

# The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

MAY 7, 2009

VOL. 360 NO. 19

## Long-Term Safety and Efficacy of Drug-Eluting versus Bare-Metal Stents in Sweden

Stefan K. James, M.D., Ph.D., Ulf Stenestrand, M.D., Ph.D., Johan Lindbäck, M.Sc., Jörg Carlsson, M.D., Ph.D., Fredrik Scherstén, M.D., Ph.D., Tage Nilsson, M.D., Ph.D., Lars Wallentin, M.D., Ph.D., and Bo Lagerqvist, M.D., Ph.D.,  
for the SCAAR Study Group\*

### ABSTRACT

#### BACKGROUND

The long-term safety and efficacy of drug-eluting coronary stents have been questioned.

#### METHODS

We evaluated 47,967 patients in Sweden who received a coronary stent and were entered into the Swedish Coronary Angiography and Angioplasty Registry between 2003 and 2006 and for whom complete follow-up data were available for 1 to 5 years (mean, 2.7). In the primary analysis, we compared patients who received one drug-eluting coronary stent (10,294 patients) with those who received one bare-metal stent (18,659), after adjustment for differences in clinical characteristics of the patients and characteristics of the vessels and lesions.

#### RESULTS

Analyses of outcome were based on 2380 deaths and 3198 myocardial infarctions. There was no overall difference between the group that received drug-eluting stents and the group that received bare-metal stents in the combined end point of death or myocardial infarction (relative risk with drug-eluting stents, 0.96; 95% confidence interval [CI], 0.89 to 1.03) or the individual end points of death (relative risk, 0.94; 95% CI, 0.85 to 1.05) and myocardial infarction (relative risk, 0.97; 95% CI, 0.88 to 1.06), and there was no significant difference in outcome among subgroups stratified according to the indication for stent implantation. Patients who received drug-eluting stents in 2003 had a significantly higher rate of late events than patients who received bare-metal stents in the same year, but we did not observe any difference in outcome among patients treated in later years. The average rate of restenosis during the first year was 3.0 events per 100 patient-years with drug-eluting stents versus 4.7 with bare-metal stents (adjusted relative risk, 0.43; 95% CI, 0.36 to 0.52); 39 patients would need to be treated with drug-eluting stents to prevent one case of restenosis. Among high-risk patients, the adjusted risk of restenosis was 74% lower with drug-eluting stents than with bare-metal stents, and only 10 lesions would need to be treated to prevent one case of restenosis.

#### CONCLUSIONS

As compared with bare-metal stents, drug-eluting stents are associated with a similar long-term incidence of death or myocardial infarction and provide a clinically important decrease in the rate of restenosis among high-risk patients.

From the Department of Cardiology, Uppsala University Hospital, Uppsala (S.K.J., L.W., B.L.); the Department of Cardiology, University Hospital Linköping, Linköping (U.S.); the Department of Cardiology, Länssjukhuset Kalmar, Kalmar (J.C.); the Department of Cardiology, Helsingborg Lasarett, Helsingborg (F.S.); Svensk PCI, Karlstad Lasarett, Karlstad (T.N.); and Uppsala Clinical Research Center, Uppsala University Hospital, Uppsala (S.K.J., J.L., L.W., B.L.) — all in Sweden. Address reprint requests to Dr. James at the Uppsala Clinical Research Center, Uppsala University Hospital, 751 85 Uppsala, Sweden, or at stefan.james@akademiska.se.

\*Members of the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) study group are listed in the Appendix.

N Engl J Med 2009;360:1933-45.

Copyright © 2009 Massachusetts Medical Society.

PROSPECTIVE, RANDOMIZED CLINICAL trials and meta-analyses have shown that rates of target-lesion revascularization are unequivocally lower with drug-eluting coronary stents than with bare-metal stents and that rates of death and myocardial infarction are similar.<sup>1-4</sup> However, no randomized trials have been prospectively designed and powered for the evaluation of rare outcome events during very-long-term follow-up. Drug-eluting stents are also widely used in broader populations than those specified by the Food and Drug Administration (FDA) and for indications that are not approved by the FDA on the basis of prospective, randomized trials. Registry studies have also suggested that rates of death and myocardial infarction with drug-eluting stents are similar to or lower than those with bare-metal stents,<sup>5-7</sup> but these studies have shown trends toward increased rates of late events with drug-eluting stents after discontinuation of clopidogrel therapy.<sup>8</sup> Although the risk of stent thrombosis is highest early after stent implantation, incomplete neointimal coverage and hypersensitivity reactions from the polymers may increase the risk of late stent thrombosis.<sup>9</sup> Therefore, very-long-term follow-up after cessation of dual antiplatelet therapy in large patient cohorts is important.

We have previously reported the outcomes among all patients who received coronary stents in Sweden during the 2003–2004 period, as recorded in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). Our results indicated that there was an increase in late mortality among patients who received a drug-eluting stent.<sup>10</sup> To obtain a more reliable estimate of the long-term outcome and efficacy, we have now extended the study to include all patients in Sweden who received a stent during the 2003–2006 period for whom at least 1 year of follow-up until the end of 2007 was available. We have also focused primarily on patients who received only one drug-eluting stent as compared with those who received one bare-metal stent, thereby allowing the adjustment for characteristics of lesions and stents in addition to characteristics of patients.

---

## METHODS

---

### STUDY POPULATION

In the present study, we included all patients in Sweden who had received a coronary stent during

the period from January 1, 2003, through December 31, 2006, and for whom follow-up data were available for at least 1 year and up to 5 years. The analyses were based on the type of stent implanted at the first recorded procedure. In the primary analysis, patients who received only one drug-eluting stent at the initial percutaneous coronary intervention (PCI) were compared with patients who received only one bare-metal stent. In a secondary analysis, all patients who received any stent were included. For these analyses, patients who received at least one drug-eluting stent were assigned to the drug-eluting–stent group, regardless of whether they received a stent of another type at any time; all other patients were assigned to the bare-metal–stent group.

### THE SCAAR DATA

The SCAAR records information on consecutive patients from all 29 centers that perform coronary angiography and PCI in Sweden. The list of the most important variables is shown in Table 1.<sup>11</sup> Patients were informed about the registration, but written informed consent is not required by Swedish law.

Long-term follow-up data were obtained by merging the SCAAR database with other national registries on the basis of the unique 10-digit personal identification number that all Swedish citizens have. Vital status and date of death were obtained from the National Population Registry, and information on the incidence of myocardial infarction (*International Classification of Diseases*, 10th revision, codes I21 and I22) was obtained from the National Public Registry (in which information on diagnoses at hospital discharge are recorded); all this information was obtained through December 31, 2007. Merging of the registries was performed by the Epidemiologic Centre of the Swedish National Board of Health and Welfare and was approved by the ethics committee at Uppsala University. Since March 1, 2004, the electronic case-report form of the SCAAR requires that information about restenosis in every implanted stent be recorded at the time of any subsequent coronary angiography for a clinical indication.

The study and the statistical analysis were designed and interpreted by the authors, all of whom contributed to the final report and participated in the decision to submit the findings for publication. No stent manufacturer had any role in the study.

**Table 1. Baseline Characteristics and Treatments in the Cohort of Patients Who Received Only One Stent and in the Cohort of All Patients Who Received One or More Stents.\***

Variable	One-Stent Cohort		Total Cohort	
	Bare-Metal Stent (N=18,659)	Drug-Eluting Stent with Adjustment for Propensity Score†	Bare-Metal Stent (N=28,286)	Drug-Eluting Stent with Adjustment for Propensity Score†
Year of treatment — % (no.)				
2003	26.2 (4882)	11.0 (1132)	26.4 (7479)	11.2 (2208)
2004	25.5 (4765)	22.7 (2334)	26.0 (7362)	22.6 (4453)
2005	21.6 (4023)	35.6 (3668)	21.2 (6006)	34.9 (6866)
2006	26.7 (4989)	30.7 (3160)	26.3 (7439)	31.3 (6154)
Mean age — yr	65.8±11.0	64.8±10.8	66.2±11.0	65.5±10.7
Male sex — % (no.)	72.2 (13,476)	70.4 (7244)	72.6 (20,541)	71.6 (14,082)
Region of Sweden — % (no.)				
North	14.4 (2684)	2.7 (281)	13.5 (3806)	2.7 (525)
Stockholm	19.3 (3596)	14.0 (1442)	18.5 (5226)	14.7 (2889)
Southeast	11.4 (2123)	14.1 (1455)	9.7 (2734)	12.4 (2431)
South	15.8 (2957)	26.1 (2689)	16.6 (4685)	26.3 (5178)
Middle	23.0 (4288)	39.1 (4029)	22.2 (6276)	39.6 (7785)
West	16.1 (3011)	3.9 (398)	19.7 (5559)	4.4 (873)
Indication — % (no.)				
Stable coronary artery disease	19.0 (3547)	26.5 (2726)	19.8 (5612)	28.5 (5618)
Unstable coronary artery disease	48.8 (9099)	52.0 (5349)	48.7 (13,789)	52.8 (10,386)
STEMI	31.2 (5820)	20.0 (2060)	30.4 (8612)	17.3 (3399)
Other	1.0 (193)	1.5 (159)	1.0 (273)	1.4 (278)
Smoking status — % (no.)				
Never smoked	37.4 (6980)	41.3 (4251)	36.8 (10,417)	41.2 (8117)
Former smoker	30.2 (5629)	32.3 (3325)	30.9 (8727)	33.0 (6488)
Current smoker	22.0 (4104)	19.4 (1998)	21.7 (6136)	18.9 (3726)
Unknown	10.4 (1946)	7.0 (720)	10.6 (3006)	6.9 (1350)
Diabetes — % (no.)	17.4 (3247)	23.8 (2447)	17.7 (5007)	24.3 (4784)
Hyperlipidemia — % (no.)				
Present	46.0 (8591)	51.4 (5286)	47.1 (13,321)	53.7 (10,564)
Absent	49.2 (9172)	44.6 (4596)	47.9 (13,561)	42.6 (8375)
Unknown	4.8 (896)	4.0 (412)	5.0 (1404)	3.8 (742)



Stent size — mm				
Diameter	3.2±0.5	2.9±0.4	3.2	
Length	16.5±5.1	18.6±6.1	16.2	
Treated vessel or procedure — % (no.)				
Right coronary artery	34.1 (6357)	18.2 (1876)	34.1	
Left main coronary artery	0.9 (159)	2.3 (236)	1.3	
Left anterior descending artery	38.9 (7256)	55.4 (5704)	39.4	
Left circumflex artery	22.9 (4264)	20.5 (2115)	21.4	
Coronary-artery bypass graft	3.3 (623)	3.5 (363)	3.9	
Stenosis type — % (no.)				
New stenosis	99.1 (18,500)	95.9 (9875)	98.4	
Restenosis	0.6 (106)	1.4 (143)	1.2	
In-stent restenosis	0.3 (53)	2.7 (276)	0.4	
Occlusion — % (no.)				
None	71.6 (13,367)	77.2 (7949)	73.6	
Within 3 mo	27.3 (5093)	19.9 (2046)	25.4	
At or after 3 mo	1.1 (199)	2.9 (299)	1.0	

\* Plus-minus values are means ±SD. COPD denotes chronic obstructive pulmonary disease, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction. Percentages in some categories may not sum to 100 because of rounding.

† The percentages represent proportions of patients in the drug-eluting-stent group when standardized according to the propensity-score distribution in the bare-metal-stent group.

‡ Some patients received more than one treatment.

## STATISTICAL ANALYSIS

The study methods have been described in detail previously.<sup>10</sup> The primary objective was to evaluate late-occurring events after the implantation of a drug-eluting stent. The primary end point was the composite of death or myocardial infarction. Secondary end points were death, myocardial infarction, and restenosis. To compensate for the nonrandomized design of this study, propensity-score methods<sup>12</sup> were used. The propensity score was defined as the conditional probability of receiving a drug-eluting stent on the basis of available variables and was estimated with a multiple logistic-regression model. All prespecified variables were included in the respective models (Table 1). To determine whether the propensity score would balance the baseline variables, a standardized mean of each variable was calculated for the drug-eluting-stent group. Standardization was performed according to the propensity-score distribution (categorized in deciles) in the bare-metal-stent group.

To provide separate descriptions of the early and late relative risks of events, we performed “landmark analyses”<sup>13</sup> with a prespecified landmark set at 6 months. Adjusted relative risks were estimated with the use of Cox regression models in which the propensity score and the stent group were entered as covariates.

The risk of restenosis was evaluated in the complete sample of patients who received only one stent and in subgroups previously found to be at an increased risk for restenosis.<sup>5,14</sup> We report the rate of restenosis at 1 year as well as the rate per 100 person-years, which was calculated as the ratio of the number of patients with an event within 1 year to the sum of the time at risk. The number of patients who would need to be treated with a drug-eluting stent to prevent one case of restenosis was calculated according to the method of Altman and Andersen.<sup>15</sup> All analyses were performed with the use of the R statistical program, version 2.7.2.<sup>16</sup>

## RESULTS

### CHARACTERISTICS OF PATIENTS AND STENTS

During the 2003–2006 period, 48,892 patients were treated with 86,552 stents during a total of 55,465 PCIs in Sweden. The 925 patients (1.9%) with incomplete baseline data were excluded from the analyses. Table 1 shows the characteristics of

the cohort of 10,294 patients who received one drug-eluting stent and 18,659 patients who received one bare-metal stent at the index procedure (one-stent cohort), as well as of the total cohort of 19,681 patients who received at least one drug-eluting stent and 28,286 patients who received one or more bare-metal stents but no drug-eluting stent. In the total cohort, the drug-eluting–stent group, as compared with the bare-metal–stent group, included a higher proportion of women and a larger number of patients who had features associated with a high risk of restenosis. In addition, more stents were implanted in the drug-eluting–stent group than in the bare-metal–stent group. Pretreatment with clopidogrel was more common and treatment with glycoprotein IIb/IIIa inhibitors was less common in the drug-eluting–stent group than in the bare-metal–stent group. The mean stent length was longer and the diameter smaller with drug-eluting stents than with bare-metal stents. On the other hand, as compared with patients in the drug-eluting–stent group, patients in the bare-metal–stent group were older and more likely to have cancer, three-vessel disease, and incomplete revascularization. Patients in the bare-metal–stent group were also treated with primary PCI for ST-segment elevation myocardial infarction considerably more often than patients in the drug-eluting–stent group (Table 1). After adjustment for the propensity score, however, the groups were similar with respect to all baseline characteristics.

Baseline characteristics for the one-stent cohort, stratified by year of inclusion in the study, are shown in Table 1 of the Supplementary Appendix (available with the full text of this article at NEJM.org). The regional differences in the use of drug-eluting stents were large and persisted over time. The frequencies of pretreatment with clopidogrel and the use of primary PCI for ST-segment elevation myocardial infarction increased in both the drug-eluting–stent group and the bare-metal–stent group over the course of the study. The average rate of use of drug-eluting stents during the entire period was 35.6% (18.8% in 2003, 32.9% in 2004, 47.7% in 2005, and 38.8% in 2006). Paclitaxel-eluting stents (TAXUS Express and TAXUS Liberté, Boston Scientific) were used in 6247 patients (21.6% of all patients in the one-stent cohort), sirolimus-eluting stents (CYPHER and CYPHER SELECT, Cordis, Johnson & John-

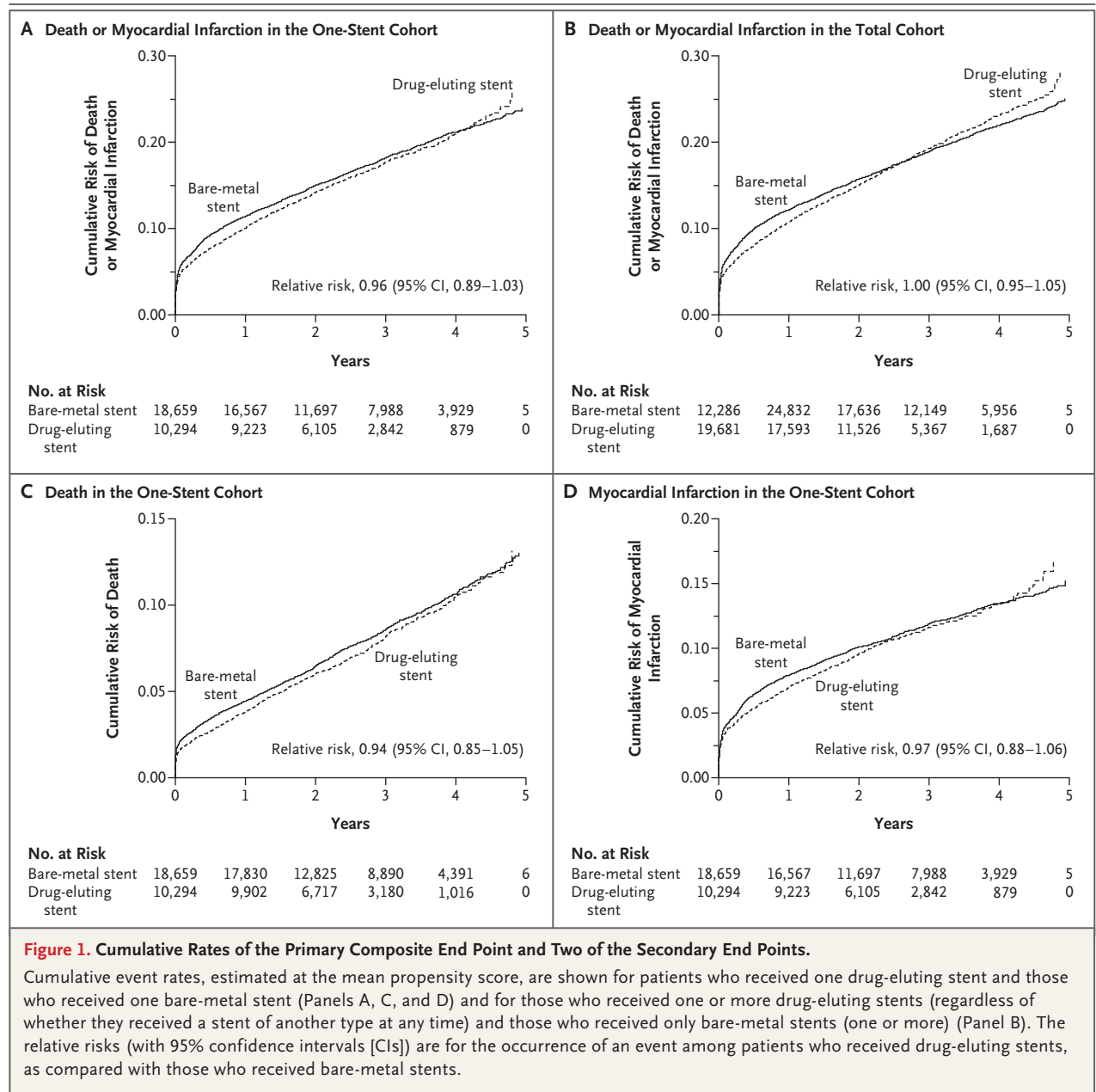
son) in 3351 (11.6%), and zotarolimus-eluting stents (Endeavor, Medtronic) in 686 (2.4%).

#### DEATH AND MYOCARDIAL INFARCTION

During the 1 to 5 years of follow-up (mean, 2.7), a total of 5578 events occurred in 5046 patients in the one-stent cohort: 3198 myocardial infarctions (2044 in the bare-metal–stent group and 1154 in the drug-eluting–stent group) and 2380 deaths (1616 and 764 in the two groups, respectively). After adjustment for the propensity score, there was no overall difference in the composite incidence of death or myocardial infarction between the two groups (Fig. 1A). During the initial 6 months, the event rate was lower in the drug-eluting–stent group than in the bare-metal–stent group (relative risk, 0.79; 95% confidence interval [CI], 0.71 to 0.87), but this difference was offset by a higher event rate in the drug-eluting–stent group thereafter (relative risk, 1.11; 95% CI, 1.01 to 1.23). There were no significant differences in event rates among patients who received paclitaxel-eluting stents, those who received sirolimus-eluting stents, and those who received zotarolimus-eluting stents (data not shown).

In the total cohort, 9812 events occurred in 8824 patients; 5565 had at least one myocardial infarction (3292 in the bare-metal–stent group and 2273 in the drug-eluting–stent group), and 4247 died (2706 and 1541 in the two groups, respectively), with no overall difference between the groups (Fig. 1B).

Adjusted mortality alone in the one-stent cohort was lower with drug-eluting stents than with bare-metal stents during the initial 6 months (relative risk, 0.76; 95% CI, 0.64 to 0.91) and was similar thereafter (relative risk, 1.08; 95% CI, 0.94 to 1.24), with the result that there was no overall long-term difference between the groups (Fig. 1C). The adjusted rate of myocardial infarction was also lower with drug-eluting stents than with bare-metal stents during the initial 6 months (relative risk, 0.79; 95% CI, 0.70 to 0.90) but was higher thereafter (relative risk, 1.16; 95% CI, 1.03 to 1.32), with the result that there was no overall difference between the groups (Fig. 1D). In addition, in the total cohort, mortality and rates of myocardial infarction were similar between the groups (relative risk of death with drug-eluting stents, 0.96; 95% CI, 0.89 to 1.03; relative risk of myocardial infarction with drug-eluting stents,



1.01; 95% CI, 0.95 to 1.08) (see Fig. 1A and 1B in the Supplementary Appendix).

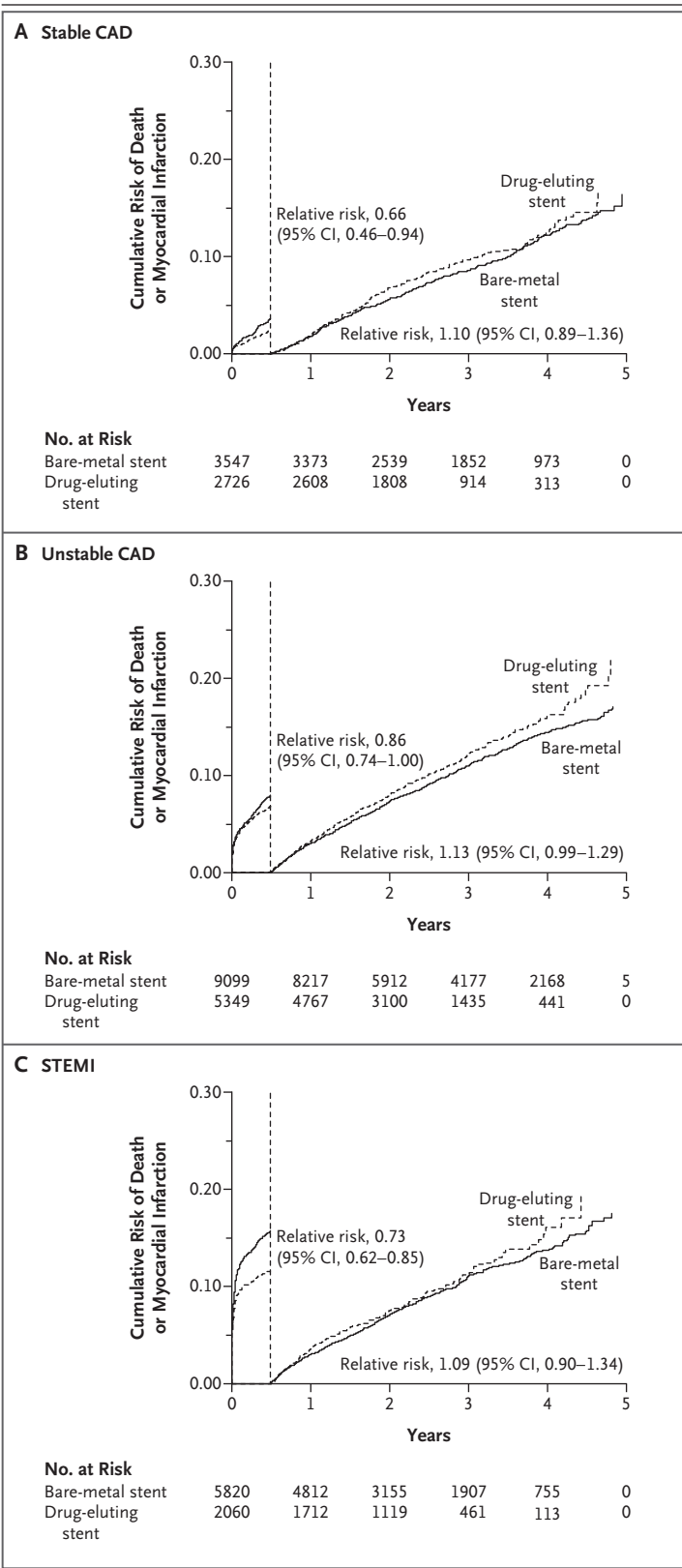
**OUTCOME STRATIFIED BY INDICATION**

In subgroups defined according to the indication for implantation of a stent, there were no significant differences in the outcomes between the drug-eluting–stent group and the bare-metal–stent group. In the one-stent cohort, the adjusted event rate for the combined end point was lower

with drug-eluting stents than with bare-metal stents during the initial 6 months but was similar during the subsequent period, with a similar pattern for all clinical indications (Fig. 2).

**OUTCOME STRATIFIED BY YEAR OF FIRST STENT IMPLANTATION**

In the one-stent cohort of patients treated in 2003, the rate of the composite end point was similar in the two groups during the initial 6 months



**Figure 2. Landmark Analyses of the Primary Composite End Point in the One-Stent Cohort, Stratified According to the Indication for Stent Implantation.**

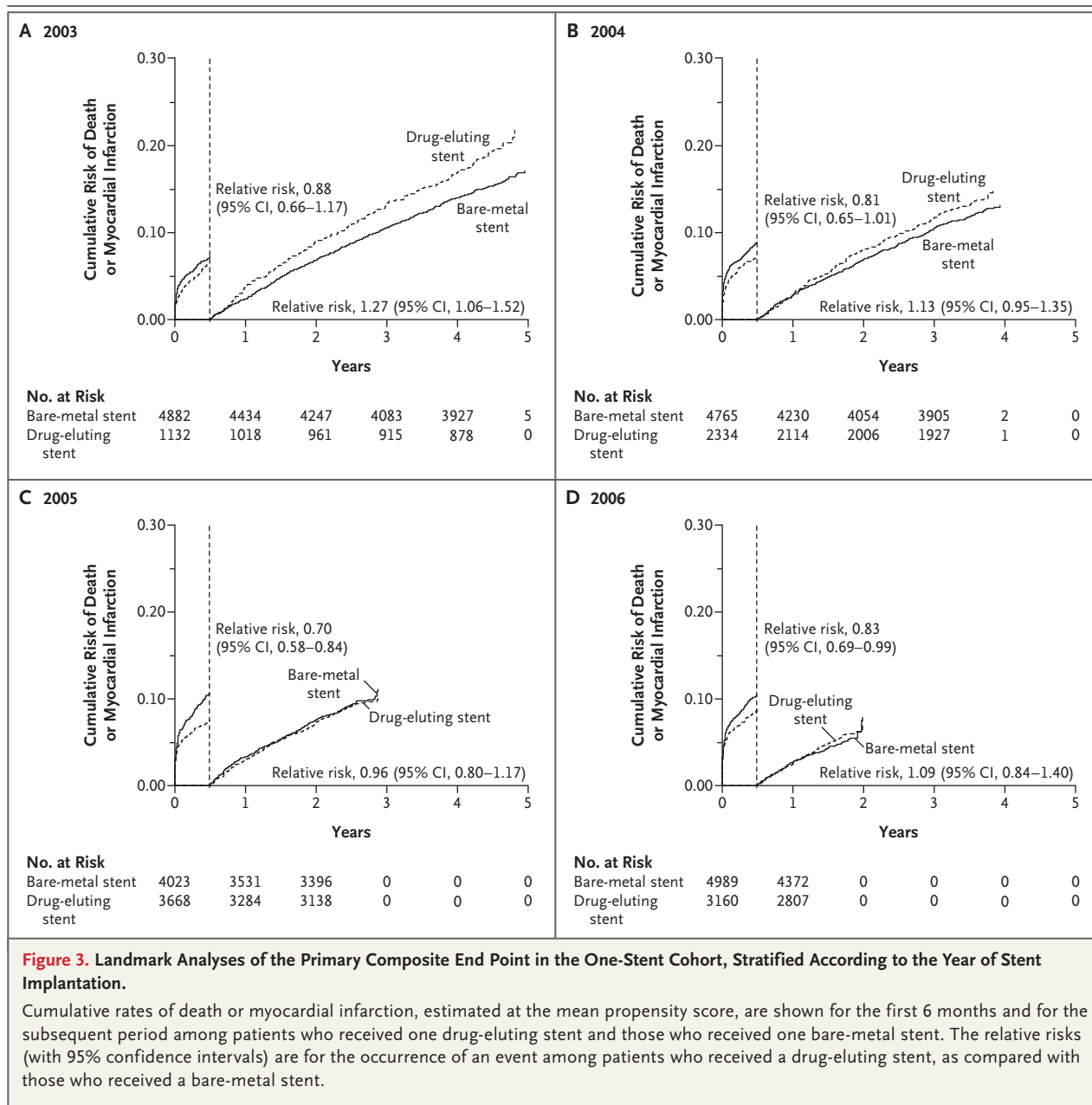
Cumulative rates of death or myocardial infarction, estimated at the mean propensity score, are shown for the first 6 months and for the subsequent period among patients who received one drug-eluting stent and those who received one bare-metal stent. The relative risks (with 95% confidence intervals) are for the occurrence of an event among patients who received a drug-eluting stent, as compared with those who received a bare-metal stent. CAD denotes coronary artery disease, and STEMI ST-segment elevation myocardial infarction.

(Fig. 3A). During the subsequent 4.5 years of follow-up, the event curves diverged, with a significantly higher rate in the drug-eluting-stent group than in the bare-metal-stent group. In the 2004 cohort, the event rates were similar during the initial 6 months (Fig. 3B), as well as during the subsequent 3.5 years of follow-up. In contrast, in the 2005 and 2006 cohorts, there were significantly lower event rates in the drug-eluting-stent group during the initial 6 months (Fig. 3C and 3D), with similar event rates thereafter.

In the 2003–2004 cohort, for whom data for up to 3 years were reported previously, extended follow-up for up to 5 years showed no significant difference in the primary event rates, because a trend toward a lower combined event rate with drug-eluting stents during the initial 6 months (relative risk, 0.89; 95% CI, 0.80 to 1.00) was offset by a higher event rate thereafter (relative risk, 1.19; 95% CI, 1.09 to 1.29) (Fig. II in the Supplementary Appendix).

**RESTENOSIS AND NEW REVASCULARIZATION**

On the basis of SCAAR data for the period from March 2004 through May 2008, restenosis occurred in 683 of 12,358 patients who received bare-metal stents (5.5%), as compared with 387 of 8648 patients who received drug-eluting stents (4.5%). In a Cox regression analysis that adjusted for differences in baseline clinical characteristics of the patients as well as characteristics of the lesions and stents at baseline, the rate of restenosis was lower among patients who received drug-eluting stents than among those who received bare-metal stents (relative risk, 0.43; 95% CI, 0.36 to 0.52) (Table 2). Accordingly, to prevent one case of restenosis per year, 39 lesions would need to be treated with drug-eluting stents. Stent diam-



eter was the most important factor contributing to the reduction in the rate of restenosis with drug-eluting stents. For stents that were less than 3 mm in diameter, the absolute rate of restenosis at 1 year was 3.6 percentage points lower with drug-eluting stents than with bare-metal stents; the corresponding adjusted risk reduction was 65%, and the number needed to treat was 22. The number needed to treat was more than twice

as high in the case of larger stents. The incidence of clinical restenosis was highest among patients with diabetes who received bare-metal stents that were 20 mm long or longer and less than 3 mm wide; the absolute rate of restenosis for this subgroup was 8.3 percentage points higher per year than the rate for patients with diabetes who received equivalent-size drug-eluting stents, and the number needed to treat was 10.

**Table 2. Restenosis in Subgroups of Patients Who Received Only One Stent.\***

Group	Patients with Restenosis at 1 Year		Event Rate		Relative Risk with Drug-Eluting Stents (95% CI) <sup>†</sup>	No. Needed to Treat <sup>†</sup>
	Bare-Metal Stents no./total no. (%)	Drug-Eluting Stents no. of events/100 person-yr	Bare-Metal Stents no. of events/100 person-yr	Drug-Eluting Stents		
Total	545/12,358 (4.4)	250/8649 (2.9)	4.7	3.0	0.43 (0.36–0.52)	39
Stent size						
<3 mm in diameter	206/3025 (6.8)	128/4020 (3.2)	7.4	3.3	0.35 (0.27–0.46)	22
≥3 mm in diameter	339/9333 (3.6)	122/4629 (2.6)	3.8	2.8	0.52 (0.41–0.66)	56
<20 mm in length	377/9068 (4.2)	133/5100 (2.6)	4.4	2.7	0.44 (0.35–0.55)	42
≥20 mm in length	168/3290 (5.1)	117/3549 (3.3)	5.5	3.5	0.42 (0.31–0.57)	33
Coronary artery disease						
Stable	98/2078 (4.7)	62/2218 (2.8)	4.9	2.9	0.42 (0.28–0.62)	37
Unstable	263/5706 (4.6)	138/4491 (3.1)	4.9	3.2	0.43 (0.34–0.56)	38
STEMI	182/4436 (4.1)	48/1800 (2.7)	4.5	2.9	0.44 (0.31–0.64)	42
No diabetes	438/10,197 (4.3)	176/6613 (2.7)	4.6	2.8	0.43 (0.35–0.53)	40
Stent diameter ≥3 mm and length <20 mm	192/5505 (3.5)	50/2041 (2.4)	3.7	2.5	0.53 (0.37–0.75)	60
Stent diameter ≥3 mm and length ≥20 mm	83/2253 (3.7)	41/1559 (2.6)	3.9	2.7	0.50 (0.32–0.78)	53
Stent diameter <3 mm and length <20 mm	118/1994 (5.9)	44/1828 (2.4)	6.3	2.5	0.33 (0.22–0.50)	25
Stent diameter <3 mm and length ≥20 mm	45/445 (10.1)	41/1185 (3.5)	11.3	3.6	0.31 (0.18–0.52)	14
Diabetes	107/2161 (5.0)	74/2036 (3.6)	5.4	3.9	0.46 (0.32–0.65)	36
Stent diameter ≥3 mm and length <20 mm	38/1094 (3.5)	13/622 (2.1)	3.7	2.2	0.43 (0.21–0.88)	49
Stent diameter ≥3 mm and length ≥20 mm	26/481 (5.4)	18/407 (4.4)	5.9	4.7	0.60 (0.30–1.23)	45
Stent diameter <3 mm and length <20 mm	29/475 (6.1)	26/609 (4.3)	6.7	4.5	0.47 (0.25–0.86)	30
Stent diameter <3 mm and length ≥20 mm	14/111 (12.6)	17/398 (4.3)	14.9	4.6	0.26 (0.11–0.59)	10

\* STEMI denotes ST-segment elevation myocardial infarction.

† The number needed to treat refers to the number of lesions.

In the group that received drug-eluting stents, 1571 patients (15.3%) underwent a repeat PCI and 222 (2.2%) underwent coronary-artery bypass grafting during the 1 to 5 years of follow-up. In the bare-metal-stent group, the corresponding numbers were 2780 (14.9%) and 501 (2.7%), respectively. Among the 1423 patients who received a second stent, the median intervals to repeat PCI were similar (696 days in the drug-eluting-stent group and 693 in the bare-metal-stent group). In a Cox regression analysis, the drug-eluting-stent group, as compared with the bare-metal-stent group, had lower adjusted rates of any repeat revascularization (relative risk, 0.89; 95% CI, 0.83 to 0.96) and of a repeat PCI (relative risk, 0.90; 95% CI, 0.84 to 0.97). In addition, the rate of coronary-artery bypass grafting tended to be lower in the drug-eluting-stent group than in the bare-metal-stent group (relative risk, 0.87; 95% CI, 0.72 to 1.06).

---

## DISCUSSION

---

In this study, we evaluated the long-term outcome with drug-eluting stents as compared with bare-metal stents in a very large cohort of unselected, consecutive patients, from all interventional centers in Sweden, in whom a coronary stent was implanted. The conclusion of our previous study<sup>10</sup> was based on the total patient population for the 2003–2004 period, which included patients who received multiple stents. With the extended study period, we were able to collect data on a sufficient number of patients (28,953) and primary-outcome events to evaluate patients who received only one stent (either a drug-eluting stent or a bare-metal stent) during the index procedure. This one-stent cohort was more than 30% larger than the total patient cohort in the earlier SCAAR study, which included patients who received any number of stents (19,771),<sup>10</sup> and the total number of patients in a network meta-analysis that included 23 randomized trials (18,023).<sup>4</sup> The one-stent cohort allowed for adjustments for lesion, vessel, and stent characteristics in the multivariable analyses, which provided a better balance between the drug-eluting-stent group and the bare-metal-stent group. The availability of this information reduced the difference in the outcome between the two cohorts, explaining in part the difference between the findings for the previous total cohort and the current one-stent cohort.

One factor that may explain the difference in the outcome between the current and previous analyses is a change in the outcome over time, with an early outcome that became gradually worse in the bare-metal-stent group and gradually better in the drug-eluting-stent group. The most important change in clinical practice during the extended study period was an increase in the use of primary PCI for patients with ST-segment elevation myocardial infarction. The proportion of such patients who received stents increased more in the bare-metal-stent group than in the drug-eluting-stent group. An increasing proportion of patients pretreated with clopidogrel, progressively higher balloon pressures, and a gradual increase in the duration of clopidogrel treatment after the implantation of drug-eluting stents might have contributed to the relatively lower rate of late events in the drug-eluting-stent group in the current study as compared with the rates in our previous study.

The average use of drug-eluting stents increased during the study period, but the variations among centers and among indications for stent implantation remained large. Although the geographic differences accounted for most of the difference in the use of drug-eluting stents, stent selection was also based on risk criteria for restenosis, as suggested by the higher percentage of patients with high-risk clinical and angiographic features in the drug-eluting-stent group.<sup>17</sup> Stent selection was also based on the clinical risk of an adverse outcome, since ST-segment elevation myocardial infarction was more common in the bare-metal-stent group. However, the multivariable propensity-score analysis was very effective in adjusting for differences in the characteristics for which we had data (Table 1).

There was no significant difference in the primary composite end point between the drug-eluting-stent group and the bare-metal-stent group during long-term follow-up. In the initial 6 months, mortality tended to be lower in the group that received drug-eluting stents than in the group that received bare-metal stents, a finding that is consistent with the results of other registry studies.<sup>5,8,18</sup> In contrast to the results of our previous study of SCAAR data, the current study shows no late-occurring increase in mortality after implantation of drug-eluting stents. This finding is consistent with the results of randomized trials, meta-analyses, and large-scale regis-

try studies.<sup>4,19,20</sup> Although late and very-late stent thromboses appear to occur infrequently,<sup>8,9</sup> they might still affect mortality.<sup>21</sup> The lower clinical need for reinterventions with drug-eluting stents (with an adjusted rate that was 10% lower than that with bare-metal stents) may, however, have led to a subsequent reduction in fatal events, offsetting a possible increase in the risk of late stent thrombosis.<sup>22</sup>

There seemed to be a trend toward a very-late increase in the rate of myocardial infarction among patients who received drug-eluting stents, a finding that is consistent with the slightly higher rate of myocardial infarction after the cessation of clopidogrel therapy in other registry studies and in extended follow-up analyses of data from randomized trials.<sup>5,8,23,24</sup> However, the upward shift in the rate of myocardial infarction that occurred very late in the drug-eluting–stent group appears to represent an increased event rate only among patients who were treated in 2003, rather than an actual increase of events in the total cohort. Unmeasured selection bias during the period when drug-eluting stents were first available may have contributed to this result. In the subgroups of patients who had stent procedures in 2004, 2005, and 2006, the event rates were similar between the drug-eluting–stent group and the bare-metal–stent group, without any signal of an increase in late events.

The average crude absolute rate of restenosis at 1 year was low with both stent types and was 1.5 percentage points lower with drug-eluting stents than with bare-metal stents, corresponding to an average 50% relative reduction in the adjusted rate of clinical restenosis. The overall absolute rate of restenosis in this study was lower than the rates in randomized clinical trials but similar to the rates in other registry studies.<sup>25-27</sup> The low rates of restenosis and of reintervention after implantation of bare-metal stents and the small absolute difference between these rates and the rates for drug-eluting stents do not support the use of drug-eluting stents in patients who are at low or intermediate risk for restenosis. On the basis of the data from the one-stent cohort, this trial clearly shows that when lesions require stents that are less than 3 mm in diameter and 20 mm or more in length, the event rate for restenosis with bare-metal stents is approximately 11

per 100 person-years in patients without diabetes and 15 per 100 person-years in patients with diabetes, a risk that is reduced with drug-eluting stents to approximately 4 in patients without diabetes and 5 in patients with diabetes. For patients with such lesions, drug-eluting stents provide a clear clinical benefit, with one case of restenosis averted for every 10 to 14 lesions treated — a number needed to treat that is reduced by a factor of four as compared with that for patients at average risk and by a factor of six as compared with that for patients at low risk for restenosis.

The inherent limitations of a nonrandomized, registry study should be acknowledged. Despite appropriate statistical adjustments, unknown confounders may have affected the results. Moreover, it is not possible to attribute individual events to the individual stents or the stented vessel. Another major limitation of our study is the lack of information about the duration of clopidogrel treatment, making it impossible to determine whether the timing of events was related to discontinuation of the drug.<sup>8</sup> Prolongation of clopidogrel treatment in later years may have contributed to the differences in the outcome over time.

In conclusion, in the present study, which included a very large, consecutive cohort of all patients who received a coronary stent in Sweden during a 4-year period and who were followed for 1 to 5 years, there was no difference in long-term survival or in the risk of myocardial infarction between the patients who received drug-eluting stents and those who received bare-metal stents. Among patients who required stents that were less than 3 mm in diameter and 20 mm or more in length, there was a relative reduction of approximately 70% and an absolute reduction of more than 10 percentage points in the rate of clinical restenosis. Thus, the use of drug-eluting stents is safe and, in patients with lesions at high risk for restenosis, is also very effective in reducing the risk of clinical restenosis.

Supported by grants from the Swedish Association of Local Authorities and Regions and the Swedish Heart–Lung Foundation (to SCAAR and the Uppsala Clinical Research Center) and the Swedish Board of Health and Welfare and the Swedish Medical Products Agency.

Dr. James reports receiving lecture fees from Boston Scientific, Cordis, and Eli Lilly; and Dr. Scherstén, consulting fees from Medtronic. No other potential conflict of interest relevant to this article was reported.

## APPENDIX

The members of the SCAAR study group are as follows: **SCAAR Steering Committee** — S. James, Uppsala (chair); B. Lagerqvist, Uppsala (vice chair); T. Nilsson, Karlstad; E. Omerovic, Göteborg; J. Carlsson, Kalmar; J. Nilsson, Umeå; N. Saleh, Stockholm; O. Fröbert, Örebro; A. Flinck, Göteborg; F. Scherstén, Helsingborg; G. Olivecrona, Lund. **Uppsala Clinical Research Center** — L. Wallentin (director); R. Svensson (system developer); O. Felton (system developer); K. Spångberg (data manager); E. Svensson (monitor). **Epidemiologic Center, Swedish Board of Health and Welfare** — M. Köster (statistician). **SCAAR hospitals and participating physicians** — Borås: L. Robertsson; Danderyd: T. Särev; Eskilstuna: F. Hjortevang; Falun: I. Sjögren; Gävle: L. Hellsten; Halmstad: P. Hårdhammar; Helsingborg: L. Sandhall; Karolinska University in Huddinge: B. Lindvall; Kalmar: J. Carlsson; Karolinska University in Solna: N. Saleh; Karlskrona: C.-M. Pripp; Kristianstad: R. Uher; Linköping University: U. Stenstrand; Lund University: B. Thorvinger; Ryhov in Jönköping: W. Puskar; Malmö University: C.-G. Gustavsson; Sahlgrenska University in Göteborg: P. Albertsson; Skövde: A. Kallryd; St. Göran in Stockholm: H. Enhörning; Sunderby in Luleå: A. Johansson; Södersjukhuset in Stockholm: M. Aasa; Trollhättan: D. Ioanes; Umeå University: J. Nilsson; Uppsala University: B. Lagerqvist; Västerås: O. Herterich; Örebro University: O. Fröbert.

## REFERENCES

1. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 2007;356:998-1008.
2. Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007;356:1030-9.
3. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007;356:989-97.
4. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet* 2007;370:937-48.
5. Tu JV, Bowen J, Chiu M, et al. Effectiveness and safety of drug-eluting stents in Ontario. *N Engl J Med* 2007;357:1393-402.
6. Mauri L, Silbaugh TS, Wolf RE, et al. Long-term clinical outcomes after drug-eluting and bare-metal stenting in Massachusetts. *Circulation* 2008;118:1817-27.
7. Marzocchi A, Saia F, Piovaccari G, et al. Long-term safety and efficacy of drug-eluting stents: two-year results of the REAL (REGistro AngiopLastiche dell'Emilia Romagna) multicenter registry. *Circulation* 2007;115:3181-8.
8. Jensen LO, Maeng M, Kaltoft A, et al. Stent thrombosis, myocardial infarction, and death after drug-eluting and bare-metal stent coronary interventions. *J Am Coll Cardiol* 2007;50:463-70.
9. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet* 2007;369:667-78.
10. Lagerqvist B, James SK, Stenstrand U, Lindbäck J, Nilsson T, Wallentin L. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. *N Engl J Med* 2007;356:1009-19.
11. Flynn MR, Barrett C, Cosio FG, et al. The Cardiology Audit and Registration Data Standards (CARDS), European data standards for clinical cardiology practice. *Eur Heart J* 2005;26:308-13.
12. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70:41-55.
13. Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response. *J Clin Oncol* 1983;1:710-9.
14. Brunner-La Rocca HP, Kaiser C, Bernheim A, et al. Cost-effectiveness of drug-eluting stents in patients at high or low risk of major cardiac events in the Basel Stent KostenEffektivitäts Trial (BASKET): an 18-month analysis. *Lancet* 2007;370:1552-9.
15. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ* 1999;319:1492-5.
16. R Development Core Team. A language and environment for statistical computing. Vienna: R-Foundation for Statistical Computing, 2006. (Accessed April 13, 2009, at <http://www.R-project.org>.)
17. Lemos PA, Hoyer A, Goedhart D, et al. Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients: an evaluation from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study. *Circulation* 2004;109:1366-70.
18. Williams DO, Abbott JD, Kip KE. Outcomes of 6906 patients undergoing percutaneous coronary intervention in the era of drug-eluting stents: report of the DEScover Registry. *Circulation* 2006;114:2154-62.
19. Kastrati A, Dibra A, Spaulding C, et al. Meta-analysis of randomized trials on drug-eluting stents vs. bare-metal stents in patients with acute myocardial infarction. *Eur Heart J* 2007;28:2706-13.
20. Schömig A, Dibra A, Windecker S, et al. A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. *J Am Coll Cardiol* 2007;50:1373-80.
21. Iakovou I, Schmidt T, Bonizzi E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;293:2126-30.
22. Doyle B, Rihal CS, O'Sullivan CJ, et al. Outcomes of stent thrombosis and restenosis during extended follow-up of patients treated with bare-metal coronary stents. *Circulation* 2007;116:2391-8.
23. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol* 2006;48:2584-91.
24. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA* 2007;297:159-68.
25. Ong AT, Serruys PW, Aoki J, et al. The unrestricted use of paclitaxel- versus sirolimus-eluting stents for coronary artery disease in an unselected population: one-year results of the Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry. *J Am Coll Cardiol* 2005;45:1135-41.
26. Ong AT, van Domburg RT, Aoki J, Sonnenschein K, Lemos PA, Serruys PW. Sirolimus-eluting stents remain superior to bare-metal stents at two years: medium-term results from the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. *J Am Coll Cardiol* 2006;47:1356-60.
27. Lemos PA, Arampatzis CA, Saia F, et al. Treatment of very small vessels with 2.25-mm diameter sirolimus-eluting stents (from the RESEARCH registry). *Am J Cardiol* 2004;93:633-6.

Copyright © 2009 Massachusetts Medical Society.