

CLINICAL RESEARCH

3-Year Clinical Outcomes in the Randomized SORT OUT III Superiority Trial Comparing Zotarolimus- and Sirolimus-Eluting Coronary Stents

Michael Maeng, MD, PhD,* Hans-Henrik Tilsted, MD,†
Lisette Okkels Jensen, MD, DMSci,‡ Anne Kaltoft, MD, PhD,*
Henning Kelbæk, MD, DMSci,§ Ulrik Abildgaard, MD, DMSci,||
Anton B. Villadsen, MD,† Lars Romer Krusell, MD,* Jan Ravkilde, MD, DMSci,†
Knud Nørregaard Hansen, MD,‡ Evald Høj Christiansen, MD, PhD,* Jens Aarøe, MD,†
Jan Skov Jensen, MD, DMSci,|| Steen Dalby Kristensen, MD, DMSci,*
Hans Erik Bøtker, MD, DMSci,* Morten Madsen, MSc,¶ Per Thayssen, MD, DMSci,‡
Henrik Toft Sørensen, MD, DMSci,¶ Leif Thuesen, MD, DMSci,*
Jens Flensted Lassen, MD, PhD*

Aarhus, Aalborg, Odense, Copenhagen, and Gentofte, Denmark

Objectives This study sought to examine the 3-year clinical outcomes in patients treated with the Endeavor (Medtronic, Santa Rosa, California) zotarolimus-eluting stent (ZES) or the Cypher (Cordis, Johnson & Johnson, Warren, New Jersey) sirolimus-eluting stent (SES) in routine clinical practice.

Background The long-term clinical outcome in patients treated with ZES in comparison with SES is unclear.

Methods The authors randomized 2,332 patients to ZES (n = 1,162) or SES (n = 1,170) implantation. Endpoints included major adverse cardiac events (MACE), a composite of cardiac death, myocardial infarction, or target vessel revascularization; the individual endpoints of MACE; and definite stent thrombosis.

Results At 3-year follow-up, the MACE rate was higher in patients treated with ZES than in patients treated with SES (148 [12.9%] vs. 116 [10.1%]; hazard ratio [HR]: 1.33, 95% confidence interval [CI]: 1.04 to 1.69; p = 0.022). Target vessel revascularization was more frequent in the ZES group compared with the SES group (103 [9.1%] vs. 76 [6.7%]; HR: 1.40, 95% CI: 1.04 to 1.89; p = 0.025), whereas the occurrence of myocardial infarction (3.8% vs. 3.3%) and cardiac death (2.8% vs. 2.8%) did not differ significantly. Although the rate of definite stent thrombosis was similar at 3-year follow-up (1.1% vs. 1.4%), very late (12 to 36 months) definite stent thrombosis occurred in 0 (0%) patients in the ZES group versus 12 (1.1%) patients in the SES group (p = 0.0005).

Conclusions Although the 3-year MACE rate is higher in patients treated with ZES versus SES, our data highlight a late safety problem concerning definite stent thrombosis with the use of SES. This finding underscores the importance of long-term follow-up in head-to-head comparisons of drug-eluting stents. (Randomized Clinical Comparison of the Endeavor and the Cypher Coronary Stents in Non-selected Angina Pectoris Patients [SORT OUT III]; NCT00660478) (J Am Coll Cardiol Intv 2012;5: 812–8) © 2012 by the American College of Cardiology Foundation

The 2 first-generation drug-eluting stents (DES), the Cypher Select+ (Cordis, Johnson & Johnson, Warren, New Jersey) sirolimus-eluting stent (SES) and the Taxus (Boston Scientific, Natick, Massachusetts) paclitaxel-eluting stent (PES), more than halved the need for new revascularizations after coronary artery stent implantation (1-3). However, both types of DES have been associated with increased risk of very late (occurring later than 12 months following the index procedure) stent thrombosis (ST) (4). The second-generation zotarolimus-eluting Endeavor stent (ZES) has been associated with an increased risk of ST within the first year after implantation as compared with SES and PES (5-7). There are, however, data indicating that ZES may be associated with fewer target lesion revascularizations (TLR) beyond the first year, but this issue has hitherto not been adequately addressed in a larger randomized study with long-term follow-up (8). The present study provides 3-year clinical outcomes in 2,332 routine clinical care patients with coronary artery disease randomized to treatment with ZES versus SES.

Methods

Patients and study design. The SORT OUT (Danish Organization for Clinical Trials with Clinical Outcome) III protocol has been previously described (5). Briefly, SORT OUT III is a multicenter, open-label, randomized, superiority trial that enrolled patients from January 2006 through August 2007 at 5 Danish high-volume PCI centers (5). Patients aged 18 years or older with an indication for DES implantation were eligible. The only exclusion criteria were inability to provide informed consent; life expectancy <1 year; allergy to acetylsalicylic acid, clopidogrel, ticlopidine, sirolimus, or zotarolimus; or participation in another randomized trial.

Patients with coronary artery disease were randomly assigned 1:1 to have either ZES (Endeavor Sprint, Medtronic, Santa Rosa, California) or SES (Cypher Select+) implanted. The recommendation for dual antiplatelet therapy included lifelong acetylsalicylic acid (75 mg daily) and clopidogrel 75 mg daily for 1 year, in accordance with Danish guidelines.

The study complied with the Declaration of Helsinki and was approved by the local ethics committee. All patients provided written, informed consent before participating in the trial.

Outcome measures and data management. Follow-up was pre-specified to take place after 9 months, 18 months, 3 years, and 5 years. We assessed major adverse cardiac events

(MACE), defined as the composite of cardiac death, myocardial infarction (MI), and target vessel revascularization (TVR). Other endpoints were all-cause death, cardiac death, MI, TVR, TLR (stent + 5-mm distal and proximal edges), symptom-driven observation of restenosis (stent + 5-mm distal and proximal edges), and angiographically verified (definite) ST. Independent study monitors blinded to treatment assignment reviewed all repeat coronary angiograms and coronary interventions (balloon angioplasty, stent implantation, and coronary artery bypass grafting). Symptom-driven restenosis and definite ST were classified based on review of angiograms and patient files. Landmark analyses were performed for all endpoints by dividing the entire follow-up period into the initial 12 months and the subsequent 24 months.

Clinical event detection. We used clinically driven event detection to avoid study-induced reinterventions (5,9). Data on mortality (cardiac and noncardiac), hospital admissions, coronary angiography, repeat percutaneous coronary intervention (PCI), and coronary bypass surgery were obtained for all randomized patients from national Danish administrative and health registries (the Danish Civil Registration system, the National Registry of Causes of Death, the National Registry of Patients, and the Danish Heart Registries). We defined new MIs as rehospitalization for MI after discharge following the index PCI. We used the original death certificates obtained from the National Registry of Causes of Deaths, combined with hospital records, and data from the patient's general practitioner to classify deaths according to the underlying cause.

An independent endpoint committee blinded to treatment assignment reviewed all events and classified all MIs and deaths.

Statistical analysis. Distributions of continuous variables in the ZES and SES groups were compared using either the 2-sample *t* test (or Cochran *t* test in the case of unequal variance) or the Mann-Whitney *U* test, depending on

Abbreviations and Acronyms

DES = drug-eluting stent(s)

HR = hazard ratio

MACE = major adverse cardiac event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

SES = sirolimus-eluting stent(s)

ST = stent thrombosis

TLR = target lesion revascularization

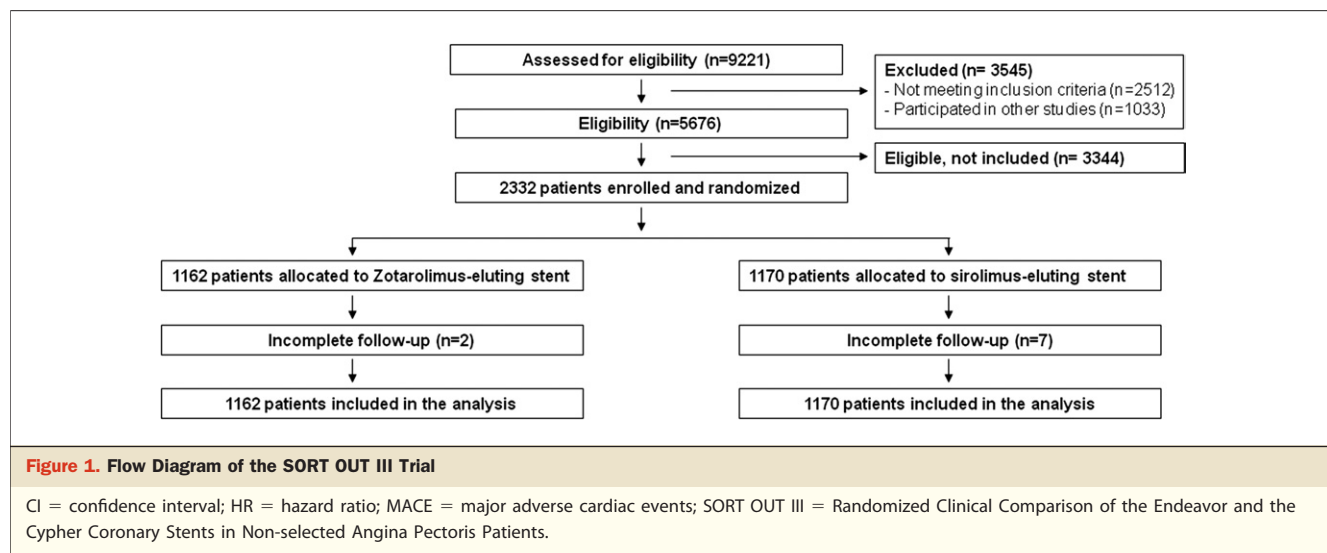
TVR = target vessel revascularization

ZES = zotarolimus-eluting stent(s)

Copenhagen University Hospital, Copenhagen, Denmark; §Department of Cardiology, Gentofte University Hospital, Gentofte, Denmark; and the ¶Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark. ¶Department of Cardiology, Odense University Hospital, Odense, Denmark; The study was supported by unrestricted research grants from Cordis and Medtronic. Both companies had no influence on the study design, data collection, data analysis, data interpretation; they did not have access to the clinical trial database, and they did not

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whether the data followed a normal distribution. We compared distributions of categorical variables using the chi-square test.

We counted endpoint events occurring during the follow-up period and compared rates for the 2 groups of patients. Follow-up began on the date of the index PCI procedure. In analyses of each outcome, follow-up continued until the date of an endpoint event, death, emigration, or until 36 months after implantation, whichever occurred first. Cumulative incidence curves were constructed based on the cumulative incidence of endpoint events, taking into account the competing risk of death. Further, landmark analyses were performed as previously noted. Differences between groups were estimated using the Cox proportional hazards model. Patients treated with SES were used as the reference in the analyses. All analyses were performed according to intention-to-treat principles. We computed the hazard ratio (HR) of MACE at 36-month follow-up for relevant patient subgroups. A value of $p < 0.05$ was considered as significant. We used SAS software version 9.2 (SAS Institute, Cary, North Carolina) for all analyses.

Results

We randomized 2,332 patients with 3,230 lesions to treatment with ZES (1,162 patients, 1,619 lesions) or SES (1,170 patients, 1,611 lesions). Of the 1,162 patients randomized to ZES and the 1,170 patients randomized to SES, 0 in the ZES group and 6 in the SES group had incomplete follow-up due to emigration and were censored on the day of emigration (Fig. 1). Complete data were available for 2,223 patients (99.6%).

Table 1 summarizes the baseline patient characteristics. The 3-year clinical outcomes and the landmark analysis of events occurring after year 1 are presented in Table 2 and illustrated for MACE, TLR, and definite ST in Figures 2,

3, and 4, respectively. The 3-year MACE rate was significantly higher in patients receiving ZES than SES. The landmark analysis showed that this difference primarily occurred during the first year, whereas no significant difference was observed for the following 2 years.

The superiority of SES with regard to MACE was due primarily to a significant disparity in TLR, and subsequently TVR, between the ZES and SES groups. The landmark analyses of TLR showed that patients receiving ZES had approximately a 4-fold higher risk of TLR during year 1, with an almost flat time-to-event curve after year 2 (Fig. 3). By contrast, the TLR rate for patients receiving SES seemed to increase steadily throughout the 3 years of follow-up.

The timing of definite ST events is illustrated in Figure 4. At 1 year, definite ST had occurred more frequently in the ZES group compared with the SES group, whereas there

Table 1. Baseline Characteristics of Patients Receiving ZES and SES at 3-Year Follow-Up in the SORT OUT III Trial

	ZES (n = 1,162)	SES (n = 1,170)
Age, yrs	64.3 ± 10.7	64.3 ± 10.8
Men	852 (73)	862 (74)
Current smoker	347 (32)	341 (32)
Diabetes mellitus	161 (15)	175 (14)
Hypertension	605 (54)	569 (51)
Hypercholesterolemia	781 (70)	757 (68)
History of myocardial infarction	285 (26)	302 (27)
Previous percutaneous coronary intervention	233 (21)	195 (17)
Previous coronary artery bypass operation	79 (7)	73 (7)
Acute coronary syndrome	506 (44)	546 (47)
Multivessel coronary artery disease	350 (31)	345 (30)

Values are mean ± SD or n (%).
SES = sirolimus-eluting stent(s); SORT OUT III = Randomized Clinical Comparison of the Endeavor and the Cypher Coronary Stents in Non-selected Angina Pectoris Patients; ZES = zotarolimus-eluting stent(s).

Table 2. Three-Year Clinical Outcomes of Patients Receiving the ZES and the SES in the SORT OUT III Trial

	ZES (n = 1,162)	SES (n = 1,170)	Hazard Ratio (95% CI)	p Value
0–36 months				
Combined endpoint (MACE)*	148 (12.9)	116 (10.1)	1.33 (1.04–1.69)	0.0223
Death	85 (7.3)	69 (5.9)	1.25 (0.91–1.72)	0.17
Cardiac death	32 (2.8)	32 (2.8)	1.02 (0.62–1.66)	0.95
Myocardial infarction	43 (3.8)	37 (3.3)	1.19 (0.77–1.85)	0.44
Definite stent thrombosis	13 (1.1)	16 (1.4)	0.83 (0.40–1.72)	0.61
Target vessel revascularization	103 (9.1)	76 (6.7)	1.40 (1.04–1.89)	0.0247
Target lesion revascularization	77 (6.8)	44 (3.9)	1.82 (1.25–2.63)	0.0016
Clinical in-stent restenosis†	66 (5.8)	33 (2.9)	2.08 (1.37–3.15)	0.0006
12–36 months				
Combined endpoint (MACE)*	55 (5.3)	70 (6.4)	0.84 (0.59–1.19)	0.32
Death	54 (4.8)	45 (3.9)	1.22 (0.82–1.82)	0.32
Cardiac death	18 (1.6)	21 (1.9)	0.88 (0.47–1.64)	0.68
Myocardial infarction	22 (2.0)	31 (2.8)	0.73 (0.42–1.26)	0.26
Definite stent thrombosis	0 (0)	12 (1.1)	—	0.0005‡
Target vessel revascularization	25 (2.4)	43 (3.9)	0.62 (0.38–1.01)	0.0551
Target lesion revascularization	15 (1.4)	28 (2.5)	0.57 (0.30–1.06)	0.0775
Clinical in-stent restenosis†	15 (1.4)	23 (2.1)	0.69 (0.36–1.32)	0.26

Values are n (%). *The composite of cardiac death, myocardial infarction, and clinically driven target vessel revascularization. †The study had no pre-planned follow-up angiography. Clinical in-stent restenosis is the detection of in-stent restenosis by repeat angiography due to stable angina pectoris or acute coronary syndromes. ‡Fisher's exact test.
CI = confidence intervals; MACE = major adverse cardiac event(s); other abbreviations as in Table 1.

were no very late ST events (0%) in the ZES group as opposed to 12 events (1.1%) in the SES group (risk difference = -1.1% , 95% confidence interval [CI]: -1.7% to -0.4% ; $p = 0.0005$) between 1 and 3 years. For very late ST, the number needed to harm was 91 with use of SES in comparison with ZES. Overall, however, there were no statistically significant difference in the number of STs at 3-year follow-up. Definite ST caused 14 (64%) of the 22 MIs observed within year 1, and 12 (23%) of the 53 MIs that occurred between 1 and 3 years of follow-up. Restenosis was observed more frequently in the SES group after 1 year.

As illustrated in Figure 5, findings concerning MACE remained consistent across subgroups categorized by age, sex, diabetes, acute coronary syndromes, lesions in left anterior descending artery, and complex lesions at 3-year follow-up.

Discussion

The SORT OUT III trial is an open-label multicenter randomized superiority trial, which compares clinical outcomes after ZES versus SES implantation in a PCI population receiving routine clinical care. The previously published 9- and 18-month results showed that ZES was inferior to the SES with regard to both safety and efficacy endpoints (5). Specifically, SES was associated with lower rates of ST at 9 months, lower rates of MI at both 9 and 18 months, and a lower rate of all-cause mortality at 18

months. The current 3-year follow-up showed that SES remained superior to ZES with regard to MACE, TVR, and TLR. This superiority was driven primarily by a reduced risk of TLR. After 3 years, the safety-related endpoints (ST, MI, and mortality) no longer differed between the ZES and SES groups. As a novel observation, however, we found that SES implantation was associated with a significantly increased risk of very late ST as compared with ZES implantation. Moreover, the HR of 2.19 (5.2% absolute MACE difference) at 18-month follow-up in favor of SES was reduced to 1.33 (2.8% absolute MACE difference) at 3-year follow-up. Combined, these results indicate that the inferiority of the ZES, as compared with the SES, decreases over time. This finding is in accordance with the 5-year results of the ENDEAVOR III study (A Randomized Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Cypher Sirolimus-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions), in which the progression of MACE was significantly more common in patients receiving SES than those receiving ZES (10). Therefore, our results highlight the importance of long-term follow-up in randomized studies evaluating new DES.

We found that SES implantation was associated with a higher risk of very late ST, occurring at a rate of approximately 0.5% per year in the SES group compared with no very late ST events in the ZES group. ZES and SES use different polymers for drug elution, elute different drugs,

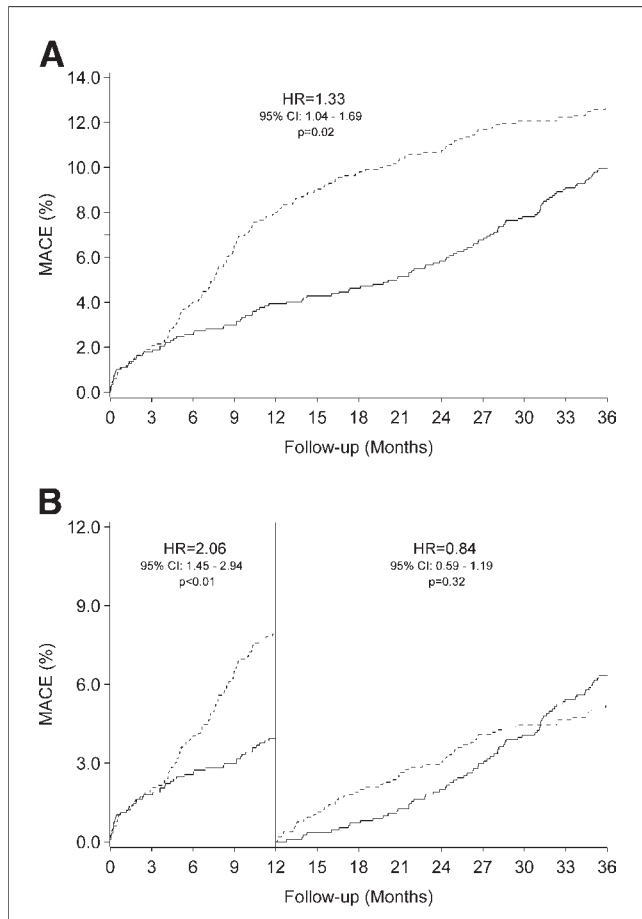


Figure 2. MACE in the SORT OUT III Trial

Event rates of MACE, the primary endpoint, a composite of cardiac death, myocardial infarction, and target vessel revascularization in the zotarolimus-eluting (**dotted line**) versus sirolimus-eluting (**straight line**) stent groups. **(A)** Event rates during the 3-year follow-up. **(B)** A landmark analysis of events occurring after year 1. Abbreviations as in Figure 1.

and differ with regard to drug release kinetics. These factors potentially explain the observed differences between these 2 types of DES. ZES elutes zotarolimus through use of a phosphorylcholine polymer. This phosphorylcholine polymer is considered a noninflammatory alternative to other polymers but has a faster drug elution rate (within 14 days) than other DES. In comparison with SES, the ZES was experimentally associated with a higher degree of inflammation in the treated vascular wall at 30 days but also less inflammation at 6 months (11). In accordance with these experimental results, human pathology studies have shown that SES is associated with localized strut hypersensitivity at late follow-up (12,13). Further, evaluation of ZES and SES using intravascular ultrasound showed that ZES induced more uniform and complete neointimal coverage of the stent struts at 8-month follow-up (14,15). This ZES-associated lack of late-acquired incomplete stent apposition is believed to protect against very late ST. Our clinical data

extend these experimental, pathological, and intravascular ultrasound findings by confirming a reduced risk of very late ST associated with ZES use. The higher risk of ST observed in the ZES group at short-term follow-up in our and other studies (6,7) may be related to an overly rapid elution of zotarolimus, whereas the higher rate of very late ST observed in the SES group may represent the, probably, polymer-related, localized strut hypersensitivity.

It should also be noted that the risk of ST was higher in our “all-comer” trial than in patients with a relatively low anatomic and clinical risk of adverse events. For example, in the ENDEAVOR III study <1% of patients experienced ST at 5-year follow-up, with no difference between ZES and SES (10). Moreover, the problem with very late ST seems unlikely to be confined to SES, as this outcome also has been reported for other newer-generation DES. In the BASKET-PROVE (Basel Stent Kosten-Effektivitäts Trial-Prospektive Validation Examination), there were 2 (0.3%) (definite and probable) very late ST events in both

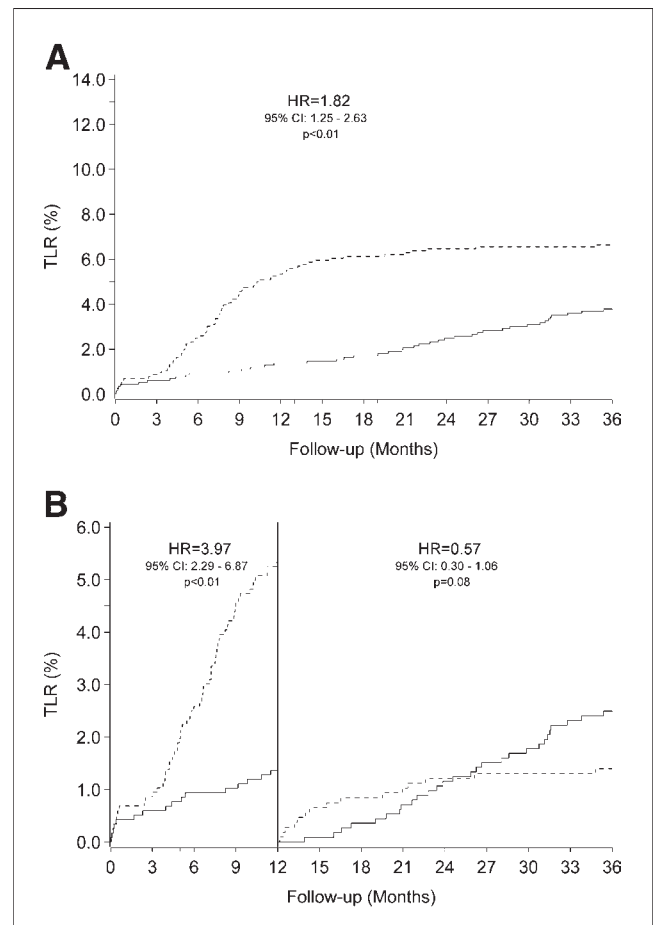


Figure 3. TLR in the SORT OUT III Trial

Event rates of target lesion revascularization (TLR) in the zotarolimus-eluting (**dotted line**) versus sirolimus-eluting (**straight line**) stent groups. **(A)** Event rates during the 3-year follow-up. **(B)** A landmark analysis of events occurring after year 1. Abbreviations as in Figure 1.

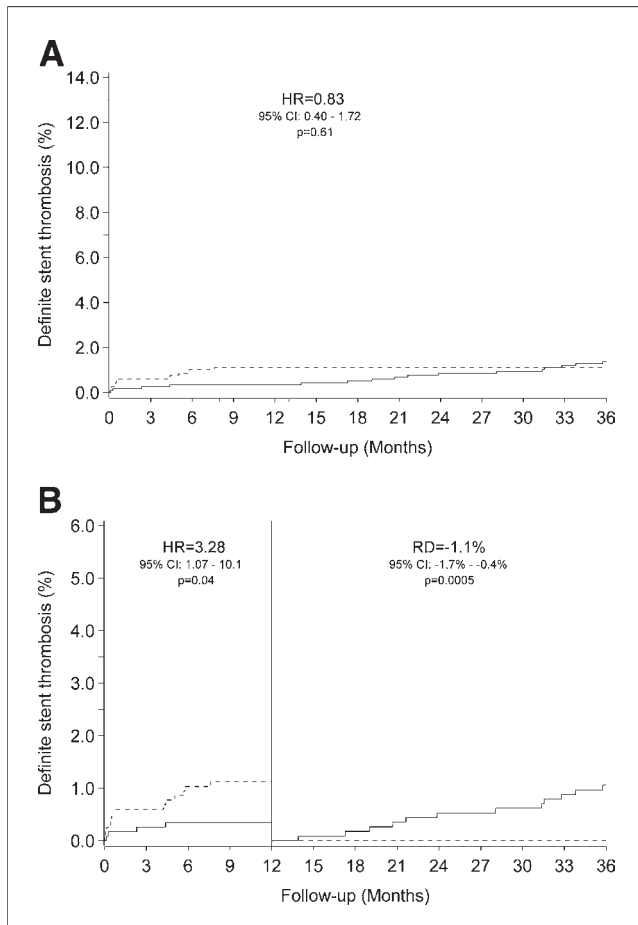


Figure 4. Definite ST in the SORT OUT III Trial

Event rates of definite stent thrombosis (ST) in the zotarolimus-eluting (ZES) (dotted line) versus sirolimus-eluting (SES) (straight line) stent groups. (A) Event rates during the 3-year follow-up. (B) A landmark analysis of events occurring after year 1. The ZES was associated with a higher rate of stent thrombosis at 1-year follow-up, whereas very late stent thrombosis events did not occur. By contrast, the SES had a steadily growing event rate of very late stent thrombosis, averaging approximately 0.5% per year. RD = risk difference; other abbreviations as in Figure 1.

the SES and the everolimus-eluting stent groups between 12 and 24 months' follow-up (16). At 2-year follow-up in the RESOLUTE All-Corers trial, which compared the Resolute ZES versus an everolimus-eluting DES, 2 (0.2%) and 3 (0.3%) definite very late ST events were reported for the 2 DES types, respectively (17). However, a noninferiority trial comparing SES with a biolimus-eluting stent using a biodegradable polymer in "all-comer" patients found a reduced risk of definite ST in patients treated with the biodegradable polymer stent due to a 5-fold reduced risk of very late ST (18). Thus, it seems that long-term follow-up, far beyond the traditional 1-year primary endpoint, in large-scale clinical trials including all-comer patients are needed to predict the long-term outcome, especially with regard to ST.

TLR reduction was the main reason for the inferiority of ZES compared with SES. The absolute TLR reduction was

4.0% at 1-year follow-up and 2.9% at 3-year follow-up. From a clinical point of view, TLR is caused either by ST or in-stent restenosis. Angiographic data have indicated a potential development of in-stent restenosis between 6 and 24 months with use of SES (8). However, the primary explanation for the reduced difference between ZES and SES at 3-year follow-up in our study was the increased risk of very late stent restenosis in the SES group, whereas symptom-driven detection of in-stent restenosis differed only numerically, but not significantly, between the 2 groups beyond 12 months.

Study limitations. It is a limitation of this study that data regarding duration of dual antiplatelet therapy was not collected. However, since November 2002, all patients treated with coronary stent implantation in Denmark have been recommended to receive 12 months dual antiplatelet therapy, and all our patients in this study received reimbursement of costs related to clopidogrel treatment for 12 months. We therefore find it unlikely that the duration of dual antiplatelet therapy differed between the groups.

Conclusions

The SES remained superior to ZES with regard to MACE, TVR, and TLR at 36-month follow-up. The SES, however, was associated with an increased risk of very late ST. Our results highlight the importance of long-term follow-up in randomized studies evaluating new DES.

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Reprint requests and correspondence: Dr. Michael Maeng, Department of Cardiology, Aarhus University Hospital, Skejby, Brendstrupgaardsvej 100, Aarhus N, Denmark. E-mail: michael.maeng@ki.au.dk.

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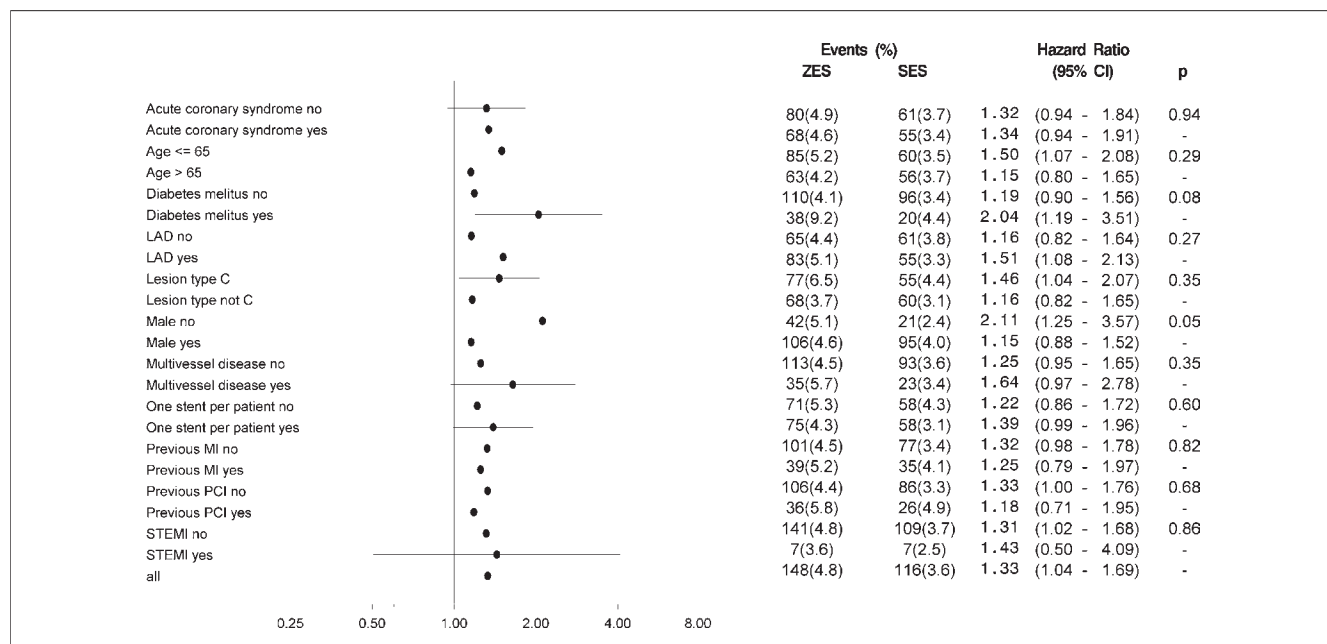


Figure 5. Pre-Specified Subgroup Analysis in the SORT OUT III Trial

The figure illustrates the hazard ratios for the primary composite endpoint of cardiac death, myocardial infarction, and target vessel revascularization at 36-month follow-up, according to baseline characteristics, among all 2,332 patients randomly assigned to percutaneous coronary intervention (PCI) with a zotarolimus-eluting (ZES) versus a sirolimus-eluting (SES) stent. The p values represent the probability for interaction among the subgroup levels. LAD = left anterior descending artery; MI = myocardial infarction; STEMI = ST-segment elevation myocardial infarction; other abbreviations as in Figure 1.

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Key Words: coronary ■ drug-eluting ■ randomized clinical trial ■ sirolimus ■ stent ■ zotarolimus.

APPENDIX

For a list of the Contributors, Coordinating Center, Independent Events Committee, and the Data Monitoring Center, please see the online version of this paper.