JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 9, NO. 21, 2016

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2016.07.021

Effects of Intravascular Ultrasound–Guided Versus Angiography-Guided New-Generation Drug-Eluting Stent Implantation

Meta-Analysis With Individual Patient–Level Data From 2,345 Randomized Patients

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate the clinical usefulness of intravascular ultrasound (IVUS)-guided new-generation drug-eluting stent (DES) implantation using a meta-analysis of individual patient-level data from randomized trials.

BACKGROUND Published randomized trials that compare IVUS-guided versus angiography-guided new-generation DES implantation are scarce.

METHODS Searches of the MEDLINE, Embase, and Cochrane databases were performed to find randomized trials that compared IVUS-guided versus angiography-guided new-generation DES implantation. A total of 2,345 patients from 3 randomized trials were identified, and all patients were treated for long lesions or chronic total occlusions. Individual patient-level data were obtained. The primary endpoint was a major adverse cardiac event, a composite of cardiac death, myocardial infarction, or stent thrombosis. An intention-to-treat analysis and per protocol analysis were performed.

RESULTS By 1 year post-procedure, major adverse cardiac events had occurred in 0.4% of the patients who underwent IVUS-guided DES implantation versus 1.2% of those who underwent angiography-guided DES implantation (hazard ratio [HR]: 0.36; 95% confidence interval [CI]: 0.13 to 0.99; $p = 0.040$). For the IVUS-guided group, favorable clinical outcomes were observed for myocardial infarction (0% vs. 0.4%; HR: 0.09; $p = 0.026$). In addition, the clinical benefit of IVUS guidance was stronger in the per protocol analysis (HR: 0.32; 95% CI: 0.12 to 0.89; $p = 0.021$).

CONCLUSIONS Compared with angiographic guidance, IVUS-guided new-generation DES implantation was associated with favorable outcomes in terms of major adverse cardiac events, the composite of cardiac death, myocardial infarction, or stent thrombosis. These findings must be interpreted only for complex lesions, because all identified patients had long lesions or chronic total occlusions. (J Am Coll Cardiol Intv 2016;9:2232–9) © 2016 by the American College of Cardiology Foundation.

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Manuscript received June 21, 2016; revised manuscript received July 11, 2016, accepted July 14, 2016.

The results of 6 recently published meta-analyses indicated that intravascular ultrasound (IVUS)-guided drug-eluting stent (DES) implantation was associated with a significant reduction in major adverse cardiac events (MACE), stent thrombosis, and target lesion revascularization (TLR) (1–6), but these studies included patients who received first-generation DES and used only study-level (not patient-level) data. In addition, 5 of these 6 meta-analyses included observational studies (1–5); the sixth study was the meta-analysis that included only randomized trial data (6).

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Because clinical outcomes between first- and new-generation DES-treated patients are clearly different (7) and the first-generation DES are not currently used in daily clinical practice, data from studies with exclusively next-generation DES-treated patients are required. Furthermore, previous randomized studies failed to prove improvement of hard clinical endpoints in IVUS-guided new-generation DES implantation (8,9). According to the IVUS-XPL (Impact of Intravascular Ultrasound Guidance on Outcomes of XIENCE PRIME Stents in Long Lesions) trial, IVUS-guided everolimus-eluting stent implantation for long coronary lesions had an approximately 50% reduction in the 1-year rate of MACEs, the composite of cardiac death, myocardial infarction, or TLR (8). However, the reduction in MACEs was driven mainly by the reduction in TLR, without between-group differences in cardiac death or myocardial infarction, which may be more clinically important events. Therefore, our objective was to conduct a meta-analysis of individual patient-level randomized trial data to evaluate whether IVUS guidance improves hard clinical endpoints in new-generation DES-treated patients.

METHODS

STUDY DESIGN AND SELECTION. The meta-analysis was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines (10). The MEDLINE, Embase, and Cochrane databases were searched for randomized trials published from 2005 through 2015 that compared IVUS-guided versus angiography-guided new-generation DES implantation. The search terms were "intravascular ultrasound" and "drug-eluting stent" (Online Appendix). Only full-paper published studies were considered for inclusion in the meta-analysis; there were no language restrictions. Studies that included the use of first-generation DES or that consisted of abstract-only data or both were excluded from our study. Information on study design, inclusion and exclusion criteria, patient and procedural characteristics, and clinical outcomes was extracted. The Cochrane bias assessment tool was used by 2 of the investigators (D.-H.S. and S.-J.H.), who independently assessed the risk for bias (11). Conflicts between the 2 investigators were resolved by consensus. The final selection for inclusion in the meta-analysis consisted of 3 randomized controlled trials (8,9,12). To obtain the individual patient-level data, the study statisticians from each trial extracted the patient-level data by direct access to the study databases. The independent statistician (D.-H.S.) collected all data from the individual trials and cross-checked them against previous publications. Data on baseline patient characteristics and procedure information, and data on clinical events, were collected. These patient data were pooled and analyzed in a single dataset.

ABBREVIATIONS AND ACRONYMS

DES = drug-eluting stent(s)

HR = hazard ratio

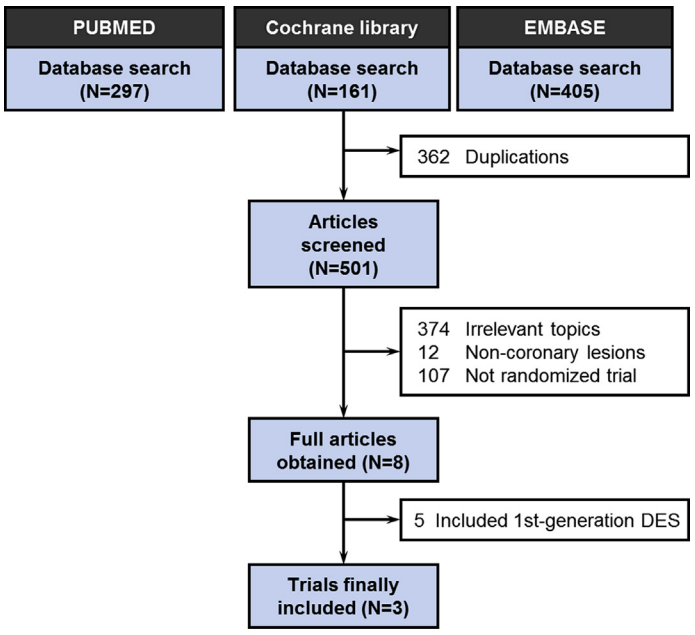
IVUS = intravascular ultrasound

MACE = major adverse cardiac event(s)

TLR = target lesion revascularization

ENDPOINTS AND DEFINITIONS. The primary endpoint in this meta-analysis was MACE of hard clinical endpoint, defined as a composite of cardiac death, myocardial infarction, and stent thrombosis. The secondary endpoint was individual components of the primary endpoint and TLR. Academic Research Consortium criteria were used to define clinical events (13); the specific endpoint definitions, as applied in each trial, were also incorporated into the study. All deaths were considered cardiac deaths unless a definite noncardiac cause could be established (13,14). Myocardial infarction during 1-year follow-up after hospital discharge was defined as the presence of clinical symptoms, electrocardiographic changes, or abnormal imaging findings that indicated myocardial infarction, combined with an increase in the creatine kinase myocardial band fraction above the upper normal limit or an increase in troponin T or troponin I to greater than the 99th percentile of the upper normal limit (8,9,12,13). Definite, probable, and possible stent thrombosis were defined according to the recommendations of the Academic Research Consortium (13,14). TLR was defined as repeat percutaneous coronary intervention or bypass surgery of target lesions with either of the following (according to each study): 1) ischemic symptoms or positive stress test results and angiographic diameter stenosis ≥50% measured by quantitative coronary angiographic analysis; or 2) angiographic diameter stenosis ≥70% measured by quantitative coronary angiographic analysis without ischemic symptoms or positive stress test results (8,9,12).

FIGURE 1 Flow Diagram



DES = drug-eluting stent(s).

STATISTICAL ANALYSIS. For the individual patient-level analysis, results for continuous variables are presented as mean ± SD. Results for categorical variables are presented as number (percentage). Continuous and categorical variable data were analyzed using Student *t* tests and chi-square tests, respectively. Cumulative incidence values were calculated using the Kaplan-Meier method and were compared using the log-rank test. Hazard ratios (HRs) were calculated using the Cox proportional hazards model, stratified by trial. Specifically, information from trials in which patients had enrolled was included as a random effect using a gamma frailty fit (15). Firth's penalized method was used if there was a convergence problem caused by lack of events (16). The analysis was performed using intention-to-treat and per protocol analysis. Subgroup analysis was performed according to the baseline characteristics. Two-sided p values were used, and a p value <0.05 was considered to indicate a statistically significant result. All analyses were performed using R version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses study flow is illustrated in Figure 1. Three randomized trials, RESET IVUS (Real Safety and Efficacy of 3-Month Dual Antiplatelet Therapy Following Endeavor Zotarolimus-Eluting Stent Implantation), CTO-IVUS (Chronic Total Occlusion Intervention With Drug-Eluting Stents Guided by Intravascular Ultrasound), and IVUS-XPL, were included in the meta-analysis (8,9,12). The study design, characteristics, and results of the 3 randomized trials are summarized in Table 1.

A total of 2,345 randomized patients were identified. These patients were randomized to undergo either IVUS-guided or angiography-guided next-generation DES implantation to treat complex coronary lesions (e.g., long lesions and chronic total occlusions). The results of the risk for bias assessment are presented in Online Figure 1. Blinding of the operator could not be performed for any of the studies, because the information from IVUS itself was the result of random allocation. Otherwise, no apparent risk for bias was found in terms of random sequence generation, allocation concealment, blinding of outcome assessment, or reporting.

The results for baseline patient characteristics and procedure information are presented in Table 2. The random allocations between the IVUS-guided and angiography-guided arms were well balanced.

The results for clinical outcomes are presented in Figure 2 and Table 3. By 1 year post-implantation, the primary endpoint (MACEs) had occurred in 0.4% of the patients who underwent IVUS-guided DES implantation versus 1.2% of those who underwent angiography-guided DES implantation (HR: 0.36; 95% confidence interval [CI]: 0.13 to 0.99; p = 0.040) (Figure 2A). In addition, the benefit of IVUS guidance was stronger in the per protocol analysis. MACEs occurred in 0.4% of the patients who underwent IVUS-guided DES implantation versus 1.3% of those who underwent angiography-guided DES implantation (HR: 0.32; 95% CI: 0.12 to 0.89; p = 0.021) (Figure 2B). Favorable clinical outcomes were observed for myocardial infarction in the patients who underwent IVUS-guided versus angiography-guided procedures (0% vs. 0.4%, respectively, p = 0.026) (Figure 2D). The occurrence of cardiac death and stent thrombosis was not significantly different between the 2 groups (Figures 2C and 2E).

The results for the subgroup analysis indicated that no statistically significant interactions were present (Figure 3). There were also no signs of between-trial heterogeneity for any of the results (Online Figure 2). A funnel plot analysis did reveal, however, that publication bias might have contributed to the result for the clinical endpoint (Online Figure 3).

TABLE 1 Main Characteristics of the Randomized Controlled Trials Included in the Meta-Analysis

Trial (Year)	Number of Patients: IVUS Guidance	Number of Patients: Angiographic Guidance	Lesion Characteristics	Stent Type	Primary Endpoint	Follow-Up Duration	Results
RESET IVUS (2013)	269	274	Long coronary lesions (implanted stent ≥28 mm long)	Everolimus-eluting stent and zotarolimus-eluting stent	MACEs (composite of cardiac death, MI, TVR, or stent thrombosis)	12 months	Superiority was not demonstrated.
CTO-IVUS (2014)	201	201	Chronic total occlusions	Biolimus-eluting stent and zotarolimus-eluting stent	Cardiac death	12 months	No difference in cardiac death, but IVUS guidance reduced the composite of cardiac death, MI, or TVR.
IVUS-XPL (2015)	700	700	Long coronary lesions (implanted stent ≥28 mm long)	Everolimus-eluting stent	MACEs (composite of cardiac death, target lesion-related MI, and ischemia-driven TLR)	12 months	IVUS reduced MACEs, driven mainly by the reduction of TLR.

CTO-IVUS = Chronic Total Occlusion Intervention With Drug-Eluting Stents Guided by Intravascular Ultrasound; IVUS = intravascular ultrasound; IVUS-XPL = Impact of Intravascular Ultrasound Guidance on Outcomes of XIENCE PRIME Stents in Long Lesions; MACE = major adverse cardiac event(s); MI = myocardial infarction; RESET IVUS = Real Safety and Efficacy of 3-Month Dual Antiplatelet Therapy Following Endeavor Zotarolimus-Eluting Stent Implantation; TLR = target lesion revascularization; TVR = target vessel revascularization.

DISCUSSION

This meta-analysis of 3 randomized trials included individual patient-level data from a total of 2,345 new-generation DES-treated patients. The analysis revealed that compared with angiography-guided DES implantation, IVUS-guided DES implantation for the treatment of complex coronary lesions was associated with a reduction in MACEs. Use of IVUS resulted in a relative risk reduction of 64% for MACE, the composite of cardiac death, myocardial infarction, and stent thrombosis at 1 year. These findings were consistent across the clinical (lesion and patient) subgroups and were stronger according to the per protocol analysis.

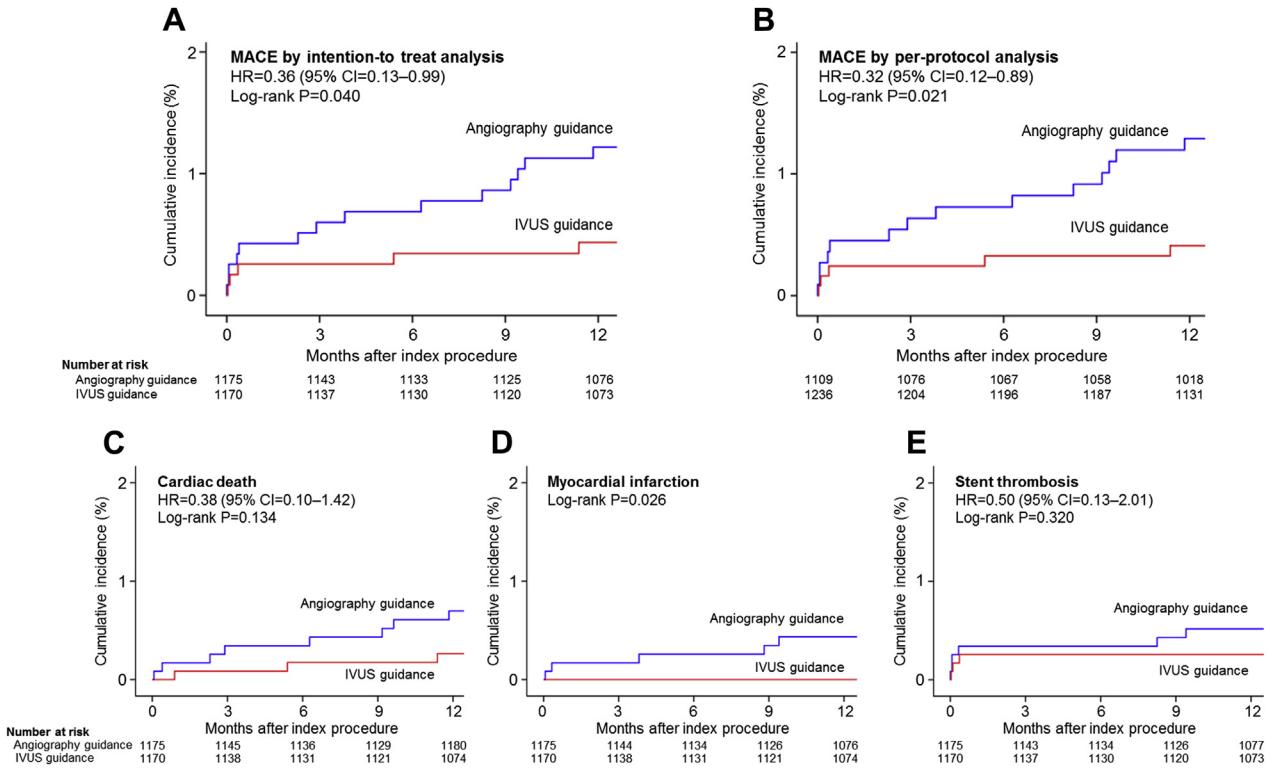
The IVUS-XPL trial was the largest randomized controlled trial performed to date. This trial revealed that 1,400 patients who underwent IVUS-guided everolimus-eluting stent implantation to treat long coronary lesions had an approximately 50% reduction in the 1-year rate of MACEs (5.8% with angiographic guidance vs. 2.9% with IVUS guidance; HR: 0.48; p = 0.007), which was due primarily to the lower risk for TLR (8). However, in that trial, the between-group differences in cardiac death or myocardial infarction were not statistically different because of the relatively low event rate in the patients treated with new-generation DES. The occurrence of cardiac death was 0.4% for the IVUS-guidance arm and 0.7% for the angiography-guidance arm (HR: 0.60; p = 0.48). Myocardial infarction occurred in only 1 patient (0.1%); this patient received an angiography-guided stent (p = 0.32) (8). In the present study, we found that the MACEs (occurrence of cardiac death, myocardial infarction, or stent thrombosis) were significantly less frequent in patients who underwent IVUS-guided DES implantation compared with those who underwent angiography-guided DES implantation (0.4% vs. 1.2%, respectively; HR: 0.36; 95% CI: 0.13 to 0.99; p = 0.040). Notably, in the present study, the primary endpoint did not include TLR.

TABLE 2 Randomized Patient Characteristics, Individual Data

	IVUS Guidance (n = 1,170)	Angiographic Guidance (n = 1,175)	p Value
Age (yrs)	62.9 ± 9.6	63.5 ± 9.4	0.142
Male	822 (70.3)	793 (67.5)	0.161
Clinical presentation			0.396
Stable angina	702 (60.0)	698 (59.4)	
Unstable angina	344 (29.4)	332 (28.3)	
Acute myocardial infarction	124 (10.6)	145 (12.3)	
Diabetes mellitus	405 (34.6)	406 (34.6)	>0.99
Hypertension	745 (63.7)	750 (63.8)	0.972
Dyslipidemia	636 (65.6)	623 (64.0)	0.21
Prior PCI	107 (11.9)	101 (11.2)	0.712
Number of diseased vessels			
1	383 (32.7)	389 (33.1)	
2	415 (35.5)	427 (36.3)	
3	372 (31.8)	359 (30.6)	
Stent type			0.994
Biolimus-eluting stent	101 (8.6)	100 (8.5)	
Everolimus-eluting stent	834 (71.3)	838 (71.3)	
Zotarolimus-eluting stent	235 (20.1)	237 (20.2)	
Number of stents per lesion	1.7 ± 0.9	1.7 ± 0.8	0.544
Total stent length (mm)	43.5 (33-60)	42 (33-56)	0.382
Multivessel PCI	323 (27.6)	314 (26.7)	0.631

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

FIGURE 2 Kaplan-Meier Estimates of Occurrence of Primary and Secondary Endpoints



CI = confidence interval; HR = hazard ratio; IVUS = intravascular ultrasound; MACE = major adverse cardiac event(s).

TABLE 3 Clinical Outcomes at 1 Year Post-Implantation

Clinical Outcomes	Events		Hazard Ratio (95% CI)	p Value by Log-Rank Test
	IVUS Guidance	Angiographic Guidance		
Intention-to-treat analysis	(n = 1,170)	(n = 1,175)		
MACE*	5 (0.4)	14 (1.2)	0.36 (0.13–0.99)	0.040
Cardiac death	3 (0.3)	8 (0.7)	0.38 (0.10–1.42)	0.134
Myocardial infarction	0	5 (0.4)	–	0.026
Stent thrombosis	3 (0.3)	6 (0.5)	0.50 (0.13–2.01)	0.320
Target lesion revascularization	35 (3.0)	57 (5.0)	0.61 (0.40–0.93)	0.020
Per protocol analysis	(n = 1,236)	(n = 1,109)		
MACE*	5 (0.4)	14 (1.3)	0.32 (0.12–0.89)	0.021
Cardiac death	3 (0.2)	8 (0.7)	0.34 (0.09–1.27)	0.090
Myocardial infarction	0	5 (0.5)	–	0.018
Stent thrombosis	3 (0.2)	6 (0.5)	0.45 (0.11–1.79)	0.243
Target lesion revascularization	35 (2.9)	57 (5.3)	0.54 (0.36–0.82)	0.004

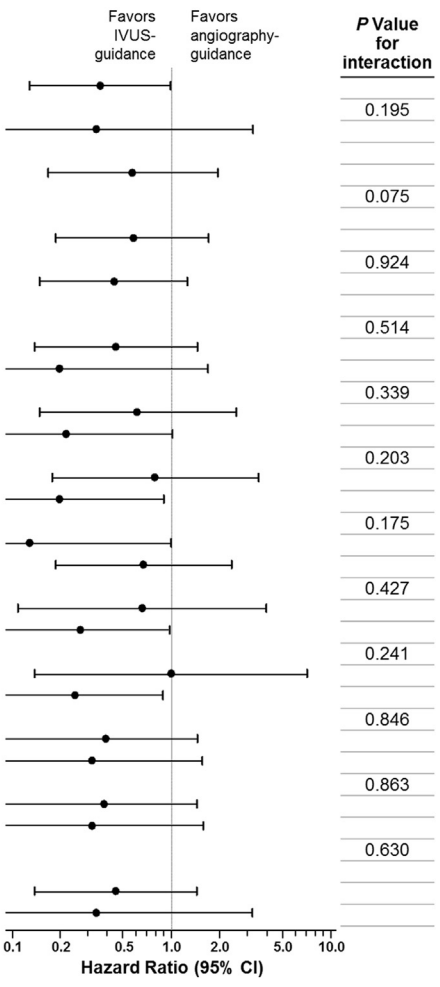
Values are n (%). *Composite of cardiac death, myocardial infarction, and stent thrombosis at 1 year.
CI = confidence interval; IVUS = intravascular ultrasound; MACE = major adverse cardiac event(s).

Therefore, different from the IVUS-XPL trial showing the benefit of IVUS due primarily to the less frequent TLR events, MACEs, even omitting the TLR events in this meta-analysis, were less frequent with IVUS guidance. In addition, consistent with the IVUS-XPL trial, the reduction in TLR with IVUS guidance versus angiographic guidance was also confirmed in the present meta-analysis. TLR was further reduced with IVUS guidance in the as-treated analysis. Therefore, reduction of TLR in complex lesions despite the use of new-generation DES is a major advantage of IVUS guidance.

The results of previous meta-analyses suggest that there was a clinical benefit to the use of IVUS during DES implantation (i.e., a significant reduction in MACEs, stent thrombosis, or TLR) (1-6). However, the proportions of first-generation (Cypher and Taxus) DES used in these studies were substantial. In 1 meta-analysis that included the largest number of DES-treated patients (n = 26,503), the proportion of new-generation DES-treated patients was <45% (4). In addition, most of the studies included in these

FIGURE 3 Subgroup Analysis of Primary Endpoints

	IVUS-guidance		Angiography-guidance		Hazard Ratio (95% CI)	*P* Value for interaction
	No. of events	No. of patients	No. of events	No. of patients		
All patients	**5**	**1170**	**14**	**1175**	**0.36 (0.13–0.99)**	
Study						0.195
RESET IVUS	1	269	3	274	0.34 (0.04–3.25)	
CTO IVUS	0	201	4	201	–	
IVUS XPL	4	700	7	700	0.57 (0.17–1.96)	
Age						0.075
<65 years	0	600	5	587	–	
≥65 years	5	570	9	588	0.58 (0.19–1.72)	
Sex						0.924
Male	5	822	11	793	0.44 (0.15–1.26)	
Female	0	348	3	382	–	
Hypertension						0.514
Yes	4	745	9	750	0.45 (0.14–1.46)	
No	1	425	5	425	0.20 (0.02–1.70)	
Diabetes mellitus						0.339
Yes	3	405	5	406	0.61 (0.15–2.56)	
No	2	765	9	769	0.22 (0.05–1.02)	
Current smoker						0.203
Yes	3	284	4	297	0.79 (0.18–3.53)	
No	2	886	10	878	0.20 (0.04–0.90)	
Clinical presentation						0.175
Stable angina	1	702	8	698	0.13 (0.02–1.00)	
Acute coronary syndrome	4	468	6	477	0.67 (0.19–2.39)	
No. of diseased vessels						0.427
One	2	383	3	389	0.66 (0.11–3.95)	
Two or three	3	787	11	786	0.27 (0.08–0.98)	
Multivessel PCI						0.241
Yes	2	323	2	314	1.00 (0.14–7.10)	
No	3	847	12	861	0.25 (0.07–0.89)	
Number of stents						0.846
<1	3	754	8	778	0.39 (0.10–1.46)	
≥2	2	416	6	397	0.32 (0.06–1.57)	
Stent length						0.863
<43 mm (median value)	3	801	8	817	0.38 (0.10–1.45)	
≥43 mm	2	369	6	358	0.32 (0.07–1.59)	
Type of drug-eluting stent						0.630
Biolimus-eluting stent	0	101	2	100	–	
Everolimus-eluting stent	4	834	9	838	0.45 (0.14–1.45)	
Zotarolimus-eluting stent	1	235	3	237	0.34 (0.04–3.23)	



CTO-IVUS = Chronic Total Occlusion Intervention With Drug-Eluting Stents Guided by Intravascular Ultrasound; IVUS-XPL = Impact of Intravascular Ultrasound Guidance on Outcomes of XIENCE PRIME Stents in Long Lesions; PCI = percutaneous coronary intervention; RESET IVUS = Real Safety and Efficacy of 3-Month Dual Antiplatelet Therapy Following Endeavor Zotarolimus-Eluting Stent Implantation; other abbreviations as in Figure 2.

meta-analyses were observational, rather than randomized controlled, studies, and significant heterogeneity was present in the analyses (1–4). The most recent updated meta-analysis did include only randomized controlled trials with 3,192 patients, but this study also included 792 patients (25%) who received first-generation DES (6). Furthermore, only a study-level analysis was performed by the investigators (6). Our study is the first meta-analysis to use individual patient-level data. It included data from 2,345 patients from randomized trials of the new-generation DES. The results indicated that the use of IVUS had clinical benefits for the hard clinical endpoint, the composite of cardiac death, myocardial infarction, and stent thrombosis.

Because the use of new-generation DES produces better clinical outcomes compared with the use of even first-generation DES, the clinical benefit of IVUS has been estimated to be smaller than previously thought (17–19). Nevertheless, a clinical benefit for the hard clinical endpoint variables was revealed by the present study. This can be partly explained in that the 3 randomized trials included in our present study enrolled patients with complex coronary lesions (e.g., chronic total occlusions and diffuse long lesions). Despite the use of new-generation DES, complex

lesions still have been associated with worse clinical outcomes (20). A randomized trial with 2,292 patients who received zotarolimus- or everolimus-eluting stents revealed that compared with patients with simple lesions, those with complex lesions had higher rates of target-lesion failure (6.3% vs. 9.3%, respectively; $p = 0.015$) and a patient-oriented composite endpoint at 1 year post-implantation (11.6% vs. 16.1%; $p = 0.004$) (20). An analysis of 8,061 everolimus-eluting stent-treated patients by Naidu et al. (21) revealed that total stent length was an independent predictor of stent thrombosis (HR per 10 mm: 1.30; $p < 0.001$). According to National Cardiovascular Data Registry results, patients with chronic total occlusions also had higher rates of MACEs compared with patients with nonchronic total occlusions (1.6% vs. 0.8%; $p < 0.001$) (22). The event rates of stent thrombosis and TLR in the present meta-analysis (0.5% and 5.3% in the angiographic-guidance arm, respectively) were generally similar to those in the previous randomized clinical trial using everolimus-eluting stents (1.0% and 2.4%, respectively) (23), and the clinical benefit in terms of MACEs in the present meta-analysis could be also attributed to the increased power from the use of randomized clinical trial and individual-level data from 2,345 patients. Patient-level meta-analyses compensate for limitations of study-level meta-analyses. This approach resulted in improved internal validity and allowed time-to-event and subgroup comparisons.

STUDY LIMITATIONS. First, the identified randomized trials enrolled only patients with complex coronary lesions. Accordingly, external generalizability should be considered limited. Second, the 1-year follow-up period may not be sufficient for the assessment of long-term clinical outcomes.

CONCLUSIONS

Compared with angiographic guidance, IVUS-guided new-generation DES implantation was associated with favorable outcomes for the composite of cardiac death, myocardial infarction, or stent thrombosis, for complex coronary lesions.

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PERSPECTIVES

WHAT IS KNOWN? Previous meta-analyses have indicated that IVUS-guided DES implantation was associated with a significant reduction in MACEs. These studies included patients who received first-generation DES and used only study-level (not patient-level) data. Published randomized trials that compare IVUS-guided versus angiography-guided new-generation DES implantation are scarce.

WHAT IS NEW? This is the first meta-analysis to use individual patient-level data in new-generation DES–treated patients, and the use of IVUS had clinical benefits for the hard clinical endpoint, the composite of cardiac death, myocardial infarction, and stent thrombosis.

WHAT IS NEXT? An individual-level meta-analysis with a greater number of randomized studies and a larger number of patients is needed to confirm these findings.

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KEY WORDS coronary artery disease, drug-eluting stent(s), intravascular ultrasound

APPENDIX For supplemental data and figures, please see the online version of this article.