549 (30.7)	
Sirolimus-eluting stent	910 (52.4)	982 (54.9)	
Complete revascularization*	531 (73.3)*	543 (75.0)*	0.47
Angiographic success	943 (98.0)	994 (97.8)	0.77
Procedural time, min*	60.88 ± 28.41	45.49 ± 26.43	<0.001
Contrast volume, ml*	178.29 ± 64.08	161.96 ± 55.44	<0.001
CIN*	57 (7.9)*	42 (5.8)*	0.12

Values are n, mean ± SD, or n (%). *n = 724. Everolimus-eluting stent: Xience V/Prime; zotarolimus-eluting stent: Endeavor Resolute; sirolimus-eluting stent: Buma, Excel, Firebird2, and Firehawk.

ACC = American College of Cardiology; AHA = American Heart Association; CIN = contrast-induced nephropathy; DES = drug-eluting stent; IVUS = intravascular ultrasound.

PRIMARY ENDPOINT BASED ON LESION-LEVEL COMPARISON. Of a total of 1,978 lesions, there were 326 type A/B1 and 636 B2/C lesions in the IVUS guidance group, and 328 type A/B1 and 688 B2/C lesions in the angiography guidance group (Tables 2 and 4). At 12 months follow-up, clinically driven TLR was performed in 9 lesions (0.9%) from 9 patients in the IVUS guidance group and 23 lesions (2.3%, p = 0.02) (Table 4) from 19 patients in the angiography guidance group. Notably, definite ST was confirmed in 4 lesions (0.4%) from 2 patients (case #5 had definite ST at 11 days after stenting single lesion in the left anterior descending coronary artery, case #1, who

TABLE 3 Intention-to-Treat Clinical Outcomes From Patient-Level Analysis

	IVUS Guidance (n = 724)	Angiography Guidance (n = 724)	Hazard Ratio (95% CI)	p Value
At 30-day follow-up				
Target-vessel failure	6 (0.8)	14 (1.9)	0.427 (0.164–1.111)	0.08
Cardiac death	1 (0.1)	3 (0.4)	0.332 (0.035–3.195)	0.32
Target-vessel MI	5 (0.7)	11 (1.5)	0.454 (0.158–1.305)	0.14
Periprocedural MI	5 (0.7)	9 (1.2)	0.555 (0.186–1.656)	0.28
Spontaneous MI	0 (0.0)	2 (0.3)	-	0.16
Clinically driven TVR	0 (0.0)	2 (0.3)	-	0.16
Clinically driven TLR	0 (0.0)	2 (0.3)	-	0.16
CABG	0 (0.0)	0 (0.0)	-	NS
Target-lesion failure	6 (0.8)	14 (1.9)	0.427 (0.164–1.111)	0.08
All-cause death	1 (0.1)	5 (0.7)	0.199 (0.023–1.707)	0.10
Definite or probable ST	1 (0.1)	5 (0.7)	0.199 (0.023–1.704)	0.10
Stroke	1 (0.1)	2 (0.3)	0.499 (0.045–5.499)	0.56
At 1-yr follow-up				
Target-vessel failure	21 (2.9)	39 (5.4)	0.530 (0.312–0.901)	0.02
Cardiac death	5 (0.7)	10 (1.4)	0.497 (0.170–1.453)	0.19
Target-vessel MI	7 (1.0)	11 (1.5)	0.634 (0.246–1.636)	0.34
Spontaneous MI	3 (0.4)	2 (0.3)	1.490 (0.249–8.917)	0.66
Clinically driven TVR	11 (1.5)	21 (2.9)	0.514 (0.248–1.066)	0.07
Clinically driven TLR	9 (1.2)	19 (2.6)	0.466 (0.211–1.030)	0.05
CABG	0 (0.0)	2 (0.3)	–	0.16
Target-lesion failure	20 (2.8)	37 (5.1)	0.533 (0.309–0.918)	0.02
Clinically driven TLR or definite ST	9 (1.2)	19 (2.6)	0.466 (0.211–1.030)	0.05
All cause death	10 (1.4)	17 (2.3)	0.584 (0.267–1.275)	0.17
Definite or probable ST	1 (0.1)	5 (0.7)	0.199 (0.023–1.704)	0.10
Definite ST	0 (0.0)	2 (0.3)	–	0.16
Probable ST	1 (0.1)	3 (0.4)	0.332 (0.034–3.188)	0.32
Stroke	5 (0.7)	4 (0.6)	1.241 (0.333–4.620)	0.75

Values are n (%), unless otherwise indicated. Data are number of events (Kaplan-Meier estimated event rate), compared by the log-rank test.

CI = confidence interval; ST = stent thrombosis; TLR = target-lesion revascularization; TVR = target-vessel revascularization; other abbreviations as in Table 1.

had 3-vessel disease, had 3 definite STs at 7 days since implantation of a DES in all lesions) in the angiography guidance group, compared with 0 definite ST in the IVUS guidance group, with a borderline p value (p = 0.050). As a result, the composite rate of clinically driven TLR and definite ST was 0.9% in the IVUS group, significantly different to 2.3% in the angiography guidance group (p = 0.02) (**Table 4, Figure 3**).

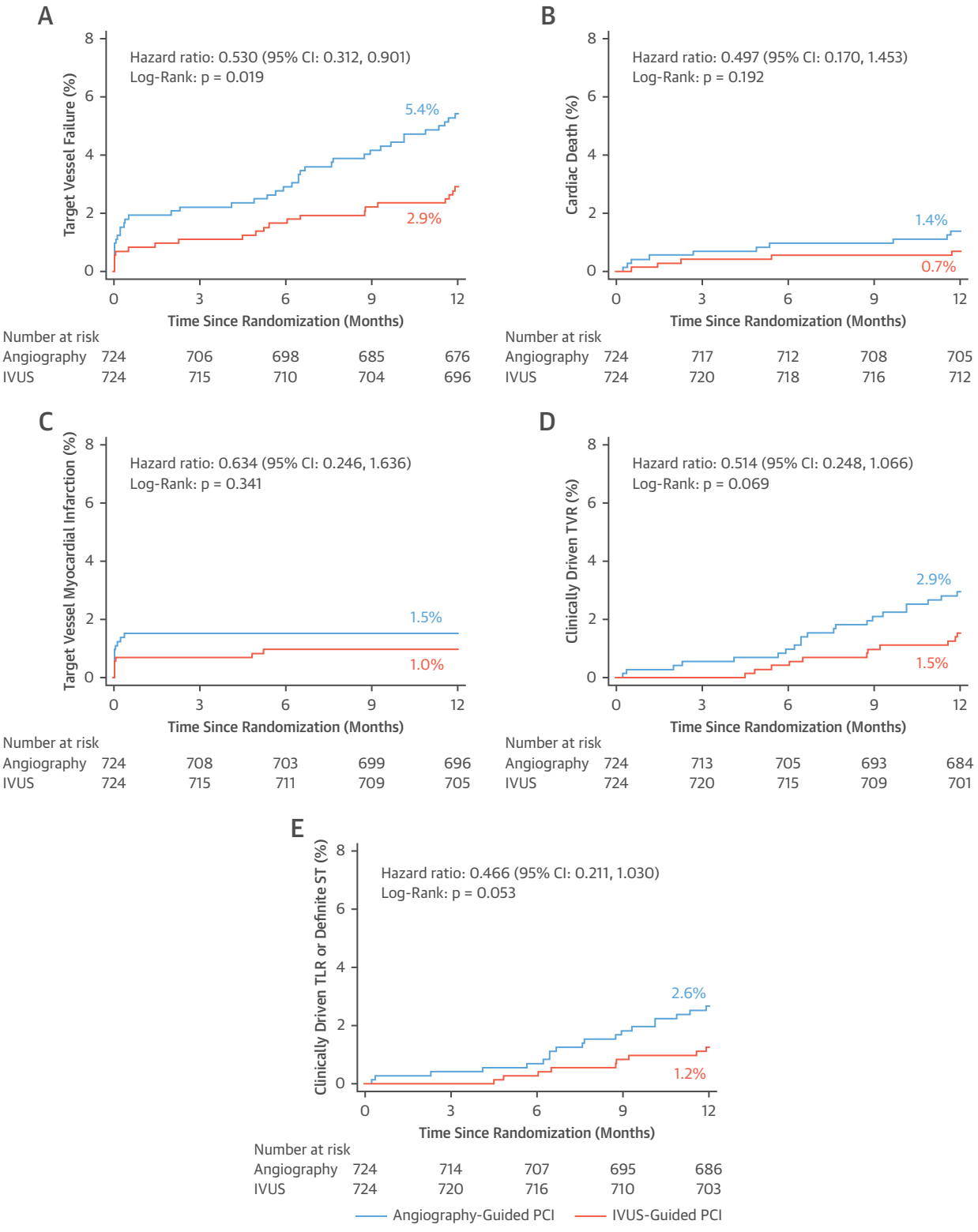
DISCUSSION

This study for the first time reports the benefit of IVUS guidance over angiography guidance from all-comers of a large population who underwent implantation of a DES. We found a significant reduction of TVF at 12 months follow-up when PCI procedures were guided by IVUS, compared with angiography-guided procedures. We also found that patients with an IVUS-defined suboptimal procedure had a higher rate of the primary endpoint, which was similar to that in the angiography guidance group. Importantly, on the basis of the lesion level analysis, IVUS guidance was associated with significant reduction of clinically driven TLR or definite ST.

On the study level, meta-analysis studies (15,16) have provided evidence of the overall beneficial effect of IVUS guidance over angiography guidance for patients who undergo PCI. Unfortunately, the presence of wider discrepancies in study design from those pooled analyses failed to show real improvement in clinical outcomes by IVUS guidance, which indicated the urgent requirement of randomized studies to confirm the benefit of IVUS guidance. In 2013, Kim et al. (12) reported their first randomized study comparing IVUS guidance versus angiography guidance. However, the high rate of crossovers in both the angiography guidance (15%) and the IVUS guidance (4.8%) groups has been considered to be as the major limitation correlated with the neutral effect of IVUS guidance, in line with the report from the HOME DES IVUS (Long-Term Health Outcome and Mortality Evaluation After Invasive Coronary Treatment Using Drug Eluting Stents with or without the IVUS Guidance) trial (14). Since then, 2 novel randomized studies (9,10) analyzed the advantage of IVUS guidance over angiography guidance for CTO-PCI, whereas our study differed with them because in-stent late lumen loss was the primary endpoint of the AIR-CTO (Study Comparing Angiography- vs. IVUS-Guided Stent Implantation for Chronic Total Occlusion in Coronary Artery) (9) and fewer than 210 patients in each group in the study by Kim et al. (10). Similarly, even though the ILUMIEN III: OPTIMIZE PCI (OPtical Coherence Tomography Compared to Intravascular Ultrasound and Angiography to Guide Coronary Stent Implantation: a Multicenter RandomIZEd Trial in Percutaneous Coronary Intervention) (20) and AVIO (Angiography Vs. IVUS Optimization) (21) studies all further confirmed the increased acute gain and less late lumen loss by IVUS guidance when compared with angiography-guided PCI, whether those anatomic benefits could be translated into clinical improvement (solid hard endpoint) was still one major concern about the efficacy of IVUS-guided PCI. Our study, coupled with others (10,11,22–24), have answered this question—that is, IVUS guidance improves clinical outcome.

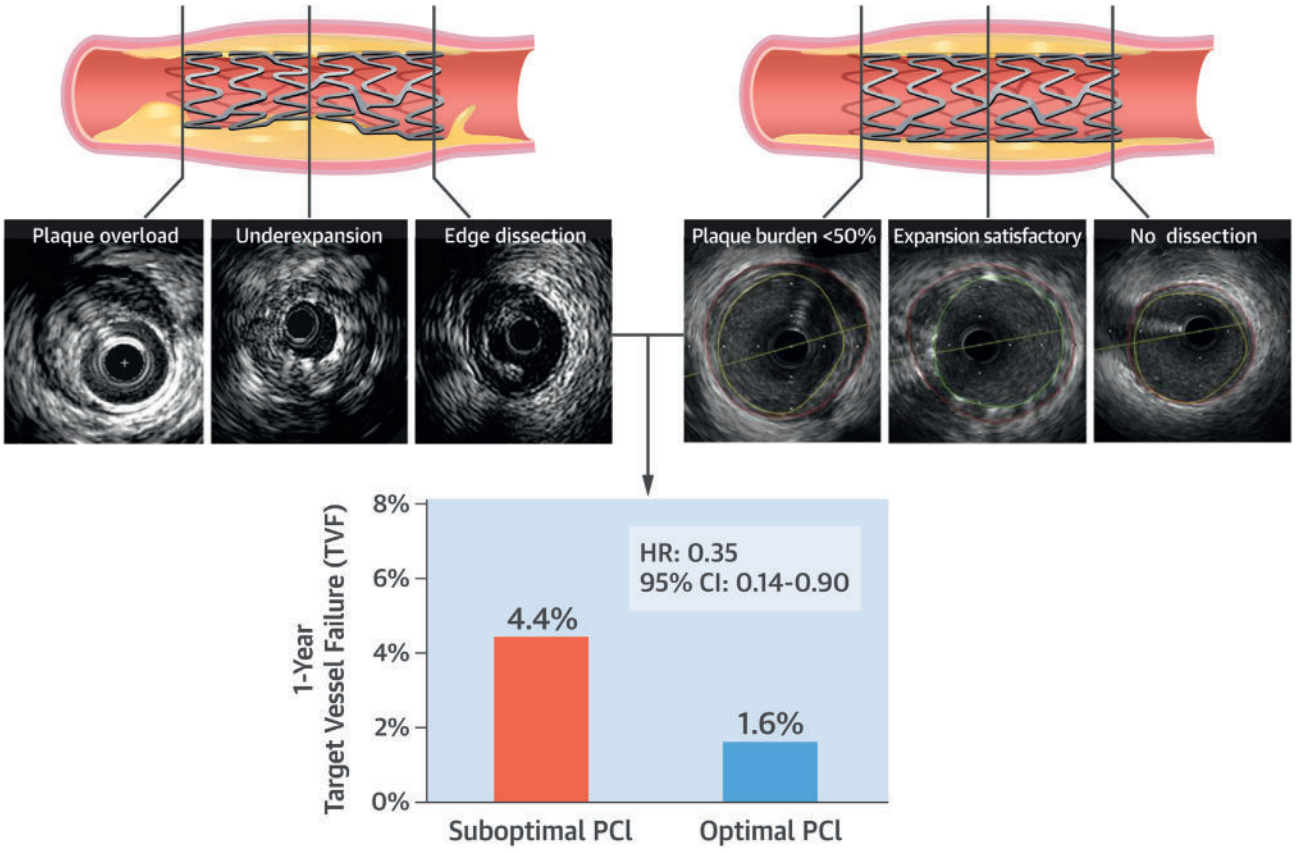
It was noted that the IVUS-XPL (Impact of Intra-Vascular UltraSound Guidance on Outcomes of Xience Prime Stents in Long Lesions) study (11) showed clinical improvement in patients who required a longer DES (minimally 28 mm in length),

FIGURE 2 Kaplan-Meier Failure Analysis at the Patient Level



(A) Target-vessel failure. **(B)** Cardiac death. **(C)** Target-vessel myocardial infarction. **(D)** Clinically driven target-vessel revascularization (TVR). **(E)** Clinically driven target-lesion revascularization (TLR) or definite stent thrombosis (ST). CI = confidence interval; other abbreviations as in Figure 1.

CENTRAL ILLUSTRATION Optimal Intravascular Ultrasound-Guided Drug-Eluting Stent Implantation



Zhang, J. et al. J Am Coll Cardiol. 2018;72(24):3126–37.

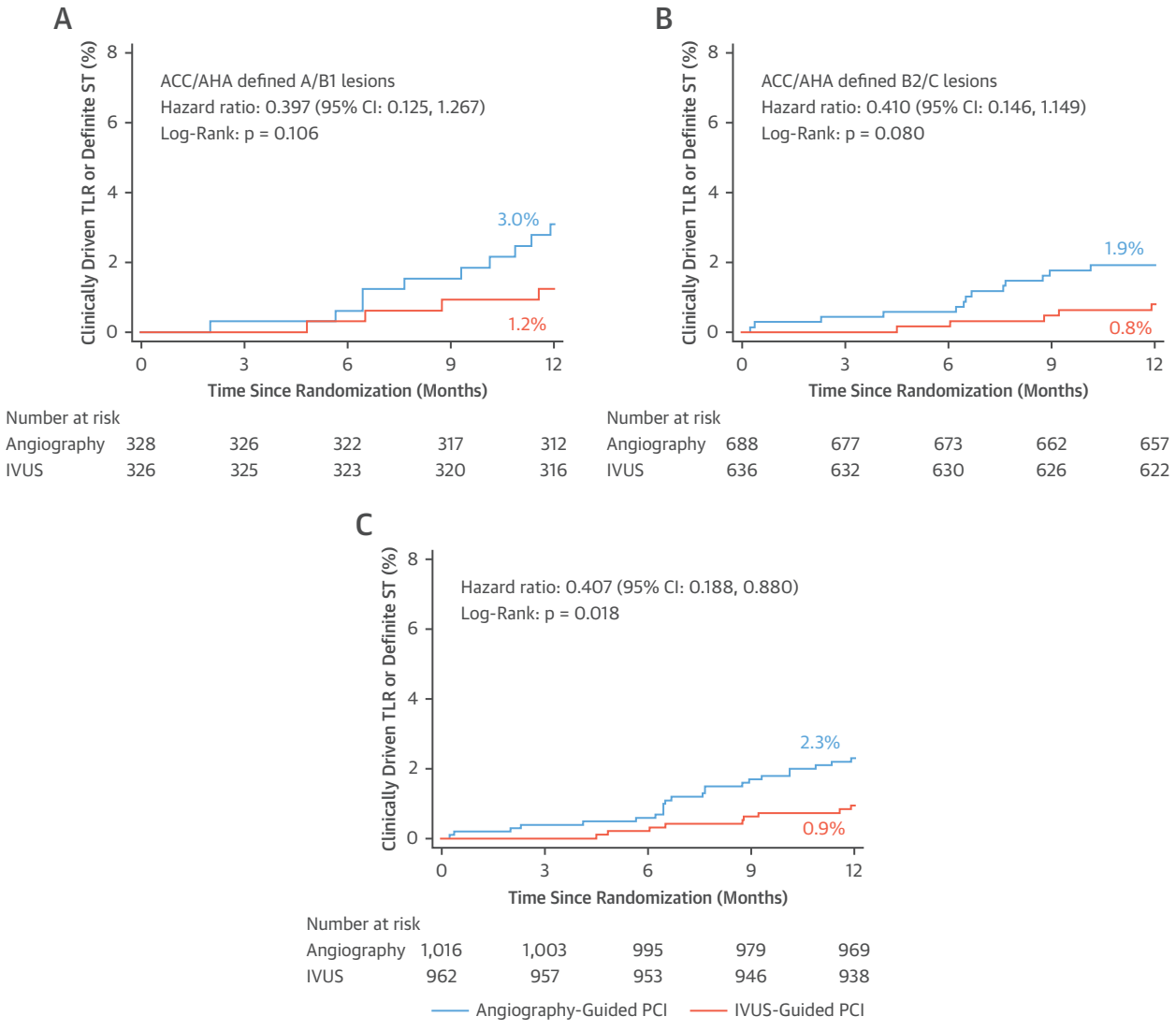
Intravascular ultrasound (IVUS) guidance was beneficial for all-comer patients who underwent implantation of a drug-eluting stent (DES), especially when IVUS-defined optimal procedures were achieved. Optimal IVUS-guided PCI **(right panel)** was defined if all 3 criteria were met: 1) the minimal lumen area (MLA) in stented segment >5.0 mm^2 or 90% of the MLA at the distal reference segments; 2) plaque burden at 5 mm proximal or distal to the stent edge <50%; and 3) no edge dissection involving media with length longer than 3 mm. Suboptimal IVUS-guided PCI **(left panel)** was defined if any of the preceding 3 criteria was not met. CI = confidence interval; HR = hazard ratio; PCI = percutaneous coronary intervention.

TABLE 4 Clinical Outcomes From Lesion-Level Analysis at 12-Month Follow-Up

	Subgroups	IVUS Guidance (n = 962)	Angiography Guidance (n = 1,016)	Hazard Ratio (95% CI)	p Value
Clinically driven TLR	Total	9 (0.9)	23 (2.3)	0.407 (0.188-0.880)	0.02
	A/B1	4/326 (1.2)	10/328 (3.0)	0.397 (0.125-1.267)	0.11
	B2/C	5/636 (0.8)	13/688 (1.9)	0.410 (0.146-1.149)	0.08
Definite ST	Total	0 (0.0)	4 (0.4)	–	0.05
	A/B1	0 (0.0)	0 (0.0)	–	NS
	B2/C	0 (0.0)	4/688 (0.6)	–	0.05
Clinically driven TLR or definite ST	Total	9 (0.9)	23 (2.3)	0.407 (0.188-0.880)	0.02
	A/B1	4/326 (1.2)	10/328 (3.0)	0.397 (0.125-1.267)	0.11
	B2/C	5/636 (0.8)	13/688 (1.9)	0.410 (0.146-1.149)	0.08

Values are n (%) or n/N (%), unless otherwise indicated. Data are number of events (Kaplan-Meier estimated event rate), compared by the log-rank test.
NS = not significant; other abbreviations as in Tables 1 and 3.

FIGURE 3 Kaplan-Meier Failure Analysis at the Lesion Level



(A) Clinically driven TLR or definite ST for ACC/AHA-defined A/B1 lesions. **(B)** Clinically driven TLR or definite ST for ACC/AHA-defined B2/C lesions. **(C)** Clinically driven TLR or definite ST for overall lesions. ACC = American College of Cardiology; AHA = American Heart Association; other abbreviations as in Figures 1 and 2.

and demonstrated a significant reduction of target-lesion failure at 1-year follow-up, largely because of the reduction of ischemia-driven TLR. Caution should be taken when comparing the IVUS-XPL study with our study, because there are many differences in study design (long lesion vs. all-comers), endpoints (ischemia-driven TLR vs. clinically driven TVR), and definitions (periprocedural MI within 48 h vs. 72 h). Most importantly, in that study (11), IVUS criteria for stent optimization after PCI was defined as a minimal lumen CSA greater than the lumen CSA at the distal reference segments, similar to the ILUMIEN III: OPTIMIZE PCI study (20) and criterion 1 in our study. However, 3 criteria were simultaneously used in this study, explaining the lower rate of optimal PCI results in the present report. Whereas we found a very similar rate of optimal PCI by our IVUS criterion 1 and criterion by the IVUS-XPL or ILUMIEN III study, our results further demonstrated the difficulty of achieving optimal PCI according to criterion 2 (both edge plaque burden <50%). On the other hand, aggressive dilation (particularly in both edge areas) commonly led to severe dissection requiring additional stents.

The complexity of coronary lesions determines the clinical outcomes after PCI based on both meta-analyses (15,16,22,23) and prospective studies (9-14,20,21,24). The AIR-CTO study (9) showed that IVUS-guided CTO-PCI resulted in a lower incidence of ISR possibly due to the optimization of stent expansion and edge dissections secondary to IVUS, but no effect on MI and CD, supported by the IVUS-XPL study (11) and our patient-level analysis.

Long lesions or CTO or bifurcation lesions do not represent all complex lesions. By contrast, ACC/AHA-defined complex lesions (17) were analyzed in this study. Our study showed that IVUS guidance was associated with a significant reduction of the composite of clinically driven TLR and definite ST relying on the lesion-level analysis, compared with angiography guidance. Although this lesion-level analysis was underpowered because only TLR and definite ST (secondary endpoints) were able to be calculated from the sample size, our results underscored the importance of IVUS guidance (risk reduction of TLR plus definite ST >60%, borderline p value for definite ST).

Although IVUS guidance was associated with improved clinical outcome, and there was a realization of the presence of different optimal criteria for IVUS guidance, the lingering question remains: how to achieve optimal IVUS-guided PCI? Technically, adjunctive post-dilatation with a noncompliant balloon can increase the MSA and decrease suboptimal stent deployment; therefore, it may reduce the frequency of TVR and ST (25). In the DES era, when the adequate post-interventional MSA of sirolimus-eluting stents was defined as >5.0 mm^2, the positive predictive value of patency was 90% (26). Foin et al. (27) found that without adjunctive balloon post-dilatation, 24% of sirolimus-eluting stents and 28% of paclitaxel-eluting stents did not achieve a final MSA of 5 mm^2. In the current study, IVUS guidance was critical to modify plaque (complex lesions), to guide post-dilation, and to minimize or to repair edge complications, subsequently leading to less composite of TVF. As a result, with the guidance of IVUS, precise selection of the right noncompliant balloon was the basis for achieving an optimal PCI.

STUDY LIMITATIONS. First, 3 IVUS criteria were simultaneously used to define optimal PCI, which would underestimate the advantages of IVUS usage. Second, we did not directly compare the rate of TVF stratified by different IVUS-defined criteria. But our results have revealed that one-third of the PCI procedures could not achieve criterion 2 (edge residual plaque burden <50%), which implied the complexity of lesions. Third, the current study does not address the cardiac events beyond 1-year follow-up; however, in order to test the long-term benefits of IVUS guidance, clinical follow-up will be continued to 5 years. Finally, the use of the sealed envelope system must be acknowledged as a suboptimal randomization procedure that does not guarantee truly concealed randomization compared with centralized web-based randomization.

CONCLUSIONS

In the present multicenter randomized trial in all-comer patients, IVUS-guided DES implantation resulted in a lower incidence of TVF at 12 months, particularly for patients who had an IVUS-defined optimal procedure, compared with angiography guidance.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Optimal deployment of coronary DESs guided by IVUS is associated with lower 12-month rates of target vessel failure than angiographically guided stenting.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine the optimum IVUS-defined criteria to guide coronary artery stenting and to examine the utility of ultrasound guidance to guide endovascular interventions in other vascular territories.

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KEY WORDS all-comers, drug-eluting stent, intravascular ultrasound, optimal criteria

APPENDIX For an expanded Methods section as well as supplemental figures and tables, please see the online version of this paper.