Clinical Trial Update on the Endeavor Stent

An overview of the completed and ongoing clinical trial program of the Endeavor zotarolimus-eluting stent platform.

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The adoption of drug-eluting stents (DES), or intracoronary stents that combine the local delivery of antirestenotic pharmacologic therapies while maintaining the mechanical advantage of bare-metal stents (BMS), has been widespread in the past decade. Designed specifically to treat the neointimal hyperplasia occurring after conventional BMS placement, DES have been remarkably successful in this regard. DES have been associated with low rates of angiographic restenosis, as well as low rates of target lesion revascularization (a surrogate of clinical restenosis) in numerous studies, with 40% to 60% relative reductions in the incidences of these endpoints compared to BMS.[1] Despite the proven efficacy of first-generation DES, there is a need for newer DES platforms. First, the stent and stent delivery system of first-generation DES do not reflect the latest advances in BMS technologies precluding optimized delivery of these devices with potential gains with respect to endpoints such as procedural success. Second, these DES have been associated with the occurrence of late stent thrombosis (LST), occurring at rates of up to 0.6% per year[2] and necessitating prolonged dual-antiplatelet therapy as a potential means of preventing LST. The risk factors for LST appear to be multifactorial, related to a combination of high-risk patient and lesion characteristics, suboptimal stent deployment, and intrinsic properties of the DES platform that might impair adequate healing of the arterial wall with the restoration of normal vasomotion and endothelial function.

As a result of these potential areas for improvement in first-generation DES technology, several second-generation DES have been developed and have recently undergone regulatory review and/or approval. The Endeavor zotarolimus-eluting stent (ZES) (Medtronic CardioVascular, Santa Clara, CA) is one such device that was approved for use in the US in February 2008. The Endeavor stent is a cobalt-based alloy stent coated with the sirolimus analogue zotarolimus delivered via a phosphorylcholine polymer. This stent has demonstrated significant reductions in angiographic restenosis and target vessel revascularization compared to BMS.[3] The hydrophilic phosphorylcholine polymer of the ZES was designed to be biocompatible, and the release kinetics of zotarolimus from the stent are somewhat unique to DES, with near-complete elution within the first month after stent placement.

COMPLETED CLINICAL TRIALS OF THE ENDEAVOR STENT

The Endeavor clinical trial program has consisted of several different clinical trials and registries performed to assess the safety and efficacy of the Endeavor stent (Figure 1). A summary of the major trials of the Endeavor stent is provided in this article.

ENDEAVOR I

The ENDEAVOR I study was a single-arm, prospective, multicenter, first-in-man trial to evaluate the performance of the ZES in 100 patients with symptomatic coronary artery disease.[4] Treated lesions were required to be single de novo lesions with a length of ≤15 mm in vessels with a reference diameter between 3 and 3.5 mm. Implanted stents were single-length stents of 18 mm, in 3- and 3.5-mm diameters, and predilation was required. Dual-antiplatelet therapy was

continued for 3 months. The primary safety endpoint of the trial was major adverse cardiac events (MACE) at 30 days, and the primary efficacy endpoint was in-stent late loss at routine 4-month angiography; patients also underwent routine 12-month angiography. Follow-up is available to 4 years and is going to 5 years.

The rate of 30-day MACE was 1%, with 100% device and procedural success achieved. Among patients undergoing angiographic follow-up, which was mandated by the protocol, at 4 months, in-segment late loss was 0.21 mm, with in-stent late loss of 0.33 mm and a binary restenosis rate of 2.1%. At 12-month angiography, the rate of binary restenosis was 5.4%, with an in-segment late lumen loss of 0.43 mm and in-stent late loss of 0.61 mm.

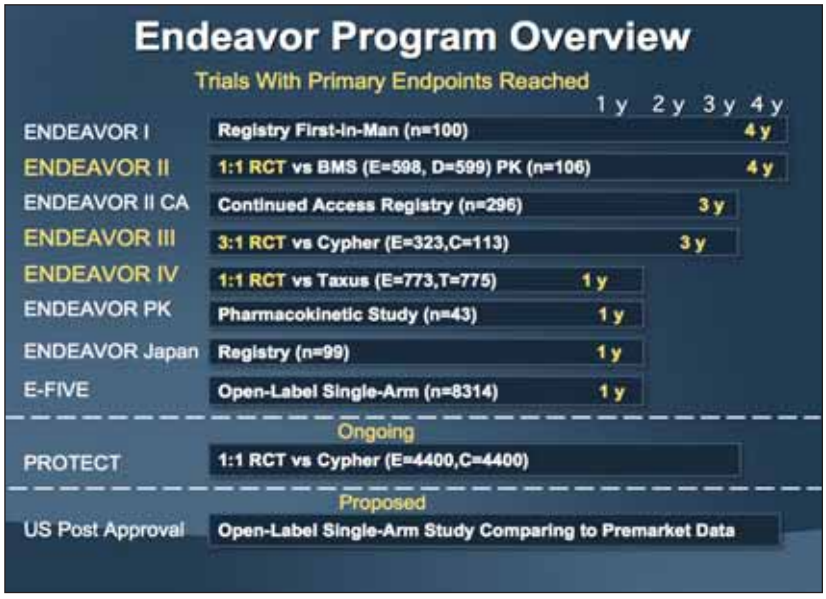

Figure 1. Endeavor clinical program overview.

The rate of clinical events in this first-in-man study was also low, with two MACE events (2%) at 12 months, consisting of a stent thrombosis at 10 days and a target lesion revascularization (TLR) at 112 days after the procedure. The rate of overall MACE has remained low out to 4 years of follow-up at 7.2%, with a 3.1% rate of TLR and an overall rate of target vessel failure (TVF) of 5.2%.[5]

ENDEAVOR II

Based upon results of the first-in-man ENDEAVOR I study, the large-scale, prospective, randomized, double-blind, multicenter ENDEAVOR II trial was designed to examine the efficacy and safety of the ZES compared to the Medtronic Driver BMS (the same stent as the ZES but without the polymer or antirestenotic agent).[6] The trial randomized patients with ischemic coronary artery disease and a single de novo coronary artery lesion to ZES (n=598) or BMS (n=599). Lesion-based inclusion criteria included a reference vessel diameter of 2.25 to 3.5 mm and a lesion length of 14 to 27 mm. Protocol-mandated angiographic follow-up was performed at 8 months in the first 600 patients enrolled in the trial. Dual-antiplatelet therapy was prescribed for a minimum of 3 months. The primary endpoint of the trial was the clinical assessment of TVF at 9 months.

Among enrolled patients, the mean lesion length was 14 mm, with a mean reference vessel diameter of 2.75 mm. At 9 months, the rate of the primary study endpoint of TVF was 7.9% with ZES versus 15.1% with BMS (P=.0001). This was largely driven by a significant reduction in TVR (5.6% vs 12.5%; P<.0001) and TLR (4.6% vs 11.8%; P=.0001); rates of myocardial infarction (MI) and death were similar in both treatment arms. Among patients undergoing routine angiographic follow-up, late loss was 0.61 mm versus 1.03 mm (P<.001), and the rate of binary angiographic restenosis was markedly reduced with ZES (9.4% vs 33.5%; P<.0001). While patients undergoing protocol-mandated angiographic follow-up had higher rates of TLR compared to those undergoing clinical follow-up alone, the differences in TLR rates between ZES and BMS were evident both among patients assigned to routine angiographic follow-up (5.8% vs 15.8%; P<.0001), as well as those assigned to clinical follow-up alone (3.4% vs 7.8%; P=.02).

Follow-up from this trial is ongoing, with data out to 4 years available at this time.[7] At 4 years, the ZES has maintained an advantage in TVF over BMS (13.6% vs 22.6%; P<.001), primarily through a persistent reduction in TVR (9.8% vs 18.8%; P<.001). The rates of other clinical endpoints have been similar in ZES- and BMS-treated patients, with a low overall rate of stent thrombosis (0.5% vs 1.2%; P=0.342) with both stents. Notably, there have been no late stent thromboses (thrombosis occurring beyond 30 days) or very late stent thromboses (occurring beyond 1 year) in this trial.

ENDEAVOR III

Although the ENDEAVOR II trial has demonstrated superior efficacy and similar safety of the ZES compared to BMS, randomized comparative data between the ZES and other approved DES have required additional trial data. ENDEAVOR III was a prospective, randomized, single-blinded multicenter angiographic trial with similar inclusion/exclusion criteria as the ENDEAVOR II trial.[8] A total of 436 patients with ischemic heart disease due to de novo native artery lesions

with reference vessel diameter 2.5 to 3.5 mm and lesion length 14 to 27 mm were randomized in a 3:1 ratio to treatment with ZES (n=323) or the Cypher sirolimus-eluting stent (SES, n=113) (Cordis Corporation, Warren, NJ). Dual-antiplatelet therapy was continued for a minimum of 3 months after the procedure. The trial was designed to show noninferiority of ZES compared to SES with respect to the primary study endpoint of in-segment late loss at routine 8-month angiographic follow-up; secondary endpoints included clinical efficacy and safety endpoints.

Similar to lesions treated in ENDEAVOR II, the mean lesion length was 15 mm, with a mean reference vessel diameter of 2.76 mm. Compared to SES, the rate of device success (a measure of deliverability) with ZES was higher (98.8% vs 94.7%; *P*=.02) and ZES-treated patients had a lower rate of in-hospital MI (0.6% vs 3.5%; *P*=.04); other short-term endpoints were similar with both stents. At 8-month angiography, in-segment late loss was significantly higher with ZES compared to SES (0.34 vs 0.13; *P*<.001 for superiority of SES; *P*=.65 for noninferiority), and the rate of binary restenosis was also higher with ZES (9.2% vs 2.1%; *P*=.02). However, at 9 months, aside from the lower rate of MI with ZES (predominantly based upon in-hospital events) the rate of MACE and the rates of the individual clinical components of MACE were similar. Long-term follow-up from this trial is ongoing as well, with data available up to 3 years. At 2 years, the rates of overall MACE and components of MACE have been similar with both stents (aside from the persistently lower rate of MI: 0.6% for ZES vs 3.6% for SES).[9] At 3 years, the rate of TVF has remained similar between both study stents (14.2% with ZES vs 13.3% with SES, log-rank *P*=.87) (unpublished data from Medtronic, 2008).

ENDEAVOR IV

Despite the higher late loss of the ZES compared to SES as observed in the ENDEAVOR III trial, a larger comparative DES trial was designed to assess the clinical performance of the ZES compared to the Taxus paclitaxel-eluting stent (PES) (Boston Scientific Corporation, Natick, MA), in part due to the similarity in clinically assessed outcomes in ENDEAVOR II. Unlike the previous trials that employed a design with a significant proportion of routine angiographic follow-up, the ENDEAVOR IV trial mandated angiographic follow-up in approximately one fifth of enrolled patients and was designed around a clinically assessed endpoint of TVF at 9 months. This study design was based in part upon observations from other comparative DES studies in which differences in angiographic endpoints did not necessarily translate into differences in clinical endpoints,[10] and in addition, upon the observation that routine angiographic follow-up is associated with greater absolute differences in rates of revascularization than those observed from clinical follow-up alone,[11] which more closely reflects actual clinical practice.

The ENDEAVOR IV trial was a pivotal, randomized, single-blind, prospective multicenter trial conducted in 1,548 patients.[12] The trial randomized patients with single de novo native artery lesions to ZES (n=774) versus PES (n=775); stent diameters were 2.5 to 3.5 mm, and included lesion lengths were 14 to 27 mm. In contrast to ENDEAVOR I, II, and III, in this trial, patients were treated with 6 months of dual-antiplatelet therapy. The primary study endpoint (comparatively assessed through a noninferiority design) was TVF at 9 months, with secondary endpoints of in-segment late loss and percent diameter stenosis at 8 months in the subset of patients assigned to routine angiographic follow-up, as well as TLR and TVR at 9 months.

The mean lesion length of enrolled patients was 13.6 mm, with a mean reference vessel diameter of 2.71 mm. Similar to that observed in ENDEAVOR III, the rate of in-hospital MI was lower with ZES compared to PES (0.8% vs 2.3%; *P*=.018); other in-hospital endpoints were similar between both stents. The rate of the primary study endpoint, TVF at 9 months, was similar in both arms (6.6% vs 7.2%; *P*=.685 for superiority; *P*<.001 for noninferiority). There were also similar rates of TVR (5.4% vs 4.9%) and TLR (4.1% vs 2.7%) with both stents. There were no differences between the two study stents in the rates of other clinical endpoints assessed at 9 months.

Updated data to 12 months are additionally available. Although a trend toward differences in 12-month TLR between the study stents was observed among patients assigned to angiographic follow-up (8.5% for ZES vs 3% for PES; *P*=.07), it was not evident among patients assigned to clinical follow-up alone (3.6% vs 3.3%; *P*=.875).[13] These findings are consistent with the angiographic findings among the subset of patients undergoing routine angiographic follow-up at 8 months, in which in-stent late loss was higher with ZES compared to PES (0.67 vs 0.42 mm; *P*<.001), and the rate of binary angiographic restenosis trended higher (13.3% vs 6.7%; *P*=.075). However, despite these angiographic differences, there have been no overall differences in the rates of TVF, TVR, TLR, or other clinical endpoints between ZES and PES, out to 12 months of follow-up. Overall, these findings suggest similarity in clinical endpoints between ZES and PES, with evidence of the oculostenotic reflex among patients undergoing protocol-mandated angiography.

ENDEAVOR Pooled Safety Analysis

Given the relative similarity of the enrolled patients and lesions across the trials in the Endeavor clinical trial program, a retrospective pooled analysis (combining the data from the ZES arms of the prior trials) has been conducted to assess long-term clinical outcomes associated with the stent.[14] In this nonrandomized analysis, out to a follow-up period of 4

years, the overall rates of death, MI, and stent thrombosis have remained low, and are comparable to—and in fact are numerically lower than—a historical control group of the Driver BMS from the ENDEAVOR II trial. For example, in this analysis, the cumulative incidence of adjudicated Academic Research Consortium defined definite/probable stent thrombosis at 4 years is 0.7% with ZES (compared to 1.5% in the nonrandomized BMS control group of ENDEAVOR II), with a .08% rate of very late stent thrombosis with ZES. Of note, this rate of stent thrombosis has been achieved with ≤6 months of dual-antiplatelet therapy in the included trials, with 29% of patients on dual-antiplatelet therapy at 1 year, 11% of patients on dual-antiplatelet therapy at 2 years, and 8.5% of patients on dual-antiplatelet therapy at 3 years.

DATA SUMMARY AND ONGOING STUDIES

In aggregate, the major trials of the Endeavor ZES have demonstrated several findings: (1) the ZES appears to be safe and effective in treating single de novo coronary artery lesions and has demonstrated angiographic and clinical superiority to its nonpolymeric and noneluting BMS comparator; (2) the ZES has demonstrated excellent deliverability and rates of procedural success, with lower rates of in-hospital MI compared to both SES and PES; (3) despite the higher late loss and greater rates of binary restenosis of ZES as assessed angiographically, clinically assessed outcomes of repeat revascularization procedures (TVR and TLR) have been similar with ZES and SES and with ZES and PES in the selected patient populations studied in head-to-head randomized studies; and (4) with follow-up to 4 years, the rates of hard clinical (safety) endpoints, including overall stent thrombosis and very late stent thrombosis, are very favorable with the Endeavor ZES and appear comparable to historical BMS data.

The critical issues that remain to be determined with the Endeavor ZES relate to its efficacy and safety in more diverse patient populations. It is presently unknown whether the relative efficacy of ZES is preserved in more complex patient and lesion subsets with potentially less tolerance for late loss (eg, longer lesions or smaller-caliber vessels). Additionally, if the safety benefits of ZES are extended to more complex patients, this may provide physicians with the ability to offset the small but potentially ongoing risk of late stent thrombosis that has been observed with first-generation DES.[2] The 8,000-patient E-FIVE registry has been designed to assess the efficacy and safety of the ZES in single and multiple coronary artery lesions ranging from 2.25 to 4 mm and utilizing stent lengths of up to 30 mm. Preliminary data from this registry have demonstrated favorable outcomes across a range of complex patient and lesion subsets, with an overall rate of 12-month TVR of 4.9%.[15] The ongoing 8,800-patient randomized multicenter PROTECT trial is designed and statistically powered to compare the overall stent thrombosis rates between ZES and PES in relatively unselected patients. Data from both these studies, as well as emerging data from the worldwide experience with the ZES, should help to better determine the performance of the ZES in general clinical use. ■

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