

Impact of postprocedure minimum stent area on long-term results following abciximab-coated stent implantation: An intravascular ultrasound analysis

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Abstract

Background: Smaller postprocedural minimum stent areas (MSA) measured by intravascular ultrasound (IVUS) have been associated with higher restenosis rates.

Methods: This was a single-center, prospective, randomized trial and we assessed the predictive value of MSA for long-term patency and the incidence and extent of incomplete stent apposition (ISA) following abciximab-coated stent ($n=69$) compared to bare metal stent (BMS) implantation ($n=69$). All patients underwent IVUS follow-up at 6 months.

Results: At follow-up coronary angiogram, the restenosis rate and late loss were 12%, 0.30 ± 0.24 mm in abciximab-coated stent group and 29%, 0.68 ± 0.36 mm in BMS group ($p=0.011$, 0.010 , respectively). At follow-up IVUS, intrastent lumen area was significantly larger and intrastent neointimal hyperplasia area was significantly smaller in abciximab-coated stent group than those in BMS group (5.9 ± 1.6 mm² vs. 4.5 ± 1.7 mm², $p=0.001$, and 1.9 ± 1.5 mm² vs. 3.3 ± 1.9 mm², $p<0.001$, respectively). Target lesion revascularization occurred in 9%, 0%, and 0% in abciximab-coated stent group and 19%, 4%, and 1% in BMS group in lesions with a MSA <6.0 mm², from 6 to 7.5 mm², and >7.5 mm², respectively. Late-acquired ISA at follow-up was observed in 7 patients and there was no difference in the incidence of ISA between both groups [abciximab-coated stent: $n=3$ (4%) vs. BMS: $n=4$ (6%), $p=0.698$].

Conclusion: Abciximab-coated stent reduced restenosis and had a considerably lower optimal MSA threshold compared to BMS and showed lower incidence of late-acquired ISA.

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1. Introduction

We previously reported that abciximab-coated stent was effective in the prevention of in-stent neointimal hyperplasia and there was no acute or subacute stent thrombosis even in patients with acute myocardial infarction and unstable angina [1].

Drug-eluting stents (DESs) have reduced the restenosis rate to $<10\%$ and appear to be a promising approach to reducing neointimal hyperplasia [2–4]. Previous studies have demonstrated that intravascular ultrasound (IVUS)-derived minimum stent area (MSA) affects the long-term need for repeat revascularization after bare metal stent (BMS) [5,6] and DES implantation [7–10].

Late-acquired incomplete stent apposition (ISA) has been reported after brachytherapy, BMS, and DES implantation [11–18]. Several studies have reported that the incidence of late ISA was 5% after BMS implantation [15], 8% after slow-

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release paclitaxel-eluting stent and 10% after moderate-release paclitaxel-eluting stent implantation [16], and 9% after sirolimus-eluting stent implantation [17].

The aim of the present study was to evaluate the predictive value of MSA for long-term stent patency and the incidence and long-term prognosis of late ISA after abciximab-coated stent implantation.

2. Methods

2.1. Study population

This was a single-center prospective, randomized trial of coronary artery disease patients who were scheduled to undergo elective coronary intervention for de novo lesions in native coronary arteries. We analyzed 138 patients with complete poststenting and follow-up IVUS studies after implantation of abciximab-coated stent ($n=69$) and BMS ($n=69$). Lesions >10 mm and <28 mm in length and vessels >2.5 mm and <4.0 mm in diameter were included. Balloon predilation was performed, followed by stent implantation. Postdilation was performed if necessary. The patients with left main disease, graft stenosis, and left ventricular dysfunction were excluded. All patients received dual therapy with clopidogrel (300 mg loading dose, followed by 75 mg daily) in addition to acetylsalicylic acid (300 mg loading dose, followed by 100 mg daily). Dual anti-platelet therapy was used up to 6 months, and thereafter acetylsalicylic acid alone was used in both groups.

2.2. Coating technology of abciximab-coated stent

MAC stent was used as platform for abciximab coating. Abciximab coating into MAC stent was performed according to the protocol previously described [1]. Briefly, a plasma polymerization reaction was performed to attach amine radicals to stent surface. For the attachment of amine radicals to the stent surface, diaminocyclohexane monomer was drifted to the tubular reactor in a constant dose, and plasma was generated with a radiofrequency power generator. The used abciximab is a human-murine chimeric antibody Fab fragment [ReoPro (Eli Lilly and Company, Indianapolis, Indiana)]. The carboxy radical of abciximab was introduced to amine radical attached to stent to achieve covalent bond and improved attachment power between stent and abciximab. Abciximab coating on the surface of the stent was confirmed by scanning electron microscopy. The amount and the median thickness of abciximab coating on the surface of the stent were 90 μg and 1 μm , respectively.

2.3. Quantitative coronary angiography (QCA)

Coronary angiogram was analyzed with validated QCA system (Phillips H5000 or Allura DCI program). Minimal luminal diameter, reference diameter were measured in

identical views before percutaneous balloon angioplasty and immediately after stent implantation and at follow-up.

2.4. IVUS imaging and analysis

All IVUS studies were performed after administration of intracoronary nitroglycerin. The IVUS catheter was advanced distal to the stent, and imaging was acquired using commercially available imaging systems with automated transducer pullback speed of 1 mm/s. We measured external elastic membrane (EEM) and lumen cross-sectional area (CSA). Plaque plus media (P&M) CSA was calculated as EEM CSA minus lumen CSA, and plaque burden was calculated as $100 \times (\text{P\&M CSA} / \text{EEM CSA})$. The EEM CSA was measured by tracing the leading edge of the adventitia; this has been shown to be a reproducible measure of total arterial CSA. The lesion was the site with the smallest lumen CSA; if there were multiple image slices with the same minimum lumen CSA, then the slice with the largest EEM and P&M was measured. Quantitative IVUS analysis was performed using computerized planimetry at ISA sections as well as stented segments with complete late apposition and reference segments. Vessel, stent, lumen, and neointimal area were computed for the stented segment. Postprocedure MSA and follow-up neointimal area at the minimum lumen area site were obtained. ISA was defined as one or more stent struts clearly separated from the vessel wall with evidence of blood speckles behind the strut in a vessel segment not associated with any side branches [12,19]. Resolved ISA was defined as ISA present after stenting but no longer present at follow-up. Persistent ISA was defined as ISA present both after stenting and follow-up. Late-acquired ISA was defined as not present at baseline but present at follow-up. Quantitative measurements of incompletely apposed sections included the EEM, stent, and lumen CSA, and were performed at the area of greatest stent–lumen separation at follow-up IVUS imaging and matched with the corresponding image from after stenting.

2.5. Clinical follow-up

Clinical status was assessed at hospital discharge and every 4 weeks after the procedure. The 6-month follow-up was an office visit together with angiographic and IVUS follow-up. The 6-month follow-up angiogram and IVUS were performed in all patients. Angiographic restenosis was defined as stenosis more than 50% of target lesion on follow-up coronary angiogram and target lesion revascularization was mandated by degree of restenosis. The 12-month follow-up was an office visit or a phone call. The 12-month clinical follow-up was completed in all patients. We observed the major adverse cardiac events including cardiac death, myocardial infarction, target lesion revascularization, and stent thrombosis in patients with persistent ISA and in patients with late-acquired ISA after both abciximab-coated stent and BMS implantation during 12-month follow-up.

Table 1
Baseline clinical and procedural characteristics

	Abciximab stent (n=69)	BMS (n=69)	p
Age (years)	57.2±10.4	58.3±11.2	0.584
Men (n)	56 (81%)	53 (77%)	0.531
Diabetes mellitus (n)	16 (23%)	13 (19%)	0.531
Hypertension (n)	35 (51%)	34 (49%)	0.865
Dyslipidemia (n)	28 (41%)	26 (38%)	0.727
Current smoker (n)	38 (55%)	37 (54%)	0.864
Unstable angina (n)	38 (55%)	37 (54%)	0.864
ST elevation myocardial infarction	19 (28%)	18 (26%)	0.848
Ejection fraction (%)	62.3±11.6	63.4±12.5	0.564
Target coronary arteries (n)			0.770
Left anterior descending artery	40 (58%)	44 (64%)	
Left circumflex artery	10 (15%)	8(12%)	
Right coronary artery	19 (28%)	17 (25%)	
ACC/AHA type (n)			0.853
B ₁	61 (88%)	59 (86%)	
B ₂	6 (9%)	8 (12%)	
C	2 (3%)	2 (3%)	
Stent size (mm)	3.28±0.36	3.29±0.43	0.785
Stent length (mm)	19.5±4.1	19.2±4.4	0.512
Use of additional high pressure balloons	23(33%)	28 (41%)	0.378
Reference vessel diameter (mm)	3.29±0.31	3.26±0.36	0.578
Minimal lumen diameter (mm)			
Preintervention	1.09±0.57	0.93±0.56	0.281
Postintervention	2.81±0.51	2.74±0.54	0.591
Follow-up	2.51±0.48	2.06±0.49	0.011
Late loss	0.30±0.24	0.68±0.36	0.010

BMS: bare metal stent, ACC/AHA: American College of Cardiology/American Heart Association.

2.6. Statistical analysis

Statistical analysis was performed with the aid of the commercially available software (SPSS Version 11). Continuous data are presented as the mean value±SD, and categorical data are presented as frequencies. Continuous variables between were compared by use of the unpaired Student *t* test. Categorical variables were compared using chi-square statistics. A value of *p*<0.05 was considered significant.

3. Results

3.1. Baseline and procedural characteristics

The patient's baseline and procedural characteristics are shown in Table 1. There were no significant differences in baseline clinical characteristics between both groups. However, minimal lumen area was larger and late loss was smaller in abciximab-coated stent group at follow-up angiogram.

3.2. IVUS results

Serial IVUS measurements are shown in Table 2. Baseline stent and reference measurements were similar

between both groups. Overall, there was a decrease in lumen CSA and an increase in neointimal hyperplasia area at follow-up in the stented segment in both groups. A net decrease in lumen CSA was smaller in the abciximab-coated stent group than that in the BMS group (*p*=0.001) and a net increase in neointimal hyperplasia area was smaller in the abciximab-coated stent group than that in the BMS group (*p*<0.001).

3.3. In-stent restenosis and target lesion revascularization according to postprocedure MSA

The postprocedure MSA was <6 mm² in 20 lesions (29%), 6 to 7.5 mm² in 20 lesions (29%), 7.5 to 10 mm² in 21 lesions (30%), and >10 mm² in 29 lesions (42%), 28 lesions (40%) in abciximab-coated stent and BMS group, respectively. Abciximab-coated stent effectively reduced the incidence of in-stent restenosis and target lesion revascularization compared with BMS (Fig. 1). Most in-stent restenosis was observed in lesions with postprocedure MSA of <6 mm² (10% in the <6 mm² group, 1% in the 6 to 7.5 mm² group, and 0% in the >7.5 mm² group) and all target lesion revascularization occurred in lesions with postprocedure MSA of <6 mm² in the abciximab-coated stent group (Fig. 2).

Table 2
Intravascular ultrasound measurements

	Abciximab stent (n=69)	BMS (n=69)	p
Preintervention			
Proximal reference EEM CSA (mm ²)	14.6±4.3	14.2±4.5	0.451
Lesion site EEM CSA (mm ²)	13.9±4.0	13.7±4.9	0.512
Lesion site lumen area (mm ²)	4.3±2.4	4.2±2.8	0.823
Lesion site P&M CSA (mm ²)	9.6±3.0	9.5±3.8	0.845
Lesion site plaque burden (%)	69.1±7.3	69.3±8.7	0.768
Distal reference EEM CSA (mm ²)	13.1±4.1	13.0±3.8	0.789
Postintervention stent CSA (mm ²)	7.9±3.2	7.7±2.5	0.712
Follow-up			
Proximal reference EEM CSA (mm ²)	14.5±4.5	14.5±3.8	0.811
Stent CSA (mm ²)	7.8±3.0	7.8±2.6	0.878
Intrastent lumen area (mm ²)	5.9±1.6	4.5±1.7	0.001
Intrastent neointimal hyperplasia area (mm ²)	1.9±1.5	3.3±1.9	<0.001
Distal reference EEM CSA (mm ²)	13.3±3.5	13.1±3.4	0.687
Serial (after intervention to follow-up) comparison			
ΔProximal reference EEM CSA (mm ²)	-0.1±0.8	0.3±1.1	0.245
ΔStent CSA (mm ²)	-0.1±1.2	0.1±1.4	0.378
ΔIntrastent lumen area (mm ²)	-2.0±1.5	-3.2±1.8	0.001
ΔIntrastent neointimal hyperplasia area (mm ²)	1.9±1.5	3.3±1.9	<0.001
ΔDistal reference EEM CSA (mm ²)	0.2±1.3	0.1±1.3	0.767

BMS: bare metal stent, EEM; external elastic membrane, CSA: cross-sectional area, P&M: plaque plus media.

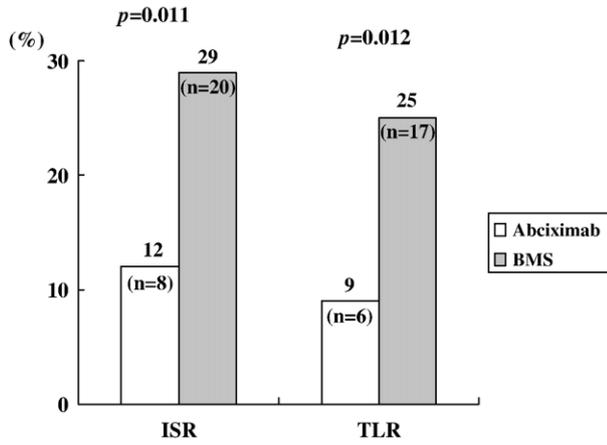


Fig. 1. Incidence of in-stent restenosis (ISR) and target lesion revascularization (TLR) at 6-month follow-up.

3.4. Incidence and clinical outcome of ISA

The incidence of ISA is shown in Table 3 according to the classification of ISA. Poststenting ISA was observed in 13 patients [abciximab-coated stent: n=7 (10%) vs. BMS: n=6 (9%)]. Of 7 instances of ISA observed after the procedure in

Table 3

Incidence of incomplete stent apposition

	Abciximab stent (n=69)	BMS (n=69)	p
Poststenting ISA (n)	7 (10%)	6 (9%)	0.771
Resolved ISA (n)	4 (6%)	3 (4%)	0.698
Persistent ISA (n)	3 (4%)	3 (4%)	1.000
Late-acquired ISA (n)	3 (4%)	4 (6%)	0.698

BMS: bare metal stent, ISA: incomplete stent apposition.

the abciximab-coated stent group, 4 were resolved at 6 months. In the BMS group, 3 of 6 were resolved. Late-acquired ISA was observed in 3 patients (4%) in abciximab-coated stent group compared to 4 patients (6%) in BMS group. 7 patients with 7 late-acquired ISA segments were assessed quantitatively. The extent of late-acquired ISA measured by length, volume is summarized in Table 4. Poststenting and follow-up EEM CSA, poststenting and follow-up stent CSA, poststenting and follow-up P&M CSA were similar between both groups. Late-acquired ISA was the result of an increase in EEM CSA from poststenting to follow-up without change in plaque behind the stent. No difference was observed in ISA length and ISA volume between both groups. At 12-month clinical follow-up, there were no cardiac death, myocardial infarction, target lesion revascularization, and subacute or late stent thrombosis in patients with persistent ISA and in patients with late-acquired ISA after both abciximab-coated stent and BMS implantation.

4. Discussion

The present study shows that postprocedure MSA affects the long-term need for repeat revascularization after abciximab-coated stent and BMS implantation, and a postprocedure MSA >6 mm² in abciximab-coated stent and >7.5 mm² in BMS may be needed to obtain an optimal IVUS result. Late-acquired ISA after abciximab-coated stent implantation was observed in 4% of patients, and this

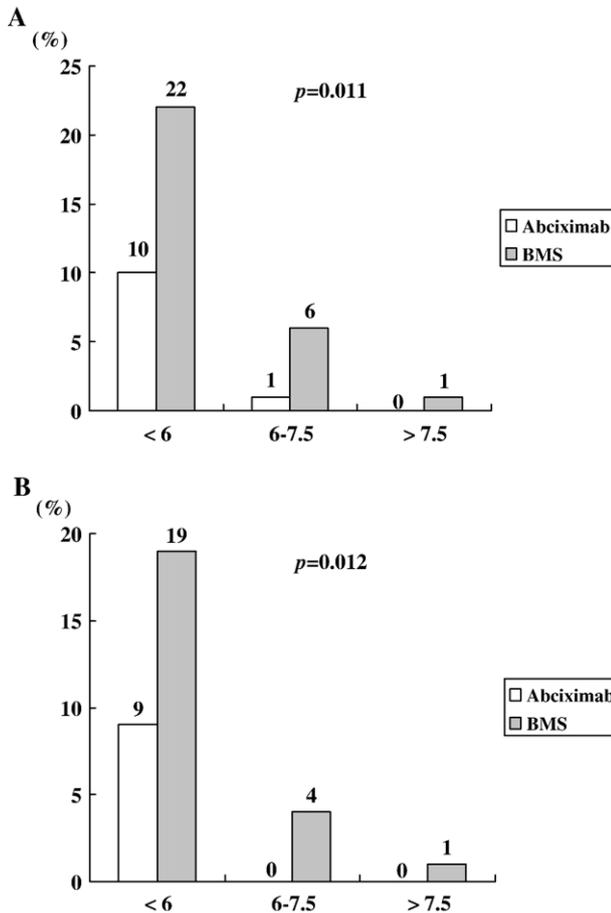


Fig. 2. Relation between final minimum stent area and in-stent restenosis (A) and target lesion revascularization (B).

Table 4

Baseline and follow-up IVUS measurements of late-acquired incomplete stent apposition

	Abciximab stent (n=3)	BMS (n=4)	p
Poststenting EEM CSA (mm ²)	14.8±3.1	14.7±3.1	0.911
Follow-up EEM CSA (mm ²)	17.5±3.7	17.7±4.0	0.787
ΔEEM CSA (mm ²)	2.7±3.9	3.0±3.8	0.643
Poststenting stent CSA (mm ²)	7.9±3.2	7.7±2.5	0.712
Follow-up stent CSA (mm ²)	7.8±3.0	7.8±2.6	0.978
Poststenting P&M CSA (mm ²)	9.6±3.0	9.5±3.8	0.898
Follow-up P&M CSA (mm ²)	9.7±3.2	9.8±3.9	0.902
ISA length (mm)	3.1±1.2	4.7±3.8	0.123
ISA volume (mm ³)	9.4±3.1	10.5±4.1	0.265

BMS: bare metal stent, EEM; external elastic membrane, CSA: cross-sectional area, P&M: plaque plus media, ISA: incomplete stent apposition.

incidence was comparable with that of BMS and the extent of ISA was similar between both groups. More than 50% of poststenting ISA resolved at follow-up. An increase of vessel area without change in plaque area was associated with the development of late-acquired ISA. Late-acquired ISA was not associated with any subsequent events.

Abciximab blocks final pathway of platelet aggregation and decreases short- and long-term event rates after percutaneous coronary intervention [20–23]. Besides blocking the effect of platelet aggregation, abciximab reacts to CD11b/CD18 of vascular endothelial cell and macrophage and inhibits inflammatory reaction and proliferation of vascular smooth muscle cells [24–28]. We previously reported that abciximab-coated stent was effective in the prevention of in-stent neointimal hyperplasia and there was no acute or subacute stent thrombosis even in patients with acute myocardial infarction and unstable angina. We suggested that the possible mechanisms responsible for inhibition of neointimal hyperplasia by abciximab might be anti-platelet, anti-inflammatory, and anti-proliferative actions [1].

DESs have considerably reduced the rate of in-stent restenosis compared with BMS by preventing neointimal growth [2–4]. The postprocedure MSA is a strong predictor of in-stent restenosis after BMS [5,6] and DES implantation [7–10]. Recently, Sonoda et al. reported that a MSA <5 mm² differentiated sirolimus-eluting stent with a follow-up minimum lumen area >4 or <4 mm² [7]. Cheneau et al. reported that the final MSA was smaller in lesions that experienced target lesion revascularization than in lesions without target lesion revascularization, and all target lesion revascularization occurred in lesions with final MSA of <6 mm² [8]. In the present study, all target lesion revascularization occurred in lesions with postprocedure MSA of <6 mm² after abciximab-coated stent implantation. Our study establishes that post-procedure MSA affects outcome after abciximab-coated stent implantation and a postprocedure MSA >6 mm² may be sufficient to obtain an optimal IVUS results following abciximab-coated stent implantation.

Late-acquired ISA has been reported after brachytherapy, BMS, and DES implantation [11–18]. Late-acquired ISA is more commonly observed after brachytherapy and DES implantation than after BMS implantation [12,14]. Several studies have reported that the incidence of late ISA was 5% after BMS implantation [15], 8% after slow-release paclitaxel-eluting stent and 10% after moderate-release paclitaxel-eluting stent implantation [16], and 9% after sirolimus-eluting stent implantation [17]. Recently, of late ISA occurred in 82 patients with 85 lesions, Hong et al. reported that there were no major adverse cardiac events in late ISA patients during a mean 10-month follow-up after detection of late ISA [18]. In the present study, no cardiac death, myocardial infarction, target lesion revascularization, and late stent thrombosis occurred in patients with persistent ISA and in patients with late-acquired ISA after abciximab-coated stent implantation at 12-month clinical follow-up. Therefore, the clinical significance of ISA is considered to be

benign, but larger cohorts are necessary to confirm this finding.

There are several limitations to be mentioned. Firstly, the results obtained are limited to vessel diameters and stent lengths. These findings should be confirmed in real-world registries that may enroll more complex lesions in smaller vessels. Secondly, this study is based on a small number of total and late-acquired ISA cases. Thirdly, this represents a time frame of 12 months. Therefore, longer-term follow-up with larger cohorts will be necessary to confirm this finding.

5. Conclusions

The postprocedure MSA >6 mm² may be sufficient to obtain an optimal IVUS result following abciximab-coated stent implantation and abciximab-coated stents do not increase the incidence of late-acquired ISA compared with BMS.

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