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Outcome of Drug-Eluting Versus Bare-Metal Stenting Used According to On- and Off-Label Criteria

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Objectives The aim of this study was to investigate the outcome of bare-metal stents (BMS) versus drug-eluting stents (DES) after on-label as well as off-label use.

Background DES lower restenosis rates while not influencing the risk for death and myocardial infarction when used in Federal Food and Drug Administration (FDA)-approved indications. It is debated whether the clinical results of this so-called on-label use might be extrapolated to off-label situations.

Methods The SCAAR (Swedish Coronary Angiography and Angioplasty Registry) was used to investigate the outcomes in 17,198 patients who underwent stenting with an on-label indication (10,431 BMS and 6,767 DES patients) and 16,355 patients in the context of an off-label indication (9,907 BMS and 6,448 DES patients). The patients were included from 2003 to 2005 with a minimum follow-up of 1 year and a maximum of 4 years. The analysis was adjusted for differences in baseline characteristics.

Results There were not significant differences between on-label DES and BMS (adjusted hazard ratio: 1.02; 95% confidence interval: 0.92 to 1.13) or between off-label DES and BMS (adjusted hazard ratio: 0.95; 95% confidence interval: 0.87 to 1.04) use with regard to the incidence of myocardial infarction and death. Off-label use of DES did not lead to significant differences in the combined risk of death and myocardial infarction compared with BMS throughout the whole spectrum of clinical indications.

Conclusions In contemporary Swedish practice, neither on- nor off-label use of DES is associated with worse outcome than use of BMS. (J Am Coll Cardiol 2009;53:1389–98) © 2009 by the American College of Cardiology Foundation

The U.S. Food and Drug Administration (FDA) approved the use of the sirolimus-eluting stent (SES) in April 2003 and the paclitaxel-eluting stent in March 2004. The approval was based on a number of pivotal randomized clinical trials investigating relatively low-risk clinical situations and therefore consequently limited to these indications as specified in the product labeling. Despite a rather limited number of "on-label" indications, the use of drug-eluting stents (DES) increased over the years to more than 80% of all stent procedures in some countries and was widespread, extending to "off-label" indications. First, in 2006, when several clinical investigations into real-world practice pointed toward specific risks with the use of DES—namely late stent thrombosis—the issue of on-label versus off-label indications was re-examined. In December 2006 an FDA hearing concluded, on the basis of all available evidence including a large number of meta-analyses, that on-label DES use is not associated with increased incidence of myocardial infarction (MI) or death, although it is associated with increased rates of very late stent thrombosis. Off-label use, in contrast, was thought to be associated with a higher risk of death or MI when compared with on-label use (1–3). This fact might be due to a patient population with a higher risk. Although the early data (2003 and 2004) of SCAAR (Swedish Coronary Angiography and Angioplasty Registry) pointed toward a higher risk of death or MI associated with DES compared with BMS use (4), this difference could no longer be seen after the inclusion of

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Abbreviations and Acronyms

BMS = bare-metal stent(s)
CABG = coronary artery bypass graft
CAD = coronary artery disease
CI = confidence interval
DES = drug-eluting stent(s)
IQR = interquartile range
MI = myocardial infarction
PCI = percutaneous coronary intervention
RR = relative risk
SES = sirolimus-eluting stent(s)
STEMI = ST-segment elevation myocardial infarction

the 2005 cohort of patients (5). Both analyses were based on a mixture of on- and off-label use in daily practice. The present report evaluates the long-term outcome of all patients who underwent stent implantation in Sweden from 2003 to 2005 with regard to on- versus off-label use of DES and BMS.

Methods

Study population. The present study included all patients in Sweden who had undergone coronary stenting from January 1, 2003, until December 31, 2005 for whom at least 1 year of follow-up was available by merging with other national registries. The analyses were based on the type of stent implanted at the first recorded procedure, where patients receiving at least 1 DES were assigned to the DES group regardless of whether they received a stent of another type at any time; otherwise they were assigned to the BMS group.

The SCAAR registry. The SCAAR registry records consecutive patients from all centers (n = 27) performing coronary angiography and percutaneous coronary interventions (PCIs) in Sweden. All consecutive patients undergoing coronary angiography and/or PCI are included. Information on restenosis has been registered for patients undergoing a subsequent coronary angiography for clinical reasons since the beginning of 2004.

The long-term follow-up was based on merging the SCAAR database with other National registries based on all Swedish citizens' unique 10-digit personal identification number. Vital statistics and date of death were obtained from the National Population registry until September 15, 2007. Hospital admission for MI (International Classification of Diseases-10th edition: I21 and I22) was obtained from the Swedish Hospital Discharge Registry until December 31, 2006. The merging of the registers was performed by the Epidemiologic Centre of the Swedish National board of Health and Welfare and approved by the local ethics committee at the Uppsala University.

Design and aim of the present study. The information states that the "sirolimus-eluting coronary stent is indicated for improving coronary luminal diameter in patients with symptomatic ischemic disease due to discrete de novo lesions of length ≤30 mm in native coronary arteries with reference vessel diameter of ≥2.5 mm to ≤3.5 mm" (6). "The paclitaxel-eluting coronary stent system is indicated for improving luminal diameter for the treatment of de novo lesions ≤28 mm in length in native coronary arteries ≥2.5 to ≤3.75 mm in diameter" (7). Patients in the present study were divided into 2 groups on the basis of the following definitions for "on-label" use: stent length ≤33 mm, diameter ≥2.5 and ≤3.75 mm, de novo lesions, non–ST-segment elevation acute myocardial infarction, no occlusion older than 3 months, no grafts, no cardiogenic shock, and not more than 2 stents in the same vessel. All other patients were assigned to the off-label group.

Then patients were then analyzed according to whether they received 1 or more DES or 1 or more BMS. Please note that for grouping of the BMS patients the same DES definitions for on- and off-label situations were used and manufacturer information about the labeled use of BMS was not taken into account for the purposes of this investigation. This led to 4 main groups of patients: DES patients with an on- or off-label indication, and BMS patients with an on- or off-label indication for stenting.

The primary aim of the investigation was to compare the outcome after DES off-label stenting versus BMS off-label stenting. Secondary aims included the comparison of on-label BMS stenting versus on-label DES stenting. Furthermore, we aimed to compare on-label versus off-label stenting irrespective of stent type.

Statistical analyses. The statistical methods used for this analysis have been published in detail in an earlier article about DES use in Sweden (4). Baseline characteristics were summarized with medians and interquartile ranges for continuous variables and percentages for discrete variables. Cumulative event rates were estimated by the Kaplan-Meier method. The primary objective was to evaluate late occurring events after stenting. The primary end point was the composite of death or MI. Secondary end points were death, MI, revascularization, and restenosis. Clinically important confounders (as presented in Table 1) were summarized in a propensity score (8). Separate propensity scores were estimated for the on- and off-label groups by fitting multiple logistic regression models. To evaluate whether the propensity score managed to balance the groups as regards the included variables, standardized means were calculated and compared before and after propensity score adjustment. Adjusted relative risks (RRs) were estimated from models where the propensity score and stent group were entered as covariates. For plotting purposes the models were then refitted with stent group as a stratification variable, and adjusted cumulative event rates were estimated at the overall average propensity score. Death was regarded as a censoring event in the analysis of MI. All analyses were done with the statistical program R version 2.6.1 (9).

Results

Patient characteristics and stents. During the years 2003 to 2005, 34,530 patients underwent stenting in Sweden. A total of 977 patients (2.8%) were excluded due to missing data about important baseline characteristics. Thus, 33,553 (97.2%) patients were included in the study and listed in

Table 1 Baseline Characteristics

	On-Label		Off-Label	
	BMS (n = 10,431)	DES (n = 6,767)	BMS (n = 9,907)	DES (n = 6,448)
Age, yrs, median (IQR)	66 (58–74)	65 (58–73)	66 (58–75)	66 (58–74)
Female sex	29.3 (3,053)	29.4 (1,991)	25.1 (2,486)	27.8 (1,790)
Region				
North	17.4 (1,810)	3.5 (235)	9.3 (925)	2.5 (160)
Stockholm	19.5 (2,029)	17.3 (1,170)	17.8 (1,766)	13.7 (881)
Southeast	9.6 (1,002)	11.8 (796)	7.7 (764)	12.1 (778)
South	13.6 (1,420)	24.0 (1,624)	21.2 (2,104)	30.2 (1,948)
Middle	23.2 (2,422)	40.6 (2,749)	24.5 (2,431)	38.3 (2,469)
West	16.8 (1,748)	2.9 (193)	19.3 (1,917)	3.3 (212)
Year				
2003	39.6 (4,128)	16.6 (1,125)	31.4 (3,110)	15.7 (1,015)
2004	34.7 (3,615)	34.2 (2,312)	36.9 (3,653)	32.4 (2,091)
2005	25.8 (2,688)	49.2 (3,330)	31.7 (3,144)	51.8 (3,342)
Stable CAD	27.8 (2,895)	32.1 (2,171)	14.3 (1,418)	26.8 (1,731)
Unstable CAD	71.1 (7,415)	66.4 (4,490)	27.6 (2,730)	38.4 (2,474)
STEMI			58.0 (5,747)	34.4 (2,219)
Other indications	1.2 (121)	1.6 (106)	0.1 (12)	0.4 (24)
Smoking				
Current	19.8 (2,066)	17.9 (1,208)	23.6 (2,337)	20.5 (1,322)
Former	33.4 (3,480)	33.0 (2,230)	28.6 (2,836)	30.8 (1,984)
Never	38.1 (3,972)	42.0 (2,844)	33.1 (3,282)	39.5 (2,549)
Unknown	8.8 (913)	7.2 (485)	14.7 (1,452)	9.2 (593)
Diabetes	16.0 (1,670)	23.3 (1,580)	15.5 (1,540)	23.3 (1,502)
Hypertension	47.7 (4,980)	48.4 (3,273)	41.4 (4,104)	46.7 (3,010)
Unknown	2.0 (213)	2.2 (148)	4.1 (408)	3.8 (248)
Previous heart failure	7.1 (744)	7.4 (503)	6.5 (647)	8.0 (514)
Previous kidney failure	1.0 (107)	1.3 (88)	1.0 (95)	1.3 (85)
Previous dialysis	0.4 (43)	0.8 (52)	0.3 (34)	0.5 (34)
Previous COPD	4.8 (496)	4.5 (306)	4.7 (464)	4.4 (282)
Previous dementia	0.1 (8)	0.0 (3)	0.1 (8)	0.1 (4)
Previous cancer	2.5 (256)	2.5 (168)	2.7 (266)	2.5 (162)
Previous PCI	10.5 (1,094)	11.2 (757)	10.0 (990)	18.3 (1,180)
Previous CABG	6.5 (677)	6.6 (448)	12.2 (1,206)	15.1 (971)
Previous MI	39.4 (4,114)	36.2 (2,451)	33.5 (3,317)	38.7 (2,495)
Previous stroke	5.6 (585)	6.0 (406)	6.6 (649)	6.7 (429)
ASA before	92.0 (9,597)	94.5 (6,396)	84.6 (8,384)	89.0 (5,738)
Clopidogrel before	66.1 (6,895)	71.3 (4,826)	49.7 (4,923)	63.0 (4,063)
GP IIb/IIIa inhibitors	24.9 (2,596)	20.7 (1,401)	54.9 (5,434)	38.5 (2,480)
No. of stents				
1	73.2 (7,631)	62.4 (4,224)	60.9 (6,033)	43.9 (2,833)
2	22.7 (2,372)	29.7 (2,013)	23.4 (2,323)	28.9 (1,863)
3	4.1 (428)	7.8 (530)	15.7 (1,551)	27.2 (1,752)
Angiographic findings				
Not significant	0.3 (28)	0.4 (30)	0.3 (28)	0.2 (15)
1-vessel	52.9 (5,514)	49.2 (3,328)	43.6 (4,318)	38.4 (2,473)
2-vessel	30.7 (3,202)	32.3 (2,188)	29.3 (2,905)	31.3 (2,020)
3-vessel	14.9 (1,556)	16.7 (1,130)	20.7 (2,046)	21.7 (1,396)
Left main	1.3 (131)	1.3 (91)	6.2 (610)	8.4 (544)

Values shown as % (n) unless otherwise stated.

ASA = acetyl-salicyl acid; BMS = bare-metal stent(s); CABG = coronary artery bypass graft; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DES = drug-eluting stent(s); GP = glycoprotein; IQR = interquartile range; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Table 1. Of the patients, 10,431 received at least 1 BMS but no DES, and 6,767 received at least 1 DES in an on-label situation; 9,907 patients received 1 or more BMS, and 6,448 received 1 or more DES for an off-label indication. Therefore, off-label clinical situations accounted for 49% of all DES use in the observation period (with little variation between 47.4% in 2003 and 50.0% in 2005), whereas of all BMS that were implanted 49% were used for off-label

indications. The average DES usage increased continuously during the study period, from 12% the first quartile of 2003 to 59% the fourth quartile of 2005. On-label indications increased the use of DES from 21.4% in 2003 to 55.3% in 2005, whereas in off-label situations the DES use was 24.6% in 2003 and 51.5% in 2005.

Table 1 shows patient characteristics in the on- and off-label groups, divided by BMS and DES.

The DES group was, on average, slightly younger and had higher proportions of diabetes mellitus compared with the BMS cohort, with regard to on-label situations. Previous MI was less often observed in the DES group, whereas previous PCI was more frequently registered. Multivessel and left main disease was more frequently observed in the DES group.

In both on- and off-label clinical situations, clopidogrel use before the procedure was more prevalent in the DES groups. Periprocedural glycoprotein IIb/IIIa inhibition was less common in the DES group, and this difference was highly significant in off-label indications, because of the inclusion of ST-segment elevation myocardial infarction (STEMI) patients. STEMI was also the single second-most-important criterion that led to inclusion in the DES off-label group, whereas the single most-important criterion was stent diameter <2.5 or >3.75 mm, followed by >2 stents/vessel, chronic occlusion, and restenotic lesion (Table 2).

After adjustment for the propensity score the DES and BMS groups were well balanced in both the on- and off-label situations (data not shown).

Death and MI. During the entire study period, 4,845 patients experienced an MI and/or died (1,255 in the on-label BMS group, and 761 in the on-label DES group; 1,836 in the off-label BMS group, and 993 in the off-label DES group).

During the entire study period, 6,660 events occurred, 3,602 MIs (956 in the on-label BMS group, and 628 in the on-label DES group; 1,223 in the off-label BMS group, and 795 in the off-label DES group) and 3,058 deaths (785 in the on-label BMS group, and 456 in the on-label DES group; 1,191 in the off-label BMS group, and 626 in the off-label DES group). The mean follow-up for the combined end point MI/death was 785 days (743 days for off-label use, and 825 days for on-label use).

Table 2 Frequency of Different Off-Label Criteria

Criteria	BMS (n = 9,907)	DES (n = 6,448)	All (n = 16,355)
STEMI	5,747 (58.0%)	2,219 (34.4%)	7,966 (48.7%)
Stent diameter <2.5 or >3.75 mm	3,393 (34.2%)	2,552 (39.6%)	5,945 (36.3%)
Stent length >33 mm	60 (0.6%)	24 (0.4%)	84 (0.5%)
More than 2 stents/coronary vessel	1,118 (11.3%)	1,102 (17.1%)	2,220 (13.6%)
Stented chronic occlusion	462 (4.7%)	712 (11.0%)	1,174 (7.2%)
Stented CABG graft	761 (7.7%)	433 (6.7%)	1,194 (7.3%)
Stented restenotic lesion	210 (2.1%)	607 (9.4%)	817 (5.0%)
Stented left main lesion	139 (1.4%)	248 (3.8%)	387 (2.4%)

Abbreviations as in Table 1.

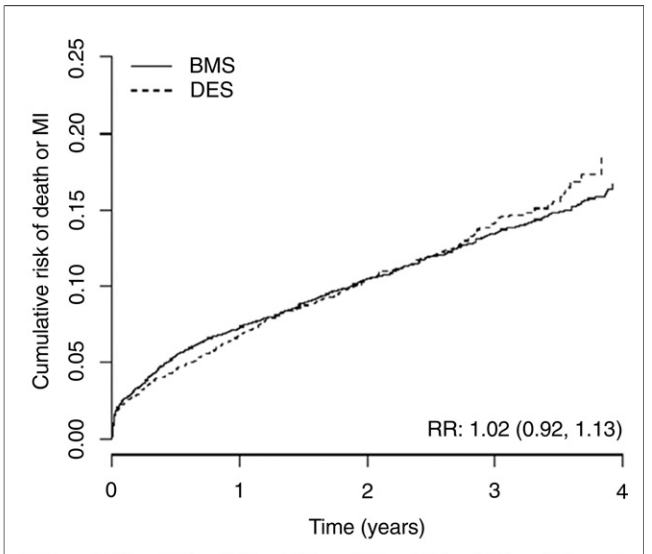

Figure 1 Death or MI: On-Label

Propensity score adjusted cumulative event rates regarding the composite of death or myocardial infarction (MI) during 4 years of follow-up after stenting for on-label indications with drug-eluting stents (DES) **(dashed line)** or with bare-metal stents (BMS) only **(solid line)**. Numbers at risk are shown **below each figure**. RR = relative risk.

There was no significant difference between the DES and BMS groups in the composite of death and MI during the 4 years follow-up period. This was true for on-label as well as off-label indications (Figs. 1 and 2).

Mortality. The total number of deaths was 3,058 (785 in the on-label BMS group, and 456 in the on-label DES group; 1,191 in the off-label BMS group, and 626 in the off-label DES group). There was not a difference in the cumulative adjusted mortality between DES and BMS in on-label situations or in off-label situations (Figs. 3 and 4).

The mean follow-up for the end point death was 1,069 days (1,029 days for off-label use, and 1,107 days for on-label use).

MI. The total number of patients experiencing at least 1 MI was 2,851 (773 in the on-label BMS group, and 494 in the on-label DES group; 988 in the off-label BMS group, and 596 in the off-label DES group). There was no difference between DES and BMS use in on-label or off-label situations over a period of 4 years. The RR for on-label use of DES was 1.00 (95% confidence interval [CI]: 0.87 to 1.14), whereas it was 0.97 (95% CI: 0.86 to 1.09) for off-label stenting (Figs. 5 and 6).

Restenosis and new revascularization. During follow-up, in the on-label group the crude rate of restenosis/year of follow-up was 3.0% for BMS (n = 319) and 1.8% for DES (n = 173), whereas in the off-label group the crude rates were 3.4%/year for BMS (n = 379) and 2.7%/year for DES (n = 246). The RR to develop a restenosis associated with

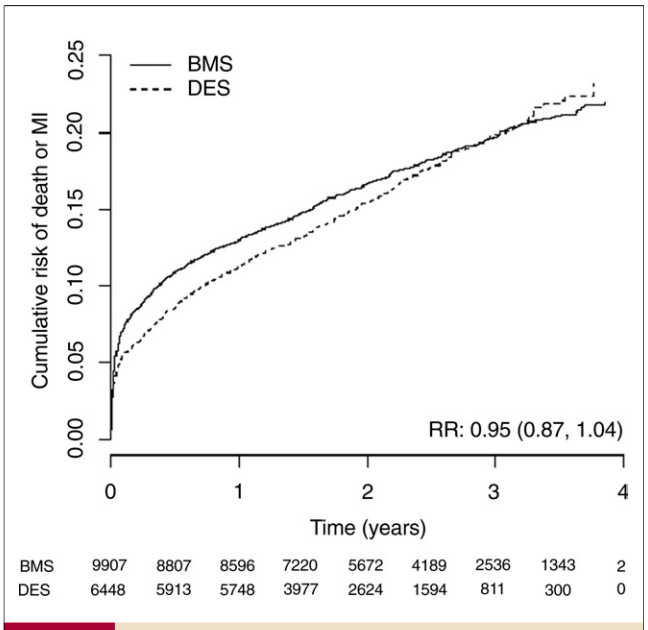

Figure 2 **Death or MI: Off-Label**

Propensity score adjusted cumulative event rates regarding the composite of death or MI during 4 years of follow-up after stenting for off-label indications with DES **(dashed line)** or with BMS only **(solid line)**. Numbers at risk are shown **below each figure**. Abbreviations as in Figure 1.

DES use was 0.57 (95% CI: 0.46 to 0.70) for on-label indications and 0.79 (95% CI: 0.65 to 0.96) for off-label indications after adjusting for differences in baseline characteristics through the propensity score.

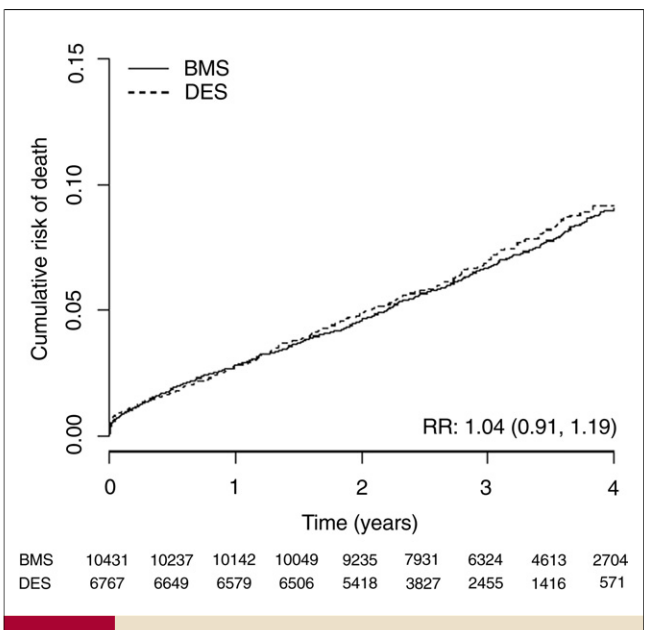

Figure 3 **Mortality: On-Label**

Propensity score adjusted cumulative mortality rates during 4 years of follow-up after stenting for on-label indications with DES **(dashed line)** or with BMS only **(solid line)**. Numbers at risk are shown **below each figure**. Abbreviations as in Figure 1.

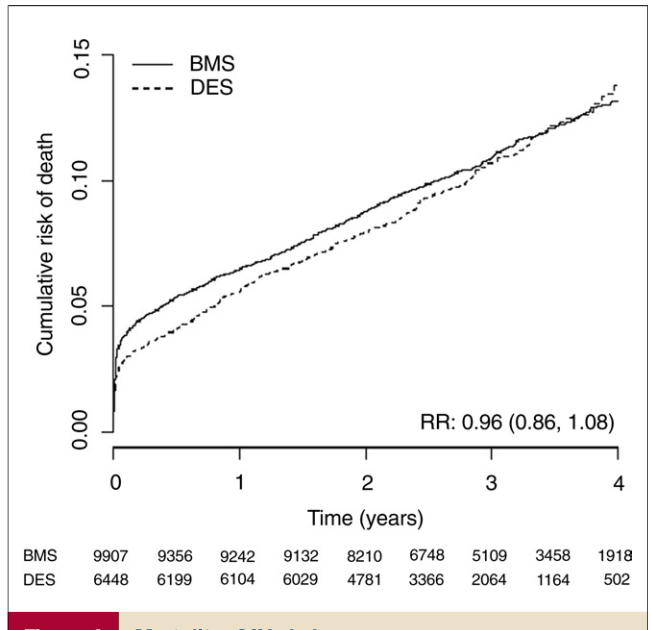

Figure 4 **Mortality: Off-Label**

Propensity score adjusted cumulative mortality rates during 4 years of follow-up after stenting for off-label indications with DES **(dashed line)** or with BMS only **(solid line)**. Numbers at risk are shown **below each figure**. Abbreviations as in Figure 1.

In the on-label BMS group, 1,481 patients (6.2%/year of follow-up) had new PCI, and 218 patients (0.8%/year) underwent coronary artery bypass graft surgery (CABG) during follow-up; in the on-label DES group, 995 (8.0%/

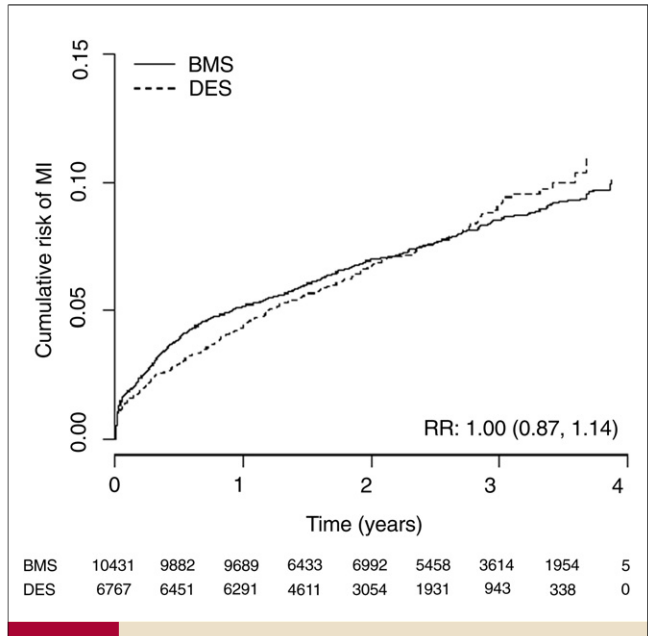

Figure 5 **MI During Follow-Up: On-Label**

Propensity score adjusted cumulative rates of MI during 4 years of follow-up after stenting for on-label indications with DES **(dashed line)** or with BMS only **(solid line)**. Numbers at risk are shown **below each figure**. Abbreviations as in Figure 1.

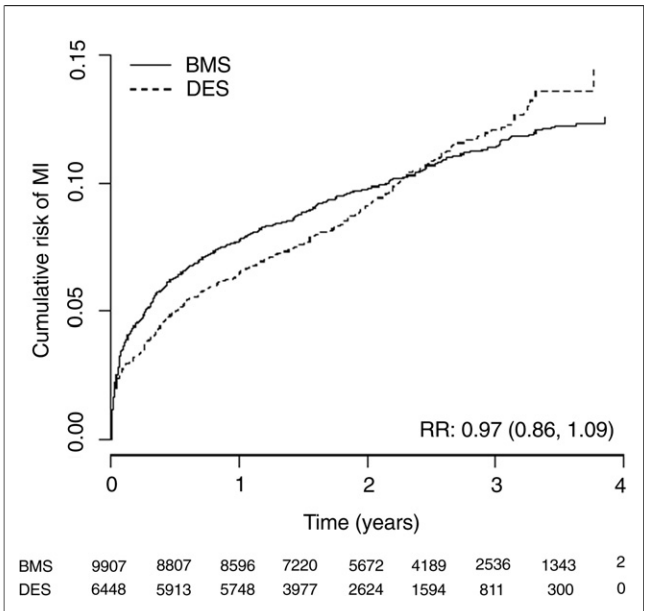

Figure 6 **MI During Follow-Up: Off-Label**

Propensity score adjusted cumulative rates of MI during 4 years of follow-up after stenting for off-label indications with DES **(dashed line)** or with BMS only **(solid line)**. Numbers at risk are shown **below each figure**. Abbreviations as in Figure 1.

year) had new PCI, and 106 (0.8%/year) underwent CABG during follow-up. In the off-label BMS group, the corresponding numbers were 1,672 (8.4%/year) for new PCI and 368 (1.6%/year) for CABG. In the off-label DES group, the corresponding numbers were 1,126 (10.3%/year) for new PCI and 162 (1.3%/year) for CABG.

Results according to indication. There were, in total, 8,215 patients with an indication of stable coronary artery disease (CAD), of which 5,066 (61.7%) fulfilled on-label criteria. The RR for the combined end point of death or MI associated with the use of DES in on-label situations was 0.93 (95% CI: 0.75 to 1.16), whereas that number for off-label stent usage was 0.95 (95% CI: 0.75 to 1.20) (Fig. 7). There was no statistically significant difference between BMS and DES regarding the end point of MI when looking at stable CAD for either the on-label situations with an RR of 0.83 (95% CI: 0.63 to 1.10) or the off-label situation with an RR of 0.98 (95% CI: 0.72 to 1.33). In addition, there were no differences in the end point of death between DES and BMS in stable patients, either in on- or off-label situations.

The biggest subgroup was patients with unstable CAD (unstable angina and non–ST-segment elevation acute myocardial infarction) with a total of 17,109 patients. Of those, 11,905 (69.6%) were treated in an on-label situation. When looking at the issue of BMS versus DES in on- and off-label situations regarding the different end points of death, death and MI, and MI alone, there were no statistically significant differences in outcome between the 2 types of stents. The adjusted hazard ratio for the combined end point of death or MI was 1.05 (95% CI: 0.93 to 1.19) in on-label situations and 1.00 (95% CI: 0.86 to 1.16) in off-label situations (Fig. 8).

STEMI was the single most important criterion to qualify a patient undergoing stenting as off-label (7,966 patients in total, accounting for 48.7% of all patients in the off-label group). There were 5,747 patients in the BMS group (58.0% of off-label BMS use) and 2,219 patients (34.4% of off-label DES use) in the DES group. As direct PCI for STEMI became more accepted under the study period, the use of DES stents increased in this off-label clinical situation from approximately 15% in 2003 to 36% in 2005. The RR for death associated with DES was 0.99 (95% CI: 0.85 to 1.16) during 4 years of follow-up for STEMI patients. Neither the combined end point of MI and death (RR: 0.92; 95% CI: 0.81 to 1.04) (Fig. 9) nor MI alone (RR: 0.93; 95% CI: 0.78 to 1.11) showed a significant difference between DES and BMS during the entire study period of 4 years.

Discussion

In the present study we evaluated the long-term outcome with DES versus BMS in a large cohort of unselected consecutive patients treated with coronary stenting at all interventional centers in Sweden. The patients were grouped according to the on- or off-label use of DES and compared with a corresponding control group of BMS patients with the same labeling categories from DES as stated in the manufacturers' information for use, which is

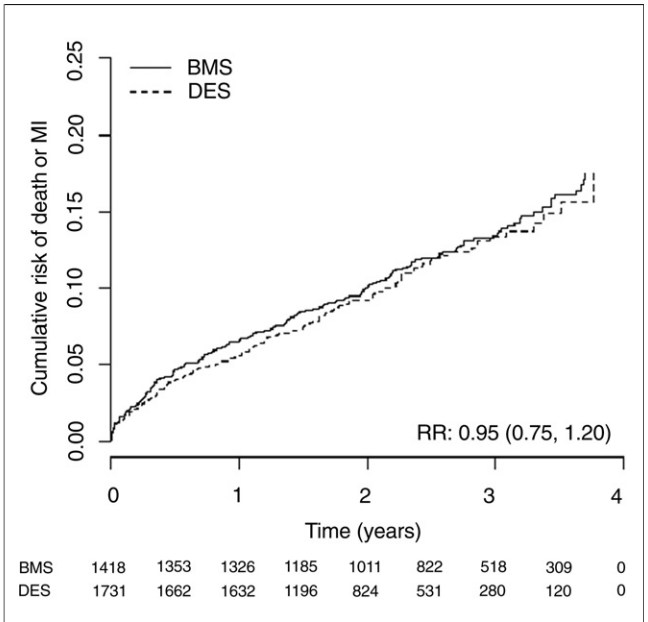

Figure 7 **Event Rates for Stable Coronary Artery Disease: Off-Label**

Propensity score adjusted cumulative event rates of death or MI during 4 years of follow-up after stenting with DES **(dashed line)** or with BMS only **(solid line)** for off-label indications. Numbers at risk are shown **below each figure**. Abbreviations as in Figure 1.

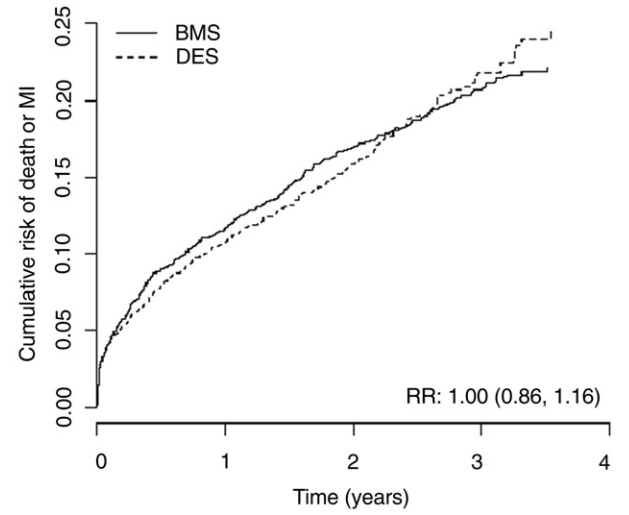

Figure 8 **Event Rates for Unstable Coronary Artery Disease: Off-Label**

Propensity score adjusted cumulative event rates of death or MI during 4 years of follow-up after stenting with DES **(dashed line)** or with BMS only **(solid line)** for off-label indications. Numbers at risk are shown **below each figure**. Abbreviations as in Figure 1.

based on the FDA approval. The FDA approval is based on the so-called pivotal trials that led to the introduction of DES. Despite the fact that the database for DES use in off-label situations is sparse, this use is estimated to comprise more than 60% of all DES use in the U.S. (1), and it was 49% in the present investigation. This figure fits well with other publications that reported between 47% (10) and 55% (11) off-label DES use.

Although we showed that death and MI are more prevalent during follow-up after off-label stenting compared with on-label use of stents, this finding was neither unexpected nor the main purpose of our investigation. Most information from the published data regarding off-label use of DES comes from registries that represent a mixture of on- and off-label indications (12–17), and none found a difference between BMS and DES with regard to mortality and MI, which is in accordance with meta-analyses of on- and off-label randomized trials (18). Our own analysis of the Swedish data from 2003 to 2004 was also a mixture of on- and off-label usage, and many analysts thought the negative results for DES were mainly due to off-label DES use (4). An analysis of patients included from 2003 to 2005 could not find the same differences between stent types without examining the on- versus off-label issue (5).

One of the registries that included all patients specifically investigated lesion characteristics that constitute off-label DES-use and did not find any difference between DES and BMS use with regard to death and MI at 1 year (17). That registry included even lesion characteristics that we could not take into account, like bifurcation lesions, presence of calcification, and thrombus (17). Abbott et al. (17) did not report any significant differences between DES and BMS with regard to mortality and MI during 1 year of follow-up.

None of the other mentioned registries investigated the on- versus off-label issue with regard to differences between BMS and DES.

Four registry reports focused on off-label DES use and compared clinical outcome data with on-label DES use (10,11,19,20). The off-label DES use accounted for between 24.1% (19) and 65.1% (20) in these studies. Two reports showed that the safety and efficacy of DES is reduced in off-label indications as compared with on-label use (10,11) while judging these results differently. One of them, the EVENT (Evaluation of Drug Eluting Stents and Ischemic Events) registry, did not include STEMI patients and did not report significant differences in mortality between the 2 groups, either during index admission or during 12 months of follow-up (10). Myocardial infarction, however, was more prevalent in the off-label DES group compared with the on-label DES group, and this difference was significant both during the index admission and 12 months of follow-up (10). When considering these results, however, it must be taken into account that Win et al. (10) systematically measured biomarkers and even excluded 1,019 patients (23.5%) because of missing baseline markers. Off-label use was also an independent predictor in multivariate analysis of worse outcome both during index hospital stay and during follow-up (10). The EVENT registry (10) as well as the D.E.S.cover registry (11) are limited by the

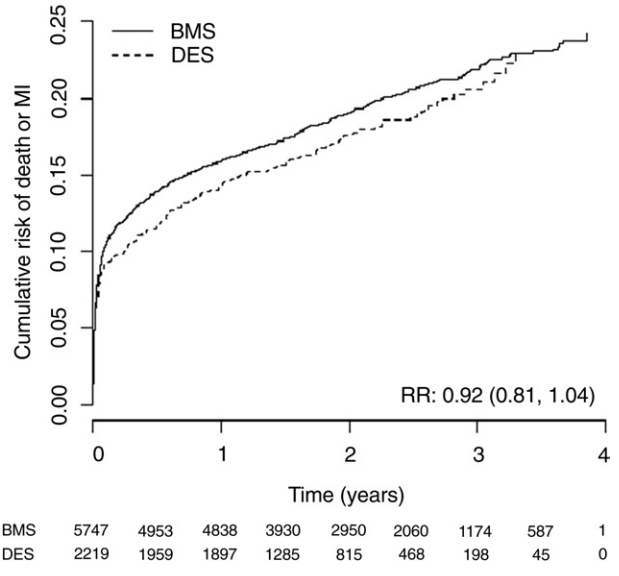

Figure 9 **Event Rates for STEMI Patients: Off-Label**

ST-segment elevation myocardial infarction (STEMI). Propensity score adjusted cumulative event rates of death or MI during 4 years of follow-up after stenting with DES **(dashed line)** or with BMS only **(solid line)**. Numbers at risk are shown **below each figure**. Abbreviations as in Figure 1.

termination of follow-up at 1 year (21); the level of events was rather low in both registries, which reported mortality rates at 1 year of 3.1% (10) and 4.3% (11), respectively, for off-label DES use. Mortality rates were lower for on-label DES use and were reported with 2.1% (10) and 2.6% (11), respectively. The crude mortality in our study after 1 year was much higher at 5% for on-label DES use and 7% for off-label DES use. We did not exclude—in contrast to the other registries—any patients from our analysis, especially not STEMI patients, like Win et al. (10) did.

Clinically, it might not be helpful to compare outcome after DES in on-label indications with outcome after off-label DES. The general opinion of commentators was that, despite the fact that on-label results obviously cannot be extrapolated to off-label use, the absolute number of short- to medium-term adverse events after off-label DES use is low. Furthermore, the significant reduction of target vessel revascularization even in off-label situations when compared with historical controls (17) or model data (18) contributes to the recommendation to use DES generally (21).

When discussing the issue of off-label DES use, it seems more important to compare results between off-label DES use and off-label BMS use. Drug-eluting stents have been shown in a number of trials that addressed single off-label indications to reduce the rates of restenosis, target vessel revascularization, and major adverse cardiac events (22–24). However, none of these trials was designed to show mortality differences, and most trials were hampered by exclusion criteria and short follow-up (21). In a meta-analysis of different randomized trials of off-label SES use versus off-label BMS use, Kastrati et al. (25) reported an RR associated with SES of 0.97 (95% CI: 0.70 to 1.33) for death and 0.88 (95% CI: 0.51 to 1.52) for stent thrombosis. They concluded that there was no evidence that off-label use of SES is associated with compromised safety compared with BMS (25). Although they concluded this from several randomized trials—some as little as including 83 patients in total—the message is in accordance with the presented data from Sweden, although we did not differentiate between SES and paclitaxel-eluting stent.

Three newer publications, 1 from a multi-center registry (26) and 2 from monocentric observations (27,28), investigated specifically the issue of BMS versus DES usage in off-label indications. All used historical control data for BMS outcome, and follow-up was between 1 (26,27) and 2 years (28), and all found that DES lowered significantly the rate of target vessel revascularization compared with BMS. Although 2 of the publications (26,27) did not find—in concurrence with our study—any significant differences in the outcome of death or MI between DES and BMS in off-label indications, 1 monocentric study with 854 historical BMS patients and 993 DES patients found that DES usage in off-label situations was associated with a significant lower incidence of death and MI during follow-up (28). However, there is always a problem comparing historical data, because interventions and adjunctive therapy tend to improve outcome in more recent years.

The rate of restenosis of between 1.8%/year (on-label DES) and 3.4%/year (off-label BMS) in our material is, as in all clinically driven investigations, much lower than in randomized studies with an angiographic end point. Patients benefit from DES in both on-label as well as off-label indications; however, the reduction of restenosis was greater for on-label indications. Because there are no registry data comparing these groups of patients in daily clinical practice, the reported numbers are not easily put into perspective. Because we cannot report on target lesion revascularization, the data on repeat angioplasty and CABG have to be interpreted with caution and cannot be used in the discussion about benefits of DES versus BMS. The numbers are in the same range as the reported on-label/off-label mixture data from Abbott et al. (17). Patient selection bias led to the finding that these rates are virtually not comparable between DES and BMS use in both labeling groups.

The analysis of the indication groups' stable CAD and unstable CAD confirms the safety of DES compared with BMS in on- and off-label situations with no differences in outcome between stent types.

In Sweden the use of DES in the situation of STEMI increased from 15% in 2003 to 36% in 2005 and was far lower than in the U.S., with a reported increase from 18% in 2003 to 85% in 2005 (29). In contrast to many other off-label indications, the use of DES in the context of STEMI has been investigated in many randomized trials, and even 2 meta-analyses of some of these trials have been published (30,31). Both meta-analyses came to the same conclusion—that the use of DES in patients with STEMI is safe and improves clinical outcomes. The total number of patients was higher in the publication of Kastrati et al. (31) and allowed analysis of DES 1,474 patients and 1,312 BMS patients in a total of 8 randomized clinical trials. However, the follow-up was limited to 12 months in 5 of the 8 trials (31). The investigation of late events, namely MI and death due to late stent thrombosis, is therefore limited by study design (31). Another shortcoming of the meta-analyses is that exclusion criteria were usually present and therefore the results cannot easily be applied to an all-comers infarct population. It has already been pointed out (32) that the only trial that did not exclude many patients because of clinical and lesion characteristics, the PASSION (Paclitaxel Eluting Stent Versus Conventional Stent in ST-segment Elevation Myocardial Infarction) trial (33), did not show an advantage in target lesion revascularization for DES versus BMS. We did not find a significant difference between DES and BMS when looking at the entire follow-up period of 4 years. A very late risk with DES cannot totally be ruled out, due to the nature and limitations of a registry study. Such a risk was seen in the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) and T-RESEARCH registries (34) as well as in the GRACE (Global Registry of Acute Coronary Events) registry (35).

Although RESEARCH and T-RESEARCH did not report any differences in MI between SES and BMS after 3 years the earlier advantage for SES at 1 year disappeared under the following 2 years in part because of a higher rate of late stent thromboses (34).

The GRACE registry delivered a totally different message than the randomized studies by finding an increased rate of late mortality between 6 months and 2 years associated with DES use, which also was thought to be related to late stent thrombosis (35). Whereas there was no difference in mortality at 6 months between DES (n = 569) and BMS (n = 1,729), GRACE reported late mortality of 8.6% versus 1.6% ($p < 0.001$) and a rate of late reinfarction of 5.4% versus 2.9% ($p = 0.046$), both to the disadvantage of DES (35). Patients receiving a DES had a lower in-hospital mortality compared with BMS patients, like in our study—a fact that is difficult to explain but most likely depends on patient selection. So neither the randomized trials nor the available registry data can totally take away the suspicion of late clinical events due to late stent thrombosis in DES, which according to other observational real-life data occurs with 0.5%/year with no tendency to abate (36). Longer follow-up than we could provide in the present study might be needed to finally settle this question.

Study limitations. The following untested situations according to the manufacturers information were not registered in SCAAR over the whole time period and could therefore not be analyzed in this investigation as off-label criteria: heavily calcified lesions, highly tortuous anatomy, bifurcation, left ventricular function <30%, and presence of definite or probable intraluminal thrombus (6,7).

Several other important limitations of the present study require comment. Bias in patient selection cannot be ruled out, as in all nonrandomized studies, although the statistical methods applied led to a good adjustment for all known clinical characteristics. However, nonrecorded characteristics (e.g., left ventricular function) could not be adjusted for. In contrast, the reported data represent daily clinical practice on an all-comers basis in a whole country with a 99.9% rate of follow-up regarding death by using the national population registry. In other words, this registry has some unique features, such as coverage of all procedures, control by monitoring visits, and independence from industry support. The long-term follow-up, up to 4 years compared with 1 year in most comparable publications (10,11), also strengthens this study.

The clinical advantages of DES, namely the reduction of restenosis and repeated revascularization, cannot be appropriately addressed in a registry like ours. This is because restenosis will only be diagnosed after clinically driven reangiography and because we cannot differentiate between restenosis and progress when it comes to repeated PCI.

Perhaps the most important limitation of the presented data is that we cannot provide data on the length of or compliance with dual-antiplatelet therapy. Dual-antiplatelet therapy has repeatedly been pointed out to be associated with outcome after DES (37–39). It cannot be estimated to what extent the results, especially DES, are influenced by the shifting length of dual antiplatelet therapy from between 3 and 6 months in the beginning of the study period to 12 months or even longer at the end. However, even this limitation is a mirror of real life practice and thus shared by almost all large observational studies of this kind.

Conclusions

In contemporary Swedish practice, neither on- nor off-label use of DES is associated with worse outcome than use of BMS. This applies to the whole clinical spectrum of CAD.

The reduction of restenosis through the use of DES was statistically highly significant for both on- and off-label indications, but the clinical benefit was higher for on-label DES compared with off-label usage.

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Key Words: BMS ■ DES ■ off-label ■ on-label ■ outcome.

APPENDIX

For a complete list of participating individuals and institutions, please see the online version of this article.