Efficacy and safety of zotarolimus-eluting and sirolimus-eluting coronary stents in routine clinical care (SORT OUT III): a randomised controlled superiority trial

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Summary

Background In low-risk patients, the zotarolimus-eluting stent has been shown to reduce rates of restenosis without increasing the risk of stent thrombosis. We compared the efficacy and safety of the zotarolimus-eluting stent versus the sirolimus-eluting stent in patients with coronary artery disease who were receiving routine clinical care with no direct follow-up.

Methods We did a single-blind, all-comer superiority trial in adult patients with chronic stable coronary artery disease or acute coronary syndromes, and at least one target lesion. Patients were treated at one of five percutaneous coronary intervention centres between January, 2006, and August, 2007. Computer-generated block randomisation and a telephone allocation service were used to randomly assign patients to receive the zotarolimus-eluting or the sirolimus-eluting stent. Data for follow-up were obtained from national Danish administrative and health-care registries. The primary endpoint was a composite of major adverse cardiac events within 9 months: cardiac death, myocardial infarction, and target vessel revascularisation. Intention-to-treat analyses were done at 9-month and 18-month follow-up. This trial is registered with ClinicalTrials.gov, number NCT00660478.

Findings 1162 patients (1619 lesions) were assigned to receive the zotarolimus-eluting stent, and 1170 patients (1611 lesions) to receive the sirolimus-eluting stent. 67 patients (72 lesions) had stent failure, and six patients were lost to follow-up. All randomly assigned patients were included in analyses at 9-month follow-up; 2200 patients (94%) had completed 18-month follow-up by the time of our assessment. At 9 months, the primary endpoint had occurred in a higher proportion of patients treated with the zotarolimus-eluting stent than in those treated with the sirolimus-eluting stent (72 [6%] vs 34 [3%]; HR 2:15, 95% CI 1:43–3:23; p=0.0002). At 18-month follow-up, this difference was sustained (113 [10%] vs 53 [5%]; 2:19, 1.58–3.04; p<0.0001). For patients receiving the zotarolimus-eluting stent and those receiving the sirolimus-eluting stent, all-cause mortality was similar at 9-month follow-up (25 [2%] vs 18 [2%]; 1:40, 0:76–2:56; p=0.035), but was significantly different at 18-month follow-up (51 [4%] vs 32 [3%]; 1:61, 1:03–2:50; p=0.035).

Interpretation The sirolimus-eluting stent is superior to the zotarolimus-eluting stent for patients receiving routine clinical care.

Funding Cordis and Medtronic.

Introduction

Introduction of sirolimus and paclitaxel drug-eluting stents more than halved the need for new revascularisations after implantation of coronary artery stents.1,4 However, the safety of these first-generation drug-eluting stents was questioned after reports of their association with an increased risk of late and very late stent thrombosis.5 This risk might be explained by insufficient healing of the vessel wall caused by delayed neointimal stent coverage, and by late-acquired incomplete stent apposition associated with inflammation and late remodelling, leaving naked stent struts as a nidus for thrombotic events.6–10 Whether adverse vessel wall reactions to implantation of drug-eluting stents are related to the type of drug eluted from the stent or to the polymer coating of the stent is unknown.6–10 Such safety concerns led to recommendations for long-term dual antiplatelet therapy after implantation of drug-eluting stents.11 In this context, the second-generation zotarolimus-eluting stent seemed to be a safer alternative to sirolimus-eluting and paclitaxel-eluting stents. The zotarolimus-eluting stent induced uniform and complete neointimal coverage of the stent struts, and was associated with a reduced occurrence of late-acquired incomplete stent apposition.12,13 Also, the polymer phosphorhyloline coating used for drug elution from the zotarolimus-eluting stent is a synthetic copy of the predominant phospholipid in the outer membrane of red blood cells and seemed to be a safer, non-inflammatory alternative to the polymers used for sirolimus-eluting and paclitaxel-eluting stents.12
Findings from the first randomised trials generated optimism regarding the clinical effectiveness of the zotarolimus-eluting stent. However, these trials were restricted to patients with a single artery stenosis, excluded complex lesions such as bifurcation lesions and chronic total occlusions, were limited by angiographic inclusion criteria, excluded patients with recent myocardial infarction, and were powered to assess only angiographic late lumen loss or target vessel failure. We therefore aimed to compare the efficacy and safety (defined by cardiac death, myocardial infarction, and stent thrombosis) of the zotarolimus-eluting stent versus the extensively used and validated sirolimus-eluting stent in a routine clinical setting with no direct follow-up.

Methods

Patients and study design

Within the framework of the Danish Organisation for Randomised Trials with Clinical Outcome (SORT OUT), we undertook a multicentre, single-blind, randomised, all-comer trial between January, 2006, and August, 2007, in five Danish high-volume percutaneous coronary intervention centres. We used data from Danish healthcare registries to compare patients who were eligible for randomisation but were and were not randomly allocated to treatment during the study period to allow us to report the trial according to the requirements of the CONSORT statement.

Eligible patients were aged 18 years or older, had chronic stable coronary artery disease or acute coronary syndromes, and had at least one target lesion, defined as a lesion needing treatment with a drug-eluting stent. If more than one lesion needed treatment, the allocated study stent had to be used in all lesions. No upper limits were imposed for the number of treated lesions, treated vessels, or lesion length. Patients were excluded if they could not provide informed consent; had a life expectancy of less than 1 year; had an allergy to aspirin, clopidogrel, ticlopidine, sirolimus, or zotarolimus; or were participants in another randomised trial.

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

Randomisation and masking

Patients were enrolled by the investigators, and were randomly allocated to treatment groups after diagnostic coronary angiography and before percutaneous coronary intervention. Block randomisation according to centre was used to assign patients in a 1:1 ratio to receive the zotarolimus-eluting stent (Endeavor, Medtronic, Santa Rosa, CA, USA) or the sirolimus-eluting stent (Cypher Select or Cypher Select Plus, Cordis, Johnson & Johnson, Warren, NJ, USA). The allocation sequence was computer-generated by an independent organisation, and stratified by sex and the presence of diabetes. Allocation was concealed and patients were assigned to treatment by use of an automated telephone allocation service. All individuals...
analysing data and all patients were masked to treatment assignment, but medical personnel were unmasked.

Procedures

Stents were implanted according to standard techniques. Stent implantation without balloon dilation before implantation (direct stenting) was allowed. Full lesion coverage with no geographical miss was attempted by implantation of one or more stents. We prohibited use of drug-eluting stents that had not been specified by the random allocation and bare-metal stents, unless the study stent could not be implanted. In such cases, other stents or balloon angioplasty without stent implantation could be used. Before implantation, patients were treated with at least 75 mg aspirin, a 300–600 mg loading dose of clopidogrel, and unfractionated heparin (5000 IU or 70–100 IU/kg). Glycoprotein IIb/IIIa inhibitors were used at the discretion of the operator. Use of the assigned study stent was encouraged in the event of additional revascularisation procedures. Dual antiplatelet regimens were lifelong 75 mg aspirin daily and 75 mg clopidogrel, and unfractionated heparin (5000 IU or 70–100 IU/kg). Glycoprotein IIb/IIIa loading dose of clopidogrel, and unfractionated heparin could be used. Before implantation, patients were treated with at least 75 mg aspirin, a 300–600 mg loading dose of clopidogrel, and unfractionated heparin (5000 IU or 70–100 IU/kg). Glycoprotein IIb/IIIa inhibitors were used at the discretion of the operator. Use of the assigned study stent was encouraged in the event of additional revascularisation procedures. Dual antiplatelet regimens were lifelong 75 mg aspirin daily and 75 mg clopidogrel daily for 1 year, in accordance with Danish guidelines.4,20

The prespecified primary endpoint was a composite of major adverse cardiac events within 9 months: cardiac death, myocardial infarction, and target vessel revascularisation. Secondary endpoints were assessed at 9 months: all-cause mortality, cardiac death, myocardial infarction, target vessel revascularisation, target lesion revascularisation, symptom-driven restenosis, and angiographically verified (definite) stent thrombosis. We also recorded 30-day follow-up of all-cause mortality, cardiac death, myocardial infarction, target vessel revascularisation, and target lesion revascularisation; and 18-month follow-up of primary and secondary endpoints. In accordance with the Academic Research Consortium definition of definite stent thrombosis, we also recorded stent thrombosis events at 30-day and 12-month follow-up to report late (30 days–1 year) and very late (>1 year) stent thrombosis.21

Independent study monitors masked to treatment assignment reviewed all repeat coronary interventions (balloon angioplasty, stent implantation, and coronary artery bypass grafting). Reinterventions were characterised as target vessel revascularisation and non-target vessel revascularisation. All target lesion revascularisations were identified and classified as caused by in-stent restenosis or stent thrombosis, based on review of angiograms and patient files. The indication for repeat intervention was identified and classified as ST-segment elevation myocardial infarction (STEMI), non-STEMI, unstable angina pectoris, or stable angina pectoris. An independent endpoint committee masked to treatment assignment reviewed all events and classified all myocardial infarctions and deaths.

Definitions

Cardiac death was defined as any death due to a cardiac cause, death related to percutaneous coronary intervention, unwitnessed death, and death from unknown causes.20 We defined myocardial infarction in accordance with the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction,20 but we excluded procedure-related myocardial infarction as an endpoint. Target vessel revascularisation was defined as any repeat percutaneous coronary intervention or surgical bypass of any segment within the entire major coronary vessel that was proximal and distal to a
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personal identifier permits an individual’s information registration number assigned at birth. This unique
In Denmark, all citizens have a personal civil intervention centres, and the Danish Heart Register).

heart registries in the five percutaneous coronary interventions. Data for mortality and coronary bypass surgeries done in Denmark. Information from the Danish Heart Register and the National Patient Registry has been validated.23

We defined new myocardial infarctions as readmission to hospital for myocardial infarction after discharge from the index percutaneous coronary intervention,26 based on admissions and readmissions for myocardial infarction (ICD-10 codes I21–I21.9) identified from the National Patient Registry.27 We also checked discharge letters from hospital admissions during the study period to assess if myocardial infarction was suspected in relation to the hospital admission. We obtained laboratory data for biomarkers (troponin and phosphocreatine kinase MB) and electrocardiograms from all relevant hospital admissions, and the diagnosis of myocardial infarction was confirmed or rejected by an independent endpoint committee which was masked to treatment allocation. Last, we checked the clinical indication for repeated coronary interventions. Hospital records for relevant readmissions to hospital were obtained and used for endpoint validation by the endpoint committee. We used original death certificates obtained from the National Registry of Causes of Deaths28 to classify deaths according to underlying cause.

Clinical event detection
We used clinically driven event detection to avoid study-induced reinterventions. Data for mortality (cardiac and non-cardiac), hospital admission, coronary angiography, repeat percutaneous coronary intervention, and coronary bypass surgery were obtained for all randomly allocated patients from national Danish administrative and health-care registries (Danish Civil Registration System, National Registry of Causes of Death, National Patient Registry, the local heart registries in the five percutaneous coronary intervention centres, and the Danish Heart Register). In Denmark, all citizens have a personal civil registration number assigned at birth. This unique personal identifier permits an individual’s information to be linked across registries and databases.23,24 The Danish Civil Registration System is updated daily and has maintained records of date of birth, death, and residence for all Danish citizens since 1968.23 The National Patient Registry maintains information for all admissions and outpatient visits to Danish hospitals. For every hospital admission, the Registry records dates of admission and discharge, surgical procedures, and up to 20 diagnoses classified according to the International Classification of Diseases, 8th revision (ICD-8) until the end of 1993, and 10th revision (ICD-10) thereafter. The Danish Heart Register and the local heart registries in the five intervention centres record patient-specific and procedure-specific information for coronary interventions and coronary bypass surgeries done in Denmark.

<table>
<thead>
<tr>
<th>Lesion location</th>
<th>Zotarolimus-eluting stent (n=1619)</th>
<th>Sirolimus-eluting stent (n=1619)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated vessels per patient</td>
<td>1.2 (0.5)</td>
<td>1.2 (0.5)</td>
</tr>
<tr>
<td>Stents per patient</td>
<td>1.7 (1.1)</td>
<td>1.7 (1.0)</td>
</tr>
<tr>
<td>Location of target lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left main artery</td>
<td>26 (2%)</td>
<td>29 (2%)</td>
</tr>
<tr>
<td>Left anterior descending artery</td>
<td>685 (42%)</td>
<td>650 (40%)</td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>395 (24%)</td>
<td>443 (27%)</td>
</tr>
<tr>
<td>Right artery</td>
<td>501 (31%)</td>
<td>479 (30%)</td>
</tr>
<tr>
<td>Saphenous vein graft</td>
<td>12 (1%)</td>
<td>10 (1%)</td>
</tr>
<tr>
<td>Lesion type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type A</td>
<td>316 (20%)</td>
<td>278 (17%)</td>
</tr>
<tr>
<td>Type B</td>
<td>710 (44%)</td>
<td>752 (47%)</td>
</tr>
<tr>
<td>Type C</td>
<td>570 (35%)</td>
<td>545 (34%)</td>
</tr>
<tr>
<td>Not classified</td>
<td>23 (1%)</td>
<td>36 (2%)</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated vessels per lesion</td>
<td>1.2 (0.6)</td>
<td>1.2 (0.6)</td>
</tr>
<tr>
<td>Treated vessels per lesion</td>
<td>12 (6.4)</td>
<td>12 (6.4)</td>
</tr>
<tr>
<td>Treated vessels per lesion</td>
<td>7 (3.4)</td>
<td>7 (3.4)</td>
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<tr>
<td>Stent length (mm)</td>
<td>180 (12.0–24.0)</td>
<td>180 (13.0–23.0)</td>
</tr>
<tr>
<td>Stent diameter (mm)</td>
<td>3.2 (0.5)</td>
<td>3.2 (0.5)</td>
</tr>
<tr>
<td>Stent delivery failure</td>
<td>30 (2%)</td>
<td>42 (3%)</td>
</tr>
<tr>
<td>Length of procedure (min)</td>
<td>260 (151–401)</td>
<td>260 (161–410)</td>
</tr>
<tr>
<td>Use of glycoprotein IIb/IIIa inhibitors*</td>
<td>188 (16%)</td>
<td>221 (19%)</td>
</tr>
</tbody>
</table>

Data are mean (SD), number of lesions (%), or median (IQR), unless otherwise indicated. *Data are for number of patients: 1162 receiving the zotarolimus-eluting stent and 1170 receiving the sirolimus-eluting stent.

Table 3: Baseline lesion and procedural characteristics

Clinical event detection
We used clinically driven event detection to avoid study-induced reinterventions. Data for mortality (cardiac and non-cardiac), hospital admission, coronary angiography, repeat percutaneous coronary intervention, and coronary bypass surgery were obtained for all randomly allocated patients from national Danish administrative and health-care registries (Danish Civil Registration System, National Registry of Causes of Death, National Patient Registry, the local heart registries in the five percutaneous coronary intervention centres, and the Danish Heart Register). In Denmark, all citizens have a personal civil registration number assigned at birth. This unique personal identifier permits an individual’s information to be linked across registries and databases.23,24 The Danish Civil Registration System is updated daily and has maintained records of date of birth, death, and residence for all Danish citizens since 1968.23 The National Patient Registry maintains information for all admissions and outpatient visits to Danish hospitals. For every hospital admission, the Registry records dates of admission and discharge, surgical procedures, and up to 20 diagnoses classified according to the International Classification of Diseases, 8th revision (ICD-8) until the end of 1993, and 10th revision (ICD-10) thereafter. The Danish Heart Register and the local heart registries in the five intervention centres record patient-specific and procedure-specific information for coronary interventions and coronary bypass surgeries done in Denmark. Information from the Danish Heart Register and the National Patient Registry has been validated.23

We defined new myocardial infarctions as readmission to hospital for myocardial infarction after discharge from the index percutaneous coronary intervention,26 based on admissions and readmissions for myocardial infarction (ICD-10 codes I21–I21.9) identified from the National Patient Registry.27 We also checked discharge letters from hospital admissions during the study period to assess if myocardial infarction was suspected in relation to the hospital admission. We obtained laboratory data for biomarkers (troponin and phosphocreatine kinase MB) and electrocardiograms from all relevant hospital admissions, and the diagnosis of myocardial infarction was confirmed or rejected by an independent endpoint committee which was masked to treatment allocation. Last, we checked the clinical indication for repeated coronary interventions. Hospital records for relevant readmissions to hospital were obtained and used for endpoint validation by the endpoint committee. We used original death certificates obtained from the National Registry of Causes of Deaths28 to classify deaths according to underlying cause.

Statistical analysis
We powered the study to test for superiority between the study groups with the primary endpoint at 9 months. Major adverse cardiac events at 9 months were estimated in 6.8% of patients receiving the sirolimus-eluting stent and 10.3% of those receiving the zotarolimus-eluting stent. With a 0.05 risk of type 1 errors and a 0.2 risk of type 2 errors, at least 1001 patients were needed in each study group to detect a significant difference. Distributions of continuous variables were compared between the study groups with the two-sample t test (or Cochran t test for cases of unequal variance) or the Mann-Whitney U test, dependent on whether the data followed a normal distribution. Distributions of categorical variables were compared with the χ² test.
We recorded and compared endpoint events occurring during the follow-up period between the study groups. Follow-up began on the date of the index percutaneous coronary intervention procedure. In analyses of every outcome, follow-up continued until the date of an endpoint event, death, emigration, or until 18 months after implantation, whichever came first. Cumulative event curves were constructed based on the cumulative occurrence of endpoint events, and accounted for the competing risk of death. Differences between groups were estimated with the Cox proportional hazards model. Patients treated with the sirolimus-eluting stent were used as the reference for all analyses. All analyses were by intention to treat. We calculated hazard ratios (HRs) for major adverse cardiac events at 9-month follow-up for prespecified patient subgroups (baseline demographic and clinical characteristics). We judged p values of less than 0·05 to be significant, and we used SAS software (version 9.2) for all analyses.

This trial is registered with ClinicalTrials.gov, number NCT00660478.

**Role of the funding source**

Cordis and Medtronic had no role in the study design, data collection, data analysis, or data interpretation; had no access to the clinical trial database; and did not have the opportunity to review or comment on the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

**Results**

Figure 1 shows the trial profile. Of 9221 patients who were screened, 3545 (38%) were excluded, 3344 (36%) were eligible for randomisation but were excluded, and 2332 (25%) with 3230 lesions were randomly assigned to receive zotarolimus-eluting or sirolimus-eluting stents. Overall, six patients were lost to follow-up because they emigrated. The randomly allocated stent was implanted in 1589 (98%) lesions allocated to the zotarolimus-eluting stent and 1569 (97%) lesions allocated to sirolimus-eluting stent (p=0·15). All patients were included in analyses at 30-day and 9-month follow-up. 18-month follow-up was completed for 2200 (94%) patients; the remaining 132 patients had not achieved 18-month follow-up at the time of our assessment.

We recorded baseline characteristics for all patients who were eligible for randomisation irrespective of whether they were randomly allocated to treatment (table 1). Age, sex, and diabetes status did not differ significantly between these patient groups. Patients who were excluded before randomisation had a higher prevalence of STEMI, fewer target lesions, fewer treated vessels, and higher mortality at 30 days, than did patients who were randomly allocated to treatment.

Baseline demographic and clinical characteristics were well balanced between the study groups (table 2). However, more patients receiving the zotarolimus-eluting stent had a history of previous percutaneous coronary intervention than did those receiving the sirolimus-eluting stent (table 2). A high proportion of patients in both groups had acute coronary syndromes, multivessel disease, and complex lesions (tables 2 and 3).

At 30-day follow-up, we recorded no differences between the study groups in all-cause mortality, cardiac death, myocardial infarction, target vessel revascularisation, or target lesion revascularisation (table 4 and figure 2). The 9-month composite primary endpoint occurred in a significantly higher proportion of patients receiving the zotarolimus-eluting stent than in those receiving the sirolimus-eluting stent (table 4 and figure 2). This difference was mainly attributable to a significant disparity in both myocardial infarction and target vessel revascularisation between the study groups. Subgroup analysis of the primary endpoint showed that findings were consistent across age-groups, sexes, diabetes status, and presence or absence of acute coronary syndromes, lesions in the left anterior descending artery, and complex lesions (figure 3). At 18-month follow-up, the significant difference in major adverse cardiac events between the study groups was caused by a sustained increased risk...
of target vessel revascularisation and myocardial infarction (table 4 and figure 2). The secondary endpoints of all-cause mortality and target lesion revascularisation were also in favour of the sirolimus-eluting stent at 18 months (table 4).

Definite stent thrombosis occurred in a higher proportion of patients receiving the zotarolimus-eluting stent than in those receiving the sirolimus-eluting stent at 9-month and 12-month follow-up (table 5 and figure 4). After 12 months, no further events of very late definite stent thrombosis occurred in patients receiving the zotarolimus-eluting stent whereas two events occurred in those receiving the sirolimus-eluting stent. Thus, at 18-month follow-up, the number of events of stent thrombosis was not significantly different between the study groups (table 5). Definite stent thrombosis caused 14 of the 22 myocardial infarctions that were recorded in the first 9 months (11 events with the zotarolimus-eluting stent vs three with the sirolimus-eluting stent), and two of the 13 myocardial infarctions that occurred during 9–18 months (zero vs two events).

Occurrence of symptom-driven restenosis was significantly higher in patients receiving the zotarolimus-eluting stent than in those receiving the sirolimus-eluting stent at 9-month and 18-month follow-up (figure 4 and table 5).

Discussion
We have shown that in routine clinical care, patients receiving the zotarolimus-eluting stent had significantly more major adverse cardiac events in 9 months than did those treated with the sirolimus-eluting stent. During 9–18 months, the sirolimus-eluting stent remained superior to the zotarolimus-eluting stent for occurrence of major adverse cardiac events, myocardial infarction, and target vessel revascularisation. Deliverability was similar for both stents.

By contrast with previously published studies of zotarolimus-eluting stents,15–17 our study included complex lesions (eg, bifurcations, ostial lesions, left main lesions, long lesions, and chronic total occlusions) and patients with acute coronary syndromes, including...
decrease in clinically driven efficacy in routine clinical care. Myocardial infarction and stent thrombosis, two effects of the zotarolimus-eluting stent 12,13,16 results in a cause of target lesion revascularisation. Thus, findings from our study show that the reduced antiproliferative effect, 12,13,16 combined with inclusion of patients with a higher risk of restenosis in our study than in previous studies. 15-27 Symptom-driven restenosis was quantitatively the most common cause of target lesion revascularisation. Thus, findings from our study show that the reduced antiproliferative effect of the zotarolimus-eluting stent 12,13,16 results in a decrease in clinically driven efficacy in routine clinical care. Myocardial infarction and stent thrombosis, two very important outcome measures, also favoured the sirolimus-eluting stent above the zotarolimus-eluting stent at 9-month follow-up. From reports of uniform neointima distribution with zotarolimus-eluting stents, 12,13 we had expected that use of these stents would reduce the risk of stent thrombosis and myocardial

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**Figure 3:** Prespecified subgroup analysis for the primary endpoint at 9-month follow-up

Data are for number of patients. Major adverse cardiac events are a composite of cardiac death, myocardial infarction, and target vessel revascularisation. STEMI=ST-segment elevation myocardial infarction. *Data are missing for three patients receiving the zotarolimus-eluting stent, and one patient receiving the sirolimus-eluting stent. †Data are missing for 25 patients receiving the zotarolimus-eluting stent, and 30 patients receiving the sirolimus-eluting stent. ‡Data are missing for 49 patients receiving the zotarolimus-eluting stent, and 52 patients receiving the sirolimus-eluting stent.
infarction. The findings from our study could differ from those of smaller previous studies because we studied more complex patient and lesion characteristics, and we did not include periprocedural myocardial infarction in our endpoint definition.

The disparities that we recorded between the study stents could be caused by different kinetics of drug release from the polymers used for drug elution. In zotarolimus-eluting stents, the phosphorylcholine polymer releases zotarolimus within the first week after implantation, whereas the sirolimus-eluting stent releases sirolimus during a 3-month period. The release kinetics of the drug from the stent could affect healing of the plaque or vessel wall, and we speculate that the high initial zotarolimus concentration impairs healing of the plaque, increases the risk of exposure of plaque material to the blood stream, and raises the risk of stent thrombosis at 9-month follow-up. Our study was neither designed nor powered to assess the long-term risk of very late (>1 year) definite stent thrombosis, and we await results from the PROTECT study to resolve our speculations.

Most patients were followed up for 18 months, which went beyond the recommended 12-month duration of dual antiplatelet treatment. 18-month follow-up showed that the sirolimus-eluting stent was superior to the zotarolimus-eluting stent in the long term.

Two small studies of angiographic outcomes after implantation of zotarolimus-eluting versus sirolimus-eluting stents both recorded increased late lumen loss with the zotarolimus-eluting stent. Although the results are not yet published, the only previous large-scale study of zotarolimus-eluting versus sirolimus-eluting stents was undertaken in Korea, and confirmed our finding that the zotarolimus-eluting stent had lower efficacy. In the Korean setting, stent thrombosis, myocardial infarction, and death did not differ significantly between the study groups, although four stent thromboses occurred in patients receiving the zotarolimus-eluting stent and none in those receiving the sirolimus-eluting stent. The Korean study relied on routine angiographic follow-up and analysed three groups of patients receiving drug-eluting stents (sirolimus, paclitaxel, or zotarolimus; 800 patients per group), but our study used two larger comparison groups and patients received only clinically driven angiography during follow-up. In the ENDEAVOR IV trial, the zotarolimus-eluting stent was compared with the paclitaxel-eluting stent in patients with a single coronary artery lesion with a reference diameter of 2.5–3.5 mm and a lesion length of 27 mm or less; complex lesions, such as ostial, bifurcation, tortuous, or thrombus-containing lesions, were excluded. Event rates were similar for the two stents. Findings from ENDEAVOR IV and our study could differ because we used the sirolimus-eluting stent as a control, which might be a better drug-eluting stent than is the paclitaxel-eluting stent, although not all studies agree on this. Furthermore, we included patients receiving routine clinical care who had lesions with increased risk of adverse events.

In clinical studies, primary endpoint definition and method of event detection might affect event frequency. For example, studies with mandated angiographic follow-up have increased occurrence of repeat revascularisation procedures. Furthermore, study-related clinical follow-up during outpatient visits or telephone contacts leads to registration of events undetected in everyday clinical practice. The SORT OUT II and III studies relied on registry-based event detection, with no study-related angiographic or clinical follow-up. Care of all patients was in accordance with normal clinical practice—ie, clinical follow-up at an outpatient visit at the referring hospital after 1–3 months.

### Figure 4: Time to event curves for definite stent thrombosis (A) and symptom-driven restenosis (B)

Vertical dashed lines show the 9-month endpoint assessment.
We believe that registry-based event detection, combined with a randomised trial design in an all-comer population with few exclusion criteria, allowed us to assess the efficacy of different percutaneous coronary intervention treatments in a context that was indicative of everyday clinical practice during the study period. Our registry-based detection of myocardial infarction might, however, underestimate occurrence of this endpoint compared with active follow-up, but the effect will probably be balanced between the study groups because of randomisation.

Our findings from the SORT OUT III trial show fewer events than were reported in the SORT OUT II trial. This difference can be explained by several factors. First, and most importantly, procedure-related myocardial infarction was part of the primary endpoint in the SORT OUT II trial, but not in the SORT OUT III trial. Second, in SORT OUT II, 17% of patients had STEMI as compared with 7% in SORT OUT III. Last, the intense debate regarding drug-eluting stents and the risk of late stent thrombosis that started in 2006—ie, during the inclusion of patients in the present study—might have affected our treatment strategy and focused our attention on the importance of 12-month dual antiplatelet therapy.

Contributors
The steering committee designed the study, which subsequently was accepted by all authors. MM, SPJ, and HTS were responsible for data management, and for design and implementation of the statistical analysis. All other authors enrolled patients and contributed to data collection. MM, LT, and JFL contributed to design of the statistical analysis and the interpretation of results. MM, LT, and JFL drafted the report, which was subsequently reviewed by all authors. All authors have seen the final submitted report and agree with its contents.

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Conflicts of interest
MMae has received speaking honoraria from Cordis, consulting fees from Medtronic, and travel grants from both companies. LOJ and AK have received speaking honoraria from Cordis, HHT has received honoraria from Medtronic (CEC member), and travel grants from Cordis and Medtronic; and his wife is a Cordis employee. EHC has received speaking honoraria and a travel grant from Cordis. HEB has received a travel grant from Medtronic. JR has received travel grants from Cordis and Medtronic. LT has received unrestricted research grants to his institution from Cordis, Medtronic, Boston Scientific, Abbott Cardiovascular; and Terumo; and travel grants from Cordis, Medtronic, and Terumo. JFL has received speaking honoraria from Cordis, Medtronic, AstraZeneca, and Abbott; and travel grants from Cordis, Medtronic, and Abbott. All other authors declare that they have no conflict of interest.

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