Trends-in-Medicine

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by Lynne Peterson

SUMMARY

The FDA Circulatory System Devices Advisory Committee has recommended unanimously that Medtronic's second-generation drug-eluting stent be approved. However, the panel attached two conditions to approval: 1) Changes to the post-marketing plan to make it larger and more rigorous, and 2) Give it the same label language on dual antiplatelet use as other drug-eluting stents. The bottom line is that Endeavor is likely to get approved but should not have a more favorable label than Johnson & Johnson's Cypher or Boston Scientific's Taxus. The stent thrombosis rate with Endeavor in the ENDEAVOR-IV trial was 0.8%, with 3 stent thromboses in the first 30 days and another 3 between 1 and 6 months, but none after that – yet.

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FDA Panel Gives Thumbs Up to Medtronic's Endeavor Drug-Eluting Stent

Gaithersburg, MD
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The FDA's Circulatory System Devices Advisory Committee voted ***unanimously*** to recommend approval of Medtronic's Endeavor drug-eluting stent (DES) – with two conditions:

1. That Medtronic conduct a post-marketing study of at least 5,000 patients, with a primary endpoint of very late stent thrombosis and a secondary endpoint of death/MI. This should be a single-arm registry using objective performance criteria (historical control) from bare metal stents (BMS), with rigorous data monitoring and at least 5-year follow-up.
2. That the Endeavor label contain language on the use of dual antiplatelet therapy consistent with prevailing FDA language (i.e., the same language Taxus and Cypher are about to get, which is in accordance with AHA/ACC/SCAI guidelines).

Endeavor is a zotarolimus-eluting, cobalt alloy Driver (3.0 mm and 3.5 mm) or Micro-Driver (2.5 mm) stent with a phosphorylcholine (PC) polymer coating (PhosphoCoat). The company is seeking approval of Endeavor with three delivery systems: over-the-wire (OTW), rapid exchange (RX), and Multi-Exchange-II (MX^2) for:

> "improving coronary luminal diameter in patients with ischemic heart disease due to *de novo* lesions of length ≤27 mm in native coronary arteries with reference vessel diameters of ≥2.5 mm to ≤3.5 mm."

The FDA is not bound to follow the advice of its advisory panels, but in this case final FDA approval appears likely, though FDA officials would not say when they could be expected to make their decision.

The key issues the panel considered – but decided were not barriers to approval – were the higher-than-usual late loss with Endeavor, the limited number of patients with long-term follow-up, and stent thrombosis. After the panel meeting, the panel chair, Dr. Clyde Yancy, medical director of the Baylor Heart and Vascular Institute, said there was adequate information for the panel to make its decision, describing the data as "orderly and consistent," and saying the data looked good in the aggregate.

During the discussions, comments by the interventional cardiologists on the panel hinted at the idea that there could be a potential safety advantage with Endeavor, but they insisted this is still theoretical and has not been proven yet. They urged Medtronic to do studies to determine this. After the meeting, Dr. Yancy urged doctors and patients to be careful about the take-away message, "My sense is that

there is nothing in this application that leverages the sponsor (Medtronic) or lets the panel say there is a decreased need for dual antiplatelet therapy with this stent. The guidelines (on dual antiplatelet use) should prevail. One panel member suggested there may be a hint of some benefit based on re-endothelialization, but we don't have the data yet. Another panel member said it may be worthwhile to attempt to prove (there is a safety advantage). But I didn't get the sense that anyone (on the panel) would walk out and say this stent doesn't require as much antiplatelet therapy as the existing drug-eluting stents."

Dr. Yancy's take-home message from the meeting is: "Endeavor works. It is evolutionary, not revolutionary. It adds another option to the field. It brings more data forward, and it provides more assurance of the safety of drug-eluting stents, but we need more data on late stent thrombosis."

Implications for Abbott's Xience stent

What lessons came out of this meeting with respect to the outlook for Abbott's Xience stent, an everolimus-eluting Vision stent which is expected to come before this same advisory committee in November 2007 (perhaps the 29th)?

- Panel members clearly want to see a **significant number of patients and two- or three-year follow-up**. With Endeavor, they would have liked more patients, but 600-700 out to two or three years proved sufficient. Xience has far fewer (~900 at 1 year, ~30 at 2 years, and none with 3 years follow-up). However, an Abbott official said the company has been capturing more long-term data and will have 200-300 patients with 2-year data for the panel. The panel likely will not like this, but it is not clear that this is a killer. If the FDA Circulatory Systems Advisory Committee meeting, tentatively scheduled for November 29th, does consider Xience that will probably send a message to panel members that more data would be nice but not necessarily a requirement for approval.
- Panel members could be swayed by **extremely consistent data** across several trials, and Xience has the SPIRIT series, but the larger numbers won't be available until at least February or March 2008.
- The panel is unlikely to challenge the **safety of everolimus** unless the FDA does so. There was no discussion at the Endeavor panel about the safety of zotarolimus.
- Panel members could be persuaded by **preclinical data** if that data are strong enough. Panel members were impressed with the Endeavor preclinical data, though they still want to see some things – like the effect of early endothelialization on the rate of very late stent thrombosis – proven clinically. Dr. Renu Virmani of CV Pathology has suggested at other meetings that the best re-endothelialization occurs with Xience.
- The panel may not get a very negative **message in the FDA briefing materials** for the Xience panel. There is no indication that the FDA will be highly critical of Xience. And remember that FDA officials previously indicated that neither Endeavor nor Xience would be held to the new, higher standards that the December 2006 FDA Advisory Committee on DES safety recommended for new stents. And that proved true with Endeavor. Three months after the December 2006 Advisory Committee meeting, an FDA official said, "For companies (with DES) in progress, there are serious issues that we do feel need to be addressed, but we also recognize that these programs went forward based on best guidance at the time, so we have been sitting down with the companies and starting to talk about the best way to address our concerns without throwing the blocks (brakes) on ongoing programs." The official said the FDA didn't intend to change the rules of the game on companies that were nearly finished with their DES application, but the Agency did plan to change them for companies that were not as far along.

Medtronic Presentation

Dr. Rick Kuntz, senior vice president of Medtronic, noted that:

- There is no signal of adverse safety events prior to 1 year or in years 1-3 with Endeavor.
- On target vessel failure (TVF), Endeavor showed superiority to a bare metal stent and non-inferiority to Taxus.
- On target lesion revascularization (TLR), Endeavor showed superiority to BMS and no difference vs. Taxus.
- Endeavor has a well-characterized drug safety profile, a polymer and non-cytotoxic drug that preserves endothelial function with low inflammation and enhanced deliverability.

Total Xience Patients Expected to Be Available for Analysis at Panel Meeting

Measurement	3 months	6 months	9 months	12 months	2 years	3 years
Number of patients	2,192	2,192	918	27	27 *	0

Source: Wachovia Capital Markets, LLC * Abbott officials said they will have 200-300 patients.

Xience Patient Follow-up Data That May Be Available for November Panel

SPIRIT-I	SPIRIT-II	SPIRIT-III	SPIRIT-III Japan	SPIRIT-IV	SPIRIT-V Diabetic	SPIRIT-V Registry
44 months = 27 patients	12 months = 223 patients 24 months: N/A	21 months = 668 patients 6 months = 80 patients with 4.0 mm stent	8 months = 88 patients	6 months = 606 patients	N/A	6 months = 500 patients 1 month = 1,800 patients

Drug and coating

Sean Salmon, vice president and general manager of Medtronic Vascular, told the panel that zotarolimus is both hydrophobic and lipophilic, eluting rapidly from the stent, with rapid arterial tissue loading and drug retention that is sustained for ~28 days. He also said the stent's PhosphoCoat is "thrombo-resistant":

- Non-thrombogenic (hemocompatible) – non-inflammatory, hydrophilic, and inhibits monocyte adhesion.
- PC-coated stents have shown less platelet adhesion compared to uncoated stents in a baboon-shunt flow model.

Preclinical experience

Dr. LeRoy LeNarz, chief medical officer and global vice president for medical affairs at Medtronic Vascular, discussed the drug and preclinical characteristics of Endeavor. He said studies found:

- No respiratory toxicity in rats.
- Non-antigenic in guinea pigs.
- No skin sensitization by lymph node assay.
- No effect on platelet aggregation at 50x the higher anticipated C_{max} for 48 mm stent length.
- No effect on heart rate, blood pressure, systemic vascular resistance, pulmonary vascular resistance, and QTc in dogs.
- No significant hemodynamic findings in conscious primates.
- Feces is the predominant path of excretion.
- Metabolism mainly by the CYP3A4 pathway, with minimal interaction with ketoconazole in dog and man.

Dr. LeNarz also said preclinical studies found:

- No medial necrosis or aneurysms.
- Low levels of drug/polymer-induced inflammation.
- Rapid, complete, and functional endothelialization.
- Biocompatibility of the drug/polymer.
- Normal endothelial coverage.
- Favorable safety margins.
- No anticipated drug-drug interaction.
- No treatment-emergent events as a combination (drug-device) product.

Clinical experience

Dr. Martin Leon, an interventional cardiologist from Columbia University, and the principal investigator for the ENDEAVOR-III and ENDEAVOR-IV trials, presented the clinical findings with Endeavor. He stressed the need to "preserve the efficacy advantage of DES while improving safety and deliverability." He called Endeavor "a highly deliverable platform."

To put the Endeavor findings in perspective, Dr. Leon reviewed the consensus observations from the December 2006 FDA Advisory Committee meeting on DES safety:

- Very late stent thrombosis occurs after 1 year at a rate of 0.2% - 0.6% per year and may represent a constant hazard.
- Little is known about DES safety for "off-label" use indications, but preliminary data suggest a higher frequency of very late stent thrombosis with on-label use.
- Dual antiplatelet therapy should be extended in some DES patients, but duration of therapy, associated risk, and impact on very late stent thrombosis is controversial.

He offered these insights on current DES:

- **Efficacy –** The relationship between late loss and TLR is non-linear, and moderate late loss may still result in low TLR. Angiographic follow-up has a profound impact on TLR.
- **Safety –** DES safety evaluations can no longer be confined to 1 year, and very late stent thrombosis is increased vs. BMS.
- **Clinical trial design –** Larger, non-inferiority randomized clinical trials vs. approved DES and even larger "real world" studies are now required.

Dr. Leon then reviewed the findings of some of the Endeavor trials:

- **ENDEAVOR-II** (vs. bare Driver) showed:
  - A similar safety profile (death, MI, and stent thrombosis) through 3 years of follow-up.
  - Improved angiographic results at 8 months follow-up (late loss and binary restenosis).
  - Superior TVF rate (by 48%), due largely to a diminished TVR requirement (by 55%), which persisted through 3 years follow-up.
- **ENDEAVOR-III** (vs. Cypher) showed:
  - Non-Q-wave rate of 0.6% with Endeavor vs. 3.5% with Cypher.
  - Higher angiographic late loss at 8 months.
  - Reduced peri-procedural non-Q-wave MIs (0.6% with Endeavor vs. 3.5% with Cypher), low rates of death, Q-wave MI, and stent thrombosis through 2 years of follow-up.
  - Similar TVF through 2 years of follow-up.
- **ENDEAVOR-IV** (vs. Taxus). This was the first presentation of this data, and it showed:
  - No important differences were seen in any measurement.

- 3 additional stent thromboses occurred in the Endeavor arm *after 30 days* – one associated with an MI and two not associated with MI.
- The Endeavor stent thrombosis rate was 0.8%.
- A post-hoc subgroup analysis found no significant difference between Endeavor and Taxus on TVF or TVR or in diabetics, but favored Endeavor on cardiac death/MI and in lesions ≥20 mm.
- Endeavor reduced peri-procedural non-Q-wave MIs and had a similar safety (death, Q-wave MI, and stent thrombosis) profile through 9 months of follow-up.
- The trial met the primary endpoint of TVF.
- Similar TVR/TLR was seen in subsets of interest through 9 months of follow-up.
- Endeavor had a higher angiographic late loss at 8 months of follow-up.

Dr. Leon concluded that the Endeavor trial results were consistent across all the studies.

- Safety profile similar to a bare Driver.
- Superior reduction in restenosis vs. a bare Driver.
- Comparable clinical outcomes (measured by TVF) vs. Taxus.
- Durable clinical outcomes during long-term follow-up (to 3 years).
- Consistent angiographic and clinical outcomes across all the randomized trials.

Safety

Dr. Laura Mauri, chief scientific officer at the Harvard Clinical Research Institute (HCRI) and a member of the Medtronic Advisory Board, reviewed the Endeavor safety findings. Her safety summary, based on the dataset of 2,132 Endeavor patients and 59 Driver patients, found:

- No evidence of increased rates of death, cardiac death, or MI vs. Driver out to 3 years.
- No evidence of increased stent thrombosis risk within 1 year (0.7% vs. 1.3% ARC definite/probable) ***or*** in years 1-3 (0.1% vs. 0.2%) with Endeavor vs. bare Driver.

Post-approval studies

Dr. Kuntz described the Endeavor post-market plans:

1. Ongoing, international PROTECT randomized clinical trial (RCT) vs. Cypher was designed to estimate very late stent thrombosis (>1 year). It will enroll 8,800 patients at >200 sites. The primary endpoint is ARC definite or probable stent thrombosis at 3 years.

ENDEAVOR-IV Results

Measurement	Endeavor n=773	Taxus n=775
30-day results		
Stent thrombosis	0.4%	0.1%
TLR	0.4%	0.8%
TVR	0.4%	0.9%
MACE	1.2%	3.0%
Q-wave MI	0.3%	0.1%
Non-Q-wave MI	0.5%	2.2%
TVF	1.0%	3.0%
MI	0.8%	2.3%
Cardiac death and MI	0.9%	2.3%
9-month results		
Stent thrombosis 0-270 days	0.8%	0.1%
Stent thrombosis 31-270 days	0.4%	0
TLR	4.2%	2.7%
TLR by angiographic follow-up	6.9%	3.0%
TVR	5.5%	5.0%
TVR by angiographic follow-up	7.6%	6.0%
Primary endpoint: TVF	6.8%	7.4% (p<.001 for non-inferiority)
MI	1.5%	2.5%
Cardiac death and MI	1.9%	2.7%
In-stent late loss	0.67 mm	0.42 mm
In-segment late loss	0.36 mm	0.23 mm
Late incomplete apposition	0.9%	3.2%

Endeavor Stent Thrombosis

Stent thrombosis *(ARC definite and probable)*	Endeavor n=773
Early (0-30 days)	0.3%
Late (31-360 days)	0.4%
Very late (361 days to 3 years)	0.1%
Cumulative	0.8%

Comparison of Stent Thrombosis Rates with DES

Drug-eluting stent	Stent thrombosis
Johnson & Johnson's Cypher	1.2%
Boston Scientific's Taxus	1.3%
Medtronic's Endeavor	0.8%

Stent Thrombosis

December 2006 FDA Advisory Committee observations	Endeavor program
An increased stent thrombosis rate >1 year for DES vs. BMS	No increased stent thrombosis seen before or after 1 year, regardless of definition
No increased risk of death or MI due to revascularization or insufficient discriminating data	Lower TLR rates without an increase in very late stent thrombosis rates, and numerically lower rates of death and MI at 3 years
Larger and longer pre-market clinical analysis was recommended	3 or more years of data sufficiently powered to show durable lower TLR rates, and safe very late stent thrombosis rates with measurable confidence boundaries
Larger and longer post-approval studies with uniform stent thrombosis definitions and monitoring of antiplatelet therapy	Large post-market RCT to test for lower very late stent thrombosis

2. E-Five, a single-arm, international, all-comers registry that will enroll 8,000 patients at 200 international sites. The primary endpoint is MACE at 12 months.
3. U.S. post-approval single-arm registry, an FDA-required U.S. post-market study. It will include ~5,300 patients (2,000 from 100 U.S. sites and ~3,000 pooled from the OUS PROTECT trial). Primary endpoints are ARC definite and probable stent thrombosis measured annually for 5 years and cardiac death/MI annually for 5 years.

Panel member questions for Medtronic

The panel appeared very impressed with the Medtronic presentation, and the tone of the questioning was generally mild and friendly, not confrontational.

Is there an advantage to Endeavor on non-Q-wave MI?

Dr. Yancy, the panel chair, asked if the difference in peri-procedural non-Q-wave MI (in favor of Endeavor) is a play of chance or due to deliverability of the Endeavor stent. Dr. Leon responded, "I don't think it was a deliverability issue…I do think it is a meaningful difference…and I think it does reflect the intrinsic properties of the stent…It is a consistent and, I think, meaningful observation."

How does Endeavor compare to Taxus?

Dr. Leon said, "We found nothing to indicate that Endeavor performed less well than Taxus…Late loss across subsets are similar…TLR is similar in all subgroups (diabetes, long lesions, small vessels, multiple stents, LAD lesions) vs. Taxus. In ENDEAVOR-IV, there really is no suggestion that there is a difference in either TLR or TVR favoring either Taxus or Endeavor…but it is a small number of patients."

How will doctors choose among available DES?

- *Dr. Leon:* "We look at three things: delivery, safety, and efficacy. I believe this device has comparable efficacy in the kinds of patients studied in these trials, but certainly superior deliverability and safety…so in a patient where I would think deliverability could be problematic, it would be my choice…In a situation where I think safety is an issue, especially in a patient where I am concerned they won't be able to extend antiplatelet therapy beyond the first few months, it would be my choice."
- *Dr. Douglas Morrison, an interventional cardiologist from Yakima Heart Center in Yakima, WA:* "How is it different in deliverability?"
- *Dr. Leon:* "That is subjective. Driver is an advanced, superior device…flexible…and an advanced stage of technology…which is not to say other devices can't be delivered, but they are older versions of stent technology."
- *Dr. Morrison:* "So, I won't be able to make the case from this data?"
- *Dr. Leon:* He pointed out that device success has been 97%-99% with Endeavor.

TLR

Dr. Judah Weinberger, an interventional cardiologist from Columbia University, asked about blinding with respect to follow-up and total TLR. Dr. Leon responded that most TLR was handled by a different interventional cardiologist from the doctor who implanted the original stent. He also said total lesion revascularization was 5.5% with Endeavor vs. 4.6% for Taxus.

Size of the trials

Dr. John Somberg, a professor of medicine and pharmacology at Rush University Medical Center, asked to be convinced that there are enough patients in these trials to make conclusions on the stent thrombosis risk, "We sat through a panel on late stent thrombosis, and initially when devices were presented with small numbers, it was not seen…And now it is established that they have a higher incidence of late stent thrombosis, and there is a safety issue…The implication I got from the Medtronic presentation is that 'We don't have this,' and I want to know the basis for that…and I don't see any justification for that (claim)." Dr. Mauri from HCRI responded that she believes the numbers are "reassuring" and the bare Driver performed consistent with historical controls…She also suggested that there were not that many more patients in other DES stent thrombosis studies, "The Stone (Dr. Gregg Stone) paper's pooled arm had 795 patients to 3 years with a bare stent and 1,106 paclitaxel patients to three years."

Late loss

Dr. Morrison said, "This was a very good presentation, but how concerned are you and should we be that in ENDEAVOR-II the stent didn't meet the late loss non-inferiority measure vs. Cypher, and in ENDEAVOR-III didn't quite meet non-inferiority late loss vs. Taxus? I think we are all reassured by the previous Driver and PC (coating) experience …but are you concerned about the late loss? Medtronic speakers insisted they are not concerned about the late loss.

Medtronic discussion with reporters

During the panel's lunch break, Medtronic hosted a media lunch during which Scott Ward, president of Medtronic Vascular, told reporters, "One of the overarching observations from the Medtronic and FDA presentations was the striking concordance of those two presentations…I think the FDA agrees with the company on every salient point…It is unusual for a panel meeting to see such concordance…And the FDA reviewers were defending the Medtronic position toward the end of the morning…which is nice but uncommon."

What is your message to interventional cardiologists if Endeavor gets approved?

Ward said: "Medtronic will say that Endeavor is a very deliverable stent, perhaps the most deliverable…We have a favorable safety profile both early and late, in comparison to both DES and BMS…and we have an efficacy profile very

similar to other DES. Some physicians can achieve the efficacy that they are seeking with DES with no compromise on long-term safety." Dr. Jeff Popma, director of invasive cardiovascular services at Caritas St. Elizabeth's Medical Center in Boston, added, "There will be an additional stent in the DES toolbox. Which you choose will depend on deliverability, and we know from Europe and the U.S. that Driver is very, very deliverable vs. what we currently have as first generation DES (Cypher and Taxus). You choose on efficacy and…you pick based on the perception of safety…(with Endeavor) as you look at all the point estimates, they are all on the right side for safety – not statistically, but directionally…so I think this will be a competitive product and will add to our toolbox."

What makes Endeavor more deliverable?

Ward said, "It is the design of Driver…It is very conformable …has very thin struts…and a softer metal cobalt chromium." Dr. Popma added that the balloon on which Endeavor is mounted is also a factor, "This is a very deliverable balloon-delivery system."

Is there really no stent thrombosis after six months?

Ward said: "Yes. The ARC definite/probable rate of stent thrombosis is 0.08% after 6 months. There were two events in that period, which is not unexpected. Stent thrombosis occurs with BMS as well."

How would you respond to a panel member suggesting that Endeavor is less effective than DES but better than BMS?

Ward focused his answer on the comparison to BMS, saying, "At the end of the day, as you look at the performance of this product, the data are really very strong…and demonstrates that Endeavor is statistically and clinically better than Driver…The Endeavor performance is very, very consistent, and the FDA loves consistency." Dr. Popma said, "Effectiveness at doing what? Compared to Taxus and Cypher, Endeavor is less effective in preventing (late loss)…but (how clinically significant is that?)…I think doctors will look at TLR, and consider that it is low (with Endeavor)…The bottom line is there is more tissue (late loss), but from a clinical standpoint they (Endeavor and Taxus) are very similar."

What does the TLR rate in ENDEAVOR-IV mean to the practicing interventionalist?

Dr. Popma said, "Clinicians will look at the totality of the package…and if you are within a 1% range of efficacy – TLR 3.5% vs. 2.7% is within 1% – and if you have a safety advantage, safety trumps everything. In clinical practice, when you have to balance safety and efficacy, safety wins today. Safety is paramount."

How should the higher late loss be considered?

Ward said, "Late loss can be considered a measure of healing in the stent…When we talk of the next generation of DES, we are trying to talk about healthy healing…where there is a balanced amount of healing to cover the stent struts, reduce inflammation, and ultimately reduce the formation of thrombosis…vs. not having so much endothelial growth that you get occlusions."

FDA Presentation

The FDA presented panel members with detailed charts of its interpretation of the Endeavor trial data. (*A few of those charts are reprinted on this and the next 2 pages*.)

The FDA's Dr. Andrew Farb reviewed all of the Endeavor trials, but there were no new data or interpretation. Interesting comments included:

- "FDA believes that clinical outcomes in diabetics should be considered in the review of the Endeavor stent program…In pooled analyses, Endeavor consistently performed better than a bare Driver in diabetics."
- "Stent thrombosis numerically favors Endeavor at all time points vs. Driver."

Dr. Farb summarized:

- Endeavor ***met*** its primary TVF superiority endpoint in ENDEAVOR-II.
- Endeavor ***met*** the primary TVR non-inferiority endpoint in ENDEAVOR-IV.
- Endeavor ***met*** the late loss endpoint vs. a bare Driver in ENDEAVOR-II.
- Endeavor ***failed to meet*** the non-inferiority late loss endpoint vs. Cypher in ENDEAVOR-III and vs. Taxus in ENDEAVOR-IV.
- Increased rates of death, cardiac death, MI, cardiac death/MI, or non-cardiac death for Endeavor vs. control have not been observed.
- Pooled analyses do not demonstrate any unanticipated safety signals.

Endeavor Patient Follow-Up

Trial	6 months	9 months	12 months	2 years	3 years	4 years
ENDEAVOR-I	100	100	100	99	99	98
ENDEAVOR-II	596	593	592	590	587	577
ENDEAVOR-II-CA	296	295	293	292	288	-
ENDEAVOR-III	323	321	321	320	313	-
ENDEAVOR-IV	770	766	740	-	-	-
ENDEAVOR-PK	43	43	42	-	-	-
Total	**2,128**	**2,118**	**2,088**	**1,301**	**1,287**	**675**

FDA View of Endeavor Safety at 9 Months

Adverse event	ENDEAVOR-I	ENDEAVOR-II		ENDEAVOR-II-CA	ENDEAVOR-III		ENDEAVOR-IV		ENDEAVOR-PK	Pooled Endeavor
		End	Driver		End	Cypher	End	Taxus		
All death	0.0%	1.2%	0.5%	0.7%	0.6%	0.0%	0.7%	0.8%	4.8%	0.9%
Cardiac death	0.0%	0.8%	0.5%	0.7%	0.0%	0.0%	0.4%	0.3%	4.8%	0.6%
MI	1.0%	2.7%	3.9%	5.1%	0.6%	3.5%	1.5%	2.5%	2.4%	2.2%
Death/MI	1.0%	3.7%	4.4%	5.5%	1.2%	3.5%	2.2%	3.3%	7.1%	3.0%
TVF	2.0%	7.9%	15.1%	13.0%	11.8%	11.5%	6.8%	7.4%	11.9%	8.6%

FDA View of Endeavor Safety at 12 Months

Adverse event	ENDEAVOR-I	ENDEAVOR-II		ENDEAVOR-II-CA	ENDEAVOR-III		ENDEAVOR-IV		ENDEAVOR-PK	Pooled Endeavor
		End	Driver		End	Cypher	End	Taxus		
All death	0.0%	1.4%	0.7%	0.7%	0.6%	0.9%	---	---	---	0.9%
Cardiac death	0.0%	1.0%	0.7%	0.7%	0.0%	0.0%	---	---	---	0.6%
MI	1.0%	2.7%	3.9%	5.5%	0.6%	3.6%	---	---	---	2.7%
Death/MI	1.0%	3.9%	4.6%	5.8%	1.3%	4.5%	---	---	---	3.5%
TVF	2.0%	10.0%	16.6%	15.8%	12.8%	11.6%	---	---	---	11.4%

FDA View of Endeavor Stent Thrombosis at 9 Months

Stent thrombosis	ENDEAVOR-I	ENDEAVOR-II		ENDEAVOR-II-CA	ENDEAVOR-III		ENDEAVOR-IV		ENDEAVOR-PK	Pooled Endeavor
		End	Driver		End	Cypher	End	Taxus		
Protocol	1.0%	0.5%	1.2%	0.0%	0.0%	0.0%	0.8%	0.1%	0.0%	0.5%
ARC definite + probable, *censored*	1.0%	0.5%	1.4%	0.0%	0.0%	0.0%	0.9%	0.1%	0.0%	0.5%
ARC definite + probable, *uncensored*	1.0%	0.5%	1.4%	0.0%	0.0%	0.0%	0.9%	0.1%	0.0%	0.5%

FDA View of Endeavor Stent Thrombosis at 12 Months

Stent thrombosis	ENDEAVOR-I	ENDEAVOR-II		ENDEAVOR-II-CA	ENDEAVOR-III		ENDEAVOR-IV		ENDEAVOR-PK	Pooled Endeavor
		End	Driver		End	Cypher	End	Taxus		
Protocol	1.0%	0.5%	1.2%	0.0%	0.0%	0.0%	---	---	---	0.3%
ARC definite + probable, *censored*	1.0%	0.7%	1.4%	0.0%	0.0%	0.0%	---	---	---	0.4%
ARC definite + probable, *uncensored*	1.0%	0.7%	1.4%	0.0%	0.3%	0.0%	---	---	---	0.5%

FDA View of Endeavor Stent Thrombosis at 24 Months

Stent thrombosis	ENDEAVOR-I	ENDEAVOR-II		ENDEAVOR-II-CA	ENDEAVOR-III		ENDEAVOR-IV		ENDEAVOR-PK	Pooled Endeavor
		End	Driver		End	Cypher	End	Taxus		
Protocol	1.0%	0.5%	1.2%	0.0%	0.0%	0.0%	---	---	---	0.3%
ARC definite + probable, *censored*	1.0%	0.7%	1.4%	0.0%	0.0%	0.0%	---	---	---	0.4%
ARC definite + probable, *uncensored*	1.0%	0.7%	1.4%	0.0%	0.3%	0.0%	---	---	---	0.5%

FDA View of Endeavor Stent Thrombosis at 36 Months

Stent thrombosis	ENDEAVOR-I	ENDEAVOR-II		ENDEAVOR-II-CA	ENDEAVOR-III		ENDEAVOR-IV		ENDEAVOR-PK	Pooled Endeavor
		End	Driver		End	Cypher	End	Taxus		
Protocol	1.0%	0.5%	1.2%	---	---	---	---	---	---	0.6%
ARC definite + probable, *censored*	1.0%	0.9%	1.4%	---	---	---	---	---	---	0.9%
ARC definite + probable, *uncensored*	1.0%	0.9%	1.6%	---	---	---	---	---	---	0.9%

FDA View of Endeavor Efficacy

Measurement	ENDEAVOR-I	ENDEAVOR-II	ENDEAVOR-II-CA	ENDEAVOR-III	ENDEAVOR-IV	ENDEAVOR-PK	ENDEAVOR-Japan
Endeavor patients	97	577	288	313	740	42	99
Diabetics	---	18.2%	---	29.7%	31.2%	---	---
Follow-up	4 years	3 years	2 years	2 years	9 months	9 months	9 months
Type of trial	Non-randomized, single-arm trial	Double-blind, superiority	Registry, single-arm, non-randomized	Single-blind, non-inferiority	Single-blind, non-inferiority	Non-randomized, single-arm trial	---
Primary endpoint	30 day MACE	Met; TVF at 9 months = 7.9% (p<.001)	30 day MACE	Not met, late loss	Met; TVF at 9 months = 6.8% (p<.001)	30-day PK parameters	TVF at 9 months
Outcomes at latest available clinical follow-up							
Death	4.1%	3.3%	1.4%	1.6%	0.7%	4.8%	---
Cardiac Death	0.0%	1.6%	0.7%	0.0%	0.4%	4.8%	---
MI	1.0%	3.3%	5.9%	0.6%	1.5%	2.4%	---
TVF	5.2%	12.8%	16.3%	14.4%	6.8%	11.9%	---
TLR	3.1%	7.3%	7.3%	7.0%	4.2%	2.4%	---
TVR	5.2%	9.5%	12.5%	13.7%	5.5%	7.1%	---

Yonghong Gao PhD, from the FDA's Division of Biostatistics, gave a statistician's view of the Endeavor data. She came to the same conclusions as Dr. Farb:

- For 9-month TVF, Endeavor showed:
  - Superiority to Driver in ENDEAVOR-II.
  - Non-inferiority to Taxus in ENDEAVOR-IV.
- For 8-month in-segment late loss, Endeavor:
  - Showed superiority to Driver in ENDEAVOR-II.
  - Failed to show non-inferiority to Cypher in ENDEAVOR-III.
  - Failed to show non-inferiority to Taxus in ENDEAVOR-IV.

Among Dr. Gao's interesting comments were:

- "Based on the results of ENDEAVOR-IV, it is uncertain whether the less effective angiographic results of the Endeavor stent will translate into a significantly greater frequency of repeat revascularization compared to Taxus in a larger study population or with longer-term follow-up."
- "From a review of the Endeavor program, cases of TLR and TVR continue to accrue over time in all treatment groups (Endeavor, Driver, and Cypher) without a pattern of reduced clinical effectiveness of the Endeavor stent."

Post-marketing studies

Hesha Duggirala PhD from the FDA's epidemiology branch, Division of Postmarket Surveillance, Office of Surveillance and Biometrics, said that, with respect to post-approval studies of all DES, "It is not known if the stent thrombosis rate plateaus or continues to increase over time."

She cited issues she believes should be considered in Endeavor post-approval studies:

- Stent thrombosis – confirm the incidence is <1% for each 12-month period after Year 1.
- 5-year patient informed consent.
- Evaluate higher risk subgroups for patient characteristics and lesion characteristics.

She asked the panel:

1. Are the objectives identified appropriate? What additional objectives should be considered?
2. Should the post-marketing study protocol be revised to address the following issues:
   - Not powered for subgroup analysis.
   - Unclear if the 5-year follow-up is sufficient for long-term stent thrombosis evaluation.
   - Potential differences on antiplatelet therapy recommendations.

Panel questions for the FDA

Does the unblinding in ENDEAVOR-III affect the data integrity?

FDA's Dr. Farb: No.

Is the FDA comfortable about bias in ENDEAVOR-IV?

Dr. Farb: Yes

How should the various Endeavor studies be weighted, or should the focus be on ENDEAVOR-III or what?

Dr. Farb: "I think the studies should be looked at individually for questions the studies address…and then look at the program as a whole with an emphasis on safety…When we think about current interventional practice, with various options,

how does this device meet the criteria for safety and efficacy vs. what is available? When you think about ENDEAVOR-II (vs. BMS), what are the relevant clinical endpoints, and how does it meet those? For angiographic substudies, those are more mechanistic kinds of questions that get to how the device works vs. other devices (BMS, DES)."

How can you justify the conclusion on stent thrombosis with the small number of patients?

Dr. Farb: "What we are looking for here are signals, rate, and confidence intervals...And what we've seen today does not rise to the level of a safety signal for increases in stent thrombosis…In the data we've seen, we don't see a safety signal for this device vs. the BMS, which is a decent stent and performed as expected."

Can Endeavor be approved if it isn't as good as Cypher or Taxus?

Dr. A. Michael Lincoff, a medical cardiologist from the Cleveland Clinic: "It is hard to say the difference (in late loss) won't later translate (into an issue)…It raises a question…If we are concerned a device may not be quite as effective (as existing DES) but more effective than a BMS, how does that fit into the regulatory decision?" Dr. Yancy, the panel chair, responded: "Our job is to look at the data as stand-alone data."

Public Witnesses

Normally, public witnesses at an FDA advisory committee meeting speak consecutively right after the lunch break. At this panel, however, there was one public speaker in the morning, before any other presentations were made, and one at the end of the day, just before the final vote on approval.

Dr. Bruce Ferguson of East Carolina Heart Institute spoke at the opening of the panel on behalf of the Society of Thoracic Surgeons (STS). He expressed concern with randomized clinical trial designs for DES, particularly inferiority and non-inferiority designs but also the use of composite endpoints and the lack of "adequate" control groups, saying these shortcomings make the data hard to translate to the "real world."

He/STS urged:

- That labeling reflect the parameters and conditions defined in the trial design, including the lack of overall clinical contract of the trial data.
- Labeling should reflect the knowledge limitations. STS is recommending "strong labeling language to adequately address the finding of the pre-market evaluation but which also addresses indication expansion."
- Post-marketing: Aggressive development of observational database procedures to evaluate safety and efficacy, with significant industry investment in these observational resources.
- Caution in the use of pivotal RCT data as the only criteria for evaluation of new technology in cardiovascular disease.

Dr. William Maisel, a cardiologist from Beth Israel Deaconess Medical Center, spoke near the end of the day about post-market surveillance, and panel members seemed to take his message to heart, saying later that it influenced their recommendation for one of the conditions attached to the Endeavor approval recommendation – changes to the company's proposed post-marketing plan. Among Dr. Maisel's recommendations were:

- Encouraging publication of more negative studies.
- Having post-marketing registries study physician bias, not just patients and stents – why physicians choose a particular stent. He suggested the Swedish DES registry, which early-on suggested an increased risk of death with DES vs. BMS but in later analysis found no overall increased deaths with DES, "could be the poster-child for registries" – what can go wrong with registries.
- Use good controls in post-marketing studies. He described Medtronic's randomized PROTECT post-marketing study as "like a statistical felony."
- Not delaying getting results to the FDA by too-long blinding. He said, "I think the blinding is unnecessary and needlessly delays results."
- Increasing the size of the Endeavor post-marketing study to at least 10,000 patients and including all-comers.
- Setting a maximum allowable very late stent thrombosis rate. He said, "A rate of 1% per year is too high…That means 4% would be acceptable at five years."

Dr. Maisel's Estimate of Potential Stent Thrombosis Cases

Stent market share	Stents that would be implanted per year	Excess very late stent thrombosis annually, based on 1% rate per year
15%	900,000	4,500
18%	1.08 million	5,400
20%	1.2 million	6,000
25%	1.5 million	7,500

Based on overall market of 6 million DES

Panel Discussion

Risk:benefit

Dr. John Hirshfeld Jr., an interventional cardiologist from the University of Pennsylvania, described Endeavor as having a little worse efficacy but similar to perhaps better safety. He said the issues for the panel to consider are what the appropriate comparator is, how any trade-off between efficacy and safety should be handled, and how Endeavor compares to Cypher and Taxus. He said, "Our approval has to be on clinical performance rather than theoretical performance…Though we have a lot of safety data, safety cannot be fully judged until the long-term, real-world experience is tabulated."

Dr. Judah Weinberger, an interventional cardiologist from Columbia University, said:

- Based on animal studies "one would expect this device, in terms of late stent thrombosis, will be safer, but will it be arrhythmogenic in larger studies?"
- "One of the questions will be what happens when real life operators get a chance to use this device…Will additional late loss translate to a loss in efficacy. In the hands of Dr. Leon and his colleagues, a 0.2 mm late loss increase did not translate into increased (events)…but it is not sure that will be the case (with the average cardiologist)."
- "It is my opinion that the signals we see…say this is a 'safe' device…However, is there sufficient safety to say the risk:benefit is acceptable?...What is a little perturbing is the repeated statement that there is a lack of a worrisome signal…The lack of a worrisome signal is not evidence of safety."

Dr. Bram Zuckerman, director of the FDA's Division of Cardiovascular Devices in the Center for Devices and Radiological Health (CDRH), pointed out: "There is no criteria that says the n+1 DES (a new DES) has to be better than other devices out there."

Deliverability

Dr. Morrison, an interventional cardiologist, said, "I think Driver is an excellent stent and deliverable…I am greatly reassured by that…by the real-world experience with the BiodivYsio stent (Abbott/Biocompatibles' phosphorycholine coated dexamethasone-eluting stent), and knowing that we have a fairly substantial amount of data with two of the components of this stent system – Driver and the PC coating. I am very excited about that."

Number of patients for which there are data

Dr. Somberg said, "I think 600 patients (long-term) is inadequate…I think 1,200-1,300 would have been better...When will that data be in? If it will take two years, are we doing this prematurely?"

Antiplatelet therapy requirements

Dr. Somberg suggested Endeavor patients should be required to get 6-12 months of dual antiplatelet therapy. "Anything other than six months of dual antiplatelet therapy would be completely inappropriate…I think this talk of 12 weeks is very disturbing because that will be taken by a lot of doctors to do it...and that may be advertising by the sponsor, and there is nothing to support that."

FDA Questions to the Panel

The FDA posed six questions to the panel, which discussed them and reached a consensus on each, but no votes were taken on these questions.

Question 1. Do the data submitted to date on the Endeavor DES provide adequate assurance of safety in the population identified in the proposed indications for use? YES

Dr. Yancy, the panel chair, offered this initial summary of the panel sentiment: "What I'm hearing the panel saying is that the data presented in aggregate do provide reasonable assurance of safety, but there are some questions about long-term safety that require long-term follow-up...and the data should be considered in how the stent was studied – single *de novo* lesions." After further discussion, he modified this to: "The panel feels that generally there is a reasonable assurance (of safety), but persistent questions vis-à-vis late stent thrombosis remain, and we understand the context of how this information was obtained gives us some reason to want to acquire information."

Question 2. If the answer to #1 is yes, does the application include adequate follow-up in a sufficient portion of the patient population? YES

Chair summary: "The ongoing plans to acquire more information will be helpful in further resolving any other questions on safety." Dr. Somberg dissented from this viewpoint.

Question 3. Do you believe that the language in the proposed Endeavor stent label adequately conveys a recommended course of dual antiplatelet therapy following Endeavor stent implantation? NO

a. Should the label explicitly state that the recommended course of dual antiplatelet therapy be at least 6 months following Endeavor stent implantation? NO

b. Following the FDA Advisory Panel Meeting on DES thrombosis in December 2006, the labels for the currently approved DES (Cypher and Taxus) had language added to their labels referencing the ACC/AHA/SCAI consensus statement recommending dual antiplatelet therapy for 12 months following DES implantation in patients who are not at high risk for bleeding. **Should this recommendation also be included in the Endeavor stent label? YES**

The panel considered mandating 12 months of dual antiplatelet therapy, with several members emphasizing that they did not want Endeavor to be labeled with a shorter course of dual antiplatelet therapy than Cypher or Taxus. They adamantly wanted a level playing field on this issue – for now. Several members suggested that dual antiplatelet therapy may not have to be as long with Endeavor, but that hasn't been proven yet and until and unless it is proven, they want a level playing field among all the approved DES. They eventually agreed that using the same language that the FDA will soon require in the Cypher and Taxus labels, which conforms to the ACC/AHA/SCAI guidelines is sufficient.

Panel member comments included:

- *Dr. Somberg:* "Three months (dual antiplatelet therapy) is not correct...One year is probably appropriate in higher risk patients…unless they (Medtronic) do a study to look at that (shorter antiplatelet use)…I think this (3 months) is misleading."
- *Dr. Michael Domanski, branch chief of atherothrombosis and coronary artery disease at the National Heart, Lung, and Blood Institute (NHLBI) and a non-voting member of the panel:* "This is a big point…If it turns out that there is a shorter duration of antiplatelet therapy (for Endeavor), that is a compelling reason for not worrying about small differences in restenosis and using this thing (Endeavor) …and that probably is a totally false impression to send… That is the wrong message to send. To have a difference in antiplatelet therapy between this and other stents is inappropriate."
- *Dr. Morrison:* "I was on the FDA panel in December (on DES safety) and would be inconsistent with myself if I didn't support 12 months (of antiplatelet therapy for Endeavor)…Labeling anything less than 12 months would give patients and doctors a false hope…I think it really doesn't make sense to label (Endeavor) other than 12 months."
- The industry representative (from Johnson & Johnson/ Biosense Webster) suggested that class labeling may be useful.

QUESTION 4. Do the data presented on the Endeavor stent provide a reasonable assurance of effectiveness? YES

a. In the ENDEAVOR-II study, the Endeavor stent was demonstrated to be superior to the bare metal Driver stent with respect to TVF along with reduced rates of TLR and TVR. **Has a reasonable assurance of effectiveness of the Endeavor stent been demonstrated vs. bare metal stent implantation? YES**

b. In the ENDEAVOR-III study, the Endeavor stent did not meet its primary non-inferiority endpoint of in-segment late lumen loss at 8 months post-stent implantation compared with the Cypher stent. In ENDEAVOR-IV, the Endeavor stent met its primary clinical endpoint of TVF, but failed to meet its major secondary non-inferiority endpoint of in-segment late lumen loss at 8 months post-stent implantation compared to the Taxus stent. **Do the data from ENDEAVOR-III and -IV demonstrate a reasonable assurance of effectiveness of the Endeavor stent? YES**

Chair summary: "The panel is saying unequivocally that Endeavor does show more than reasonable assurance of efficacy vs. bare stents and vs. Cypher and Taxus, that there is at least one DES with which it has similarity based on non-inferiority, but there are differences in late loss, and there is a reasonable assurance the device will achieve a clinical result that is reasonable."

Product labeling

One aspect of the premarket evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify potential adverse events with the use of the device, and explain how the product should be used to maximize benefits and minimize adverse effects. Please address the following questions regarding the product labeling.

QUESTION 5:

a. Please comment on the INDICATIONS FOR USE section as to whether it identifies the appropriate patient populations for treatment with this device.

Chair summary: "The majority of the panel believes, in general, that the statement that already exists as a proposed indication is reasonable, but within the label we can develop language from individual trials and make specific reference that the trial was in single vessels."

However, one panel member was very outspoken in his disagreement with this summary finding and asked for a vote, which was not granted at that time. He indicated there are at least two dissenters from this position.

b. Please comment on the CONTRAINDICATIONS section as to whether there are conditions under which the device should not be used because the risk of use clearly outweighs any possible benefit. Acceptable as proposed.

c. Please comment on the WARNING/PRECAUTIONS section as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events. Acceptable as proposed.

d. Please comment on the OPERATOR'S INSTRUCTIONS as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events. Reasonably acceptable as proposed.

e. Given the information on the drug substance proposed for inclusion in the labeling, please comment whether modifications are needed or whether any additional information should be added to the labeling to maximize benefits and minimize adverse events. No comments.

f. Please comment on the remainder of the labeling as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events. No particular comments.

Chair summary: "My sense is these can be worked out in a more deliberative way (by the FDA and the company)."

Post-market evaluation

The post-market study has been designed to:

- Identify rate of stent thrombosis through 5 years.
- Assess rates of cardiac death and MI to confirm long-term safety of the Endeavor stent when implanted in accordance with its labeled indications for use compared to the Driver bare metal stent.
- Evaluate use of the Endeavor stent for potential safety signals associated with higher risk lesion and patient subsets, recognizing from published literature that such patients are likely to receive drug-eluting stents in clinical practice.

QUESTION 6:

a. **Are the objectives identified above appropriate? Should additional objectives be considered?**

b. **Does the plan provided by the sponsor adequately address the objectives?**

c. **If not, how should the sponsor's plan be modified?**

Chair summary: "We are comfortable with a single-arm registry vs. objection performance criterion – probably vs. BMS data. Reasonable follow-up is indicated with use of standard stent thrombosis definitions (e.g., ARC definite/probable)."

The key issues for the FDA were (a) whether antiplatelet use and duration will be adequately captured and (b) pooling of data in the post-marketing analysis. The panel was very concerned with getting data on antiplatelet use, and it recognized that the post-marketing PROTECT trial is already underway, so it is too late to really modify it significantly.

THE PANEL VOTED FOR APPROVAL WITH CONDITIONS

The panel had three options: to vote to approve Endeavor, approve it with conditions, or not approvable (that the data did not provide reasonable assurance of safety or efficacy). The panel voted unanimously in favor of approval with conditions:

1. Change Medtronic's proposed **post-marketing program** to require:
   - A single-arm registry.
   - At least 5,000 patients.
   - Very late stent thrombosis as the primary endpoint.
   - Death/MI as the secondary endpoint.
   - Objective performance criteria (OPC) from bare metal stents as the comparator.
   - Rigorous data monitoring.
   - At least 5-year follow-up.
2. Language be included in the Endeavor label on the use of **dual antiplatelet therapy** consistent with prevailing FDA language (i.e., the same language Taxus and Cypher are ***about to get***, which is in accordance with AHA/ACC/SCAI guidelines).

There was some discussion about mandating a control arm in the post-marketing study, but that idea ultimately failed to gain any traction with panel members. A suggestion that the post-marketing study evaluate duration of antiplatelet therapy also died. A third proposal – to restrict use to single *de novo* lesions since that is what was studied in the randomized trials – was voted down, with just two votes in favor.

Panel members offered explanations for their vote:

- *Dr. Lincoff:* "I think (approval with conditions) is reasonable, based on ENDEAVOR-II and ENDEAVOR-IV and that the data for safety on late stent thrombosis are appropriate for reasonable safety."
- *David Naftel PhD, a statistician and professor of surgery from the University of Alabama at Birmingham:* "I believe the analyses have painted a very clear picture and totally helped me understand how Endeavor compares to BMS and DES…All the studies are incredibly consistent."
- *Dr. JoAnne Lindenfeld, medical director for cardiac transplant at the University of Colorado Health Science Center in Denver:* "I think safety has been shown."
- *Dr. Somberg, an interventional cardiologist:* "I voted reluctantly for approval, not because of an inherent lack of efficacy or a safety signal…I think the sponsor should be congratulated…I've seen all kinds of devices with much more meager material…This is robust (data)…The marketplace will be the most important check on inappropriate use…Certainly, post-marketing studies in this area are needed; otherwise we go to class labeling, and that means we just don't know…There is a good hypothesis here that this DES may prevent late stent thrombosis and may not need as long dual antiplatelet therapy."
- *Dr. Domanski (non-voting)*: "Safety and efficacy were reasonably demonstrated."
- *Dr. Morrison, interventional cardiologist:* "I'm impressed that the emphasis from the Agency (FDA) is first on safety…It seems to me Driver is an excellent stent…I'm trying to quell the desire to be excited about the possibility of reduced early MI…I think this is potentially a very useful product…I am not as nearly concerned about the surrogate endpoint outcome (late loss) in ENDEAVOR-III and ENDEAVOR-IV as I thought I might be…and if the post-marketing surveillance works the way we hope, this could be a big win for patients."
- *Dr. Weinberg, an interventional cardiologist:* "This device has a real place in the DES universe…For the patient where the likelihood is not good of continuing antiplatelet therapy, this device may have a role…Clearly, it is better than BMS…For a patient who can tolerate antiplatelet therapy out as long as 1-2 years, I don't have a strong reason to prefer this…There is a smell (hint) in the data that you may get away with less antiplatelet therapy, but without data, it will be up to individual practitioners."

- *Dr. Norman Kato, a cardiothoracic surgeon from California:* "I still have reservations on the total number of patients followed…(and) I am still a little bit unsure where the product fits in the grand scheme of DES…I guess at the end of the day I hope the sponsor and the FDA work diligently to do the post-marketing study and get the data out as quickly as possible."
- *Dr. Yancy, the panel chair:* "The most intriguing thing was the data of early endothelialization (with Endeavor). With pre-existing DES platforms, significant concern has been raised (about late endothelialization or non-endothelialization) which may promote stent thrombosis…I have yet to see a post-marketing study come back to this panel in a way that was reasonably done and relatively straightforward to interpret. A lot of effort has been put into those post-marketing studies (design and requirements), and it is our expectation that this will be followed through."

♦