Zotarolimus-eluting versus sirolimus-eluting coronary stent implantation

The safety and efficacy of coronary stents, utilized for treatment of ischemic heart disease, have been evaluated extensively. In comparison with bare-metal stents, first-generation drug-eluting stents more than halved the need for target lesion revascularization, but long-term safety has been questioned, as the first-generation drug-eluting stents seem 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 stent, Endeavor™, was believed to represent a safer alternative. We present an overview of the currently available data comparing Endeavor with the first-generation sirolimus-eluting stent, Cypher™. We also present the limited results with the next-generation of zotarolimus- and sirolimus-eluting stents.

KEYWORDS: drug eluting ■ efficacy ■ safety ■ sirolimus ■ stent ■ zotarolimus

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The introduction of the sirolimus-eluting Cypher™ stent (Cordis, Johnson & Johnson, NJ, USA) and the paclitaxel-eluting Taxus™ stent (Boston Scientific Corp., MA, USA) more than halved the need for new revascularizations after coronary artery stent implantation [1–4]. However, the safety of these first-generation drug-eluting stents (DESs) was questioned following reports of their association with an increased risk of late and very-late stent thrombosis (ST) [5,6]. 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 remodeling, leaving naked stent struts as a nidus for thrombotic events [7,8]. Whether adverse vessel wall reactions to implantation of DESs are related to the type of drug eluted from the stent, or to the polymer coating of the stent, is currently unknown.

The second-generation zotarolimus-eluting stent, Endeavor™ (Medtronic, CA, USA), was supposed to represent a safer alternative to Cypher and Taxus. The Endeavor stent induced uniform and complete neointimal coverage of the stent struts, and was associated with a lower incidence of late-acquired incomplete stent apposition [9,10]. In addition, the polymer phosphorylcholine (PC) drug carrier used for controlling drug elution from Endeavor is a synthetic copy of the predominant phospholipid in the outer membrane of red blood cells, and appears to be a safer noninflammatory alternative to the polymers used for Cypher and Taxus [11,12].

This article presents an overview of the current data on zotarolimus-eluting and sirolimus-eluting stents.

Zotarolimus-eluting stents

The Endeavor drug-eluting coronary stent is a thin strut (0.0036-inch or 91-µm diameter) cobalt-based alloy stent, with a PC polymer and zotarolimus dose concentration of 10 µg/mm stent length [12]. The Endeavor PC coating is a synthetic copy of the predominant phospholipid in the outer membrane of red blood cells, has high biovascular compatibility, and is considered to be noninflammatory [11,12]. A potential limitation of the use of the PC coating for antiproliferative drug elution is the elution of the drug within days. The next-generation zotarolimus-eluting Resolute™ DES (Medtronic, CA, USA), utilizes the same drug, drug dose and stent, but employs the BioLinx® tripolymer permanent coating for extended drug elution. The Resolute elutes 85% of its zotarolimus content during the first 60 days after implantation, and the remainder of the drug is completely eluted by 180 days [13].

Sirolimus-eluting stents

The Cypher stent was the first available DES and, so far, no other DESs has been shown to obtain better outcomes than this one. The Cypher is a bare-metal stent (0.0055 inch), coated with a permanent polymer that elutes more than 90% the sirolimus during the first 28 days after implantation [14]. The next-generation sirolimus-eluting

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stent is the NEVO™ stent (Cordis, Johnson & Johnson), which is a dedicated thin-strut (0.0039 inch) cobalt–chromium alloy DES. The NEVO stent elutes sirolimus to the abluminal side from reservoirs in the stent, utilizing a bioabsorbable polymer. The drug-elution kinetics of the two sirolimus-eluting stents are similar [14].

Endeavor clinical trial program

The ENDEAVOR I first-in-man study tested the Endeavor stent in 100 patients with *de novo* coronary stenosis. The study lesion should be no more than 15 mm in length, and have a diameter of 3.0–3.5 mm [15]. Patients could have multivessel disease, but only one lesion could be treated with the Endeavor stent. Major exclusion criteria were low (<30%) left ventricular ejection fraction (LVEF) and myocardial infarction (MI) within 72 h. At 5-year follow-up, seven patients (7%) had experienced a major adverse cardiac event (MACE); this included three target lesion revascularizations (TLRs), one definite ST after 10 days and four noncardiac deaths [15].

The ENDEAVOR II study randomized 1197 patients with a single, *de novo* stenosis of 14–27 mm in length, and a diameter between 2.25 and 3.5 mm in a native coronary artery [16]. Patients with low LVEF, recent MI and higher-risk lesions, such as left main, ostial, bifurcation, tortuous and severely calcified lesions, were excluded. Compared with bare-metal stents, the Endeavor stent reduced TLR from 11.8 to 4.6% ($p = 0.0001$). ST rates were 1.2 and 0.5%, respectively [16]. Thus, these results indicated that, compared with bare-metal stents, the Endeavor stent was safe, and more than halved TLR rates.

The ENDEAVOR III trial was the first study to compare the Endeavor stent versus the gold-standard Cypher stent. Major inclusion and exclusion criteria were similar to ENDEAVOR II [17,18]. Patients were randomized 3:1 to Endeavor ($n = 323$) and Cypher ($n = 113$). In-stent late lumen loss was 0.60 mm in the Endeavor arm versus 0.15 mm in the Cypher arm ($p < 0.001$); binary restenosis was increased in the Endeavor group (11.7%) compared with the Cypher group (4.3%), and there was a trend towards higher TLR rates (6.3 vs 3.5%) [18]. There were no ST events in both stent groups at 9-month follow-up [18]. After 3 years of follow-up, the Endeavor stent was associated with a trend towards higher rates of target vessel revascularization (TVR; 17.9 vs 12.2%; $p = 0.23$) while there were no differences in cardiac death (one vs two events) or ST (three vs two events) [17]. TLR was reported in the primary publication, but not in the 3-year publication. The Endeavor stent 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 [17].

The ENDEAVOR IV study was a randomized 1:1 comparison of Endeavor versus the paclitaxel-eluting Taxus, which included 1548 patients. Major inclusion and exclusion criteria were similar to ENDEAVOR II and III. The 12-month and 2-year results have been published [19,20]. TLR at 2 years was similar for both groups (Endeavor 5.9% vs Taxus 4.6%). ST at 2 years was also similar (definite ST: six events in both groups; definite/probable ST: Endeavor eight events vs Taxus seven events). The STs in the Endeavor group occurring primarily within the first year (definite: 5:6; definite/probable: 7:8), while occurring primarily during the second year in the Taxus group (definite: 5:6; definite/probable: 6:7).

The E-five registry is a prospective, nonrandomized, multicenter global registry without angiographic follow-up, conducted at 188 centers worldwide [21]. This study demonstrated that 74% of the registry patients did not fit the inclusion/exclusion criteria in the ENDEAVOR II–IV trials, and that this extended-use group had higher rates of adverse events. Overall, TLR was 4.5% [21].

■ Resolute stent

There are currently limited data available for The Resolute DES. A total of 139 patients, with criteria similar to ENDEAVOR II, were primarily followed by angiography at 9 months. Late lumen loss was 0.22 mm, one patient (1%) had in-stent restenosis and two patients (2%) had in-segment restenosis. TLR at 9 and 12 months were 0 and 1%, respectively. Compared with a matched cohort from ENDEAVOR II, the delayed elution of zotarolimus reduced late lumen loss by 0.39 mm ($p < 0.001$) [13]. The 2-year follow-up suggested sustained efficacy and safety. These results suggest that the delayed elution of zotarolimus from the Resolute stent improves the angiographic outcome compared with the faster elution from the Endeavor stent, and the results of a large randomized trial showed noninferiority in comparison with an everolimus-eluting stent [22].

■ NEVO stent

The first clinical results with the NEVO stent showed that the NEVO had a lower late lumen loss (0.13 ± 0.31 mm) than the Taxus stent (0.36 ± 0.46 mm) at 6-month follow-up [14]. A large randomized all-comer trial is planned.

Randomized comparisons of Endeavor & Cypher

The major adverse cardiac event rates in the four largest head-to-head randomized trials are presented in Table 1. The aforementioned ENDEAVOR III study was the first head-to-head comparison of Endeavor and Cypher. This study was limited by selective inclusion criteria, and was powered to assess an angiographic end point. The Danish Organization on Randomized Trials with Clinical Outcome (SORT OUT) III was the first randomized trial that aimed to compare clinical end points between Endeavor and Cypher [23]. We included 2332 routine clinical-care patients, and followed them for 18 months. Inclusion criteria were indications for a DES, and exclusion criteria were inability of informed consent, life expectancy of less than 1 year and allergy to aspirin/clopidogrel. The primary end point, MACE, was a composite of cardiac death, MI and TVR, and occurred in 113 (9.7%) versus 53 (4.5%) patients ($p < 0.0001$). Secondary end points were each of the MACE end points: all-cause mortality, TLR and definite ST. In general, use of the Endeavor stent doubled the rates of the secondary outcomes (Table 1). The Intracoronary Stenting and Antithrombotic Regimen: Test Efficacy of Three 'limus-Eluting Stents (ISAR-TEST) 2 trial compared three different DESs, two of which were Endeavor and Cypher [24]. This study did also include routine clinical-care patients. The primary end point was binary restenosis after 6–8 months. The Endeavor arm had 19.3% restenosis at follow-up, while Cypher had 12%. Similarly, the secondary end point of TLR at 12 months was also doubled (Endeavor 13.6 vs Cypher 7.2%) [24]. The 2-year results, with 2-year angiographic follow-up in 67% of the patients, showed no signal of a differential safety profile across the groups throughout the 2 years, but showed a potential decrement in angiographic and clinical antirestenotic efficacy with the Cypher (2-year TLR rates: Endeavor 14.3 vs Cypher 10.7%; 2-year restenosis rates: Endeavor 20.9 vs Cypher 18.6%). It is noteworthy that a similar signal was neither observed in ENDEAVOR III, where TVR tended to be increased in the Endeavor group [17,18], nor observed in ENDEAVOR IV, where TLR was performed in 1.4% in both groups between year 1 and 2 [20]. Moreover, it remains a question whether the intense angiographic follow-up in the ISAR-TEST 2 trial affected the TLR and binary restenosis rates, since these rates are much higher than reported in ENDEAVOR IV [19,20], and are also higher than those obtained in high-risk groups, such as diabetes patients, patients with ST-segment elevation MI and bifurcation lesions treated with the Cypher stent [25–28]. The Comparison of the Efficacy and Safety of Zotarolimus-Eluting Stent versus Sirolimus-Eluting Stent and Paclitaxel-Eluting Stent for Coronary Lesions (ZEST) randomized 2645 patients to Endeavor, Cypher, or Taxus [29]. It was an all-comer study, except for the exclusion of patients with ST-segment elevation MI, left main disease, in-stent restenosis after previous DES implantation, renal failure or life expectancy of less than 1 year. The primary end point was a composite of death, MI and TVR at 12 months, and occurred in 10.1 versus 8.3% ($p = 0.25$) in Endeavor versus Cypher, respectively. Death or MI rates were similar in the Endeavor and Cypher arms, but TVR was significantly higher ($p < 0.001$) in patients randomized to treatment with Endeavor (5.2%) than to treatment with Cypher (1.9%). Definite ST was also significantly increased ($p = 0.046$) in the Endeavor (0.5%) versus the Cypher (0%) group. ZEST-AMI randomized 328 patients with ST-segment elevation MI to Endeavor, Cypher or Taxus [28]. The primary end point was similar to ZEST, and occurred in 11.3 and 8.2% for Endeavor and Cypher, respectively. The ZEST-AMI study was severely underpowered for the assessment of clinical end points, and no conclusions can be drawn with regard to the primary end point or the secondary clinical end points. Angiographic in-stent restenosis, a secondary end point, was present in 15.9% in the Endeavor group compared with 1.4% in the Cypher group [28].

Why is there more restenosis & stent thrombosis with Endeavor?

The PC polymer of the Endeavor releases zotarolimus within the first week after implantation, while the Cypher releases sirolimus over a 3-month period. The lower efficacy associated with coronary implantation of the Endeavor is most likely to be related to the fast release rate of zotarolimus, since the Resolute stent, utilizing the same drug but with a slower release, has a lower late lumen loss. Other possible explanations include differences in stent design and differences between the various 'limus drugs. The release kinetics of the drug from the stent may also influence the healing of the plaque/vessel

Table 1. Major adverse clinical outcomes in the four largest randomized comparisons of Endeavor™ versus Cypher™.

	Follow-up (months)	Endeavor™ n (%)	Cypher™ n (%)	p-value	Ref.
Cardiac death					
SORT OUT III†	18	18 (1.6)	12 (1.0)	0.27	[23]
ENDEAVOR III	36				[17]
ISAR-TEST-2‡	12	6 (1.8)	8 (2.4)		[24]
ZEST‡	12	5 (0.6)	3 (0.3)		[29]
Myocardial infarction					
SORT OUT III	18	24 (2.1)	11 (0.9)	0.029	[23]
ENDEAVOR III	36	? (0.6)	? (4.5)	0.005	[17]
ISAR-TEST-2	12	11 (3.2)	12 (3.6)		[24]
ZEST	12	47 (5.3)	55 (6.3)	0.40	[29]
Definite stent thrombosis					
SORT OUT III	18	13 (1.1)	6 (0.5)	0.13	[23]
ENDEAVOR III	36	3	2		[17]
ISAR-TEST-2	12	2 (0.6)	3 (0.9)		[24]
ZEST	12	4 (0.5)	0	0.046	[29]
TLR					
SORT OUT III	18	71 (6.1)	20 (1.7)	<0.0001	[23]
ENDEAVOR III	36				[17]
ISAR-TEST-2	12	57 (13.6)	30 (7.2)		[24]
ZEST	12	43 (4.9)	12 (1.4)	<0.001	[29]

†SORT OUT III was the only study that did not perform angiographic follow-up as part of the study protocol, and this study did not include periprocedural myocardial infarction in their myocardial infarction definition.
‡ISAR-TEST-2 and ZEST included three different stents in their studies and separate comparisons of Endeavor versus Cypher were not always reported.
ISAR-TEST: Intracoronary Stenting and Antithrombotic Regimen: Test Efficacy of three 'Limus-Eluting Stents; SORT OUT: Danish Organization on Randomized Trials with Clinical Outcome; TLR: Target-lesion revascularization; ZEST: Zotarolimus-Eluting Stent versus Sirolimus-Eluting Stent and Paclitaxel-Eluting Stent for Coronary Lesions.

wall, and we speculate that the high initial zotarolimus concentration might impair plaque healing, increase the risk of exposing plaque material to the blood stream, and give rise to the observed increased risk of ST after 9–12-month follow-up in SORT OUT III.

Registry data comparing Endeavor with Cypher

There are only few data on this issue. The Swedish Coronary Angiography and Angioplasty Registry (SCAAR) showed that the Endeavor had a 45% increased relative risk of restenosis compared with the Cypher stent [30], and our data from the Western Denmark Heart Registry (WDHR) confirmed the results from the randomized trials (i.e., showing a doubling of TLR in the Endeavor group) [31].

Conclusion

In comparison with Cypher, the Endeavor stent has less efficacy with regard to neointima formation, which, as a uniform finding across all studies, leads to a higher risk of TVR/TLR at midterm follow-up. Thus, the Endeavor stent appears inferior with regard to efficacy end points. Moreover, the currently available midterm data indicate that the Endeavor may be associated with a higher risk of clinical safety outcomes (death, MI and ST) than the Cypher stent in routine clinical-care patients. However, the uniform neointima formation, and the lack of stent malapposition after 9 months, may protect against very late ST. The adequately powered Patient-Related Outcomes with Endeavor Versus Cypher Stenting Trial (PROTECT) study will answer this question [32].

Future perspective

In comparison to Endeavor, the next-generation zotarolimus-eluting stent, Resolute, has a slower drug elution, lower late lumen loss, and clinical outcomes that makes this DES look promising.

The next-generation sirolimus-eluting stent, the NEVO stent, utilizes an absorbable polymer, which may be a safer alternative to the

permanent polymers used by first- and second-generation DES. Moreover, DES without polymers are being developed and tested. In the future, we will probably have DESs that are as effective as the Cypher stent but without the rare occurrences of very late ST. Until then, large, randomized comparisons in routine clinical patients are needed to discover the best DES.

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Executive summary

- Drug-eluting stents have more than halved the need for new revascularizations after coronary artery stent implantation.
- First-generation drug-eluting stents, especially the paclitaxel-eluting stent, seem to be associated with an increased risk of very late (>12 months after index implantation) stent thrombosis.
- Stent thrombosis is probably caused by an inflammatory reaction in the vessel wall.
- The zotarolimus-eluting stent, Endeavor™, was supposed to represent a safer alternative, because of uniform and complete neointimal coverage of the stent struts. This full-stent coverage was obtained at the expense of greater neointima formation and larger angiographic late lumen loss.
- The Danish Organization on Randomized Trials with Clinical Outcome (SORT OUT) III study was the first randomized comparison of Endeavor and Cypher™ that was powered to assess clinical end points.
- SORT OUT III showed that Endeavor was inferior to Cypher with regard to both safety and efficacy end points.
- The inferior efficacy of Endeavor, observed in SORT OUT III, is in line with smaller randomized comparisons of Endeavor versus Cypher.
- Contrary to expectations, Endeavor seems associated with a higher risk of stent thrombosis with the first year but this issue awaits confirmation.

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