Differential clinical outcomes after 1 year versus 5 years in a randomised comparison of zotarolimus-eluting and sirolimus-eluting coronary stents (the SORT OUT III study): a multicentre, open-label, randomised superiority trial

Michael Maeng, Hans Henrik Tilsted, Lisette Okkels Jensen, Lars Romer Krusell, Anne Kaltoft, Henning Kelbæk, Anton B Villadsen, Jan Ravkilde, Knud Nørregaard Hansen, Evald Høj Christiansen, Jens Aarøe, Jan Skov Jensen, Steen Dalby Kristensen, Hans Erik Bøtker, Leif Thuesen, Morten Madsen, Per Thayssen, Henrik Toft Sørensen, Jens Flensted Lassen

Summary

Background In head-to-head comparisons of coronary drug-eluting stents, the primary endpoint is traditionally assessed after 9–12 months. However, the optimum timepoint for this assessment remains unclear. In this study, we assessed clinical outcomes at up to 5 years' follow-up in patients who received two different types of drug-eluting stents.

Methods We undertook this multicentre, open-label, randomised superiority trial at five percutaneous coronary intervention centres in Denmark. We randomly allocated 2332 eligible adult patients (≥18 years of age) with an indication for drug-eluting stent implantation to the zotarolimus-eluting Endeavor Sprint stent (Medtronic, Santa Rosa, CA, USA) or the sirolimus-eluting Cypher Select Plus stent (Cordis, Johnson & Johnson, Warren, NJ, USA). Randomisation of participants was achieved by computer-generated block randomisation and a telephone allocation service. The primary endpoint of the SORT OUT III study was a composite of major adverse cardiac events—cardiac death, myocardial infarction, and target vessel revascularisation—at 9 months' follow-up. In this study, endpoints included the occurrence of major adverse cardiac events and definite stent thrombosis at follow-up times of up to 5 years. Analysis was by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT00660478.

Findings We randomly allocated 1162 patients to receive the zotarolimus-eluting stent and 1170 to the sirolimus-eluting stent. At 5-year follow-up, rates of major adverse cardiac events were similar in patients treated with both types of stents (zotarolimus-eluting stents 197/1162 [17·0%] *vs* sirolimus-eluting stents 182/1170 [15·6%]; odds ratio [OR] 1·10, 95% CI 0·88–1·37; p=0·40). This finding was indicative of the directly contrasting results for rates of major adverse cardiac events at 1-year follow up (zotarolimus 93/1162 [8·0%] *vs* sirolimus 46/1170 [3·9%]; OR 2·13, 95% CI 1·48–3·07; p<0·0001) compared with those at follow-up between 1 and 5 years (104 [9·0%] *vs* 136 [11·6%]; OR 0·78, 95% CI 0·59–1·02; p=0·071). At 1-year follow-up, definite stent thrombosis was more frequent after implantation of the zotarolimus-eluting stent (13/1162 [1·1%]) than the sirolimus-eluting stent (4/1170 [0·3%]; OR 3·34, 95% CI 1·08–10·3; p=0·036), whereas the opposite finding was recorded for between 1 and 5 years' follow-up (zotarolimus-eluting stent 1/1162 [0·1%] *vs* sirolimus-eluting stent 21/1170 [1·8%], OR 0·05, 95% CI 0·01–0·36; p=0·003). 26 of 88 (30%) target lesion revascularisations in the zotarolimus-eluting stent group occurred between 1 and 5 years' follow-up, whereas 54 of 70 (77%) of those in the sirolimus-eluting stent group occurred during this follow-up period.

Interpretation The superiority of sirolimus-eluting stents compared with zotarolimus-eluting stents at 1-year follow-up was lost after 5 years. The traditional 1-year primary endpoint assessment therefore might be insufficient to predict 5-year clinical outcomes in patients treated with coronary drug-eluting stent implantation.

Funding Cordis and Medtronic.

Lancet 2014; 383: 2047–56

Published Online March 14, 2014 http://dx.doi.org/10.1016/S0140-6736(14)60405-0

See Comment page 2024

Department of Cardiology, Aarhus University Hospital, Skejby, Aarhus, Denmark (M Maeng MD, L R Krusell MD, A Kaltoft MD, E H Christiansen MD, Prof S D Kristensen MD, Prof H E Bøtker MD, L Thuesen MD, J Flensted Lassen MD); **Department of Cardiology, Aarhus University Hospital, Aalborg Hospital, Aalborg, Denmark** (H H Tilsted MD, A B Villadsen MD, J Ravkilde MD, J Aarøe MD); **Department of Cardiology, Odense University Hospital, Odense, Denmark** (L O Jensen MD, K N Hansen MD, P Thayssen MD); **Department of Cardiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark** (H Kelbæk MD); **Department of Cardiology, Gentofte University Hospital, Hellerup, Denmark** (Prof J S Jensen MD); **and Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark** (M Madsen MSc, Prof H T Sørensen MD)

Correspondence to: Dr Michael Maeng, Department of Cardiology, Aarhus University Hospital, Skejby, Brendstrupgaardsvej 100, 8200 Aarhus N, Denmark **michael.maeng@ki.au.dk**

Introduction

The first commercially available drug-eluting stents for the treatment of coronary artery disease more than halved the need for new revascularisations after coronary artery stent implantation when compared with the use of bare-metal stents.[1–3] In-stent restenosis was the main limitation of percutaneous coronary intervention with bare-metal stents, and carefully undertaken studies were designed mainly to address the angiographic and clinical endpoints related to this complication.[2–5] About 5 years after the introduction of drug-eluting stents, safety concerns also arose about increased risk of stent thrombosis, myocardial infarction, and death.[6–8] These concerns led to the design of all-comer studies that were powered to address clinical endpoints in patients in routine clinical practice within predefined long-term follow-up.[9–14]

The second-generation zotarolimus-eluting Endeavor stent (Medtronic, Santa Rosa, CA, USA) was initially believed to be a safer choice than first-generation drug-eluting stents (ie, the sirolimus-eluting Cypher stent[1,5] and the paclitaxel-eluting Taxus stent[3]) because of formation of larger and more uniform neointima. However, the three largest randomised studies that compared zotarolimus-eluting stents with the first-generation sirolimus-eluting Cypher stent (Cordis, Johnson & Johnson, Warren, NJ, USA) all showed an increased risk of definite stent thrombosis in the zotarolimus-eluting stent group within the first year after implantation.[11,15,16] Additionally, studies that used the traditional primary endpoint assessment at 9 or 12 months reported that zotarolimus-eluting stents increased the risk of target lesion revascularisation.[11,15,17] Follow-up results presented for two of these trials through to 3 years indicated the possibility of opposite outcomes when results within the first year were compared with those during the following 2 years.[11,16]

In this Article, we present 5-year clinical outcomes for 2332 patients with coronary artery disease receiving routine clinical care and randomly allocated to treatment with zotarolimus-eluting stents or sirolimus-eluting stents. The study was done to describe long-term clinical performance of the study stents and to address the issue of length of follow-up in studies of drug-eluting stents.

Methods

Study design and participants

The study protocol of Danish Organization of Randomized Trials With Clinical Outcome (SORT OUT) III has previously been described in detail.[18] Briefly, SORT OUT III is a multicentre, open-label, randomised superiority trial that enrolled patients between January, 2006, and August, 2007 at five high-volume percutaneous coronary intervention centres in Denmark. Patients aged 18 years or older with an indication for drug-eluting stent implantation were eligible for inclusion. The only exclusion criteria were inability to provide informed consent; life expectancy of less than 1 year; allergy to aspirin, clopidogrel, ticlopidine, sirolimus, or zotarolimus; or participation in another randomised trial.

In accordance with Danish guidelines, dual antiplatelet therapy was recommended for all participants, including lifelong aspirin (75 mg daily) and clopidogrel 75 mg daily for 1 year.

The trial complied with the Declaration of Helsinki and was approved by the local ethics committee. All patients provided written, informed consent before enrolment.[18]

Randomisation and masking

Participants were randomly allocated to treatment groups after diagnostic coronary angiography and before percutaneous coronary intervention. Block randomisation

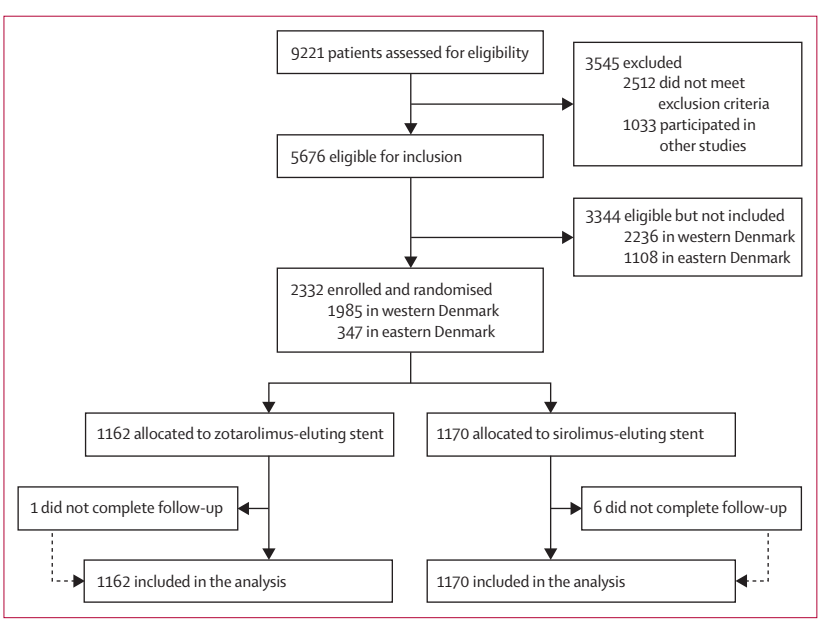

Figure 1: **Trial profile of the SORT OUT III trial**

	Randomised patients (n=1985)	Non-randomised patients (n=2236)
Age (years)	64 (11)	64 (12)
Men	1471 (74%)	1625 (73%)
Diabetes mellitus	284 (14%)	198 (9%)
Smoking history		
Active	587 (30%)	559 (25%)
Previous	763 (38%)	559 (25%)
Indication for percutaneous coronary intervention		
STEMI	170 (9%)	930 (42%)
NSTEMI or UAP	761 (38%)	626 (28%)
Stable angina	989 (50%)	624 (28%)
Other	65 (3%)	56 (3%)
Target lesions per patient		
1	1273 (64%)	1570 (70%)
2	478 (24%)	488 (22%)
≥3	227 (11%)	178 (8%)
Treated vessels per patient		
1	1462 (74%)	1801 (81%)
2	426 (21%)	381 (17%)
3	89 (5%)	53 (2%)
1-year all-cause mortality	40 (2%)	147 (7%)
5-year all-cause mortality	243 (12%)	373 (17%)

Data are mean (SD) or n (%). STEMI=ST-segment elevation myocardial infarction. NSTEMI=non-ST-segment elevation myocardial infarction. UAP=unstable angina pectoris. *Only patients from western Denmark are included here because in this 5-year analysis we could identify and compare 5-year mortality only in randomised and non-randomised patients in western Denmark, who accounted for 85% of patients in the SORT OUT III trial. We could not do this comparison for non-randomised patients in eastern Denmark.

Table 1: **Baseline, clinical, and angiographic characteristics of randomised and non-randomised patients in western Denmark***