

EDITORIAL COMMENT

The “Final Voyage” of the Endeavor Stent*

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The “final” 5-year outcomes of combined trials with the Endeavor zotarolimus-eluting stent (E-ZES) by Kandzari et al. (1), published in this issue of *JACC: Cardiovascular Interventions*, might be considered a companion to the Kirtane et al. (2) publication in the issue last month of *JACC: Cardiovascular Interventions*, which reported on the “final” 5-year follow-up of the ENDEAVOR IV (A Randomized, Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Taxus Paclitaxel-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions) study. Both papers represent an opportunity to place the long-term clinical results of the Endeavor stent in perspective for the here-and-now.

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But before plowing into the data and the implications of these 2 studies, let us digress with a bit of history. The percutaneous coronary intervention device industry, over the years, has come up with some colorful names to highlight and sell their products. The term “Endeavor” (American English spelling) for the Medtronic second-generation ZES ranks among one of the more intriguing device names that has a basis in history. The sailing ship of Captain James Cook on his first voyage of discovery in the South Seas (1768 to 1771) was named the “HMS Endeavour” (British English spelling). Over 200 years later and of a vastly different travel destination, the Command Module of the Apollo 15 moon mission was also named “Endeavour.” And most recently, we can remember the striking images last year of the retired Space Shuttle “Endeavour” riding piggy back on a jumbo 747 airliner on its “final” voyage across the United States and then towed through the streets of Los

Angeles to a resting place at the California Science Center. So, in a sense, with these reports on the “final” 5-year follow-ups of the Endeavor stent, we might consider this the “final voyage” of this interesting stent design.

The E-ZES stent program was born after the unbridled enthusiastic use of first-generation drug-eluting stents (DES) in the early 2000s was tempered by disturbing reports of late stent thrombosis (3). Even though a meta-analysis of randomized multicenter trials and registry data demonstrated reasonable safety and efficacy of first-generation DES compared with bare-metal stents (BMS) (4), there continued to be major issues of cost-effectiveness, late stent thrombosis, and the lack of a robust mortality benefit with DES in more complex coronary lesions. Potential problems in the first-generation DES, such as thick stent struts, inflammation-inducing release polymers, and the effectiveness of different anti-proliferative agents, set the stage for improved second-generation concepts. The E-ZES consists of a cobalt-based alloy stent with a phosphorylcholine polymer and a dose concentration of 10 $\mu\text{g}/\text{mm}$ stent length of zotarolimus, a sirolimus-like anti-proliferative agent (5). It was speculated that the biocompatibility of the phosphorylcholine polymer would lead to more gentle anti-proliferation and better endothelialization of the stent without the potential of inflammatory reactions and exposure of stent struts to late stent thrombosis.

The E-ZES system was then assessed in various trials comparing it with BMS, paclitaxel-eluting stents (PES), and sirolimus-eluting stents (SES). The major multicenter trials consisted of ENDEAVOR I (First-in-human study of the Endeavor ABT-578-eluting phosphorylcholine-encapsulated stent system in de novo native coronary artery lesions) (E-ZES first in man) (5), ENDEAVOR II (Randomized Controlled Trial to Evaluate the Safety and Efficacy of the Medtronic AVE ABT-578 Eluting Driver Coronary Stent in De Novo Native Coronary Artery Lesions) (E-ZES vs. BMS) (6), ENDEAVOR III (A Randomized Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Cypher Sirolimus-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions) (E-ZES vs. SES) (7), and ENDEAVOR IV (E-ZES vs. PES) (8). These 4 trials, at endpoints of 9 months to 1 year, consistently found that E-ZES had greater surrogates of late lumen loss (LLL) and angiographic restenosis compared with either SES or PES. However, for the short-term these did not seem to translate into deleterious separate or composite endpoints for E-ZES.

Nevertheless, extended long-term outcomes with the variety of DES in clinical practice is an important practice to assure safety and effectiveness for the patient, particularly in light of the potential for adverse signals of late and very late stent thrombosis (VLST). The papers by Kirtane et al. (2) and by Kandzari et al. (1) reflect the strong commitments by

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the sponsor, Medtronic (Minneapolis, Minnesota), and the dedicated clinical investigators to submit the ENDEAVOR trials to extended and structured 5-year clinical follow-up.

Last month in *JACC: Cardiovascular Interventions*, Kirtane et al. (2) reported on the “final” 5-year follow-up of the ENDEAVOR IV randomized trial that compared E-ZES with PES. This 5-year cumulative and landmark analysis of clinical outcomes was performed in 722 (93.4%) E-ZES patients and 718 (92.6%) PES patients. Overall rates of target lesion revascularization (TLR) and target vessel failure were similar. The incidence of cardiac death or myocardial infarction (MI) was lower with E-ZES compared with PES (6.4% vs. 9.1%, $p = 0.048$), primarily driven by a lower rate of MI (2.6% vs. 6%, $p = 0.002$). Overall definite/probable stent thrombosis rates were similar between stents (1.3% vs. 2%, $p = 0.42$). But rates of VLST in E-ZES compared with PES (0.4% vs. 1.8%, $p = 0.012$) and late MI events (1.3% vs. 3.5%, $p = 0.008$) were significantly lower with E-ZES. The authors concluded that E-ZES had durable long-term safety and efficacy compared with PES. There were no late signals of adverse events with E-ZES. The authors properly acknowledged that the subsets of significantly reduced VLST and late MI with E-ZES should be hypothesis-generating, given the limited statistical power of the trial.

As an interesting sequel, the paper by Kandzari et al. (1) also reports on a “final” 5-year clinical follow-up of the ENDEAVOR clinical trial program, which consisted of 5 trials: ENDEAVOR I (100 patients); ENDEAVOR II (1,194 patients); ENDEAVOR III (436 patients); ENDEAVOR IV (1,548 patients); and an ENDEAVOR II Continued Access Registry (9) (296 patients). The authors intended to assess whether the higher short-term incidence of LLL and angiographic restenosis translated to late adverse clinical events in the combined ENDEAVOR trials. The study cohort consisted of a total of 3,616 percutaneous coronary intervention patients, of which 2,132 received E-ZES, 888 received first-generation DES (775 PES, 113 SES), and 596 received BMS. The authors found that, when E-ZES was compared with a parallel cohort of patients treated with first-generation DES and BMS, 5-year rates of cardiac death/MI (5.8% vs. 8.8% DES, $p = 0.003$, vs. 8.4% BMS, $p = 0.02$) and major adverse cardiac events (16.1% vs. 20.6% DES, $p = 0.009$, vs. 24.6% BMS, $p < 0.001$) were significantly lower with E-ZES. There were similar TLR rates when E-ZES was compared with overall DES (7.4% vs. 8.1%, $p = 0.63$). The TLR in E-ZES compared with BMS was significantly lower (7.4% vs. 16.3%, $p < 0.001$). The most striking finding was that, despite higher E-ZES TLR in the first year compared with DES, the rates of cardiac death/MI, TLR, and definite/probable stent thrombosis were significantly lower with E-ZES in the 5-year time frame. The authors concluded that rates of clinical restenosis and safety events, including stent thrombosis beyond the first year of revascularization remain stable with E-ZES, leading to significant differences compared with first-generation DES. Again, because there are

issues with the limited statistical power of these combined trials, the results of these subset analyses should be considered hypothesis-generating and not clear-cut mandates for safety or efficacy.

The shortcomings of the E-ZES system rest in the nondurable rapid release polymer, resulting in completed elution of the active zotarolimus agent within 10 days (5). As a result, the perceived Achilles heel of the E-ZES has always been the increased LLL compared with other first-generation and second-generation DES platforms. By contrast, the heightened re-endothelialization and incorporation of the E-ZES in the coronary lumen has been touted as a potentially “safer” stent by reducing the risk of late stent thrombosis and VLST. In essence, the E-ZES can be considered intermediate between BMS and other limus-like DES systems.

Regardless, in the current world, the E-ZES stent architecture has now been eclipsed by the Resolute zotarolimus-eluting stent (R-ZES) system. The R-ZES polymer is a mixture of a hydrophilic biocompatible component that faces the endoluminal surface and a hydrophobic component that is attached to a cobalt alloy stent surface and serves as a drug reservoir. This results in a sustained release of zotarolimus, one-half of the load over 10 to 14 days, and the remainder more gradually over 8 to 10 weeks (10). The clinical results of the R-ZES have been found to be comparable to contemporary everolimus-eluting stents in an “all-comers” trial (11).

Is the E-ZES a safer stent? The data from these 2 5-year follow-ups would indicate long-term safety compared with first-generation DES. But this is not definitive, due to the limited statistical power of both of these analyses. We do know for sure that E-ZES is not harmful in the long run. But we should keep in mind that these studies were in simple de novo coronary lesions. Is the E-ZES a superior stent compared with SES or PES? Absolute superiority is hard to prove—so the answer is no. But, one could conclude that the E-ZES stent might be somewhat better than first-generation DES, particularly in long-term clinical outcomes. Is there a role for E-ZES as a work horse stent in our current practice? Due to the march of time and even newer DES platforms, the answer again is no. If a zotarolimus-elution is preferable, the current choice would be R-ZES in view of the improved elution dynamics and newer underlying stent architecture. Thus, in final perspective, the Endeavor stent was an interesting transition from first-generation to second-generation stents but one whose time has now passed.

These “final” 5-year reports on the long-term outcomes of the ENDEAVOR trials closes another chapter or “voyage” on the meticulous conduct of these and other large-scale multicenter randomized trials assessing various DES platforms and elution schemes. Although the ENDEAVOR trials dealt with older comparative stent designs that are not often used in

current clinical practice, the priority for publication and dialogue of these 2 papers are justified by the importance of the concept of a 5-year follow-up. There is a benefit to an extended follow-up of randomized DES patients to assure that there are no late-late deleterious signals that could result in harm. This commitment to long-term follow-up also helps to develop hypothesis-generating principles of improved polymer compatibility and elution dynamics to guide the next generations of DES, such as total bioabsorbable stents and unidirectional abluminal drug-elution stent platforms. So, in the end, the long “final voyage” of the Endeavor stent and the long-term information gained was well worth the journey.

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REFERENCES

1. Kandzari DE, Leon MB, Meredith I, Fajadet J, Wijns W, Mauri L. Final 5-year outcomes from the endeavor zotarolimus-eluting stent clinical trial program: comparison of safety and efficacy with first-generation drug-eluting and bare-metal stents. *J Am Coll Cardiol Intv* 2013;6:504-12.
2. Kirtane AJ, Leon MB, Ball MW, et al. The “final” 5-year follow-up from the ENDEAVOR IV trial comparing a zotarolimus-eluting stent with a paclitaxel-eluting stent. *J Am Coll Cardiol Intv* 2013;6:325-33.
3. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 2007;356:998-1008.
4. Kirtane AJ, Gupta A, Iyengar S, et al. Safety and efficacy of drug-eluting and bare metal stents: comprehensive meta-analysis of randomized trials and observational studies. *Circ* 2009;119:3198-206.
5. Meredith IT, Ormiston J, Whitbourn R, et al. First-in-human study of the endeavor ABT-578-eluting phosphorylcholine-encapsulated stent system in *de novo* native coronary artery lesions: endeavor I trial. *Eurointerv* 2005;1:164.
6. Fajadet J, Wijns W, Laarman GJ, et al. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. *Circulation* 2006;114:798-806.
7. Kandzari DE, Mauri L, Popma JJ, et al. Late-term clinical outcomes with zotarolimus- and sirolimus-eluting stents. 5-year follow-up of the ENDEAVOR III (A Randomized Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Cypher Sirolimus-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions). *J Am Coll Cardiol Intv* 2011;4:543-50.
8. Leon MB, Nikolsky E, Cutlip DE, et al. Improved late clinical safety with zotarolimus-eluting stents compared with paclitaxel-eluting stents in patients with *de novo* coronary lesions: 3-year follow-up from the ENDEAVOR IV (Randomized Comparison of Zotarolimus- and Paclitaxel-Eluting Stents in Patients With Coronary Artery Disease) trial. *J Am Coll Cardiol Intv* 2010;3:1043-50.
9. Schultheiss HP, Grube E, Kuck KH, et al. Safety of direct stenting with the endeavor stent: results of the endeavor II continued access registry. *Eurointerv* 2007;3:81.
10. Meredith IT, Worthley S, Whitbourn R, et al. Clinical and angiographic results with the next-generation resolute stent system: a prospective, multicenter, first-inhuman trial. *J Am Coll Cardiol Intv* 2009;2:977-85.
11. Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med* 2010;363:136-46.

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