Impact of Stent Size Selection on Acute and Long-Term Outcomes After Drug-Eluting Stent Implantation in De Novo Coronary Lesions

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Background—Although significant undersizing often results in incomplete stent apposition or underexpansion, the possible impact of oversized stent implantation on arterial wall injury has not been systematically investigated with drug-eluting stents. The aim of this study was to investigate the impact of stent oversizing on acute and long-term outcomes after drug-eluting stents implantation in de novo coronary lesions.

Methods and Results—Serial (baseline and 6–12 months) coronary angiography and intravascular ultrasound were performed in 2931 lesions treated with drug-eluting stents (355 sirolimus, 846 paclitaxel, 1387 zotarolimus, and 343 everolimus). The percentage of stent oversizing to angiographic reference vessel diameter (RVD) was calculated as (nominal stent diameter–RVD)/RVD×100 (%). Clinical outcomes, including target lesion revascularization and stent thrombosis, were followed for 1 year. Overall, smaller preintervention RVD was associated with higher percentage of stent oversizing (P<0.001). The significant oversizing group underwent less post-dilatation (P=0.002) but achieved greater stent expansion (P<0.001) and less incomplete stent apposition (P<0.001) without increase of edge dissection after procedure. When stratified by vessel size and stent oversizing, progressive decreases of restenosis (P=0.002) and target lesion revascularization rates (P=0.007) were found in favor of larger vessel size and oversized stents. Stent thrombosis was observed the most in small RVD with low percentage of stent oversizing group among the subgroups (P=0.040).

Conclusions—The positive impact of stent oversizing was documented on procedural and clinical outcomes. In particular, small vessels treated with smaller stents were associated with greater adverse events, suggesting that aggressive selection of larger stents, with appropriate attention to edge effects, may optimize long-term outcomes, even in drug-eluting stents implantation. **(*Circ Cardiovasc Interv*. 2017;10:e004795. DOI: 10.1161/CIRCINTERVENTIONS.116.004795.)**

Key Words: dilatation ■ drug-eluting stent ■ everolimus ■ stents ■ thrombosis

In the bare-metal stent era, numerous studies have shown a strong association between small final stent dimensions at post-deployment and in-stent restenosis at follow-up,[1–3] which led to the so-called bigger-is-better strategy for bare-metal stent optimization. After the introduction of drug-eluting stents (DES), several studies have consistently demonstrated that DES have considerably lower optimal thresholds of final stent dimensions to predict subsequent restenosis because of significant suppression of neointimal proliferation within the stent.[4] Combined with the fact that some early DES trials demonstrated a relatively high incidence of restenosis at the stent edge segment, the stenting procedure in the DES era has changed from the aggressive to the adequate strategy. In clinical settings, however, final stent expansion often fails to meet expected stent dimensions after DES implantation.[5] Furthermore, there is compelling clinical evidence that significant stent undersizing of DES often ends up with suboptimal results, particularly stent underexpansion, which can lead to adverse clinical events, such as restenosis and stent thrombosis.[6–8] Therefore, selection of proper device size relative to the target vessel may be considered as important as post-deployment optimization strategy. Recently, the importance of accurate device sizing has also gained further attention due to the introduction of bioresorbable scaffold technology into the clinical arena because polymer-based devices cannot be overly dilated after implantation.

At the other end of this spectrum, however, potential effects of oversized stent implantation on arterial wall injury and vascular response have not been systematically evaluated. Thus, the aim of this study was to investigate the impact of stent oversizing on acute and long-term outcomes after DES implantation in de novo coronary lesions.

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WHAT IS KNOWN

- Final stent expansion often fails to meet expected stent dimensions after drug-eluting stent implantation, and suboptimal stent expansion can lead to adverse clinical events.
- Although selection of drug-eluting stent size relative to the target vessel is considered as important as postdeployment optimization strategy, the impact of oversized stent implantation on acute and long-term outcomes remains unclear.

WHAT THE STUDY ADDS

- Aggressive selection of larger drug-eluting stent, with appropriate attention to edge effects under intravascular ultrasound guidance, may result in greater stent expansion, without significant increase in residual edge dissection.
- Furthermore, long-term adverse events may be reduced by stent oversizing, especially in small vessels, without accelerated restenosis or plaque progression at the stent edge.

Methods

Study Population

The original study data were pooled at both patient and lesion levels from 14 DES trials with similar inclusion and exclusion criteria: SIRIUS (A Multicenter, Randomized, Double-Blind Study of the Sirolimus-Coated BX VELOCITY Balloon-Expandable Stent in the Treatment of Patients With De Novo Coronary Artery Lesions),[4] NEVO ResElution-I (A Randomized, Multi-Center, Single-Blind Comparison of the Conor Cobalt Chromium Reservoir Based Stent With Sirolimus Elution Versus the TAXUS Liberte Paclitaxel-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions),[9] J-DESsERT (A Japanese Prospective, Randomized, Multi-Center Trial Comparing the TAXUS Stent and the CYPHER Stent in Patients With Coronary Artery Disease Eligible for PCI),[10] ZoMaxx I and ZoMaxx II (A Randomized, Controlled Trial to Evaluate the Safety and Efficacy of the ZoMaxx Drug Eluting Coronary Stent System Compared to the TAXUS Express2 Paclitaxel-Eluting Coronary Stent System in de Novo Coronary Artery Lesions),[11] ENDEAVOR I (The Clinical Evaluation of the Medtronic AVE ABT-578 Coated Driver Coronary Stent in De Novo Native Coronary Artery Lesions),[12] ENDEAVOR II (Randomized Controlled Trial to Evaluate the Safety and Efficacy of the Medtronic AVE ABT-578 Eluting Driver Coronary Stent in De Novo Native Coronary Artery Lesions),[13] ENDEAVOR II Continued Access (Randomized Controlled Trial to Evaluate the Safety and Efficacy of the Medtronic AVE ABT-578 Eluting Driver Coronary Stent in De Novo Native Coronary Artery Lesions Continued Access),[14] ENDEAVOR III (A Randomized Controlled Trial of the Medtronic Endeavor Drug Eluting Coronary Stent System Versus the Cypher Sirolimus-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions),[15] ENDEAVOR IV (A Randomized, Controlled Trial of the Medtronic Endeavor Drug Eluting Coronary Stent System Versus the Taxus Paclitaxel-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions),[16] RESOLUTE FIM (The Clinical Response Evaluation of the Medtronic Endeavor CR ABT-578 Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions),[17] RESOLUTE US (A Clinical Evaluation of the Medtronic Resolute Zotarolimus-Eluting Coronary Stent System in the Treatment of De Novo Lesions in Native Coronary Arteries With a Reference Vessel Diameter of 2.25 mm to 4.2mm),[18] and SPIRIT III and SPIRIT III Japan (A Clinical Evaluation of the Investigational Device XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects With De Novo Native Coronary Artery Lesions)[19] (Table I in the Data Supplement). The study designs and primary results have been previously reported. These trials were conducted in accordance with virtually identical inclusion and exclusion criteria. In brief, they were prospective, multicenter, randomized, or nonrandomized trials to evaluate the safety and efficacy of DES in stable or unstable angina patients with 1 or 2 de novo lesions in native coronary arteries with a diameter of 2.25 to 4.25 mm. The major exclusion criteria of these trials included acute myocardial infarction, stroke, impaired left ventricular function (ejection fraction 30%), ostial or left main lesions, and previously treated lesions. In these trials, the intravascular ultrasound (IVUS) cohorts were configured with volumetric IVUS studies prescheduled at baseline and midterm (6–12 months) follow-up. From these IVUS cohorts, patients with analyzable quantitative coronary angiography (QCA) data, who had undergone successful treatment with Cypher sirolimus-eluting stents, Taxus paclitaxel-eluting stents, Endeavor/Resolute/ZoMaxx zotarolimus-eluting stents, or Xience V everolimus-eluting stents, were enrolled in this analysis. Clinical outcomes, including target lesion revascularization (TLR) and stent thrombosis, were followed for 1 year. TLR was defined as any repeat percutaneous coronary intervention for the target lesion or bypass surgery of the target vessel, and stent thrombosis included definite and probable events according to Academic Research Consortium definitions.[20] The study protocol for each clinical trial was approved by the institutional review board at each participating site, and eligible patients signed written informed consent before the interventional procedure.

QCA Analysis

Coronary angiograms performed at baseline and follow-up were reviewed by an independent angiographic core laboratory in each trial (Cardiovascular Research Foundation, New York, NY, or Beth Israel Deaconess Medical Center, Boston, MA) using a standard manner. Reference vessel diameter (RVD) and minimum lumen diameter were measured in the target segment. Percent diameter stenosis (%DS) was calculated as (1−minimum lumen diameter/RVD)×100. In the DES trials included in this analysis, angiographic end points were standard binary restenosis (%DS ≥50%) and late loss (minimum lumen diameter at post-intervention−minimum lumen diameter at follow-up) by QCA.

IVUS Analysis

IVUS was performed in a standard fashion using automated 0.5 mm/s pullback with a commercially available imaging system (40-MHz IVUS catheter, Boston Scientific Corp, Natick, MA; or 20-MHz IVUS catheter, Volcano Corp, San Diego, CA) at baseline and follow-up. IVUS analysis was conducted in an independent core laboratory (Stanford Cardiovascular Core Analysis Laboratory, Stanford, CA), and analysts were blinded to clinical characteristics, angiographic information, and randomization assignments. Volumetric measurements were performed using validated software (echoPlaque; Indec Systems, Santa Clara, CA). Volume index (VI, volume/length, mm^3/mm) was calculated for the vessel, lumen, plaque, stent, and neointima in the stented segment. Vessel, lumen, and plaque VI were also obtained for the stent margins, 5 mm proximal and distal to the stent. Percent neointimal volume was calculated as neointimal volume divided by stent volume (%). Cross-sectional narrowing (%) was defined as neointimal area divided by stent area. Incomplete stent apposition (ISA) was defined as ≥1 stent strut clearly separated from the vessel wall, with evidence of blood speckles behind the strut in a vessel segment not associated with any side branches. Late-acquired ISA was defined as newly developed ISA at follow-up in the segment where struts were completely apposed to the vessel wall at baseline. Any edge dissection detected as a fissure or separation within intima or plaque was counted. Stent expansion at baseline was calculated as minimum stent area divided by the average of proximal and distal reference lumen areas.

Percent Stent Oversizing

For evaluating the degree of stent oversizing relative to the vessel size, the percentage of stent oversizing (%SO) against angiographic pre-intervention RVD was calculated as (nominal stent diameter–RVD)/RVD×100 (%). In lesions with >1 stents overlapped, average nominal stent diameter was applied for the calculation. Because preintervention RVD itself is known as one of the determinants of clinical outcomes, possible impact of stent oversizing was further investigated by stratifying the lesions by vessel size (ie, small versus large RVD lesions).

Statistical Analysis

Statistical analysis was performed using JMP 10.0 (SAS Institute, Cary, NC). Categorical variables are presented as numbers and percentages and were compared using χ^2 test or Fisher exact test. All pairwise comparisons among the 4 stratified groups were conducted using χ^2 test with a Bonferroni correction. Continuous variables are presented as mean±SD. Comparisons of the mean of continuous variables among the 4 stratified groups were done with the general F test for ANOVA with a post hoc comparison using the Tukey honestly significant difference test. When the homoscedasticity was not verified by the Levene test, the mean of continuous variables was compared using Welch ANOVA with a post hoc comparison using Welch t test with a Bonferroni correction. Correlation between preintervention RVD and %SO was examined using a polynomial regression model. A nominal P<0.05 was considered statistically significant. Forward stepwise multivariate logistic regression models were used to determine independent predictors of TLR and stent thrombosis. Major clinical, procedural, angiographic, and IVUS variables with P<0.05 in univariate models were included simultaneously in multivariate models. For predictors of TLR, because the incidence of TLR decreased stepwise in favor of larger vessel size and oversized stents, the 4 groups were scored as 1 to 4 to be included in these models. For predictors of stent thrombosis, the small RVD with low %SO was used as a binary parameter because of its remarkably high incidence of stent thrombosis compared with the other 3 groups. The variables representing vessel, lumen, and stent dimensions were excluded because of their significant correlations with 4 stratified subgroups by RVD and %SO. In addition, number of stents, rate of multiple stent implantations, and lesion length were excluded because these variables were strongly correlated with total stent length.

Results

Study Population and Clinical Characteristics

A total of 2931 lesions in 2808 patients treated with sirolimus-eluting stents (n=335), paclitaxel-eluting stents (n=846), zotarolimus-eluting stents (n=1387 [Endeavor, n=853; Resolute, n=211; and ZoMaxx, n=323]), and everolimus-eluting stents (n=343) were enrolled in the present study. Patient characteristics in the overall population are shown in Table 1. The mean age was 62.8 years old, 71.4% of patients were men, and 41% presented with unstable angina.

Table 1. Patient Characteristics

	Total Patients (n=2808)
Age, y	62.8±10.7
Male (%)	71.4
Unstable angina (%)	41.1
Hypertension (%)	74.6
Hyperlipidemia (%)	80.1
Diabetes mellitus (%)	27.3
Prior myocardial infarction (%)	23.4
Prior PCI (%)	24.1
Prior bypass surgery (%)	5.4
Current smoking (%)	24.4
Family history of coronary artery disease (%)	39.3

PCI indicates percutaneous coronary intervention.

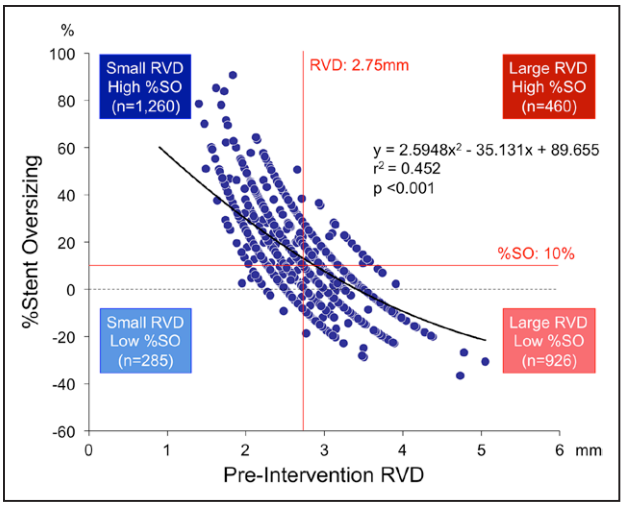

Figure 1. Relationship between reference vessel diameter (RVD) and %stent oversizing (%SO). Overall, smaller preintervention RVD was significantly associated with higher %SO. For further analysis, lesions were stratified into 4 groups by vessel size (RVD ≥ or < 2.75 mm) and stent oversizing (%SO ≥ or < 10%).

Relationship Between RVD and %SO, and Stratification Into 4 Groups

Overall, smaller preintervention RVD significantly correlated with higher %SO (r^2=0.452; P<0.001; Figure 1). Significant stent oversizing (high %SO, defined as %SO ≥10%) was found in 82% of the small RVD (<2.75 mm) group and 33% of the larger RVD (≥2.75 mm) group. For further analysis, lesions were stratified into 4 groups by vessel size (RVD ≥ or < 2.75 mm) and stent oversizing (%SO ≥ or < 10%). Among the 4 groups, DES type did not differ (P=0.525) while there were several differences in lesion and other procedural characteristics (Table 2). Of note, the lesions with low %SO included more type B2/C lesions and underwent more overall and upsizing post-dilatations. The total number of stents used and total stent length were not significantly different among the 4 groups, whereas the use of multiple stents was most frequent in the small RVD with low %SO group (Table 2).

QCA Results

QCA results were summarized in Table 3. Despite the similar %DS at pre-intervention among the 4 groups, %DS at post-intervention was significantly higher in lesions with low %SO compared with those with high %SO. At follow-up, %DS was also numerically (small RVD groups) or significantly (large RVD groups) higher in lesions with low %SO compared with those with high %SO. The rate of binary restenosis at follow-up was significantly lower in lesions with large RVD than those with small RVD and the lowest in the large RVD with high %SO group (Figure 2). With respect to edge effect,

Table 2. Lesion and Procedural Characteristics

	Total (n=2931)	Small RVD Low %SO	Small RVD High %SO	Large RVD Low %SO	Large RVD High %SO	*P* Value
Stent type (SES/PES/ZES/EES, %)	12/29/47/12	12/28/46/14	12/29/47/12	12/31/47/10	13/25/49/13	0.525
Target vessel (LAD/LCX/RCA, %)	45/23/32	40/35/25	51/26/22*	41/18/40*†	38/14/48*†	<0.001
Type B2/C (%)	70.1	73.1	65.0	75.6†	71.1	<0.001
Total number of stents (n)	1.18±0.44	1.22±0.49	1.19±0.44	1.16±0.44	1.17±0.43	0.161
Multiple stents used (%)	15.4	18.6	16.8	13.1	14.6	0.044
Mean stent diameter, mm	3.06±0.38	2.56±0.17	2.93±0.31*	3.18±0.30*†	3.51±0.11*†‡	<0.001
Total stent length, mm	23.2±9.3	24.0±9.5	23.2±9.1	23.2±9.9	22.7±8.3	0.370
Post-dilatation (%)	54.1	55.7	51.0	58.2†	53.3	0.010
Upsizing post-dilatation (%)	42.9	49.8	37.0*	52.7†	34.8*‡	<0.001
Maximum balloon diameter, mm	3.22±0.75	2.82±1.08	3.02±0.36*	3.40±0.47*†	3.65±1.28*†‡	<0.001
Maximum balloon pressure, atm	15.4±3.2	15.5±3.3	14.9±3.1	16.1±3.1†	15.5±3.3†	<0.001

EES indicates everolimus-eluting stents; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; PES, paclitaxel-eluting stents; RCA, right coronary artery; RVD, reference vessel diameter; SES, sirolimus-eluting stents; SO, stent oversizing; and ZES, zotarolimus-eluting stents.

*P<0.05 vs the small RVD with low %SO group, †P<0.05 vs the small RVD with high %SO group, ‡P<0.05 vs the large RVD with low %SO group.

no significant difference was observed in binary restenosis at adjacent reference segments among the 4 groups (Figure 2).

IVUS Results

At baseline, progressive increases of lumen and stent VI and minimum lumen area (MLA) were in favor of larger vessel size and oversized stents (Table 4). The high %SO groups achieved greater stent expansion (P<0.001) and less ISA (P<0.001), without a significant increase of edge dissection after implantation (Figure 3). At follow-up, in lesions with small RVD, the greater stent expansion achieved at baseline compensated the slightly greater in-stent neointimal proliferation (P<0.001 for neointimal VI and percent neointimal volume; P=0.042 for %max cross-sectional narrowing) observed in the high %SO group, resulting in significantly larger lumen dimensions at follow-up (P=0.002 for lumen VI; P=0.012 for MLA) compared with the low %SO group. In lesions with large RVD, the greater stent expansion at baseline in the high %SO group directly translated into the larger lumen dimensions at follow-up (P<0.001 for both lumen VI and MLA) because of the similar neointimal proliferation observed between the high versus low %SO groups. With respect to possible edge effect of stent oversizing, no significant difference was observed in reference segment IVUS parameter changes (Δ from baseline to follow-up) in both small and large RVD lesions, indicating comparable plaque

Table 3. Quantitative Coronary Angiography Results

	Total	Small RVD Low %SO	Small RVD High %SO	Large RVD Low %SO	Large RVD High %SO	*P* Value
Pre-intervention						
Lesion length, mm	14.8±6.6	15.8±7.1	14.1±6.5*	15.5±6.6†	14.8±6.5	<0.001
RVD, mm	2.74±0.46	2.49±0.16	2.37±0.26*	3.19±0.34*†	2.99±0.14*†‡	<0.001
MLD, mm	0.86±0.38	0.75±0.30	0.75±0.30	0.99±0.42*†	0.96±0.40*†	<0.001
%DS (%)	68.7±12.3	69.9±11.7	68.6±12.0	69.2±12.5	67.7±13.3	0.077
Baseline (post-intervention)						
RVD, mm	2.82±0.46	2.55±0.21	2.45±0.26*	3.25±0.35*†	3.05±0.18*†‡	<0.001
MLD, mm	2.67±0.42	2.36±0.25	2.42±0.33*	2.94±0.35*†	2.97±0.25*†	<0.001
%DS (%)	3.96±9.57	6.50±8.79	0.89±9.80*	8.10±8.53†	2.31±7.71*†‡	<0.001
Follow-up						
RVD, mm	2.73±0.46	2.46±0.23	2.41±0.32	3.12±0.38*†	3.00±0.26*†‡	<0.001
MLD, mm	2.22±0.61	1.97±0.49	1.97±0.55	2.47±0.60*†	2.53±0.51*†	<0.001
%DS (%)	18.3±19.3	20.1±19.9	17.9±20.8	20.0±18.1	14.8±16.1*†‡	<0.001
Late lumen loss, mm	0.45±0.50	0.37±0.48	0.43±0.49	0.48±0.54*	0.45±0.46	0.039

DS indicates diameter stenosis; MLD, minimum lumen diameter; RVD, reference vessel diameter; and SO, stent oversizing.

*P<0.05 vs the small RVD with low %SO group, †P<0.05 vs the small RVD with high %SO group, ‡P<0.05 vs the large RVD with low %SO group.

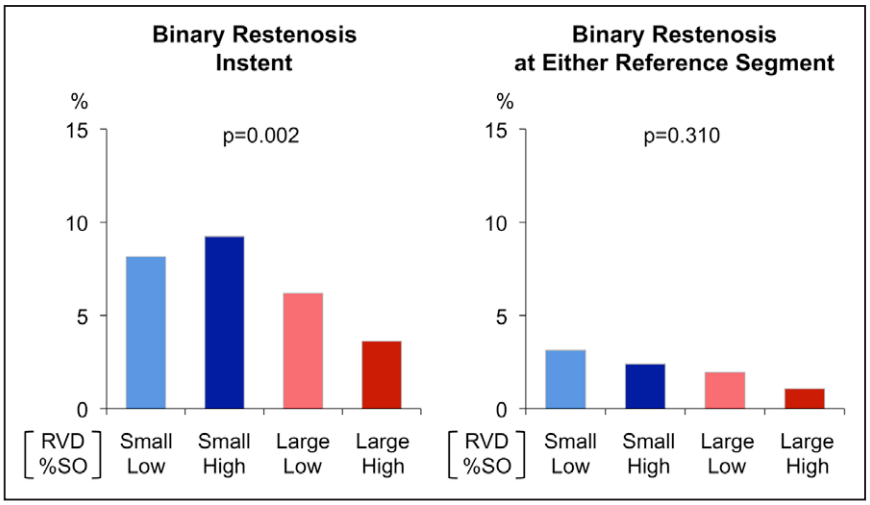

Figure 2. Angiographic binary restenosis. In-stent angiographic binary restenosis at follow-up was significantly lower in lesions with large reference vessel diameter (RVD) than those with small RVD and was lowest in the large RVD with high %stent oversizing (%SO) group. In contrast, no significant difference was observed in binary restenosis localized at the adjacent reference (stent edge) segment.

proliferation and vessel remodeling between high versus low %SO groups (Table II in the Data Supplement).

Clinical Outcomes in 1 Year

In this analysis, the data of clinical outcomes were obtained in 2869 vessels (97.9%) at 1-year follow-up. Progressive decrease of TLR rate was found in favor of larger vessel size and oversized stents at 1 year after implantation (Figure 4). The incidence of definite/probable stent thrombosis was significantly higher in the small RVD with low %SO group than in the other 3 groups. The multivariate model using variables with $P<0.05$ in univariate models determined 4 independent predictors of TLR: diabetes mellitus, prior bypass surgery, total stent length, and stratified groups by RVD and %SO (Table III in the Data Supplement). For stent thrombosis, the multivariate model determined 3 independent predictors: diabetes mellitus, current smoking, and lesions with small RVD and low %SO (Table IV in the Data Supplement). In terms of effect-modification by age-group or sex, no statistically significant interactions were found to the TLR rate among the 4 groups or to the rate of stent

Table 4. IVUS Results at the Stented Segment

	Total	Small RVD Low %SO	Small RVD High %SO	Large RVD Low %SO	Large RVD High %SO	*P* Value
Baseline (post-intervention)						
Lumen VI, mm³/mm	7.1±2.1	5.3±1.3	6.1±1.6*	8.3±2.1*†	8.8±1.3*†‡	<0.001
Vessel VI, mm³/mm	14.0±4.3	10.8±2.9	11.9±3.2*	16.5±4.3*†	17.0±3.2*†	<0.001
Plaque VI, mm³/mm	6.9±2.7	5.5±2.1	5.8±2.1	8.3±2.8*†	8.1±2.4*†	<0.001
Stent VI, mm³/mm	7.1±2.1	5.3±1.3	6.1±1.6*	8.3±2.1*†	8.8±1.3*†‡	<0.001
MLA, mm	5.9±1.9	4.4±1.2	5.1±1.4*	6.9±1.9*†	7.5±1.4*†‡	<0.001
Follow-up						
Lumen VI, mm³/mm	6.3±2.1	4.8±1.2	5.4±1.5*	7.2±2.1*†	8.0±1.5*†‡	<0.001
Vessel VI, mm³/mm	14.3±4.4	10.7±2.6	12.1±3.2*	16.7±4.4*†	17.7±3.0*†‡	<0.001
Plaque VI, mm³/mm	7.2±2.7	5.5±1.9	6.1±2.2*	8.6±2.8*†	8.6±2.3*†	<0.001
MLA, mm	5.0±1.9	3.7±1.1	4.1±1.4*	5.7±2.1*†	6.3±1.8*†‡	<0.001
Neointimal VI, mm³/mm	0.8±0.8	0.5±0.5	0.8±0.7*	0.9±0.8*	1.0±1.0*†	<0.001
%NIV (%)	11.4±10.3	8.8±8.0	12.5±10.7*	10.8±10.1†	11.2±10.7	<0.001
%Max CSN (%)	26.3±17.1	23.9±15.2	28.0±16.8*	25.4±17.5†	25.0±17.6	0.005
Change from baseline to follow-up						
ΔLumen VI, mm³/mm	−0.7±1.0	−0.4±0.6	−0.7±0.8*	−0.8±1.0*	−0.8±1.2*	<0.001
ΔVessel VI, mm³/mm	0.3±1.2	0.4±0.9	0.4±1.1	0.2±1.4	0.3±1.1	0.579
ΔPlaque VI, mm³/mm	0.3±1.0	0.4±0.7	0.3±1.0	0.2±1.2	0.2±0.8	0.086
ΔMLA, mm	−1.0±1.2	−0.7±0.8	−0.9±1.0*	−1.1±1.3*	−1.1±1.5*	<0.001

CSN indicates cross-sectional narrowing; ISA, incomplete stent apposition; MLA, minimum lumen area; NIV, neointimal volume; RVD, reference vessel diameter; and SO, stent oversizing; and VI, volume index.

*$P<0.05$ vs the small RVD with low %SO group, †$P<0.05$ vs the small RVD with high %SO group, ‡$P<0.05$ vs the large RVD with low %SO group.

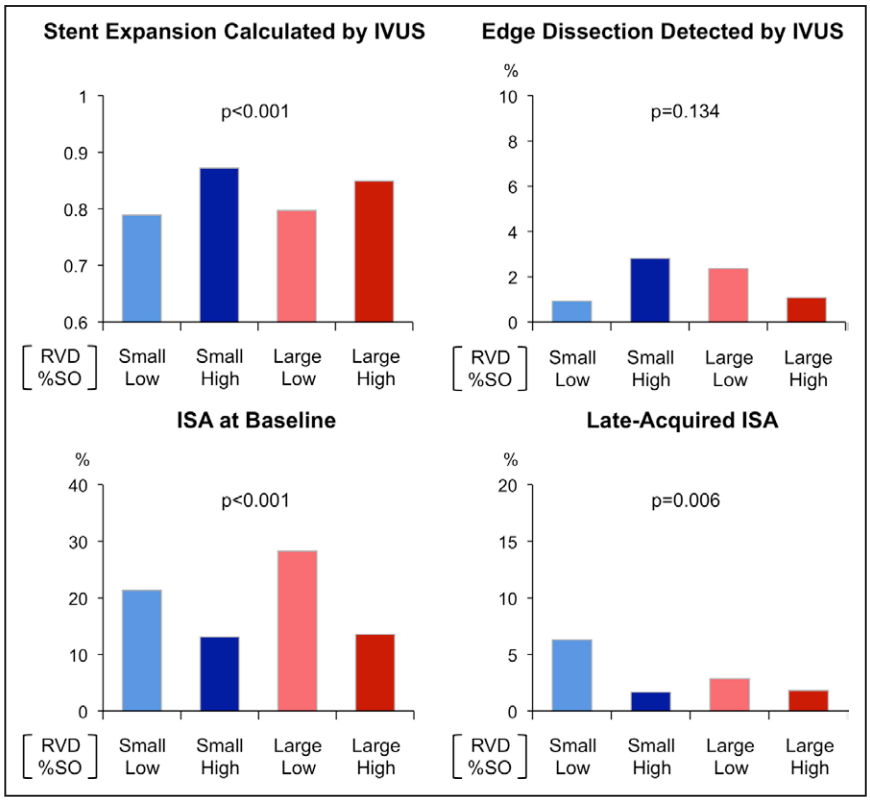

Figure 3. Comparisons of IVUS parameters. The high %stent oversizing (%SO) groups achieved greater stent expansion and less incomplete stent apposition (ISA), without a significant increase of edge dissection after implantation. Late-acquired ISA was observed more frequently in the small reference vessel diameter (RVD) with low %SO group than in the other 3 groups.

thrombosis between the small RVD and low %SO group and the other 3 groups (Table VA–VD in the Data Supplement).

Effect of Very High Oversizing

The additional analyses were conducted with further stratification into 3 groups: low (%SO <10%), high (10%–30%), and very high (>30%) oversizing to explore the upper limit of stent oversizing (Table VI in the Data Supplement). In small vessels, the very high oversizing achieved the greatest stent area at post-procedure, which resulted in the largest lumen VI and MLA at follow-up, despite the greatest neointimal proliferation. Importantly, the very high oversizing did not lead to increased edge dissections at post-procedure compared with the low and high oversizing groups. As a result, the vessels with very high %SO tended to have the lowest incidence of TLR. In large vessels, however, there were only 4 cases in the very high oversizing (%SO >30%) category. Although statistical analysis would not be feasible, these 4 cases had no edge dissection at post-procedure and no TLR or stent thrombosis at follow-up.

Discussion

The main findings of this analysis are as follows: (1) Overall, stent size selection was affected by the reference vessel dimension; (2) Lesions with significant stent oversizing underwent less post-dilatation but achieved greater stent expansion and less ISA, without increasing edge dissection after procedure; (3) When stratified by vessel size and stent oversizing, progressive decreases of angiographic binary restenosis and TLR rates were found in favor of larger vessel size and oversized stents, with no difference in restenosis or plaque progression at the stent edge between lesions with and without stent oversizing; and (4) Stent thrombosis was observed the most in small vessels without stent oversizing among the subgroups.

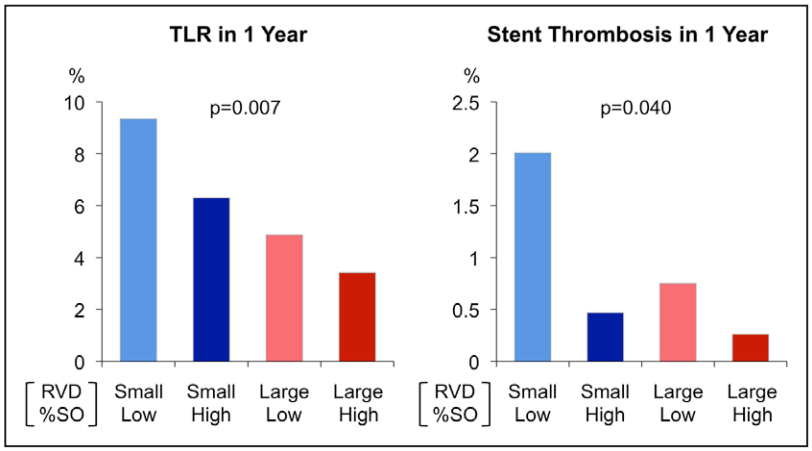

Figure 4. Clinical outcomes at 1 year. Progressive decrease of target lesion revascularization (TLR) rate was found in favor of larger vessel size and oversized stents in 1 year after implantation. The incidence of definite/probable stent thrombosis was significantly higher in the small reference vessel diameter (RVD) with low %stent oversizing (%SO) group than in the other 3 groups.

Stent Size Selection and Final Stent Expansion

There have been few studies systemically investigating the impact of stent size selection on final stent expansion after coronary stent implantation. In the present study, the selected stent size relative to RVD varied depending on the vessel size. In small vessels, a relatively larger stent might have been intentionally selected to achieve sufficient stent expansion. In large vessels, however, the operators tended to select a relatively smaller stent because adequate stent expansion might have been considered easier to achieve, even without aggressive stent dilation. At post-intervention, the lesions with significant stent oversizing achieved greater stent expansion and less ISA, without increase of edge dissection, despite the less frequent upsizing post-dilatation, compared with those without stent oversizing. The current results may suggest that aggressive selection of a larger stent might be an effective option to obtain better stent expansion while avoiding aggressive post-dilatation. Of note, however, there may be some lesions in which the oversized stent implantation is considered inappropriate because of increased risks of coronary perforation, such as chronic total occlusion,[21,22] severe calcification,[21–23] or eccentric lesions.[21,23] Further investigation involving detailed assessment of lesion or plaque characteristics would be warranted to confirm this hypothesis.

Vascular Response to Stent Oversizing at Adjacent Edge Segment

Although oversized stents can potentially cause vascular injury at the adjacent edge segment,[24] the current study demonstrated relatively low and comparable incidences of post-stent edge dissection across the 4 subgroups. This may be, in part, because the operators were allowed to use IVUS for the guidance of stent implantation and optimization in this study population. Final IVUS assessment at post-procedure can also underestimate the occurrence of initial edge dissection if additional bailout stent implantation is performed in response to the postdeployment IVUS observation. In the present study, however, the total number of stents implanted per lesion did not differ between the lesions with and without stent oversizing. In addition, multiple stent implantation was not more frequent in lesions with stent oversizing, suggesting that aggressive selection of a larger stent may not necessarily lead to a significant increase in residual edge dissection if appropriate attention to edge effect is given.

A previous study evaluating first-generation sirolimus-eluting stents also reported that edge restenosis could be induced by vessel overstretching because of stent overexpansion.[25] In the present study with various types of DES including newer generation stents, however, neither increased edge restenosis nor significant plaque progression in the adjacent reference segment was observed in the oversizing groups compared with the nonoversizing groups.

Effect of Stent Oversizing on Neointimal Proliferation

Although the bigger-is-better strategy has been the widely accepted principle in the bare-metal stent era, it has also been reported that overly aggressive stent deployment can lead to increased neointimal proliferation,[26,27] which is likely related to vessel injury caused by overstretching.[27–29] Although one study reported that arterial injury as assessed by the balloon-to-artery ratio was not associated with the amount of neointimal hyperplasia in sirolimus-eluting stents and paclitaxel-eluting stents,[30] the exact impact of stent oversizing has not been well investigated in DES. In the present study, stent oversizing resulted in no significant increase of neointimal proliferation in large target vessels. However, in small vessels, stent oversizing was associated with a slight but significantly greater amount of neointima, suggesting that small target vessels might be more susceptible to overstretch injury, which could promote neointimal proliferation even after DES implantation. Overall, however, current DES technology seems to offer a sufficiently potent antiproliferative effect so that the disadvantage of vessel injury was counterbalanced by the advantage of larger final stent dimensions achieved with oversized stents, resulting in significantly larger follow-up lumen in the oversizing group of the present study.

Long-Term Outcomes

It is well recognized that vessel size is one of the strongest determinants of long-term outcomes after coronary stenting. Specifically, smaller target vessel dimensions have been reported as an independent predictor of restenosis and repeat revascularization even after DES implantation.[31] In addition, it has also been reported that final stent expansion is related to subsequent adverse clinical events, including restenosis and stent thrombosis.[6,32,33] However, it remained unclear whether optimal selection of DES size itself could contribute to the improvement of long-term clinical outcomes. In the present study, the incidences of angiographic restenosis, TLR, and stent thrombosis were all highest in small vessels without stent oversizing, and the results suggest possible benefits of oversized stent selection, especially in small vessels. Although the limited number of patients in the very high oversizing group in large vessels precludes direct comparison of benefits and limitations of higher oversizing, small vessels seem to tolerate higher oversizing well, demonstrating no increased complications in this analysis. In the trials included in this analysis, operators were allowed to use IVUS information to guide stent deployment and optimization, which may, in part, account for the favorable results.

During the past few years, bioresorbable scaffold technology has evolved,[34,35] and its advent has refocused attention to accurate device size selection because overdilation of undersized biodegradable stents can damage the polymer struts. Conversely, a recent study also reported that implantation of an oversized bioresorbable scaffold in a relatively small vessel appeared to be associated with a higher 1-year adverse event rate,[36] which is inconsistent with our results with metallic DES. It is reasonable that proper implantation methods may vary according to the design and material of device. Thus, the appropriate selection of device size and deployment strategy for each type of device should be individually established to derive the best clinical benefits from specific devices.

Study Limitations

There were several limitations in this study. First, this is a retrospective study from pooled analyses, raising a possibility of

selection bias. Also, the data collected from a large number of participating sites may have enhanced the generalizability of the current results but at the expense of possibly increased variability in outcomes. Second, there is an imbalance of sample size among the 4 stratified groups. Third, detailed medical therapy information was not available in all the investigated patients. Fourth, the lesions' composition can be an important variable affecting the outcome. However, the present study is a pooled data analysis of clinical DES trials with common exclusion criteria, such as severely calcified lesions, thrombus-containing lesions, ST-segment–elevation myocardial infarction, etc. Also, although preprocedural IVUS imaging would be required for accurate lesion composition assessment, most trial protocols mandated IVUS interrogation only at post-intervention and follow-up. Fifth, detailed patient-level data on peri-procedural complications, such as slow/no reflow phenomenon, and anticoagulant/antiplatelet therapy, were not fully available in some of the trials. As supportive information about peri-procedural complications, however, there was no significant difference in the rate of myocardial infarction on the date of percutaneous coronary intervention among the 4 stratified groups (P=0.168). Sixth, preprocedural IVUS imaging could provide more accurate reference diameter measurements that would allow more aggressive oversizing. Practically, however, the use of preprocedural IVUS for device sizing in every stent case would not be warranted in most countries where angiography-guided percutaneous coronary intervention is still dominantly performed in the majority of patients. The potential benefit of further aggressive oversizing with IVUS guidance certainly represents a clinically important question, especially in complex lesions/patients or with particular devices, such as bioresorbable scaffolds, and therefore would warrant further systematic investigations. Finally, possible differences among DES types could not be fully evaluated because of insufficient statistical power when each group was further divided into DES subgroups.

Conclusions

In this pooled data analysis, the positive impact of stent oversizing was documented with respect to procedural and clinical outcomes. Long-term adverse events appeared to be related to not only the vessel size itself but also the selection of a stent larger than the vessel size. In particular, small vessels treated with a smaller stent were associated with greater adverse events, suggesting that aggressive selection of larger stents, with appropriate attention to edge effects, may optimize long-term outcomes, even in DES implantation.

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Disclosures

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Impact of Stent Size Selection on Acute and Long-Term Outcomes After Drug-Eluting Stent Implantation in De Novo Coronary Lesions

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SUPPLEMENTAL MATERIAL

Supplementary Table 1. Trial List

Trial	Stent type	Stent	QCA/IVUS follow-up (months)	Number of lesions
SIRIUS	SES	Cypher	8	96
J-DESsERT	SES	Cypher	8	152
	PES	Taxus		142
NEVO	PES	Taxus	6	50
ENDEAVOR I	ZES	Endeavor	12	100
ENDEAVOR II	ZES	Endeavor	8	175
ENDEAVOR II Continued Access	ZES	Endeavor	8	74
ENDEAVOR III	ZES	Endeavor	8	306
	SES	Cypher		107
ENDEAVOR IV	ZES	Endeavor	8	198
	PES	Taxus		211
RESOLUTE FIM	ZES	Resolute	9	103
RESOLUTE US	ZES	Resolute	8	108
ZoMaxx I	ZES	ZoMaxx	9	129
	PES	Taxus		131
ZoMaxx II	ZES	ZoMaxx	9	194
	PES	Taxus		197
SPIRIT III	EES	Xience V	8	241
	PES	Taxus		115
SPIRIT III Japan	EES	Xience V	8	102

EES, everolimus-eluting stent; IVUS, intravascular ultrasound; PES, paclitaxel-eluting stent; QCA, quantitative coronary angiography; SES, sirolimus-eluting stent; ZES, zotarolimus-eluting stent.

Supplementary Table 2. IVUS Results at the Reference Segment

	Total	Small RVD Low %SO	Small RVD High %SO	Large RVD Low %SO	Large RVD High %SO	p
Baseline (post-intervention)						
Proximal						
Lumen VI (mm^3/mm)	8.1±3.0	6.7±2.2	6.7±2.1	10.0±3.2*†	9.5±2.2*†	<0.001
Vessel VI (mm^3/mm)	14.9±4.6	12.4±3.4	12.8±3.7	17.7±4.6*†	17.3±3.6*†	<0.001
Plaque VI (mm^3/mm)	6.9±2.7	5.7±2.1	6.1±2.5	7.9±2.8*†	7.9±2.6*†	<0.001
Distal						
Lumen VI (mm^3/mm)	6.4±2.5	4.7±1.5	5.3±1.8*	7.9±2.7*†	8.1±1.9*†	<0.001
Vessel VI (mm^3/mm)	10.9±4.5	8.0±2.8	8.8±3.2*	13.4±4.6*†	13.7±3.6*†	<0.001
Plaque VI (mm^3/mm)	4.5±2.7	3.3±1.8	3.5±2.1	5.7±2.8*†	5.7±2.7*†	<0.001
Follow-up						
Proximal						
Lumen VI (mm^3/mm)	7.6±2.8	6.3±2.1	6.2±2.1	9.2±3.1*†	8.8±2.3*†	<0.001
Vessel VI (mm^3/mm)	14.5±4.5	11.9±3.5	12.4±3.6	17.1±4.5*†	16.9±3.4*†	<0.001
Plaque VI (mm^3/mm)	7.0±2.8	5.7±2.2	6.2±2.5	7.9±2.8*†	8.2±2.6*†	<0.001

Distal						
Lumen VI (mm^3/mm)	6.3±2.5	4.5±1.4	5.1±1.6	7.5±2.8*†	7.9±2.0*†	<0.001
Vessel VI (mm^3/mm)	10.9±4.5	7.8±2.6	8.7±3.0	13.3±4.8*†	14.2±3.8*†	<0.001
Plaque VI (mm^3/mm)	4.7±2.7	3.3±1.8	3.7±2.1	5.9±2.9*†	6.2±2.8*†	<0.001
Change from baseline to follow-up						
Proximal						
ΔLumen VI (mm^3/mm)	-0.5±1.4	-0.4±1.0	-0.4±1.1	-0.5±1.6	-0.8±1.6†	0.046
ΔVessel VI (mm^3/mm)	-0.3±1.5	-0.2±1.3	-0.2±1.3	-0.5±1.7	-0.5±1.7	0.060
ΔPlaque VI (mm^3/mm)	0.1±1.2	0.2±0.9	0.2±1.1	-0.02±1.3	0.3±1.2	0.111
Distal						
ΔLumen VI (mm^3/mm)	-0.2±1.2	-0.2±0.9	-0.2±0.9	-0.2±1.3	-0.4±1.7	0.584
ΔVessel VI (mm^3/mm)	0.01±1.4	0.1±0.9	0.01±1.0	0.03±1.6	-0.1±1.9	0.857
ΔPlaque VI (mm^3/mm)	0.2±0.9	0.3±0.6	0.2±0.7	0.2±1.1	0.3±1.0	0.777

VI: volume index.

* $p<0.05$ vs. the small RVD with low %SO group, † $p<0.05$ vs. the small RVD with high %SO group, ‡ $p<0.05$ vs. the large RVD with low %SO group.

Supplementary Table 3. Univariate and Multivariate Logistic Regression Analyses of the Variables Associated with TLR

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p value	OR	95% CI	p value
Age	0.995	0.980-1.010	0.502			
Male	0.807	0.569-1.145	0.235			
Unstable angina	0.923	0.638-1.336	0.672			
Hypertension	1.388	0.922-2.090	0.106			
Hyperlipidemia	1.138	0.743-1.745	0.547			
Diabetes	1.559	1.107-2.196	0.011	1.542	1.051-2.262	0.027
Prior bypass surgery	3.035	1.752-5.258	<0.001	2.657	1.520-4.644	<0.001
Current smoking	0.882	0.593-1.312	0.535			
Zotarolimus-eluting stent	1.287	0.928-1.784	0.130			
Left anterior descending artery	1.341	0.871-2.065	0.182			
Type B2/C	1.259	0.854-1.857	0.245			
Total stent length	1.020	1.006-1.035	0.006	1.021	1.005-1.037	0.010
Post-dilatation	0.846	0.609-1.176	0.320			
Maximum balloon pressure	0.942	0.883-1.005	0.069			
Minimum lumen diameter at pre-intervention	0.803	0.513-1.257	0.337			
%DS at post-intervention	0.999	0.982-1.017	0.959			
Plaque VI at post-intervention	0.972	0.873-1.083	0.609			
Stent expansion calculated by IVUS	1.485	0.376-5.863	0.573			
ISA at post-intervention	1.068	0.675-1.690	0.780			
Stratified groups by RVD and %SO	0.720	0.593-0.874	<0.001	0.724	0.580-0.904	0.004

DS, diameter stenosis; ISA, incomplete stent apposition; IVUS, intravascular ultrasound; RVD, reference vessel diameter; SO, stent oversizing; VI, volume index.

Supplementary Table 4. Univariate and Multivariate Logistic Regression Analyses of the Variables Associated with Stent Thrombosis

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p value	OR	95% CI	p value
Age	0.971	0.930-1.015	0.195			
Male	0.577	0.219-1.523	0.277			
Unstable angina	1.435	0.537-3.836	0.473			
Hypertension	1.112	0.361-3.421	0.852			
Hyperlipidemia	1.793	0.406-7.913	0.408			
Diabetes	3.028	1.164-7.876	0.023	3.683	1.357-9.995	0.011
Current smoking	3.145	1.176-8.415	0.023	3.557	1.319-9.588	0.012
Sirolimus-eluting stent	0.931	0.212-4.089	0.925			
Left anterior descending artery	0.614	0.134-2.812	0.530			
Type B2/C	1.282	0.412-3.989	0.668			
Total stent length	1.013	0.967-1.062	0.584			
Average stent size	0.286	0.078-1.039	0.057			
Post-dilatation	1.549	0.571-4.202	0.390			
Maximum balloon pressure	0.974	0.813-1.168	0.779			
%DS at post-intervention	1.005	0.956-1.058	0.834			
Plaque VI at post-intervention	0.763	0.502-1.102	0.161			
Stent expansion calculated by IVUS	0.015	0.0002-8.578	0.194			
ISA at post-intervention	1.720	0.537-5.509	0.361			
Lesions with small RVD and low %SO	3.955	1.383-11.313	0.010	4.304	1.470-12.606	0.008

DS, diameter stenosis; ISA, incomplete stent apposition; IVUS, intravascular ultrasound; RVD, reference vessel diameter; SO, stent oversizing; VI, volume index.

Supplementary Table 5A. Interaction of Age-Group to TLR Rates Among the 4 Groups

Group	All		Age <65	Age ≥65	
	TLR (%)	p-value (group difference)	TLR (%)	TLR (%)	p-value (interaction)
Small RVD / Low %SO	8.7	0.009	11.8	5.8	0.512
Small RVD / High %SO	5.9		6.4	5.4	
Large RVD / Low %SO	4.5		4.5	4.7	
Large RVD / High %SO	3.3		4.0	2.6	

RVD, reference vessel diameter; SO, stent oversizing; TLR, target lesion revascularization

Supplementary Table 5B. Interaction of Gender to TLR Rates Among the 4 Groups

Group	All		Male	Female	
	TLR (%)	p-value (group difference)	TLR (%)	TLR (%)	p-value (interaction)
Small RVD / Low %SO	8.7	0.009	8.5	9.3	0.620
Small RVD / High %SO	5.9		5.2	7.4	
Large RVD / Low %SO	4.5		4.6	4.4	
Large RVD / High %SO	3.3		3.7	2.6	

RVD, reference vessel diameter; SO, stent oversizing; TLR, target lesion revascularization

Supplementary Table 5C. Interaction of Age-Group to ST Rates Between the Small RVD and Low %SO group and the Other 3 Groups

Group	All		Age <65	Age ≥65	
	ST (%)	p-value (group difference)	ST (%)	ST (%)	p-value (interaction)
Small RVD / Low %SO	1.9	0.022	3.0	0.8	0.178
Other 3 groups	0.5		0.5	0.5	

RVD, reference vessel diameter; SO, stent oversizing; ST, stent thrombosis

Supplementary Table 5D. Interaction of Gender to ST Rates Between the Small RVD and Low %SO group and the Other 3 Groups

Group	All		Male	Female	
	ST (%)	p-value (group difference)	ST (%)	ST (%)	p-value (interaction)
Small RVD / Low %SO	1.9	0.022	0.6	4.2	0.068
Other 3 groups	0.5		0.5	0.4	

RVD, reference vessel diameter; SO, stent oversizing; ST, stent thrombosis

Supplementary Table 6. Additional Analysis with Further Stratification into 3 Groups in Small Vessels: Low (<10%), High (10-30%), and Very High (>30%) Oversizing

	Low %SO (<10%) (n=285)	High %SO (10-30%) (n=921)	Very High %SO (>30%) (n=339)	p
IVUS measurements at baseline (post-intervention)				
Lumen VI (mm^3/mm)	5.3±1.3	5.9±1.4*	6.5±2.0*†	<0.001
Vessel VI (mm^3/mm)	10.8±2.9	11.8±3.1*	12.1±3.5*	0.004
Plaque VI (mm^3/mm)	5.5±2.1	5.9±2.1	5.6±2.1	0.109
Stent VI (mm^3/mm)	5.3±1.3	5.9±1.4*	6.5±2.0*†	<0.001
MLA (mm)	4.4±1.2	4.9±1.3*	5.4±1.8*†	<0.001
Edge dissection (%)	0.92	2.78	2.89	0.226
IVUS measurements at follow-up				
Lumen VI (mm^3/mm)	4.8±1.2	5.3±1.4*	5.7±1.9*†	<0.001
Vessel VI (mm^3/mm)	10.7±2.6	12.1±3.1*	12.2±3.5*	<0.001
Plaque VI (mm^3/mm)	5.5±1.9	6.2±2.2*	5.8±2.0	0.003
MLA (mm)	3.7±1.1	4.1±1.3*	4.4±1.7*	<0.001
Neointimal VI (mm^3/mm)	0.5±0.5	0.7±0.7*	0.9±0.8*	<0.001
%NIV (%)	8.8±8.0	12.1±10.6*	13.5±11.0*	<0.001
%Max CSN (%)	23.9±15.2	27.9±16.8*	28.3±16.8*	0.024
Clinical outcomes at 1 year				
TLR (%)	9.34	6.93	4.51	0.084
Stent thrombosis (%)	2.01	0.25	0.36	0.007

CSN, cross-sectional narrowing; ISA, incomplete stent apposition; IVUS, intravascular ultrasound; MLA, minimum lumen area; NIV, neointimal volume; RVD, reference vessel diameter; SO, stent oversizing; TLR, target lesion revascularization; VI, volume index.

* $p<0.05$ vs. the low %SO group, † $p<0.05$ vs. the high %SO group.