New Drugs and Technologies

Overview of the 2007 Food and Drug Administration Circulatory System Devices Panel Meeting on the Endeavor Zotarolimus-Eluting Coronary Stent

Tina L. Pinto Slottow, MD; Ron Waksman, MD

Initial trials comparing stenting with balloon angioplasty demonstrated improved angiographic and clinical outcomes with the former.1–3 The main clinical problem with bare metal stents (BMS) became the development of in-stent restenosis.4–6 Early data suggested that drug-eluting stents (DES) could mitigate, if not abolish, this problem.7–9 Since the approval of DES, these devices have become the predominant stents used in percutaneous coronary interventions, regardless of indication. As of September 2007, the Cypher sirolimus-eluting stent (SES) (Cordis Johnson & Johnson, Miami Lakes, Fla) had been deployed in >3 million patients worldwide,10 and the millionth Taxus paclitaxel-eluting stent (PES) (Boston Scientific, Natick, Mass) was implanted as of January 2005.11 Over the past 2 years, numerous reports of very late stent thrombosis (ST) with first-generation DES have surfaced. This highly morbid complication and data proving efficacy end points are presented in Table 2.15 ZES demonstrated a reasonable level of safety and effectiveness, with clinical benefits clearly outweighing short- and long-term risks of ZES use. Important efficacy end points included ischemia-driven target lesion revascularization (TLR) or target vessel revascularization (TVR); safety end points included death, MI, and ST.

Endeavor ZES System

The Endeavor ZES is a combination product comprising 3 components: (1) a low-profile, thin-strut, cobalt-alloy Driver stent (Medtronic Vascular, Santa Rosa, Calif); (2) a phosphorylcholine polymer; and (3) zotarolimus, an antiproliferative drug that is a synthetic analog of sirolimus with a similar mechanism of action.14 The phosphorylcholine polymer is a hydrophilic biomimetic polymer that resembles erythrocyte membranes. A dose concentration of 10 μg zotarolimus per 1 mm stent length, with 98% of the zotarolimus eluted within 14 days, provides treatment level doses in tissue for >28 days after implantation. ZES are available in diameters of 2.5 to 3.5 mm and in lengths of 8 to 30 mm.

ENDEAVOR Trials

The sponsor14 and the FDA15 presented data from the randomized trials (ENDEAVOR II, ENDEAVOR III, and ENDEAVOR IV) and registries (ENDEAVOR I, ENDEAVOR II Continued Access [CA], and ENDEAVOR Pharmacokinetics [PK]) that have been conducted to date (Table 1). The trials conducted in the United States, namely ENDEAVOR III and ENDEAVOR IV, compared ZES with SES and PES because the sponsor thought that enrollment in a trial of ZES versus BMS would not be possible given the availability of other DES. Of the 2232 patients enrolled in the ENDEAVOR trials, 2-year follow-up is available on 1287 patients and 3-year follow-up on 675 patients. The sponsor’s presentations aimed to demonstrate the desired properties of ZES, namely improved efficacy, ie, lower rates of restenosis than BMS; safety similar to that of BMS; and noninferiority compared with available DES. End points included late loss (LL), TLR, TVR, death, MI, ST, and target vessel failure (TVF). TVF is a clinical end point composed of efficacy (TVR) and safety (cardiac death and MI not proved to be due to a vessel other than the target vessel) end points. For noninferiority, a prior TVF rate of 7.6% was assumed for both arms with a margin of 3.8%. The protocol definition of ST was angiographically or pathologically confirmed thrombosis in the setting of acute coronary syndrome, unexplained death within 30 days of implantation, or target vessel MI within 30 days of implantation without confirmation of an alternative culprit. The ST protocol definition excluded patients who had undergone TLR.

Efficacy

Data from the 3 randomized trials on TVF and revascularization end points are presented in Table 2.15 ZES demon-
strated consistent LL across the ENDEAVOR I, II, III, and IV trials, including in the subsets of patients and lesions in these trials. ZES achieved superiority compared with BMS in ENDEAVOR II in both angiographic (LL) and clinical (TLR/TVR) end points at up to 3 years of follow-up. In ENDEAVOR III, ZES did not achieve noninferiority compared with SES angiographically. TLR, TVR, and TVF were not significantly different, although the trial was not powered for these end points. In ENDEAVOR IV, ZES demonstrated clinical outcomes comparable to PES as evaluated by TVF. ENDEAVOR IV is the first trial comparing 2 different DES platforms that is powered for clinical (TVF) and angiographic (LL) end points. It met its primary end point: ZES was noninferior to PES in TVF at a 9-month clinical follow-up. It did not meet its LL goal, however, because ZES did not achieve noninferiority compared with PES at the 8-month angiographic follow-up. This disparity in outcomes was addressed by Dr Martin Leon. Dr Leon spoke about the false belief that LL would be a reliable surrogate for clinical TLR with a linear relationship between the 2, citing an evaluation by Dr Stuart Pocock that used patients from 11 randomized trials of DES versus BMS16 (Figure 1). The slope appears to be nearly flat at LL of 0 and 0.7 and then becomes linear at LL values >0.7, leading him to conclude that moderate LL may still result in low TLR. In addition, angiographic follow-up has been shown to have a profound impact on revascularization rates. In the ENDEAVOR IV trial, TLR and TVR rates were similar in patients who had clinical follow-up yet different in those who underwent angiographic follow-up14 (Figure 2). These arguments are limited by the 9-month follow-up of ENDEAVOR IV. Assessment of TLR at later time points is essential to determine whether these theories will be borne out.

Specific concerns about the trials themselves were addressed. The results of ENDEAVOR III did not change when a propensity analysis was conducted to account for the differences in baseline characteristics, namely more men in the SES arm.15 Likewise, concerns about bias resulting from the single-blind nature of the ENDEAVOR IV trial were assuaged by the sponsor, who stated that core laboratory analysis found operators’ approaches to lesions to be independent of stent type.

At the latest available follow-up of all of these trials, ZES maintained significantly lower revascularization rates compared with BMS and nonsignificant differences in revascularization rates compared with SES and PES15 (Table 3).

Safety
Initial assumptions based on experience with BMS led investigators to believe that ST would be limited to the first year after DES deployment; however, multiple reports of very late ST led to changes in trial design. Follow-up beyond 1 year is now imperative for the verification of DES safety. Furthermore, although no stent can be completely safe and

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**Table 1. Summary of Premarket Trials**

<table>
<thead>
<tr>
<th>ENDEAVOR Trials</th>
<th>n</th>
<th>Type</th>
<th>Follow-Up, mo</th>
<th>DAP, mo</th>
<th>Angiographic Follow-Up, Planned/% Obtained</th>
<th>Device Success, %</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>100</td>
<td>Registry</td>
<td>48/97</td>
<td>3</td>
<td>...</td>
<td>...</td>
<td>Feasibility trial</td>
</tr>
<tr>
<td>II–ZES arm</td>
<td>598</td>
<td>DB-S</td>
<td>36/97</td>
<td>3</td>
<td>50/89</td>
<td>99</td>
<td>ZES superior to BMS: lower LL at 8 mo, lower TVR at 3 y; safety similar at 3 y</td>
</tr>
<tr>
<td>II–BMS arm</td>
<td>599</td>
<td>DB-S</td>
<td>36/97</td>
<td>3</td>
<td>50/88</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>II CA</td>
<td>296</td>
<td>Registry</td>
<td>24/97</td>
<td>3</td>
<td>...</td>
<td>...</td>
<td>Assess safety, performance</td>
</tr>
<tr>
<td>III–ZES arm*</td>
<td>323</td>
<td>SB-NI</td>
<td>24/97</td>
<td>3</td>
<td>100/86</td>
<td>99</td>
<td>More men in SES arm (65% vs 81%; ( P=0.001 )); ZES LL inferior to SES; TVF similar; safety similar at 2 y</td>
</tr>
<tr>
<td>III–SES arm*</td>
<td>113</td>
<td>SB-NI</td>
<td>24/99</td>
<td>3</td>
<td>100/83</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>IV–ZES arm*</td>
<td>773</td>
<td>SB-NI</td>
<td>9/96</td>
<td>6</td>
<td>20/88</td>
<td>97</td>
<td>ZES TVF noninferior to PES; ZES LL higher than PES; TLR and TVR similar; safety similar at 9 mo</td>
</tr>
<tr>
<td>IV–PES arm*</td>
<td>775</td>
<td>SB-NI</td>
<td>9/95</td>
<td>6</td>
<td>20/82</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>PK*</td>
<td>43</td>
<td>Registry</td>
<td>9/98</td>
<td>3</td>
<td>...</td>
<td>...</td>
<td>Assess drug elution</td>
</tr>
</tbody>
</table>

DAP indicates minimum recommended duration of dual antiplatelet therapy; DB-S, double-blind, superiority randomized trial; and SB-NI, single-blind, noninferiority randomized trial.

*US trial.

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**Table 2. Efficacy Data**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>F/U, mo</th>
<th>ENDEAVOR II</th>
<th>ENDEAVOR III</th>
<th>ENDEAVOR IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ZES</td>
<td>BMS</td>
<td>ZES</td>
</tr>
<tr>
<td>TVF, %</td>
<td>9</td>
<td>7.9</td>
<td>15.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TLR, %</td>
<td>9</td>
<td>4.6</td>
<td>11.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TVR, %</td>
<td>9</td>
<td>5.6</td>
<td>12.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LL, mm</td>
<td>8</td>
<td>0.36±0.46</td>
<td>0.72±0.61</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

F/U indicates follow-up.

*Test for superiority, †test for noninferiority.
efficacious, there might be an optimal LL that maximizes both qualities. For the time being, the FDA sought assurances that ZES would have a safety profile on par with BMS.

Animal models evaluating for safety have been promising. Tests of endothelial function with endothelial nitric oxide synthase staining and acetylcholine have demonstrated a return to normal vasodilatory response by 28 days, as is seen with BMS. This is in contrast to SES and PES, for which endothelial dysfunction at up to 6 months after implantation has been noted. Histopathological analyses in porcine models at 180 days after ZES implantation have demonstrated low inflammation scores and complete endothelialization. Even at drug concentrations up to 6 times that eluted by a single stent, eosinophils and lymphocytes have not been seen, and complete strut coverage was noted by 28 days after deployment. This is not completely reassuring, however, because animal models of SES and PES reported limited inflammation and complete endothelialization, but human autopsy studies have revealed delayed healing.

In the 3 randomized ENDEAVOR trials, ZES had death, MI, and ST rates similar to BMS at the 3-year follow-up (Table 3). The ENDEAVOR II trial demonstrated no ST event in the ZES group between 30 days and 2 years. At the 9-month follow-up of the ENDEAVOR IV trial, there was a numerically higher incidence of protocol-defined ST in the ZES arm compared with PES (0.8% [6 events] versus 0.1% [1 event], respectively; \( P = \text{NS} \)). Nevertheless, this study was not powered to show significance.

The FDA noted that the individual trials were underpowered to detect differences in clinical outcomes. Pooled analysis of ZES patients from the randomized trials and registries demonstrated a similar incidence of the safety end points (Figure 3). Subgroup analysis of pooled diabetic ZES patients from all 6 trials compared with diabetic patients in the BMS arm in ENDEAVOR II demonstrated similar rates of death, MI, and ST (protocol and Academic Research Consortium [ARC] definition) at the 3-year follow-up. The 95% upper confidence bound for the pooled ZES definite/probable (DP) ST rate for 1 to 3 years’ follow-up is 0.32%. This upper bound is lower than the published DPST range of 0.4% to 0.9% from 1 to 4 years from the pivotal trial data for both the SES and PES randomized clinical trial programs. The implication, then, is that the ZES will prove to be a safer stent because it will not be possible for ENDEAVOR ZES arm patients to experience rates of DPST similar to those of patients from the randomized SES and PES trials at any point in the future. The lack of protocol-defined ST after 6 months in any of the ENDEAVOR trials also is encouraging. More data are required, however, to be absolutely certain that ST frequency after 1 year is equivalent to BMS.

Finally, because the randomized trials are not powered to detect differences in ST alone as an end point, the sponsor is currently enrolling 8800 unrestricted patients in the Patient Related Outcomes With Endeavor Versus Cypher Stenting Trial (PROTECT), a multicenter randomized trial powered for superiority with a primary end point of DPST at 3 years compared with SES.

Antiplatelet Therapy

Dual antiplatelet therapy in the ENDEAVOR trials was recommended for at least 3 months with 1 exception. Because PES require 6 months of dual antiplatelet therapy, the protocol for ENDEAVOR IV recommended at least 6 months of aspirin and thienopyridine. Actual practice was at the discretion of the treating physician, however, so it is unclear how decisions on length of dual antiplatelet therapy were made. At 6 months, the majority of patients in ZES arms remained on a thienopyridine (Table 4). Among the patients in the ENDEAVOR I, II, and II CA trials, 29% were adherent
with dual antiplatelet therapy at 1 year and 12% were adherent at 2 years after stent deployment (Figure 4). In the proposed device labeling, no required duration of antiplatelet therapy was endorsed because of the range of thienopyridine use. Rather, details from the randomized trials were described, and the decision was left to the individual physician. Some panel members thought that although there were no data to support a shorter duration of thienopyridine therapy, ZES may require less given the suggestion of higher LL and complete endothelialization. Thus, ZES might fill the niche in practice when a DES would be preferred over a BMS because of restenosis risk in a patient in whom prolonged dual antiplatelet therapy is going to be problematic, be it because of bleeding risk, planned procedures, or limited ability to adhere to thienopyridine therapy.

**Postapproval Trials**

Postapproval studies are intended to evaluate real-world use of a device over a longer time period than required for premarket approval. The intent is not to evaluate important safety issues that should have been addressed during the premarket process. For the purposes of a postapproval DES registry, the FDA established a goal of DPST incidence of 1%/y and 5-year informed consent to allow a follow-up period long enough to truly determine safety. This incidence and follow-up would place ZES on par with currently available DES and be more likely to uncover the effect of very late ST on cardiac death and MI. Analysis of more complex patient and lesion subsets also was requested. The FDA raised concerns about the sponsor’s planned registries, namely that they were not powered for subgroup analysis or for providing clear guidelines on duration of antiplatelet therapy.

Two postapproval trials are ongoing outside the United States: PROTECT and E-Five. PROTECT has goals of randomizing 8800 patients 1:1 to ZES or SES and determining very late ST incidence at a 3-year follow-up. It also is monitoring the duration of dual antiplatelet therapy. The E-Five single-arm registry has enrolled 8000 patients who received ZES and will evaluate 1-year major adverse cardiovascular events.

The planned postapproval US registry would aim to enroll 2000 patients and pool their data with those from 3300 patients from PROTECT with primary end points of DPST incidence each year for 5 years and the composite of cardiac death and MI each year for 5 years. The goals are to demonstrate a rate of DPST of <1%/y and a rate of cardiac death and MI that is noninferior to that experienced by patients in the BMS arm of ENDEAVOR II.

Dr William Maisel raised concerns about the proposed postmarketing surveillance analysis. The “acceptable” very late DPST rate as defined by the FDA of <1%/y would result in thousands of events if, as expected, ZES were implanted in millions of patients. Recording the reasons that an operator chose ZES over other DES or BMS would be illuminating in defining the clinical judgments that influence these decisions. Moreover, a registry on the order of 10 000 patients with at least 3 years of follow-up would be required to guarantee adequate power to detect meaningful differences in rare events like ST. Dr Maisel concluded by recommending that these concerns be incorporated into the required conditions of postmarket analysis if the panel voted to approve ZES.

![Figure 3. Cumulative incidence of clinical events at the 3-year follow-up.](http://circ.ahajournals.org/)

Table 3. Clinical Outcomes at Latest Available Follow-Up<sup>15</sup>

<table>
<thead>
<tr>
<th>ENDEAVOR</th>
<th>I</th>
<th>II-ZES</th>
<th>II-BMS</th>
<th>II CA</th>
<th>III-ZES</th>
<th>III-SES</th>
<th>IV-ZES</th>
<th>IV-PES</th>
<th>PK</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>97</td>
<td>577</td>
<td>579</td>
<td>288</td>
<td>313</td>
<td>112</td>
<td>740</td>
<td>734</td>
<td>42</td>
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<tr>
<td>Follow-up, mo</td>
<td>48</td>
<td>36</td>
<td>36</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Death, %</td>
<td>4.1</td>
<td>3.3</td>
<td>4.5</td>
<td>1.4</td>
<td>1.6</td>
<td>4.5</td>
<td>0.7</td>
<td>0.8</td>
<td>4.8</td>
</tr>
<tr>
<td>Cardiac death, %</td>
<td>0</td>
<td>1.6</td>
<td>2.4</td>
<td>0.7</td>
<td>0</td>
<td>0.9</td>
<td>0.4</td>
<td>0.3</td>
<td>4.8</td>
</tr>
<tr>
<td>MI, %</td>
<td>1</td>
<td>3.3</td>
<td>4.3</td>
<td>5.9</td>
<td>0.6</td>
<td>3.6</td>
<td>1.5</td>
<td>2.5</td>
<td>2.4</td>
</tr>
<tr>
<td>TVF, %</td>
<td>5.2</td>
<td>12.8</td>
<td>21.4*</td>
<td>16.3</td>
<td>14.4</td>
<td>13.4</td>
<td>6.8</td>
<td>7.4</td>
<td>11.9</td>
</tr>
<tr>
<td>TLR, %</td>
<td>3.1</td>
<td>7.3</td>
<td>14.7*</td>
<td>7.3</td>
<td>7.0</td>
<td>4.5</td>
<td>4.2</td>
<td>2.7</td>
<td>2.4</td>
</tr>
<tr>
<td>TVR, %</td>
<td>5.2</td>
<td>9.5</td>
<td>4.8*</td>
<td>12.5</td>
<td>13.7</td>
<td>9.8</td>
<td>5.5</td>
<td>5.0</td>
<td>7.1</td>
</tr>
<tr>
<td>ST, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Protocol definition</td>
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<td>1.2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.8</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>DPST (TLR censored)</td>
<td>1</td>
<td>0.9</td>
<td>1.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.9</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>DPST (TLR uncensored)</td>
<td>1</td>
<td>0.9</td>
<td>1.6</td>
<td>0</td>
<td>0.3</td>
<td>0</td>
<td>0.9</td>
<td>0.1</td>
<td>0</td>
</tr>
</tbody>
</table>

*P<0.001.
Other Considerations

With any device, risks must outweigh benefits, and DES efficacy should be evaluated in the context of long-term safety as defined by rates of death, MI, and ST. The sponsor concluded that the submitted data included more patients than the SES and PES premarket approval applications combined with 3 times the length of follow-up. Clinical and angiographic superiority of ZES compared with BMS was present up to the 3-year follow-up. ZES was clinically noninferior compared with PES but angiographically inferior to both SES and PES. The data density available on ZES compares well to that currently available for SES and PES that first led to an appreciation of the risk of very late ST. No signal of increased very late ST (protocol or ARC definition) or increased death and MI was noted at the 3-year follow-up among patients receiving ZES compared with patients in the BMS arm of ENDEAVOR II (Figure 3).

In response to concerns from the panel about what niche ZES would fill, given the current availability of BMS, SES, and PES, Dr Leon noted potential advantages. There was high device and procedural success in the ENDEAVOR II, III, and IV trials with no significant difference in deployment of ZES compared with the Driver BMS or PES. There was some improved deliverability of ZES compared with SES in the ENDEAVOR III trial (98.8% versus 94.7%; P<0.05). He stated that ZES is likely to be as effective at preventing restenosis while being safer than SES or PES. It also might become the preferred choice among patients who cannot adhere to long-term thienopyridine therapy.

Panel Recommendations

At the conclusion of these presentations, the CSDP was in general agreement that the data submitted on ZES provided reasonable assurance of safety in the target population, although ongoing follow-up is imperative to prove this. The panel also thought that the data demonstrated a reasonable level of effectiveness compared with BMS. As clinical noninferiority was achieved compared with PES, the consensus was that there was a reasonable likelihood that ZES will achieve a clinically meaningful end point when used in patients.

Significant concerns were raised about the proposed language regarding the recommended duration of dual antiplatelet therapy. The FDA CSDP recommendation from December 2006 advocated a minimum of 12 months of dual antiplatelet therapy in patients at low risk for bleeding complications, as per the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions guidelines. Given this endorsement and the lack of data on duration of clopidogrel use in the ENDEAVOR trials, a condition was added stating that the product labeling should be consistent with the guidelines (Table 5).

With regard to the proposed postmarket evaluation, the CSDP was comfortable with a single-arm registry with 5-year follow-up compared with historical BMS patients, namely the 600 patients from the ENDEAVOR II trial. Objective end points using the standardized ARC ST definitions were endorsed. The number of patients was stated to be inadequate. A condition was added specifying that at least 5000 patients are required (Table 5).

Table 4. Antiplatelet Therapy at 6 Months in ZES Arms

<table>
<thead>
<tr>
<th>Medication, % (n)</th>
<th>ENDEAVOR II (n=598)</th>
<th>ENDEAVOR II CA (n=296)</th>
<th>ENDEAVOR III (n=323)</th>
<th>ENDEAVOR IV (n=773)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>96.9 (561/579)</td>
<td>95.1 (272/286)</td>
<td>95.9 (303/316)</td>
<td>95.8 (713/744)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>65.5 (377/576)</td>
<td>59.4 (170/286)</td>
<td>90.1 (264/293)</td>
<td>94.8 (697/735)</td>
</tr>
<tr>
<td>Aspirin + thienopyridine</td>
<td>64.8 (375/579)</td>
<td>55.9 (161/288)</td>
<td>81.6 (258/316)</td>
<td>92.3 (687/744)</td>
</tr>
</tbody>
</table>

Dual antiplatelet therapy was higher at 6 months in the US trials (ENDEAVOR III and IV).

Table 5. FDA CSDP Recommendations

- Premarket approval application is approved with 2 conditions
  - Completion of a postmarketing registry that meets the following criteria
    - Single arm
    - 5-year follow-up
    - At least 5000 patients
    - Compared with the historical BMS arm (from ENDEAVOR II trial)
    - Objective end points
      - Primary: very late ST
      - Secondary: all-cause death and MI
    - Rigorous data monitoring
- Product labeling should endorse dual antiplatelet therapy for a minimum of 12 mo as stated in the ACC/AHA/SCAI guidelines, consistent with the recommendations arrived at during the December 2006 FDA CDSP meeting

ACC/AHA/SCAI indicates American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions.
Conclusions

The panel voted unanimously to approve the premarket application for the Endeavor ZES stent with the 2 conditions mentioned previously. The sponsor was able to convincingly demonstrate to the CSDP that the ZES is reasonably effective and reasonably safe for the proposed indication. The FDA does not require that the sponsor prove that a device is better than similar devices on the market to gain approval. The FDA is not required to follow the recommendations of the panel but typically does. If the ZES is approved, the postmarketing surveillance analysis and registries from other centers will help to elucidate whether the safety and efficacy of ZES are an improvement over available DES. Performance of this stent in real-world use in more complex lesions over the long term remains to be seen.

Disclosures

None.

References


Key Words: drug-eluting stents • heart disease • atherosclerosis
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