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ORIGINAL PAPER

The risk of definitive stent thrombosis is increased after "off-label" stent implantation irrespective of drug-eluting stent or bare-metal stent use

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Abstract
Introduction A limitation of drug-eluting stent (DES) use to FDA-approved indications has been suggested to reduce the risk of stent thrombosis. This study evaluated predictors of stent thrombosis in clinical practice after the use of drug-eluting as well as bare-metal stents (BMS), including adherence to the FDA indications for DES.
Methods Between July 2002 and October 2006 percutaneous coronary intervention (PCI) was performed on 5,945 patients using BMS (68%) or DES (32%). Patients had 1-year follow-up for definitive stent thrombosis (ARC criteria). 76 patients (1.27%) developed definitive stent thrombosis. Clinical, procedural, and angiographic parameters were related to those of 786 patients without stent thrombosis to define predictors of stent thrombosis. Off-label or on-label implantation of stents according to the FDA-approved indications for DES was included as parameter in the analysis.
Results In 434 patients, stent implantation was performed within FDA-approved indications and in 428 patients outside of FDA-approved indications for DES. Predictors of stent thrombosis were PCI in acute myocardial infarction (OR = 4.51, $P < 0.001$), treatment of bifurcation lesions (OR = 4.43, $P < 0.001$), stent length per mm (OR = 1.07, $P < 0.001$), implantation of multiple stents (OR = 3.67, $P < 0.001$), and stent implantation outside of FDA indications (OR = 6.13, $P < 0.001$). The risk was increased for DES as well as BMS. In a multivariate analysis, PCI in acute myocardial infarction (OR = 2.56, $P = 0.014$), LV-EF < 30% (OR = 3.60, $P < 0.001$), treatment of bifurcation lesion (OR = 3.65, $P = 0.004$), stent length in mm (OR = 1.04, $P = 0.015$), and implantation of multiple stents (OR = 2.64, $P = 0.002$) remained predictors of stent thrombosis. Off-label stent implantation was no independent additional predictor as it is a combined parameter of the above-mentioned predictors.
Conclusions Implantation of coronary stents outside of the FDA-approved indications for DES is associated with an increased risk of stent thrombosis using DES and BMS.

Keywords Drugs · Myocardial infarction · Stents · Stent thrombosis

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Introduction

Drug-eluting stents (DES) have been proved in randomized clinical trials of selected patients to reduce the incidence of angiographic and clinical restenosis compared to bare-metal stents (BMS). Recent reports have suggested an increased rate of stent thombosis (ST) with the use of DES [7, 10, 21]. Delayed healing after DES placement and impaired growth of neointima have been proposed as mechanisms for ST [15, 22]. Stent thrombosis is associated with a high mortality and the risk of ST after DES

implantation appears to be increased when used outside of approved indications ("off-label") [5, 25, 27]. To reduce the risk of ST with the implantation of DES, limitation of DES use to the indications approved by the Food and Drug Administration (FDA) based on recent randomized studies ("on-label") has been suggested [17]. A FDA panel raised concern about the use of DES outside of the approved indications. Approval of BMS for the treatment of coronary stenosis has also been the consequence of randomised studies with limited inclusion criteria [12, 23]. Whether the implantation of DES outside of the FDA indication criteria for DES ("off-label") is associated with an increased ST rate, while use of BMS in these indications is associated with less ST risks, is incompletely evaluated.

This study evaluated (1) predictors of definitive ST (based on the Academic Research Consortium criteria) including adherence to the FDA indications for DES and (2) whether implantation of BMS outside of the FDA-approved indications for DES is associated with an increased risk of ST during a 1-year follow-up period.

Methods

All patients treated by percutaneous coronary intervention (PCI) with BMS or DES implantation at the University Clinic Aachen, Aachen, Germany, between January 2002 and October 2006, were included in the analysis. A total of 5,945 patients were identified, 4,512 patients with implantation of a BMS and 1,433 patients with implantation of a DES. The study was approved by the local ethical committee of the University Clinic Aachen.

Percutaneous coronary intervention was performed according to standard techniques. The BMS stent group was composed of patients treated by Multilink™ or Vision™ stents, $n = 3{,}145$ (Guidant, Indianapolis, IN, USA), Liberte™ or Express™ stents $n = 959$ (Boston Scientific, Billerica, MA, USA), and Driver™ stents $n = 408$ (Medtronic AVE, Santa Rosa, CA, USA). The DES group was composed of $n = 609$ patients treated by sirolimus-eluting stents (Cypher™, Cordis, Johnson & Johnson, Warren, NJ, USA); $n = 770$ patients treated by paclitaxel eluting stents (TAXUS™, Boston Scientific Corp) and $n = 54$ patients treated by a sirolimus and a paclitaxel-eluting stent. No specific rules were formulated at this hospital during the period of stent implantation when to use or not to use drug-eluting stents. Anticoagulation during PCI was accomplished with unfractionated heparin per standard protocol. Patients received glycoprotein IIb/IIIa receptor inhibitor according to usual protocol with Abciximab or Tirofiban at the discretion of the operator. All patients were treated with aspirin 100 mg/day before PCI and indefinitely afterwards. Clopidogrel loading dose of 300 or 600 mg was given prior to PCI and continued at 75 mg/day for 4 weeks after elective PCI using BMS, for 6 months after elective PCI using DES and for 9 months after PCI for troponine positive acute coronary syndrome.

Clinical and procedural data were obtained in the analysed patients by a research nurse using hospital charts. Quantitative angiographic data were obtained by the use of the CASS II system. Minimal lumen diameter before and after stent placement, reference vessel diameter and lesion length were determined by quantitative coronary angiography.

Stent thrombosis was defined following the recommendations of the Academic Research Consortium (ARC) [21]. Only definitive ST, defined as angiographic or pathologic evidence of ST in a patient presenting with acute coronary syndrome, was included in this analysis. On-label stent use was defined as follows: single de novo native coronary artery lesion <30 mm in length in vessels of 2.5–3.5 mm diameter, without thrombus, no myocardial infarction within 7 days prior to the procedure, no bifurcation lesion, no severe left ventricular dysfunction (ejection fraction <30%), no main stem lesion, and no chronic total occlusion. These criteria are related to the criteria formulated by the FDA [11] which are based on the randomized DES studies for the Cypher™ and TAXUS™ stent resulting in their approval [19, 26]. Stent use in all other patients was defined as off-label. Nonfatal myocardial infarction was defined as symptomatic presentation with a CK-MB >2 times the upper normal limit.

The University Hospital Aachen is the only hospital providing interventional treatment in the community. Thus, the overwhelming majority of patients treated by PCI can be expected to present for repeat angiography during follow-up if needed. A total of 76 patients (1.27%) with definitive ST within 1 year after stent implantation were identified. To determine clinical, procedural and angiographic predictors of ST, a representative consecutive subgroup of patients treated by PCI using BMS or DES during the time period between January 2005 and July 2005 was included in the analysis in addition to all patients with a definitive ST. Thus, among 786 patients, 471 treated with BMS and 315 treated with DES were included in addition to all patients with definitive ST. Thus, a total of 862 patients were included in the analysis of clinical, procedural, and angiographic predictors of ST.

Statistics

Continuous variables are presented as mean ± SD and were compared using Student *t*-test, Wilcoxon test, or ANOVA as appropriate. Dichotomous variables were compared using chi-square statistics or Fisher's exact test. Univariate and multivariate logistic regression analyses

were performed to define predictors of ST. Age, gender, diabetes, hypertension, hypercholesterinemia, renal insufficiency, lesion length, vessel diameter, total stent length, number of stents, bifurcation lesion, lesion in LAD, DES versus BMS, concordance to FDA indication for DES ("on-label" use), intervention for AMI, and LV-function with ejection fraction <25% were included in the analysis. Only univariate parameters with $P < 0.2$ were included in the multivariate analysis. Odds ratios (OR) are presented along with their 95% confidence intervals (CI). Kaplan–Meier plots of ST free survival were constructed for all stents implanted at the University Aachen. All tests were two-sided and assessed at the 5% significance level. All statistical analyses were performed using SAS Release 9.13 (SAS Institute Inc., Cary, NC, USA).

Results

At 30 days, 59 patients (0.99%) had definitive stent thrombosis. A total of 76 patients (1.27%) with definitive ST within 1 year after stent implantation were identified. 56 patients of all 4,512 BMS patients had definitive ST (1.24%) and 20 patients of all 1,433 DES patients had definitive ST (1.39%). Consequences of definitive ST were death in 12 patients and non-fatal myocardial infarction in 45 patients. Figure 1 demonstrates Kaplan–Meier plots of definitive ST free survival during 1-year follow-up for all patients treated at the University Aachen.

Clinical, procedural, and angiographic baseline characteristics for 76 patients with ST as well as the consecutive 786 patients without ST treated between January and July 2005 are given in Tables 1 and 2. 434 patients (51%) were treated on-label and 428 patients (49%) were treated off-label. Off-label use was related to PCI in acute myocardial infarction in 243 patients, treatment of bifurcation lesions

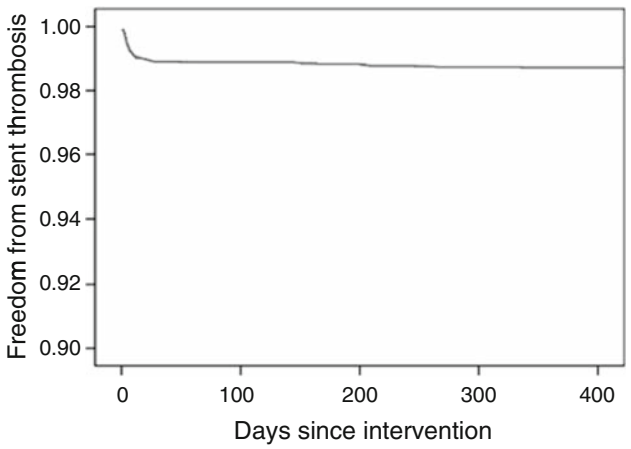

Fig. 1 Kaplan–Meier plots of stent thrombosis free survival during 1-year follow-up for all 5,945 patients included in the analysis

Table 1 Clinical baseline characteristics for the 76 patients with stent thrombosis as well as the $n = 786$ patients without stent thrombosis

	Stent thrombosis ($n = 76$)	No stent thrombosis ($n = 786$)	*P*
Age	61 ± 9	62 ± 10	0.893
Male gender	60 (79%)	621 (79%)	1.000
Diabetes	24 (31%)	173 (22%)	0.084
Hypertension	55 (73%)	550 (70%)	0.766
Hypercholesterinemia	53 (69%)	622 (79)%	0.054
Renal insufficiency	16 (21%)	212 (27%)	0.331
Intervention for AMI	46 (60%)	197 (25%)	<0.001
STEMI	24 (32%)	87 (11%)	<0.001
NSTEMI	22 (29%)	110 (14%)	<0.001
Medication			
Beta-blocker therapy	68 (89%)	377 (48%)	<0.001
ACE inhibitor	45 (59%)	362 (46%)	0.040
Nitrates	39 (51%)	259 (33%)	0.003

AMI Acute myocardial infarction, *DES* drug-eluting stent, *FDA* Food and Drug Administration, *NSTEMI* None ST-elevation myocardial infarction, *STEMI* ST-elevation myocardial infarction

Table 2 Procedural and angiographic baseline characteristics for the 76 patients with stent thrombosis as well as the $n = 786$ patients without stent thrombosis

	Stent thrombosis ($n = 76$)	No stent thrombosis ($n = 786$)	*P*
LV-Ejection fraction <30%	31 (41%)	102 (13%)	<0.001
Bifurcation lesion	21 (27%)	63 (8%)	<0.001
Chronic occlusion	19 (25%)	66 (8%)	<0.001
Vessel diameter (mm)	2.97 ± 0.32	2.86 ± 0.272	0.002
Number of stents	1.7 ± 0.9	1.2 ± 0.4	<0.001
Total stent length (mm)	27.6 ± 16.8	16.8 ± 8.0	<0.001
Drug-eluting stent	24 (31%)	291 (37%)	0.416
FDA DES "on-label"			
Indication	9 (12%)	419 (54%)	<0.001

in 84 patients, treatment of restenosis in 47 patients, treatment of chronic total occlusion in 85 patients, lesion length >30 mm in 90 patients. Table 3 provides clinical, procedural, and angiographic characteristics of the patients treated on-label versus the patients treated off-label. Patients treated off-label had more frequent diabetes, had longer lesions, a higher stent number. There was no difference in the frequency of DES between off-label use and on-label use of stents (37% vs 36%, $P = 0.990$). Patients treated off-label had a higher rate of ST than patients treated on-label. The higher stent thrombosis frequency for off-label use as compared to on-label use was found for

Table 3 Clinical, procedural and angiographic characteristics of patients treated "on label" versus patients treated "off label"

	Concordant to FDA DES indications ($n = 434$)	Non-concordant to FDA DES indications ($n = 428$)	*P*
Age	62 ± 9	61 ± 10	0.847
Male gender	351 (81%)	330 (77%)	0.202
Diabetes	82 (19%)	115 (27%)	0.007
Hypertension	312 (72%)	293 (68%)	0.305
Hypercholesterinemia	321 (74%)	354 (82%)	0.003
Renal insufficiency	81 (19%)	147 (34%)	0.004
Intervention for AMI	0 (0%)	243 (57%)	<0.001
Restenosis	0 (0%)	47 (11%)	<0.001
Bifurcation lesion	0 (0%)	84 (19%)	<0.001
Chronic occlusion	0 (0%)	85 (20%)	<0.001
Lesion length >30 mm	0 (0%)	90 (21%)	<0.001
Ejection fraction <30%	0 (0%)	133 (31%)	<0.001
Vessel diameter (mm)	2.86 ± 0.26	2.90 ± 0.31	0.181
Number of stents	1.2 ± 0.3	1.4 ± 0.6	<0.001
Total stent length (mm)	15.6 ± 6.2	20.6 ± 13.2	<0.001
Drug-eluting stent	158 (36%)	157 (37%)	0.990
Stent thrombosis*	17 (4%)	59 (14%)	<0.001
BMS	12 (4%)	44 (16%)	<0.001
DES	5 (3%)	15 (10%)	0.039

AMI Acute myocardial infarction, *BMS* bare-metal stent, *DES* drug-eluting stent

* High stent thrombosis rates due to special selection of patients included in this study (all stent thrombosis patients + selected control group)

BMS implantation as well as for DES implantation (Table 3).

Predictors of stent thrombosis

Considering all patients PCI for AMI, bifurcation lesion, number of stents, stent length, and off-label implantation of stent were found to be univariate predictors of ST. PCI for AMI, bifurcation lesion, number of stents, and stent length remained to be independent predictors of ST (Table 4). Off-label implantation of BMS and DES stents was not an independent predictor of ST. Considering only patients with DES, PCI for AMI, bifurcation lesions, number of stents, diabetes, stent length, and off-label stent implantation were univariate predictors of ST. Bifurcation lesion, diabetes and stent length remained independent predictors of ST (Table 5). Predictors of ST were similar in the group of patients treated with BMS. In these patients, PCI for AMI, bifurcation lesion, number of stents, stent length, and off-label stent implantation were univariate predictors of ST.

Table 4 Univariate and multivariate predictors of stent thrombosis considering all patients included in the analysis

Variable	OR	*P*	CI
Univariate predictors			
PTCA for AMI	4.51	<0.001	2.80–7.25
Bifurcation lesion	4.43	<0.001	2.69–7.67
Number of stents	3.67	<0.001	2.59–5.51
LV-EF <30%	3.34	<0.001	2.11–5.26
Diabetes	1.58	0.069	0.97–2.59
Stent length (per mm)	1.07	<0.001	1.05–1.09
"On-label" stent use	0.17	<0.001	0.10–0.30
Multivariate predictors			
LV-EF <30%	3.60	<0.001	2.01–6.37
PTCA for AMI	2.56	0.014	1.19–5.48
Number of stents	2.64	0.002	1.39–4.95
Bifurcation lesion	3.65	0.004	1.49–3.31
Stent length (per mm)	1.04	0.015	1.01–1.07

Table 5 Univariate and multivariate predictors of stent thrombosis considering only patients treated with drug-eluting stents

Variable	OR	*P*	CI
Univariate predictors			
PTCA for AMI	3.25	0.009	1.35–7.86
Bifurcation lesion	4.17	0.004	1.56–10.81
Number of stents	3.21	0.001	1.62–5.76
Diabetes	3.18	0.009	1.32–7.70
Stent length (per mm)	1.07	<0.001	1.04–1.10
"On-label" stent use	0.146	<0.001	0.05–0.40
Multivariate predictors			
Bifurcation lesion	2.26	0.034	1.08–4.89
Diabetes	3.65	0.010	1.35–9.69
Stent length (per mm)	1.06	0.007	1.02–1.10

Among the 76 patients who developed definite ST, $n = 66$ patients (87%) received dual antiplatelet therapy consisting of aspirin and clopidogrel at the time of ST. The 12-month cumulative incidence of non-fatal MI was also higher in the off-label group compared to the on-label group 36 versus 13 patients, respectively ($P < 0.001$).

Discussion

The results of this study show that (1) definitive ST during a 1-year follow-up occurs at a similar frequency in DES as compared to BMS, (2) off-label use of stents is associated with an increased rate of ST compared to on-label use, (3) the increased risk of ST in off-label use relates to BMS as

well as to DES, and (4) off-label stent implantation is no independent predictor of ST beyond PCI for AMI, stent number, stent length, and bifurcation lesion.

The incidence rate of definite ST for all patients included in this analysis was in the range of the previously reported studies [3, 14, 18]. A high rate of patients treated for acute coronary syndromes may have contributed to a slightly higher rate than reported in some of previously reported studies. The finding of a similar frequency of ST in the DES group as compared to the BMS group differs from the findings of the BASKET-LATE (BAsel Stent Kosten Effektivitäts Trial—LAte Thrombotic Events) study, in which there was a higher rate of ST in the DES group [21]. The implantation of stents off-label was found to be associated with an increased rate of ST compared to on-label implantation. This finding is in agreement with previous studies as well as a large registry analysis on the use of paclitaxel eluting TAXUS stents [1, 3, 5]. The registry on 7,000 patients also found significantly increased rates of ST, mortality, and myocardial infarction in patients treated for off-label indications as compared to on-label use. However, off-label stent implantation was not found to be an independent risk factor of definitive ST. Several previous studies have evaluated the risk factors for stent thrombosis [2, 14, 18, 20]. Number of stents, stent length, stent implantation for treatment of acute coronary syndromes, renal insufficiency, treatment of bifurcation lesions, cessation of clopidogrel administration, prior brachytherapy, and treatment of chronic total occlusions are the most frequently defined risk factors of ST. Some of these previously defined risk factors could be confirmed in this study. Most of these predictors relate to patient, lesion, and interventional characteristics which have been exclusion criteria in previous randomized clinical trials comparing DES with BMS and resulting in the approval of DES. This confirms that the patients treated for on-label indications belong to a low-risk group. The combination of previously defined risk factors encompasses the off-label indications. It is therefore not surprising that the off-label use of stent therapy was not found to be an independent predictor of ST in addition to the known predictors of ST. Importantly, our study evaluated whether the use of BMS for off-label indications of DES is also associated with an increased risk of ST. This issue is of special importance as confinement of DES use to on-label indications has been proposed to reduce the risk of stent thrombosis [17]. The greater risk of ST even with the use of BMS in DES off-label indications is an important finding indicating that BMS use may not solve the problem of ST if the operator is encountered with a situation requiring stent implantation outside the on-label indications for DES. Other techniques to reduce ST including scoring of patients for their risk to develop ST, intensified search for resistance to antiplatelet therapy and intensified antiplatelet therapy in case of drug resistance may be indicated [4, 6, 8, 9, 13, 16, 24].

Limitations

This study did not include a complete analysis of all patients without stent thrombosis. This may result in an overestimation of the hazard ratios of predictors of ST. The follow-up period for ST included only during a 1-year period. Thus, very late ST could not be assessed in this study. Only definitive stent thrombosis was included in this analysis. However, it is very likely that ST defined as possible or likely will occur at a similar ratio between off-label and on-label indications as define ST. Thus, off-label use of stents is likely to be a predictor of these forms of stent thrombosis although not an independent one.

Information of clopidogrel use during follow-up was available only for the 76 patients with stent thrombosis, while no systematic information was available in the other patients. This parameter was therefore not evaluated in the analysis on predictors of ST.

Conclusion

Implantation of coronary stents outside of the FDA-approved indications for drug-eluting stents is associated with an increased risk of ST using drug-eluting as well as bare-metal stents.

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