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NEW RESEARCH PAPERS

CORONARY

3-Year Outcomes of the ULTIMATE Trial Comparing Intravascular Ultrasound Versus Angiography-Guided Drug-Eluting Stent Implantation

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ABSTRACT

OBJECTIVES The aim of this study was to explore the difference in target vessel failure (TVF) 3 years after intravascular ultrasound (IVUS) guidance versus angiographic guidance among all comers undergoing second-generation drug-eluting stent (DES) implantation.

BACKGROUND The multicenter randomized ULTIMATE (Intravascular Ultrasound Guided Drug Eluting Stents Implantation in "All-Comers" Coronary Lesions) trial showed a lower incidence of 1-year TVF after IVUS-guided DES implantation among all comers compared with angiographic guidance. However, the 3-year clinical outcomes of the ULTIMATE trial remain unknown.

METHODS A total of 1,448 all comers undergoing DES implantation who were randomly assigned to either IVUS guidance or angiographic guidance in the ULTIMATE trial were followed for 3 years. The primary endpoint was the risk for TVF at 3 years. The safety endpoint was definite or probable stent thrombosis (ST).

RESULTS At 3 years, TVF occurred in 47 patients (6.6%) in the IVUS-guided group and in 76 patients (10.7%) in the angiography-guided group ($p = 0.01$), driven mainly by the decrease in clinically driven target vessel revascularization (4.5% vs. 6.9%; $p = 0.05$). The rate of definite or probable ST was 0.1% in the IVUS-guided group and 1.1% in the angiography-guided group ($p = 0.02$). Notably, the IVUS-defined optimal procedure was associated with a significant reduction in 3-year TVF relative to that with the suboptimal procedure.

CONCLUSIONS IVUS-guided DES implantation was associated with significantly lower rates of TVF and ST during 3-year follow-up among all comers, particularly those who underwent the IVUS-defined optimal procedure compared with those with angiographic guidance. (Intravascular Ultrasound Guided Drug Eluting Stents Implantation in "All-Comers" Coronary Lesions; NCT02215915) (J Am Coll Cardiol Intv 2021;14:247-57) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CI = confidence interval

DES = drug-eluting stent

HR = hazard ratio

IVUS = intravascular ultrasound

MI = myocardial infarction

PCI = percutaneous coronary intervention

TLR = target lesion revascularization

TVF = target vessel failure

TVMI = target vessel myocardial infarction

TVR = target vessel revascularization

Intravascular ultrasound (IVUS) guidance has emerged as the recommended treatment modality for selected patients with complex coronary lesions undergoing drug-eluting stent (DES) implantation, with both randomized and observational studies having confirmed the clinical benefits of IVUS guidance in patients with unprotected left main disease (1–5), long lesions (6–8), chronic total occlusion (9,10), and complex bifurcation lesions (11,12). In the randomized ULTIMATE (Intravascular Ultrasound Guided Drug Eluting Stents Implantation in "All-Comers" Coronary Lesions) trial (13), we also found a lower 1-year risk for target vessel failure (TVF) in the IVUS-guided group compared with that in the angiography-guided group among all-comer patients undergoing second-generation DES implantation. However, the long-term effect of IVUS guidance beyond 2 years in the modern DES era has scarcely been reported in randomized trials. Accordingly, the purpose of this study was to assess the 3-year clinical outcomes of IVUS guidance compared with those of angiographic guidance among all comers from the ULTIMATE trial with dedicated long-term follow-up.

TABLE 1 Clinical, Angiographic, and Procedural Characteristics

	IVUS Guidance (n = 724)	Angiographic Guidance (n = 724)	p Value
Clinical			
Age, yrs	65.2 ± 10.9	65.9 ± 9.8	0.19
Male	535 (73.9)	530 (73.2)	0.77
Hypertension	512 (70.7)	521 (72.0)	0.60
Diabetes	217 (30.0)	226 (31.2)	0.61
Hyperlipidemia	389 (53.7)	400 (55.2)	0.56
Acute coronary syndrome	569 (78.6)	567 (78.3)	0.90
Angiographic			
Number of lesions	962	1,016	
Left main or LAD lesion*	552 (57.4)	561 (55.2)	
Multivessel disease	381 (52.6)	414 (57.2)	0.08
Chronic total occlusion*	85 (8.8)	91 (9.0)	0.93
Bifurcation lesion*	226 (23.5)	269 (26.5)	0.13
Procedural			
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
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

Values are mean ± SD or n (%). Modified with permission from Zhang et al. (13). *n = lesion number in each group.
IVUS = intravascular ultrasound; LAD = left anterior descending coronary artery.

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METHODS

TRIAL DESIGN. The trial design has been described previously (13,14). Briefly, the ULTIMATE trial was a prospective, investigator-initiated, randomized trial to compare IVUS-guided versus angiography-guided DES implantation among all-comer patients at 8 Chinese centers. The trial protocol was approved by the ethics committee of each participating center, and written informed consent was obtained from all patients.

Patients were eligible to participate in this trial if they had silent ischemia, stable or unstable angina, or myocardial infarction (MI) with more than 24 h between onset of chest pain and admission and de novo coronary lesions requiring DES implantation. A total of 1,448 patients were enrolled from August 2014 to May 2017 and randomly assigned to undergo IVUS-guided or angiography-guided DES implantation in a 1:1 ratio immediately after coronary angiography. The detailed protocols for IVUS and angiographic guidance were reported previously (13). Of note, the IVUS-defined optimal criteria for DES implantation in this trial included: 1) minimum luminal area in the stented segment more than 5.0 mm^2 or 90% of the minimal luminal area at the distal reference segments; 2) plaque burden 5 mm proximal or distal to the stent edge <50%; and 3) no edge dissection involving the media with length more than 3 mm. IVUS-defined optimal procedures were identified only if all 3 criteria were simultaneously met. Otherwise, the percutaneous coronary intervention (PCI) was defined as a suboptimal procedure.

MEDICATIONS. All patients were prescribed a loading dose of aspirin (300 mg) and a $P2Y_{12}$ inhibitor (clopidogrel 600 mg or ticagrelor 180 mg) if not receiving antiplatelet therapy before the procedure. After the procedure, all patients were treated with 100 mg/day aspirin indefinitely and 75 mg/day clopidogrel (or ticagrelor 90 mg twice a day) for at least 1 year. Other medications for secondary prevention of coronary disease, including statins, angiotensin-

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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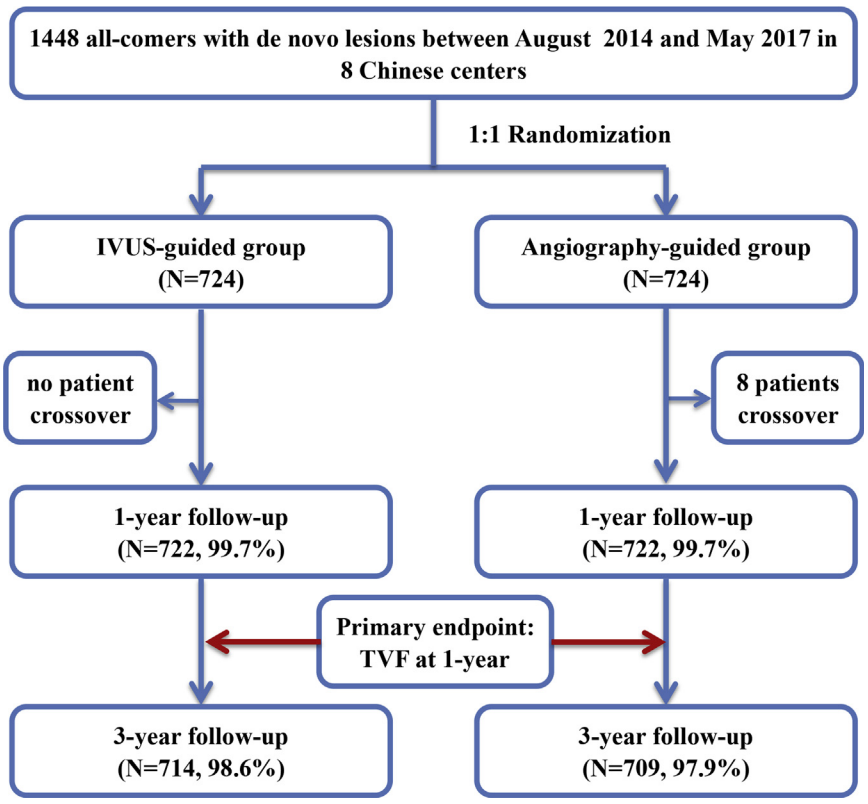
FIGURE 1 Study Flowchart



A total of 1,448 all comers were randomly assigned to either intravascular ultrasound (IVUS) guidance or angiographic guidance. TVF = target vessel failure.

converting enzyme inhibitors, and β-blockers, were prescribed according to current guidelines.

STUDY ENDPOINTS AND DEFINITIONS. The primary endpoint was the occurrence of TVF at 3 years after the index procedure, which included cardiac death, target vessel MI (TVMI), and clinically driven target vessel revascularization (TVR). The safety endpoint was definite or probable stent thrombosis. All deaths were considered to be cardiac deaths unless there was a clear noncardiac cause. TVMI was defined as any MI without clear evidence of a nontarget vessel. Protocol-defined peri-procedural MI was defined as a peak creatine kinase-MB ≥10 times the upper limit of normal measured within 72 h after the procedure or ≥5 times the upper limit of normal plus: 1) new pathological Q waves in 2 or more contiguous leads or new left bundle branch block; 2) angiographically documented coronary artery or graft occlusion or new severe stenosis with thrombosis; or 3) imaging evidence of new regional wall motion abnormality or new loss of viable myocardium. Spontaneous MI was defined previously (13). Clinically driven TVR was defined as the presence of angina or objective signs of ischemia referable to the target vessel requiring any repeat revascularization (PCI or coronary artery bypass grafting). The composite of clinically driven target lesion revascularization (TLR) and definite stent thrombosis was the endpoint of the lesion-level comparison. All clinical events were assessed by an independent committee blinded to group information using original medical documents.

STATISTICAL ANALYSIS. The sample size calculation was described previously (13). The Kolmogorov-Smirnov test was used to evaluate the distributions of continuous variables. Continuous variables are reported as mean ± SD for normally distributed data and were compared using Student's *t*-test; data not normally distributed are expressed as medians and were compared using the Mann-Whitney *U* test. Categorical variables are expressed as frequency (percentage) and were compared using the chi-square test

TABLE 2 Clinical Outcomes at 1, 2, and 3 Years

	IVUS Guidance (n = 724)	Angiographic Guidance (n = 724)	Hazard Ratio (95% CI)	p Value
1-yr follow-up				
Number of patients	722	722		
Target vessel failure	21 (2.9)	39 (5.4)	0.53 (0.31–0.90)	0.02
Cardiac death	5 (0.7)	10 (1.4)	0.50 (0.17–1.45)	0.19
Target vessel MI	7 (1.0)	11 (1.5)	0.63 (0.25–1.64)	0.34
Clinically driven TVR	11 (1.5)	21 (2.9)	0.51 (0.25–1.07)	0.07
All-cause death	10 (1.4)	17 (2.3)	0.58 (0.27–1.28)	0.17
Clinically driven TLR	9 (1.2)	19 (2.6)	0.47 (0.21–1.03)	0.05
Target lesion failure	20 (2.8)	37 (5.1)	0.53 (0.31–0.92)	0.02
Definite/probable ST	1 (0.1)	5 (0.7)	0.20 (0.02–1.70)	0.10
2-yr follow-up				
Number of patients	718	719		
Target vessel failure	43 (6.0)	65 (9.0)	0.65 (0.44–0.95)	0.03
Cardiac death	9 (1.3)	16 (2.2)	0.56 (0.25–1.26)	0.16
Target vessel MI	7 (1.0)	14 (1.9)	0.50 (0.20–1.23)	0.12
Clinically driven TVR	31 (4.3)	42 (5.8)	0.72 (0.45–1.15)	0.17
All-cause death	24 (3.3)	27 (3.8)	0.88 (0.51–1.53)	0.65
Clinically driven TLR	26 (3.6)	40 (5.6)	0.63 (0.39–1.04)	0.07
Target lesion failure	38 (5.3)	63 (8.8)	0.59 (0.39–0.88)	0.01
Definite/probable ST	1 (0.1)	7 (1.0)	0.14 (0.02–1.15)	0.03
3-yr follow-up				
Number of patients	714	709		
Target vessel failure	47 (6.6)	76 (10.7)	0.60 (0.42–0.87)	0.01
Cardiac death	13 (1.8)	19 (2.7)	0.68 (0.34–1.38)	0.28
Target vessel MI	7 (1.0)	15 (2.1)	0.46 (0.19–1.14)	0.09
Clinically driven TVR	32 (4.5)	49 (6.9)	0.64 (0.41–1.00)	0.05
All-cause death	31 (4.3)	31 (4.4)	0.99 (0.60–1.63)	0.98
Clinically driven TLR	27 (3.8)	45 (6.3)	0.59 (0.36–0.94)	0.03
Target lesion failure	42 (5.9)	72 (10.2)	0.57 (0.39–0.83)	0.003
Definite/probable ST	1 (0.1)	8 (1.1)	0.12 (0.02–0.99)	0.02

Values are n (%). The p values are from the log-rank test.

CI = confidence interval; IVUS = intravascular ultrasound; MI = myocardial infarction; ST = stent thrombosis; TLR = target lesion revascularization; TVR = target vessel revascularization.

or Fisher exact test. Time-to-first event curves were generated using the Kaplan-Meier method and compared using the log-rank test. The Cox proportional hazards model was used to evaluate the differences in primary and secondary endpoints between 2 randomized groups; hazard ratios (HR), 95% confidence interval (CIs), and p values are reported. In a post hoc analysis, we evaluated the effect of IVUS guidance over angiographic guidance using piecewise hazards models separately for landmark analyses (2 intervals: 0 to 1 year and >1 to 3 years). Net treatment effects of IVUS guidance versus angiographic guidance were tested using post hoc milestone analyses, and the difference in TVF between the 2 groups that occurred each day during the 3-year follow-up period was reported. We also performed pre-specified subgroup analysis to explore the potential heterogeneity of the effects in the Cox proportional hazards model. All principal analyses were performed in the intention-to-treat population, and on-treatment and per-protocol analyses were also performed for sensitivity analyses. Another sensitivity analysis including lesion-level comparison was also used. A 2-tailed p value <0.05 was considered to indicate statistical significance. All analyses were conducted using Stata version 14.0 (StataCorp, College Station, Texas).

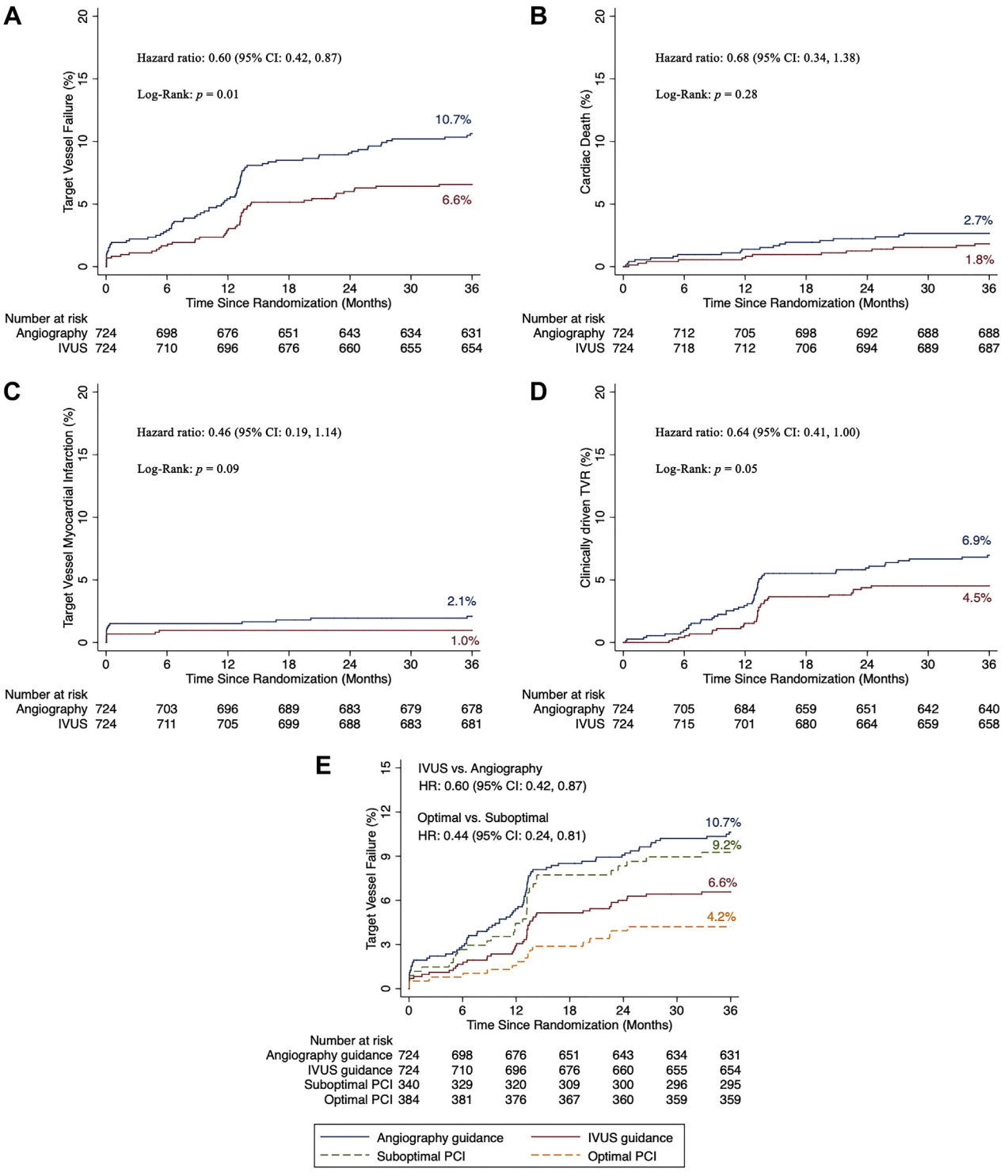
RESULTS

BASELINE CLINICAL, ANGIOGRAPHIC, AND PROCEDURAL CHARACTERISTICS. The baseline characteristics (Table 1) were well matched between the 2 groups (13). Diabetes was present in 30.6% of enrolled patients, and 78.5% of patients presented with acute coronary syndromes (ACS). Multivessel disease was found in 54.9% of patients. Larger stents were implanted in the IVUS guidance group, with more frequent post-dilation using larger noncompliant balloons at higher pressures.

CLINICAL OUTCOMES. Clinical follow-up was completed in 1,444 patients (99.7%) at 1 year and in 1,423 patients (98.3%) at 3 years (Figure 1). The median duration of follow-up was 3 years (interquartile range: 3 to 3 years). At 3 years, dual-antiplatelet therapy was prescribed to 274 patients (37.8%) in the angiographic guidance group and 263 patients (36.3%) in the IVUS guidance group (p = 0.55). Angiographic follow-up was completed in 488 patients (67.4%) in the angiography group and 507 patients (70.0%) in the IVUS group at 3 years after the index procedure (p = 0.28).

Clinical outcomes are shown in Table 2 and Figure 2. At 1-year follow-up, TVF was more frequent (5.4%) in the angiographic guidance group than in the IVUS guidance group (2.9%; p = 0.02). At the 2- and 3-year follow-up, the risk for TVF was 9.0% and 10.7% in the angiographic guidance group (HR: 0.65; 95% CI: 0.44 to 0.95; p = 0.03) and 6.0% and 6.6% in the IVUS guidance group (HR: 0.60; 95% CI: 0.42 to 0.87; p = 0.01), respectively, driven mainly by the increased occurrence of TVR (5.8% vs. 4.3% [p = 0.17] and 6.9% vs. 4.5% [p = 0.05]) in the angiographic guidance group. Milestone analysis showed that the sustained 3-year benefit of IVUS guidance over time was in decreased TVF risk (Supplemental Figure 1). For those without 13-month angiographic follow-up, the rates of 3-year TVF were 14 of 217 (6.5%) in the IVUS group and 17 of 236 (7.2%) in the angiography group (p = 0.75). The results were similar for the per-protocol and on-treatment populations (Supplemental Table 1). Moreover, by 3 years after the index procedure, the risk for definite or probable stent thrombosis was 1.1% in the angiographic

FIGURE 2 Kaplan-Meier Failure Analysis at 3-Year Follow-Up



(A to D) IVUS guidance was associated with significantly lower rate of TVF and clinically driven target vessel revascularization (TVR) compared with angiographic guidance. There were no statistical differences in cardiac death and target vessel myocardial infarction. **(E)** IVUS-defined optimal percutaneous coronary intervention was associated with less TVF compared with suboptimal PCI. CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 1.

TABLE 3 Landmark Analyses of Clinical Outcomes Between IVUS and Angiographic Guidance

	IVUS Guidance (n = 724)	Angiographic Guidance (n = 724)	Hazard Ratio (95% CI)	p Value	p Value for Interaction
Target vessel failure					
≤1 yr	21 (2.9)	39 (5.4)	0.53 (0.31–0.90)	0.02	0.50
>1 to 3 yrs	26 (3.7)	37 (5.5)	0.68 (0.41–1.12)	0.13	
Cardiac death					
≤1 yr	5 (0.7)	10 (1.4)	0.50 (0.17–1.45)	0.19	0.81
>1 to 3 yrs	8 (1.1)	9 (1.3)	0.88 (0.34–2.29)	0.80	
Target vessel MI					
≤1 yr	7 (1.0)	11 (1.5)	0.63 (0.25–1.64)	0.34	0.92
>1 to 3 yrs	0	4 (0.6)	0.02 (0–47.04)	0.04	
Clinically driven TVR					
≤1 yr	11 (1.5)	21 (2.9)	0.51 (0.25–1.07)	0.07	0.46
>1 to 3 yrs	21 (3.0)	28 (4.1)	0.73 (0.41–1.29)	0.27	
All-cause death					
≤1 yr	10 (1.4)	17 (2.3)	0.58 (0.27–1.28)	0.17	0.08
>1 to 3 yrs	21 (2.9)	14 (2.0)	1.49 (0.76–2.93)	0.24	
Clinically driven TLR					
≤1 yr	9 (1.2)	19 (2.6)	0.47 (0.21–1.03)	0.05	0.47
>1 to 3 yrs	18 (2.6)	26 (3.8)	0.67 (0.37–1.23)	0.19	
Target lesion failure					
≤1 yr	20 (2.8)	37 (5.1)	0.53 (0.31–0.92)	0.02	0.74
>1 to 3 yrs	22 (3.2)	35 (5.2)	0.61 (0.36–1.04)	0.06	
Definite/probable ST					
≤1 yr	1 (0.1)	5 (0.7)	0.20 (0.02–1.70)	0.10	0.93
>1 to 3 yrs	0	3 (0.4)	0.02 (0–163.01)	0.08	

Values are n (%). The p values are from the log-rank test.
Abbreviations as in Table 2.

guidance group and 0.1% in the IVUS guidance group (p = 0.02) (Supplemental Table 2).

Landmark analyses of clinical outcomes between the IVUS and angiographic guidance groups are presented in **Table 3 and Figure 3A**. Between 1 and 3 years, 63 TVFs occurred, 26 (3.7%) in the IVUS group and 37 (5.5%) in the angiography group (HR: 0.68; 95% CI: 0.41 to 1.12; p = 0.13). No interaction between IVUS guidance and time was found for TVF (p = 0.50). A total of 384 patients (53%) who met all 3 protocol-defined criteria were regarded as having undergone IVUS-defined optimal PCI. Baseline characteristics between the optimal PCI and suboptimal PCI groups are summarized in Supplemental Table 3. Patients with IVUS-defined optimal PCI had a lower risk for 3-year TVF (4.2%) than those with suboptimal PCI (9.2%) (HR: 0.44; 95% CI: 0.24 to 0.81; p = 0.01) (**Figure 2E, Central Illustration**). Multivariate Cox regression showed that optimal PCI (HR: 0.50; 95% CI: 0.26 to 0.93; p=0.03), ACS (HR: 3.00; 95% CI: 1.08 to 8.38; p = 0.04), and stent length (per 10 mm) (HR: 1.12; 95% CI: 1.00 to 1.24; p = 0.04) were independent predictors of 3-year TVF in the IVUS guidance group. Landmark analyses between IVUS-defined optimal and suboptimal groups are shown in **Table 4 and Figure 3B**. There was no interaction between treatment effect and time for TVF (p = 0.51).

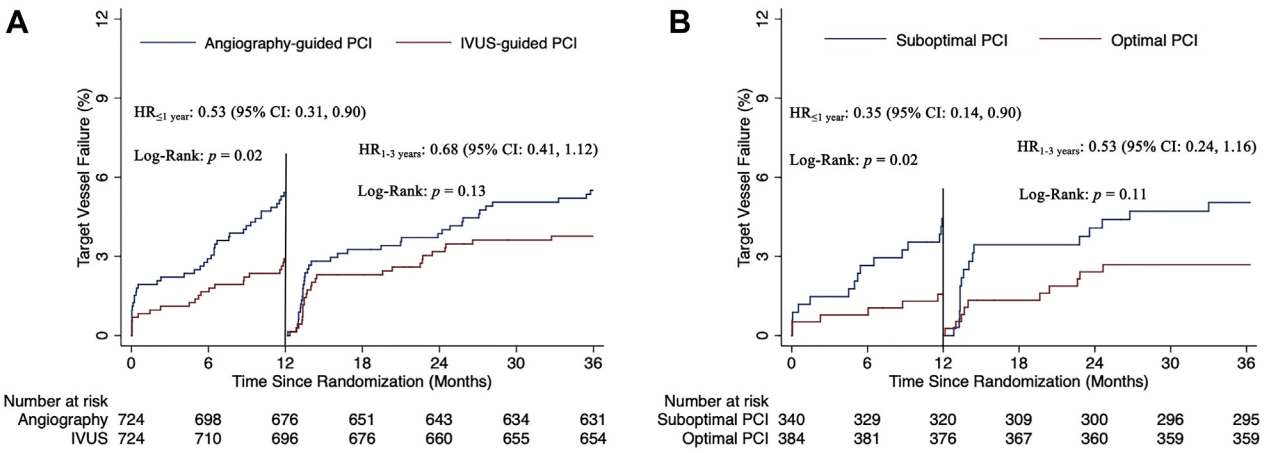
Pre-specified subgroup analysis revealed a consistently lower 3-year rate of TVF in the IVUS guidance group across numerous subgroups, with a tendency for patients with ACS, chronic kidney disease, multivessel disease, type B2/C lesions, or bifurcation lesions to possibly benefit from IVUS guidance (**Figure 4**). Post hoc analysis suggested that IVUS guidance provided greater benefit in complex PCI, although no interaction existed (Supplemental Table 4). Lesion-level analysis showed that the 3-year rate of clinically driven TLR or definite stent thrombosis in the IVUS guidance group was significantly lower than that in the angiographic guidance group (HR: 0.50; 95% CI: 0.32 to 0.77; p = 0.001) (Supplemental Figure 2).

DISCUSSION

The ULTIMATE trial evaluated clinical outcomes after IVUS guidance compared with angiographic guidance among all comers undergoing implantation of second-generation DES for the first time. The present study demonstrated that the reduction of TVF with IVUS guidance was sustainable and became more significant throughout the 3-year clinical follow-up period. Notably, we found that patients with IVUS-defined optimal PCI had better clinical outcomes than those who underwent nonoptimal IVUS.

It has been established that IVUS guidance could improve the 1-year clinical benefit in complex lesion subsets (5–7,9,10) and high-risk patients (12,15,16) undergoing DES implantation. However, the long-term effects of IVUS guidance remain unknown in the modern era of DES. Several studies have reported long-term clinical outcomes with IVUS guidance in patients undergoing DES implantation. The ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) registry, enrolling 8,582 all comers, found that the benefits of IVUS guidance increased from 1 to 2 years, especially in reducing TVMI and revascularization (17). A retrospective, single-center registry (18) including 6,005 consecutive patients with complex coronary artery lesions showed that IVUS-guided PCI was related to a lower risk for cardiac death and ischemia-driven TLR compared with angiography-guided PCI during more than 5 years of follow-up. A nationwide population-based registry (2) demonstrated better clinical outcomes with IVUS guidance when performing unprotected left

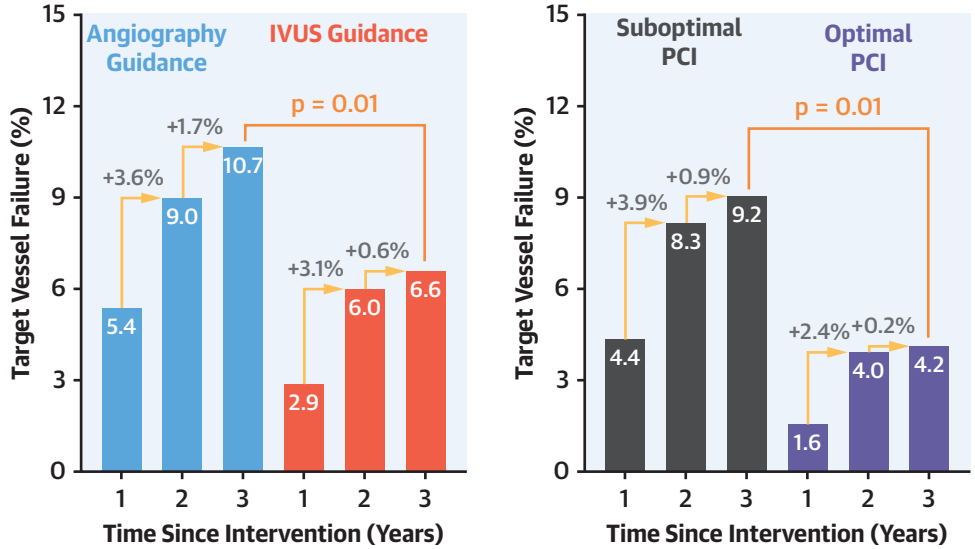
FIGURE 3 Landmark Analyses of Target Vessel Failure



(A) Landmark analyses for all patients. **(B)** Landmark analyses for patients in the IVUS guidance group. Abbreviations as in Figures 1 and 2.

main coronary artery stenting during more than 5 years of follow-up. Recently, an American Medicare cohort (19) showed that IVUS was used in only 5.6% of all PCI patients, and IVUS use was associated with lower long-term mortality and repeat revascularization over a median follow-up duration of 3.7 years. Our results, coupled with those of these registries, demonstrate that

CENTRAL ILLUSTRATION 3-Year Follow-Up of the IVUS-Guided Drug-Eluting Stents Implantation in All-Comers Coronary Lesions Trial



Gao, X.-F. et al. J Am Coll Cardiol Intv. 2021;14(3):247-57.

Intravascular ultrasound (IVUS) guidance improved 3-year clinical outcomes among all-comer patients who underwent implantation of drug-eluting stents, especially when IVUS-defined optimal procedures were achieved. IVUS-guided optimal percutaneous coronary intervention (PCI) was defined if all 3 criteria were met: 1) minimal luminal area (MLA) in the 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 the media with length longer than 3 mm. IVUS-guided suboptimal PCI was defined if any of these 3 criteria was not met.

TABLE 4 Clinical Outcomes Between IVUS-Defined Optimal and Suboptimal PCI

	Optimal PCI	Suboptimal PCI	Hazard Ratio (95% CI)	p Value	p Value for Interaction
Target vessel failure					
≤1 yr	6/382 (1.6)	15/340 (4.4)	0.35 (0.14–0.90)	0.02	0.51
>1 to 3 yrs	10/371 (2.7)	16/317 (5.0)	0.53 (0.24–1.16)	0.11	
Cardiac death					
≤1 yr	1/382 (0.3)	4/340 (1.2)	0.22 (0.03–1.97)	0.14	0.30
>1 to 3 yrs	4/376 (1.1)	4/328 (1.2)	0.87 (0.22–3.47)	0.84	
Target vessel MI					
≤1 yr	2/382 (0.5)	5/340 (1.5)	0.35 (0.07–1.82)	0.19	1.00
>1 to 3 yrs	0/374	0/323	–	–	
Clinically driven TVR					
≤1 yr	3/382 (0.8)	8/340 (2.4)	0.33 (0.09–1.23)	0.08	0.75
>1 to 3 yrs	7/373 (1.9)	14/320 (4.4)	0.42 (0.17–1.05)	0.06	

Values are number of events/number of patients (%). The p values are from the log-rank test. Two patients at 1 year and 5 patients at 1 to 3 years were lost to clinical follow-up in the IVUS-defined optimal PCI group, while 3 patients at 1 to 3 years were lost to follow-up in the suboptimal PCI group.

PCI = percutaneous coronary intervention; other abbreviations as in Table 2.

IVUS-guided DES implantation improves long-term clinical outcomes.

A recent meta-analysis (20) including 9 randomized trials and 4,724 patients demonstrated that IVUS-guided DES implantation could reduce the risk for cardiac death, coronary revascularization, and stent thrombosis compared with angiographic guidance. Unfortunately, the wide differences in study design and follow-up duration among these randomized trials results in a failure to show real long-term improvement of clinical outcomes when using IVUS guidance in the era of DES. Of the 9 randomized trials, only the IVUS-XPL (Impact of Intra-Vascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions) study demonstrated lower 5-year major adverse cardiac event rates with IVUS guidance than with angiographic guidance, mainly because of a reduction in ischemia-driven TLR. There are many differences when comparing our study with the IVUS-XPL study with respect to enrolled patients (all comers vs. those with long lesions), study endpoints (clinically driven TVR vs. ischemia-driven TLR), peri-procedural MI definition (within 72 h vs. 48 h), loss to follow-up (1.7% at 3 years vs. 15% at 5 years), and IVUS criteria (3 criteria vs. 1 criterion). Another important finding in our study is that the differences in TLR, TVR, and stent thrombosis between the IVUS- and angiography-guided groups, which were statistically nonsignificant at 1-year follow-up, were significant at 3-year follow-up. Neoatherosclerosis, characterized by lipid foamy macrophage accumulation within the neointima, could occur several years after DES implantation, which might contribute to in-stent restenosis and thrombosis. Our study, in line with other studies (4,8,12), showed that IVUS guidance could optimize stent implantation and reduce the rates of repeat revascularization and stent thrombosis compared with that when using angiographic guidance.

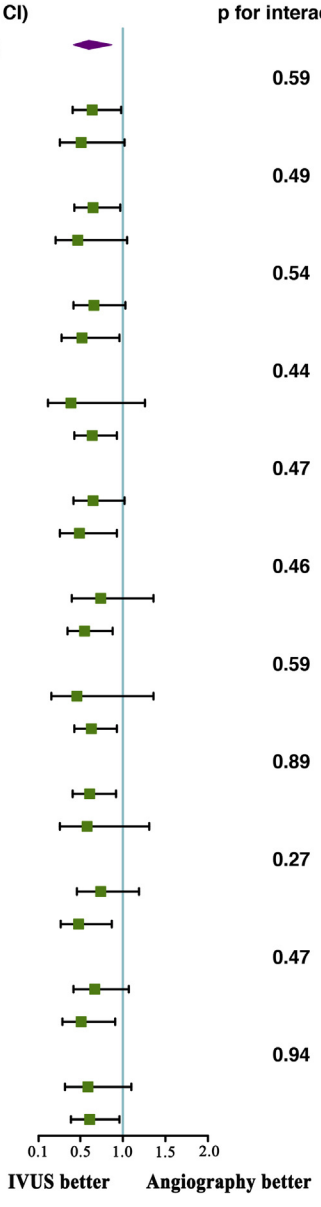
Landmark analysis found a lower trend of TVF, TVMI, and definite or probable stent thrombosis with IVUS guidance compared with angiographic guidance between 1 and 3 years after DES implantation; however, this difference was not statistically significant. This might be because of a significantly low risk for TVR, spontaneous MI, and stent thrombosis after 1 year in the 2 groups due to the low event rate among all-comer patients and second-generation DES deployment. Moreover, increased clinically driven TVR between 12 and 18 months after DES implantation was observed, which might be related to follow-up protocol. However, repeat angiography was performed only for patients with suspected chest pain, or angina, or confirmed evidences of abnormal biomarkers or ischemia. As we noted, clinically driven revascularization, assessed by an independent committee blinded to allocation, was defined as an event. The rates of angiographic follow-up were comparable between the 2 groups. Therefore, the optional angiographic follow-up did not influence the comparison of IVUS guidance and angiographic guidance.

Despite the different IVUS criteria used in randomized trials, the aforementioned meta-analysis (20) showed that patients with IVUS-defined optimal procedures had a significant 67% reduction in 1-year major adverse cardiovascular events over those who underwent suboptimal procedures. More important, our study, in line with the IVUS-XPL study, demonstrated that IVUS-guided optimal DES deployment could provide long-term clinical benefit over a suboptimal procedure. A prospective registry (12) comparing IVUS guidance and angiographic guidance in DES implantation for patients with ACS showed that patients who did not achieve IVUS-defined optimal results had a higher risk for cardiac events than those with optimal procedures and similar to that with angiographic guidance. Recently, the IRIS-DES (Interventional Cardiology Research In-Cooperation Society-Drug-Eluting Stents) registry (21) found that only 35.4% of patients in real-word clinical practice underwent IVUS guidance for all 3 stages of pre-dilation, stent sizing, and post-dilation during DES implantation in complex coronary artery stenosis, and those patients had a lower risk for 3-year cardiac events.

Both the IVUS-XPL trial and our study verified the gradually increasing clinical benefits of IVUS-guided DES implantation; however, IVUS was used in only

FIGURE 4 Subgroup Analysis for 3-Year Target Vessel Failure

Subgroup	IVUS guidance Events/ total patients	Angiography guidance Events/ total patients	Hazard Ratio (95% CI)	p for interaction
All patients	**47/724**	**76/724**	**0.60 (0.42–0.87)**	
Age				**0.59**
<75 yrs	34/557	54/573	0.64 (0.41–0.98)	
≥75 yrs	13/167	22/151	0.51 (0.26–1.02)	
Sex				**0.49**
Male	38/535	57/530	0.65 (0.43–0.97)	
Female	9/189	19/194	0.47 (0.21–1.05)	
Diabetes mellitus				**0.54**
No	32/507	47/498	0.66 (0.42–1.03)	
Yes	15/217	29/226	0.52 (0.28–0.96)	
Acute coronary syndrome				**0.44**
No	4/155	10/157	0.39 (0.12–1.26)	
Yes	43/569	66/567	0.64 (0.43–0.93)	
Chronic kidney disease				**0.47**
No	32/543	49/551	0.65 (0.42–1.02)	
Yes	15/180	27/169	0.49 (0.26–0.93)	
Multi–vessel disease				**0.46**
No	19/343	23/310	0.74 (0.40–1.36)	
Yes	28/381	53/414	0.55 (0.35–0.88)	
ACC/AHA classification				**0.59**
A/B1	5/219	10/203	0.46 (0.16–1.36)	
B2/C	42/505	66/521	0.63 (0.43–0.93)	
Chronic total occlusion				**0.89**
No	38/641	60/635	0.61 (0.41–0.92)	
Yes	9/83	16/89	0.58 (0.26–1.31)	
Bifurcation lesions				**0.27**
No	31/509	38/469	0.74 (0.46–1.19)	
Yes	16/215	38/255	0.48 (0.27–0.87)	
Moderate to severe calcification				**0.47**
No	29/517	43/521	0.67 (0.42–1.07)	
Yes	18/207	33/203	0.51 (0.29–0.91)	
Lesion length				**0.94**
<25 mm	16/290	27/293	0.59 (0.32–1.10)	
≥25 mm	31/434	49/431	0.61 (0.39–0.96)	



ACC = American College of Cardiology; AHA = American Heart Association; other abbreviations as in Figure 1 and 2.

5.6% of all PCI patients (19). In view of the evidence from randomized trials, it is time to overcome the barriers, including cost, availability, expertise, and procedure prolongation, to promote IVUS use in daily clinical practice. Further randomized studies are also warranted to identify the most optimal criteria for IVUS guidance and how to achieve these IVUS-defined optimal criteria. Moreover, after the benefits of IVUS guidance have been established in chronic total occlusion, left main disease, long lesions, and all comers, the DKCRUSH VIII (IVUS Guided DK Crush Stenting Technique for Patients with Complex Bifurcation Lesions) study comparing IVUS-guided versus an angiography-guided systematic 2-stent strategy for complex bifurcation lesions is expected.

STUDY LIMITATIONS. First, the sealed-envelope system is not an optimal randomization method

when compared with centralized web-based randomization. Second, relatively high-risk patients (78% with ACS) and complex coronary lesions were enrolled in the ULTIMATE trial, which reflects the typical characteristics of high-volume PCI centers in China. Subgroup analysis also indicated that the benefit of IVUS guidance was not limited to ACS and complex lesions. Third, a procedure was considered optimal only if all 3 criteria were met, which might underestimate the long-term clinical benefits of IVUS guidance. We did not directly compare the clinical outcomes stratified by different IVUS-defined criteria. Finally, a nonsignificant p value for TVF after 1 year should be interpreted cautiously, mainly because of the small sample size and relatively short follow-up duration.

CONCLUSIONS

In the present multicenter randomized trial, IVUS guidance was associated with a lower risk for 3-year TVF, particularly for patients with IVUS-defined optimal procedures, relative to angiographic guidance among all comers undergoing second-generation DES implantation.

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PERSPECTIVES

WHAT IS KNOWN? IVUS guidance improves 1-year clinical outcomes among all comers undergoing DES implantation.

WHAT IS NEW? IVUS-guided DES implantation, especially an IVUS-defined optimal procedure, is associated with a lower risk for TVF for up to 3 years among all comers compared with that following angiographic guidance.

WHAT IS NEXT? Further studies are warranted to identify the most optimal IVUS-defined criteria and how to achieve these IVUS criteria.

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KEY WORDS all-comers, drug-eluting stent, intravascular ultrasound, target vessel failure

APPENDIX For supplemental figures and tables, please see the online version of this paper.