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Factors that Predict Target Lesion Revascularization in Patients with Paclitaxel–eluting Stent Implantation

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Abstract：The purpose of this study was to evaluate the predictors of target lesion revascularization (TLR) after Paclitaxel–eluting stent (PES) implantation in three hundred twenty nine lesions of 250 patients with coronary artery disease. All pre– and post–procedural images were analyzed using a CMS–GFT system (MEDIS, The Netherlands). The incidence of insulin–treated diabetes mellitus was significantly higher in the TLR group than in the non–TLR group (15.9% vs. 4.17%, p=0.03). The lesion length was longer and the reference diameter was smaller in the TLR group than in the non–TLR group (19.8±11.3 mm vs. 15.3±8.1 mm, p=0.03, 2.48±0.47 mm vs. 2.88±0.6 mm, p=0.01, respectively). The incidence of severe calcification was higher in the TLR group than in the non–TLR group (33.3% vs. 8.3%, p=0.027). A multivariate analysis showed that stent length and calcification were strong predictors of TLR after PES implantation in this study ; stent length was associated with a 1.3– to 14.4–fold higher relative risk of TLR, while patients with calcification were associated with a 2.0– to 26.5–fold higher risk of TLR relative to those without calcification.

Key words：**Paclitaxel–eluting stent, Restenosis, Target lesion revascularization**

Introduction

A Drug–Eluting Stent (DES) drastically reduces angiographic restenosis after percutaneous coronary intervention. However, the incidence of Target Lesion Revascularization (TLR) after Paclitaxel –eluting stent (PES) implantation is 1–12.0%[1)–3)], and previous large trials have identified some factors that predict restenosis. The aim of this study was to evaluate predictors of TLR after PES implantation in a single hospital in Brazil.

Subjects and Methods

Subjects

Three hundred twenty–nine lesions (250 patients) were treated with PES at Hospital Cardiologico Costantini, Brazil, from 3/28/2003 to 10/20/2004. Forty three of these lesions required clinically driven TLR. This study compared the patient and angiographic characteristics of the TLR cases to those in the non–TLR cases. The mean follow–up period was 286.7±123.1 days. Any patients with myocardial infarction were excluded from the study.

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PCI procedure

Several surgeons performed DES implantation according to the standard technique using intravascular ultrasonography. The endpoint of the procedure for the main vessel was a final value of TIMI (Thrombolysis in Myocardial Infarction)of 3, angiographic percent diameter stenosis (%DS)＜10% and no major dissection that would compromise the flow of the vessel. Provisional stenting was performed for side-branch treatment.

Medication

Dual antiplatelet therapy with aspirin (100 mg daily) and clopidogrel (75 mg daily) was started at least 48 hours before the procedure. Aspirin was continued for an indefinite period, and the same dose of clopidogrel was continued for at least 6 months. Myocardial infarction (MI) was defined as CK-MB or Tn-T elevation above the normal limit with the development of new pathological Q-waves in two or more leads (Q-wave myocardial infarction) or the elevation of CK-MB or Tn-T alone without new pathological Q-waves (non-Q-wave myocardial infarction).

Quantitative coronary angiographic evaluation

An angiographic core laboratory at Fukuoka University Hospital analyzed all pre- and post-procedural images using a CMS-GFT system (MEDIS, The Netherlands). All measurements were performed on angiographic images that were recorded after the intracoronary administration of nitroglycerin. The target lesion was defined as the stented lesion and 5 mm proximal and 5 mm distal to the edge of the stent. Calcification was defined as" readily apparent densities seen within the artery wall and the site of the lesion as an x-ray-absorbing mass," and was classified as none/mild, moderate (densities noted only during the cardiac cycle before contrast injection), or severe (radiopacity noted without cardiac motion before contrast injection generally involving both sides of the arterial wall).

Statistical Analysis

All statistical analyses were performed using the SAS (Statistical Analysis System) Software Package (Version 9.1, SAS Institute, CA, USA) at Fukuoka University. The distribution of variables was examined by the Shapiro-Wilk test. Differences in categorical variables between TLR and non-TLR cases were examined by the Chi-square test. Differences in continuous variables between TLR and non-TLR cases were examined by an analysis of variance and/or the Wilcoxon rank-sum test. Correlations between variables were examined by the Spearman correlation. The odds ratio and 95% confidence interval (CI) are given. All p values are two-tailed. The significance level was considered to be 5% unless indicated otherwise. A multivariate logistic regression analysis was used to identify independent predictors of TLR after PES implantation.

Results

Patient and Lesion Characteristics

The baseline patient characteristics are shown in Table 1. There were no significant differences in age or the prevalence of male or diabetic patients between the TLR and non-TLR groups. The incidence of insulin-treated diabetes mellitus was significantly higher in the TLR group than in the non-TLR group (15.9% vs. 4.17%, p=0.03). Although the incidence of prior MI tended to be higher in the TLR group, this difference was not statistically

Table 1 Patient characteristics in the TLR and non-TLR groups

	TLR (N=43)	Non-TLR (N=286)	P-value
Mean age (years)	64.8±10.4	64.4±11.7	N.S
Male	38 (88.7%)	216 (75.7%)	N.S
Prior MI	13 (30.2%)	70 (24.6%)	0.06
Prior CABG	10 (23.2%)	62 (21.8%)	N.S
Current Smoker	16 (36.4%)	104 (36.4%)	N.S
Dys-lipidemia	29 (68.2%)	179 (62.6%)	N.S
Hypertension	29 (68.8%)	188 (65.9%)	N.S
Family history	17 (40.1%)	130 (45.8%)	N.S
LVEF-UCG	27 (62.3%)	188 (66%)	N.S
Renal failure	0 (0%)	1 (0.4%)	N.S
Current Smoker	15 (36.4%)	104 (36.4%)	N.S
BMI	28.7	27.2	N.S
Diabetes Mellitus (%)	14 (31.8%)	75 (26.4%)	N.S
Insulin therapy	7 (15.9%)	12 (4.17%)	0.003
Oral agents	7 (15.9%)	60 (20.8%)	N.S

TLR : target lesion revascularization
MI : myocardial infarction
CABG : coronary-artery bypass graft
LVEF-UCG : Left ventricular ejection fraction
BMI body mass index

significant. The lesion characteristics are shown in Table 2. The lesion length was longer and the reference diameter was smaller in the TLR group than in the non-TLR group (19.8±11.3 mm vs. 15.3 ±8.1 mm, p=0.03, 2.48±0.47 mm vs. 2.88±0.6 mm, p =0.01, respectively). The incidence of severe calcification was higher in the TLR group than in the non-TLR group (33.3% vs. 8.3%, p=0.027)

Procedural results

Procedural results are shown in Table 3. The stent length was greater (29.7±10.8 mm vs. 23.0± 10.1 mm, p=0.014) and in-lesion %DS after the procedure was greater (27.9±12.4% vs. 21.0±10.6%, p= 0.008) in the TLR group than in the non-TLR group.

Table 2 Lesion characteristics in the TLR and non-TLR groups

	TLR (N=43)	Non-TLR (N=286)	P-value
Lesion length (mm)	19.8±11.3	15.3±8.1	0.03
Reference (mm)	2.48±0.47	2.88±0.66	0.01
%DS	59.8	60.6	N.S
MLD (mm)	1.03±0.47	1.14±0.48	N.S
Proximal normal (mm)	3.27±0.48	3.32±0.77	N.S
Distal normal (mm)	2.25±0.47	2.49±0.50	N.S
ACC type B2/C (%)	66.2	66.4	N.S
ISR (%)	23.8	17.4	N.S
LMT (%)	0	8.24	0.055
Blush grade 3 (%)	85.7	80.9	N.S
Calcification (%)	33.3	8.3	0.0027
Eccentric (%)	38.1	29.7	N.S
Tortuosity (%)	4.7	8.3	

TLR : target lesion revascularization
%DS : % diameter stenosis, MLD : minimum lumen diameter
ISR : in stent re-stenosis, LMT : left main trunk

Table 3 Procedural results in the TLR and non-TLR groups

	TLR (N=43)	Non-TLR (N=286)	P-value
MLD (In-lesion : mm)	1.97±0.47	2.22±0.56	0.06
%DS (In-lesion : %)	27.9±12.4	21.0±10.6	0.008
Min proximal edge (mm)	2.72±0.66	2.94±0.62	N.S
Min distal edge	2.13±0.55	2.35±0.59	N.S
MLD (In-stent)	2.58±0.47	2.71±0.50	N.S
%DS (In-stent : %)	13.5	11.7	N.S
Stent Length (mm)	29.7±10.8	23.0±10.1	0.014

TLR : target lesion revascularization
%DS : % diameter stenosis, MLD : minimum lumen diameter

In-hospital and follow-up clinical outcomes

Table 4 shows the in-hospital and long-term clinical outcomes. The incidences of death and MI due to definite or possible stent thrombosis were 0.3% and 0.6%, respectively. During the follow-up period, the incidences of death and MI were 1.9% and 0.9%. There was no stent thrombosis after discharge. Clinically-driven TLR was performed in 11.1% of all patients.

Predictors of TLR

A multivariate analysis demonstrated that calcification and stent length were factors that predicted TLR after PES implantation in this study. As shown in Table 5, patients with calcification were associated with a 2.0- to 26.5-fold higher risk of TLR relative to those without calcification. Stent length was associated with a 1.3- to 14.4-fold higher relative risk of TLR.

Discussion

PES drastically reduces restenosis and TLR after PCI by preventing negative remodeling by a metal stent and by suppressing neointimal hyperplasia by anti-proliferative agents. In this study, the incidence of TLR at 6 months after PES implantation was 11.1%, which was higher than the values in major PES trials. However, this study included a higher proportion of complex patient and lesion characteristics, such as more frequent left ventricu-

Table 4 In-hospital and long-term clinical outcomes

	In-hospital	Follow-up
Death	1 (0.3%)	6 (1.9%)
MI	2 (0.6%)	3 (0.9%)
CVA	1 (0.3%)	0 (0%)
TLR	1 (0.3%)	36 (11.1%)
Stent thrombosis	2 (0.6%)	7 (2.2%)

MI : myocardial infarction, CVA : cerebrovascular accident,
TLR : target lesion revascularization

Table 5 Factors that predict TLR after PES implantation as assessed by multivariate analysis

	Odds ratio	P-value
Calcification	7.2 (2.0-26.5)	0.002
Stent length	4.3 (1.3-14.4)	0.01

TLR : target lesion revascularization

lar dysfunction, smaller reference vessel diameter or longer lesions, in comparison to other trials. Although some factors such as diabetes mellitus (DM), long lesion, small reference vessel, and small final MLD (minimal lumen diameter) have been reported as predictors of TLR after BMS, it is unclear whether these factors also predict TLR after DES implantation. Lee and Park reported post–intervention MLD, and lesion length was an independent predictor of restenosis after PES implantation.[4)–5)] Similarly, the lesion length was greater and the post–intervention %DS was higher in the TLR group than in the non–TLR group in the current study.

Calcification was identified as an independent predictor of TLR in the present study. Calcification interrupts stent expansion to result in restenosis and TLR.[6)] Although rotational atherectomy has improved the immediate results of angioplasty in calcified arteries, it has not reduced the incidence of TLR.[4)–5)] Kawaguchi reported that the incidence of TLR was significantly higher in calcified lesions than in non–calcified lesions after sirolimus–eluting stent (SES) implantation (7.3% vs. 2.8%; $P<0.05$).[7)–8)] Patients with heavily calcified lesions have been excluded from enrollment in most major randomized trials of drug–eluting stents.[9)–11)] The TAXUS–II sub–study, which demonstrates that PES reduces the 12–month TLR and TVR by about 65%, showed that the implantation of PES significantly reduced restenosis in patients with and without calcified lesions.

However, patients with moderate to severe calcification were excluded in the TAXUS–II. Damage to the polymer coating of a drug–eluting stent may occur when a DES is delivered through a calcified artery and this might be one of the reasons why calcification was a predictor of TLR.[8)12)]

The length of a stented segment in the bare metal stent era, was reported to be an independent predictor of TLR.[13)] Aoki reported that a stent length of 64 mm with DES for de novo coronary artery lesions is associated with a low incidence of TVR without an increase in adverse cardiac events at 1 year.[14)] Although the incidence of TLR was also reduced by DES in long lesions in the current study, stent length still predicted TLR after PES implantation.

Although no difference was observed in the incidence of TLR between all diabetic mellitus patients and non–diabetic patients, there were more insulin–treated diabetic patients in the TLR group than in the non–TLR group in the present study. A more diffuse and accelerated form of atherosclerosis accompanied by a smaller vessel size may contribute to the increased risk for restenosis after bare metal stent implantation in patients with diabetes. Diabetes mellitus also influences remodeling, not only in the lesion in which negative remodeling has been demonstrated but also in the reference segment, which may show inadequate positive remodeling.[15)16)] However, diabetes mellitus was not a predictor of TLR in the current study. This result suggests that paclitaxel might play an important role in reducing TLR in patients with diabetes mellitus, similar to non–diabetic patients. The primary mechanism of action of paclitaxel is the prevention of microtubule depolymerization, which is required for mitosis to progress through anaphase. Since paclitaxel modulates cell mitogenesis downstream from Ras/Raf/MAP kinase, independent of PI3 kinase/PKb/mTOR signal–transduction pathways, it may be particularly effective in the diabetic with insulin resistance by inhibiting both insulin–dependent and –independent pathways that mediate neointimal hyperplasia.[17)] There were more cases of insulin–treated DM in the TLR group than in the non–TLR group in the current study. Insulin–treated diabetes may be associated with an increased frequency of negative remodeling.[18)–19)] A more–diseased vessel with a small vessel size may contribute to an increased risk of TLR in patients with insulin–treated diabetes mellitus.

Limitations

The most important limitation of this study is the small number of patients. Since the incidence of TLR after DES implantation is thought to be low, the number of patients in this study has limited the power to identify predictors of TLR after DES implantation. In addition, this study did not evaluate whether the risk factors were well controlled. Serum lipid profiles, HbA1c and other important markers should be tested. The details

of medical treatment should therefore be checked as well.

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