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Impact of Post-Intervention Minimal Stent Area on 9-Month Follow-Up Patency of Paclitaxel-Eluting Stents

An Integrated Intravascular Ultrasound Analysis From the TAXUS IV, V, and VI and TAXUS ATLAS Workhorse, Long Lesion, and Direct Stent Trials

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Objectives We investigated the predictive value of the intravascular ultrasound (IVUS) measured post-intervention minimum stent area (MSA) on 9-month follow-up paclitaxel-eluting stent (PES) patency compared with bare-metal stents (BMS).

Background Stent underexpansion is a strong predictor for restenosis after sirolimus-eluting stent implantation, but the implication of underexpansion in PES is still unknown.

Methods From the combined TAXUS IV, V, and VI and TAXUS ATLAS Workhorse, Long Lesion, and Direct Stent trials, 1,580 patients (PES 1,098, BMS 482) in IVUS substudies were analyzed. The MSA that best predicted angiographic in-stent restenosis (ISR) (% diameter stenosis ≥50%) was determined.

Results The post-intervention IVUS MSA was similar in PES and BMS (6.6 ± 2.5 mm^2 vs. 6.7 ± 2.3 mm^2, $p = 0.92$). At 9-month follow-up, ISR was lower in the PES group versus the BMS group (10% vs. 31%, $p < 0.0001$). Using multivariable logistic regression analysis, post-intervention IVUS MSA was the independent predictor of subsequent ISR in both the PES and BMS groups ($p = 0.0002$ for PES and $p = 0.0002$ for BMS). The ability of the post-intervention IVUS MSA to predict ISR was further assessed using receiver operating characteristic analysis. The post-intervention IVUS MSA was found to be a faithful discriminator between patients with and without ISR in both PES ($c = 0.6382$) and BMS ($c = 0.6373$). Finally, the optimal thresholds of post-intervention IVUS MSA that best predicted stent patency at 9 months were 5.7 mm^2 for PES and 6.4 mm^2 for BMS.

Conclusions Post-intervention MSA measured by IVUS can predict 9-month follow-up stent patency after both PES and BMS implantation. (Randomized Trial Evaluating Slow-Release Formulation TAXUS Paclitaxel-Eluting Coronary Stents to Treat De Novo Coronary Lesions; NCT00301522) (Direct Stenting of TAXUS Liberté-SR Stent for the Treatment of Patients With de Novo Coronary Artery Lesions; NCT00371423) (A Study of the TAXUS Liberté Stent for the Treatment of Long De Novo Coronary Artery Lesions; NCT00371475) (A Study of the TAXUS Liberté Stent for the Treatment of de Novo Coronary Artery Lesions in Small Vessels; NCT00371748) (J Am Coll Cardiol Intv 2009;2:1269–75)

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Drug-eluting stents (DES) have dramatically decreased in-stent restenosis (ISR) compared with bare-metal stents (BMS) (1,2). However, previous reports indicate that stent underexpansion measured by intravascular ultrasound (IVUS) remains a strong predictor for mid-term sirolimus-eluting stent (SES) patency whether patency is defined by angiography or IVUS criteria (3–5).

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Once intimal hyperplasia is suppressed by the drug, stent underexpansion as a cause of restenosis appears to be magnified. To address this issue in paclitaxel-eluting stents (PES), we have used data from the major TAXUS Express and TAXUS Liberté trials, each of which had an IVUS substudy (2,6–9). In this report we evaluate the IVUS parameters that best predicted 9-month follow-up PES patency defined angiographically.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
ISR = in-stent restenosis
IVUS = intravascular ultrasound
MLA = minimal lumen area
MSA = minimum stent area
PES = paclitaxel-eluting stent(s)
ROC = receiver-operator characteristic
SES = sirolimus-eluting stent(s)
TLR = target lesion revascularization

Methods

Patient population and protocol. The TAXUS IV, V, and VI trials, were prospective, double-blind, BMS-controlled trials in which patients with a single de novo native coronary artery lesion were randomly assigned to treatment with a PES or an otherwise identical BMS (both Boston Scientific, Natick, Massachusetts) (2,6,7). The TAXUS IV and V studies used the TAXUS Express stent with the paclitaxel slow-release (commercially available) formulation; whereas the TAXUS VI study used the TAXUS Express stent with the moderate-release (not commercially available) formulation. TAXUS ATLAS WH (Workhorse), LL (Long Lesion), and DS (Direct Stent) were prospective, single-arm studies comparing the new generation, thin-strut TAXUS Liberté stent (Boston Scientific), versus TAXUS Express historical control subjects from the TAXUS IV and V studies (8,9). Both stents, TAXUS Express SR and TAXUS Liberté, have identical polymer coating and paclitaxel slow release formulation. Of the 4,184 patients enrolled in the 6 trials, 1,580 patients (1,098 PES and 482 BMS) were enrolled in IVUS substudies and were included in the current analyses; clinical sites were selected based on their IVUS experience, volume, and willingness to enroll all of their patients in the IVUS substudy. IVUS substudy patients within each trial were enrolled until the pre-specified numbers were obtained. All pre-specified IVUS substudy patients were scheduled for follow-up angiography and IVUS at 9 months. The IVUS substudy data from these trials were analyzed at a single core laboratory (MedStar Research Institute, Washington Hospital Center, Washington, DC) (10), and the angiographic studies were analyzed at a single core laboratory (Brigham and Women's Hospital, Boston, Massachusetts) (9).

Angiographic analysis. Two or more angiographic projections of the stenosis after intracoronary nitroglycerin were acquired with repetition of identical angiographic projections of the lesion at the time of follow-up angiography. With the contrast-filled injection catheter as the calibration source, quantitative coronary angiographic analysis was performed using a validated automated edge-detection algorithm (CMS, Medis, Neunen, the Netherlands) by a technician who was unaware of the clinical or IVUS findings and who was blinded to the treatment arm. Significant angiographic ISR was defined as % diameter stenosis $\geq$50%.

IVUS protocol and analysis. IVUS imaging was performed after intracoronary administration of 0.1 to 0.2 mg nitroglycerin using motorized pullback (0.5 mm/s) and contemporary, commercial scanners. Images were recorded continuously throughout the stent and at least 5 mm reference segments distal and proximal to the stent. Images were recorded onto s-VHS videotape or onto digital media for offline analysis at a single, independent core laboratory by a technician who was unaware of treatment assignment or patient clinical outcomes. With the use of computerized planimetry (TapeMeasure, Indec Systems, Mountain View, California), stent and lumen borders were manually traced every 1 mm. Post-intervention minimum stent area (MSA) was defined as the smallest stent area within the length of the stent.

Statistical analysis. Individual patient data were integrated from the 3 TAXUS Express trials (TAXUS IV, TAXUS V de novo, and TAXUS VI) into 1 common database representing outcomes across 2 paclitaxel release formulations (slow release and moderate release). For binary data, homogeneity of the odds ratios across the 3 TAXUS Express studies was assessed with the Breslow-Day test, which tests the null hypothesis that the odds ratios of the treatment effect of PES over BMS across studies are equal. If the p value was more than 0.05, then a treatment effect was homogeneous across studies. Indeed, the p value of the Breslow-Day tests in theses trials was 0.37, indicating that pooling of these TAXUS trials was justified. Furthermore, the stent type effect of TAXUS Express versus TAXUS Liberté was not statistically significant for ISR, and TAXUS ATLAS studies were poolable as well. Categorical variables were summarized as frequencies and percentages and were compared between groups using chi-square statistics or Fisher exact test, as appropriate. Continuous variables were presented as mean $\pm$ 1 SD and compared between groups using 2-tailed, unpaired *t* tests or, if parameters were

Table 1. Baseline Clinical and Angiographic Findings and Procedural Details

	PES (n = 1,098)	BMS (n = 482)	p Value
Age, yrs	62.3 ± 10.7	62.6 ± 10.5	0.57
Women	312 (28)	148 (31)	0.36
Diabetes	283 (26)	137 (28)	0.27
Hypertension	763 (70)	324 (67)	0.37
Hyperlipidemia	802 (73)	334 (69)	0.13
Smoking	259 (29)	99 (21)	<0.001
Prior myocardial infarction	341 (31)	153 (32)	0.79
Unstable angina	382 (35)	149 (31)	0.13
Ejection fraction, %	55.8 ± 9.8	56.9 ± 10.5	0.14
Vessel			
Left anterior descending	465 (42)	209 (43)	0.71
Left circumflex	294 (27)	127 (26)	0.86
Right	336 (31)	143 (30)	0.71
Pre-intervention angiographic findings			
Type B2/C lesion	803 (73)	353 (74)	0.85
Lesion length, mm	16.4 ± 8.1	16.4 ± 8.8	0.94
Reference vessel diameter, mm	2.77 ± 0.48	2.75 ± 0.53	0.33
Minimal lumen diameter, mm	0.9 ± 0.4	0.9 ± 0.4	0.82
Diameter stenosis, %	68.8 ± 11.1	68.3 ± 11	0.42
Post-intervention angiographic findings			
In-stent minimal lumen diameter, mm	2.63 ± 0.45	2.64 ± 0.46	0.94
In-stent diameter stenosis, %	6.0 ± 9.6	4.1 ± 10.9	0.01
Procedural details			
Maximum inflation pressure, atm	15.3 ± 3.4	14.4 ± 4.2	<0.0001
Stent length, mm	25.2 ± 11.1	26.6 ± 12.0	0.035
Stent/lesion length ratio	1.7 ± 0.7	1.8 ± 0.9	0.0013
Stent/artery ratio	1.15 ± 0.15	1.15 ± 0.17	0.48
Post-dilation performed, %	66.3%	71.5%	0.0424

Values are mean ± SD or n (%).
BMS = bare-metal stent(s); PES = paclitaxel-eluting stent(s).

not normally distributed per Kolmogorov-Smirnov test, then using the Wilcoxon 2-sample test. Differences were considered to be statistically significant when the p value was <0.05. Multivariate analysis was used to determine predictors of angiographic ISR. All clinical, angiographic, and IVUS covariates listed in Table 2 were modeled univariately for each outcome and multivariately using a stepwise logistic regression. A goodness-of-fit test (Hosmer and Lemeshow, a global model fitting) was used to evaluate the fit of the model; the p value was >0.5 indicating a good fit of the model (little difference between the observed value and the expected values). Statistical significance of the multivariate analysis was set at a value of $p < 0.05$. Receiver-operator characteristic (ROC) analysis was used to measure the ability of post-intervention MSA to discriminate between those subjects with and without 9-month angiographic ISR. The ROC curves plot the probability of detecting true positive fraction (sensitivity) against false positive fraction (1-specificity) of 9-month ISR over the entire range of observed MSAs. In general: 1) ROC = 0.5 suggests no discrimination; 2) $0.7 \leq ROC < 0.8$ is considered acceptable discrimination; 3) $0.8 \leq ROC < 0.9$ is considered excellent discrimination; and 4) $ROC \geq 0.9$ is considered outstanding discrimination. However, to determine the IVUS MSA cutoff point value for each treatment group that best predicted 9-month angiographic ISR or stent patency, the cross point of sensitivity and specificity curves was used. No adjustments for differences between BMS and PES were used.

Results

Baseline clinical and lesion characteristics comparing PES and BMS treatment groups are shown in Table 1. In addition, while there were no differences in age, sex, and coronary risk factors between patients with and without IVUS in the combined TAXUS IV, V, and VI and TAXUS ATLAS Workhorse, Long Lesion, and Direct Stent trials, lesions in the IVUS substudy had larger baseline reference vessel diameter (2.77 ± 0.50 mm vs. 2.66 ± 0.54 mm, $p < 0.0001$), longer lesion length (16.4 ± 8.3 mm vs. 15.7 ± 7.9 mm, $p = 0.0058$), greater % diameter stenosis (68.7 ± 11.1% vs. 67.3 ± 11.3%, $p = 0.0001$), and more frequent type B2/C lesion types (modified American College of Cardiology/American Heart Association lesion classification, 73.4% vs. 69.1%, $p = 0.0022$) than those not in the IVUS substudy. Among the PES group in the IVUS cohort, hyperlipidemia (77% vs. 68%, $p = 0.0013$) and smoking (37% vs. 23%, $p < 0.001$) were more frequent in the LIBERTÉ subgroup compared with the EXPRESS subgroup. The EXPRESS subgroup had a smaller baseline reference vessel diameter (2.74 ± 0.49 mm vs. 2.80 ± 0.48 mm, $p = 0.034$) and a longer lesion length (17.0 ± 8.6 mm vs. 16.0 ± 7.7 mm, $p = 0.030$) compared with the LIBERTÉ subgroup despite less frequent type B2/C lesion characteristics (modified American College of Cardiology/

Table 2. Univariate and Multivariate Predictors of ISR in TAXUS-Treated Patients

Variable	Coefficient	Standard Error	Odds Ratio (95% CI)	p Value
Univariate analysis				<0.05
Pre-RVD (mm)	−0.9945	0.2455	0.37 (0.23–0.60)	<0.0001
Post-intervention IVUS MSA (mm^2)	−0.2597	0.0688	0.77 (0.67–0.88)	0.0002
Sex	0.6088	0.2219	1.84 (1.19–2.84)	0.0061
Multiple study stents Implanted	0.5898	0.2464	1.80 (1.11–2.92)	0.0167
Multivariate analysis				
Post-intervention IVUS MSA (mm^2)	−0.2597	0.0703	0.77 (0.67–0.89)	0.0002

CI = confidential interval; ISR = in-stent restenosis; IVUS = intravascular ultrasound; MSA = minimal stent area; RVD = reference vessel diameter.

American Heart Association lesion classification, 67% vs. 78%, $p < 0.001$).

Patient and lesion characteristics and angiographic and IVUS findings post-intervention. Baseline clinical and lesion characteristics were similar in both PES- and BMS-treated groups (Table 1). Post-intervention quantitative coronary angiography in-stent diameter stenosis measured 6.0 ± 9.6% in the PES group and 4.1 ± 10.9% in the BMS group ($p = 0.01$), and IVUS MSA measured 6.6 ± 2.5 mm^2 in the PES group and 6.7 ± 2.3 mm^2 in the BMS group ($p = 0.92$).

Angiographic findings at 9-month follow-up. At 9 months of follow-up, quantitative coronary angiography in-stent minimum lumen diameter measured 2.2 ± 0.7 mm in the PES group and 1.7 ± 0.7 mm in the BMS group ($p < 0.001$), and quantitative coronary angiography in-stent diameter stenosis measured 20.5 ± 20.0% in the PES group and 38.2 ± 22.2% in the BMS group ($p < 0.001$). Overall, 10% of patients in the PES group had angiographic ISR compared with 31% of patients in the BMS group ($p < 0.001$).

IVUS predictors of 9-month angiographic restenosis. Table 2 shows the univariate predictors ($p < 0.05$) of angiographic ISR after PES implantation. Subsequent multivariate analysis identified the post-intervention IVUS MSA as the only independent predictor of angiographic ISR (odds ratio: 0.77 [95% confidence interval: 0.67 to 0.89], $p = 0.0002$). ROC analysis was then performed to determine the ability of the post-intervention IVUS MSA to discriminate between PES-treated patients with versus without 9-month angiographic ISR over the entire range of MSA values (Fig. 1). The c-statistic for PES-treated patients was 0.6382 (close to acceptable discrimination) (Fig. 1); however, the p value in the Hosmer and Lemeshow test was 0.5211, indicating that pre-intervention MSA was a faithful discriminator between patients with and without ISR at 9 months post-stent implantation. The single post-intervention MSA value that best separated patients with 9-month angiographic ISR from those with no ISR was 5.7 mm^2 (Fig. 1). Using this cut-point to separate the patient population into subgroups revealed that the rate of angiographic ISR was 7.2% for patients with an IVUS MSA ≥5.7 mm^2 compared with 14.5% in patients with an IVUS MSA <5.7 mm^2 ($p = 0.0016$); and the positive and negative predictive values were 13.6% and 92.0%, respectively. Comparing the patients with an IVUS MSA <5.7 mm^2 with those with an IVUS MSA ≥5.7 mm^2: 1) diabetes mellitus was more frequent (29% vs. 23%, $p < 0.0001$); 2) baseline reference vessel diameter was smaller (2.47 ± 0.31 mm vs. 3.04 ± 0.42 mm, $p < 0.0001$); 3) baseline minimal lumen diameter was smaller (0.77 ± 0.29 mm vs. 0.97 ± 0.37 mm, <0.0001 for minimal lumen diameter); and 4) post-intervention minimal lumen diameter was smaller (2.34 ± 0.30 vs. 2.90 ± 0.35, $p < 0.0001$). Of note, the results were almost identical when analyzing just the slow-release formulation (MSA of 5.6 mm^2); however, there were not enough patients to analyze just the moderate release formulation.

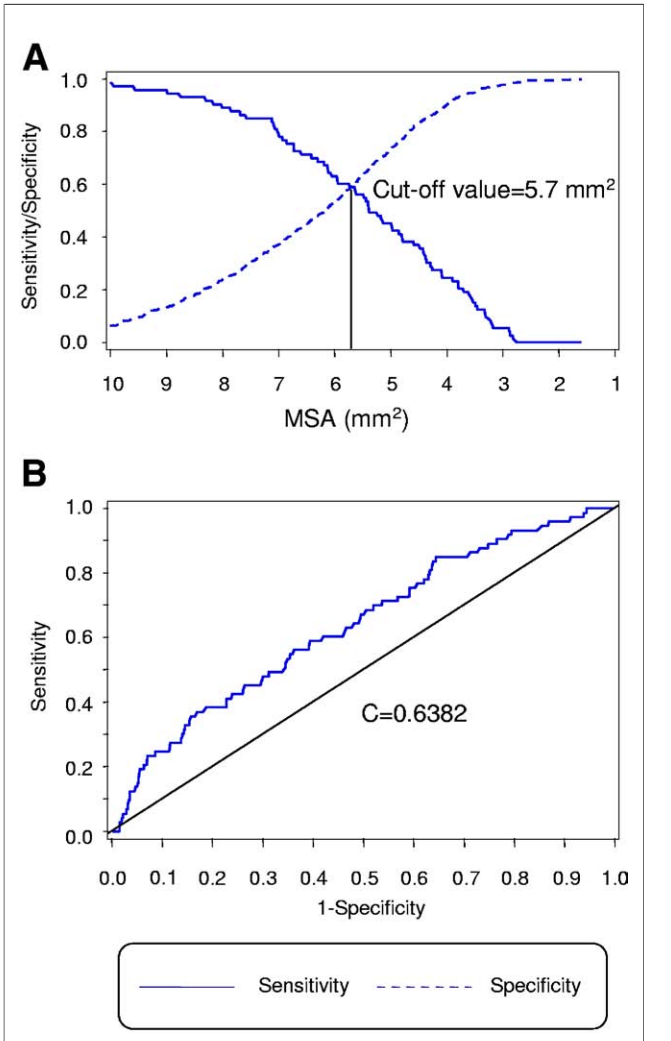

Figure 1. Optimal MSA in PES

(A) Sensitivity and specificity curves for intravascular ultrasound minimum stent area (MSA) predicting angiographic in-stent restenosis (ISR) in paclitaxel-eluting stent (PES)-treated patients. The single post-intervention MSA value that best separated patients with 9-month angiographic ISR from those with no ISR was 5.7 mm^2 in PES-treated patients. **(B)** Receiver-operator characteristic analysis of the intravascular ultrasound MSA for angiographic ISR in PES-treated patients. Receiver-operator characteristic analysis was performed to determine the ability of the post-intervention intravascular ultrasound MSA to discriminate between PES-treated patients with versus without 9-month angiographic ISR over the entire range of MSA values. The c-statistic for PES-treated patients was 0.6382.

When a similar analysis was performed for BMS-treated patients, independent predictors of BMS restenosis included post-intervention IVUS MSA (odds ratio: 0.77 [95% confidence interval: 0.67 to 0.88], $p = 0.0002$) and implantation of multiple BMS (Table 3). The c-statistic for the MSA was 0.6373 (close to acceptable discrimination) (Fig. 2);

however, the p value of the pre-intervention IVUS MSA in the Hosmer and Lemeshow test was 0.9033, indicating that pre-intervention MSA was a faithful discriminator between patients with and without ISR at 9 months post-stent implantation. The single MSA value that best separated patients with 9-month ISR from those with no ISR was 6.4 mm^2 (Fig. 2); the rate of ISR in patients with an IVUS MSA $\geq$6.4 mm^2 was 25% compared with 40% in patients with an IVUS MSA $<$6.4 mm^2 ($p < 0.001$), and the positive and negative predictive values were 40.0% and 75.6%, respectively.

Discussion

The current analysis explored the predictors of angiographic restenosis after PES implantation and, in particular, the relationship between angiographic restenosis and baseline IVUS MSA in more than 1,500 patients, more than 1,000 treated with PES and almost 500 treated with BMS.

The importance of stent expansion in the BMS era. IVUS studies in the BMS era showed that stents were often underexpanded despite adequate angiographic results and that post-intervention MSA measured by IVUS predicted subsequent target lesion revascularization (TLR) or mid-term stent patency (defined as IVUS minimal lumen area [MLA] $\geq$4.0 mm^2) (3,11,12). Castagna et al. (11) reported the incidence of stent underexpansion in 1,090 patients with ISR after BMS implantation; in this single-center cohort, 38% of BMS restenosis lesions had an MSA $<$6.0 mm^2, and 20% had an MSA $<$5.0 mm^2. Using data from the CRUISE (Can Routine Intravascular Ultrasound Influence Stent Expansion) trial, Morino et al. (12) showed that an MSA of 6.5 mm^2 best separated TLR from no TLR at 9-month follow-up; the TLR rate was 16.7% in patients with an MSA of $<$6.5 mm^2 and 5.8% in patients with an MSA of $\geq$6.5 mm^2 ($p < 0.0001$). This cutoff value was supported by Sonoda et al. (3) using data from the SIRIUS (SIRolImUS-Eluting Balloon Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions) trial; an MSA of 6.5 mm^2 for BMS best separated IVUS patency from nonpatency, but with a positive predictive value of only 56%. This cutoff value was

Table 3. Univariate and Multivariate Predictors of ISR in BMS-Treated Patients

Variable	Coefficient	Standard Error	Odd Ratio (95% CI)	p Value
Univariate analysis				<0.05
Multiple stents implanted	1.4394	0.2397	4.22 (2.64–6.75)	<0.0001
Lesion length (mm)	0.0551	0.0121	1.06 (1.03–1.08)	<0.0001
Pre-RVD (mm)	−0.7807	0.2155	0.46 (0.30–0.70)	0.0003
Post-intervention IVUS MSA (mm^2)	−0.2353	0.0643	0.79 (0.70–0.90)	0.0003
Pre-MLD (mm)	−1.0638	0.3405	0.35 (0.18–0.67)	0.0018
Diabetes requiring medication	0.5471	0.2328	1.73 (1.10–2.73)	0.0188
Multivariate analysis				
Multiple stents implanted	1.2784	0.3056	3.59 (1.97–6.54)	<0.0001
Post-intervention IVUS MSA (mm^2)	−0.2677	0.0709	0.77 (0.67–0.88)	0.0002

BMS = bare-metal stent(s); MLD = minimal lumen diameter; other abbreviations as in Table 2.

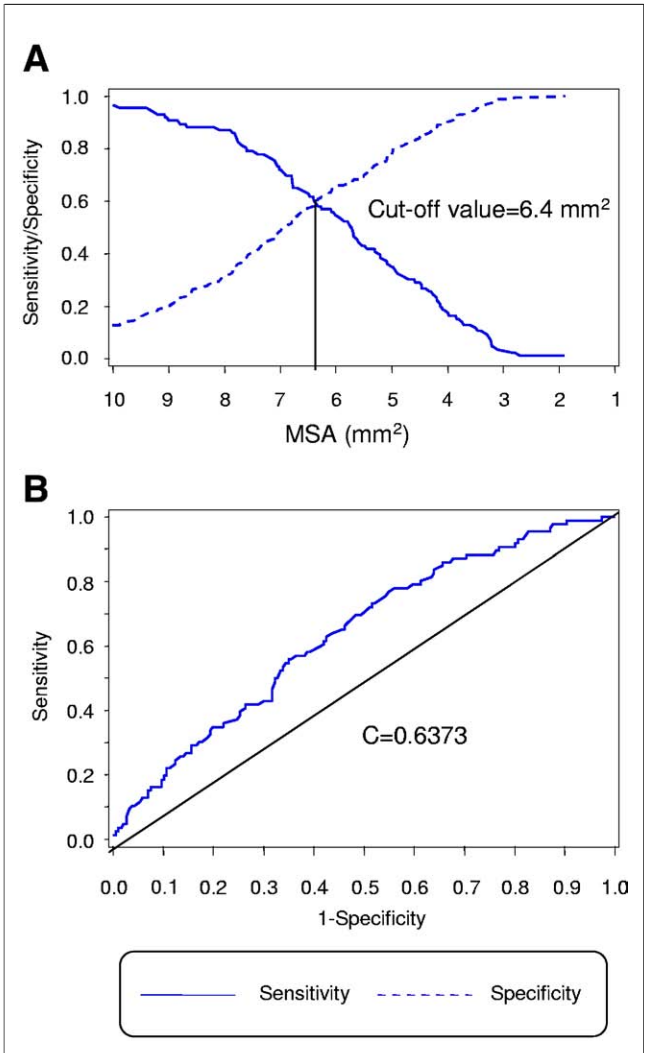

Figure 2. Optimal MSA in BMS

(A) Sensitivity and specificity curves for intravascular ultrasound MSA predicting angiographic ISR in bare-metal stent (BMS)-treated patients. The single post-intervention MSA value that best separated patients with 9-month angiographic ISR from those with no ISR was 6.4 mm^2 in paclitaxel-eluting stent-treated patients. **(B)** Receiver-operator characteristic analysis of the intravascular ultrasound MSA for predicting angiographic ISR in BMS-treated patients. Receiver-operator characteristic analysis was performed to determine the ability of the post-intervention intravascular ultrasound MSA to discriminate between BMS-treated patients with versus without 9-month angiographic ISR over the entire range of MSA values. The c-statistic for BMS-treated patients was 0.6373. Abbreviations as in Figure 1.

also substantiated in the BMS arm of the current analysis in which an IVUS MSA of 6.4 mm^2 best separated 9-month angiographic restenosis from no restenosis, with a negative predictive value of 75.6%, but a low positive predictive value of 40.0%. While a post-intervention MSA >6.4 mm^2 demonstrated good ability to identify patients with stent patency at 9 months post-BMS implantation, there was a limited value of MSA <6.4 mm^2 in predicting subsequent restenosis. This, along with c-statistics of 0.6373, indicates that other lesion or patient factors may also significantly influence BMS restenosis at 9 months. Nevertheless, the multivariate analysis demonstrated that both MSA and multiple stents implantation were significant predictors of angiographic ISR.

The importance of stent underexpansion in the DES era. Stent underexpansion assessed by IVUS seems to be a stronger predictor for mid-term stent patency after SES implantation compared with BMS implantation (3–5). In the IVUS substudy of the SIRIUS trial, a significant positive correlation was observed between IVUS follow-up MLA and IVUS post-intervention MSA in both the SES and BMS groups (3); however, the correlation was higher for SES than for BMS indicating that stent expansion influenced mid-term patency more in SES than BMS. Sonoda et al. (3) (using IVUS MLA end points) and Hong et al. (4) (using angiographic restenosis end points) showed that the post-intervention MSA that best separated mid-term patency from nonpatency after SES implantation was 5.0 to 5.5 mm^2. The SIRIUS trial enrolled relatively low-risk patients, while Hong et al. (4) included both low- and high-risk patients in their single-center registry. The study by Hong et al. (4) also reported that a stent length of >40 mm best separated angiographic restenosis from no restenosis. When patients were divided into 4 groups according to the MSA and stent length, the angiographic restenosis rates were 0.4% (MSA >5.5 mm^2, stent length <40 mm), 2.4% (MSA <5.5 mm^2, stent length <40 mm), 8.6% (MSA >5.5 mm^2, stent length <40 mm), and 17.7% (MSA <5.5 mm^2, stent length >40 mm). Another IVUS study of 169 lesions in 138 patients treated with SES showed that a post-intervention MSA of 5.0 mm^2 and a stent length of >30 mm were independent predictors for angiographic restenosis (5).

The current analysis extends these observations to PES-treated patients. A post-intervention IVUS MSA >5.7 mm^2 can predict subsequent PES patency with a negative predictive value of 92%. Like SES, PES also decreases intimal hyperplasia compared with BMS, albeit to a lesser extent (13,14). The less profound effect of paclitaxel on intimal hyperplasia compared with sirolimus may be one possible explanation for the somewhat larger MSA that best separated restenosis from nonrestenosis in PES (5.7 mm^2) in the current study compared with SES in previous studies (5.0 to 5.5 mm^2). A slightly larger MSA may be needed to accommodate a little more intimal hyperplasia in PES versus SES just as a much larger MSA is necessary to accommodate significantly more intimal hyperplasia in BMS versus DES.

Is a DES MSA of 5.0 or 5.7 mm^2 large enough in all situations? Probably not and for many reasons. First, the SIRIUS and TAXUS trials enrolled relatively low-risk patients compared with real-world cohorts. Studies have consistently showed a relationship between increasing patient and lesion complexity and increased risk of restenosis.

Second, sensitivity/specificity curve analysis identified a single number for MSA that best separates the subsequent presence of an event from no event; however, this cutoff was selected from the MSA values observed only in the current trials, and, therefore, cannot be generalized. Third, multivariate analysis demonstrated that the post-intervention MSA was a significant predictor of ISR at 9 months, with identical risk reduction with a larger MSA for both PES and BMS. Also, the ROC analysis showed virtually an identical ability of MSA for both PES and BMS to discriminate between 9-month ISR and stent patency. In the current analysis, c-statistics were virtually identical for DES and BMS, and a c-statistic of 0.64 is better than chance, less than perfect. The c-statistics in the current analysis took all IVUS MSA values into consideration; they were not related to any specific cut-point, but to MSA as a continuous variable. Of note, c-statistics were not reported by Sonoda et al. (3) or Hong et al. (4) in their previous reports. Conversely, when it comes to individual MSA values, the negative or positive predictive values show the accuracy of the selected MSA cut-points as "diagnostic" tests. In the current study, both cut-points are accurate in predicting stent patency, but the cut-points are not good in predicting restenosis. If the MSA is larger than the cut-point, then the chance of not developing restenosis is high. If the MSA is less than the cut-point, then restenosis may or may not occur. In addition, other factors—strut fracture, nonhomogeneous stent-strut distribution, and so on—must be taken into account. Fourth, in all of the studies cited in the preceding text as well as in the current analysis, there was a stepwise relation between the post-intervention MSA and the likelihood of restenosis; a post-intervention MSA larger than the cut-point was associated with a greater chance of 9-month follow-up patency. Fifth, interventional cardiologists routinely use the manufacturer-supplied compliance charts to target final stent dimensions on the basis of stent size and inflation pressures. However, a comprehensive IVUS analysis showed that stents—whether BMS or DES—achieve only 75 ± 10% of predicted minimum stent diameter and 66 ± 17% of predicted MSA (15).

Finally, if "one size fit all," theoretically an MSA of 6.5 mm^2 would be achieved by 100% expansion of any 2.5 to 3.0 mm BMS, and an MSA of 5.0 to 5.7 mm^2 would be achieved by 100% expansion of any 2.5 to 2.75 mm DES. Thus, manufacturers would only have to make one size stent for all vessels

with reference diameter ≥2.5 mm, and one size would fit all situations. This was not the case in the early SES experience when shortages in larger stent sizes lead to the use of undersized stents in larger vessels with a high rate of adverse events.

Study limitations. First, the results obtained are limited to vessel diameters and stent lengths used in the TAXUS IV, V, and VI and TAXUS ATLAS Workhorse, Long Lesion, and Direct Stent trials. These trial cohorts may include relatively lower risk patients in comparison with real-world practice, and this might limit the use of the suggested MSA cutoff values in clinical practice. Second, this was a post-hoc analysis, and the comparison between BMS and PES was nonrandomized and unadjusted. However, the objective of this analysis was to determine post-procedural MSA values for PES and BMS that best predict ISR at 9 months rather than to compare the stents. Finally, the definition of ISR is based on a protocol-driven 9-month angiographic follow-up and may differ from clinically defined restenosis.

Conclusions

In the combined IVUS analysis of the TAXUS IV, V, and VI and TAXUS ATLAS Workhorse, Long Lesion, and Direct Stent trials, post-intervention MSA measured by IVUS can predict 9-month follow-up stent patency after both PES and BMS implantation. Thus, post-intervention IVUS may help to achieve optimal stent expansion after PES or BMS implantation to reduce underexpansion-related complications such as early/late thrombosis and restenosis.

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