Journal of the American College of Cardiology Vol. 53, No. 18, 2009

Published by Elsevier Inc.
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.01.054

Differences in Restenosis Rate With Different Drug-Eluting Stents in Patients With and Without Diabetes Mellitus

A Report From the SCAAR (Swedish Angiography and Angioplasty Registry)

Ole Fröbert, MD, PhD,* Bo Lagerqvist, MD, PhD,† Jörg Carlsson, MD, PhD,‡ Johan Lindbäck, MS,§ Ulf Stenestrand, MD, PhD,‖ Stefan K. James, MD, PhD†

Örebro, Uppsala, Kalmar, and Linköping, Sweden

Objectives Our aim was to evaluate restenosis rate of drug-eluting stents (DES) in patients with and without diabetes mellitus (DM) in a real-world setting.

Background DES seem less effective in patients with DM.

Methods The SCAAR (Swedish Coronary Angiography and Angioplasty Registry) includes all patients undergoing percutaneous coronary intervention in Sweden. From April 1, 2004, to April 20, 2008, all restenoses detected at a subsequent angiography and all DES types implanted at more than 500 occasions were assessed using Cox regression.

Results Four DES types qualified for inclusion. In total, 35,478 DES were implanted at 22,962 procedures in 19,004 patients and 1,807 restenoses were reported over a mean 29 months follow-up. In the entire population, the restenosis rate per stent was 3.5% after 1 year and 4.9% after 2 years. The adjusted risk of restenosis was higher in patients with DM compared with that in patients without DM (relative risk [RR]: 1.23, 95% confidence interval [CI]: 1.10 to 1.37). In patients with DM, restenosis was twice as frequent with the zotarolimus-eluting Endeavor stent (Medtronic, Minneapolis, Minnesota) compared with that in the other DES types. The Endeavor stent and the sirolimus-eluting Cypher stent (Cordis, Johnson & Johnson, Miami, Florida) had higher restenosis rates in patients with DM compared with those in patients without DM (RR: 1.77, 95% CI: 1.29 to 2.43 and RR: 1.25, 95% CI: 1.04 to 1.51). Restenosis rate with the paclitaxel-eluting Taxus Express and Liberté (Boston Scientific, Natick, Massachusetts) stents was unrelated to DM. Mortality did not differ between different DES.

Conclusions Restenosis rate with DES was higher in patients with DM compared with that in patients without DM. There seem to be important differences between different brands of DES. (J Am Coll Cardiol 2009;53:1660–7)

Coronary artery stenting in patients with diabetes mellitus (DM) is associated with higher rates of restenosis and repeat revascularization compared with those seen in patients without DM (1,2). Randomized trials (3,4) and results from registries (5) seem to favor the use of drug-eluting stents (DES) over bare-metal stents (BMS) for better clinical and angiographic outcome. Most data on patients with DM and DES are available for the sirolimus-eluting Cypher stent (Cordis, Johnson & Johnson, Miami, Florida) and the paclitaxel-eluting Taxus stent (Boston Scientific, Natick, Massachusetts) (3,5–9). However, with more players on the market for DES, other stent platforms, drugs, and polymers are introduced. The zotarolimus-eluting Endeavor stent (Medtronic, Minneapolis, Minnesota) was approved by the U.S. Food and Drug Administration for coronary revascularization in the U.S. in early 2008 while this stent has already been used in other countries since 2003 (10).

It is important to look at real-world data when evaluating treatment strategies; both because "off-label" use of DES is widespread and not part of clinical trials and because

From the *Department of Cardiology, Örebro University Hospital, Örebro, Sweden; †Department of Cardiology, Uppsala University Hospital Uppsala, Uppsala, Sweden; ‡Department of Medicine, Kalmar Hospital, Kalmar, Sweden; §UCR, Uppsala Clinical Research Center, Uppsala, Sweden; and the ‖Department of Cardiology, Linköping University Hospital, Linköping, Sweden. Supported by funds from the Swedish Association of Local Authorities and Regions and the Swedish Heart-Lung Foundation (to SCAAR and the Uppsala Clinical Research Center) (all Stockholm, Sweden).

Manuscript received September 23, 2008; revised manuscript received January 22, 2009, accepted January 27, 2009.

randomized head-to-head comparisons of all different DES types are unrealistic. We determined that the evaluation of large clinical registries might provide useful information concerning the long-term efficacy and safety of DES. Therefore, we evaluated the restenosis rate in all patients, stratified for DM status, who underwent stent implantation in Sweden from April 2004 to April 2008, as recorded in the SCAAR (Swedish Coronary Angiography and Angioplasty Registry).

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CI = confidence interval
DES = drug-eluting stent(s)
DM = diabetes mellitus
PCI = percutaneous coronary intervention
RR = relative risk

Methods

Study population. Our study included all patients in Sweden who had received coronary stents from April 1, 2004, to April 20, 2008. The analyses were based on the type of stent implanted at the first recorded procedure. Patients who received at least 1 DES were included in the analysis, regardless of whether they had received another type of stent at any time. In order to be included in this analysis only DES types implanted on more than 500 occasions during the study period were assessed. Data from 1 small center was excluded from the analysis due to incomplete registration of coronary angiographies.

The SCAAR data. The SCAAR holds data on consecutive patients from all 26 centers that perform coronary angiography and percutaneous coronary intervention (PCI) in Sweden. The registry is sponsored by the Swedish Health Authorities and is independent of commercial funding. The technology is developed and administered by the Uppsala Clinical Research Center. Since 2001, SCAAR has been Internet-based, with recording of data online through an Internet interface in the catheterization laboratory; data are transferred in an encrypted format to a central server at the Uppsala Clinical Research Center. All consecutive patients undergoing coronary angiography or PCI are included. Information with respect to restenosis has been registered for patients undergoing any subsequent coronary angiography for a clinical reason since the beginning of 2004. Because of the nature of this study using real-life registry data, all restenoses identified by repeat angiography did not lead to repeat revascularization. Accordingly, in this study, restenosis is not identical to "target lesion revascularization" as defined in other publications. Throughout the study we use the terminology "restenosis" defined as angiographically significant restenosis detected at any repeat angiography because of ischemic symptoms. The Internet-based system provides each center with immediate and continuous feedback on processes and quality-of-care measures. Monitoring and verification of registry data have been performed in all hospitals since 2001 by comparing 50 entered variables in 20 randomly selected interventions per hospital and year with the patients' hospital records. The overall correspondence of data during the study period was 95.2%.

Statistical analysis. We summarized baseline characteristics of the patients with means and standard deviations for continuous variables and percentages for discrete variables. Cumulative event rates were estimated by the Kaplan-Meier method. The primary objective was to evaluate restenosis rates after the implantation of DES. The primary end point was clinically driven restenosis rate. The secondary end point was death. The cumulative adjusted relative risk (RR) of the primary end point was calculated using Cox proportional hazard method. All factors in Tables 1 and 2 were forced into the model together with information on treating hospital, year of procedure, and complete revascularization. Diabetes was dichotomized to yes/no as the variable diabetes treatment was not known for the first part of the study period.

Statistical interaction was tested by introducing the interaction terms diabetes*stent name and diameter of stent*stent name in the used model. Difference in adjusted mortality between the different stents was analyzed using the same model in a subgroup of patients with only 1 stent (DES) implanted where only the first PCI during the study period was included. Vital status and date of death was obtained from the National Population Registry until April 15, 2008. Hospitalizations due to myocardial infarction were available until December 31, 2007, from the Swedish registry of inhospital diagnosis. The merging of the registries 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. In the majority of analyses the statistical unit was stent and not the patient. However, in the subgroup analyses of mortality and rehospitalizations with a diagnosis of myocardial infarction the statistical unit was patient. And here only data from the first PCI during the study period in patients with only 1 stent were analyzed. All reported p values are 2-sided. All analyses were performed with the use of SPSS statistical software (version 15.0, SPSS Inc., Chicago, Illinois).

Results

During the study period, 35,478 DES were implanted at 22,962 procedures in 19,004 patients. Baseline characteristics are listed in Table 1. Patients with DM compared with patients without DM were more often women, less often smokers, and had more often hyperlipidemia, hypertension, and previous coronary artery disease. Angiographic data are shown in Table 2. Minor, but significant, differences were found with respect to multivessel disease, lesion type, restenotic lesion, chronic total occlusion, and stent diameter. Follow-up time was 29.1 ± 11.1 months.

Restenosis was reported in 3.5% of all stents after 1 year and in 4.9% of all stents 2 years after implantation. The restenosis rates after 1 and 2 years, respectively, were 3.3% and

JACC Vol. 53, No. 18, 2009
May 5, 2009:1660–7

Table 1 Baseline Characteristics

	Patients With Diabetes					Patients Without Diabetes			
	Cordis Cypher	Boston Taxus Express	Boston Taxus Liberté	Medtronic Endeavor	All Patients With Diabetes	Cordis Cypher	Boston Taxus Express	Boston Taxus Liberté	Medtronic Endeavor
n	2,615	2,182	2,553	881	8,231	8,667	7,447	8,483	2,650
Age, yrs, mean ± SD	65.1 ± 10.4	65.6 ± 9.9	66.6 ± 9.8	66.7 ± 10.6	65.9 ± 10.1	65.1 ± 10.8	65.2 ± 10.8	66.2 ± 10.6	65.7 ± 10.9
Female sex, n (%)	782 (29.9)	747 (34.2)	746 (29.2)	304 (34.5)	2,579 (31.4)	2,283 (26.3)	1,880 (25.2)	2,253 (26.6)	691 (26.1)
Indication, n (%)									
Stable coronary artery disease	896 (34.3)	732 (33.5)	851 (33.4)	280 (31.8)	2,760 (33.5)	3,047 (35.2)	2,460 (33.0)	2,835 (33.4)	883 (33.3)
Unstable coronary artery disease	1,413 (54.0)	1,157 (53.0)	1,338 (52.4)	509 (57.8)	4,417 (53.7)	4,315 (49.8)	3,795 (51.0)	4,115 (48.5)	1,395 (52.6)
STEMI	262 (10.0)	269 (12.3)	301 (11.8)	80 (9.1)	912 (11.1)	1,176 (13.6)	1,096 (14.7)	1,361 (16.0)	333 (12.6)
Other	44 (1.7)	24 (1.1)	62 (2.4)	12 (1.3)	142 (1.7)	129 (1.5)	96 (1.3)	172 (2.0)	39 (1.5)
Diabetes mellitus, n (%)									
Insulin treatment	1,182 (45.2)	698 (32.0)	1,236 (48.4)	412 (46.8)	3,528 (42.9)				
Noninsulin treatment	1,186 (54.4)	742 (34.0)	1,317 (51.6)	469 (53.2)	3,714 (45.1)				
Unknown treatment	247 (9.4)	742 (34.0)	0	0	989 (12.0)				
Smoking status, n (%)									
Current smoker	337 (12.9)	325 (14.9)	337 (13.2)	148 (16.8)	1,147 (13.9)	1,543 (17.8)	1,407 (18.9)	1,518 (17.9)	467 (17.6)
Former smoker	990 (37.9)	772 (35.4)	1,002 (39.2)	319 (36.2)	3,084 (37.5)	3,208 (37.0)	2,534 (34.0)	3,070 (36.2)	936 (35.3)
Never smoked	1,124 (43.0)	907 (41.6)	1,071 (42.0)	344 (39.0)	3,446 (41.9)	3,523 (40.6)	3,078 (41.3)	3,583 (42.2)	1,094 (41.3)
Unknown	164 (6.3)	177 (8.1)	143 (5.6)	70 (7.9)	554 (6.7)	393 (4.5)	432 (5.8)	312 (3.7)	153 (5.8)
Hyperlipidemia, n (%)	1,941 (74.2)	1,544 (70.8)	1,866 (73.1)	694 (78.8)	6,045 (73.4)	5,206 (60.1)	4,138 (55.6)	4,792 (56.5)	1,632 (61.6)
Hypertension, n (%)	1,745 (66.7)	1,461 (67.0)	1,907 (74.7)	619 (70.3)	5,733 (69.7)	4,120 (47.5)	3,319 (44.6)	4,358 (51.4)	1,305 (49.2)
Previous myocardial infarction, n (%)	1,105 (42.3)	928 (42.5)	1,042 (40.8)	384 (43.4)	3,459 (42.0)	2,991 (34.5)	2,486 (33.4)	2,714 (32.0)	902 (34.0)
Previous coronary angioplasty, n (%)	950 (36.3)	657 (30.1)	892 (34.9)	296 (33.6)	2,795 (34.0)	2,791 (32.2)	1,877 (25.3)	2,493 (29.4)	750 (28.3)
Previous CABG, n (%)	435 (16.6)	354 (16.2)	451 (17.7)	210 (23.8)	1,450 (17.6)	917 (10.6)	804 (10.8)	897 (10.6)	333 (12.6)

All variables differed statistically significantly between the different stents ($p = 0.001$) except indication ($p = 0.140$) in the diabetes mellitus group and female sex ($p = 0.261$) and previous coronary artery bypass grafting (CABG) ($p = 0.095$) in the nondiabetes mellitus group.
STEMI = ST-segment elevation myocardial infarction.

4.9% for Cypher stents, 3.7% and 5.1% for Taxus Express stents, 3.2% and 4.1% for Taxus Liberté stents, and 4.9% and 6.5% for Endeavor stents. There were considerable differences between the different stents in both patients with DM and in patients without DM (Fig. 1). In patients with DM the adjusted RR of restenosis was twice as high with the Endeavor stent compared with the other types of DES (Table 3). There were no statistically significant differences between other stent types in patients with DM. In patients without DM there were smaller but significant differences in restenosis rate; with the Endeavor and the Taxus Express stents the adjusted restenosis rates were 20% to 30% higher than with the Cypher and Taxus Liberté stents. It is also noteworthy that in patients without DM the adjusted risk of restenosis was significantly higher with the Taxus Express than with the Taxus Liberté stent (Table 3).

The adjusted risk of restenosis was higher in patients with DM than in patients without DM (RR: 1.23, 95% confidence interval [CI]: 1.10 to 1.37). This difference was also found for the zotarolimus-eluting Endeavor stent (Fig. 2A) and the sirolimus-eluting Cypher stent (Fig. 2B) with higher rates of restenosis in patients with DM compared with those in patients without DM (RR: 1.77, 95% CI: 1.29 to 2.43 and RR: 1.25, 95% CI: 1.04 to 1.51, respectively). With the paclitaxel-eluting Taxus Express stent (Fig. 2C) the incidence of restenosis was similar in patients with DM compared with that in patients without DM (RR: 1.10, 95% CI: 0.91 to 1.34) and with Taxus Liberté stent (Fig. 2D) there was a trend to a higher rate of restenosis in patients with DM (RR: 1.19, 95% CI: 0.94 to 1.49). The therapeutic decision in the 1,370 cases in which a restenosis was detected was repeat PCI in 80.1%, coronary artery bypass grafting in 9.4%, and no coronary intervention in 10.4%.

Information about diabetes treatment has been registered in the SCAAR database from May 1, 2005 and onward. From this date and to the end of the study period, 26,020 stents were implanted resulting in 1,214 restenoses. There was no statistically significant difference in restenosis rate in stents placed in patients with insulin-treated DM (n = 3,018) compared with that in stents placed in patients with noninsulin-treated DM (n = 3,061) (RR: 0.84, 95% CI: 0.67 to 1.04). Adjusted risks of restenosis were more than doubled (significant) in Endeavor compared with those in Taxus Liberté and compared with those in Taxus Express stents both in insulin-treated and in noninsulin-treated patients. Also in comparison with the Cypher stent the adjusted risk of restenosis was more than doubled (significant) for Endeavor in noninsulin-treated patients. Endeavor

Table 2 Angiographic and Lesion Characteristics

	Patients With Diabetes					Patients Without Diabetes				
	Cordis Cypher	Boston Taxus Express	Boston Taxus Liberté	Medtronic Endeavor	All Patients With Diabetes	Cordis Cypher	Boston Taxus Express	Boston Taxus Liberté	Medtronic Endeavor	All Patients Without Diabetes
Number of stents per procedure, mean ± SD	1.69 ± 0.96	1.71 ± 0.94	1.74 ± 1.00	1.74 ± 0.98	1.72 ± 0.96	1.70 ± 0.94	1.70 ± 0.96	1.78 ± 1.02	1.73 ± 0.94	1.72 ± 0.97
Findings on angiography, n (%)										
Not significant	13 (0.5)	10 (0.5)	12 (0.5)	4 (0.5)	39 (0.5)	27 (0.3)	28 (0.3)	47 (0.6)	11 (0.4)	109 (0.4)
1-vessel disease	786 (30.1)	667 (30.6)	760 (29.8)	245 (27.8)	2,458 (29.9)	3,501 (40.4)	3,978 (40.0)	3,404 (40.0)	1,012 (38.2)	10,895 (40.0)
2-vessel disease	946 (36.2)	741 (34.0)	882 (34.5)	279 (31.7)	2,848 (34.6)	2,989 (34.4)	2,432 (32.7)	2,816 (33.2)	930 (35.1)	9,167 (33.6)
3-vessel disease	695 (26.6)	607 (27.8)	683 (26.8)	283 (32.1)	2,268 (27.6)	1,625 (18.7)	1,448 (19.4)	1,652 (19.5)	530 (20.0)	5,255 (19.3)
Left main coronary artery disease	129 (4.9)	131 (6.0)	193 (7.6)	58 (6.6)	511 (6.2)	391 (4.5)	451 (6.1)	479 (5.6)	129 (4.9)	1,450 (5.3)
Stent diameter, mean ± SD	2.81 ± 0.39	2.87 ± 0.47	2.85 ± 0.46	2.90 ± 0.47	2.85 ± 0.44	2.82 ± 0.41	2.91 ± 0.49	2.87 ± 0.46	2.89 ± 0.45	2.87 ± 0.45
Stent length, mean ± SD	19.7 ± 7.3	18.1 ± 6.4	18.0 ± 6.5	18.1 ± 6.5	18.6 ± 6.8	19.7 ± 7.4	18.2 ± 6.6	18.3 ± 6.5	18.6 ± 6.8	18.7 ± 6.9
Restenotic lesion, n (%)	335 (12.8)	188 (8.6)	228 (8.9)	69 (7.8)	820 (10.0)	1,058 (12.2)	533 (7.2)	640 (7.5)	207 (7.8)	2,438 (8.9)
Chronic total occlusion, n (%)	128 (4.9)	98 (4.5)	139 (5.4)	40 (4.5)	405 (4.9)	602 (6.9)	311 (4.2)	524 (6.2)	155 (5.8)	1,592 (5.8)
Treated vessel, n (%)										
Right coronary artery	666 (25.5)	602 (27.6)	664 (26.0)	221 (25.1)	2,153 (26.2)	2,102 (24.3)	1,729 (23.2)	2,155 (25.4)	691 (26.1)	6,677 (24.5)
Left main coronary artery	45 (1.7)	59 (2.7)	63 (2.5)	20 (2.3)	187 (2.3)	136 (1.6)	214 (2.9)	174 (2.1)	50 (1.9)	574 (2.1)
Left anterior descending coronary artery	1,205 (46.1)	906 (41.5)	1,027 (40.2)	347 (39.4)	3,485 (42.3)	4,330 (50.0)	3,690 (49.6)	3,922 (46.2)	1,216 (45.9)	13,158 (48.3)
Left circumflex coronary artery	606 (23.2)	505 (23.1)	667 (26.1)	226 (25.7)	2,004 (20.3)	1,885 (21.7)	1,550 (20.8)	1,987 (23.5)	610 (23.0)	6,032 (22.1)
CABG	93 (3.5)	110 (5.1)	132 (5.2)	67 (7.6)	402 (4.9)	214 (2.4)	264 (3.6)	245 (2.9)	83 (3.1)	806 (3.0)
Lesion classification, n (%)										
Type A	279 (10.7)	205 (9.4)	267 (10.5)	108 (12.3)	859 (10.4)	910 (10.5)	711 (9.5)	940 (11.1)	303 (11.4)	2,864 (10.5)
Type B1	794 (30.4)	658 (30.2)	857 (33.6)	270 (30.6)	2,579 (31.3)	2,324 (26.8)	2,134 (28.7)	2,892 (34.1)	872 (32.9)	8,222 (30.2)
Type B2	710 (27.2)	602 (27.6)	770 (30.2)	261 (29.6)	2,343 (28.5)	2,623 (30.3)	2,060 (27.7)	2,498 (29.4)	823 (31.1)	8,004 (29.4)
Type C	716 (27.4)	512 (23.5)	657 (25.7)	240 (27.2)	2,125 (25.8)	2,408 (27.8)	1,810 (24.3)	2,129 (25.1)	641 (24.2)	6,988 (25.6)
Unknown	116 (4.4)	205 (9.4)	2 (0.1)	2 (0.2)	325 (3.9)	402 (4.6)	732 (9.8)	24 (0.3)	11 (0.4)	1,169 (4.3)

All variables differed statistically significant between the different stents ($p < 0.001$) except for number of stents per procedure ($p = 0.456$) and chronic total occlusion ($p = 0.493$) in the group of patients with diabetes mellitus.
CABG = coronary artery bypass grafting.

JACC Vol. 53, No. 18, 2009
May 5, 2009:1660–7

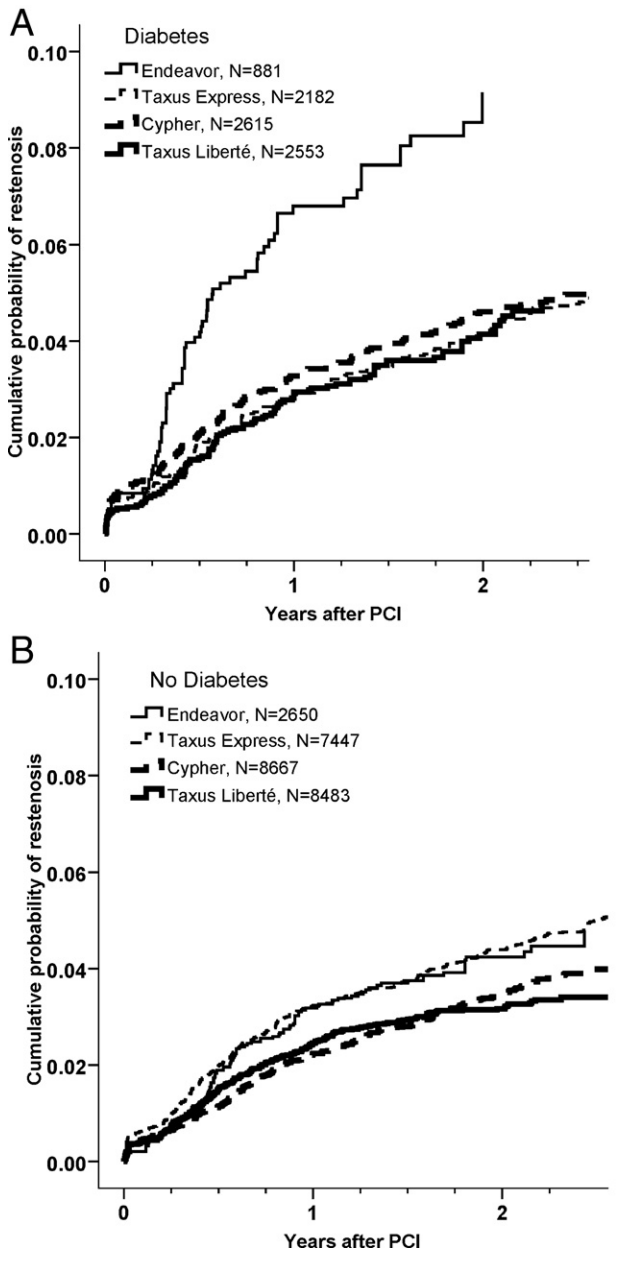

Figure 1 Estimated Cumulative Event Rates

A shows propensity score adjusted probability of restenosis in patients with diabetes mellitus and **B** shows the same for patients without diabetes mellitus. Risk ratios (with 95% confidence intervals) are for occurrence of restenosis with 1 stent type compared with another stent type. PCI = percutaneous coronary intervention.

compared with Cypher in insulin-treated patients demonstrated an insignificant trend (RR: 1.55, 95% CI: 0.98 to 2.47).

In the statistical model, stent diameter was independently associated with a lower risk of restenosis (RR: 0.58, 95% CI: 0.46 to 0.74). Stent length, assessed as a 1-mm increase, was not associated with an increased risk of restenosis (RR: 1.01, 95% CI: 0.99 to 1.01). Stents placed in chronic total occlusions had a higher risk of restenosis than stents placed in nonoccluded lesions (RR: 1.29, 95% CI: 1.06 to 1.57). There was a statistically significant interaction between type of DES and diabetes status ($p = 0.006$) but no statistically significant interaction between type of DES and stent diameter. In a subgroup analysis the material was divided into 2 groups of equal size with a cutoff at the median stent diameter. In patients with DM the higher risk of restenosis remained with Endeavor stents compared with that in all the other DES in the group of smaller stents (≤2.75 mm) as well as in the group of stents with larger diameter (>2.75 mm) (detailed results not shown).

Of all patients, 3.9% died within 1 year after stent implantation and 6.0% died within 2 years. The incidence of reported myocardial infarctions was 7.3% and 10.2% after 1 and 2 years, respectively. Stent-specific information on death and myocardial infarction is reported for patients in whom only 1 DES was implanted. Definite information regarding death was available in 9,860 patients (52% of all patients) of whom 674 died during the follow-up period. Information regarding rehospitalizations to Swedish hospitals with a diagnosis of myocardial infarction was available in 9,273 patients (49% of all) of whom 925 had a myocardial infarction before the end of 2007. Mortality (Fig. 3) or myocardial infarction rates did not differ between different DES ($p = 0.933$ and $p = 0.793$, respectively).

Discussion

The main findings of this national registry study on DES in patients with DM are: 1) The rate of restenosis with DES

Table 3 Adjusted RR of Restenosis Pairwise Comparison Between Stents

	RR	95% Confidence Interval
Patients with diabetes		
Endeavor vs. Taxus Liberté	2.18	1.55–3.07
Endeavor vs. Taxus Express	2.08	1.43–3.00
Endeavor vs. Cypher	1.99	1.43–2.77
Taxus Express vs. Taxus Liberté	1.05	0.76–1.44
Cypher vs. Taxus Liberté	1.10	0.82–1.46
Cypher vs. Taxus Express	1.04	0.80–1.36
Patients without diabetes		
Endeavor vs. Taxus Liberté	1.31	1.03–1.67
Endeavor vs. Taxus Express	0.99	0.77–1.28
Endeavor vs. Cypher	1.23	0.97–1.55
Taxus Express vs. Taxus Liberté	1.32	1.10–1.60
Cypher vs. Taxus Liberté	1.07	0.90–1.28
Cypher vs. Taxus Express	0.81	0.68–0.95
All patients		
Endeavor vs. Taxus Liberté	1.55	1.28–1.89
Endeavor vs. Taxus Express	1.26	1.03–1.56
Endeavor vs. Cypher	1.45	1.20–1.76
Taxus Express vs. Taxus Liberté	1.23	1.04–1.45
Cypher vs. Taxus Liberté	1.07	0.92–1.81
Cypher vs. Taxus Express	0.87	0.76–1.001

RR = relative risk.

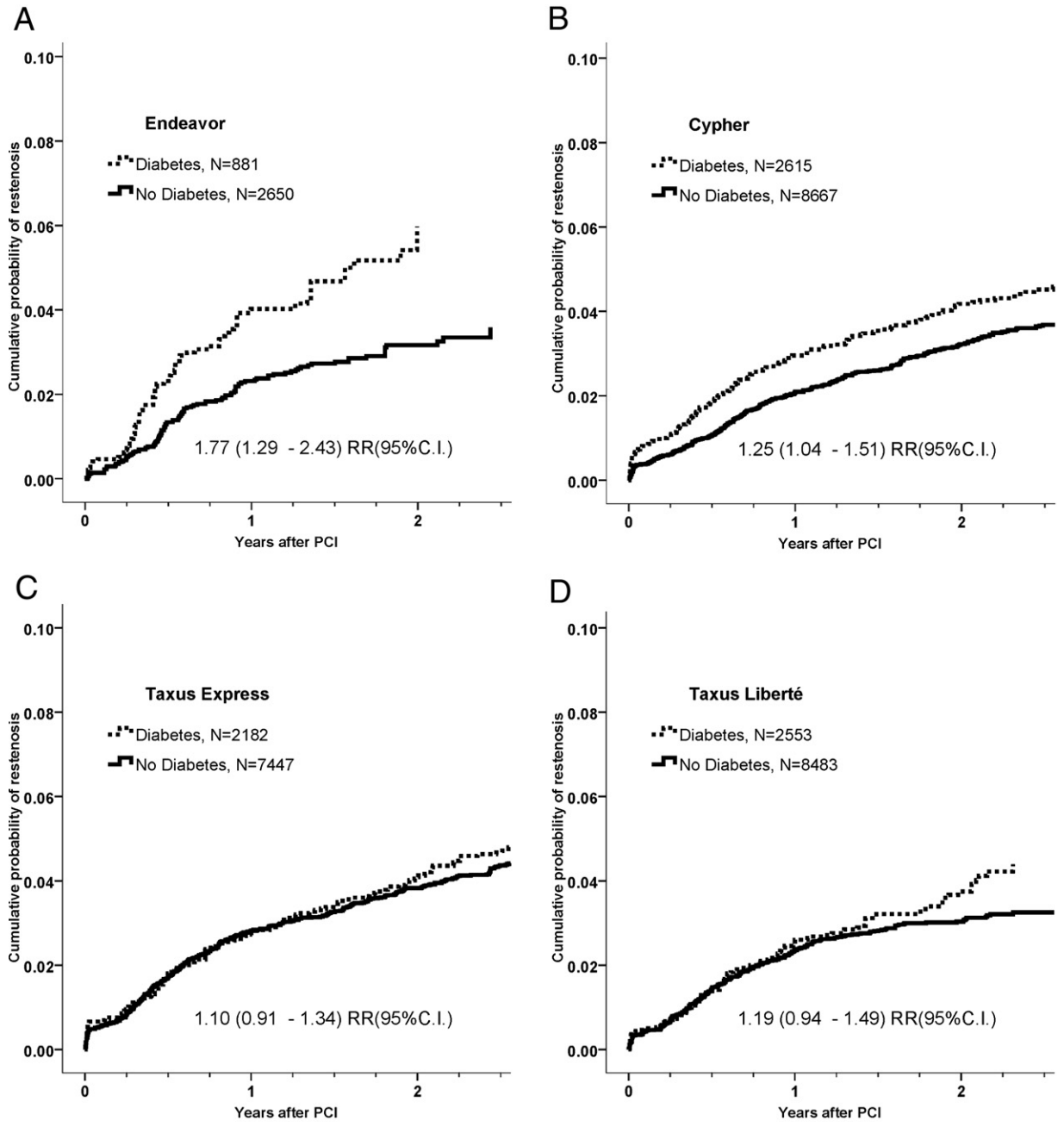

Figure 2 **Estimated Cumulative Rates of Restenosis With Respect to Stent Type**

Estimated cumulative event rates in patients with diabetes mellitus (DM) and patients without DM for the 4 different stent types **(A to D)** analyzed. Risk ratios (RRs) (95% confidence intervals [CIs]) are for occurrence of restenosis in patients with DM compared with patients without DM. PCI = percutaneous coronary intervention.

was higher in patients with DM compared with patients without DM. 2) There seems to be significant differences in restenosis rate between different stents. The zotarolimus-eluting Endeavor stent was associated with a restenosis rate in patients with DM twice the rate in patients without DM. The sirolimus-eluting Cypher stent had a 30% increased restenosis risk in patients with DM. 3) There were no differences in mortality between patients with DM receiving different DES.

Experiences from many previous randomized stent trials have shown that patients with DM respond with less favorable outcome than do patients without DM. Patients with DM have a higher risk of death and higher restenosis rates after stenting compared with patients without DM (1,2). Moreover,

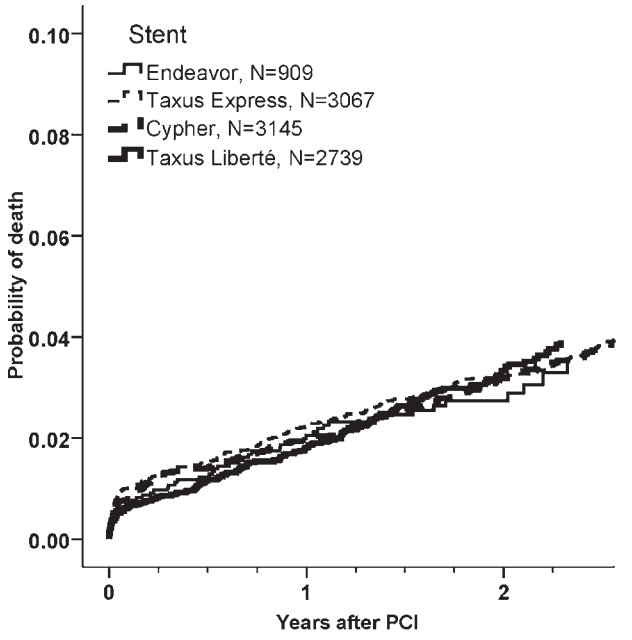

Figure 3 **Adjusted Risk of Death With Respect to Stent Type**

Adjusted risk of death with the 4 different drug-eluting stents (DES) in a subpopulation of patients who only had 1 DES implanted. PCI = percutaneous coronary intervention.

the advantage of DES on restenosis compared with BMS is not as apparent in patients with DM (7).

One of the problems in acquiring data on patients with DM after stenting is to achieve high enough numbers of patients in clinical trials. While the effect of DES compared with that of BMS in patients with DM has been investigated in some clinical trials (3,4,11) only few dedicated studies comparing different DES in patients with DM are available. The ISAR-DIABETES (Paclitaxel-Eluting Stent Versus Sirolimus-Eluting Stent for the Prevention of Restenosis in Diabetic Patients With Coronary Artery Disease) study randomized 125 patients with DM to the sirolimus-eluting Cypher stent and 125 patients with DM to the paclitaxel-eluting Taxus stent. Target lesion revascularization at 9 months was 6.4% in the Cypher arm versus 12.0% in Taxus ($p = 0.13$) but the trial was not powered for clinical restenosis (8). In the DM subgroup of the SIRTAX (Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularization) trial at 2 years these numbers were 7.4% and 17.2% ($p = 0.03$) (7). In an elegant head-to-head comparison, patients with DM and 2-vessel coronary artery disease were randomized to Cypher stent in 1 vessel and Taxus stent in the other (6). Late loss at 8 months was 0.26 mm in Cypher lesions versus 0.50 mm in Taxus lesions ($p = 0.01$). However, results from smaller registries contrast the above findings. Three different reports on, respectively, 1,320, 293, and 260 consecutive patients with DM receiving sirolimus- or paclitaxel-eluting stents found no statistically significant differences in death, major adverse cardiac events, or revascularization between stent types (9,12,13). In line with these findings and in contrast to the clinical studies cited above it is evident that the Cypher stent performs equivalent compared with Taxus stents in clinically driven restenosis in patients with DM in the present study. In a recent meta-analysis incorporating most available randomized clinical trials and registry data of more than 11,000 patients with DM receiving sirolimus- or paclitaxel-eluting stents, revascularization and major adverse cardiac events estimates were similar (14). However, follow-up time in all the studies included in this meta-analysis ranged between 6 to 12 months thus leaving out long-time effects (14).

Almost all comparative data on DES in patients with DM are available only for Cypher and Taxus stents. With more than 20 different DES having received a CE mark approval, randomized head-to-head comparisons of all stent types are unrealistic. This study represents the first large-scale evaluation of the zotarolimus-eluting Endeavor stent in patients with DM and underlines the importance of continuous registry monitoring of new coronary stents. We found the Endeavor stent to be associated with restenosis twice the rate in patients with DM compared with that in patients without DM. This alarming finding should of course be verified in a prospective randomized clinical trial before any conclusion can be drawn and the result of the PROTECT (Prophylaxis of Thromboembolism in Critical Care) trial including 8,800 patients in a comparison of Cypher and Endeavor stents is awaited. However, of notice, in the 1,197 patients Endeavor II trial (comparing a Driver BMS with the Endeavor DES) among patients who received an Endeavor stent, in-stent restenosis after 8 months was 7.8% for patients without DM, 16.7% for noninsulin-dependent DM patients, and 20.0% for insulin-dependent patients (15).

Differences in findings between clinical trial and registry studies underline that some surrogate end points used in clinical trials, such as late loss, have shortcomings in comparison with real-world information. An advantage of the present registry study compared with that of clinical trials is that advanced age and stenting of left main coronary artery and stenting in acute myocardial infarction were included in contrast to what is often the case in trials. Registry data cannot substitute randomized clinical trials. However, the SCAAR is particularly valuable because it provides PCI data from an entire country with complete and continuous registration of all deaths and all repeat PCIs. To our knowledge the present report is the largest on DES and restenosis in patients with DM. It is also one of the first reports to include data on more than 2 different DES and the follow-up time of almost two and one-half years is longer than in most previous publications on restenosis and DM.

In order to look into explanations for our findings, technical aspects must be considered. The 4 stents in this

study release small amounts of pharmacological agents with antirestenosis properties at the implantation site. All 4 stents have polymer coating as a drug carrier in order to slow the release of drug to prevent restenosis for as long a time as possible. A difference in the mechanism of action of paclitaxel and sirolimus in diabetic patients has been hypothesized (14) but it is important to realize that not only type of drug and type of polymer contribute to restenosis. As can be seen from the Taxus data in this study, despite the same polymer coating containing 1 $\mu g/mm^2$ of paclitaxel, the Taxus Liberté stent with a flexible cell geometry, thin struts, and uniform cell distribution had a lower restenosis rate at 2 years compared with the older, more rigid Taxus Express stent with a different geometry.

Study limitations. Inherent limitations are associated with the interpretation of registry data. Despite appropriate statistical adjustments, differences in baseline characteristics or selection criteria that might not have been recorded could remain. Potential alternative explanations exist for differences in event curves, for example, multiple selection biases, such as unrecognized propensity to use one type of DES instead of another in certain patients. It is also a possible confounder, although unlikely a systematic one, that patients with more than 1 type of DES in the coronary arteries were included. Ideally we would like to have included information on insulin treatment because this group of patients with DM may have a more rapid progression of atherosclerosis (3,5). However, this information was not available for the entire time period we studied. It is a limitation to our study, which covers 2004 to 2008, that data on stent thrombosis in the SCAAR database were not introduced until a late stage in the study period. Therefore, relevant data for stent thrombosis were not available for most of the study period.

Conclusions

We conclude that the rate of restenosis with DES is higher in patients with DM compared with that in patients without DM. There seem to be important differences between different brands of DES. Our findings reinforce the need of large prospective randomized trials with head-to-head comparisons between different DES, especially in patients with DM.

Reprint requests and correspondence: Dr. Ole Fröbert, Department of Cardiology, Örebro University Hospital, Södra Grev Rosengatan, 701 85 Örebro, Sweden. E-mail: ole.frobert@orebroll.se.

REFERENCES

1. Elezi S, Kastrati A, Pache J, et al. Diabetes mellitus and the clinical and angiographic outcome after coronary stent placement. J Am Coll Cardiol 1998;32:1866–73.
2. Feld S, Almagor Y, Vaughn WK, Leon MB, Serruys PW. Predictors of clinical outcome following NIR stent implantation for coronary artery disease: analysis of the results of the First International New Intravascular Rigid-Flex Endovascular Stent Study (FINESS trial). J Interv Cardiol 2002;15:1–6.
3. Kirtane AJ, Ellis SG, Dawkins KD, et al. Paclitaxel-eluting coronary stents in patients with diabetes mellitus: pooled analysis from 5 randomized trials. J Am Coll Cardiol 2008;51:708–15.
4. Sabate M, Jimenez-Quevedo P, Angiolillo DJ, et al. Randomized comparison of sirolimus-eluting stent versus standard stent for percutaneous coronary revascularization in diabetic patients: the diabetes and sirolimus-eluting stent (DIABETES) trial. Circulation 2005;112:2175–83.
5. Ortolani P, Balducelli M, Marzaroli P, et al. Two-year clinical outcomes with drug-eluting stents for diabetic patients with de novo coronary lesions: results from a real-world multicenter registry. Circulation 2008;117:923–30.
6. Tomai F, Reimers B, De LL, et al. Head-to-head comparison of sirolimus- and paclitaxel-eluting stent in the same diabetic patient with multiple coronary artery lesions: a prospective, randomized, multicenter study. Diabetes Care 2008;31:15–9.
7. Billinger M, Beutler J, Taghetchian KR, et al. Two-year clinical outcome after implantation of sirolimus-eluting and paclitaxel-eluting stents in diabetic patients. Eur Heart J 2008;29:718–25.
8. Dibra A, Kastrati A, Mehilli J, et al. Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. N Engl J Med 2005;353:663–70.
9. Kuchulakanti PK, Chu WW, Torguson R, et al. Sirolimus-eluting stents versus paclitaxel-eluting stents in the treatment of coronary artery disease in patients with diabetes mellitus. Am J Cardiol 2006;98:187–92.
10. Meredith IT, Ormiston J, Whitbourn R, et al. Four-year clinical follow-up after implantation of the endeavor zotarolimus-eluting stent: ENDEAVOR I, the first-in-human study. Am J Cardiol 2007;100:56M–61M.
11. Baumgart D, Klauss V, Baer F, et al. One-year results of the SCORPIUS study: a German multicenter investigation on the effectiveness of sirolimus-eluting stents in diabetic patients. J Am Coll Cardiol 2007;50:1627–34.
12. Ong AT, Aoki J, van Mieghem CA, et al. Comparison of short- (one month) and long- (twelve months) term outcomes of sirolimus- versus paclitaxel-eluting stents in 293 consecutive patients with diabetes mellitus (from the RESEARCH and T-SEARCH registries). Am J Cardiol 2005;96:358–62.
13. Stankovic G, Cosgrave J, Chieffo A, et al. Impact of sirolimus-eluting and paclitaxel-eluting stents on outcome in patients with diabetes mellitus and stenting in more than one coronary artery. Am J Cardiol 2006;98:362–6.
14. Mahmud E, Bromberg-Marin G, Palakodeti V, Ang L, Creanga D, DeMaria AN. Clinical efficacy of drug-eluting stents in diabetic patients: a meta-analysis. J Am Coll Cardiol 2008;51:2385–95.
15. Fajadet J, Wijns W, Laarman GJ, et al. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. Circulation 2006;114:798–806.

Key Words: angioplasty ■ coronary artery disease ■ diabetes mellitus ■ drug-eluting stents.