INTERVENTIONAL CARDIOLOGY

Target lesion revascularisation in patients treated with a sirolimus-eluting or paclitaxel-eluting stent

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Objective: To identify risk factors for clinical-driven target lesion revascularisation (TLR) in patients treated with sirolimus-eluting (Cypher) or paclitaxel-eluting (Taxus) stents in a real-world scenario.

Design: From 1 January 2003 to 18 May 2005, all patients treated with a Cypher or Taxus stent were consecutively registered and followed for 9 months. Re-intervention was driven by clinical symptoms.

Setting: Western Denmark Heart Registry.

Patients: 4432 patients with 6102 lesions treated with a Cypher (n=3791 lesions) or Taxus (n=2311 lesions) stent.

Interventions: Percutaneous coronary intervention.

Main outcome measures: TLR, defined as either new percutaneous coronary intervention or coronary artery bypass graft operation of the target lesion, within 9 months from the index procedure.

Results: TLR within 9 months was performed in 2.5% of lesions treated with the Cypher stent and in 3.3% of lesions treated with the Taxus stent (OR 1.36, 95% CI 1.00 to 1.84). After adjustment by multivariate logistic regression, Taxus stent implantation was an independent predictor of TLR (OR 1.43, 95% CI 1.05 to 1.95). Implantation of >1 stent per lesion (OR 1.62, 95% CI 1.13 to 2.33) and reference diameter <2.8 mm (OR 1.42, 95% CI 1.00 to 2.02) were also identified as independent predictors of TLR.

Conclusions: These data from the registry reflect a real-world clinical scenario with operator-driven use of drug-eluting stents and symptom-driven re-intervention. In this setting, use of the Taxus stent, implantation of multiple stents per lesion and stent implantation in small vessels were independent predictors of TLR.

Randomised controlled trials of the sirolimus-eluting Cypher stent (Cypher) and the paclitaxel-eluting Taxus stent (Taxus) have demonstrated that these drug-eluting stents (DESs) significantly reduce neointima formation when compared with bare metal stents, as evidenced by reduced angiographic late loss and binary restenosis rate.¹⁻³ This resulted in improved clinical outcomes with reduced target lesion revascularisation (TLR).²⁻⁴ Currently, few studies have compared the first commercially available DESs, the Taxus and Cypher stents.⁵⁻¹⁰ Available data indicate that the Cypher stent has less angiographic late lumen loss than the Taxus stent.⁷⁻¹¹ Furthermore, in high-risk populations, the Cypher stent seems to reduce TLR.^{7-9, 11-13} The question that remains to be answered is whether the superiority observed in randomised studies can be translated into less TLR in a real-world scenario.

The aim of this study was to compare the TLR rates of the Cypher and Taxus stents in all DES interventions in Western Denmark over a 26-month period.

METHODS

Data registration

The Danish Data Management Council approved the registry. Western Denmark has a population of 2.97 million people. In the Western Denmark Heart Registry, all coronary angiograms and coronary interventions including coronary artery bypass graft operation within this region are recorded. All three interventional cardiology hospitals in this region (Skejby, Aalborg and Odense) report to the registry. Thus, all patients who had a coronary intervention in Western Denmark were registered. The Central Personal Registration number (a unique identification number given to all Danish citizens at birth) was used to identify the patients. Data were collected prospectively and included pre-procedure clinical and procedural data. Re-admission for repeated

percutaneous coronary intervention (PCI) or coronary artery bypass graft was registered in the same database. Information on death within 9 months of follow-up was obtained from the Danish Central Personal Registry. Data regarding acute myocardial infarction during follow-up were not recorded in the registry. The angiographic data (lesion type, lesion length, reference diameter and percentage of diameter stenosis) were based on visual estimates by the operator using the guiding catheter, the pre-dilatation balloon and the guidewire markers as reference according to normal clinical practice at the three hospitals.

Patients and study period

All patients treated with a DES from 1 January 2003 to 18 May 2005 were included in the study. During the inclusion period, both study stents were routinely used. If the patients had a TLR within 9 months (the last patient was followed to 18 February 2006), it was registered as an end point.

Procedures and post-intervention drugs

The participating centres were high-volume centres performing >1500 PCI procedures per year. Interventions were performed according to current standards, with the interventional strategy (including balloon angioplasty, pre-dilatation or post-dilatation, choice of stent, direct stenting, periprocedural glycoprotein IIb/IIIa inhibitor) left to the operator's discretion. However, the operators were not allowed to implant DESs in all patients owing to financial restrictions. Thus, DESs were in general used in patients with an anticipated higher risk of restenosis. Patients were advised to maintain lifelong aspirin (at least 75 mg/day) and were treated with 300 mg clopidogrel, followed by 75 mg clopidogrel for 6-12 months for all stent implantations.

Abbreviations: DES, drug-eluting stent; PCI, percutaneous coronary intervention; TLR, target lesion revascularisation

Table 1 Baseline characteristics of patients

	Cypher	Taxus	p Value
Patients (n)	2728	1704	
Procedures (n)	2897	1781	
Lesions (n)	3791	2311	
Age (inter quartile range; years)	63 (55–71)	63 (35–72)	0.120
Male (%)	72.7	74.0	NS
Family history of IHD (%)	39.3	44.2	<0.001
Treatment for hypertension (%)	40.3	41.9	0.163
Treatment for hypercholesterolaemia (%)	52.3	56.9	0.001
Active smoking (%)	31.2	33.4	NS
Diabetes (%)	14.1	17.1	0.001
Previous MI (%)	28.8	28.2	NS
Previous PCI (%)	19.4	21.9	0.023
Previous CABG (%)	6.2	7.6	0.036
Indication for stent implantation			
Stable angina pectoris (%)	66.4	70.9	NS
Acute coronary syndrome (%)	33.6	29.1	NS

CABG, coronary artery bypass grafting; IHD, ischaemic heart disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Endpoint definition

The primary end point was TLR within 9 months after the index procedure. TLR was defined as re-PCI or coronary artery bypass graft of the index lesion. In both groups, follow-up angiography was clinically driven by symptoms or signs suggestive of myocardial ischaemia, or in a few cases decided by the operator at the end of the index procedure, predominantly following treatment of the left main stem.

Statistics

Categorical data were presented as counts and percentages, and compared by the Pearson χ^2 test or Fisher's exact test. Continuous data were expressed as either mean (SD) or median (interquartile range) and compared by t test or Mann-Whitney U test, respectively. All statistical tests were two tailed. Separate logistic regression analyses were performed to identify univariate predictors of TLR, and a subsequent stepwise (backward conditional) regression analysis was performed with entry and removal criteria of 0.05 and 0.10, respectively. Logistic regression analyses were presented as odds ratio (OR) with 95% CIs. Missing values were registered as "normal" values—that is, placed in groups with the lowest risk of TLR. A p value ≤ 0.05 was considered significant. p Values >0.20 were considered NS. p Values between 0.05 and 0.20 were noted since they could represent a trend towards a difference between parameters. All analyses were performed in SPSS V.11.5.

RESULTS

We identified 4432 patients who received a Cypher (n = 2728) or Taxus (n = 1704) stent during the study period. A total of 137 (3.09%) patients died within 9 months (Cypher, 79 (2.90%) patients with 112 lesions; Taxus, 59 (3.46%) patients with 91 lesions). The entire database in this period included 15 419 stented lesions in 9709 patients—that is, 46% of the patients and 40% of the lesions were treated with one of the two studied DESs.

Baseline and procedural characteristics

Table 1 shows the baseline clinical characteristics of patients. The Taxus group had higher percentages of family history of ischaemic heart disease, treatment for hypercholesterolaemia, diabetes and previous coronary interventions. Table 2 shows the lesion and treatment characteristics. The Cypher stents were implanted in smaller vessels and in longer lesions treated with longer and/or additional stents.

Table 2 Lesion and treatment characteristics

	Cypher	Taxus	p Value
Mean (SD) lesion length (mm)	17.9 (13.6)	16.6 (12.5)	<0.001
Complex lesions (type B2/C ^o ; %)	23.2	21.9	NS
Restenotic lesion (%)	8.4	9.0	NS
Stenosis pre-PCI (%)	86.5	86.3	NS
Stenosis post-PCI (%)	0.14	0.38	0.010
Mean (SD) stent length (mm)	22.1 (14.1)	20.3 (12.3)	<0.001
Mean (SD) reference diameter (mm)	3.1 (0.5)	3.3 (0.5)	<0.001
≥ 2 Stents implanted (%)	19.1	14.2	<0.001
Glycoprotein IIb/IIIa inhibitor (%)	45.7	44.2	NS

PCI, percutaneous coronary intervention.

Predictors of TLR

TLR was 2.5% after a Cypher stent implantation and 3.3% after a Taxus stent implantation (p = 0.05). Logistic regression was used to assess the independent predictors of TLR at 9 months. Table 3 lists the parameters examined using univariate logistic regression analysis.

As observed from table 3, only the use of the Taxus stent (OR 1.36, 95% CI 1.00 to 1.84) and multiple stent implantation (OR 1.53, 95% CI 1.07 to 2.19) were significantly associated with an increased TLR at 9 months. Stent implantation in restenotic lesions (OR 1.42, 95% CI 0.88 to 2.28) and stent implantation in arteries with a reference diameter <2.8 mm (OR 1.33, 95% CI 0.94 to 1.89) showed a trend towards increased TLR. Diabetes (OR 0.96, 95% CI 0.63 to 1.45) and stent implantation in complex lesions (OR 1.04, 95% CI 0.73 to 1.49) did not significantly influence TLR. Analysis of the same parameters but excluding missing values did not change the significance of the parameters. To adjust for differences in baseline risk and lesion factors, we performed a stepwise logistic regression analysis including parameters with a p value <0.20 —that is age (<70 vs ≥ 70 years), reference diameter (<2.8 vs ≥ 2.8 mm), number of stents implanted (1 vs ≥ 2 stents), restenotic lesions (yes/no) and type of stent (Taxus vs Cypher). After adjustment, reference diameter <2.8 mm, multiple stent implantation and Taxus stent implantation were found to be independent predictors of TLR at 9 months (table 4).

If the lesions were divided into subgroups according to reference and number of stents implanted (table 5), the greatest differences in TLR between the two DESs were observed in small vessels.

DISCUSSION

The major new finding of this study was that use of the Taxus stent was an independent predictor of TLR in a real-world population of patients treated with the first two commercially available DESs (Cypher and Taxus). The greatest difference in TLR between the two DESs was observed in small arteries. The TLR rate, however, was low in both DES groups.

The strengths of this study were the large number of lesions included in the analysis, the unique follow-up owing to the Danish Central Personal Registration number, the inclusion of all patients treated with a DES during a 29-month period in an entire region and the fact that the re-interventions were driven by clinical symptoms.

There are, however, several methodological problems that warrant caution in the interpretation of the findings. First, this was a retrospective analysis of prospectively collected registry data. Although the risk of selection bias due to the lack of randomisation can be reduced by logistic regression analysis, as performed in this study, factors not included in this analysis could influence the results. However, previous studies comparing the results of randomised trials and observational studies

Table 3 Univariate predictors of target lesion revascularisation

	OR (95% CI)	p Value
Age <70 years	0.80 (0.53 to 1.08)	0.125
Male	0.90 (0.60 to 1.23)	NS
Family history of IHD	1.09 (0.80 to 1.49)	NS
Treatment for hypertension (%)	0.97 (0.71 to 1.32)	NS
Treatment for hypercholesterolaemia	0.89 (0.66 to 1.21)	NS
Current smoking	1.02 (0.73 to 1.41)	NS
Diabetes (%)	0.96 (0.63 to 1.45)	NS
Complex lesions (type B2/C)	1.04 (0.73 to 1.49)	NS
Restenotic lesion	1.42 (0.88 to 2.28)	0.151
Stent length >19 mm	1.25 (0.92 to 1.69)	0.156
Reference diameter <2.8 mm	1.33 (0.94 to 1.89)	0.105
Stents implanted (≥2)	1.53 (1.07 to 2.19)	0.019
Stent type (Taxus)	1.36 (1.00 to 1.84)	0.050

IHD, ischaemic heart disease.

NS, p value >0.20.

An odds ratio >1 indicates a higher risk of target lesion revascularisation.

comparing two competing interventions have concluded that the treatment effects are not qualitatively different and that the observational studies do not overestimate the magnitude of the treatment effects.^{14, 15} A recent meta-analysis of six randomised trials comparing the Cypher and the Taxus stents included 3669 patients,¹¹ which is a smaller number of patients than included in this study. Angiographic follow-up was performed in most patients.¹¹ The meta-analysis reported that use of the Taxus stent was associated with increased TLR.¹¹ This study indicated that the superiority of the Cypher stent in selected randomised patients was transferred to clinical reality in a large real-world population treated with DESs without angiographic follow-up.

The use of a clinical end point such as TLR may be considered to be a potential limitation. Without systematic clinical or angiographic follow-up at later time points, the obtained TLR may underestimate the “true” clinical restenosis rate. It is, however, noteworthy that the Scandinavian study of Cypher versus bare metal stents in complex lesions (Stenting Coronary Arteries in Non-stress/benestent Disease)¹⁶ included clinical and angiographic follow-up but showed an almost similar rate of TLR of 2.4% in the Cypher group, thereby supporting the validity of our study.

This study is the third registry study that compares Cypher versus Taxus stents. Ong *et al*⁵ reported registry results with Cypher and Taxus stents. A total of 1084 patients with de novo coronary artery disease were registered. Similar to our results, a tendency towards increased target vessel revascularisation after Taxus stent implantation was observed (hazard ratio 1.33, 95% CI 0.82 to 2.15),⁵ with the lack of significance potentially being due to a statistical type 2 error. There are a number of differences between the study of Ong *et al*⁵ and our study. First, the use of DESs were unrestricted in all patients in the study of Ong *et al*,⁵ whereas the operators in our study were restricted by financial considerations. The study of Ong *et al*⁵ may reflect the future, although it is as yet unclear whether DESs should be implanted in all lesions; our study reflects the current clinical reality in most catheterisation laboratories. Secondly, Ong and colleagues used DESs only in de novo coronary artery lesions whereas our registry included patients with restenosis and arterial and vein coronary artery bypass grafts. Thirdly, they studied two sequential registries separated by a 4-month interval, whereas we compared stent implantation within the same time period. Ong *et al*'s⁵ study precludes confounding by operators' preferences, but may be affected by changes in the patient population in the direction of more complex lesions, whereas this study depends on the operators' choice of stent. Another limitation of using sequential registries is that the last group (in this case the Taxus stent⁵) had

Table 4 Multivariate regression analysis

	OR (95% CI)	p Value
Stent type (Taxus)	1.43 (1.05 to 1.95)	0.022
Reference diameter <2.8 mm	1.42 (1.00 to 2.02)	0.049
Stents implanted (≥2)	1.62 (1.13 to 2.33)	0.008

An OR >1 indicates a higher risk of target lesion revascularisation.

the advantage of more experienced operators with a greater experience with implantation of DESs (eg, awareness of covering all balloon-treated segments with the DES). Finally, our data included interventions performed at three centres versus the single-centre study of Ong *et al*.⁵

A recent study by Kastrati *et al*¹⁷ reported the outcome of 1845 patients with 2093 target lesions treated at two German centres. That study used a combination of data from several randomised trials, and angiographic follow-up was performed in >80% of patients. Similar to the results obtained in this study, Kastrati *et al*¹⁷ found that the most important predictors of TLR were vessel type and use of the Taxus stent. TLR was performed in 9.2% of treated lesions,¹⁷ which was three times higher than in our registry with symptom-driven re-intervention, probably because routine follow-up angiography increases the re-intervention rate.¹⁸

Limitations

The visual estimates of reference diameters in this report were greater than those reported in other studies using quantitative coronary angiography and hamper direct comparison with those studies. Our analysis was performed on a per-lesion analysis since neither Kastrati *et al*,⁷ Ong *et al*⁵ nor this analysis showed that patient-specific factors were associated with TLR. No routine ischaemia tests were used, and thus the low TLR observed might partly be explained by treatment of vessels supplying parts of the myocardium that did not induce recurrent symptoms despite development of in-stent restenosis. However, the presence of silent ischaemia is unlikely to be related to the selected type of DES. Finally, some operator bias may have been present in the study, as there were significant differences between the two DES groups with regard to baseline clinical parameters and lesion characteristics.

CONCLUSIONS

These registry data reflect a real-world scenario with operator-driven use of DESs and symptom-driven re-intervention. The TLR rate was low in both DES groups. Use of the Taxus stent, implantation of multiple stents per lesion and stent implantation in small vessels were independent predictors of TLR.

Table 5 Unadjusted target lesion revascularisation according to reference diameter and number of stents implanted

Parameter (number of lesions)	Cypher	Taxus	p Value
Reference diameter			
<2.8 mm (1267)	2.9%	4.8%	0.046
≥2.8 mm (4835)	2.4%	3.0%	NS
No. of stents			
1 (5049)	2.2%	3.1%	NS
≥2 (1053)	3.6%	4.6%	NS
Reference diameter + number of stents			
<2.8 mm+1 (1109)	2.6%	4.9%	0.047
<2.8 mm+≥2 (158)	4.8%	3.8%	NS
≥2.8 mm+1 (3940)	2.1%	2.7%	NS
≥2.8 mm+≥2 (895)	3.4%	4.7%	NS

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IMAGES IN CARDIOLOGY

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Metastatic squamous cell carcinoma causing right ventricular outflow tract obstruction

A 50-year-old woman presented with two syncopal episodes 7 months after resection of squamous cell carcinoma (SCC) of the base of the mouth. Investigation for metastatic disease at the time of diagnosis was negative. She had been immunosuppressed for 19 years with azathioprine and prednisolone after renal transplantation. A new loud ejection systolic murmur was noted in the pulmonary area.

Transthoracic echocardiography showed a large mass (6×5 cm) attached to the right ventricular wall and extending into the main pulmonary artery, obliterating the right ventricular cavity (panels A and B). Coronary angiography showed neovascularisation from the right coronary artery (panels C). Computed tomographic scan of the chest showed the mass extensively involving the ventricular wall, as well as probable tumour emboli in the right pulmonary artery (panel D). Transvenous biopsy of the mass confirmed SCC. The patient started receiving radiotherapy, but died 6 days later.

Cardiac metastatic disease has been reported in up to 8% of patients who die from cancer, although it rarely results in clinical symptomatology. In particular, right ventricular outflow tract obstruction from SCC is extremely rare. We postulate that the patient's immunosuppression may have contributed to aggressive tumour progression.

(A,B) Transthoracic echocardiograms. Large mass in right ventricle (RV) obstructing right ventricular outflow tract. LA, left atrium; PA, pulmonary artery; RA, right atrium.

(C) Coronary angiogram—left anterior oblique view of the right coronary artery showing neovascularisation (arrows). (D) Computed tomography angiogram of the chest. Large right ventricular (RV) mass and evidence of likely tumour embolus to the right pulmonary artery.

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