Review of Registry and Randomised Comparisons of Zotarolimus-eluting and Sirolimus-eluting Coronary Stents in Western Denmark

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ABSTRACT

The safety and efficacy of coronary stents utilised for treatment of ischaemic heart disease have been extensively evaluated. In comparison with bare metal stents, first-generation drug-eluting stents more than halved the need for target lesion revascularisation (TLR). However, the long-term safety has been questioned as the first-generation drug-eluting stents seemed to be associated with a small, but increased, risk of (very) late stent thrombosis. The latter may be related to an inflammatory reaction caused by the polymer used for drug release control. The second-generation zotarolimus-eluting Endeavor® stent was believed to represent a safer alternative. We present an overview of our results from a large randomised trial and a large registry, both of which compared clinical outcomes with the Endeavor® and the first-generation sirolimus-eluting Cypher® stent. Both studies indicated that the Endeavor® stent had higher risks of adverse outcomes. We discuss these data in the light of the current available data from other randomised comparisons of these two drug-eluting stents.

INTRODUCTION

The introduction of the sirolimus-eluting Cypher® (Cordis, Johnson & Johnson, Warren, NJ) stent (SES) and the paclitaxel-eluting Taxus® (Boston Scientific Corp, Natick, MA) stent (PES) more than halved the need for new revascularisations after coronary artery stent implantation. [1-4] The safety of these first-generation drug-eluting stents (DES), however, was questioned following reports of their association with an increased risk of late and very late stent thrombosis (ST). [3,5] 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. [6,7] Whether adverse vessel wall reactions to implantation of DES are related to the type of drug eluted from the stent or to the polymer coating of the stent are currently unknown.

The second-generation zotarolimus-eluting Endeavor® (Medtronic, Santa Rosa, Ca) stent (ZES) was supposed to represent a safer alternative to SES and PES. The ZES induced uniform and complete neointimal coverage of the stent struts and was associated with a lower incidence of late-acquired incomplete stent apposition. [8,9] Also, the polymer phosphorylcholine (PC) drug carrier used for controlling drug elution from the ZES is a synthetic copy of the predominant phospholipid in the outer membrane of red blood cells and appeared to be a safer noninflammatory alternative to the polymers used for SES and PES. [10,11]

The present report provides a brief overview of our randomised [12] and registry [13] results with ZES and SES in western Denmark. We chose SES as the gold-standard DES based on meta-analyses, [14,15] registry data, [3,16] and randomised trials, [17,18] which have obtained better results with the SES than the PES.

The Zotarolimus-Eluting Endeavor Stent

The ZES is a thin strut (0.0036 inch = 91 µm diameter) cobalt-based alloy stent with a PC polymer and zotarolimus dose concentration of 10µg/mm stent length. [11] The PC coating is a synthetic copy of the predominant phospholipid in the outer membrane of red blood cells and has high biovascular compatibility and is considered to be non-inflammatory. [10,11] A potential limitation of the use of the PC coating for antiproliferative drug elution is the short duration of elution of the drug (within days).

The Sirolimus-Eluting Cypher Stent

The SES was the first available DES and so far no other DES has been shown to obtain better outcomes. The SES is a bare metal (0.0055 inch = 140 µm diameter) stent coated with a permanent polymer that elutes >90% of the sirolimus during the first 28 days after implantation. [19]

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The Sort Out III Trial

The Danish Organisation for Randomised Trials with Clinical Outcome (SORT OUT) III was a multicentre, single-blind, randomised, all-comer, superiority trial comparing ZES and SES in 2,332 patients.[12] The study was performed at the five university hospitals in Denmark. The study was the first study powered to assess clinical endpoints and, in contrast to previously published studies of ZES,[20-23] SORT OUT III included complex lesions (eg, bifurcations, ostial lesions, left main lesions and chronic total occlusions) and complex patients. In SORT OUT III, 7% of the patients presented with ST-segment elevation myocardial infarction, 25% had multi-vessel intervention, and 35% had complex type C lesions.

The primary endpoint was a composite of major adverse cardiac events (MACE) within nine months: cardiac death, myocardial infarction (MI) and target vessel revascularisation (TVR). Secondary endpoints included individual MACE endpoints plus all-cause mortality and definite ST. Intention-to-treat analyses were done at nine-month and 18-month follow-up, and the results are shown in *Table 1*.

The nine-month composite primary endpoint favoured the SES above the ZES mainly caused by a reduced risk of TLR, but also due to a lower incidence of myocardial infarction and ST. Most patients were followed for 18 months, which went beyond the recommended 12 month duration of antiplatelet therapy. At 18-month follow-up SES remained superior to ZES.

Table 1: Clinical Outcomes in the SORT OUT III Trial

Pro	ZES (N= 1162)	SES (N= 1170)	Hazard ratio (95% CI)	P-value
Events at 9 months*				
Composite endpoint†	72 (6.2%)	34 (2.9%)	2.15 (1.43-3.23)	0.0002
Death	25 (2.2%)	18 (1.5%)	1.40 (0.76-2.56)	0.28
Cardiac death	12 (1.0%)	6 (0.5%)	2.01 (0.76-5.36)	0.16
Myocardial infarction	18 (1.5%)	4 (0.3%)	4.55 (1.54-13.4)	0.006
Definite stent thrombosis	13 (1.1%)	4 (0.3%)	3.28 (1.07-10.1)	0.048
Target vessel revascularisation	62 (5.3%)	28 (2.4%)	2.25 (1.44-3.51)	0.0004
Target lesion revascularisation	50 (4.3%)	12 (1.0%)	4.25 (2.26-7.97)	<0.0001
Events at 18 months‡				
Composite endpoint†	113 (9.7%)	53 (4.5%)	2.19 (1.58-3.04)	<0.0001
Death	51 (4.4%)	32 (2.7%)	1.61 (1.03-2.50)	0.035
Cardiac death	18 (1.6%)	12 (1.0%)	1.51 (0.73-3.14)	0.27
Myocardial infarction	24 (2.1%)	11 (0.9%)	2.22 (1.09-4.53)	0.029
Definite stent thrombosis	13 (1.1%)	6 (0.5%)	2.19 (0.83-5.77)	0.13
Target vessel revascularisation	92 (7.9%)	39 (3.3%)	2.42 (1.67-3.52)	<0.0001
Target lesion revascularisation	71 (6.1%)	20 (1.7%)	3.66 (2.23-6.01)	<0.0001

* Number (Cumulative incidence).

† Primary endpoint = The composite of cardiac death, myocardial infarction, and clinically driven target vessel revascularisation (MACE).

‡ Number (estimated cumulative incidence).

MI; myocardial infarction.

The finding that the ZES was associated with increased frequency of TLR is probably indicative of the stent's reduced antiproliferative effect, combined with the inclusion of all-comer patients with a higher risk of restenosis than in previous studies. 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. The PC coating of the ZES releases >90% of the zotarolimus within the first few days after the implantation, whereas the SES releases >90% of sirolimus within 30 days. Beyond the documented efficacy difference with regard to neointima formation and TLR in favour of SES, we speculate that high initial zotarolimus concentration impairs endothelialisation, increases the risk of exposure of plaque material to the blood stream and raises the risk of ST at nine month follow-up.

The Comparison of the Efficacy and Safety of Zotarolimus-Eluting Stent versus Sirolimus-Eluting Stent and Paclitaxel-Eluting Stent for Coronary Lesions (ZEST) trial [24] seemed to confirm a potential increased risk of ST as the investigators found a significant increased risk of definite ST in the ZES arm compared to the SES arm (ZES 0.7%, PES 0.5%, SES 0.0%). Moreover, the ENDEAVOR IV trial, comparing ZES with the paclitaxel-eluting PES, reported 0.7% definite ST in the ZES arm versus 0.1% in the PES arm at 12-month follow-up. Although we have to await results from the PROTECT study to resolve our speculations, [25] it is noteworthy that the next-generation ZES (the Resolute™ stent) have been constructed to provide a slower release of zotarolimus, seemingly leading to improved outcomes. [26,27]

ZES Versus SES in the Western Denmark Heart Registry

SORT OUT III indicated that ZES, as compared to SES, had lesser efficacy and a potential increased risk of safety outcomes. Although the SORT OUT III had very few exclusion criteria, less than 50% of eligible patients were randomised. Since the external validity of randomised trials is limited by selection bias, it is of importance that data from randomised trials can be reproduced in observational studies. [28] We therefore used the Western Denmark Heart Registry (WDHR) to compare ZES and SES in order to see if the randomised SORT OUT III data could be extended to a large cohort of consecutive patients. The WDHR is a clinical database within the Danish health care system.

The WDHR is based on an internet-based online system with a common interface form that secures standardised data collection from the cardiac centres. The WDHR includes all adult patients referred for cardiac intervention in western Denmark. Between August 1, 2005 and October 1, 2007, we treated 6181 patients with ZES (n=2,300) or SES (n=3,881) and followed these patients for up to 27 months. [13] The main outcome parameters are given in *Table 2*. This large registry-based study confirmed the main findings in the SORT OUT III trial by showing that ZES was associated with increased mortality, TLR and a trend towards a doubled risk of definite ST. [13]

Table 2: Clinical Outcomes in the Western Denmark Heart Registry Comparison of Zotarolimus-Eluting Stents (SES) in Western Denmark

Endpoint	Period (days)	ZES		SES		Adjusted HR* (95% CI)	P
		No. of events	No./100 person-year	No. of events	No./100 person-year		
		N=2,282		N=3,840			
Death	0-823	135	6.3	159	3.3	1.35 (1.05 - 1.73)	0.018
Cardiac death	0-823	57	2.7	59	1.2	1.33 (0.89 - 2.00)	0.183
Myocardial infarction	31-823	66	3.5	108	2.5	0.99 (0.69 - 1.42)	0.964
Stent thrombosis	0-823	26	1.2	24	0.5	2.01 (0.76 - 5.34)	0.159
Target lesion revascularisation	0-823	110	5.3	91	1.9	2.16 (1.36 - 3.42)	0.001

*Analyses were adjusted for age, gender, diabetes, Charlson's comorbidity score, diabetes mellitus, indication, procedure time, no. of treated lesions, total stent length and total no. of stents.

Other Randomised Comparisons of ZES and SES

The ENDEAVOR III trial was the first study to compare the ZES versus SES. Patients with a single, de novo stenosis of 14 to 27mm length and a diameter between 2.25 and 3.5mm in a native coronary artery were included, whereas patients with low left ventricular ejection fraction (LVEF), recent MI, and higher-risk lesions, such as left main, ostial, bifurcation, tortuous, and severely calcified lesions, were excluded. [29,20] ENDEAVOR III thus included patients with low-risk lesions, and the patients were randomised 3:1 to ZES (n=323) and SES (n=113). In-stent late lumen loss was 0.60-mm in the ZES arm versus 0.15-mm in the SES arm (p<0.001), binary restenosis was increased in the ZES group (11.7%) as compared to SES group (4.3%), and there was a trend towards higher TLR rates (6.3% versus 3.5%) in the ZES group. [20]

There were no ST events in any of the patient groups at nine-month follow-up. [20] After three years follow-up, the ZES was associated with a trend towards higher rates of TVR (17.9% vs. 12.2%, p=0.23) while there were no differences in cardiac death (1 vs. 2 events) or ST (3 vs. 2 events). [29] TLR was reported in the primary publication (20) but not in the three-year publication. [29] The ZES was associated with a lower rate of MI (0.6% vs. 4.5%, p=0.005), which reportedly were non-Q-wave and occurred primarily during the index hospital stay. [29]

The Intracoronary Stenting and Antithrombotic Regimen: Test Efficacy of 3 limus-Eluting Stents (ISAR-TEST) 2 trials compared three different DES, two of which were ZES and SES. [30] The primary endpoint was binary restenosis evaluated by quantitative coronary angiography after 6-8 months. The ZES arm had 19.3% restenosis at follow-up while SES had 12%. Likewise, the secondary endpoint of TLR at 12 months also was doubled (ZES 13.6% vs. SES 7.2%). [30] The ZEST trial (24) has not yet been published but the data are available online *(assets.cardiosource.com/ZEST_Park.ppt)*. ZEST randomised a total of 2640 patients to ZES, SES or PES. ZEST included complex lesions but excluded patients with ST-segment elevation MI, left main disease, in-stent restenosis after previous DES implantation, renal failure or life expectance <1-year.

The primary endpoint was a composite of death, MI and TVR at 12-month, and occurred in 10.1% vs. 8.3% (p=0.25) in ZES and SES, respectively. Death or MI were similar in the ZES and SES arms, but TVR was significantly higher (p<0.001) in patients randomised to treatment with ZES (5.2%) than to treatment with SES (1.9%). Definite ST also was significantly increased (p=0.046) in the ZES (0.5%) vs. the SES (0%) group. ZEST-AMI [31] randomised 328 patients with ST-segment elevation MI to ZES, SES, or PES. The primary endpoint was similar to ZEST, and occurred in 11.3% and 8.2 for ZES and SES, respectively. The ZEST-AMI study was severely underpowered for assessment of clinical endpoints and no conclusions can be drawn with regard to the primary endpoint and the secondary clinical endpoints. Angiographic in-stent restenosis, a secondary endpoint, was present in 15.9% in the ZES group as compared to 1.4% in the SES group. [31]

CONCLUSION

In comparison to SES, the ZES has lesser efficacy with regard to inhibition of neointima formation; which, as a uniform finding across all studies, leads to a higher risk of TVR/TLR. The ZES stent thus seems inferior with regard to efficacy endpoints. Moreover, the currently available medium-term data indicate that the ZES may be associated with a higher risk of clinical safety outcomes (death, MI, ST) than the SES in routine clinical care patients. However, the uniform neointima formation and the better stent apposition after nine months may protect against very late ST. The adequately powered Patient Related Outcomes With Endeavor Versus Cypher Stenting Trial (PROTECT) study will probably answer this question. [25]

FUTURE PERSPECTIVE

In comparison to the ZES, the next-generation zotarolimus-eluting Resolute [26,27] stent has a slower drug elution and a lesser late lumen loss, which makes this DES look promising. The next-generation sirolimus-eluting stent, the NEVOTM stent, utilises an absorbable polymer, which may be a safer alternative to the permanent polymers used by first and second generation DES. [19] Moreover, DES without polymers are being developed and tested. [30] In the future, we will hopefully have DES that are as effective as the SES but without the rare occurrences of very late ST. There is, however, still a need for large, randomised comparisons in routine clinical patients ("all-comers") as well as large-scale well-validated long-term registry follow-up to sort out the best DES for our patients.

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