The effect of drug-eluting stents on target lesion revascularization in native coronary arteries: results from the NORSTENT randomized study.

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Short title: Mølstad et al. TLR in DES vs. BMS

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ABSTRACT

Background. The NORSTENT trial randomized 9013 patients to percutaneous coronary intervention (PCI) with drug-eluting or bare metal stents with five years follow-up. No difference was found in the composite primary outcome of death from any cause and nonfatal spontaneous myocardial infarction after a median of 5 years of follow-up. Secondary outcomes included repeat revascularizations, which were reduced by drug-eluting stents. The present study reports the occurrence of target lesion revascularization (TLR) in time and across demographic and clinical subgroups in patients with lesions in native coronary arteries (n = 8782).

Results. Clinically driven TLR was performed in 488 (5.6%) of the 8782 patients during 5 years of follow-up. Male gender, older age, visible thrombus in the lesion and larger stent diameters were associated with less TLR, whereas multivessel disease and longer stents were associated with higher risk of TLR. There was a substantial and highly significant reduction in the hazard for any TLR after 5 years in the drug-eluting stent group (HR 0.44, [95% CI 0.36 – 0.52], $p < .001$). The effect of drug-eluting stents on TLR was limited in time to the first 2 years in the study without evidence of a later rebound effect. The reduction in TLR by drug-eluting stents was consistent across subgroups defined by gender, age, diabetes status, renal function, and lesion and stent characteristics. The number needed to treat with drug-eluting stents compared to bare metal stents to prevent one TLR ranged from 4 to 110 across clinically relevant subgroups.

Conclusion. Drug-eluting stents have a time limited effect on the rate of TLR, but with a substantial and highly significant reduction in the first 2 years after the procedure. This effect was found to be consistent across all important clinical subgroups.

INTRODUCTION

Percutaneous coronary interventions (PCI) with implantation of bare metal (BMS) or drug-eluting stents (DES) are frequently performed with millions of patients treated each year worldwide [1, 2]. DES generally reduce the rate of restenosis after intervention compared to BMS [1, 3]. The Norwegian Coronary Stent Trial (NORSTENT) randomized 9013 patients to DES or BMS (ClinicalTrials.gov number, NCT00811772) and reported no significant difference between DES and BMS for the main composite endpoint of death of any cause and non-fatal spontaneous myocardial infarction [4]. The rates of revascularization were significantly lower after the use of DES compared to BMS with a hazard ratio (HR) for target lesion revascularization (TLR) of 0.47 (95 % confidence interval [95% CI] 0.40 – 0.56). Several studies have reported predictors for TLR with variable results. Younger age, diabetes and lesion complexity including stent length and multiple lesions have been suggested in some studies to be risk factors for TLR [5-9], but not all [10]. We have not identified larger randomized studies reporting predictors for TLR with second generation DES compared to thin strutted BMS, and no studies evaluating separate predictors for DES and BMS.

The aim of the present study was to evaluate the effects of DES versus BMS on TLR for heterogeneity across demographic and clinical subgroups, lesion characteristics and follow-up time in native coronary arteries. Further, we aimed to estimate multivariable models to predict TLR in important clinical subgroups and to investigate potential risk factors for TLR separately and together for DES and BMS.

METHODS

NORSTENT was a multicenter, randomized trial conducted at all centers in Norway performing PCI. The main study including the study protocol has previously been reported [4]. The trial was funded by the Norwegian Research Council and other non-profit organizations and approved by the Norwegian Regional Committee for Medical and Health Research Ethics – Region North. The patients were included in the study from September 15, 2008 to February 14, 2011. NORSTENT was an "all-comer" trial with broad inclusion criteria and few exclusion criteria [4]. Double platelet inhibition with aspirin and clopidogrel was prescribed for 9 months regardless of randomized assignment. Clinical follow-up was performed according to the routine practice at each center without any routine follow-up with coronary angiography. The manual for definitions and classifications of outcomes was provided in the Supplementary Appendix to the main study. Definite stent thrombosis was defined according to the Academic Research Consortium Criteria [11]. Non-fatal outcomes were collected by linkage to the Norwegian Patient Registry through December 31, 2014, with use of the unique 11-digit Norwegian national identification number for each patient. The date and cause of death were obtained by linkage to the Norwegian Causes of Death Registry. All outcomes were adjudicated by an end-point committee consisting of clinical and interventional cardiologists and an epidemiologist blinded for the patients' treatment assignment.

The endpoint TLR was defined as clinically driven PCI of the target lesion for restenosis or other complication of the index lesion or coronary artery bypass surgery (CABG) to the target vessel. The patient level outcomes were evaluated in the whole cohort excluding patients with treated vein grafts or arterial grafts (n = 229). The lesion level outcomes were assessed in the subgroup with only one lesion treated in a native coronary artery to ensure that the actual characteristics of that lesion were those related to TLR. When more than one lesion was

treated in the index procedure the TLR data did not allow the identification of which lesion had to be retreated.

Statistical analyses

Differences among categorical variables at baseline were tested with Fishers exact test or chi-square test in case of excessive permutations. The purpose of the remaining analyses was to compare the rates and risk factors for TLR across subgroups in patients randomized to treatment with BMS or DES.

Subgroup analyses

Cumulative failure rates at specific time points were estimated with the Kaplan-Meier method and cumulative incidence functions. Subgroup-specific hazards were identified using Cox regressions which were all stratified for study center. The presence of important heterogeneity of the treatment effect of DES versus BMS on TLR across subgroups was assessed by including treatment-subgroup interactions as cross product terms in the model, requiring $p<0.01$ for claiming significance due to many comparisons. Cox regression and Royston-Parmar models were used to identify time-dependent effects [12]. The best fitting Cox model was identified based on maximum log-likelihood. The assumption of proportional hazards was tested using Schoenfeld residuals and continuous variables were tested for linearity on the hazard scale by quartile plots.

Multivariable TLR prediction model.

The Royston-Parmar model was used to compare multivariable survival between DES and BMS overall and in each stent group. A basic prediction model was built from the demographic and clinical covariates by backwards elimination, and thereafter adding

variables describing properties of the stents and lesions, model selection being guided by likelihood-ratio tests. Martingale residuals were used to assess goodness-of-fit. The final model was tested for time varying covariates and for interaction between covariates, as well as recasted as a competing risk model to assess any impact of all-cause mortality on the estimated hazards for TLR. The number needed to treat for benefit (NNT) was calculated as the reciprocal value of the survival difference. All analyses were performed in STATA v.14 (Collage Station, Tx, USA) and the STATA programs stpm2 and stpm2cr were used for calculating the Royston-Parmar models.

RESULTS

Subgroup analyses

In the complete cohort of 9013 patients, 226 had their index lesion in vein grafts, three in arterial graft and one patient had missing information, leaving 8782 patients in the study. In this cohort target lesion revascularization was performed in a total of 575 patients (6.5%) of which 488 patients (5.6%) were treated with PCI and 87 treated with CABG. The sum of TLR from both treatments in the cohort with lesions in native coronary arteries was used as the endpoint in the analyses. Lesion and stent characteristics in relation to TLR were analyzed in the subgroup of patients with only one lesion treated (n= 6087) in native arteries. In that cohort there were 277 (4.6%) patients treated with PCI and 56 (0.9%) treated with CABG. In the DES group 83.5% of the stents implanted at baseline were everolimus-, 11.6% zotarolimus-, 2.5% sirolimus- and 2.4% paclitaxel-eluting stents. Thus, the number of first-generation drug-eluting stents were too few to warrant separate analyses.

During a median of 59 months of follow-up TLR occurred in 3.5 % vs 7.6 % of patients in the DES and the BMS group, respectively ($p < .001$), see Table 1. The distribution of the clinical indications for TLR treated with PCI only, differed in the DES and the BMS groups. Myocardial infarction occurred relatively more frequently, and stable angina occurred less frequently in the DES group than in the BMS group ($p = .001$, Table 1). No difference in the use of platelet inhibition between the DES and BMS groups could be detected from a questionnaire 6 months after the index procedure ($p= 0.84$).

Multivariable Cox regression with all significant baseline variables on patient level revealed that TLR was neither related to all-cause mortality (HR 0.90, [95% CI 0.63 – 1.28], $p = .56$), nor to cardiac mortality (HR 0.72, [CI 0.35 – 1.46], $p = .36$) in the population with lesions in the native arteries ($n = 8782$).

In the total population with TLR in native coronary arteries there was a substantial and highly significant reduction in the rate of any TLR in the DES group after 5 years (HR 0.44, [0.36 – 0.52], $p < .001$). In the subgroup with only one treated lesion the HR for DES was 0.40 (0.31 – 0.50, $p < .001$). Kaplan-Meier failure estimate was used to calculate the rate of TLR events in baseline subgroups at specific time points. The influence of total mortality as competing event was assessed with the same Kaplan-Meier estimate in the subgroup without mortality, yielding virtually identical results. In addition, competing risk regression with total mortality as competing event yielded comparable results to the Kaplan-Meier estimate. The cumulative rates of TLR for DES and BMS in different baseline subgroups after 5 years are depicted in Table 2 on patient level and in Table 3 on lesion level. The influence of each baseline variable on TLR rates together with the p-value of the interaction term between stent type and covariate on patient level and lesion level is given in Table 1 and Table 2 in Supplementary appendix. The rate of TLR seems to decrease with increasing age and more so in the BMS group. However, the interaction term between age and randomized stent was not significant ($p = 0.90$). The impact of diabetes on TLR rate was modest and elevated values of serum creatinine had no effect. Number of diseased vessels increased the absolute TLR rate without significantly affecting the HR for randomized stent. The TLR rate increased with longer stent lengths and decreased with increasing stent diameter and the presence of visible thrombus in the index lesion without affecting the HR for the effect of DES versus BMS. No interaction term was significant at the 0.01 level.

Time varying effect of randomized stent type

In Cox regression with type of stent as the only covariate the interaction with time was highly significant ($p < .001$) with time split at 500 days as the best fitting model. Landmark analysis revealed HR for DES of 0.29 (0.23 – 0.36, $p < .001$) in the first 500 days and 1.07 (0.79 – 1.45, $p = .66$) after 500 days with proportional hazard within each time period. A Royston-

Parmar model on the hazard scale with randomized stent as the only covariate, allowed to vary over time revealed similar results, and is illustrated in Figure 1. The HR is initially very low (HR 0.25) indicating a substantial initial effect of DES on the risk of TLR rate, but the HR increases with the elapse of time and the effect of DES compared to BMS is no longer significantly different after about one to two years.

Multivariable TLR prediction model

The model was constructed in the patient cohort with only one treated lesion in native coronary arteries (n = 6087), as described under statistics. The final model contained 7 significant baseline covariates. In this model height could be viewed as a proxy for gender and substituting gender for height affected the model minimally as judged by the log likelihood. Randomized stent was the only covariate with a statistically significant interaction with time. None of the interactions between the covariates were more than of borderline significance and with minimal impact on the predictions. For simplicity the model is therefore presented without interactions. An identical model analyzed with all-cause mortality as competing risk gave virtually identical results (not shown). The HRs for the final model are given in Table 4. A plot of baseline hazard for DES and BMS from this model indicated increased hazard for BMS up to about 2 years with identical hazards thereafter (Figure 1, Supplementary appendix). Separate modelling of predictors for TLR in BMS and DES patients basically revealed similar predictors, but with less importance of stent diameter in DES and increased TLR in chronic occlusion in BMS but not in DES (Supplementary appendix table 3 and 4). The test for interaction between chronic occlusion and stent treatment was not significant in the full model (p=0.16). When forced into either of these models diabetes and serum creatinine were not significant predictors.

Number-needed-to-treat in clinical subgroups

From the model in table 4 a wide range of NNT after 5 years can be calculated from the covariate values. Selecting realistic clinical values for the covariates the range of NNT is from about 4 to 110. Figure 2 shows examples of differences in survival free of TLR in a 75-year-old male and 50-year-old female in one- two- and three-vessel disease with short stents (15 mm) with a large diameter (3.5) and no visual thrombus in the lesion with NNT indicated in each case.

DISCUSSION.

DES have consistently been shown to reduce the rate of restenosis and target vessel revascularization in multiple studies [13-15, 1, 3]. However, randomized trials have had limited generalizability and statistical power due to sample size and selection of patients [16-18]. Our study was large with 9013 randomized patients. That amounted to 43.6 % of all PCI procedures in Norway performed in the study period and included 72.5 % of all eligible patients. The most frequent criteria for ineligibility was previous stent treatment [4].

In our study DES caused a consistent, significant and substantial reduction in TLR across all subgroups (Table 2 and 3) and with no evidence of heterogeneity across subgroups when tested for interaction in a Cox regression. In addition, TLR seemed to be a benign event causing no increase in all-cause or cardiac mortality during a follow-up period of 5 years even though a considerable percent of indications for TLR was myocardial infarction (Table 1). This is in contrast to previous observations [19, 9, 20]. The reason for this discrepancy is not immediately apparent. A type II error can never be completely ruled out, but it is of note that in the study of Palmerini et al. [20] the excess mortality of TLR was only slightly increased (HR 1.23, [CI 1.04 – 1.45], p = .02) and Parasca et al. [9] found significant differences in the composite endpoint, but not in total mortality. Thus, our observation might not be so much at odds with previous reports in claiming that TLR is a relative benign event.

Interestingly the indications for TLR differed in the two stent groups (Table 1). The clinical presentation in DES treated patients was more often myocardial infarction than in BMS. If collapsing the categories of unstable angina and myocardial infarction so that the indications just were stable and unstable situations no difference between the indications of stent types was observed. Thus, it seems that the process leading up to TLR more often ends up in an infarction in DES treated patients and this did not seem to be related to the use of platelet inhibition. Differences in angioscopic appearance and tendency of thrombus development

between BMS and DES as well as pathological studies might explain that observation [21-23].

Our analyses revealed that the effect of DES on the reduction in the rate of TLR development lasted up to 1.5 – 2 years with no additional benefit after that time, and with no indication of "catch-up" in TLR by BMS later in the observation period. Thus, the duration of the clinical effect of DES concerning TLR in this study seems to be in concert with previous reports [6, 24].

Concerning predictors for TLR the variables in table 4 have also been described as significant in other reports [25, 8], except for visible thrombus in the index lesion. We have only found one report with a limited study population where thrombus in the lesion was included as a baseline variable [25]. They reported a non-significant trend towards less restenosis in lesions with thrombi. The reason for this is not obvious but could possibly be related to the occurrence of thrombi also in otherwise moderate plaques. Further studies are needed to corroborate this observation. Separate modelling of predictors in the BMS and DES group revealed similar results except for chronic total occlusion which was a significant predictor in BMS but not in DES patients and lesser influence of stent diameter in DES patients. We have found no previous report describing this in a randomized study, but they seem to be in concert with previous observations [6, 26, 8].

In the full multivariable model, no significant interaction between randomized stent and the other variables was found, consequently the use of drug-eluting stent would be beneficial in all subgroups with a reduced hazard ratio for the development of TLR. The magnitude of the absolute difference in survival free of TLR would depend on the underlying baseline hazard rate in each subgroup and can be evaluated with calculations of NNT. The model indicates less benefit in the older and male population, and as expected with short stents with large diameters, in concert with previous observations [25, 8]. We calculated the range of NNT in

selected clinically relevant subgroups from 4 to 110, a range comparable to Tu et al. [6]. Since the TLR procedure does not seem to carry any additional mortality risk in our study the reasons to not use DES would be mainly economic and patient inconvenience for a new intervention. To decide what number needed to treat should indicate that one could use BMS instead of DES is a matter of subjective judgement, but it might be justified to claim that with an NNT in the region of 50-60 the benefit of using DES is negligible. Thus, the clinical benefit from using DES in elderly men with large stents is definitely limited (figure 2). However, as stated we have found no subgroup where DES does not perform better than BMS.

Our results are based on the largest randomized study of DES versus BMS reported, and it is not likely that a study of the same size will ever be conducted again. It is therefore of great interest that no evidence of heterogeneity in the effect of DES compared to BMS for TLR was found. Subgroup analyses of the primary end-point were reported in the main article [4], and are basically repeated here for the development of TLR. All subgroup analyses must be viewed as hypothesis generating and not as solid evidence and the individual p-values must be viewed with caution. Nevertheless, the consistency of the DES effect on TLR is impressive and despite the high number of analyses performed, not in a single comparison was BMS better than DES.

In conclusion our study showed a consistent effect of DES in preventing TLR across all subgroups. The effect was time limited vanishing after about 1.5 years, but with no evidence of rebound phenomenon after that time and up to 5 years of observation. The baseline hazard for the development of TLR varied considerably as reflected in the wide range of observed number needed to treat. In recent guidelines [27] new-generation DES is in general preferred to BMS. However, since TLR seems to be a benign event without excess mortality the clinical benefit of using DES in the low risk subgroups for TLR is limited.

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Legend to figures.

Legend to figure 1.

The figure shows the Royston-Parmar model on the hazard scale with randomized stent as a time varying covariate. HR, hazard ratio; CI, confidence interval.

Legend to figure 2.

Survival free of TLR in subgroups with short stents (15 mm) with relatively large diameters (3.5 mm), and no visual thrombus. NNT, number needed to treat for benefit.

Figure 1.

Figure 2.

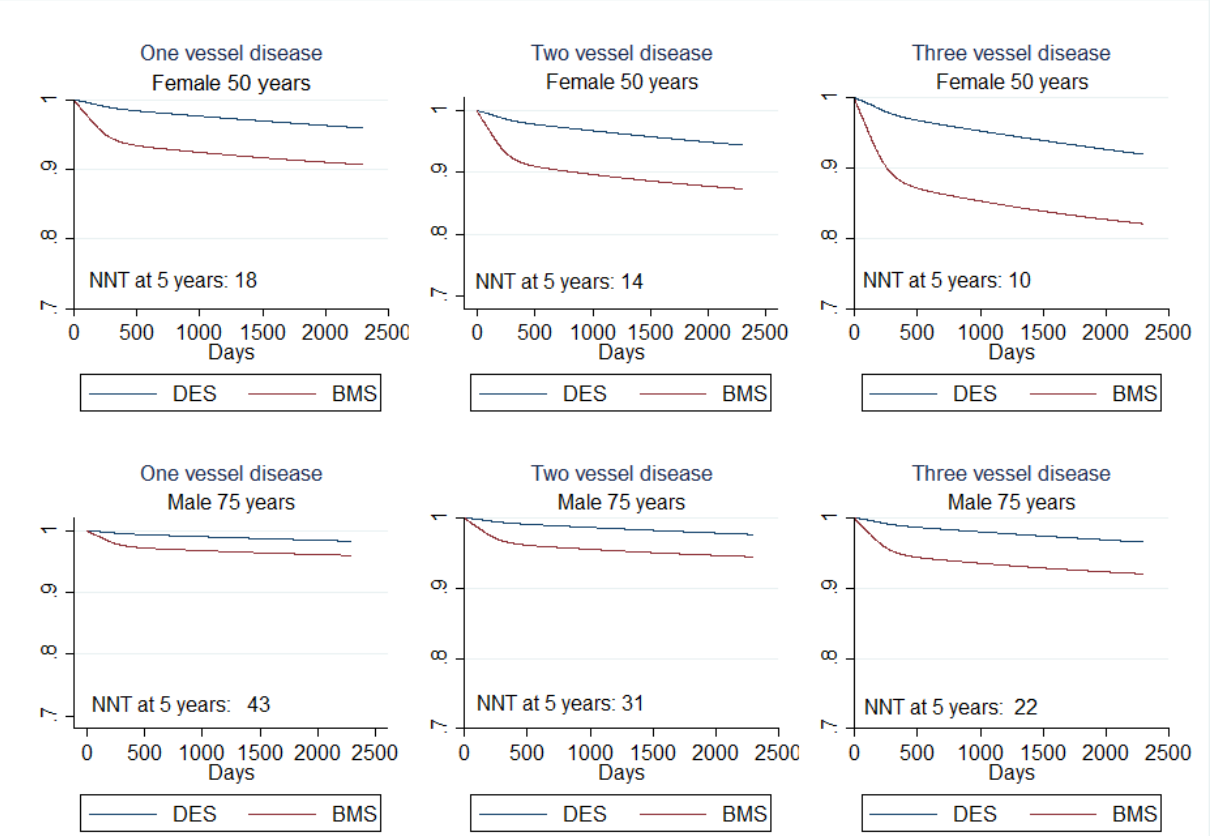
One vessel disease
Female 50 years
NNT at 5 years: 18
Two vessel disease
Female 50 years
NNT at 5 years: 14
Three vessel disease
Female 50 years
NNT at 5 years: 10
One vessel disease
Male 75 years
NNT at 5 years: 43
Two vessel disease
Male 75 years
NNT at 5 years: 31
Three vessel disease
Male 75 years
NNT at 5 years: 22
.7
.8
.9
1
0
500
1000
1500
2000
2500
Days
DES
BMS

Table 1. Clinical indication for target lesion revascularization with PCI in patients with lesions in native coronary arteries.

	Total population n (%)/N *	**DES n (%)/N**	**BMS n (%)/N**
All TLRs	488 (5.6)/8782	156 (3.5)/4403	332 (7.6)/4379
Stable angina	221 (45.3)/488	65 (41.7)/156	156 (47.0)/332
Unstable angina	94 (19.3)/488	19 (12.2)/156	75 (22.6)/332
MI (all)	165 (33.8)/488	70 (44.9)/156	95 (28.6)/332
MI with stent thrombosis	45 (9.2)/488	20 (12.8)/156	25 (7.5)/332
MI without stent thrombosis	120 (24.5)/488	50 (32.1)/156	70 (21.1)/332
Unknown indication	8 (1.6)/488	2 (1.3)/156	6 (1.8)/332

Abbreviations: DES, drug-eluting stent; BMS, bare-metal stent; MI, myocardial infarction

* n = number of events during follow-up in indicated group and percent experiencing the event in brackets (%), N = sample size in indicated group. P=0.001 (Fishers exact test) for distribution of indications between stent types.

Table 2. Target lesion revascularization in baseline variables at patient level after 5 years in native coronary arteries.

	TLR rates *			DES vs. BMS †	
	All N=8782	DES N=4403	BMS N=4379		
Subgroup	n (%)	n (%)	n (%)	HR (95% CI)	p
Total population	560 (6.6)	174 (4.1)	386 (9.1)	0.44 (0.36 - 0.52)	<0.001
Age					
<60 years	234 (7.1)	74 (4.5)	160 (9.6)	0.45 (0.34 – 0.59)	<0.001
60-79 years	303 (6.5)	90 (3.9)	213 (9.1)	0.41 (0.32 – 0.52)	<0.001
>79 years	23 (4.7)	10 (3.9)	13 (5.7)	0.68 (0.30 – 1.57)	0.37
Gender					
Male	406 (6.4)	123 (3.9)	283 (8.9)	0.42 (0.34 – 0.52)	<0.001
Female	154 (7.3)	51 (4.9)	103 (9.7)	0.47 (0.34 – 0.66)	<0.001
Current smoker					
Yes	183 (6.1)	57 (3.9)	126 (8.2)	0.45(0.33 – 0.62)	<0.001
No	332 (7.0)	97 (4.1)	235 (10.0)	0.39 (0.31 – 0.50)	<0.001
BMI					
<25 kg/m^2	163 (6.3)	49 (3.9)	114 (8.6)	0.43 (0.31 – 0.61)	<0.001
25-35 kg/m^2	358 (6.8)	110 (4.2)	248 (9.5)	0.42 (0.33 – 0.52)	<0.001
>35 kg/m^2	27 (7.3)	10 (5.7)	17 (8.7)	0.63 (0.29 – 1.39)	0.25
Height					
<172 cm	201(7.6)	68 (5.2)	133 (9.9)	0.51 (0.38 – 0.68)	<0.001
172- 179 cm	171(7.0)	54 (4.2)	117 (9.2)	0.45 (0.33 – 0.62)	<0.001
>179 cm	188 (5.8)	52 (3.2)	136 (8.4)	0.38 (0.28 – 0.52)	<0.001
Treated hypertension					
Yes	266 (7.5)	83 (4.6)	191 (10.5)	0.41 (0.32 – 0.53)	<0.001
No	292 (6.0)	91 (3.8)	201 (8.1)	0.46 (0.36 – 0.58)	<0.001
Treated hyperlipidemia					
Yes	321 (7.1)	106 (4.8)	215 (9.3)	0.48 (0.38 – 0.61)	<0.001
No	232 (6.1)	67 (3.5)	165 (8.8)	0.39 (0.29 – 0.51)	<0.001
Diabetes					
Yes	82 (7.9)	30 (5.7)	52 (9.2)	0.52 (0.33 – 0.82)	0.004
No	477 (6.5)	144 (3.9)	333 (9.0)	0.42 (0.35 – 0.51)	<0.001
Previous MI					
Yes	63 (8.3)	22 (6.2)	41 (10.1)	0.57 (0.34 – 0.95)	0.031
No	495 (6.5)	151 (3.9)	344 (9.0)	0.42 (0.35 – 0.51)	<0.001
Previous stroke					
Yes	22 (6.7)	8 (4.9)	14 (8.7)	0.52 (0.22 – 1.24)	0.14

No	535 (6.5)	165 (4.1)	370 (9.1)	0.43 (0.36 – 0.52)	<0.001
Previous CABG					
Yes	40 (10.6)	16 (8.2)	24 (13.2)	0.57 (0.30 – 1.07)	0.08
No	520 (6.4)	158 (4.0)	362 (8.9)	0.42 (0.35 – 0.51)	<0.001
Serum creatinine					
<100 µmol/l	479 (6.6)	150 (4.2)	329 (9.1)	0.44 (0.36 – 0.53)	<0.001
100 -120 µmol/l	35 (6.0)	11 (3.9)	24 (8.1)	0.47 (0.23 – 0.95)	0.037
> 120 µmol/l	14 (5.3)	2 (1.6)	12 (9.1)	0.17 (0.04 – 0.75)	0.020
No. of diseased vessels					
One vessel	294 (5.6)	88 (3.4)	206 (7.8)	0.42 (0.33 – 0.54)	<0.001
Two vessels	165 (7.2)	46 (3.9)	119 (10.6)	0.36 (0.26 – 0.51)	<0.001
Three vessels	101 (10.9)	40 (9.0)	61 (12.8)	0.61 (0.41 – 0.90)	0.01

Abbreviations: BMS, bare-metal stent; DES, drug-eluting stent; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; p, p-value; TLR, target lesion revascularization; BMI, body mass index.

* Number of events (cumulative rate). The cumulative outcome rates (expressed as number (n) and percentages (%)) were calculated with the use of Kaplan-Meier the method. The sum of events (n) vary due to missing observations for some variables.

† Hazard ratios and p-values were adjusted for study center in the Cox proportional hazard model.

Table 3. Target lesion revascularization in stent- and lesion related variables after 5 years in patients with a single lesion treated.

	TLR rates *			**DES vs. BMS** †	
	All	DES	BMS		
	N=6087	N=3030	N=3057		
Stent/lesion variables	n (%)	n (%)	n (%)	HR	p
Total population	327 (5.6)	94 (3.3)	233 (7.9)	0.40 (0.31 – 0.50)	<0.001
Stent length					
<20 mm	176 (5.0)	47 (2.7)	129 (7.1)	0.37 (0.27 – 0.52)	<0.001
20 – 34 mm	99 (5.8)	28 (3.3)	71 (8.4)	0.39 (0.25 – 0.60)	0.001
>34 mm	47(8.4)	16 (5.5)	31 (11.7)	0.43 (0.23 – 0.79)	0.006
Stent diameter					
< 3 mm	106 (7.0)	27 (3.6)	79 (10.6)	0.31 (0.20 – 0.47)	<0.001
3 – 3.9 mm	197 (5.3)	57 (3.1)	140 (7.3)	0.42 (0.31 – 0.57)	<0.001
>3.9	19 (3.6)	7 (2.5)	12 (4.9)	0.46 (0.18 – 1.16)	0.099
Delivery pressure					
<15 bars	51 (6.1)	16 (3.4)	35 (8.7)	0.46 (0.25 – 0.83)	0.01
15 -19 bars	94 (5.4)	27 (3.4)	67 (7.2)	0.42 (0.27 – 0.63)	<0.001
>19 bars	18 (5.7)	6 (3.7)	12(7.7)	0.51 (0.19 – 1.40)	0.19
Ostial lesion					
Yes	22 (7.9)	8 (5.6)	14 (10.5)	0.50 (0.21 – 1.22)	0.13
No	305 (5.5)	86 (3.1)	219 (7.8)	0.39 (0.30 – 0.50)	<0.001
Visible thrombus					
Yes	52 (3.8)	16 (2.2)	36 (5.3)	0.44 (0.25 – 0.80)	0.007
No	275 (6.2)	78 (3.6)	197 (8.7)	0.39 (0.30 – 0.51)	<0.001
Visible calcification					
Yes	77 (6.8)	24 (4.2)	53 (9.5)	0.43 (0.26 – 0.69)	0.001
No	250 (5.3)	70 (3.2)	180 (7.5)	0.39 (0.29 – 0.51)	<0.001
Bifurcation lesion					
Yes	46 (7.2)	11 (3.5)	35 (10.7)	0.32 (0.16 – 0.63)	0.001
No	281 (5.4)	83 (3.2)	198 (7.6)	0.41 (0.32 – 0.53)	<0.001

Chronic occlusion					
Yes	18 (11.8)	3 (4.0)	15 (20.5)	0.19 (0.05 – 0.66)	0.009
No	309 (5.4)	91 (3.2)	218 (7.6)	0.41 (0.32 – 0.53)	<0.001
Lesion type					
A	36 (4.6)	4 (1.1)	32 (7.3)	0.15 (0.05 – 0.42)	<0.001
B1	142 (5.5)	48 (3.7)	94 (7.2)	0.50 (0.36 – 0.71)	<0.001
B2	67 (5.6)	12 (2.2)	55 (8.8)	0.22 (0.12 – 0.41)	<0.001
C	82 (6.5)	30 (4.4)	52 (8.9)	0.48 (0.31 – 0.76)	0.002
Degree of stenosis					
<81%	116 (5.8)	35 (3.7)	81 (7.8)	0.45 (0.30 – 0.67)	<0.001
81-94%	100 (6.2)	28 (3.5)	72 (9.1)	0.36 (0.23 – 0.56)	<0.001
95-100%	111 (4.9)	31 (2.7)	80 (7.1)	0.37 (0.25 – 0.56)	<0.001
TIMI flow ǂ					
0	71 (5.5)	19 (2.9)	52 (8.0)	0.33 (0.19 – 0.55)	<0.001
1	13 (5.9)	4 (3.7)	9 (8.0)	0.52 (0.16 – 1.70)	0.27
2	37 (5.2)	10 (2.8)	27 (7.5)	0.37 (0.18 – 0.77)	0.008
3	206 (5.7)	61 (3.4)	145 (7.9)	0.41 (0.31 – 0.56)	<0.001
Use of GPI					
Yes	60 (4.9)	19 (3.1)	41 (6.6)	0.45 (0.26 – 0.78)	0.004
No	267 (5.8)	75 (3.3)	192 (8.3)	0.38 (0.29 – 0.50)	<0.001

Abbreviations: BMS, bare-metal stent; DES, drug-eluting stent; GPI; Glycoprotein IIb/IIIa inhibitor.HR, hazard ratio; TIMI, thrombolysis in myocardial infarction; p, p-value; TLR, target lesion revascularization. * Number of events (cumulative rate). The cumulative outcome rates (expressed as number (n) and percentages (%)) were calculated with the use of Kaplan-Meier the method.

† Hazard ratios and p-values were adjusted for study center in the Cox proportional hazard model. ǂ Preintervention TIMI flow

Table 4. Predictors for target lesion revascularization in patients with one treated lesion in native coronary arteries and time-dependent effect of type of stent.

Time invariant variables	HR	95 % CI	p
Age (/5years)	0.89	0.84 – 0.94	<0.001
Gender *	0.76	0.59 – 0.97	0.025
Two vessels disease ┼	1.39	1.04 – 1.86	0.027
Three vessels disease	2.02	1.42 – 2.87	<0.001
Visible thrombus in the lesion	0.59	0.44 – 0.79	<0.001
Stent length (/5 mm)	1.11	1.08 – 1.16	<0.001
Stent diameter (mm)	0.62	0.49 – 0.79	<0.001
Covariate with time-dependent effect			
DES/BMS ǂ			
At 6 months	0.22	0.16 – 0.31	<0.001
At 1 year	0.38	0.29 – 0.50	<0.001
At 2 years	0.77	0.53 – 1.12	0.17
At 5 years	0.96	0.62 – 1.48	0.90

Abbreviations: CI, confidence interval; HR, hazard ratio; p, p-value

* Female gender as reference group

┼ One vessel disease as reference group.

ǂ BMS as reference group