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ORIGINAL RESEARCH

Intravascular Ultrasound vs Angiography-Guided Drug-Coated Balloon Angioplasty

The ULTIMATE III Trial

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ABSTRACT

BACKGROUND Drug-coated balloon (DCB) angioplasty seems a safe and effective option for specific de novo coronary lesions. However, the beneficial effect of intravascular ultrasound (IVUS)-guided DCB angioplasty in de novo lesions remains uncertain.

OBJECTIVES This study aimed to assess the benefits of IVUS guidance over angiography guidance during DCB angioplasty in de novo coronary lesions.

METHODS A total of 260 patients with high bleeding risk who had a de novo coronary lesion (reference vessel diameter 2.0-4.0 mm, and lesion length ≤15 mm) were randomly assigned to either an IVUS-guided or an angioplasty-guided DCB angioplasty group. The primary endpoint was in-segment late lumen loss (LLL) at 7 months after procedure. The secondary endpoint was target vessel failure at 6 months.

RESULTS A total of 2 patients in the angiography-guided group and 7 patients in the IVUS-guided group underwent bailout stent implantation ($P = 0.172$). The primary endpoint of 7-month LLL was 0.03 ± 0.52 mm with angiography guidance vs −0.10 ± 0.34 mm with IVUS guidance (mean difference 0.14 mm; 95% CI: 0.02-0.26; $P = 0.025$). IVUS guidance was also associated with a larger 7-month minimal lumen diameter (2.06 ± 0.62 mm vs 1.75 ± 0.63 mm; $P < 0.001$) and a smaller diameter stenosis (28.15% ± 13.88% vs 35.83% ± 17.69%; $P = 0.001$) compared with angiography guidance. Five target vessel failures occurred at 6 months, with 4 (3.1%) in the angiography-guided group and 1 (0.8%) in the IVUS-guided group ($P = 0.370$).

CONCLUSIONS This study demonstrated that IVUS-guided DCB angioplasty is associated with a lower LLL in patients with a de novo coronary lesion compared with angiography guidance. (Intravascular Ultrasound Versus Angiography Guided Drug-Coated Balloon [ULTIMATE-III]; NCT04255043) (J Am Coll Cardiol Intv 2024;■:■-■) © 2024 by the American College of Cardiology Foundation.

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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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ABBREVIATIONS AND ACRONYMS

DCB = drug-coated balloon

DES = drug-eluting stent(s)

ITT = intention-to-treat

IVUS = intravascular ultrasound

LLL = late lumen loss

MI = myocardial infarction

MLD = minimal lumen diameter

PCI = percutaneous coronary intervention

PP = per-protocol population

TVF = target vessel failure

Percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation stands as the most prevalent method for revascularizing coronary artery disease. Unfortunately, concerns persist regarding stent thrombosis and in-stent restenosis, which have spurred the development and clinical use of drug-coated balloon (DCB).[1] The efficacy and safety of DCB have been comprehensively investigated in the context of in-stent restenosis[2,3] and de novo small vessel disease.[4,5] Additionally, emerging studies[6-9] have shown promising outcomes for DCB in the treatment of bifurcation lesions, de novo large vessel disease, and patients at high risk of bleeding.

It has been well-established that intravascular ultrasound (IVUS) guidance could improve clinical outcomes in patients with unprotected left main disease,[10,11] long lesions,[12,13] chronic total occlusion,[14,15] bifurcation lesions,[16,17] and complex lesions[18] undergoing DES implantation. The ULTIMATE (Intravascular Ultrasound Guided Drug Eluting Stents Implantation in "All-Comers" Coronary Lesions) trial[19,20] further confirmed the clinical benefits of IVUS-guided DES implantation in all-comer patients. More recently, a patient-level meta-analysis[21] of 2 large, randomized trials found the use of IVUS-guided DES implantation, in comparison to angiography guidance, improved the long-term cardiac survival. However, the safety and efficacy of IVUS-guided DCB angioplasty have not been systematically assessed in a randomized study. Accordingly, we designed the present multicenter, randomized ULTIMATE III trial to investigate the outcomes of IVUS guidance compared with angiography guidance in patients at high risk of bleeding undergoing DCB angioplasty.

METHODS

TRIAL DESIGN. The ULTIMATE III trial was a prospective, multicenter, randomized, controlled, open-label study to compare IVUS-guided with angiography-guided DCB angioplasty for de novo coronary lesions in patients with high bleeding risk. The trial was registered at ClinicalTrials.gov (NCT04255043). The trial was conducted at 4 centers in China, rigorously adhered to the principles outlined in the Declaration of Helsinki, and received approval from the institutional ethics committees at each participating center. Written informed consent for participation in the trial was obtained from all subjects.

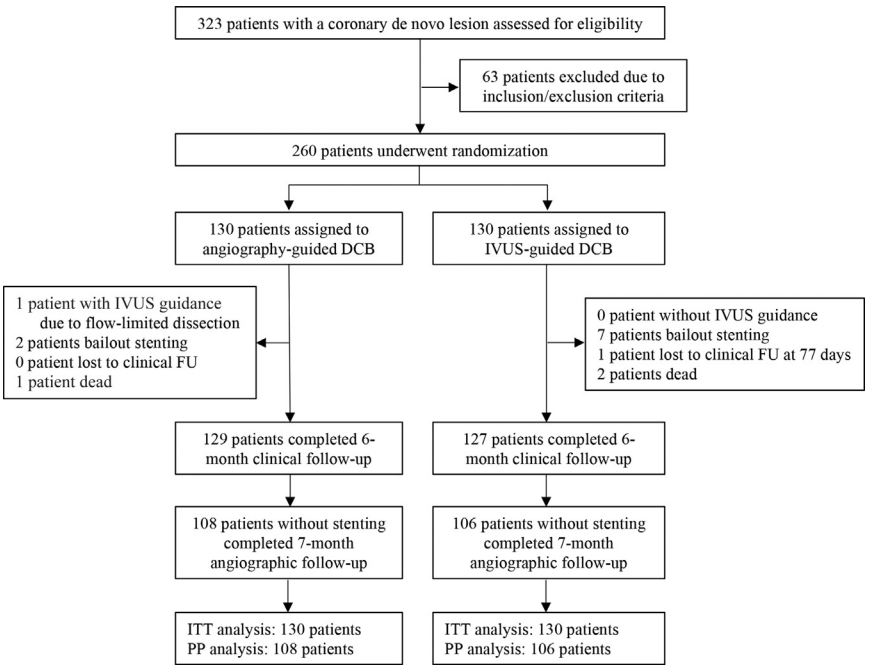
PATIENT SELECTION. Adult patients with an indication for PCI due to silent ischemia, chronic stable or unstable angina, or myocardial infarction (MI) >48 hours before treatment were screened. The patients with high bleeding risk and a de novo coronary lesion (reference vessel diameter 2.0-4.0 mm, and lesion length ≤15 mm) suitable for angioplasty by a DCB were eligible for enrollment. Patients were considered to be at high bleeding risk if at least 1 major or 2 minor criteria were met according to the Academic Research Consortium for High Bleeding Risk (ARC-HBR) consensus.[22] Major and minor criteria for high bleeding risk at the time of PCI were also summarized in Supplemental Table 1. Nontarget lesions were treated at least 1 month before target lesions, and only subjects with nontarget lesions without any clinical events after treatment were included. Patients would be excluded if they had: 1) target lesion length >15 mm; 2) severe calcified lesions; 3) left main disease; 4) ostial lesions; 5) multivessel disease; 6) target vessel received stent implantation; 7) chronic total occlusion lesion not recanalized; 8) intolerant of antithrombotic therapy; 9) hemodynamic instability; or 10) comorbidity with a life expectancy <12 months.

RANDOMIZATION AND MASKING. All eligible subjects were randomly assigned in a 1:1 ratio to receive either IVUS-guided or angiography-guided DCB angioplasty after the pre-PCI angiogram using a central interactive web-based computerized system. Concealed randomization was stratified based on enrolling sites with a block size of 6 for 2 groups. Neither the patients nor the treating physicians were blinded to the treatment procedures, whereas outcome and core laboratory assessors were masked to the allocated group.

PROCEDURES. All procedures were performed according to current guidelines and local practices. Clopidogrel 300 mg (or ticagrelor 180 mg) was administered at least 6 hours before the index procedure and then maintained at 75 mg/day (or ticagrelor 90 mg twice per day). Either unfractionated heparin or bivalirudin was administered during procedure to maintain the activated clotting time at 250 to 350 seconds. Upon discharge from the hospital, all patients received a recommendation for continuing either clopidogrel or ticagrelor for a minimum of 1 month, and the choice between aspirin or a novel oral anticoagulant (dabigatran or rivaroxaban) was at the discretion of the attending physician.

Our protocol mandated very careful lesion predilation, and the predilation was regarded as successful if visual residual stenosis was ≤30%,

FIGURE 1 Study Flowchart



A total of 260 patients with a de novo coronary lesion were randomly assigned to either the intravascular ultrasound (IVUS)-guided drug-coated balloon (DCB) angioplasty group or angiography-guided DCB angioplasty group. FU = follow up; ITT = intention-to-treat; PP = per protocol.

dissection type ≤B, and TIMI flow grade 3. In cases with decreased blood flow (TIMI flow grade ≤2) or type C or worse dissection after predilation, DES implantation was recommended for rescue treatment. DCB angioplasty was performed using all commercially available paclitaxel-eluting balloon in China (SeQuent Please, Braun; Swide, ShenQi Medical; Restore, Cardionovum; Bingo, Yinyi Biotech; Atheris, InnoMed). The technical data of these DCB are listed in Supplemental Table 2. DCB, which had to be 2 to 3 mm longer on each side than the predilation balloon, was inflated at least nominal pressure for a minimal time of 30 seconds, unless there was severe ischemia. Postdilation was not allowed after DCB application. If there was decreased blood flow (TIMI flow grade ≤2) or severe angiographic dissection (type C to F) after DCB angioplasty, bailout stenting with DES was also recommended.

In the angiography-guided group, types of predilation balloon, balloon size, DCB size, and dilation pressure were chosen by visual estimation, with the recommended ratio of balloon/distal reference diameter of 0.8 to 1.0. Angiographic success was defined as TIMI flow grade 3, residual stenosis <30%, and the absence of type ≥ B dissection.

In the IVUS-guided group, the IVUS catheter was advanced at least 10 mm distal to the lesion following the intracoronary administration of nitroglycerin (100-200 mg). IVUS images were acquired using automated pullback, employing a commercially available imaging system equipped with a 40-MHz mechanical transducer (Boston Scientific). Subsequently, all IVUS images were saved onto a DVD for offline analysis. Several key parameters were assessed onsite, including the minimal lumen diameter (MLD), minimal lumen area, reference lumen area, and plaque burden. The minimum lumen area site was identified as the slice with the smallest lumen area. Lesion length was defined as the distance between the distal and proximal reference segments. The reference segment was characterized as a cross-sectional image adjacent to the lesion with <50% plaque burden. Lastly, the maximum diameter of predilation balloon and DCB was determined based on the distal reference, with a ratio of 0.8 to the media diameter or 1:1 to the lumen diameter.

TABLE 1 Baseline Clinical Characteristics

	Angiography Group (n = 130)	IVUS Group (n = 130)	*P* Value
Age, y	67.60 ± 9.91	68.36 ± 9.95	0.537
Age >75 y	45 (34.6)	47 (36.2)	0.795
BMI, kg/m^2	25.64 ± 3.19	25.17 ± 3.13	0.228
Male	105 (80.8)	103 (79.2)	0.756
Hypertension	92 (70.8)	97 (74.6)	0.486
Hyperlipidemia	92 (70.8)	89 (68.5)	0.686
Diabetes mellitus	43 (33.1)	37 (28.5)	0.420
Current smoker	37 (28.5)	38 (29.2)	0.891
Clinical presentation			
Silent ischemia	2 (1.5)	4 (3.1)	0.684
Stable angina	19 (14.6)	14 (10.8)	0.352
Unstable angina	95 (73.1)	96 (73.8)	0.888
NSTEMI	6 (4.6)	11 (8.5)	0.210
STEMI	8 (6.2)	5 (3.8)	0.393
Prior myocardial infarction	11 (8.5)	12 (9.2)	0.827
Prior PCI	22 (16.9)	24 (18.5)	0.745
Prior malignant tumor	3 (2.3)	3 (2.3)	1.000
Prior stroke			
Ischemic stroke	14 (10.8)	9 (6.9)	0.475
Hemorrhagic stroke	1 (0.8)	2 (1.5)	
LVEF, %	60.79 ± 9.23	60.66 ± 8.92	0.906
Peptic ulcer	6 (4.6)	7 (5.4)	0.776
Atrial fibrillation with long-term OAC	14 (10.8)	19 (14.6)	0.352
Lab examination			
Hemoglobin <11 g/dL	18 (13.8)	17 (13.1)	0.856
Hemoglobin 11-12.9 g/dL for men and 11-11.9 g/dL for women	25 (19.2)	32 (24.6)	0.294
Platelet count <100,000/m^3	11 (8.5)	17 (13.1)	0.230
eGFR <60 mL/min/1.73 m^2	21 (16.2)	18 (13.8)	0.602

Values are mean ± SD or n (%).

BMI = body weight index; eGFR = estimated glomerular filtration rate; IVUS = intravascular ultrasound; LVEF = left ventricular ejection fraction; NSTEMI = acute non-ST-segment elevation myocardial infarction; OAC = oral anticoagulation treatment; PCI = percutaneous coronary intervention; STEMI = acute ST-segment elevation myocardial infarction.

FOLLOW-UP. Clinical follow-up was performed through office visits or telephone interviews at 1 and 6 months. Follow-up would be continued annually to 3 years after the index procedure. Follow-up coronary angiography was scheduled at 7 months. Procedural and clinical data were entered into electronic case report forms, verified by independent on-site monitoring, and transmitted to a central database at Nanjing Medical University.

QUANTITATIVE CORONARY ANALYSIS. Quantitative coronary analysis was conducted by skilled technicians who were blind to the study design at a centralized core lab, utilizing the CAAS II system (Pie Medical Imaging). This process, as detailed previously,[23,24] included meticulous angiographic recordings during all pivotal phases. Essential to the protocol were a minimum of two orthogonal projections for initial angiograms, precise angiograms marking the DCB's position dilation, and corresponding post-procedural angiograms. Follow-up angiograms were consistently captured at angles mirroring those used during procedure to ensure comparability. Key metrics such as lesion length, reference vessel diameter, MLD, percentage diameter stenosis, and type of coronary dissection were systematically quantified at baseline, postprocedure, and during follow-up assessments.

STUDY ENDPOINTS AND DEFINITIONS. The primary endpoint of this study was the in-segment late lumen loss (LLL) measured at 7 months following the index procedure. LLL was defined as the difference between the postprocedural MLD and the MLD observed at the time of angiographic follow-up. The major secondary endpoint was target vessel failure (TVF) at 6 months, a composite of cardiac death, target vessel MI, and ischemia-driven target vessel revascularization. Additional secondary endpoints included acute coronary occlusion, spontaneous MI, ischemia-driven target lesion revascularization, bleeding, and the individual components of TVF. Bleeding was defined in accordance to the Bleeding Academic Research Consortium (BARC) classification.[25] Other endpoints were defined according to ULTIMATE trial.[19,20] An independent events committee who was blinded to study design and randomization results (excluded from the original medical documents) assessed all clinical events.

STATISTICAL ANALYSIS. The sample size estimation was performed according to the primary endpoint of LLL. We hypothesized that the 7-month LLL would be 0.20 ± 0.31 mm in the IVUS guidance group and 0.35 ± 0.46 mm in the angiography guidance group on the basis of previous studies and the experts' experience.[26-29] Accordingly, a total of 218 patients were needed to detect a 2-sided alpha level of 0.05 and 80% power. Anticipating a dropout rate of 20% for angiographic follow-up, the planned total sample size of was 130 in each group (260 patients in total).

The intention-to-treat (ITT) population was defined as all patients meeting inclusion and no exclusion criteria who provided informed consent, and were randomized to a treatment group. To form the per-protocol population (PP), we excluded patients from the ITT population with major protocol violations (DES implantation, optical coherence tomography guidance, IVUS usage in angiography guidance group due to complications, or no IVUS usage in the IVUS guidance group), or patients lost to angiographic follow-up. The PP population was the main population for reporting angiographic data

(primary endpoint), and the ITT population was used to report clinical events (secondary endpoint).

Continuous variables are presented as mean ± SD and categorical variables as counts and percentages. We used the Student's *t*-test to compare normally distributed continuous variables. Chi-square or Fisher's exact tests were used to compare categorical variables. Time-to-first event curves were generated using the Kaplan-Meier analysis and compared using the log-rank test. Cox regression was also used to compare the differences in secondary endpoints, with outputs of HR, 95% CI, and *P* values. The 95% CIs presented for secondary endpoints are not adjusted for multiple testing, and inferences drawn from these might not be reproducible. A sensitivity analysis in the ITT population was conducted, and missing data for individuals who did not return for angiographic follow-up were imputed with the mean of valid surrounding values. All statistical analyses were performed at a 2-sided significance level of 0.05 using SAS version 9.4 (SAS Institute).

RESULTS

BASELINE CLINICAL CHARACTERISTICS. From February 2020 to December 2022, a total of 260 patients from 323 screened patients with de novo coronary lesions from 4 Chinese centers were randomized to either IVUS-guided (n = 130) or angiography-guided (n = 130) DCB angioplasty (**Figure 1**). According to the ARC-HBR consensus, there were 128 patients (98.5%) in the IVUS guidance group and 126 patients (96.9%) in the angiography guidance group who were at high risk of bleeding ($P = 0.409$). Of 260 patients in the ITT analysis, 7 patients in the IVUS guidance group and 2 patients in the angiographic guidance group underwent bailout stent implantation ($P = 0.172$), and 1 patient in the angiography guidance group was crossed over to the IVUS guidance group due to flow-limiting dissection after predilation. Finally, 106 patients in the IVUS guidance and 108 patients in the angiography guidance group were enrolled in the PP analysis after excluding patients lost to angiographic follow-up. Baseline clinical characteristics were well matched between the 2 groups (**Table 1**, Supplemental Table 3). The mean age was 68 years. Diabetes and unstable angina were present in 30.8% and 73.5% of the patients, respectively.

LESIONS AND PROCEDURAL CHARACTERISTICS. Baseline lesion characteristics were very similar between the 2 groups (**Table 2**, Supplemental Table 4). The number and type of predilation balloon were matched, but the maximum balloon diameter used for predilation was significantly larger in the IVUS guidance group (2.73 ± 0.47 mm) than that in the angiography guidance group (2.57 ± 0.50 mm; $P = 0.009$). Moreover, IVUS guidance was associated with a larger DCB diameter (2.74 ± 0.46 mm vs 2.56 ± 0.48 mm; $P = 0.005$) and a higher DCB inflation pressure (8.50 ± 1.76 atm vs 7.80 ± 1.85 atm; $P = 0.003$) compared with the angiography guidance group. Baseline lesion features assessed by IVUS are summarized in Supplemental Table 5. Finally, bailout stenting in total was required in 5.4% of patients in the IVUS guidance group and 1.5% of patients in the angiography guidance group ($P = 0.172$).

QUANTITATIVE CORONARY ANALYSIS. Baseline angiographic analyses indicated that lesion length,

TABLE 2 Baseline Lesion and Procedural Characteristics

	Angiography Group (n = 130, 130 Lesions)	IVUS Group (n = 130, 130 Lesions)	*P* Value
Target vessel			
LAD	60 (46.2)	60 (46.2)	0.308
LCx	44 (33.8)	35 (26.9)	
RCA	26 (20.0)	35 (26.9)	
Chronic total occlusion	13 (10.0)	15 (11.5)	0.842
True bifurcation lesion	4 (3.1)	9 (6.9)	0.155
Predilation	130 (100)	130 (100)	NS
Semicompliant balloon	97 (74.6)	90 (69.2)	0.334
Noncompliant balloon	25 (19.2)	37 (28.5)	0.081
Scoring balloon	73 (56.2)	63 (48.5)	0.214
Cutting balloon	7 (5.4)	11 (8.5)	0.328
Number of predilation balloons	1.55 ± 0.57	1.54 ± 0.57	0.914
Maximum balloon diameter, mm	2.57 ± 0.50	2.73 ± 0.47	0.009
Bailout stenting after predilation	1 (0.8)	5 (3.8)	0.213
DCB treatment	129 (99.2)	125 (96.2)	0.213
Paclitaxel-coating balloon	129 (100)	125 (100)	NS
DCB brand			
SeQuent	71 (55.0)	70 (56.0)	0.878
Chinese domestic DCB	58 (45.0)	55 (44.0)	
Swide	15 (25.9)	13 (23.6)	0.990
Restore	6 (10.3)	6 (10.9)	
Bingo	26 (44.8)	26 (47.3)	
Atheris	11 (19.0)	10 (18.2)	
DCB diameter, mm	2.56 ± 0.48	2.74 ± 0.46	0.005
DCB inflation pressure, atm	7.80 ± 1.85	8.50 ± 1.76	0.003
DCB inflation time, s	54.38 ± 7.58	54.04 ± 7.34	0.717
Bailout stenting after DCB	1 (0.8)	2 (1.6)	0.618
Bailout stenting in total	2 (1.5)	7 (5.4)	0.172
Final dissection type,[a] n	128	123	
No dissection	67 (52.3)	56 (45.5)	0.460
Type A	51 (39.8)	54 (43.9)	
Type B	7 (5.5)	12 (9.8)	
Type C	2 (1.6)	1 (0.8)	
Type D	1 (0.8)	0	

Values are n (%) or mean ± SD unless otherwise indicated. [a]Patients with bail-out stenting are excluded in the analysis of dissection type.

DCB = drug-coated balloon; IVUS = intravascular ultrasound; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

TABLE 3 Quantitative Coronary Analysis

	Angiography Group (n = 130)	IVUS Group (n = 130)	*P* Value
Baseline			
Lesion length, mm	16.41 ± 6.15	17.53 ± 6.44	0.170
Minimum lumen diameter, mm	0.98 ± 0.54	0.99 ± 0.51	0.881
Reference vessel diameter, mm	2.69 ± 0.61	2.76 ± 0.63	0.317
Diameter stenosis, %	63.50 ± 17.79	63.61 ± 17.92	0.959
Postprocedure,[a] n	128	123	
Minimum lumen diameter, mm	1.78 ± 0.48	1.93 ± 0.54	0.019
Reference vessel diameter, mm	2.69 ± 0.57	2.80 ± 0.62	0.135
Diameter stenosis, %	33.68 ± 11.53	31.16 ± 11.74	0.088
Acute lumen gain, mm	0.80 ± 0.47	0.93 ± 0.58	0.038
Angiographic follow-up[b]	108 (83.1)	106 (81.5)	0.745
Angiographic follow-up time, d	222.38 ± 36.94	228.0 ± 36.87	0.267
Coronary dissection type			
No dissection	106 (98.1)	102 (96.2)	0.239
Type A	1 (0.9)	4 (3.8)	
Type B	1 (0.9)	0	
Minimum lumen diameter, mm	1.75 ± 0.63	2.06 ± 0.62	<0.001
Reference vessel diameter, mm	2.71 ± 0.58	2.86 ± 0.61	0.081
Diameter stenosis, %	35.83 ± 17.69	28.15 ± 13.88	0.001
Late lumen loss, mm	0.03 ± 0.52	−0.10 ± 0.34	0.025

Values are mean ± SD or n (%) unless otherwise indicated. [a]Patients with bailout stenting are excluded. [b]Patients with bailout stenting, all-cause death, and lost to angiographic follow-up are excluded.
IVUS = intravascular ultrasound.

MLD, reference vessel diameter, and diameter stenosis were well matched in the 2 groups (**Table 3**). The acute postprocedural result was better in the IVUS guidance group than that in the angiography guidance group, with a larger final in-segment MLD (1.93 ± 0.54 mm vs 1.78 ± 0.48 mm; $P = 0.019$) and acute lumen gain (0.93 ± 0.58 mm vs 0.80 ± 0.47 mm; $P = 0.038$).

Seven-month angiographic follow-up was available in 106 patients (81.5%) in the IVUS guidance group and 108 patients (83.1%) in the angiography guidance group, with the matched angiographic follow-up time (231 [210-253] days vs 224 [206-249] days; $P = 0.185$). The primary endpoint of 7-month LLL was 0.03 ± 0.52 mm with angiography guidance vs −0.10 ± 0.34 mm with IVUS guidance (mean difference 0.14 mm; 95% CI: 0.02-0.26; $P = 0.025$) (**Central Illustration**). Sensitivity analysis found 7-month LLL was 0.04 ± 0.49 mm in the angiography-guided group and −0.11 ± 0.32 mm in the IVUS-guided group ($P = 0.007$) by imputing missing data in the ITT population. IVUS guidance was also associated with a larger 7-month MLD (2.06 ± 0.62 mm vs 1.75 ± 0.63 mm; $P < 0.001$) (Supplemental Figure 1) and a smaller diameter stenosis (28.15% ± 13.88% vs 35.83% ± 17.69%; $P = 0.001$) compared with angiography guidance. Furthermore, the brand of DCB did not affect the primary endpoint outcome (SeQuent vs others: −0.051 ± 0.457 mm vs −0.014 ± 0.436 mm; $P = 0.549$).

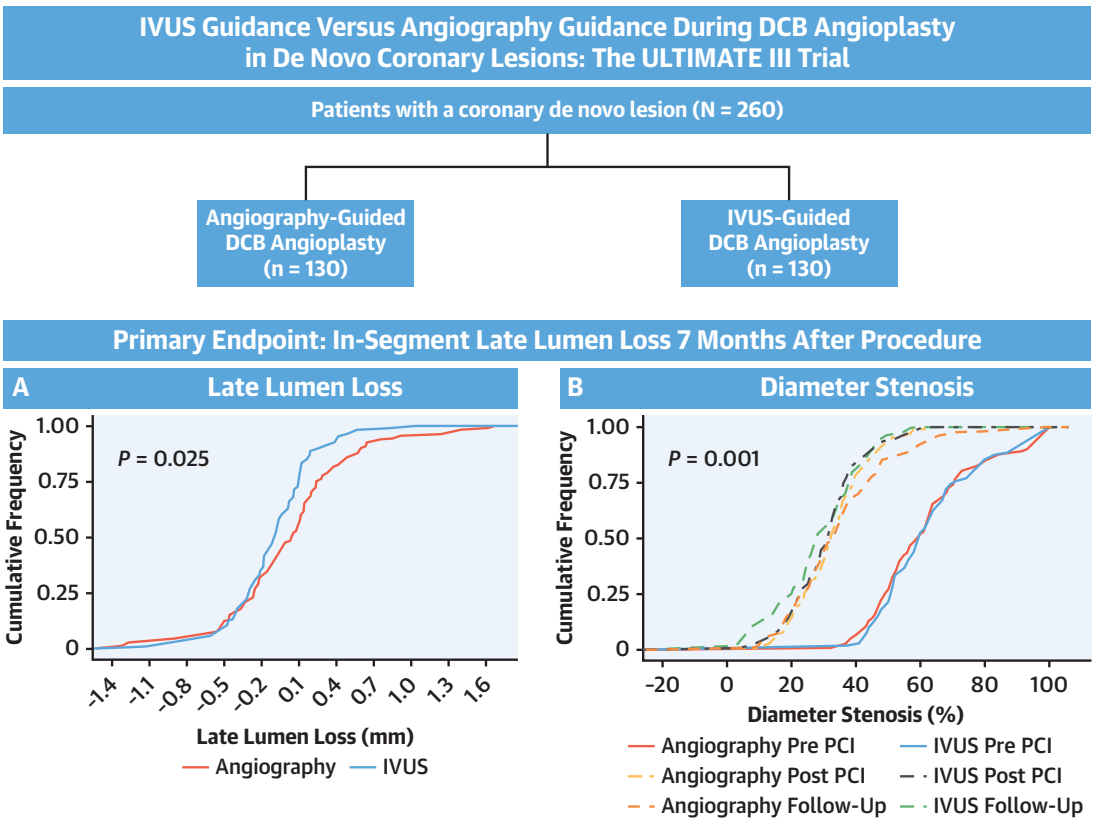
CLINICAL OUTCOMES. During the hospitalization, no death and acute coronary occlusion after procedure occurred (**Table 4**). Only 1 patient in the IVUS guidance group was lost to clinical follow-up at 77 days after the index procedure. In the angiography guidance group, dual antiplatelet therapy was maintained in 80% of patients at 30 days, 53.8% of patients at 90 days, and 16.9% of patients at 180 days, while the corresponding percentages in the IVUS guidance group were 73.8% ($P = 0.239$), 49.2% ($P = 0.457$), and 17.7% ($P = 0.870$), respectively. By 180 (180-180) days after the index procedure, 5 TVFs were observed, with 4 (3.1%) in the angiography guidance group and 1 (0.8%) in the IVUS guidance group ($P = 0.370$). The detailed information of all-cause death and TVF are summarized in Supplemental Table 6. Differences in cardiac death, target vessel MI, ischemia-driven target lesion revascularization, and bleeding (BARC type 2, 3, and 5) were also insignificant between the 2 groups.

DISCUSSION

To our knowledge, the current trial reports for the first time the benefit of IVUS guidance over angiography guidance in patients with a de novo coronary lesion who underwent DCB angioplasty. We found a significant improvement of LLL at 7-month follow-up when DCB angioplasty was guided by IVUS, compared with angiography-guided procedures. It seems there are no apparent between-group differences in the incidence of procedure-related safety events.

The motivation not to leave the metal behind remains, and with the reduction in use of bioresorbable vascular scaffolds, DCB remains an attractive option to meet this goal. DCB offers several advantages over DES, as DCB do not leave behind a metallic mesh, ensuring a uniform drug distribution, promoting positive vessel remodeling (larger MLD observed during the follow-up), and potentially allowing for a shorter duration of dual antiplatelet therapy.[1,6] Clinical studies employing DCB have yielded promising results in the treatment of in-stent restenosis,[2,30,31] and more recent study has shown that DCB demonstrates equivalent safety and efficacy to DES in cases of de novo small vessel disease.[4,5] However, to date, the available data do not support broad usage of DCB for de novo lesions. In our current study, we found favorable results, with only an 0.8% incidence of periprocedural MI, no occurrences of acute coronary occlusion, and only a 1.9% rate of TVF at 6 months following paclitaxel DCB angioplasty with a mean reference vessel diameter of 2.73 mm. Our study shows that paclitaxel DCB angioplasty appears to be a

CENTRAL ILLUSTRATION **Intravascular Ultrasound- or Angiography-Guided Drug-Coated Balloon Angioplasty in Patients With a De Novo Coronary Lesion**



The curves depict the cumulative distribution functions for the primary endpoint, late lumen loss (A), and the diameter stenosis preprocedure, postprocedure, and at follow-up (B). The provided *P* values represent the comparison between intravascular ultrasound (IVUS)-guided and angiography-guided drug-coated balloon (DCB) angioplasty at the 7-month follow-up. ULTIMATE III = Intravascular Ultrasound Guided Drug Eluting Stents Implantation in "All-Comers" Coronary Lesions.

safe and feasible option for specific patients at high risk of bleeding with low rates of procedure-related complications and 6-month TVF.

Currently, no clinical trials have investigated the clinical outcomes of IVUS-guided DCB angioplasty for de novo coronary lesions. A previous study[32] has reported that adequate lesion preparation before DCB angioplasty is associated with improved long-term outcomes. A large inflation pressure with the predilation balloon may lead to severe dissection, whereas insufficient inflation may result in worsening long-term outcomes.[32] Larger predilation balloon diameter and DCB diameter were used in the IVUS guidance group, with larger DCB dilation at higher pressures, resulting in a larger MLD post-DCB angioplasty, which could be the most important reason for the improved 7-month LLL (an extensively used surrogate efficacy endpoint) in the IVUS guidance group. Importantly, patients in the IVUS guidance group had a higher trend of rescuing stent implantation after more aggressive dilation compared with angiography guidance. Fortunately, very few patients required bailout stenting, and the risk of procedure-related safety events were comparable between the 2 groups. Moreover, although the difference was not statistically significant, we found a lower trend of TVF with IVUS guidance compared with angiography guidance during 6-month follow-up after DCB

TABLE 4 Clinical Follow-Up

	Angiography Group (n = 130)	IVUS Group (n = 130)	*P* Value
In-hospital events			
All-cause death	0	0	NS
Periprocedural MI	1 (0.8)	1 (0.8)	1.000
Acute coronary occlusion after procedure	0	0	NS
TLR	0	0	NS
6-mo follow-up[a]			
Target vessel failure	4 (3.1)	1 (0.8)	0.370
All-cause death	1 (0.8)	2 (1.5)	1.000
Cardiac death	0	0	1.000
Target vessel MI	1 (0.8)	1 (0.8)	1.000
Spontaneous MI	0	0	NS
Ischemia-driven TLR	1 (0.8)	0	1.000
Ischemia-driven TVR	3 (2.3)	0	0.247
Bleeding (BARC type 2, 3, and 5)	10 (7.7)	12 (9.2)	0.656

Values are n (%). [a]One patient in the intravascular ultrasound (IVUS) guidance group was lost to clinical follow-up at 77 days after procedure.

BARC = Bleeding Academic Research Consortium; DAPT = dual-antiplatelet therapy; MI = myocardial infarction; TLR = target lesion revascularization; TVR = target vessel revascularization.

angioplasty. Of note, we do not know whether the benefits of LLL in IVUS-guided group over angiograph guidance can translate to the improvement of clinical outcomes. A large, randomized trial with long-term clinical follow-up could find the improved clinical outcomes of IVUS guidance during DCB angioplasty.

The primary objective of this trial was to enroll patients deemed at high risk for bleeding and unsuitable for prolonged dual antiplatelet therapy. All eligible patients with relatively simple lesion were also candidates for DCB angioplasty, with the intention of reducing the duration of dual antiplatelet therapy. Despite the fact that the majority of patients (85%) presented with acute coronary syndrome, only 17.3% of them continued dual antiplatelet therapy at 6 months postprocedure. As anticipated in this high-risk population, the 6-month bleeding rate was substantial, with 7.3% of patients meeting the criteria for BARC types 2 to 5 bleeding. Importantly, this bleeding rate was similar in both study groups. It is noteworthy that the optimal duration of antiplatelet therapy for patients with high bleeding and ischemic risk undergoing DCB angioplasty remains uncertain. Consequently, there is a pressing need for further randomized trials to investigate the safety and efficacy of DCB angioplasty in these high-risk patients, and also explore whether the duration of dual antiplatelet therapy can be further shortened.

STUDY LIMITATIONS. First, it is important to note that the primary endpoint of this study was angiographic. Further investigation is needed in larger trials that are adequately powered to detect differences in clinical endpoints. Second, only patients with de novo coronary lesions were enrolled in this trial. As a result, the findings may not be broadly applicable to patients with in-stent restenosis. Third, all DCBs used in this study were paclitaxel DCBs. Consequently, the effect of IVUS-guided newer sirolimus DCBs for the treatment of de novo lesions remains uncertain. Fourth, patients with relatively simple lesions and with high bleeding risk were enrolled in the current study, so the results cannot be generalized to those with complex lesions and non-high bleeding risk.

CONCLUSIONS

Our study showed that paclitaxel DCB angioplasty appears to be a safe and feasible option for specific patients at high risk of bleeding with low rates of procedure-related complications and 6-month TVF. In the present multicenter randomized trial in patients with a de novo coronary lesion, IVUS-guided DCB angioplasty resulted in a lower LLL at 7 months compared with angiography guidance.

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PERSPECTIVES

WHAT IS KNOWN? IVUS guidance improves clinical outcomes in patients undergoing DES implantation, especially in coronary complex lesions.

WHAT IS NEW? IVUS-guided DCB angioplasty is associated with a lower late lumen loss in patients with a de novo coronary lesion compared with that following angiography guidance.

WHAT IS NEXT? Further randomized trials are warranted to investigate whether IVUS-guided DCB angioplasty could improve clinical outcomes.

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KEY WORDS de novo coronary lesion, drug-coated balloon, intravascular ultrasound, late lumen loss

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