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**Drug-eluting versus bare metal stents in saphenous vein grafts compared to native coronary vessels. The NORSTENT study.**

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Short title: Drug-eluting stents in vein grafts vs. native vessels.

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## **Abstract.**

### *Background.*

Drug-eluting stents (DES) reduce target lesion revascularization (TLR) with no effect on mortality or myocardial infarction (MI) compared to bare metal stents (BMS) in native vessels. Randomized stent studies in saphenous vein grafts (SVG) are few and the reported effects are ambiguous. The NORSTENT study is the first to randomize lesions to percutaneous coronary intervention (PCI) in native vessels and SVG.

### *Aims.*

To compare rate of mortality, MI and TLR across stent and vessel types.

### *Methods.*

In this substudy 6087 patients with a single lesion in native vessels and 164 in SVG, were followed for 5 years.

### *Results.*

MI was more frequent in SVG (subdistributional hazard ratio (SHR) 4.95 (3.75 – 6.54,  $p < 0.001$ ), but not affected by stent type. In the first 500 days DES reduced TLR in native vessels (SHR 0.21 (0.15 – 0.30)  $p < 0.001$ ) and SVG (SHR 0.18 (0.04 – 0.80)  $p = 0.02$ ). Thereafter DES and BMS were equivalent in native vessels, but DES had a higher TLR rate than BMS in SVG (SHR 3.31 (1.23 – 8.94)  $p = 0.02$ ). After 5 years the TLR rate was still significantly lower for DES in native vessels (3.2 % versus 7.8 %,  $p < 0.001$ ) but not in SVG (21.4 % vs 18.4%).

### *Conclusion:*

In SVG no difference in TLR between DES and BMS was observed after 5 years in contrast to persistent benefit in native vessels. The high rate of TLR and myocardial infarction in SVG makes treatment of native vessels a preference whenever feasible and better treatment options for SVG are warranted.

## **Introduction.**

Percutaneous coronary intervention in saphenous vein grafts is common and has accounted for 5 to 15% of all PCI procedures [1, 2]. DES used in native coronary arteries have consistently showed reduction in the need for repeat revascularization when compared to BMS [3, 4], with no effect on mortality or cardiovascular morbidity. However, the effects of DES compared to BMS when used in SVG, are not established since the results of randomized trials [5-8, 2, 9, 10] and meta-analyses [11, 12, 1, 13-15] of these trials have been inconsistent.

Among the seven randomized trials reported, six employed first generation DES (sirolimus and paclitaxel coated)[5-7, 2, 9, 10]. The trials were small [5-7, 9] and the follow-up period often short. The one study with second generation DES found no benefit of DES on the composite endpoint of cardiac death, target vessel myocardial infarction and target vessel revascularization (TVR) after a median of 2.7 years follow-up [8]. All randomized trials except one [8] found a reduction in MACE and TLR by DES in short term follow-up (1 - 2.5 years). After 5 years one study showed consistent benefit of DES on MACE (cardiac death, non-fatal myocardial infarction and TVR) [10], while another reported an elimination of the initial beneficial effect of DES [2]. A recent meta-analysis of 7 studies with a total of 1639 patients with 32 months follow-up revealed no benefit by using DES neither on mortality nor on revascularization [15]. No previous randomized trial has been designed to compare stent effects in native coronary arteries and vein graphs.

The Norwegian Coronary Stent Trial (NORSTENT) randomized 9013 patients with acute or stable coronary lesions in native coronary arteries or vein grafts to PCI with second generation DES or BMS. There was no significant difference between the treatment arms for the main composite endpoint of all-cause death and non-fatal spontaneous myocardial

infarction [3], but the rate of target lesion revascularization (TLR) was lowered from 9.1 % with BMS to 4.1 % with DES after 5 years [4]. The aim of the present prespecified substudy is to compare the long-term risk of mortality, spontaneous myocardial infarction, and target lesion revascularization among patients treated with DES or BMS in SVG compared to patients treated in native coronary arteries.

## **Methods.**

NORSTENT (ClinicalTrials.gov number NCT00811772) was a multicentre, randomized trial comparing the long-term effects of PCI with DES or BMS in 9013 patients with stable or acute coronary disease and de novo lesions in native coronary arteries or vein grafts. The main methods and study protocol have been reported previously [3]. 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 (reference number REKNORD 40/2008). The primary outcome for the main study was a composite of death from any cause and nonfatal spontaneous myocardial infarction after a median of 5 years of follow-up. Secondary outcomes included repeat revascularization. Patients were included in the study from September 15, 2008 to February 14, 2011 and followed to December 31, 2014. All patients in Norway undergoing PCI were evaluated for enrolment with broad inclusion and few exclusion criteria. Clinical follow-up was performed according to routine practice at each centre without any scheduled coronary angiography. Double-platelet inhibition with aspirin and clopidogrel was prescribed for 9 months regardless of randomized assignment. The manual for definitions and classifications of outcomes was provided in the Supplementary Appendix to the main study [3]. All outcomes were adjudicated by an end-point committee consisting of clinical and interventional cardiologists, in addition to an epidemiologist blinded for the patients' treatment assignment.

The present analyses include patients who were treated for a single de novo lesion in a native coronary vessel or SVG.

## **Statistical analyses.**

The distribution of baseline covariates among stent and vessel types was evaluated with analysis of variance for continuous variables and logistic regression for categorical variables, including ordered and multinomial logit models when appropriate. In continuous variables with markedly skewed distribution based on normal probability plots Box-Cox transformation was performed before analysis of variance. Multivariable regression models assessing adjusted effects were developed based on directed acyclic graphs (DAG) created at [daggity.net](http://daggity.net) [16, 17] and by evaluating confounding, which was defined as more than 10 % change in the exposure variable by an added covariate.

Cumulative incidence curves for spontaneous myocardial infarction and TLR with all-cause mortality as competing risk was calculated in each stent and vessel group, and differences between the groups evaluated with Pepe-Mori's test. Multivariable analyses accounting for baseline differences were performed with the Cox proportional hazard regression method for all-cause mortality and competing risk regression with subdistribution hazard ratios (SHR) for cardiac and non-cardiac deaths, myocardial infarction, and TLR. Royston-Parmar multivariable competing risk model was used for TLR prediction. Continuous variables were tested for linearity in log hazard by quartile plots and evaluated with fractional polynomials for best fit. The proportional hazard assumptions were evaluated by a test based on Schoenfeld residuals, by log-log survival plots and by interaction with time and time-split at different points of time. Robust standard errors were used in the regression models. For meta-analysis pooled risk ratio (RR) and 95% confidence interval (CI) was calculated using random-effects models with Mantel-Haenszel method. Heterogeneity between studies was calculated using  $I^2$  statistic. Forest plots were generated to show the relative effect size of DES versus BMS in each study. All analyses were performed in STATA v.14 (College Station, Tx, USA) including the programs `stcompet` for cumulative incidence functions,

stpm2cr for Royston-Parmar multivariable competing risk models and metan for the random effect meta-analysis.



## **Results.**

A total of 6251 patients were included in the analyses, of which 164 had a single lesion in SVG and 6087 had a single lesion treated in native vessels.

The distribution of demographic, clinical, laboratory and lesion characteristics are given in Table 1. The DES and BMS groups were well balanced within each vessel type. Patients treated in SVG were older, less likely to smoke, had more comorbid conditions, were less likely to be treated for STEMI at the index event, and differed significantly in several lesion and stent characteristics. No reflow was more frequent in SVG than native vessels but did not vary between stent types. Body mass index, previous stroke, and the use of glycoprotein IIb/IIIa inhibitor did not vary between the groups. Neither did preintervention flow (TIMI grades), frequency of visual thrombus in the lesion, total occlusion, nor stent delivery pressure (overall mean  $\pm$  SD :  $16 \pm 3$  bars). In patients with lesion exclusively in SVG, 76 (46.3 %) were treated with DES and 88 (53.7 %) with BMS. The coating on the DES employed in all lesions was everolimus in 83.1 %, zotarolimus in 11.9 %, paclitaxel in 2.5 % and sirolimus in 2.6 % with no difference between native vessels and SVG ( $p=0.08$ ).

After 6 months 85.8 % of the patients used aspirin on a daily basis with no difference between vessel and stent types. Daily clopidogrel was reported used in 68.2 % in patients with BMS in SVG versus 77.6 % in the three other groups ( $p=0.04$ ) with no individual difference between them.

### *Mortality analyses.*

The cumulative incidence of all-cause mortality was 15.7 % with DES and 20.4 % with BMS in SVG and 8.4 % and 7.2 % in native vessels, respectively (Table 2). All-cause mortality analyzed with Cox regression revealed a HR of 1.19,  $p=0.07$  for DES versus BMS and 2.31,

$p < 0.001$  for SVG versus native vessels (Table 3). The interaction term between stent and vessel type was not significant. The excess mortality in SVG was reduced when adjusting for age (HR 1.57, 95% CI 1.03 – 2.38,  $p = 0.03$ ). There was no significant difference between the DES and the BMS group in cardiac mortality in neither SVG nor native vessels (data not shown).

#### *Spontaneous myocardial infarction.*

The overall cumulative incidence of myocardial infarction after 5 years was 32.9 % (95% CI 25.7 – 40.4) in patients treated in SVG with 37.0 % in the BMS group and 28.3 % in the DES group ( $p = 0.23$ ). In patients treated in native vessels the cumulative incidence of myocardial infarction was 7.5 % (95% CI 6.0 – 8.2) with 7.8% and 7.3 % in BMS and DES groups ( $p = 0.15$ ). The difference in incidence of myocardial infarction between patients treated in SVG vs patients treated in native vessels was highly significant ( $p < 0.001$ ) (Table 3 and Figure 1A). There was no significant interaction between type of stent and vessel ( $p = 0.38$ ) on the rate of myocardial infarction. The unadjusted SHR in patients treated in SVG versus native vessels was 4.95 (95% CI 3.75 - 6.54,  $p < 0.001$ ). The difference remained significant after adjusting for age, gender, number of diseased vessels, diabetes, hyperlipidaemia, and previous myocardial infarction based on DAG analysis.

The subgroup of patients with previous coronary artery bypass surgery (CABG) ( $n = 444$ ), 280 were treated in native vessels and 164 in SVG. In this subgroup the unadjusted SHR for myocardial infarction was 2.52 (95% CI 1.67 – 3.78,  $p < 0.001$ ) in patients treated in SVG vs patients treated in native vessels.

Type of stent had no significant impact on the rate of myocardial infarction in any of the analyses (not shown).

Definite stent thromboses were diagnosed in 40 (0.6 %) of patients treated in native vessels versus 3 (1.8 %) of patients treated in SVG ( $p = 0.26$ ).

*Target lesion revascularization.*

The overall cumulative 5 years incidence of TLR was much higher in SVG (19.9 %) than in native vessels (5.5 %) ( $p < 0.001$ ). In patients treated in SVG TLR was 21.4 % for DES and 18.4 % for BMS ( $p = 0.52$ ) with corresponding figures in native vessels of 3.2 % for DES and 7.8 % for BMS ( $p < 0.001$ ) (Table 2). The shapes of the curves for TLR (Figure 1B) showed considerable time dependent effect variation of stent type depending on vessel type. In native coronary arteries the risk of TLR remained lower after DES than after BMS throughout the whole period of follow-up with no sign of late catch-up in the DES group. In vein grafts, however, an initial benefit of DES was reversed during follow-up so that no significant difference existed after 5 years.

Regression modelling of TLR revealed a highly significant interaction with time and BMS/DES ( $p < 0.001$ ). The best model had a time split at 500 days as judged by the log likelihood of the models. A landmark analysis at 500 days showed a significant lower TLR rate for DES both in SVG ( $p = 0.009$ ) and native vessels ( $p < 0.001$ ) for the first 500 days. Analyses after 500 days revealed no difference in native vessels ( $p = 0.23$ ), but a significant higher TLR rate for DES in SVG ( $p = 0.01$ ) (Figure 2, Table 2).

Controlling for age, gender, number of diseased vessels, diabetes, hyperlipidaemia, prior myocardial infarction, current smoking, and hypertension in analyses of TLR during the first 500 days had no significant effect on the SHR for DES vs BMS (data not shown) but lowered the SHR for vessel type from 2.32 (95 % CI 1.36 – 3.95;  $p = 0.002$ ) to 1.35 (95 % CI 0.72 – 2.54;  $p = 0.35$ ). There was no significant interaction between stent and vessel types.

A similar analysis of TLR after 500 days revealed a significant interaction between stent and vessel types ( $p=0.039$ ), with 3-fold higher TLR with DES compared to BMS in SVG versus similar rates of the two stent types in native arteries (Table 3). Controlling for age, gender, number of diseased vessels, diabetes, hyperlipidaemia, prior myocardial infarction, current smoking, and hypertension, had no significant effect on the SHR for stent type or vessel type (data not shown). After 500 days the TLR rate in SVG versus native vessels was considerably higher for DES with SHR = 11.7 (95% 6.50 – 21.3,  $p<0.001$ ) compared to BMS with SHR = 3.48 (1.25 – 9.66,  $p=0.017$ ).

A subgroup analysis including only patients with previous CABG ( $n= 444$ ) showed similar contrasts between PCI of SVG vs. native arteries as described for the whole study group (data not shown). Modelling predictors for TLR in SVG alone from all covariates in table 1 only recipient vessel was found significant with a reduced risk in grafts to RCA (SHR=0.38, 95% CI 0.16 – 0.87,  $p=0.02$ ).

A multivariable competing risk Royston-Parmer model for TLR prediction was constructed from all variables in Table 1 testing for significance and confounding. Seven variables (age, gender, number of diseased vessels, visible thrombus in the lesion, stent length and stent diameter) were included in the model in addition to stent type (DES/BMS), the dichotomous variable SVG/native vessel and interaction term between vessel and type of stent. Stent type was the only variable that interacted significantly with time. This model was used to visualize the cumulative incidence of TLR for DES/BMS in SVG and native vessels with 95 % confidence interval for DES (Figure 3). The model predicts a higher rate of long-term TLR with DES in SVG than in any of the other groups.

The clinical indication for TLR was stable coronary artery disease for 28.1 % and unstable coronary artery disease for 71.5 % of the patients, with no significant difference depending on stent and vessel type (data not shown).

Selecting recently published studies with long-term follow-up report rate of TLR in SVG, only two reports were found [8, 2]. A meta-analysis of these including the present study is shown in Figure 4. All studies found 23 % higher rates of TLR with DES compared to BMS, and the pooled risk ratio (1.23, 95% CI 1.00 – 1.52) was of borderline significance.

## **Discussion.**

The NORSTENT trial provided a unique opportunity to compare long-term rates of clinically driven revascularization after the implantation of DES or BMS in saphenous vein grafts and native coronary arteries in patients included in the same randomized study. This direct comparison between the treatment results in the two vessel types has to our knowledge never been reported before. The study was initiated in 2008 and patients followed through 2014. Since then, the use of BMS has decreased, but not been eliminated [18]. Second generation DES with everolimus or zotarolimus was used in 95.0 % of the patients randomized to PCI with DES are still in use and the results are pertaining to stents with these coatings. Patients with a single treated lesion were selected to reduce inhomogeneity between treatment groups and to make it possible to relate lesion characteristics to the need for TLR.

The cumulative 5-year incidence of TLR was much higher in SVG (21.4 % for DES and 18.4 % for BMS), than in native vessels (3.2 % for DES and 7.8 % for BMS). The higher rate of TLR in SVG is in concert with previous reports [6-8, 2, 9, 10]. Both the shape of the cumulative incidence function curves and formal analyses with Cox and competing risk regressions showed a strong time-dependent effect of stent type. During the first 500 days, DES had a lower TLR rate than BMS in both vein grafts and native coronary arteries. However, after 500 days, DES and BMS appear to be equivalent in native vessels whereas in SVG DES have a higher TLR rate than BMS. The competing risk cumulative incidence starting after 500 days (Figure 2), the Royston-Parmer model (Figure 3), and the pooled risk ratio estimate from the present and two other relevant studies (Figure 4) indicate no benefit of DES on TLR during long-term follow-up. The pooled estimate suggests a 23 % increase in long-term risk of TLR after implantation of DES in SVG as compared to BMS.

The present study is consistent with the results reported by Colleran et al. [2], the long-term results from Brilakis et al. [8], but in contrast to the study of Fahrni et al [10]. The study of

Colleran et al. was a post-hoc analysis of the ISAR-CABG trial. In the randomized trial of Fahrni et al. DES showed a sustained improved efficacy during long-time follow-up regarding TVR while TLR was not reported. The marked discrepancy to our results is not easily explained, but their overall follow-up was only 70% with more patients lost in the DES group, which the authors indicated could have influenced their outcome. Our results are in also in concert with the most recently published meta-analysis [15].

The total number of deaths in SVG treated patients was limited (n=34), but there was no indication of difference between the stent types in concert with the cited recent studies [8, 2]. Nor was there any difference in the occurrence of spontaneous myocardial infarction, but the rate of occurrence was much higher in SVG than in native vessels (Table 3).

Thus, PCI in SVG has a high long-term complication rate of both TLR and myocardial infarction and our results underline the poor prognosis of a degenerated SVG. This observation is in keeping with previous studies [6-8, 2, 9, 10]. In addition, the only predictor for TLR in vein grafts (recipient vessel) contrasts to what is found in native vessels [4]. Obviously SVG differs in many ways in structure compared to a native vessel [19-21]. Atherosclerotic lesions in SVG have been characterized by large haemorrhagic necrotic cores and delayed endothelial healing particularly after DES implantation [22]. Histologic studies have shown accelerated progression of atherosclerosis in SVG possibly due to macrophage derived foam cells, in contrast to pathologic intimal thickening which is mainly seen in native vessels [23]. The pathological and physiological differences between native coronary arteries and SVG, indicate that DES may have different effects on the vessel wall and healing process after stent deployment in SVG compared to native vessels

Our results could be interpreted as a postponement of DES failure in SVG rather than a different effect of DES in the early and late follow-up period. On the other hand, one could envision that the initial phase is the well-known effect of the drug elution as seen in native

vessels and speculate that the long-term effect is due to a reaction to the remaining polymer. That would indicate the possibility of obtaining better long-term results using DES with biodegradable polymers in SVG [24]. Furthermore, treating degenerated SVG may invoke a different logic compared to treating restenosis in native arteries as lesion severity in the SVG might influence the decision to treat the SVG or the corresponding native vessel. This may also influence the results in the study.

The study has several limitations. First, although NORSTENT was a large, randomized study, treatment of SVG accounted for only 2 % of the patients, thus limiting the power of the substudy. Randomization was not stratified by vessel type, but important prognostic factors were well balanced among the DES and BMS groups at baseline. Baseline differences between SVG and native vessels were adjusted with multivariable methods and corroborated by comparisons made in the subgroup consisting only of previously CABG operated patients. Secondly, although this was a pre-specified analysis, results of subgroup analyses should always be interpreted with caution. Thirdly, it was an open label study where the operator was not blinded to the randomization and a variety of devices was used in both treatment arms adding to possible heterogeneity. The difference in the occurrence of STEMI in SVG versus native vessels (Table 1) may have multiple explanations like differences in hemodynamic situation and/or presence of chronic ischemia and might affect the comparisons within each type of indication. It is however unlikely to have any effect on any overall endpoints reported. We also lack information on the age of SVG and frequency in the use of distal protection device.

In conclusion we could not find any persistent clinical benefit from the use of DES in SVG compared to BMS as judged by rate of mortality, spontaneous myocardial infarction or TLR. After an initial period of benefit, it appears that the rate of TLR is accelerated for DES compared to BMS in SVG in contrast to what is observed in native vessels. Several



mechanisms have been suggested to explain the results. In addition, our study underlines the treatment challenges with a degenerated SVG. A substantially higher rates of TLR and myocardial infarction regardless of stent type are observed in SVG compared to the native vessels. Lesions in native arteries that have been bypassed with SVG probably tend to be more complex than our average single lesion and the results therefore cannot directly be compared. It is nevertheless reasonable to conclude that improved treatment alternatives in SVG are warranted, and that our results also indicate that intervention on the native vessel rather than the SVG should be preferred whenever feasible.

## **Legend to figures.**

### **Figure 1.**

Cumulative incidence functions for spontaneous myocardial infarction (MI (A) and target lesion revascularization (TLR) (B) for DES and BMS in saphenous vein grafts (SVG) and native vessels. For myocardial infarction no significant difference exists in incidence between DES and BMS in SVG or in native vessels. In SVG, the cumulative incidence of TLR did not differ between DES and BMS, whereas in native vessels the difference was highly significant ( $p < 0.001$ ). The incidence was higher for both DES and BMS in SVGs than in native vessels both for MI and TLR ( $p < 0.0001$ ).

### **Figure 2.**

Landmark analysis showing cumulative incidence of target lesion revascularization (TLR) before and after 500 days separately in native vessels and saphenous vein grafts (SVG). In the first 500 days the TLR rate for DES was significantly lower than for BMS both in SVG ( $p = 0.003$ ) and native vessels ( $p < 0.001$ ). After 500 days there was no difference in TLR between DES and BMS in native vessels ( $p = 0.22$ ), but a significantly higher rate for DES than for BMS in SVGs ( $p > 0.001$ ).

### **Figure 3.**

Royston-Parmar model for cumulative incidence of TLR with all-cause mortality as competing risk with 95 % confidence interval for DES. The model contains 9 covariates (age, gender, number of diseased vessels, graft/native vessel, stent type, interaction term type of vessel and type of stent, visible thrombus, stent length, stent diameter). The dichotomous variables are set to 0 and the continuous variables to their mean values for predictions.

**Figure 4.**

Forest plot for target lesion revascularization (TLR) with DES vs BMS in saphenous vein grafts showing risk ratio (RR) in three individual studies including the present, and a pooled effect estimate. Test for overall effect  $RR=1$ ,  $z=1.93$ ,  $p=0.05$ . Heterogeneity:  $I^2=0.0\%$ .

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**Drug-eluting versus bare metal stents in saphenous vein grafts compared to native coronary vessels. The NORSTENT study.**

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Short title: Drug-eluting stents in vein grafts vs. native vessels.

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**Abstract.***Background.*

Drug-eluting stents (DES) reduce target lesion revascularization (TLR) with no effect on mortality or myocardial infarction (MI) compared to bare metal stents (BMS) in native vessels. Randomized stent studies in saphenous vein grafts (SVG) are few and the reported effects are ambiguous. The NORSTENT study is the first to randomize lesions to percutaneous coronary intervention (PCI) in native vessels and SVG.

*Aims.*

To compare rate of mortality, MI and TLR across stent and vessel types.

*Methods.*

In this substudy 6087 patients with a single lesion in native vessels and 164 in SVG, were followed for 5 years.

*Results.*

MI was more frequent in SVG (subdistributional hazard ratio (SHR) 4.95 (3.75 – 6.54,  $p < 0.001$ ), but not affected by stent type. In the first 500 days DES reduced TLR in native vessels (SHR 0.21 (0.15 – 0.30)  $p < 0.001$ ) and SVG (SHR 0.18 (0.04 – 0.80)  $p = 0.02$ ). Thereafter DES and BMS were equivalent in native vessels, but DES had a higher TLR rate than BMS in SVG (SHR 3.31 (1.23 – 8.94)  $p = 0.02$ ). After 5 years the TLR rate was still significantly lower for DES in native vessels (3.2 % versus 7.8 %,  $p < 0.001$ ) but not in SVG (21.4 % vs 18.4%).

*Conclusion:*

In SVG no difference in TLR between DES and BMS was observed after 5 years in contrast to persistent benefit in native vessels. The high rate of TLR and myocardial infarction in SVG makes treatment of native vessels a preference whenever feasible and better treatment options for SVG are warranted.

## Introduction.

Percutaneous coronary intervention in saphenous vein grafts is common and has accounted for 5 to 15% of all PCI procedures [1, 2]. DES used in native coronary arteries have consistently showed reduction in the need for repeat revascularization when compared to BMS [3, 4], with no effect on mortality or cardiovascular morbidity. However, the effects of DES compared to BMS when used in SVG, are not established since the results of randomized trials [5-8, 2, 9, 10] and meta-analyses [11, 12, 1, 13-15] of these trials have been inconsistent.

Among the seven randomized trials reported, six employed first generation DES (sirolimus and paclitaxel coated)[5-7, 2, 9, 10]. The trials were small [5-7, 9] and the follow-up period often short. The one study with second generation DES found no benefit of DES on ~~the target vessel failure~~ (composite endpoint of cardiac death, target vessel myocardial infarction and target vessel revascularization (TVR)) after a median of 2.7 years follow-up [8]. All randomized trials except one [8] found a reduction in MACE and TLR by DES in short term follow-up (1 - 2.5 years). After 5 years one study showed consistent benefit of DES on MACE (cardiac death, non-fatal myocardial infarction and TVR) [10], while another reported an elimination of the initial beneficial effect of DES [2]. A recent meta-analysis of 7 studies with a total of 1639 patients with 32 months follow-up revealed no benefit by using DES neither on mortality nor on revascularization [15]. No previous randomized trial has been designed to compare stent effects in native coronary arteries and vein graphs.

The Norwegian Coronary Stent Trial (NORSTENT) randomized 9013 patients with acute or stable coronary lesions in native coronary arteries or vein grafts to PCI with second generation DES or BMS. There was no significant difference between the treatment arms for the main composite endpoint of all-cause death and non-fatal spontaneous myocardial



infarction [3], but the rate of target lesion revascularization (TLR) was lowered from 9.1 % with BMS to 4.1 % with DES after 5 years [4]. The aim of the present prespecified substudy is to compare the long-term risk of mortality, spontaneous myocardial infarction, and target lesion revascularization among patients treated with DES or BMS in SVG compared to patients treated in native coronary arteries.

## **Methods.**

NORSTENT (ClinicalTrials.gov number NCT00811772) was a multicentre, randomized trial comparing the long-term effects of PCI with DES or BMS in 9013 patients with stable or acute coronary disease and de novo lesions in native coronary arteries or vein grafts. The main methods and study protocol have been reported previously [3]. 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 (reference number REKNORD 40/2008). The primary outcome for the main study was a composite of death from any cause and nonfatal spontaneous myocardial infarction after a median of 5 years of follow-up. Secondary outcomes included repeat revascularization.

Patients were included in the study from September 15, 2008 to February 14, 2011 [and followed to December 31, 2014](#). All patients in Norway undergoing PCI were evaluated for enrolment with broad inclusion and few exclusion criteria. Clinical follow-up was performed according to routine practice at each centre without any scheduled coronary angiography. Double-platelet inhibition with aspirin and clopidogrel was prescribed for 9 months regardless of randomized assignment. The manual for definitions and classifications of outcomes was provided in the Supplementary Appendix to the main study [3]. All outcomes were adjudicated by an end-point committee consisting of clinical and interventional cardiologists, in addition to an epidemiologist blinded for the patients' treatment assignment.

The present analyses include patients who were treated for a single de novo lesion in a native coronary vessel or SVG.

### **Statistical analyses.**

The distribution of baseline covariates among stent and vessel types was evaluated with analysis of variance for continuous variables and logistic regression for categorical variables, including ordered and multinomial logit models when appropriate. In continuous variables with markedly skewed distribution based on normal probability plots Box-Cox transformation was performed before analysis of variance. Multivariable regression models assessing adjusted effects were developed based on directed acyclic graphs (DAG) created at [daggity.net](http://daggity.net) [16, 17] and by evaluating confounding, which was defined as more than 10 % change in the exposure variable by an added covariate.

Cumulative incidence curves for spontaneous myocardial infarction and TLR with all-cause mortality as competing risk was calculated in each stent and vessel group, and differences between the groups evaluated with Pepe-Mori's test. Multivariable analyses accounting for baseline differences were performed with the Cox proportional hazard regression method for all-cause mortality and competing risk regression with subdistribution hazard ratios (SHR) for cardiac and non-cardiac deaths, myocardial infarction, and TLR. Royston-Parmar multivariable competing risk model was used for TLR prediction. Continuous variables were tested for linearity in log hazard by quartile plots and evaluated with fractional polynomials for best fit. The proportional hazard assumptions were evaluated by a test based on Schoenfeld residuals, by log-log survival plots and by interaction with time and time-split at different points of time. Robust standard errors were used in the regression models. For meta-analysis pooled risk ratio (RR) and 95% confidence interval (CI) was calculated using random-effects models with Mantel-Haenszel method. Heterogeneity between studies was calculated using  $I^2$  statistic. Forest plots were generated to show the relative effect size of DES versus BMS in each study. All analyses were performed in STATA v.14 (College Station, Tx, USA) including the programs `stcompet` for cumulative incidence functions,

stpm2cr for Royston-Parmar multivariable competing risk models and metan for the random effect meta-analysis.

## Results.

A total of 6251 patients were included in the analyses, of which 164 had a single lesion in SVG and 6087 had a single lesion treated in native vessels.

The distribution of demographic, clinical, laboratory and lesion characteristics are given in Table 1. The DES and BMS groups were well balanced within each vessel type. Patients treated in SVG were older, less likely to smoke, had more comorbid conditions, were less likely to be treated for STEMI at the index event, and differed significantly in several lesion and stent characteristics. No reflow was more frequent in SVG than native vessels but did not vary between stent types. Body mass index, previous stroke, and the use of glycoprotein IIb/IIIa inhibitor did not vary between the groups. Neither did preintervention flow (TIMI grades), frequency of visual thrombus in the lesion, total occlusion, nor stent delivery pressure (overall mean  $\pm$  SD :  $16 \pm 3$  bars). In ~~the~~ patients with lesion exclusively in SVG, 76 (46.3 %) ~~patients~~ were treated with DES and 88 (53.7 %) with BMS. The coating on the DES employed in all lesions was everolimus in 83.1 %, zotarolimus in 11.9 %, paclitaxel in 2.5 % and sirolimus in 2.6 % with no difference between native vessels and SVG ( $p=0.08$ ).

After 6 months 85.8 % of the patients used aspirin on a daily basis with no difference between vessel and stent types. Daily clopidogrel was reported used in 68.2 % in patients with BMS in SVG versus 77.6 % in the three other groups ( $p=0.04$ ) with no individual difference between them.

### *Mortality analyses.*

The cumulative incidence of all-cause mortality was 15.7 % with DES and 20.4 % with BMS in SVG and 8.4 % and 7.2 % in native vessels, respectively (Table 2). All-cause mortality analyzed with Cox regression revealed a HR of 1.19,  $p=0.07$  for DES versus BMS and 2.31,

$p < 0.001$  for SVG versus native vessels (Table 3). The interaction term between stent and vessel type was not significant. The excess mortality in SVG was reduced when adjusting for age (HR 1.57, 95% CI 1.03 – 2.38,  $p = 0.03$ ). There was no significant difference between the DES and the BMS group in cardiac mortality in neither SVG nor native vessels (data not shown).

#### *Spontaneous myocardial infarction.*

The overall cumulative incidence of myocardial infarction after 5 years was 32.9 % (95% CI 25.7 – 40.4) in patients treated in SVG with 37.0 % in the BMS group and 28.3 % in the DES group ( $p = 0.23$ ). In patients treated in native vessels the cumulative incidence of myocardial infarction was 7.5 % (95% CI 6.0 – 8.2) with 7.8% and 7.3 % in BMS and DES groups ( $p = 0.15$ ). The difference in incidence of myocardial infarction between patients treated in SVG vs patients treated in native vessels was highly significant ( $p < 0.001$ ) (Table 3 and Figure 1A). There was no significant interaction between type of stent and vessel ( $p = 0.38$ ) on the rate of myocardial infarction. The unadjusted SHR in patients treated in SVG versus native vessels was 4.95 (95% CI 3.75 - 6.54,  $p < 0.001$ ). The difference remained significant after adjusting for age, gender, number of diseased vessels, diabetes, hyperlipidaemia, and previous myocardial infarction based on DAG analysis.

~~In a~~ **The** subgroup of patients with previous coronary artery bypass surgery (CABG) ( $n = 444$ ), 280 were treated in native vessels and 164 in SVG. In this subgroup the unadjusted SHR for myocardial infarction was 2.52 (95% CI 1.67 – 3.78,  $p < 0.001$ ) in patients treated in SVG vs patients treated in native vessels.

Type of stent had no significant impact on the rate of myocardial infarction in any of the analyses (not shown).

Definite stent thromboses were diagnosed in 40 (0.6 %) of patients treated in native vessels versus 3 (1.8 %) of patients treated in SVG ( $p = 0.26$ ).

*Target lesion revascularization.*

The overall cumulative 5 years incidence of TLR was much higher in SVG (19.9 %) than in native vessels (5.5 %) ( $p < 0.001$ ). In patients treated in SVG TLR was 21.4 % for DES and 18.4 % for BMS ( $p = 0.52$ ) with corresponding figures in native vessels of 3.2 % for DES and 7.8 % for BMS ( $p < 0.001$ ) (Table 2). The shapes of the curves for TLR (Figure 1B) showed considerable time dependent effect variation of stent type depending on vessel type. In native coronary arteries the risk of TLR remained lower after DES than after BMS throughout the whole period of follow-up with no sign of late catch-up in the DES group. In vein grafts, however, an initial benefit of DES was reversed during follow-up so that no significant difference existed after 5 years.

Regression [modelling](#) of TLR revealed a highly significant interaction with time and BMS/DES ( $p < 0.001$ ). The best model had a time split at 500 days as judged by the log likelihood of the models. A landmark analysis at 500 days showed a significant lower TLR rate for DES both in SVG ( $p = 0.009$ ) and native vessels ( $p < 0.001$ ) for the first 500 days. Analyses after 500 days revealed no difference in native vessels ( $p = 0.23$ ), but a significant higher TLR rate for DES in SVG ( $p = 0.01$ ) (Figure 2, Table 2).

Controlling for age, gender, number of diseased vessels, diabetes, hyperlipidaemia, prior myocardial infarction, current smoking, and hypertension in analyses of TLR during the first 500 days had no significant effect on the SHR for DES vs BMS (data not shown) but lowered the SHR for vessel type from 2.32 (95 % CI 1.36 – 3.95;  $p = 0.002$ ) to 1.35 (95 % CI 0.72 – 2.54;  $p = 0.35$ ). There was no significant interaction between stent and vessel types.

A similar analysis of TLR after 500 days revealed a significant interaction between stent and vessel types ( $p=0.039$ ), with 3-fold higher TLR with DES compared to BMS in SVG versus similar rates of the two stent types in native arteries (Table 3). Controlling for age, gender, number of diseased vessels, diabetes, hyperlipidaemia, prior myocardial infarction, current smoking, and hypertension, had no significant effect on the SHR for stent type or vessel type (data not shown). After 500 days the TLR rate in SVG versus native vessels was considerably higher for DES with  $SHR = 11.7$  (95% 6.50 – 21.3,  $p<0.001$ ) compared to BMS with  $SHR = 3.48$  (1.25 – 9.66,  $p=0.017$ ).

A subgroup analysis including only patients with previous CABG ( $n= 444$ ) showed similar contrasts between PCI of SVG vs. native arteries as described for the whole study group (data not shown). Modelling predictors for TLR in SVG alone from all covariates in table 1 only recipient vessel was found significant with a reduced risk in grafts to RCA (SHR=0.38, 95% CI 0.16 – 0.87,  $p=0.02$ ).

A multivariable competing risk Royston-Parmer model for TLR prediction was constructed from all variables in Table 1 testing for significance and confounding. Seven variables (age, gender, number of diseased vessels, visible thrombus in the lesion, stent length and stent diameter) were included in the model in addition to stent type (DES/BMS), the dichotomous variable SVG/native vessel and interaction term between vessel and type of stent. Stent type was the only variable that interacted significantly with time. This model was used to visualize the cumulative incidence of TLR for DES/BMS in SVG and native vessels with 95 % confidence interval for DES (Figure 3). The model predicts a higher rate of long-term TLR with DES in SVG than in any of the other groups.



The clinical indication for TLR was stable coronary artery disease for 28.1 % and unstable coronary artery disease for 71.5 % of the patients, with no significant difference depending on stent and vessel type (data not shown).

Selecting recently published studies with long-term follow-up ~~that~~ reporting rate of TLR in SVG, only two reports were found [8, 2]. A meta-analysis of these including the present study is shown in Figure 4. All studies found 23 % higher rates of TLR with DES compared to BMS, and the pooled risk ratio (1.23, 95% CI 1.00 – 1.52) was of borderline significance.

## Discussion.

The NORSTENT trial provided a unique opportunity to compare long-term rates of clinically driven revascularization after the implantation of DES or BMS in saphenous vein grafts and native coronary arteries in patients included in the same randomized study. This direct comparison between the treatment results in the two vessel types has to our knowledge never been reported before. [The study was initiated in 2008 and patients followed through 2014.](#) [Since then, the use of BMS has decreased, but not been eliminated](#) [18]. Second generation DES with everolimus or zotarolimus was used in 95.0 % of the patients randomized to PCI with DES [are still in use and the](#) ~~The results are thus~~ [pertaining to stents with](#) these coatings. Patients with a single treated lesion were selected to reduce inhomogeneity between treatment groups and to make it possible to relate lesion characteristics to the need for TLR.

The cumulative 5-year incidence of TLR was much higher in SVG (21.4 % for DES and 18.4 % for BMS), than in native vessels (3.2 % for DES and 7.8 % for BMS). The higher rate of TLR in SVG is in concert with previous reports [6-8, 2, 9, 10]. Both the shape of the cumulative incidence function curves and formal analyses with Cox and competing risk regressions showed a strong time-dependent effect of stent type. During the first 500 days, DES had a lower TLR rate than BMS in both vein grafts and native coronary arteries. However, after 500 days, DES and BMS appear to be equivalent in native vessels whereas in SVG DES have a higher TLR rate than BMS. The competing risk cumulative incidence starting after 500 days (Figure 2), the Royston-Parmar model (Figure 3), and the pooled risk ratio estimate from the present and two other relevant studies (Figure 4) indicate no benefit of DES on TLR during long-term follow-up. The pooled estimate suggests a 23 % increase in long-term risk of TLR after implantation of DES in SVG as compared to BMS.

The present study is consistent with the results reported by Colleran et al. [2], [the long-term results from Brilakis et al.](#) [8], but in contrast to the study of Fahrni et al [10]. The study of

Colleran et al. was a post-hoc analysis of the ISAR-CABG trial. In the randomized trial of Fahrni et al. DES showed a sustained improved efficacy during long-time follow-up regarding TVR while TLR was not reported. The marked discrepancy to our results is not easily explained, but their overall follow-up was only 70% with more patients lost in the DES group, which the authors indicated could have influenced their outcome. Our results are in also in concert with the most recently published meta-analysis [15].

The total number of deaths in SVG treated patients was limited (n=34), but there was no indication of difference between the stent types in concert with the cited recent studies [8, 2]. Nor was there any difference in the occurrence of spontaneous myocardial infarction, but the rate of occurrence was much higher in SVG than in native vessels (Table 3).

Thus, PCI in SVG has a high long-term complication rate of both TLR and myocardial infarction and our results underline the poor prognosis of a degenerated SVG. This observation is in keeping with previous studies [6-8, 2, 9, 10]. In addition, the only predictor for TLR in vein grafts (recipient vessel) contrasts to what is found in native vessels [4].

Obviously SVG differs in many ways in structure compared to a native vessel [19-21]. Atherosclerotic lesions in SVG have been characterized by large haemorrhagic necrotic cores and delayed endothelial healing particularly after DES implantation [22]. Histologic studies have shown accelerated progression of atherosclerosis in SVG possibly due to macrophage derived foam cells, in contrast to pathologic intimal thickening which is mainly seen in native vessels [23]. The pathological and physiological differences between native coronary arteries and SVG, indicate that DES may have different effects on the vessel wall and healing process after stent deployment in SVG compared to native vessels

Our results could be interpreted as a postponement of DES failure in SVG rather than a different effect of DES in the early and late follow-up period. On the other hand, one could envision that the initial phase is the well-known effect of the drug elution as seen in native

vessels and speculate that the long-term effect is due to a reaction to the remaining polymer.

That would indicate the possibility of obtaining better long-term results using DES with biodegradable polymers in SVG. Our results could also be interpreted as a postponement of DES failure in SVG rather than a different effect of DES in the early and late follow-up period and indicate the possibility of obtaining better results using DES with biodegradable polymer [24]. Furthermore, treating degenerated SVG may invoke a different logic compared

to treating restenosis in native arteries as lesion severity in the SVG might influence the decision to treat the SVG or the corresponding native vessel. This may also influence the results in the study.

The study has several limitations. First, although NORSTENT was a large, randomized study, treatment of SVG accounted for only 2 % of the patients, thus limiting the power of the substudy. Randomization was not stratified by vessel type, but important prognostic factors were well balanced among the DES and BMS groups at baseline. Baseline differences between SVG and native vessels were adjusted with multivariable methods and corroborated by comparisons made in the subgroup consisting only of previously CABG operated patients. Secondly, although this was a pre-specified analysis, results of subgroup analyses should always be interpreted with caution. Thirdly, it was an open label study where the operator was not blinded to the randomization and a variety of devices was used in both treatment arms adding to possible heterogeneity. The difference in the occurrence of STEMI in SVG versus native vessels (Table 1) may have multiple explanations like differences in hemodynamic situation and/or presence of chronic ischemia and might affect the comparisons within each type of indication. It is however unlikely to have any effect on any overall endpoints reported. We also lack information on the age of SVG and frequency in the use of distal protection device.

In conclusion we could not find any persistent clinical benefit from the use of DES in SVG compared to BMS as judged by rate of mortality, spontaneous myocardial infarction or TLR. After an initial period of benefit, it appears that the rate of TLR is accelerated for DES compared to BMS in SVG in contrast to what is observed in native vessels. Several mechanisms have been suggested to explain the results. In addition, our study underlines the treatment challenges with a degenerated SVG. A substantially higher rates of TLR and myocardial infarction regardless of stent type are observed in SVG compared to the native vessels. Lesions in native arteries that have been bypassed with SVG probably tend to be more complex than our average single lesion and the results therefore cannot directly be compared. It is nevertheless reasonable to conclude that improved treatment alternatives in SVG are warranted, and that our results also indicate that intervention on the native vessel rather than the SVG should be preferred whenever feasible.

**Legend to figures.**

**Figure 1.**

Cumulative incidence functions for spontaneous myocardial infarction (MI (A) and target lesion revascularization (TLR) (B) for DES and BMS in saphenous vein grafts (SVG) and native vessels. For myocardial infarction no significant difference exists in incidence between DES and BMS in SVG or in native vessels. In SVG, the cumulative incidence of TLR did not differ between DES and BMS, whereas in native vessels the difference was highly significant ( $p < 0.001$ ). The incidence was higher for both DES and BMS in SVGs than in native vessels both for MI and TLR ( $p < 0.0001$ ).

**Figure 2.**

Landmark analysis showing cumulative incidence of target lesion revascularization (TLR) before and after 500 days separately in native vessels and saphenous vein grafts (SVG). In the first 500 days the TLR rate for DES was significantly lower than for BMS both in SVG ( $p = 0.003$ ) and native vessels ( $p < 0.001$ ). After 500 days there was no difference in TLR between DES and BMS in native vessels ( $p = 0.22$ ), but a significantly higher rate for DES than for BMS in SVGs ( $p > 0.001$ ).

**Figure 3.**

Royston-Parmar model for cumulative incidence of TLR with all-cause mortality as competing risk with 95 % confidence interval for DES. The model contains 9 covariates (age, gender, number of diseased vessels, graft/native vessel, stent type, interaction term type of vessel and type of stent, visible thrombus, stent length, stent diameter). The dichotomous variables are set to 0 and the continuous variables to their mean values for predictions.

**Figure 4.**

Forest plot for target lesion revascularization (TLR) with DES vs BMS in saphenous vein grafts showing risk ratio (RR) in three individual studies including the present, and a pooled effect estimate. Test for overall effect  $RR=1$ ,  $z=1.93$ ,  $p=0.05$ . Heterogeneity:  $I^2=0.0\%$ .

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**Table 1.****Baseline characteristics according to treatment groups.**

Variable	SVG		Native vessels		p-value DES vs. BMS	p-value SVG vs. native vessels
	DES (n=76)	BMS (n=88)	DES (n=3030)	BMS (n=3057)		
<i>Patient characteristics.</i>						
Age years (mean ± SD)	68.2 ± 8.9	68.8 ± 9.3	61.9 ± 10.8	61.7 ±10.9	0.46	<0.001
Gender (male) %	88.2	77.3	73.9	73.8	0.74	0.02
Current smoker %	13.2	22.7	35.4	37.0	0.13	<0.001
Treated hypertension %	56.6	61.2	42.1	39.4	0.04	<0.001
Treated hyperlipidaemia %	82.9	79.1	51.8	52.4	0.67	<0.001
Previous MI %	38.7	44.1	8.1	9.2	0.11	<0.001
Diabetes mellitus %	15.8	26.1	12.8	11.5	0.23	0.001
Creatinine µmol/l	87 ±25	86 ±26	78 ±25	78 ±27	0.83	<0.001*
Number of diseased vessels						
One vessel disease %	13.2	17.2	76.7	78.0		
Two vessels disease %	17.1	9.2	15.8	14.7		
Three vessels disease %	69.7	73.6	7.5	7.4	0.30§	<0.001§
HbA1c %	6.4 ± 1.4	6.5 ±0.9	6.1 ±0.9	6.1 ±1.0	0.10*	<0.001*

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*Indication for  
index procedure*

Stable coronary disease %	34.2	26.1	27.3	28.5		
Unstable angina %	22.4	22.7	13.0	12.0		
NSTEMI %	32.9	38.6	30.6	30.5		
STEMI %	10.5	12.5	29.1	29.0	0.78§	<0.001§
Troponin T before procedure (ng/l) (median (IQR≠))	13 (1 - 110)	21 (10 -140)	24 (10 - 222)	26 (10 – 242)	0.36*	0.009*

*Stent and lesion  
characteristics*

Total number of stents used						
Mean ±SD	1.2 ± 0.5	1.2 ± 0.7	1.2 ± 0.5	1.2 ± 0.5	0.82	0.44

Recipient  
vessel/ treated  
vessel n (%)

Left anterior descending coronary artery	16 (21.3)	20 (22.7)	1326 (43.4)	1394 (45.6)		
Circumflex coronary artery	28 (37.3)	37 (42.1)	654 (21.6)	631 (20.6)		
Right coronary artery	31 (41.3)	31 (35.2)	1060 (35.0)	1032 (33.8)	0.05 §	<0.001

Stent length

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mean $\pm$ SD	21.9 $\pm$	20.7 $\pm$	21.3 $\pm$	20.5 $\pm$	0.003	0.68
mm	13.8	14.6	11.4	10.7		
Stent diameter						
mean $\pm$ SD	3.5 $\pm$ 0.5	3.2 $\pm$ 0.5	3.1 $\pm$ 0.5	3.1 $\pm$ 0.5	0.48	<0.001
mm						
Ostial lesion n (%)	9 (11.8)	7 (8.0)	159 (5.3)	144 (4.7)	0.26	0.007
Visible calcification n (%)	7 (9.2)	14 (15.9)	603 (19.9)	576 (18.9)	0.39	0.04
Bifurcation lesion n (%)	1 (1.3)	4 (4.6)	340 (11.2)	354 (11.6)	0.59	0.002
Lesion type B2 or C n (%)	36 (47.4)	52 (59.1)	1331 (43.9)	1263 (41.3)	0.07	0.005
Degree of stenosis % (mean $\pm$ SD)	83 $\pm$ 14	89 $\pm$ 8	88 $\pm$ 12	87 $\pm$ 12	0.37*	0.02*
No reflow %	5.3	10.2	1.9	1.6	0.75	<0.001

Variables were tested for equality between groups using analysis of variance for continuous variables and logistic regression for categorical variables. \* After Box-Cox transformation of dependent variable. § tested for the whole distribution of diseased vessels/indications for index procedure, † IQR, interquartile range. Total number of observations are varying due to missing observations.



**Table 2.**

**Five years cumulative incidence of all-cause mortality, spontaneous myocardial infarction, and target lesion revascularization by stent and vessel type.**

	SVG		p-value	Native vessels		p-value
	DES n=76	BMS n=88		DES n=3030	BMS n=3057	
All-cause mortality n (%) (95% CI) 0 - 5 years	10 (15.7) (8.4 – 28.3)	13 (20.4) (11.0 – 36.1)	0.76	212 (8.4) (7.3 – 9.6)	177 (7.2) (6.1 – 8.4)	0.06
Myocardial infarction n (%) (95 % CI) 0 - 5 years	22 (28.3) (18.5 – 38.8)	42 (37.0) (26.7 – 47.4)	0.23	211 (7.3) (6.4 – 8.3)	228 (7.8) (6.8 – 8.8)	0.15
TLR n (%) (95 % CI) 0 – 5 years	19 (21.4) (13.0 – 31.3)	23 (18.4) (11.1 – 27.2)	0.52	94 (3.2) (2.6 – 3.8)	233 (7.8) (6.9 - 8.8)	<0.001
TLR 0 - 500 days %	3 (2.6) (0.5 – 8.2)	13 (13.8) (7.5 – 21.8)	0.009	40 (1.3) (1.0 – 1.8)	185 (6.1) (5.3 - 6.9)	<0.001
TLR n (%) 500 days – 5 years %	16 (19.6) (11.3 – 29.5)	5 (5.7) (1.8 – 12.7)	0.01	57 (1.9) (1.5 – 2.5)	50 (1.9) (1.4 – 2.4)	0.23

SVG saphenous vein graft, TLR target lesion revascularization



**Table 3****Hazard and subhazard ratios for stent and vessel types with 5 years follow-up.**

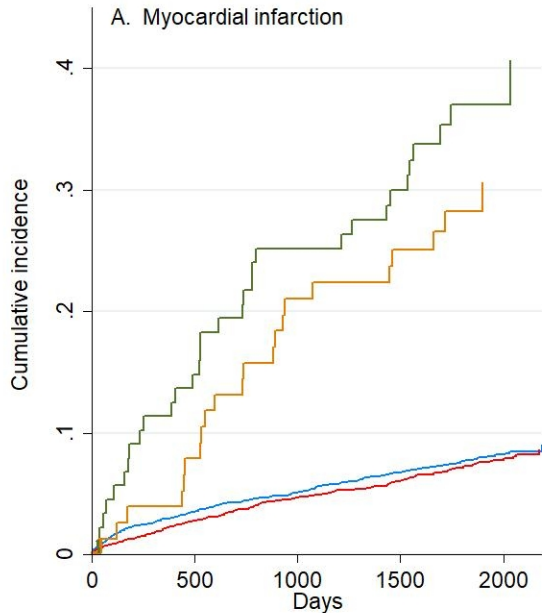
	SVG DES vs. BMS (95 % CI) p-value	Native vessels DES vs. BMS (95 % CI) p-value	All vessels DES vs. BMS (95 % CI) p-value	All stents SVG vs. native vessels (95 % CI) p-value
All-cause mortality	0.88 (0.39 – 1.96) p=0.76	1.21 (1.00 – 1.48) p=0.06	1.19 (0.98 – 1.44) p=0.07	2.31 (1.53 – 3.47) p<0.001
Myocardial infarction	0.72 (0.42 – 1.23) p=0.23	0.94 (0.78 – 1.12) p=0.47	0.91 (0.77 – 1.08) p=0.27	4.95 (3.75 – 6.54) p<0.001
TLR 0 – 500 days	0.18 (0.04 – 0.80) p=0.02	0.21 (0.15 - 0.30) p<0.001	0.21 (0.15 – 0.29) p<0.001	2.32 (1.36 – 3.95) p=0.002
TLR 500 days – 5 years	3.40 (1.25 – 9.23) p=0.02	1.10 (0.75 – 1.61) p=0.62	1.29 (0.91- 1.82) p=0.16	8.36 (5.24 – 13.3) p<0.001

SVG saphenous vein graft, TLR target lesion revascularization

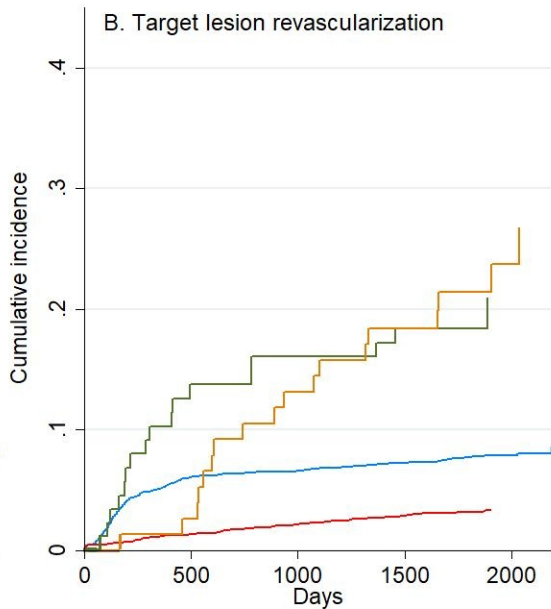




A. Myocardial infarction

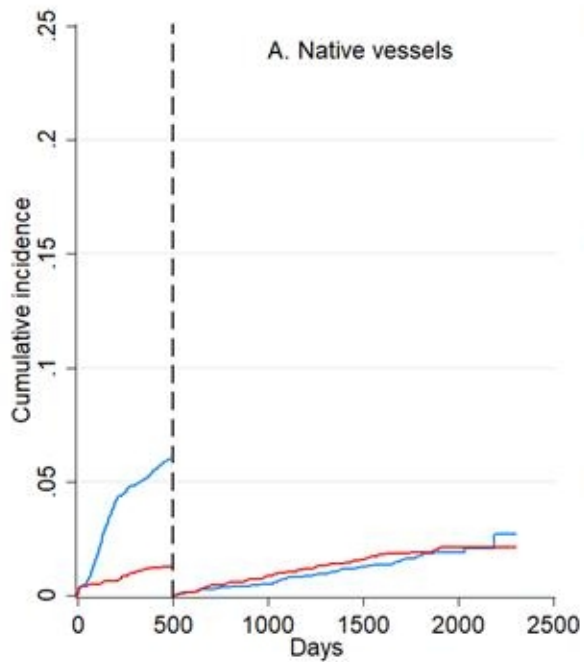


B. Target lesion revascularization

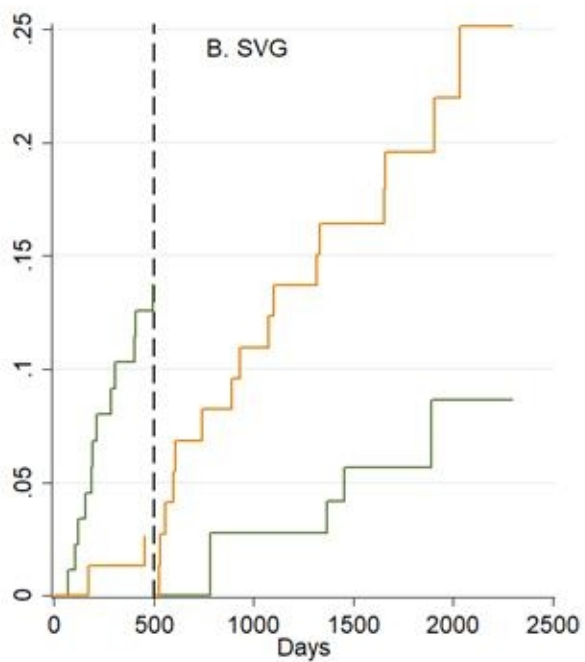


— BMS native vessel  
— BMS vein graft

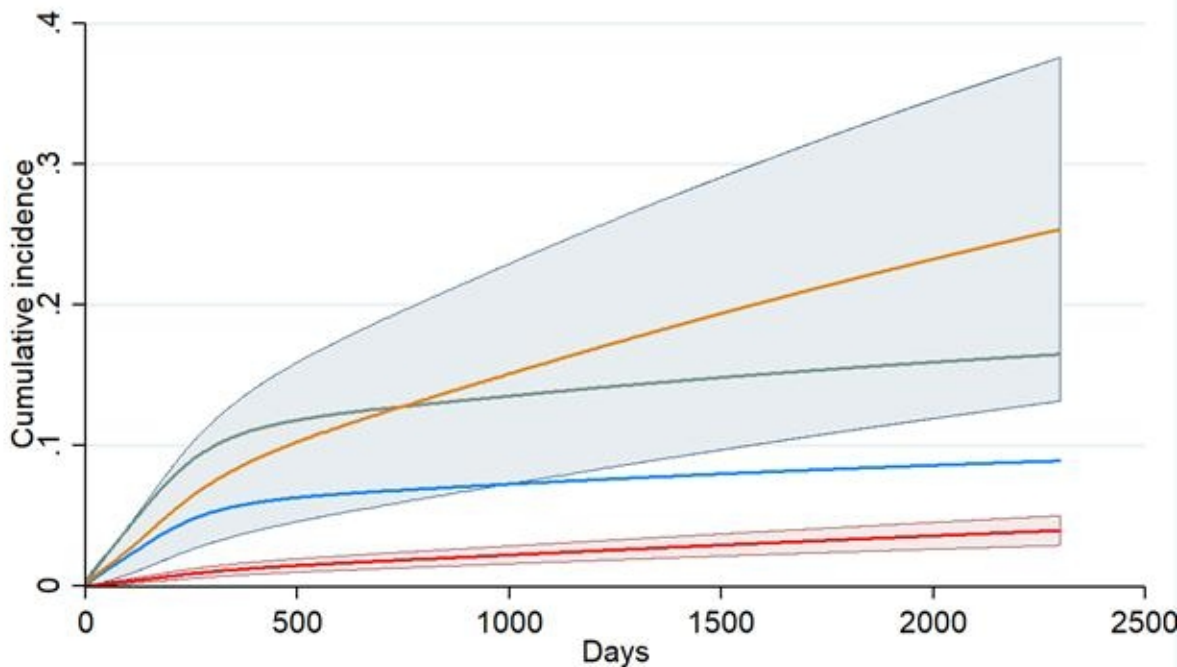
— DES native vessel  
— DES vein graft



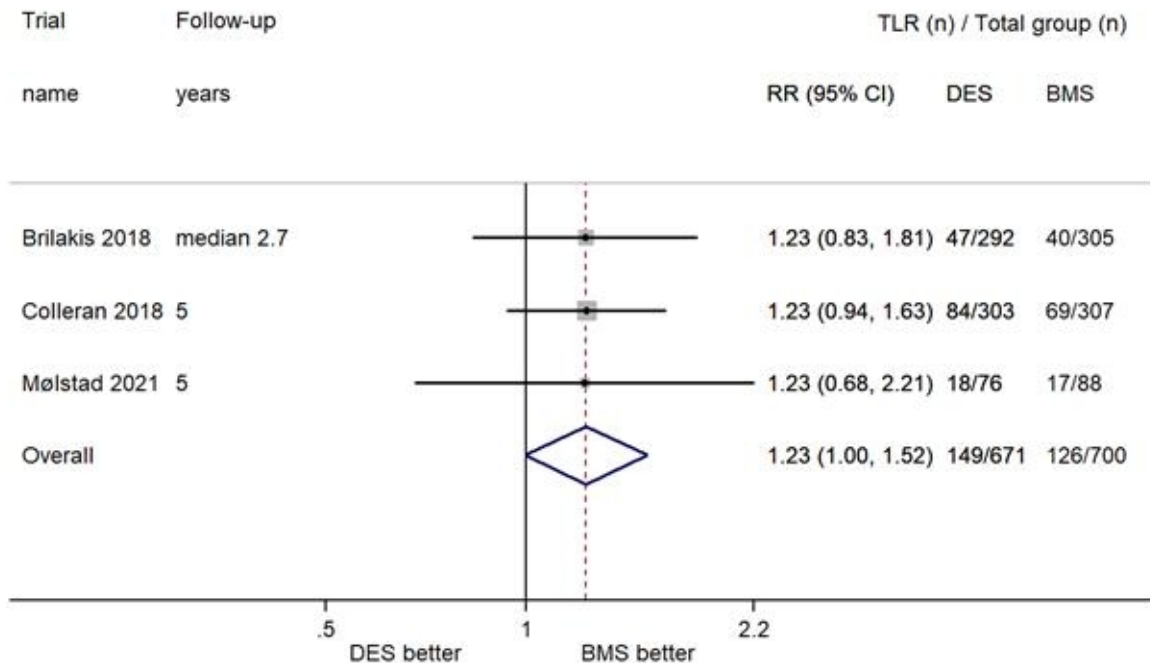
— BMS — DES



— BMS — DES



- 95 % CI DES in vein grafts
- 95 % CI DES in native vessels
- BMS in native vessels
- DES in native vessels
- BMS in vein grafts
- DES in vein grafts



The editor

Cardiology

We appreciate the valuable comments and critics from the reviewers and have responded and altered our article according to the suggestions made. Below is a detailed response to every item raised:

Response to reviewers:

**Reviewer 1:**

1. “Avoid to present data BMS vs. DES.”

The advice assumes that BMS is practically not in use anymore. We do agree that BMS are used to a far lesser extent than before. However even recent publications indicate that the use is far from discarded and therefore the results are still of interest [1-3]. First, to state the obvious, results from long-term follow-up studies necessary will have to take some time to be gathered and reported and clinical practice might have changed somewhat in the meantime. That does not imply that the scientific results obtained cannot be applied to the altered clinical practice. In our case in addition to be of interest for the continuing use of BMS in itself, one can also see the late BMS results in vein grafts as a proxy for drug-eluting stents with bio-resorbable polymers and lending credence to the further investigation of such stents in vein grafts. This is alluded to in the discussion (p.13). The majority of DES stents used in our study was coated with either everolimus or zotarolimus and are still in use. Thus, we think that it is valuable to report the BMS results versus DES as they might indicate a different reaction in vein grafts to the coating and /or polymer than observed in native vessels. In addition, the advice to avoid the BMS data will not be in concert with the request from some of the other reviewers. For these reasons we are still reporting the BMS results, though we appreciate and understand the background for the suggestion.

2. “Please report the temporal window of the NORSTENT and its implication in terms of devices, techniques and medical treatments.”

The temporal window has been included in the method and discussion sections. Description of stent used and the implication for interpretation of results are given in the discussion. Medical treatment of hypertension and hyperlipidemia is given in Table 1. The use of glycoprotein IIb/IIIa inhibitor did not differ between groups and that is mentioned in the results section. Concerning anti-thrombotic treatment, the guidelines for the study is described in the method section and the adherence to the regimen after 6 months is included in the result section. The anti-thrombotic treatment consisted basically of aspirin and clopidogrel for 9 months as stated in the method section. We do not think that newer guidelines for medical treatment of coronary disease is likely to distort the results we obtained to any significant extent.

3. Focus the attention of the comparison of performance SVG vs. native vessels.

This is partly answered above with our rebuttal of avoiding presentation of BMS data. However, we do agree that the comparison of results in SVG versus native vessels is an important part of the paper and we have alluded to that both in the abstract, discussion and conclusion in accordance with the view of the reviewer.

4. “Report predictors of PCI failure in SVG.”

This is included in the results section and commented on in the discussion.

## **Reviewer 2.**

1.” As you know, medication is one of the essential points for the patients after PCI. Do you have any data of other medication? (for instance; statin, ACE-I, ARB...) If the data lacked, it is one of the limitations of the study.”

The data on medical treatment has been described in point 2 in the answer to reviewer 1. We do have the data on the treatment of hypertension and hyperlipidemia, although not detailed down to each drug.

2. “In Results section; You mentioned, After 500 days the TLR rate in SVG versus native vessels was considerably higher for DES with SHR = 11.7 (95% 6.50 – 21.3, p However, these results were not described in Tables. Please consider that resume Table 3. (for instance; DES ~SVG vs. native vessels~, BMS ~SVG vs native vessels~)”

The reason for not including these results in the table is that they cannot be given in such a manner that the headlines would be correct for the comparisons (i.e. we do not have a headline for a column of BMS alone or DES alone). We therefore think that the table would be more crowded, and the results more easily misinterpreted (or not understood) in a table than in free text. Anyway, the results are given.

3. “In Results and Discussions section; This study reported clinical difference between DES and BMS for SVG, and the reasons were well discussed. However, the mechanism of the difference between in early phase (within 500 days) and in chronic phase (after 500 days) should be more discussed. Do you have any reasons or speculations?”

We have altered our discussion to contain the following:

Our results could be interpreted as a postponement of DES failure in SVG rather than a different effect of DES in the early and late follow-up period. On the other hand, one could envision that the initial phase is the well-known effect of the drug elution as seen in native vessels and speculate that the long-term effect of DES is due to a reaction to the remaining polymer. That would indicate the possibility of obtaining better long-term results using DES with biodegradable polymers in SVG.

Minor concerns:

1. In Introduction section;

The Norwegian Coronary Stent Trial (NORSTENT) randomized 9013 patients with acute or stable coronary lesions in native coronary arteries or vein grafts to PCI...

→I think this is not "graphs" but "grafts". Please confirm.

We have corrected this error.

2. In Results section;

In Figure 1A and 1B, it seems that green and yellow line (BMS vein graft/DES vein graft) is not started from the origin. Does it has any reasons? If possible, please resume the Figures.

This was a error that has been corrected.

### **Reviewer 3:**

1. Line 40 to 41 : The one study with second generation DES found no benefit of DES on target vessel failure (composite possibly change to The one study with second generation DES found no benefit of DES on a composite of

The sentence has been altered according to the suggestion.

2. Line 152 : In a subgroup possibly change to The subgroup

This has been done.

3. it could be useful to mention if there was no reflow and how often as well as the usage of intracoronary adenosine, nitroglycerine, verapamil etc.

The occurrence of no reflow has been included in table 1, and a sentence included in the results section : “ No reflow was more frequent in SVG than native vessels but did not vary between stent types.” We do not have the details of treatment of each episode with no reflow and therefore do not have the data about how often nitroglycerine, adenosine and verapamil were used.

4. In the limitations of the study it could be mentioned an underdiagnosis of STEMI in cases of occluded SVGs as the ECG changes are not typical and in the current study the STEMI cases in the SVG subgroup differ significantly...

It is correct that in vein grafts STEMI occurs more rarely than in native vessels with a 100 % occlusion of target lesion (excluding known chronic occlusion). This is corroborated in our data and is probably the reason for the difference in STEMI between SVG and native vessels. How this can influence our results is rather difficult to assess, but we have included a sentence about that in the section of study limitations: “The difference in the occurrence of STEMI in SVG versus native vessels may have multiple explanations like differences in hemodynamic situation and/or presence of chronic ischemia and might affect the comparisons within each type of indication. It is however unlikely to have any effect on any overall endpoints reported.”

5. In Figure 4 I would include also previously mentioned studies [references 5-10] . I think that the publication of Brilakis had TVF and not TLR.



Since we have reported TLR throughout the paper we felt it was most appropriate to do the pooled analyses with that as an endpoint. The publication of Brilakis reported both TLR and TVR and could therefore be included in our TLR meta-analysis (using of course their TLR data). We wanted to make the pooled estimate of recently published studies with long term follow-up as we had strong indication for a time dependent effect of DES vs. BMS. Older studies and studies with a follow-up shorter than 2 years would therefore not be included in our analyses. Fahrni's study [4] did not report TLR and was therefore not included. The selection of studies is described in the result section.

However, we have also done a pooled analyses of TVR with and without the study of Fahrni. The results without the study are practically identical to the TLR analysis. The pooled RR was 1.29 (1.07 – 1.57,  $p=0.009$ ) and variation in RR attributable to heterogeneity 0%. Including the study of Fahrni using a random effect model we obtained a pooled RR of 1.01 (0.66 – 1.55  $p=0.95$ ), but with a significant and substantial heterogeneity with  $I^2$  of 74.1 %. Thus, the study of Fahrni is really at odds to the other three (which is obvious merely from evaluating the results) and the value, validity and information gained by including the study in a meta-analysis is questionable. Instead of including the study in a somewhat dubious meta-analysis and reporting that, we have tried to give explanations for the different effect in the discussion (albeit it is difficult to have a strong opinion about the reason why the results vary that much).

A few minor alterations have been done throughout the paper to improve the language and narrative.

We hope that these alterations make our study acceptable for publication in your journal.

1. Rymer JA, Harrison RW, Dai D, Roe MT, Messenger JC, Anderson HV, et al. Trends in Bare-Metal Stent Use in the United States in Patients Aged  $\geq 65$  Years (from the CathPCI Registry). *Am J Cardiol.* 2016 Oct 1;118(7):959-66.
2. Biswas S, Duffy SJ, Lefkovits J, Andrianopoulos N, Brennan A, Walton A, et al. Australian Trends in Procedural Characteristics and Outcomes in Patients Undergoing Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction. *Am J Cardiol.* 2018 Feb 1;121(3):279-88.
3. Costa F, Brugaletta S, Pernigotti A, Flores-Ulmanzor E, Ortega-Paz L, Cequier A, et al. Does Large Vessel Size Justify Use of Bare-Metal Stents in Primary Percutaneous Coronary Intervention? *Circ Cardiovasc Interv.* 2019 Sep;12(9):e007705.

4. Fahrni G, Farah A, Engstrøm T, Galatius S, Eberli F, Rickenbacher P, et al. Long-Term Results After Drug-Eluting Versus Bare-Metal Stent Implantation in Saphenous Vein Grafts: Randomized Controlled Trial. *J Am Heart Assoc.* 2020 Oct 20;9(20):e017434.