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Possible Predictors of Target Lesion Revascularization After Drug-Eluting Stent Implantation

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Abstract

Background. A small number of patients still need target lesion revascularization (TLR) after drug-eluting stent (DES) implantation. It is important for the management of coronary artery disease to assess the predictors of TLR after DES implantation.

Methods and Results. Two hundred ninety-seven patients (325 lesions) were treated with Cypher™ sirolimus-eluting and/or TAXUS™ paclitaxel-eluting stent implantation at four centers in Japan and Brazil. Among these centers, 20 patients (24 lesions) needed clinically driven TLR. The clinical and angiographic characteristics of TLR patients were compared to those of non-TLR patients. Hemodialysis, prior myocardial infarction (MI) and prior coronary artery bypass grafting (CABG) were more frequent in TLR patients than in non-TLR patients. An ostial stenosis was more frequent in the TLR group than in the non-TLR group (41.7% vs 19.9%, $p=0.012$). In addition, post-procedure in-stent percentage diameter stenosis (%DS) was higher in TLR patients (21.9% vs 13.3%, $p=0.002$). Stepwise logistic regression analysis indicated that all of these variables were independent predictors of TLR after DES implantation.

Conclusions. Hemodialysis, prior MI, prior CABG, ostial lesion location and high in-stent %DS may be independent predictors of TLR after DES implantation.

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Key Words

■**Stent (drug-eluting)** ■**Revascularization**

INTRODUCTION

Both Cypher™ sirolimus-eluting stent (SES) and TAXUS™ paclitaxel-eluting stent (PES) have been proven to reduce restenosis after percutaneous coronary intervention (PCI) and to improve the clinical outcome in patients with PCI in many clinical trials.[1–3] However, a small number of patients still

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experience restenosis after SES or PES implantation and require target lesion revascularization (TLR). Although some factors such as diabetes, long lesion or small vessel[4,5] are well known to predict TLR after bare metal stent (BMS) implantation, such predictors after drug-eluting stent (DES) implantation have not yet been clarified. The purpose of this study was to identify possible predictors of TLR after DES implantation and to clarify their possible significance in the management of coronary artery disease.

SUBJECTS AND METHODS

Study design

Consecutive patients who had been treated with SES or PES and who had more than 6 months of clinical follow-up at the Clinica Cardiologico C. Costantini (Curitiba, Brazil) between May 2003 and June 2004, or at Fukuoka University Hospital, Fukuoka University Chikushi Hospital and White Cross Hospital between August 2004 and July 2005, were enrolled in this study. Clinical characteristics, lesion characteristics, interventional procedure and clinical events were compared between 20 patients (24 lesions) with TLR (TLR group) and 277 without TLR (non-TLR group) in a total of 297 patients (192 SES, 134 PES) with 325 lesions to evaluate the predictors of TLR after DES implantation. Patients with acute myocardial infarction (MI) within 24 hr after the onset were excluded from this study. Clopidogrel or ticropidine was prescribed for at least 6 months. Clinical follow-up information was obtained by telephone contact or by reviewing hospital records. During follow-up, coronary angiography was performed only as clinically indicated in Brazil and routinely in Japan. TLR was basically performed when the percentage diameter stenosis (%DS) of the target lesion was more than 50 and myocardial ischemia was documented in the target vessel area by a noninvasive method. Acute MI was defined by a rise in the creatine kinase level of more than twice the upper normal limit with an increased creatine kinase-MB or Troponin-T. This study was approved by the ethics committee of Fukuoka University Hospital.

The angiographic laboratory at Fukuoka University Hospital analyzed all procedural and post-procedural angiographic images using CMS-GFT (MEDIS). The angiographic laboratory was unaware of the treatment assignment. All measurements were performed on angiographic images recorded after the intracoronary administration of nitroglycerin. The target lesion was defined as the stent and 5 mm proximal and distal to the edge of the stent. Ostial lesions were those that began within 3 mm of the major epicardial artery ostium.

Statistical analysis

All statistical analyses were performed using the SAS (Statistical Analysis System) Software Package (Version 9.1, SAS Institute) at Fukuoka University. The distribution of variables was examined by the Shapiro-Wilk test. Differences in categorical variables between the TLR and non-TLR groups were examined by the chi-square test. Differences in continuous variables between the TLR and non-TLR groups were examined by analysis of variance and/or the Wilcoxon rank-sum test. Correlations between variables were examined by the Spearman correlation. Stepwise multiple regression analysis was used to examine the independent variables that predicted TLR. The significance of the variables that predicted TLR after controlling for other related variables was examined by multivariate logistic regression analysis using dummy variables. The odds ratio and 95% confidence interval are given. All p values are two-tailed. The significance level was considered to be 5% unless indicated otherwise.

RESULTS

Clinical and lesion characteristics

The mean follow-up period in all patients was 174.6 ± 72.7days. There was no death and 1 (0.4%) MI because of stent thrombosis during this period (**Table 1**). Baseline patient characteristics are shown in **Table 2**. There were no significant differences in age or the incidence of male or diabetic patients between the TLR and non-TLR groups. The prevalences of prior MI, prior coronary artery bypass grafting (CABG) and hemodialysis were higher in the TLR group than in the non-TLR group (60.0% vs 27.5%, $p = 0.004$, 45.0% vs 18.7%, $p = 0.009$, 8.3% vs 0.7%, $p = 0.028$, respectively). Although lesion length in the TLR group was greater than that in the non-TLR group, this difference was not statistically significant. Ostial stenosis was more frequent in the TLR group than in the non-TLR group (41.7% vs 19.9%, $p = 0.012$; **Table 3**).

Table 1 Overall clinical events

	In hospital	After discharge
Follow-up period(days)		174.6±72.7
Death	0	0
MI	0	1(0.4%)
TLR PCI	0	20(6.7%)
TLR CABG	1(0.4%)	0
Stent thrombosis	1(0.4%)	1(0.4%)

MI=myocardial infarction; TLR=target lesion revascularization; PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting.

Table 2 Clinical characteristics

	TLR group (n=20)	Non-TLR group (n=277)	p value
Age(yr, mean±SD)	65±11	63±11	NS
Male(%)	90	77.8	NS
DM(%)	35.0	23.8	NS
HT(%)	85.0	68.7	NS
HL(%)	60.0	70.6	NS
UAP(%)	25.0	29.1	NS
Prior MI (%)	60.0	27.5	0.004
Prior CABG(%)	45.0	18.7	0.009
HD(%)	8.3	0.7	0.028

DM= diabetes mellitus; HT=hypertension; HL=hyperlipidemia; UAP=unstable angina pectoris; HD=hemodialysis. Other abbreviations as in Table 1.

Table 3 Lesion characteristics

	TLR group (n=24)	Non-TLR group (n=301)	p value
Ostial lesion(%)	41.7	19.9	0.012
ISR(%)	25.0	21.3	NS
Bifurcation(%)	66.8	48.3	NS
SVG graft (%)	8.3	2.0	NS
Multivessel disease(%)	65.0	62.4	NS
Type B_2 / C lesion(%)	87.5	71.4	NS
Brush grade 3(%)	66.7	70.0	NS
Lesion length(mm)	21.8±13.6	17.1±9.6	NS
Reference(mm)	2.6±0.7	2.7±0.6	NS
MLD pre(mm)	1.0±0.7	1.0±0.4	NS
%DS pre(%)	63.0	62.8	NS

Continuous values are mean±SD.
ISR=in-stent restenosis; SVG=saphenous vein graft; MLD=minimum lumen diameter; %DS=percentage diameter stenosis. Other abbreviation as in Table 1.

Table 4 Procedural results

	TLR group (n=24)	Non-TLR group (n=301)	p value
MLD(insegment)(mm)	1.8±0.4	2.0±0.6	NS
Final MLD(instent)(mm)	2.2±0.5	2.5±0.5	<0.01
Stent %DS final (%)	21.9	13.3	0.002
%DS final (%)	26.7	24.2	<0.01
%DS proximal edge(%)	17.1	14.9	NS
%DS distal edge(%)	20.4	18.7	NS
Stent length(mm)	30.8±15.4	24.0±10.0	0.012
Stent/lesion ratio	1.3±0.4	1.6±0.7	NS
Balloon/artery ratio	1.56±0.38	1.49±0.51	NS

Continuous values are mean±SD.
Abbreviations as in Tables 1, 3.

Table 5 Multivariate predictors of target lesion revascularization

	Odds ratio(95% CI)	p value
Prior MI	3.5(1.3−9.1)	<0.01
Hemodialysis	2.9(1.0−8.3)	<0.05
Prior CABG	2.8(1.1−7.5)	<0.05
Ostial location	2.6(1.1−6.3)	<0.05
Final %DS(in stent)	3.1(1.2−8.2)	<0.05

CI=confidence interval. Other abbreviations as in Tables 1, 3.

Procedural results(Table 4)

Stent length was greater in the TLR group than in the non-TLR group(30.8±15.4 vs 24.0±10.0 mm, $p=0.012$), whereas the stent / lesion length ratio was not significantly different between the two groups. After the procedure, in-stent %DS in the TLR group was higher than that in the non-TLR group(21.9% vs 13.3%, $p=0.002$). Among 8 TLR lesions with ostial lesion treatment, the ostium was fully covered by DES in 7 lesions. Eighteen TLR lesions in Japanese patients were completely followed by angiographic analysis, which showed restenosis in 8 focal body lesions, 8 marginal lesions and 2 multifocal lesions. One of these patients suffered stent fracture.

Predictors of TLR(Table 5)

Stepwise multiple regression analysis indicated that hemodialysis, prior MI, prior CABG, ostial lesion, and post-procedural %DS were independent predictors of TLR, and these variables were interdependent by multivariate logistic regression analy-

sis. As shown in **Table 5**, patients with prior MI were associated with about a 3.5-fold higher risk of TLR compared to those without prior MI. Hemodialysis was associated with about a 2.9-fold higher relative risk of TLR.

DISCUSSION

Both SES and PES have been shown to drastically reduce restenosis and TLR after PCI. The extent of neointimal hyperplasia after SES or PES implantation is known to be different between the two types of DESs because of the different types of drugs and polymers. However, the mechanism by which restenosis is reduced is similar between the two DES methods; negative remodeling is prevented by the metal stent and neointimal hyperplasia is suppressed by the anti-proliferative agents. Thus, we analyzed combined SES and PES data to determine the predictors of TLR. The TLR rate for SES 9 months after PCI was 4.1% in the SIRIUS trial[3] and that for PES was 3.0% in the TAXUS-Ⅳ trial.[1] In the present study, the TLR rate at 6 months after DES implantation was 7.4%, which was higher than in the SIRIUS and TAXUS-Ⅳ trials. However, complex clinical and lesion characteristics such as renal failure, left ventricular dysfunction, small vessel or long lesions were excluded in both SIRIUS and TAXUS IV trials. In contrast, in this study, we enrolled most patients except those with acute MI. Thus, the possible reason of higher incidence of TLR in this study is that patients with complex clinical and lesion characteristics were included.

Although some factors such as diabetes mellitus, long lesion, small reference vessel, ostial lesion location or small final minimum lumen diameter have been reported to be predictors of TLR after BMS implantation,[4,6,7] it is unclear whether these factors can also predict TLR after DES implantation. In the present study, hemodialysis was identified as one of the predictors. Stent under-expansion seems to be more frequent in hemodialysis than in non-hemodialysis patients because of the more intense coronary artery calcification in hemodialysis patients.[8,9] Two of 14 TLR lesions in patients with prior CABG were in saphenous vein grafts. Although it is not clear why restenosis is frequent in patients with prior CABG or prior MI, one of the possible reasons is that these patients had more severe atherosclerosis compared to those without such conditions. Meanwhile, diabetes mellitus was not a predictor of TLR which showed intensely suppressed neointimal hyperplasia with DES. Thus, a possible mechanism of restenosis may be unfavorable stent expansion rather than neointimal hyperplasia. In fact, smaller final %DS was also a possible predictor of TLR in our study.

One of the Japanese TLR cases showed stent fracture at follow-up coronary angiography. Ostial lesions are known to have high rates of restenosis after bare metal stent implantation because of the technical difficulty of accurate stent positioning and the high elasticity of the ostium: [10,11] 7 of 8 ostial lesions with TLR were completely covered by DES. Stent under-expansion just after the procedure was seen in one patient. Mechanical problems such as chronic recoil rather than neointimal hyperplasia might be important in ostial restenosis. DES with higher radial force might be effective for the treatment of ostial lesions.

Study limitations

The most important limitation of this study is the number of patients. Since the incidence of TLR after DES implantation is low, there is a limitation with the number of patients in this study to statistically identify predictors of TLR after DES implantation. Instead, we observed each patient with TLR in detail. Another limitation of this study is the difference in the follow-up methodology : angiographic follow-up was performed in most patients in Japan whereas only clinical follow-up was performed in Brazil. However, the determination of TLR was also clinically driven in Japan. The difference in race between the two countries does not seem to be a big issue for identifying predictors of TLR because the two groups are thought to have a similar mechanism of restenosis after DES implantation.

CONCLUSIONS

Hemodialysis, prior MI, prior CABG, ostial lesion location and small in-stent %DS are possible predictors of TLR after DES implantation. A possible mechanism of restenosis could be unfavorable stent expansion.

要　　約

薬物溶出性ステント留置後の再血行再建術施行予測因子の検討

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背　景: 薬剤溶出性ステント(DES)留置後に標的病変再血行再建(TLR)を必要とする症例を少数例ではあるが経験する．TLRの予測因子を検討することは，虚血性心疾患の治療方針を決定するうえで重要である．

方法と結果: 日本とブラジルの4施設において297例の患者(325病変)に対してCypher™シロリムス溶出性ステントまたはTAXUS™パクリタキセル溶出性ステントが留置された．これらのうち20例(24病変)は，臨床的にTLRが必要であった．今回我々はTLRを要した患者群とそうでなかった患者群の間で，患者背景，病変背景を比較検討した．その結果，TLR群では透析患者，心筋梗塞および冠動脈バイパス術の既往のある患者が非TLR群に比べて多かった．またTLR群では，非TLR群に比べて入口部病変が多く認められ(41.7% vs 19.9%, $p = 0.012$)，さらには手技後のステント内径狭窄率が高値であった(21.9% vs 13.3%, $p = 0.002$)．多変量解析の結果，これらの因子はDES留置後のTLRの独立した予測因子であった．

結　論: 透析，心筋梗塞および冠動脈バイパス術の既往，入口部病変と術後にステント内径狭窄率が高いことは，DES留置後TLRの予測因子となりうる可能性が示唆される．

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