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by Lynne Peterson

SUMMARY

The FDA advisory panel was mostly an opportunity for doctors on all sides of the drug-eluting stent safety debate to let off steam. FDA officials indicated that there will not be a black box on current DES, and the ARC definitions of stent thrombosis will be the Agency's preferred method. The panel:

- ♦ Agreed there is an increased risk of stent thrombosis with DES vs. BMS.
- ♦ Recommended 12 months of dual anti-platelet therapy for most DES patients.
- ♦ Urged trials be longer and larger in the future and that registries should have a control arm.
- ♦ Found no significant difference in risk between Johnson & Johnson's Cypher and Boston Scientific's Taxus.
- ♦ Did not appear to recommend anything that would delay approvals of new DES in the near pipeline.

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FDA'S CIRCULATORY SYSTEM DEVICES ADVISORY COMMITTEE MEETING ON DRUG-ELUTING STENTS

Gaithersburg, MD
December 7-8, 2006

The FDA advisory committee meeting on drug-eluting stent (DES) safety started on Pearl Harbor day, but industry managed to stay afloat. Experts spent two days reviewing the safety of DES, but few changes are likely to result from the meeting. The 21-member panel was well balanced, with 7 interventional cardiologists, 3 cardiac surgeons, 6 medical cardiologists, 1 electrophysiologist, an NIH expert, a statistician, an industry representative, and a consumer representative. A panel member called the meeting a "steam valve" that let everyone vent on the topic. And there were plenty of opinions for the panel to consider; more than 40 speakers provided their own data analyses or points of view.

Following are key concerns going into the meeting, and a summary of what the panel recommended on each of these.

1. Will the panel recommend any FDA action – label changes (e.g., black box, market withdrawal, etc.) – that would seriously impact the penetration of DES?

No, the only substantive change was a recommendation for 12 months of dual antiplatelet therapy, which is already the recommendation of professional societies.

2. How will the regulatory path for new stents change?

No significant change for stents in the near term – except for longer and larger post-marketing studies.

Dr. William Maisel, chair of the panel and an electrophysiologist at Brigham & Women's Hospital, said, "We talked about what future trials and future approvals would require. The consensus was that any new DES that comes on the market should be safe and effective and the stent thrombosis issue should be addressed… That typically means more patients and longer study duration."

Dr. Daniel Schultz, Director of the FDA's Center for Devices and Radiologic Health (CDRH), said, "We will look at their data and…see if they meet our regulatory threshold as to reasonable safety and effectiveness. That is what we would have done two days ago, and it is what we will do tomorrow. Obviously, we will listen to what the panel talked about…and look at those aspects of their data relating to these topics. But our threshold of data hasn't changed."

Panel members also indicated they were impressed with Medtronic's post-marketing plans for Endeavor.

The expectation is that the FDA will not change the requirements for DES that are close to approval, but the post-marketing requirements will be much tougher for

them. The Circulatory Systems Devices advisory panel is likely to expect:

- Safety data >1 year, especially in a high risk cohort.
- Data on the adequacy of antiplatelet therapy.
- Post-marketing data over at least 3 years in 5,000+ patients (which could be registries with a control arm).
- If the bar for late stent thrombosis becomes 0.6%/year, the new stent won't be able to be worse than that.
- The new stent ***should*** bring new information to the FDA, particularly on the adequacy of antiplatelet therapy, and perhaps on incorporating the use of platelet function tests.

3. Will one of the currently approved DES get a better label or some other advantage over the other DES?

No, Cypher and Taxus came out of the panel pretty equally. At one point each day it looked as if Cypher might be put at a disadvantage, but in each case the crisis passed:

- **Day 1:** The panel flirted with the idea that Cypher has a worse thrombosis rate, particularly in diabetics, but J&J officials contended the negative data in diabetics were an anomaly, and, in the end, the panel decided the risk is probably equivalent in both DES.
- **Day 2:** The panel was highly critical of J&J for stopping its post-marketing registry after one year. Panel members thought the company had been asked to run it for five years but stopped too soon. J&J was finally "rescued" by an FDA official who pointed out that the FDA approved a one-year post-marketing plan because, at the time, that seemed sufficient.

4. How will DES use/penetration change after the advisory committee meeting?

The panel didn't discuss this, but it appears there will be a **decrease in DES use, but not significantly.** Most interventional cardiologists on the panel – and that was almost half the members – didn't think there would be major changes in their practice after the meeting, but they admitted they may think twice about using DES in some situations, and medical cardiologists may refer a few less patients.

Dr. Maisel summarized the panel sentiments: "There appears to be a numerical excess of very late stent thrombosis in DES. The magnitude of risk is uncertain based on available data. Importantly, there does not appear to be an increased rate of death or MI when DES are used on-label vs. BMS. Use of DES off-label is associated with increased risk of stent thrombosis, death, and MI compared to on-label use, and the same can be said for BMS. We all agree we need more and better data – more patients and longer studies."

Dr. Schultz offered his own concluding remarks at the end of the panel meeting:

- "This meeting needed to happen. One of the things I've certainly taken away is it is important to bring some of these controversial issues to this kind of open forum. In the past we (the FDA) have sometimes shied away from bringing these controversial issues (to a panel)...but I've seen this is the best way, maybe the only way, to move forward if not get resolution."
- "I'd say we've learned:
  - The review process works.
  - There was unanimous agreement that on-label – what we regulate are on-label indications – the risk:benefit ratio, even given current new information, is still appropriate.
  - We need to update information to patients and physicians based on new information, and it is our responsibility to be sure information is kept current.
  - We need to continue to monitor this particular safety issue as well as add issues we may not even be aware of yet, so a focus on post-market surveillance is something that we can't afford to neglect.
  - We need to work closely with industry, academia, and other governmental agencies to encourage the design and performance of well-designed studies to take the very diverse practice of medicine and convert those different practices to on-label indications when we have the data to do so."

Immediately after the panel concluded, Dr. Maisel and Dr. Schultz spoke with reporters. The key takeaways from that session were:

Dr. Maisel:

- "The message from the panel was that DES, when used off-label, are associated with an increased risk of adverse outcomes – stent thrombosis, death, and MI, as compared to on-label use. The same could be said about BMS. We also talked about antiplatelet regimens, and the panel felt those regimens should be extended for at least 12 months, consistent with current ACC/AHA/SCAI guidelines. Those were the two main take-home messages."
- "The consensus on the label change was that physicians need to understand that if they use a device (DES) in an off-label manner, they won't get the results they see in on-label use because the data in off-label are not as robust…The consensus was that this message should be conferred in the label, but we leave it to the FDA on how to do that."
- "Off-label patients who get DES do not fare as well (as on-label patients). That is not a surprise, but it is an important message because about 60% of DES use is off-label. If DES is used outside the label, you will get slightly different results than on-label. The risk of death, MI, and heart attack is higher with off-label use…Patients don't care if something is off-label. They want to know how the stent compares to CABG or medical therapy, and the panel felt there was insufficient evidence to make judgments about that."

- "My biggest change (when I go home) is that antiplatelet therapy should be continued for 12 months at least in these patients, particularly in the off-label population. That is the biggest change I will take away (from this meeting)."
- "(Stent thrombosis) is a signal to be concerned about. There is no conclusive evidence of increased death or MI rates, but that needs to be answered in these patients."
- "I think we would like to see off-label (DES use) go down in overlapping stents, bifurcations, and potentially lesions with already thrombosis in them…We need more data. There are not enough data for recommendations."
- "The panel feels there should be more studies of dual antiplatelet use. The appropriate duration is unknown. The panel felt at least 12 months is appropriate, but we don't know if that is the right time."

Dr. Schultz:

- "One of the things we are committed to is the design of clinical programs that start on the pre-market side and continue almost seamlessly into the post-marketing side."
- "We heard a lot about controls and comparators…All that will be helpful not only for DES but for other products."
- On the timeframe for FDA action, particularly label changes for approved Cypher and Taxus: "(We will act) as quickly as possible, but we need to get it right…There were a lot of discussions and not all were in agreement. Now, we need to go back and look at all the documents and see exactly what fits into a label, what fits into a notification, what part fits into the types of communications we have. At the end of the day, what I heard is we need to do a better job in communicating to patients and doctors the best and latest information on what we know for this and other products."
- "We will go back to our internal experts to sit down and go through, in great detail, all the different discussion points…We asked specific questions. Now, we need to apply the answers to our regulatory tools. Where there may be a need to update labeling, we will look at that. Where there is a need for a public message, we will look at what the public message will look like…Where additional studies were suggested, we would say, 'What are those and where are the holes in the data we need to start looking for answers to?'…There was a consensus that this information needs to be transmitted very quickly."
- "We clearly need to talk (with CDER) more about continuing use of DES with antiplatelet therapy."

THE FDA PERSPECTIVE

In the briefing documents, the FDA said DES thrombosis concerns have "important public health implications that warrant an open dialogue among the DES manufacturers, investigators, physicians, and the FDA." The Agency wrote: "Recent presentations at scientific meetings have suggested a small but significant increase in the rates of: (1) death or myocardial infarction (possibly due to stent thrombosis) and (2) non-cardiac mortality in DES-treated patients compared to patients treated with bare metal stents." The FDA also made a number of points, including:

- **Bare metal stents (BMS).**
  - Restenosis rates with BMS are ~25%.
  - Before DES, stent thrombosis mortality with BMS was 17% - 20.8%.
  - Stent thrombosis ranges from 0.5% - 1.8%, varying by patient subset.
- **FDA has approved 2 DES so far:**
  - **Cypher** is approved by the FDA for *de novo* lesions ≤30 mm in native coronary arteries ≥2.5 mm to ≤3.5 mm in diameter.
  - **Taxus** is approved by the FDA for *de novo* lesions ≤28 mm in native coronary arteries ≥2.5 mm to ≤3.75 mm in diameter.
- **DES usage.** DES are used in ~80% of U.S. procedures, and the FDA believes >60% of DES are for off-label uses, where the rate of serious adverse events (*including subacute **and** late stent thrombosis*) is expected to be greater. "Information is emerging that suggests increased rates of DES thrombosis in more complex patient and lesion subsets, including bifurcation lesions, thrombus-containing lesions (acute MI), multiple stents per vessel, and in patients with diabetes, multivessel disease, and renal dysfunction."
- **DES risks.** The FDA wrote, "Whether or not there is an increased risk of stent thrombosis with DES use compared to other revascularization techniques, there is a clear consensus that stent thrombosis is a clinically relevant adverse outcome." The therapeutic benefit of restenosis prevention with DES has to be balanced with:
  - Reduced endothelialization (delayed arterial healing), resulting in a prolongation of the window of risk for stent thrombosis.
  - Increased inflammation.
  - Increased per-strut fibrin deposition.
  - Rare very late stent thrombosis associated with aneurysm formation and a hypersensitivity-like reaction (possibly in response to the DES non-biodegradable polymer).
  - Cases of severe in-stent restenosis caused by aggressive neointimal thickening.
  - Possible resistance to antiplatelet therapy.

- **Stent thrombosis mortality.** DES stent thrombosis is associated with a 31% - 45% fatality rate.

- **Definitions.** The FDA participated in the development of standardized definitions of stent thrombosis by the Academic Research Consortium (ARC), and those are the definitions the FDA used for the panel meeting. The FDA asked each company to provide a minimum set of analyses using the ARC definitions. Those definitions are:
  - **Early** stent thrombosis: 0-30 days post stent implantation.
  - **Late** stent thrombosis (LaST): >30 days - 1 year post stent implantation.
  - **Very late** stent thrombosis: >1 year post stent implantation.
  - **Definite** stent thrombosis: acute coronary syndrome ***and*** angiographic confirmation of thrombus or occlusion ***or*** pathologic confirmation of acute thrombosis.
  - **Probable** stent thrombosis: unexplained death within 30 days ***or*** target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesion.
  - **Possible** stent thrombosis: unexplained death after 30 days.

- **Benefits of DES are reduction in TVR, not death or MI.** "For both approved DES (Cypher and Taxus)…the difference in outcome of DES vs. bare metal stents was essentially due to a reduction in the rate of ischemia-driven repeat revascularization. There were no differences in the rates of death and MI between treatment groups at 9 to 12 months post stenting; death and MI rates in DES studies have been relatively low, and these studies have not been powered to detect differences in these endpoints. No claims have been made in the device label that myocardial infarctions (MIs) and death are prevented with DES use. Similarly, there are no labeled claims of reduced death or MI rates with the other approved PCI (percutaneous coronary interventions) revascularization techniques (balloon angioplasty and bare metal stents)."
  - The FDA did not equate reduction in repeat revascularization with death or MI. The Agency wrote, "Given the high case fatality and MI rates associated with stent thrombosis, it is reasonable to re-assess the risk:benefit ratio of reduced repeat revascularization rates if there is a significant increase in DES thrombosis-induced death and MI."
  - Restenosis is not necessarily benign.

- **FDA MAUDE adverse event reports.** The FDA found no discernable trend in reports of thrombosis (or associated events) for either Cypher or Taxus.
  - 1,570 thromboses with Cypher, 23% of Cypher reports.
  - 882 thromboses with Taxus, 16% of Taxus reports.

- **Antiplatelet therapy.** The FDA has been evaluating the use patterns of Sanofi-Aventis's Plavix (clopidogrel). The Agency wrote, "Although the duration of clopidogrel use appeared to be adequate for the selected patient population in the original clinical trials that supported FDA approval, the optimal duration of clopidogrel in more complex patients has not been established."

  The current ACC/AHA/SCAI PCI Practice Guidelines recommend clopidogrel therapy for at least 3 months after Cypher and at least 6 months after Taxus, and ideally up to 12 months in patients who are not at high risk of bleeding. The European Society of Cardiology recommends clopidogrel administration for 6 to 12 months. However, the Agency wrote, "It is not clear that extended duration of dual antiplatelet therapy will prevent late thrombosis…A consideration for a longer duration of dual antiplatelet therapy must weigh a potential benefit of a reduction in the incidence of stent thrombosis vs. a potential increase in the risk of major bleeding."

The FDA briefing document conclusions

1. When used on-label, Cypher and Taxus are "associated with a small but significant risk of late stent thrombosis (emerging 1-year post stent placement) compared to BMS." The total number of patients ≥3 years post stenting remains relatively small, and it is uncertain whether cases of late stent thrombosis will continue to accrue with longer-term follow-up.

2. Whether DES are associated with an overall long-term increased rate of death or MI is an area of uncertainty. Meta-analyses based on published literature suggest an increased death or MI risk associated with the Cypher stent. In contrast, meta-analyses based on patient-level databases from the DES manufacturers have not shown an increased risk with either Cypher or Taxus.

3. The majority of current DES use is in patient and lesion subsets that are more complex than those represented in the randomized trials. Increased rates of stent thrombosis have been observed in more complex patient and lesion subsets (e.g., bifurcation lesions, multiple stents per vessel, diabetics, and patients with acute MI, multivessel disease, and renal dysfunction). However, most data are from single-armed registries of DES use and lack a control group for comparison, and few long-term data (≥1 year) are available.

4. The optimal duration of dual antiplatelet therapy particularly in more complex patient and lesion subsets that may be inherently at increased risk of late stent thrombosis is unknown.

5. It is not known whether an extended course of dual antiplatelet therapy will prevent late thrombosis. Consideration for a longer duration of dual antiplatelet therapy must weigh a potential benefit of a reduction in the

incidence of stent thrombosis vs. a potential increase in the risk of major bleeding.

6. There is consensus among investigators, the NIH, and FDA that randomized controlled trials (RCTs) are the best approach to address optimal revascularization strategies in certain high risk patient cohorts. Ongoing trials include:

   a. **SYNTAX** trial is exploring multivessel revascularization (including left main disease) with DES (Taxus) vs. CABG.

   b. **FREEDOM** trial is comparing multivessel stents (Cypher or Taxus) vs. CABG.

   c. **HORIZONS-AMI** trial is comparing Taxus to a bare Express stent in STEMI patients.

7. Since stent thrombosis is a serious adverse event associated with high rates of death and MI, continued efforts to clarify the mechanisms of stent thrombosis and interventions to reduce the risk of its occurrence will have public health benefits.

The FDA presentaton to the Advisory Committee

Dr. Takahiro Uchida, CDRH, Office of Drug Evaluation (ODE), gave the FDA opening summary, describing current trials and the approval process for them. He emphasized that "the FDA does not regulate the practice of medicine but is responsible for any use of a device that raises a public health concern."

Dr. Andrew Farb, CDRH, ODE, reviewed the pathology of restenosis with DES and described in more detail the key results of the pivotal approval studies for Boston Scientific's Taxus and Johnson & Johnson's Cypher. He described their current approved indications and the pathophysiology of late DES thrombosis. He said the clinical importance of stent thrombosis is death and MI, which ranges from 17% - 21% with BMS and 25% - 45% with DES.

Dr. Farb then reviewed all the data on stent thrombosis (*See chart on page 7*). He commented that the stent thrombosis rate is higher for both approved DES vs. BMS but that both DES companies report statistical analyses that show no statistically significant difference on death (all death, cardiac death, non-cardiac death, or MI). But he cautioned that post hoc analyses should be considered with caution. He said the FDA finds the ARC definitions as acceptable and asked sponsors to apply them when and where possible.

Hesha Duggirala PhD, CDRH, discussed considerations in the interpretation of available data. She said the FDA was seeking panel input on whether currently mandated post-approval studies should be modified. She then briefly described the Nordmann meta-analysis and the limitations of that study, and preferred meta-analysis methods, which include:

- Patient-level analysis.
- Pre-specified study hypothesis and study protocol.
- Complete data capture – published and unpublished trials.
- Consistent data extraction methods.
- Accurate definitions of outcomes.
- Quantitative data synthesis.
- Methods vetted in peer-review process.

Dr. Robert Fiorentino, CDRH, discussed stent thrombosis with DES. He noted that three patient subsets that ***may*** influence the risk of stent thrombosis are:

1. Diabetes (insulin and non-insulin dependent)
2. Renal dysfunction
3. Multivessel disease

Specific lesion subsets that may influence the risk of stent thrombosis:

- Left main disease
- Bypass grafts
- Chronic total occlusions
- In-stent restenosis
- Bifurcation lesions
- Long lesions and overlapping DES
- Small vessels (<2.5 mm diameter)
- Acute MI
- Multiple stents per vessel

Challenges in data interpretation are:

1. Frequent overlap between subsets and their definitions.
2. Variable and/or evolving clinical practice patterns.
3. Lack of adequate control arms.
4. Data may not capture adherence to antiplatelet therapy.
5. Studies may be underpowered for patient- and lesion-specific subset analyses.
6. Meta-analyses may fail to capture patient-level data.
7. Definition of stent thrombosis is variable, and there is a need for standardization.
8. Length of follow-up varies across studies.
9. Few long-term data are available.

FDA presentation conclusions

- When used in accordance with their labeled intended uses, data available to the FDA indicate that the currently approved DES are associated with a small but significantly increased risk of late stent thrombosis compared to BMS.
- It has not been established whether these thrombosis events translate into increased rates of death and MI.

- The total number of patients ≥3 years post stenting remains relatively small, and it is uncertain whether cases of late stent thrombosis will continue to accrue with longer-term follow-up.
- Multiple studies indicate increased rates of DES thrombosis, MI, or mortality associated with premature discontinuation of dual antiplatelet therapy.
- The optimal duration of dual antiplatelet therapy, particularly in more complex patient and lesion subsets, is unknown.
- It is not known whether an extended course of dual antiplatelet therapy will prevent late thrombosis.
- Since stent thrombosis is associated with high rates of death and MI, continued efforts to clarify the mechanisms of stent thrombosis and interventions to reduce the risk of its occurrence will have public health benefits.

Panel questions for the FDA

Dr. Eric Topol, a medical cardiologist from Scripps Clinic: He asked about the mismatch between stent thrombosis and the events of death/MI. "This is a critical disconnect because one would expect if there is an excess of stent thrombosis, there ought to be an excess of death/MI. There are 2 possible explanations: (1) circular reasoning and (2) there are other events that are actually resulting in death/MI."

FDA's Dr. Farb responded: "It could be the numbers are too small to show a difference…It may be that studies were not powered to show any difference, and the other possibility is that there are other confounders and difficulties with determining cause and effect…There can be noise from non-cardiac deaths, etc…It is a trade-off between a known pathophysiology, even though that is dramatic when it occurs, and applying that important clinical effect to datasets where it is more difficult to determine cause and effect…Maybe there just isn't a relationship between thrombosis and death/MI."

Panel member: "How do we factor in stopping (dual) antiplatelet therapy?"

Dr. Farb: "Even patients maintained on antiplatelet therapy have had events. We shouldn't think indefinite prescription of clopidogrel forever will solve this (stent thrombosis) problem."

Dr. Steve Nissen, a medical cardiologist from the Cleveland Clinic and President of the American College of Cardiology: "The critical question is: Is there an attenuation of the risk of late stent thrombosis over time? Do you see any evidence of that over time? Is it less in Year 3 than Year 1, or does it look to be constant?"

Dr. Farb: "That is difficult to say with available data. There are signals on both sides. Some RCT data seem to group in the 1-3 year range, but then we have the European Wenaweser data with a 0.6%/year increase. The question we have is if that is leveling off or if that will continue to accrue."

Dr. Nissen: "In contemporary CV medicine, some of these patients will have a 20-year life expectancy, so we need to know if the risk is constant…And what about dual antiplatelet therapy compliance? Do we have pill-based compliance measures?"

Dr. Farb: "If we knew then what we know now, we would have different types of accounting (for compliance)."

Panel member: "What is a clinically meaningful difference in thrombosis? Clinically, what is the effect size where you worry about the difference between BMS and DES? Is it a 1%, a relative rate?"

Dr. Bram Zuckerman, Director of the FDA's Division of Cardiovascular Devices: "I suggest we need to put the shoe on the other foot. That is why we have a large and distinguished advisory panel. That is the type of input we are looking to get…It is a key concern. My only comment is: When looking at the delta, we also need to put it in perspective with the totality of the data. If there is a certain difference in stent thrombosis (between BMS and DES), but it is not translated into a delta in terms of death/MI, that is another question of utmost importance."

Panel member: "I have no sense of what stent thrombosis rate today is for BMS."

Dr. Farb: "The issue has to do with the timing of stent thrombosis…What we are seeing is that there appears to be increased (stent thrombosis) rates after >1 year in DES groups, and we can extrapolate that that is a clinically meaningful problem and improvements or prevention strategies will be useful."

Dr. John Hirshfeld, an interventional cardiologist with the Hospital of the University of Pennsylvania: "How much should we focus on pivotal trial follow-up vs. observational data on real-world experience? It appears to me that adverse events globally are at least double the adverse event rates in tightly controlled trials. So, if you are going to have a good sense of the actual problem, it seems we should focus on the real-world experience."

Dr. Farb: "I agree."

Dr. Douglass Morrison, an interventional cardiologist with the University of Arizona: "As a clinician I guess I'm scared to think there is a strong connection between thrombosis and infarction…When we see patients come back who have stopped clopidogrel and are presenting with infarction, pretty nearly all the time we see ST elevation associated with occlusion…(But) people may be thrombosing and not presenting with infarction…Is there an association between stent thrombosis and infarction?"

FDA Review of Stent Thrombosis Rates

Stent thrombosis	**Cypher vs. Control**	**Taxus vs. Control**
	Pivotal trials for FDA approval	
Trial	SIRIUS	TAXUS-IV
Definition	---	More inclusive
Subacute (<30 days)	0.2% vs. 0.2%, Nss	0.3% vs. 0.6%, Nss
Late (30-360 days)	0.2% vs. 0.6%, Nss	0.3% vs. 0.2%, Nss
Total (0-360 days)	0.4% vs. 0.8%, Nss	0.6% vs. 0.8%, Nss
	Other trials and studies	
Stent thrombosis	RAVEL: 0 4-year SIRIUS: 0.8% vs. 0.6%, Nss	TAXUS-IV at 3 years: 1.2% vs. 0.8%, Nss TAXUS-V at 1 year: 0.7% vs. 0.7%, Nss TAXUS-V high risk patients at 1 year: 0.6% vs. 1.8%, Nss
Late stent thrombosis (0-360 days)	E-CYPHER U.S. registry: 0.2% E-CYPHER OUS registry: 0.2%	ARRIVE-I registry: 1.0% in uncomplicated patients, 2.6% in complicated patients
MACE (0-360 days)	E-CYPHER U.S. registry: 7.3% E-CYPHER OUS registry: 5.8%	ARRIVE-I registry: 4.0% in uncomplicated patients, 8.4% in complicated patients
Dr. Pocock's analysis of Cypher and Taxus combined	14 stent thrombosis with DES vs. 2 with BMS, p=0.01 (1:500 patient-years of follow-up)	
Time period	**Camerzind meta-analysis: Death/Q-wave MI**	
6-9 months	1.7% vs. 0.9%, p=0.21	1.6% vs. 1.5%, p=0.88
1 year	2.3% vs. 1.4%, p=0.30	1.7% vs. 1.6%, p=0.80
2 years	3.7% vs. 2.0%, p=0.09	2.6% vs. 2.8%, p=0.78
3 years	6.0% vs. 4.0%, p=0.06	3.5% vs. 3.1%, p=0.60
Through latest available follow-up	6.3% vs. 3.9%, **p=0.03**	2.6% vs. 2.3%, p=0.68
Mortality	**Nordmann meta-analysis: Death/Q-wave MI**	
Cardiac	Nss	Nss
Non-cardiac	2 years: OR 2.74 with Cypher, p<.05 3 years: OR 2.04 with Cypher, p<.05	Nss
Time period	**Stent thrombosis in trial data analyses by Dr. Greg Stone and Dr. Marty Leon**	
1-4 years	0.6% Cypher (~0.2%/year)	0.5% Taxus (~0.15%/year)
Type of lesion/patient	**Stent thrombosis rates by lesion/patient subset at 1 year**	
	Cypher in E-CYPHER U.S.	**Taxus in ARRIVE-I**
Long lesions	0.5%	3.7%
Patients with multiple DES	N/A	3.4%
Lesions with multiple DES	N/A	4.1%
Overlapping stents	0.7%	N/A
Multiple vessel stenting	2.7%	3.8%
Bifurcations	1.6%	3.5%
AMI	0.6%	2.9%
Diabetics	1.1%	3.1% (1.7% angiographically-confirmed, 1.3% assumed)
Insulin-requiring diabetics	---	6.3%
Stent-related cardiac events	**Stent-related cardiac event rates by lesion/patient subset at 1 year**	
	Cypher in E-CYPHER U.S.	**Taxus in ARRIVE-I**
Total	2.3%.	8.4%
Cardiac deaths	---	1.9%
MI	2.6%	2.9%
In insulin-requiring diabetics	---	13.0%
In diabetics	3.0%	8.4%
Study/author	**Stent thrombosis in additional "real-world" trials**	
Ong, ***JACC***, 2005	Overall incidence: 0.35%	
Iakovu, ***JAMA***	1.3%	1.7%
Hoye et al, ***JACC***, 2006	4.3% DES at 9 months	
Kuchulakanti et al, ***Circulation***, 2006	1.27% DES by angiography	
BASKET and BASKET-LATE (Pfisterer et al, in press ***JACC***, 2006)	2.6% DES vs. 1.3% BMS, Nss (18 month death/MI: 8.4% vs. 7.5%, p=0.63; non-infarct TVR: 7.5% vs. 11.6%, p=0.05)	
DEScover registry (Williams et al, ***Circulation*** in press, 2006)	Death/MI: 5.2% Cypher Stent thrombosis: 0.5% vs. 0.8%	Death/MI: 5.3% Taxus Stent thrombosis: 0.8% vs. 0.8%
Wenaweser registry analysis	Annual rate of 0.6%/year, with ACS and diabetes the only independent predictors. 30 days: 1.2%, 1 year: 1.7%, 2 years: 2.3%, 3 years: 2.9%	

Dr. John Somberg, a medical cardiologist with Rush University Medical Center: "The FDA makes the statement that there is a significant but small increase in late stent thrombosis…Are you certain of that conclusion from your data? I didn't see sufficient p-values to say there is increased stent thrombosis?"

Dr. Farb: "Looking at the totality of the data, that is where we land…Putting together what we know pathophysiologically with what we see in trials, we think there is a small but significant increase in late stent thrombosis."

Dr. Christopher White, an interventional cardiologist from the Ochsner Clinic: "I get sense there is a difference in (stent thrombosis) rates, with events more likely in off-label use than on-label use. What is off-label use of BMS? My sense is BMS are never used off-label."

Dr. Farb: "We have approval for BMS for AMI.

Dr. Norman Kato, a cardiothoracic surgeon from California: "Most of the studies you are talking about are not powered to identify adverse events <1%, but you are asking for global recommendations based on very, very small numbers. I, too, have a sense there is something going on…It sounds like something is going on…The pathophysiology makes sense… But we are still trying to grasp the statistical significance. Are we going down the road of making a mistake on a public policy question and compounding the problem?"

Dr. Farb: "At the end of the day, we do perceive this as a global public health question...We will be interested in how you are able to walk that line and give the best advice to address that limitation."

FDA Review of Antiplatelet Use and Stent Thrombosis Rates

Stent thrombosis	Patients on dual antiplatelet therapy	Patients not on dual antiplatelet therapy
1 Year ARRIVE-I	1.9% by patient 1.8% by vessel	3.8% by patient 5.2% by vessel
Kuchulakanti et al	Clopidogrel discontinuation was an independent predictor of stent thrombosis, p=0.0003	
PREMIER registry (Sperus et al, ***Circulation***, 2006)	Patients who stopped dual antiplatelet therapy by 30 days were more likely to die during the next 11 months	

INDUSTRY PRESENTATIONS: JOHNSON & JOHNSON AND BOSTON SCIENTIFIC

JOHNSON & JOHNSON/CORDIS

Dr. Campbell Rogers, Chief Technology Officer at Cordis, reviewed the benefits of Cypher stents in >45,000 patients studied worldwide. He emphasized that the J&J clinical data analysis was done exclusively by outside, non-Cordis data management centers like Harvard Clinical Research Institute (HCRI) and Cardialysis in Rotterdam, Netherlands.

J&J View of Stent Thrombosis from Cypher RCTs at 4 Years

Measurement	Cypher	BMS	p-value
Any stent thrombosis	3.5%	3.3%	0.894
Definite or probable stent thrombosis	1.5%	1.8%	N/A
Death	6.8%	5.5%	0.27
MI	6.5%	6.3%	0.92
Death or non-fatal MI	11.9%	10.7%	0.44
Protocol-defined stent thrombosis	1.1%	0.6%	0.30

Among the key points Dr. Rogers made were:

- J&J supports the ARC definitions.
- "p-value-driven discussions are not the whole story."
- There is "strong evidence of safety and efficacy of Cypher in a wide variety of clinical settings…Physicians should be confident in prescribing Cypher for all patients they believe will benefit from the therapy."
- "We recommend patients and physicians be educated to clinical guidelines of one year of dual antiplatelet therapy."
- In the IVUS subset of patients, the thrombosis rates were identical whether patients had malapposition or didn't have malapposition.
- J&J will continue to work with the FDA on:
  - Physician (primary care, gastroenterologists, and dentists) and patient education on stent thrombosis with DES and on antiplatelet therapy guidelines.
  - Generating appropriate data to understand better how to reduce the risk of stent thrombosis.
  - Endorse the dual antiplatelet guidelines, that dual antiplatelet therapy should be continued up to 12 months in appropriate patients.
  - Conduct a Cypher post-marketing study with randomization to two durations of antiplatelet therapy, pending the recommendation of this panel.
  - Expand the follow-up in the 3 SIRIUS trials from 5 to 8 years.

Dr. Dennis Donohoe, vice president of clinical research at J&J, reviewed the safety data on Cypher, using patient-level data based on a four-year, pooled analysis of four RCTs. He noted that there are numerically more events within the first year for BMS, and numerically more events related to Cypher after one year post stent implantation.

Among the key points Dr. Donohoe made were:

- "A significant difference was found in the diabetic subgroup that we think was a statistical anomaly."
- No significant differences were found in stent thrombosis, death (cardiac and non-cardiac), or MI, but the need for repeat intervention is reduced by more than 70%.

Dr. Sidney Cohen, Group Director of Clinical Research at J&J/Cordis offered a pooled meta-analysis of Cypher RCTs.

Pooled Meta-Analysis of Cypher RCTs

Measurement	4 Cypher RCTs at 1 year: Cypher vs. BMS	6 post-marketing Cypher registries: Cypher range
Death	1.3% vs. 0.8%, Nss	2.2% - 4.1%
Death in patient/lesion subgroups	N/A	2.1% - 9.0% *
TLR	79% reduction, p<.0001	N/A
MI	3.3% vs. 3.4%, Nss	1.0% - 2.0%
MI in patient/lesion subgroups	N/A	N/A
Stent thrombosis	0.6% vs. 0.6%, Nss	0.3% - 0.9%
ARC definite + probable stent thrombosis	N/A	0.5% - 1.2%
Any ARC stent thrombosis	0.8% vs. 1.7%	N/A

*** 9.0% was in chronic renal insufficiency patients.**

Dr. Laura Mauri, an interventional cardiologist at Brigham & Women's Hospital and Chief Scientific Officer of HCRI, presented an analysis of Cypher RCT data based on ARC definitions.

Stent Thrombosis in Cypher RCTs at 4-5 Years by ARC Definitions

Measurement	Cypher	BMS	p-value
Any stent thrombosis	4.1%	5.1%	0.795
Definite or probable stent thrombosis	1.7%	1.9%	0.703
ST by protocol	1.2%	0.6%	0.216
ST	6.5%	6.3%	0.92
Death or non-fatal MI	11.9%	10.7%	0.44
Protocol-defined stent thrombosis	1.1%	0.6%	0.30

Among the comments Dr. Mauri made were:

- Among the trial patients, 7 of 10 BMS patients with a stent thrombosis had prior brachytherapy, but none of the Cypher patients who had had prior brachytherapy experienced a stent thrombosis.
- There is a similar overall risk of stent thrombosis with Cypher or a BMS over four years – and to last follow-up beyond four years.
- Clinical outcomes following stent thrombosis were similar for Cypher and BMS.

There appeared to be a sense that J&J did not do as good a job as Boston Scientific in its panel presentation. Panel members also were very concerned about J&J's lack of long-term registry data on Cypher. Among the panel questions/ comments and company responses were:

- *Chair to J&J:* "I appreciate there is little registry data beyond 1 year…When the panel approved Cypher, a condition of approval was a post-marketing registry because of the concern on long-term safety…Now, it is 3 years later, and you've failed to provide any information from a registry beyond one year. Taxus was approved later (than Cypher) and has provided 2-year registry data…I'm at a loss why you failed to show that data. Either (1) you chose not to show us the data, which I doubt is true, or (2) you haven't done your due diligence in analyzing this data and providing it to the panel."
- *Dr. Donohoe:* "If we had it, it would have been presented. The follow-up was only for 1 year. It was approved on (a requirement for) one-year follow-up."
- *Chair:* "So, your contention is that Cordis doesn't have registry data beyond 1 year?"
- *Dr. Donohoe:* "The ones we have control over are 1 year except in Japan, which is still underway."
- *Chair:* "I find that concerning."
- *Dr. Somberg:* "Are you saying this (registry) protocol design was for 1 year, and the FDA approved 1-year follow-up?"
- *Dr. Donohoe:* "Yes."
- *FDA's Dr. Zuckerman:* "When post-marketing approval studies are planned, there is always a balance between getting all the data we all would like to see vs. doing something that is reasonable and can answer the safety questions at hand. If we harken back to 2003, the knowledge base at that time, which was incomplete…was that stent thrombosis was something that would occur primarily within the 1-year timeframe, using the BMS stent model…And that is why the register was designed as Dr. Donohoe explained. In retrospect, certainly the Agency and Cordis would like to have done it differently. But that doesn't mean…if there are legitimate safety concerns right now that continued work in the post-

marketing arena can't be done with this particular sponsor or others…The BMS model used at that time (for RCTs) was follow-up to 5 years, and the sponsor is doing that… What is new here…is that we are in a different day and age, where we are truly reckoning with transforming technology that has reshaped the landscape for interventional cardiology and our understanding of that science. And if we do need to make adjustments in post-approval strategies, that is more than legitimate if that is the advice of the advisory panel."

- *Dr. Michael Domanski, branch chief of atherothrombosis and coronary artery disease at the National Heart, Lung, and Blood Institute (NHLBI):* "We would like to have more data, but I worry about the sense that could go out that this is criticism of the FDA or the sponsor. That doesn't seem fair."
- *Dr. Somberg:* "In the future I would like to see large registries, followed a long time."

BOSTON SCIENTIFIC

Dr. Donald Baim, vice president and Chief Medical and Scientific Officer of Boston Scientific, pointed out that stent thrombosis was initially an issue with bare metal stents but was resolved by better deployment and use of a thienopyridine (e.g., Plavix or ticlopidine). Among the other points he made were:

- With DES, "We may be seeing an emergence of ~0.5% very late stent thrombosis."
- "I believe that if there is a mechanistic difference between DES and BMS in terms of late stent thrombosis, it is our obligation to treat this like all problems in interventional cardiology over the last 25-30 years, and look for ways to identify who is vulnerable and look for ways to mitigate that risk."
- "I think we've spent too much time thinking about the hole (late stent thrombosis) and forgetting about the donut (whether the patient is going to have death or MI)…Late stent thrombosis is just one of several causes of late death and MI."

Dr. Baim took issue with the ARC definitions, arguing that the "possible" category is too broad and may dilute any true safety signal. He also insisted that Taxus has no significant increase in stent thrombosis by ***any*** definition. He provided the panel with an analysis of stent thrombosis viewed several different ways – per protocol, by ARC definite/probable, ARC possible, censoring for TLR, by subgroup, etc. – and in each case the difference in risk was not statistically significant between Taxus and BMS. Panel members indicated they were very impressed with Dr. Baim's analysis, calling it very thorough.

Difference in Death and MI with Taxus vs. BMS in Subgroups

Subgroup	Deaths	MI	Q-wave MI	ARC definite/ probable stent thrombosis at 1 year
Diabetics	1.5% less	0.2% less	0.8% less	0.8% increase
Small vessels	0.6% higher (Nss)	N/A	Nss	0.9% higher but TLR significantly reduced
Long lesions	3% numerically lower	9.5% increase (p=0.01)	N/A	0.3% less and TLR reduced 18.2% (p<.05)
Multiple stents	4% lower	N/A	N/A	21% reduction in TLR

Boston Scientific View of Stent Thrombosis from Taxus RCTs

Measurement	Taxus-SR	BMS	p-value
Cumulative at 4 years in Taxus RCTs			
Any stent thrombosis per protocol	1.3%	0.8%	0.057
ARC definite and probable stent thrombosis	1.8%	1.1%	0.081
ARC possible stent thrombosis	1.6%	2.3%	0.28
ARC all	3.5%	3.6%	0.786
All death	7.1%	7.4%	0.78
Cardiac death	2.7%	3.1%	0.64
Non-cardiac death	4.5%	4.4%	0.97
TLR reduction at 4 years			
Diabetics	-11.5%	---	<.001
Small vessels (≤2.5 mm)	-13.2%	---	<.001
Long lesions (≥28 mm)	-18.2%	---	<.001
Multiple stents per vessel	-23.1%	---	<.001
Other Taxus results at 1 year			
Mortality hazard	1.71%/year	1.87%/year	---
Possible stent thrombosis	0.36%/year	0.53%/year	---

Boston Scientific View of ARC Definitions

ARC definition	Primary with TLR censored	Total with post-TLR retained
Definite stent thrombosis	Too narrow	Too broad
Definite + probable stent thrombosis	Best balance	Too broad
Definite, probable, and possible stent thrombosis	Too broad	Too broad

Boston Scientific Comparison of BMS and Taxus

Side effect	BMS	Taxus
TLR	1 death in 260 TLRs	0 deaths in 118 TLRs
Stent thrombosis (ST)	3 deaths in 10 STs	3 deaths in 16 STs
Stent-related deaths	4	3
Conclusions	More TLR events and fewer ST-related events	Fewer TLRs and more ST-related events
Likeliness of death or large heart attack	Lower with Taxus than BMS	

Duration of dual antiplatelet therapy also may be a factor in interpreting stent thrombosis data, Dr. Baim pointed out. He said that 93.6% of patients in the Taxus RCTs were on dual antiplatelet therapy at 4 months, 83.2% at 6 months (the trial requirement), 31.2% at 2 years, 18.2% at 3 years, and 15.1% at 4 years.

Dr. Baim also presented the 7,000-patient ARRIVE-I and II registry data for Taxus, which showed comparable outcomes to patients with similar lesions in the RCTs. The more complex registry patients had, as expected, higher rates of adverse events, but the rates of death and MI were equivalent or better than those for CABG, though the CABG data used appeared to be old and higher than what surgeons claim it is today. He said, "One could make the point that the results of real-world ARRIVE patients are comparable to other registries and also comparable to or lower than that seen with alternative revascularizations that might be used in these patients. MI rate is somewhat lower, stent thrombosis we don't have historical controls for, but TVR is in the range of bypass surgery and far below what is seen historically with angioplasty.

Some panel members were critical of Dr. Baim's characterization of the safety of CABG. Dr. Kato commented, "I'm concerned with historical CABG data that is almost decades old at this point."

Perhaps most compelling, though, was one slide Dr. Baim provided to the panel detailing, in a patient-level analysis, all the deaths in the Taxus RCTs, their timeframe and cause. The panel asked J&J to do the same for the Cypher RCTs, and J&J officials later offered more data on this but did not have an identical per-patient analysis.

After the panel meeting Boston Scientific said the key take-aways from their presentation were:

- A meta-analysis of 2,797 patients from the Taxus RCTs with up to 4-year follow-up showed a statistically significant reduction in TLR and a trend (Nss) towards less death and Q-wave MI with Taxus vs. BMS.
- There was no statistically significant increase in ARC definite/probable stent thrombosis with Taxus vs. BMS out to 4 years.

Other Industry Presentations

Abbott Vascular

Dr. Krishna Sudhir, Medical Director of Global Clinical Science at Abbott Vascular, didn't present any stent thrombosis data on the Abbott Xience V human clinical program, saying it was too early to do that, but he emphasized:

- DES are not a class effect. In particular, he suggested the difference in strut thickness may be a factor in stent thrombosis, not just the platform, polymer, drug, and elution rate.
- Questions were raised by the panel about whether the endothelial lining that forms over DES stents is actually functional, and he said, "In general, the parameters go up favorably in Xience stents…At 360 and 720 days, there is minimal chronic inflammation in the wall of the pig coronary artery, and there is no difference from a (bare) Vision stent."
- There has been no stent thrombosis in SPIRIT-First out to two years in either arm (DES or BMS). In SPIRIT-II, there was 1 event in each group within 60 days (0.5% vs. 1.3% with Taxus) out to 9 months. The ARC adjudication is not yet complete.

Biolimus A-9 programs

Dr. Mauri of HCRI proposed that the FDA allow 4 different companies – **Biosensor, Devax, Terumo, and Xtent,** all of which use the biolimus and the same biodegradable polymer but different stent designs and different delivery systems – be allowed to have their safety data pooled and analyzed by an independent agency in a mega-analysis. She said that this would provide data on >5,000 patients, offering better adverse event rate data than any of these companies could provide alone and would increase the power to detect rare events.

This would be a secondary safety analysis, not a replacement for regulatory approval requirements. The individual data would remain with each company; they wouldn't all share their data, but the outside agency could have access to all of it to do the safety analysis. A statistician on the panel commented that she really liked this proposal.

Medtronic

Endeavor was submitted to the FDA for approval on November 16, 2006. Dr. Rick Kuntz, senior vice president of Medtronic, presented an analysis of Endeavor safety data based on 1,300 patients for 2-3 years using both the per-protocol and ARC definitions.

Medtronic Endeavor Safety Analysis

Measurement	Endeavor	BMS (Driver)
Protocol definition ≤3 years		
Any stent thrombosis	0.30%	---
Early stent thrombosis (≤30 days)	0.5% - 1%	---
LaST (>30-365 days)	0	---
ARC definitions ≤3 years		
Definite/probable	0.54%	2.3%
Any stent thrombosis	0.97%	3.3%
Stent thrombosis in patients with TLR vs. no TLR	0.9% vs. 0.9%	1.0% vs. 2.6%
Other results		
All-cause mortality at 2 years	2.0% Nss	3.1%
Late incomplete apposition	0.2% *	---

* 1 patient in ENDEAVOR-III

Among the points he made were:

- Adherence to antiplatelet therapy at 12 months is 29.4% in ENDEAVOR-II.
- Available Endeavor data have demonstrated prevention of restenosis without an increased safety risk under ARC definitions.
- Any increased incidence in late stent thrombosis appears to be offset by a reduction in downstream revascularization events prevented by DES.
- Medtronic is committed to ongoing follow-up and new post-market studies. The international PROTECT trial will follow 8,000 patients for 5 years, with ARC definite/probable stent thrombosis at 3 years the primary endpoint.
- DES are not a class – there are different platforms, drugs, polymers, etc.

The completed Endeavor trials used three months of dual antiplatelet therapy, and going forward the company plans to mandate six months of therapy (in the head-to-head PROTECT trial vs. Cypher). This raised some panel and FDA eyebrows. The FDA's Dr. Zuckerman asked if the company is re-thinking this (to move to longer dual antiplatelet therapy) in light of the testimony at this panel, but Dr. Kuntz said not really, "Probably we could justify longer dual antiplatelet use because the risk is higher (since this is an all-comer trial), but right now the plan is for 6 months."

Dr. Kuntz agreed with J&J and Boston Scientific officials that all DES should not be lumped into a class, "While historically, there might not have been complete exchangeability, I think there will be less a view of exchangeability going forward."

PUBLIC WITNESSES

More than 40 public witnesses addressed the panel, many with their own analyses of stent thrombosis data. Following is a brief synopsis of some of these.

➢ **Dr. Herman Gold, an interventional cardiologist from Massachusetts General Hospital,** presented on behalf of pathologist, Dr. Renu Virmani of CV Pathology. He said that preclinical evaluation of DES – Cypher and Taxus – showed delayed healing at 28 days in pigs and rabbits, indicating early-on that late stent thrombosis with DES was a potential problem. He concluded, "The potentially avoidable factors for late stent thrombosis include malapposition, bifurcations, and long lesions." During a break in the panel meeting, he explained that when malapposition occurs with DES, there is an increased risk of stent thrombosis.

Asked if there are any clinical characteristics that might predict stent thrombosis, Dr. Gold said, "The one thing that came out of our analysis…(was) the number of uncovered struts per stent…If 37% of struts per stent were uncovered, there was (several-fold) increase of stent thrombosis compared to stents with full coverage. That technology is theoretically possible with high-resolution IVUS." In the absence of that, he suggested limiting (DES in) patients with long lesions and in complicated patients.

➢ **Dr. Alan Michelson a professor of pediatrics at the University of Massachusetts Medical School** discussed antiplatelet resistance, contending that platelet function testing be considered. The predictive value of this testing, and whether altering therapy based on the tests would rescue patients, still needs to be done. But he suggested the role of platelet function testing could be to monitor for:

- Patient non-compliance.
- Resistance or hypo-responsiveness to aspirin and/or Plavix.
- Platelet hyperfunction after discontinuation (rebound).

➢ **Dr. Donald Cutlip, a cardiologist at Beth Israel Deaconess Medical Center, Chief Medical Officer of HCRI, and the first author on the ARC definitions,** reviewed the definitions and stressed that it is important "not to get too concerned about p-values." He also recommended that stent thrombosis be examined at different time periods, and he defended the inclusion of "possible" stent thromboses. He added, "Stent thrombosis as a mechanism impacting overall safety remains critical even if there is no measurable effect on mortality or MI outcomes."

Asked by a panel member for his views on whether there is a true late stent thrombosis increase, he said, "There certainly is a problem with late stent thrombosis. I don't know what events we are seeing. We are struck with the prior TLR. That makes a difference. And many of the prior TLR events occur after treatment for restenosis that includes brachytherapy. The relevance of that to modern therapy is a question. The events when they occur are dramatic and it is possible we are missing silent events. Given the dramatic nature, I find it hard to believe we are missing very many of them."

Asked about who funded ARC, Dr. Cutlip said each industry sponsor paid $1,000, and HCRI gave $1,000, but he did not know who paid for a second ARC meeting in Dublin. After that, there was no outside funding.

➢ **Dr. Gregg Stone of Columbia University Medical Center, the Taxus principal investigator,** offered his own personal review of all DES. He called DES a "remarkable advance" that have improved the quality of life for hundreds of thousands of patients. But he noted that "like any medical advance, DES have side effects the most concerning of which is a increased incidence of primary late stent thrombosis of ~2 per 1,000 patients per year compared to BMS, but he said this is offset by an excess rate of secondary thrombotic events from treatment of BMS restenosis.

Why is there no increase in death/MI with DES despite an increase in late stent thrombosis? Dr. Stone suggested three possibilities:

1. The excess in death and MI from LaST with DES is *offset* by a reduction of death and MI by preventing restenosis.
2. The causes of death/MI in DES patients are multifactorial and often remote from the stent site. A relatively small excess risk of late stent thrombosis leading to death or MI might be lost against this greater non-stent-related background rate.
3. The definition of stent thrombosis used in the pivotal trials *censored thrombotic events after TLR*, biasing against DES.

Patient-Level Meta-Analysis of DES Stent Thrombosis at 4 Years

Measurement	Cypher vs. BMS	Taxus vs. BMS
Freedom from stent thrombosis (by protocol)	98.8% vs. 99.4% p=0.20	98.7% vs. 99.1% p=0.30
Freedom from all-cause death	93.3% vs. 94.7% p=0.23	93.9% vs. 93.4% p=0.68
Freedom from MI	93.6% vs. 93.8% p=0.86	93.0% vs. 93.7% p=0.66
Deaths	6.7% vs. 5.3%	6.1% vs. 6.6% p=0.68
MI	6.4% vs. 6.2%	7.0% vs. 6.3% p=0.66
Stent thrombosis	1.2% vs. 0.6% p=0.20	0.6%
Death or MI	8.4%	7.3%

Dr. Stone made an impassioned argument against long-term use of Plavix in DES patients without data to support that. He said, "In the U.S. we don't change practice recommendations based on hope or need without firm evidence-based medicine. Therefore, pending the completion of an adequately powered randomized trial, the FDA-regulated 'label' mandate (3 months for Cypher, 6 months for Taxus) shouldn't change. The ACC/AHA guidelines currently recommend 1 year of clopidogrel for DES, which is sufficient." Among the points he made were:

- The CURE and CREDO clinical trials found an increased major bleeding risk with Plavix of 1.0% - 2.1% at one year, and the CHARISMA trial reported an increased risk of 1.2% over 2.5 years.
- Plavix is expensive – averaging $1,500 per year. This means that 4 million U.S. patients with DES taking Plavix would cost ~$6 billion.
- Whether long-term clopidogrel would reduce late stent thrombosis, thus warranting the risks and cost, is completely unknown.

He also urged the panel and the FDA not to modify the requirements for approval of new DES. He said, "To modify approval trials to be powered for safety or to require longer-term follow-up is unnecessary and would be excessively burdensome." Instead, he recommended more rigorous post-market surveillance, an FDA "Dear Doctor" letter to reinforce the need to carefully weigh the risks and benefits of DES on a per patient basis, especially when considering off-label use.

➢ **Dr. Patrick Serruys of the Thoraxcenter in the Netherlands** reviewed the data from the Rotterdam/Bern analysis presented at the World Congress of Cardiology meeting in Barcelona in September 2006 which found a 0.6% annual rate of stent thrombosis with DES. He said there is clearly a need for large-scale studies in diabetics, but he doesn't believe that Cypher is more dangerous than Taxus in diabetic patients, though he suggested that Cypher in diabetic patients should be re-evaluated by a pooled analysis incorporating the long-term results of the most recently completed randomized studies – including TYPHOON, PRISON-II, and others.

➢ **Burt Cohen, editor of Angioplasty.org** (an independent website devoted to interventional cardiology), made a plea for regulators to pay more attention to patient reports of DES problems, such as hypersensitivity, and to better inform patients about DES safety. He said, "I think the time has come for the FDA to find a way to 'fit' real world, anecdotal, self-reported patient experience, into its information gathering and post-market safety monitoring…Is DES hypersensitivity a safety issue? I don't know, but we have over 200 postings from patients whose doctors cannot explain their severe and on-going symptoms, all of which started after DES implantation, and many don't seem medication-related. We may have the largest informal registry of such individuals – and hypersensitivity may impact late stent thrombosis."

Cohen said a key concern of patients is about Plavix use with DES, "We are now hearing every single day from stent patients who have questions about Plavix…When we approached the makers of Plavix for a grant to help us inform the hundreds of thousands of stent patients who come to our site to learn about this drug, we were stunned to discover that these companies were not legally permitted to participate in educational projects like ours. Why? Because Plavix after PCI and stenting in patients outside of acute coronary syndrome is an off-label use of the drug…So the drug companies aren't allowed to support this kind of public education, and the device companies are not required by FDA to educate patients proactively about the drugs that are essential to their survival …I believe that drug-eluting stents have been a wonderful advance for many, many patients. But stents plus Plavix is a package deal. The public deserves responsive communication, participatory patient education, and on-going patient support. But, given current policies, where will the money come from to improve compliance strategies and to support proven effective education initiatives like ours?"

➢ **Dr. Antonio Colombo of Italy** reviewed his study of 3,021 consecutive DES patients. The stent thrombosis rate in these patients was 1.9%. Among these patients, 44.6% were on dual antiplatelet therapy at 6-12 months and 25.6% were on

it at 18 months. Half the patients experienced stent thrombosis during the first 30 days post-implantation. He said the prevalence of stent thrombosis was higher in patients not taking dual antiplatelet therapy in the first six months after getting a DES, but after six months the benefits of dual antiplatelet therapy were less clear, "In the first 6 months, in patients without dual antiplatelet therapy, the risk (of stent thrombosis) is quite high and is clearly very different compared to the patients on antiplatelet therapy, but after six months, the two curves become parallel…Discontinuation of dual antiplatelet therapy was the most powerful predictor of stent thrombosis during the first six months after stent implantation. Discontinuation of clopidogrel treatment after six months from stenting did not increase the risk of stent thrombosis."

➢ **Dr. Lars Wallentin of Sweden** presented the independent SCAAR registry data, an observational study of 61,894 patients (37,380 BMS and 24,514 DES). Based on this study, DES use in Sweden dropped to ~25%. Dr. Wallentin said, "(The findings) were published in the general papers. They were called the 'Death Studies.' It was very dramatic."

Researchers found that over 2.5 years:

- No significant difference in the composite of death and MI.
- Increased mortality.
- No significant difference in MI.

After 6 months, the DES vs. BMS showed:

- 20% relative ***increase*** in death/MI (yearly absolute increased risk of 0.5% - 1%).
- 32% relative ***increase*** in mortality (yearly absolute increased risk of ~0.5%).
- 12% relative ***increase*** in MI (yearly absolute increased risk of 0.3% - 0.5%).
- Unchanged ***increase*** in risk from 6 months to 3 years.
- Half the restenosis risk (absolute risk reduction of ~3%).

Panel members were impressed with this study because (1) the findings were so dramatic, (2) it was a countrywide study, (3) compliance with dual antiplatelet therapy is less of a problem in Sweden because the medication is free. Dr. Wallentin guessed that most had dual antiplatelet therapy for six months, but he stressed this was only a guess.

➢ **Dr. Roxana Mehran of Columbia University Medical Center** reviewed the interim results of the first 1,521 patients in the MATRIX trial, a prospective, single-arm, physician-initiated study. Stent thrombosis in this study was 1.2% at two years. Dual antiplatelet compliance was 60% at two years, though aspirin compliance remained above 90% for two years. She said the study found the frequency of early and late adverse events were similar and low. Patients with diabetes, CKD, or more than 3 stents had higher rates of death, MI, and TLR, but not ARC definite/probable stent thrombosis compared to controls without those conditions.

➢ **Dr. Alexandre Abizaid of Brazil** presented a prospective registry of 1,800 DES patients in his country, 75% Cypher and 25% Taxus. At four years, the stent thrombosis rate was 1.32%, death 3.4%, MI 2.2%, and TLR 2.1%. He said they found that late acquired incomplete apposition is one of the explanations for late stent thrombosis.

➢ **Dr. Takeshi Kamura of Japan** reviewed the J-CYPHER registry of the Japanese real-world experience with Cypher, comparing the results to what was reported in the European E-CYPHER registry. He reported that extending dual antiplatelet therapy up to 1 year vs. discontinuing it did not lower the stent thrombosis rate.

J-CYPHER Results

Measurement	Stent thrombosis rate with Cypher		
	30 days	180 days	365 days
ARC definite/probable stent thrombosis	0.32%	0.53%	0.62%
ARC definite stent thrombosis	0.24%	0.45%	0.52%
ARC probable stent thrombosis	0.8%	0.08%	0.1%
One-year all-cause mortality	0.66%	2.12%	3.57%
Cardiac mortality	0.36%	N/A	1.41%
Stent thrombosis in patients who discontinued Ticlid	---	---	0.23%
Stent thrombosis in patients who continued Ticlid	---	---	0.45%

➢ **Gerrit-Anne van Es, PhD, of the Netherlands** reviewed stent thrombosis in the ARTS-II trial using ARC definitions.

Stent Thrombosis in ARTS-II by ARC Definitions

Stent thrombosis	0-30 days	0-365 days	0-3 years
ARC definite	0.7%	1.0%	2.0%
ARC probable	0.5%	1.2%	2.3%
ARC definite/probable	1.2%	2.1%	4.3%

➢ **Dr. Gregory Mishkel, an interventional cardiologist with Prairie Cardiovascular Consultants,** presented the results of their 5,280-patient DES registry, in which 75% of patients got a Cypher stent, primarily off-label. He reported no difference between Cypher and Taxus on survival. Smokers, bifurcations, and overlapping stents were over-represented in patients who had a stent thrombosis, and a "large" number were on Plavix at the time of the stent thrombosis. He concluded that the stent thrombosis rate over 3 years was 1.9%, with unadjusted definite/probable stent thrombosis at 1.1%, giving an annual rate of definite stent thrombosis of 0.45%/year. As a result of these analyses, he said their DES use has dropped to close to 80%.

➢ **Dr. David Kong of Duke University** compared DES to BMS in Duke's practice-based cardiovascular registry. He found that DES was associated with reduced TVR compared to BMS, and death/MI were higher for DES patients stopping Plavix therapy at six months.

A panel member asked Dr. Kong to comment on the "surprising" finding that DES patients on Plavix did the best of the four groups studied. Dr. Kong responded, "Certainly, the leading hypothesis is antiplatelet therapy reduced the likelihood of late thrombotic events. Whether that is actually the mechanism or not requires further study. What is reassuring is that, albeit we were not powered to detect mortality, there is a non-significant ~23% reduction in mortality associated with taking Plavix for an extended time …One of the key differences from the Swedish analysis is that we were able to have reasonably detailed clopidogrel use in the four arms (of the study)…If we look at reports of clopidogrel use…it became apparent that there may be patients using clopidogrel for extended periods…I thought it was interesting that Dr. Baim showed similar parameters… There does appear to be a sufficiently robust signal."

Asked if he can make a recommendation on how long Plavix should be used, Dr. Kong said, "The optimal duration of clopidogrel use is something that is yet to be determined. In my opinion…because we have detected a mortality difference in patients on extended clopidogrel vs. those not on extended clopidogrel, it is reasonable that a 12-month minimum would provide more optimum reduction in risk."

➢ **Cardiologist Dr. Ralph Brindis and emergency medicine specialist Dr. David Magid, both of Kaiser Permanente,** said a review of their databases found that DES off-label was associated with increased risk of adverse events and that Plavix may have a protective effect in the first 12 months post-implantation but had no protective effect after that.

➢ **Dr. David Williams, an interventional cardiologist from Rhode Island Hospital,** reviewed the NHLBI Dynamic registry and the DEScover registry. He said the findings in these two registries was similar – no signal of excess death or MI in DES patients but a substantial reduction in the rates of TVR with DES. Then, he presented new data about on- and off-label DES use. He said off-label patient outcomes were worse than on-label outcomes, and BMS off-label use had the worst results, with the best results from DES on-label use.

On-Label vs. Off-Label DES Use

Measurement	On-label	Off-label
DES 1-year cumulative mortality	2.6%	4.5%
BMS 1-year cumulative mortality	3.3%	5.8%
DES stent thrombosis	0.5%	1.6%

➢ **Dr. Ron Waxman of Washington Hospital Center** told the panel that a registry of patients at his hospital, using ARC definitions, found a higher stent thrombosis in off-label use. He recommended giving different weights to definite, probable, and possible stent thromboses: 1.0 for definite, 0.8 for probable, and 0.3 for possible. He said, "A warning about late stent thrombosis should be considered for the current DES when used off-label, diabetics with multivessel disease should be liberally referred to bypass, and dual antiplatelet therapy beyond six months is not proven to prevent stent thrombosis …We think one of the explanations for the difference in the stent thrombosis rates between Taxus and Cypher may be clopidogrel compliance…We have now reduced our use of DES to 68%."

➢ **Dr. Jeffrey Moses, an interventional cardiologist from Columbia University Medical Center,** described the current environment as "difficult because of the negative characterization portrayed by the press," adding, "What should we do? We recommend a more considered use of DES, adherence to antiplatelet therapy guidelines, and a lower threshold for BMS in situations where prolonged dual antiplatelet therapy is problematic…There are new DES technologies which may reduce the late safety concerns."

➢ **Dr. Robert Guyton, a cardiothoracic surgeon from Emory University,** argued that DES are being overused and patients under-informed and that more RCTs and registries are not the answer. He said, "We need robust, comprehensive databases in multivessel patients, not more RCTs in selected, low-risk patients. DES is inferior to CABG in multivessel disease. Do we not need a DES labeling change to reflect this fact? Yes. At the very least, better patient information is of paramount importance."

➢ **Dr. Bruce Ferguson, speaking on behalf of the Society of Thoracic Surgeons,** offered three recommendations:

1. Informed consent that is accurate and complete, including all available data, not just RCT data. And the informed consent should be provided by a multidisciplinary team, after diagnosis but before intervention.
2. FDA should develop data partnerships with professional society-led databases to provide data on important new technologies where appropriate. He described the STS database as a major observational database, and according to that database, overall CABG mortality is <0.2% and multivessel mortality is <1%.
3. Active robust comprehensive databases should be developed through partnerships between FDA and professional societies.

Asked about the overall mortality of CABG in all-comers, Dr. Ferguson said, "STS has shown a steady decline in operative mortality overall and in every single subset of patients. In the latest analysis, which is a composite of three years, risk-

adjusted 30-day mortality from 700 hospitals overall is 1.95%, and for elective cases, which are predominantly multivessel disease now, it is just under 1%."

➢ **Dr. James Gustafson, vice president of research and development at Possis Medical,** outlined for the panel how his company's AngioJet can be used to "turn a high risk off-label use (of DES) into a lower risk on-label use" by reducing thrombus in the vessel.

➢ **Dr. James Dove, president-elect of the American College of Cardiology (ACC),** said, "The College, as a professional society, is willing to step in and help with the decision-making processes. Where it becomes important to educate doctors, we certainly want to be at the table to help do that…And we want to be involved in helping to educate patients…We caution presenters and the panel about data hysteria – taking small results and blowing them way out of proportion…We ought to stick to science and not magnify projections of outcomes by trying to state something not proven or true. In very publicized events like this meeting, it is critical to watch the words we use…Words like 'significant' and 'extraordinary' sometimes overstate the literature. We need to be careful and not upset the public."

The ACC also offered some recommendations to the panel:

1. Short term
   - Reiteration of patient selection criteria for BMS, DES, and medical therapy.
   - Reiterate approved indications for limited subsets.
   - Recommendations on duration of antiplatelet therapy.
   - Strategies to improve patient compliance.
   - Education of all healthcare personnel on the need to continue antiplatelet among patients with DES.

2. Near term strategy
   - Better define patient selection, particularly off-label.
   - Informed consent.
   - Risk:benefit discussion.
   - Carefully look at what we know and don't know.
   - Design new trials.

3. Longitudinal database needed with
   - Unique patient identifier to track patients.
   - Common data standards.
   - Independent funding – consider a surcharge on devices and pharmaceuticals.
   - Build on a platform similar to the STS and ACC databases.
   - The ACC/NCDR (American College of Cardiology/ National Cardiovascular Data Registry) database is considering a longitudinal database. "A longitudinal database will benefit more patients than anything we have discussed here so far."

➢ **Dr. Frederick Grover, a cardiothoracic surgeon at the University of Colorado Health Sciences Center and president of the Society of Thoracic Surgeons,** claimed, "We are focusing too much on technology and not the patients themselves. There are 3,000 excessive deaths/year in patients with multivessel disease who receive DES instead of CABG. There are 2,200 additional deaths/year from stent thrombosis …And we now face $7 billion a year in additional costs with Plavix…Approval of DES was based on a 'straw man' – BMS instead of CABG."

Dr. Grover said cardiac surgeons are concerned about a lack of adequate consent after the diagnosis and before an interventional procedure, "And there is misrepresentation of current CABG results…Personally, I try to be as honest as I can about the various options and try not to push the procedure I do myself. Six of the last 50 patients (12%) receiving a cardiac transplant at Duke had stent thrombosis of DES…Off-label use of DES, particularly in multivessel disease, is a major public health problem causing unnecessary deaths."

He offered several recommendations:

- A labeling change for DES to reflect safety and efficacy in multivessel disease has not been established.
- Adequate informed consent by a multidisciplinary team.
- Use of robust, comprehensive databases.
- A stronger FDA/specialty society partnership.

➢ **Dr. Sidney Smith, a past president of the American Heart Association (AHA),** said the AHA/ACC/SCAI guidelines committee may consider revising the guidelines for antiplatelet therapy, patient selection, etc., in conjunction with DES, "It is inappropriate for me to predict the outcome (of the guidelines committee), but we will follow this panel and convene our group after this to determine if a change in guidelines might be necessary…The guidelines group will look carefully at your deliberations, weigh all the evidence, and see if a change or additional guidelines are necessary. I wouldn't want to pre-empt that process by saying what I think would happen, but one possibility is a better definition of subsets and changes in the recommendations for the duration of dual antiplatelet therapy."

Asked if the guidelines committee will make recommendations on the choice of BMS vs. DES, Dr. Smith said, "If evidence emerges where that is important, we will…I think there might well be a refinement of recommendations on stent selection that would apply to certain clinical conditions."

➢ **A patient** who had participated in a DES clinical trial (Abbott's SPIRIT trial) told the panel that there is a lack of information and support services for DES patients experiencing either physical or emotional effects, "Did I ask questions (when asked to join the trial)? No. Did I fully comprehend what was going on? No. I only knew that I wanted to live. I signed all the forms they had…Patients get the device and are left to figure out the rest themselves."

PANEL DISCUSSION OF GENERAL ISSUES

Registries. The panel statistician said using the existing registries to analyze DES safety is very difficult because most have no control. She said, "If someone is going to mandate registries to be collected, then I argue they need a control arm." By the end of the meeting, she had convinced most other panel members of the importance of a registry control.

ARC definitions. The panel was not asked to vote on – or even comment on – whether or not the ARC definitions should be adopted. However, the panel did discuss the value of the ARC definitions.

- *Dr. Somberg:* "It is very hard to give advice when there are no definitions…I think one has to consider what is the empiric data on each question. What does our clinical experience say – in the context that there may be no answer at this point?"
- *Chair:* "ARC definitions have drawbacks, but they try to unify definitions, so there is some value in that."
- *Dr. Nissen:* "I'm not necessarily saying the ARC definitions aren't good, but I'm not pleased with the process. Professional societies frequently define these things, through consensus task forces. I'm concerned with a process where industry funds people to define something with such profound public health import…It would have been far better to have this done independently than an industry-funded group…The most powerful analysis is the per-protocol analysis because that is prospective…It is analogous to changing the rules of the game while the game is going on. I just worry that when you use the new definitions – that have never been tested prospectively and are unverified – you might produce results that are different when you use some other set of definitions. The definitions the investigators chose have a certain validity, but an arbitrary set of definitions that may have a big impact on how we see the hazards that come later when you know the results really is a potential problem…I recognize it is retrospective, but it is changing the rules of the game after it has started."
- *Dr. Domanski:* "If we are going to use ARC, I would use definite/probable…(But) I'm concerned about writing them in stone."
- *Sharon Lise-Normand, PhD, a statistician with Harvard School of Public Health:* "I would go with definite/probable…At least it is clear…It is just wrong to say we can't use the ARC definitions because they are retrospective."
- *FDA's Dr. Zuckerman:* "What this panel has to grapple with is the current reality, which is we are faced with a real-time post-approval conundrum, where the Agency and investigators throughout the world are trying to better understand the dataset. From a practical perspective, I can say the so-called protocol definitions used in the trials are of a somewhat limited nature. Certainly, we would be interested in hearing about any other suggestions – and there is always that opportunity – but for the proceedings today, the Agency did specifically ask the companies to try to use these (ARC) definitions as a way to get a sense of the totality of the data and the totality of the problem."
- *Dr. Zuckerman again:* "We are enthusiastic at the Agency to participate in any future research or efforts by professional societies, but I would urge the panel to utilize this framework (ARC) as well as the original protocol-defined definition because it does allow us to put more of the data on a common ground today."
- *Industry representative*: "For ARC to come up with standardized terms and to ask companies to re-analyze data was leveling and a good thing. It allows us to make judgments based on a level playing field."

QUESTIONS TO THE ADVISORY COMMITTEE AND PANEL RECOMMENDATIONS

On-Label Use of DES

1. **Risk level with DES. When used in accordance with their labeled indications, are DES associated with an increased rate of stent thrombosis, death, or myocardial infarction compared to BMS? YES.**

Chair summary: "Panel members range from feeling not sure, not certain to worry, to probably and a strong signal. So, we are all over the place, but none of us feel this is conclusive data. Further studies are crucial…I'm not saying there isn't a potential issue, but right now there is no evidence of excess of death or MI with DES."

Panel comments included:

- *Dr. Judah Weinberger, an interventional cardiologist at Columbia University Medical Center:* "I'm quite concerned if we define a particular risk, that it be defined as a risk rate…I'm okay with 0.5% lifetime stent thrombosis risk, but completely unhappy with 0.5% per year rate."
- *Dr. Somberg:* "I would say all stent thrombosis is important…I think the issue is, is there a problem? Is it a building problem? Maybe you can improve stents with changes in design, drugs, etc., not what level of death is acceptable."
- *Dr. Topol:* "It is a small risk. It may be significant if it were a large enough population under study…There is a numerical excess of late stent thrombosis. Whether that is statistically significant is immaterial."
- *Dr. Nissen:* "I agree there is pretty unequivocal evidence …and considering the totality of the evidence, it probably is statistically significant. But the confidence intervals are so broad that we can't state with reasonable certainty the magnitude of the risk except to say it is statistically significant."

- *Dr. Hirshfeld:* "If you extrapolate between Years 2-4, and the preponderance (of evidence) doesn't level off, then we will have a very significant difference down the road."
- *Dr. White:* "I think the numbers speak for themselves. I'm not certain that the rate of stent thrombosis is elevated. I'm worried that it is, but I'm not certain that it is, and I don't think death and MI are elevated."
- *Dr. Richard Page, a cardiologist at the University of Washington School of Medicine:* "I'm seeing a strong signal of something going on with stent thrombosis but not death and MI. Why the disconnect?...Just because we don't see an increase in death and MI, we shouldn't ignore the stent thrombosis signal."
- *Dr. Kato:* "While emotionally I think there may be something there, from an evidence-based position, I don't think I can say one way or the other."
- *Dr. Robert Harrington, Director of cardiovascular clinical trials at Duke Clinical Research Institute and a member of the FDA's Cardio-Renal Advisory Committee:* "There is probably an increased risk of stent thrombosis …I'm not completely convinced, but I have a high degree of confidence that stent thrombosis appears to be increased with DES, particularly when not taking long-term Plavix."

1a. What is the relationship, if any, between stent thrombosis and clinical endpoints such as myocardial infarction or cardiac death?

No relationship has been proven.

Chair summary: We are all over the place, but none of us feel this is conclusive data. Further studies are crucial…I'm not saying there isn't a potential issue, but right now there is no evidence of excess of death or MI with DES…**There is a numerical excess but there is uncertainty as to the magnitude of the risk, how it will change over time, and whether that numerical excess is of any importance is unclear.**

1b. Compared to BMS, are DES associated with an increased rate of all-cause mortality?

No, that has not been proven.

Dr. Topol commented, "There may be a late clotting problem, but this does not appear to be associated with an excess of fatal heart attacks."

1c. Do the safety concerns apply equally to both of the currently approved DES? YES.

1d. Do the safety concerns outweigh the benefits for DES compared to BMS (i.e., reduction in repeat revascularization procedures)? NO.

1e. Should the current labeling (indications, contraindications, warnings, or precautions) be modified?

YES, they should be modified to include the latest data in the clinical trials section.

Panel comments included:

- *Dr. L. Henry Edmunds, a cardiothoracic surgeon and editor of the **Annals of Thoracic Surgery**:* "We are going to try to give full disclosure of what we know now. That is all we can talk about to patients. We need to tell patients the question of late stent thrombosis is undecided, but there is no conclusive evidence at this time that they are at any increased risk."
- *Dr. Jeffrey Brinker, an interventional cardiologist at Johns Hopkins Hospital:* "I think the label is made for the doctor, not the patient. I think the label should have any take-homes from this rather than a reproduction of all the study analyses. I think there should be a public statement by the FDA concerning current thoughts on this and other information on the risk for patients in terms they would understand. I think there should be labeling changes for the doctor, and it will take a lot of work to iron them out. But it should include ongoing concern about delayed stent thrombosis and that the RCTs are not clear, but perhaps there is a signal that the rate of stent thrombosis (is increased)."
- *Chair:* "I hesitate to say anything on the label on the risk of stent thrombosis other than to say to reduce it, you should take antiplatelet therapy."
- *FDA's Dr. Zuckerman:* "What we are seeing here is a need to update our clinical trials section."

2. On-label dual antiplatelet use. Current data indicate that termination of dual antiplatelet therapy prior to the duration as recommended in the DES label is associated with a higher risk of stent thrombosis. Current ACC/AHA/SCAI PCI Practice Guidelines recommend clopidogrel therapy for at least 3 months after Cypher stent implantation, at least 6 months after Taxus stent implantation (reflecting the recommendations in the present label for the Cypher and Taxus stents, respectively), and ideally up to 12 months in patients who are not at high risk of bleeding (Class IB recommendation). The European Society of Cardiology recommends clopidogrel (Sanofi-Aventis's Plavix) administration for 6 to 12 months after DES implantation (Class IC recommendation).

2a. Duration of Plavix. Do the current data support a recommendation for an extended duration of dual antiplatelet therapy?

YES – at least 12 months, in accordance with professional society guidelines.

While the panel seemed reluctant to recommend indefinite use of dual antiplatelet therapy, that is exactly what some members said they would do if they had a DES. Dr. White commented, "I'm loathe to change the antiplatelet recommendation, to make that kind of emotional response without evidence." However, asked by the chair, Dr. Maisel, how long he would take dual antiplatelet therapy if he had a DES, he responded, "Indefinitely," to which the chair added, "Me, too."

Other panel comments included:

- *Dr. Topol:* "DES with antiplatelet therapy fare the best; DES without antiplatelet therapy fare the worst. And BMS is in the middle. I think there is a bit of a conundrum here…I find Dr. Baim's analysis suggesting that at least through 12 months, staying on therapy appears to be preferential."
- *Dr. Warren Lasky, medical cardiologist at the University of New Mexico School of Medicine:* "Beyond a year, the stuff we saw this morning is patients almost as likely to develop stent thrombosis on antiplatelet therapy as off. There wasn't that much difference on and off...so I'm not so sure."
- *Dr. Harrington:* "I find the BASKET-LATE results compelling…There does appear to be an accumulation of risk in DES patients off clopidogrel…(The) comment that (panel members) would stay on it indefinitely is what I give my patients now – with a discussion about bleeding …I would like to see it specified in the label what percent of patients in the trials continued their dual antiplatelet therapy beyond 3-6 months. I think there is a fallacy that patients were on it 3 months and stopped or 6 months and stopped. In Taxus (trials), half were on it for a year."
- *Dr. Somberg:* "I think it would be correct to have a risk continuum mentioned. In Cypher (dual antiplatelet use) is 3 months, with Taxus 6 months…Right now I don't continue dual antiplatelet therapy for life for everyone, but for some people it is probably necessary – multiple vessels, bifurcations, prior brachytherapy, diabetics, etc...I think physicians need to individualize."
- *Dr. Nissen:* "I think we are all saying the same thing – we can't make a hard recommendation on how long to give clopidogrel."
- *Statistician:* "I don't think data from observational studies should be in the label...I think we are mixing data."
- *Dr. Domanski:* "I understand observational data. It is what we have, and it is compelling…I don't see anything wrong with having the label help out with the education."
- *FDA's Dr. Zuckerman:* "I think the general tenor here is that an additional statement would be helpful regarding the current guidelines, and a truthful statement regarding just how long patients continued on clopidogrel in a particular trial…I think it should be recognized that observational data are often included in device trials and would not set a precedent if well constructed."

2a (1). What duration of administration would you recommend, and what data support this recommendation?

12 months.

The panel recommended that the label should be changed to include the latest recommendations of the professional societies, which is 12 months. However, individual panel members commented that if they themselves had a DES, they would continue dual antiplatelet therapy ***indefinitely***. The chair concluded: "We have seen no data to (1) change the label or (b) override or overturn national guidelines."

2a (2). Would you recommend restarting dual antiplatelet therapy in stable patients who have already stopped clopidogrel? NO.

2b. Stopping Plavix. If antiplatelet therapy needs to be stopped due to a concurrent compelling medical condition, what strategies do you recommend to reduce the risk of DES thrombosis until antiplatelet therapy can be reinstituted?

The recommendation was to try not to stop Plavix.

If the patient were to remain on only one of the two antiplatelet agents (aspirin or clopidogrel), which agent should be continued?

Aspirin, but Plavix is considered critical.

Panel comments included:

- *Dr. Somberg:* "I'd leave it to physician decisions. I don't think there should be a recommendation…(But) patients should consult a physician before stopping antiplatelet therapy."
- *Chair:* "It is incumbent on us to educate other healthcare providers, for industry to advertise where appropriate, and for professional societies to educate."
- *FDA's Dr. Zuckerman:* "The Cypher label says a patient should talk with the interventionalist. I think this reflects the current dilemma where we are a nation with many physicians who don't understand DES and the risks that come with this technology…This is a big issue."

Real-World Clinical Use of DES

3. Safety of DES. The pivotal randomized trials of CYPHER and TAXUS submitted for FDA approval primarily involved use of DES in non-complex patients and lesions. Following these approvals, it is estimated that a majority of DES are implanted in lesions outside of their current indications for use, such as in-stent restenosis lesions, bifurcation lesions, coronary artery bypass grafts, acute myocardial infarction, chronic total occlusions, overlapping and multiple stents per vessel and in patients with multivessel disease and chronic renal insufficiency. **Given currently available data, are there safety concerns regarding stent thrombosis, death, and myocardial infarction rates for DES use in these complex patients and lesions?**

Most panel members said YES.

The chair summarized the sentiment as: The rates of stent thrombosis, death, and MI are higher with DES used off-label vs. on-label.

3a. Can lesion subsets or patient populations at a particularly higher risk of DES thrombosis within the "off-label" patient population be identified?

No, though there are concerns with overlapping stents, bifurcations, and vessels with thrombosis already which may be at higher risk. However, the panel did not feel there are sufficient data to make sweeping recommendations.

Panel member comments included:

- *Dr. Nissen:* "I think there is (a difference in safety)…In the real world, patients are less compliant. RCTs are probably a best case scenario. I would have to conclude there are differences (between on- and off-label). What we saw in RCTs, which was equivalence, is likely to be the best we will see. The problem with almost all the registry data is there is no comparator, but there are some data that aren't single arm – like the Swedish data. And if you look at that critically, there is approximately a 20% higher mortality in real-world use in individuals who got DES vs. BMS. So I can't exclude that there is an increase in patients who get DES in the real world."
- *Dr. Somberg:* "I would view it differently. I noticed an increased risk of stent thrombosis in certain patient subsets, with both BMS and DES. There is a difference between European/Scandinavian and U.S. databases. While the Swedish database was large, there are smaller ones that show incremental increases in risk that are multi-times the U.S. risk…There is a risk. It should be so stated."
- *Dr. Harrington:* "I'm troubled by the state of the data. There are a lot of small, underpowered registries, with poor follow-up in many. Despite the weakness of the data, there is no consistency that off-label DES use is associated with a worse outcome than on-label use. Then there is the question of the Swedish data, a mix of on- and off-label, where the survival curves separate at ~1 year. What is surprising about the Swedish data is that they have a large enough size to detect very small differences, and they showed a 0.5%/year increased risk of mortality. I think that is something that needs to be thought about. I would also include that the off-label risk has not been well-characterized."
- *Dr. Eric Topol:* "The issue we have to confront is the inconsistencies in the data. Although there is no question DES were a great advance, they also created a new entirety, some would say a new monster – this late thrombosis."
- *Panel statistician:* She repeatedly asked about the comparator in the many studies that were presented to the panel. "Compared to what?" she wanted to know. "In simple patients, I understand using BMS as the comparator, but in off-label use, who is the best comparator? I don't think it is BMS."
- *Dr. Kato:* "This is very new technology, transformational technology, which has really grabbed both clinicians and patients. The concern with off-label use is very important for DES as well as devices in general…I think it is fairly safe to say on-label use is safe and effective, but I don't think we have enough data to say the other reasons for putting in a DES are safe and effective, so it needs to be said more forcefully – contraindicated, the equivalent of a black box warning in the drug world...We just don't know enough to say they are safe."
- *Dr. Edmunds:* "I'm worried that (the message) will go out to the public and suggest that DES isn't the right thing to use."
- *Dr. Weinberger:* "The obligation of the package insert is to let patients know that if they don't fit into the dataset in the package insert, they can't expect to get that outcome. What the outcome is is poorly defined, given the data we have today…I think the purpose of the package insert is to say, 'If you are in Class A, you get the outcomes explained, but if you are in Class B, the outcomes are not as good.'"
- *Dr. White:* "Nothing I heard here will change my practice when I go home unless there is a subset of patients in which we should be very worried – perhaps bifurcations. My first bifurcations won't get two DES. I won't argue. I need more information, and I am concerned about the Swedish data."
- *Dr. George Vetrovec, an interventional cardiologist from the Medical College of Virginia:* "It seems to me when I go back (to my cath lab) and have to decide about stents, what I carry with me is recognition that I should try to simplify everything I do and that less stent is probably better, but I'm not sure I will change any patient I treat."

- *Dr. Nissen:* "I think our surgical colleagues made a fairly impressive case that we know a lot about (CABG), that it has life-saving ability in some subsets of patients. It is extremely well-categorized. In making comparisons, we have to be careful because we have an established therapy with a profound effect that we understand extremely well…What is driving off-label use is DES in multivessel disease as an alternative to CABG. We know what CABG does long-term, but we don't know what stenting does long-term."
- *Dr. Hirshfeld:* "If we looked at pooled data in off-label, there probably would be a small group that probably had injury due to DES, but there may be a very large number that had a positive outcome because of DES…and we can't say yet who is in which cohort...My sense is that there are a lot of people out there we treated off-label, and they've been benefited by DES."
- *Dr. Clyde Yancy, a medical cardiologist at Baylor University Medical Center:* "I hope the message (after the panel) is that any application of stent technology off-label should give someone pause…I wouldn't say restrict it."

3b. Antiplatelet use for off-label DES. Among the "off-label" population, would the antiplatelet therapy modifications discussed previously for on-label use apply differently to this population or include other patient subgroups?

No. The panel agreed that DES patients should be on dual antiplatelet therapy for 12 months.

Panel member comments included:

- *Dr. Nissen:* "I was persuaded…that up to 12 months (of dual antiplatelet therapy) is probably beneficial…I think risk:benefit looks pretty good up to 12 months. I don't see any compelling data beyond 12 months…so I think it is reasonable to suggest DES patients, if not experiencing complications from treatment, should be treated up to 12 months…Before the meeting, there was a lot of talk that long-term clopidogrel could mitigate the risk of DES. Up to 12 months, it very well may benefit patients, but we should not send the message that going beyond 12 months eliminates the residual risk of DES."
- *Dr. Harrington:* "I feel uncertain (recommending anti-platelet therapy) after a year. I would like to change to a year's recommendation because I think that will give people pause to say, 'Do I really think people will take it for a year?'"
- *Dr. Kato:* "I think it is important to proactively state that the continuation of antiplatelet therapy may or may not be associated with stent thrombosis risk."
- *Dr. Topol:* "One year is very arbitrary…There are no data to support that. Duke didn't stop at one year…That is pulling it out of the air."
- *Dr. Somberg:* "Right now there is a growing body of data saying people who can tolerate 12 months should receive it…The recommendation for 3-6 months (3 months with Cypher and 6 months with Taxus is in the FDA label for those products) isn't based on much but this (12 month recommendation) is based on data….Those people with off-label (DES) uses should consider staying on dual antiplatelet therapy for longer than 12 months. Patients at the lowest risk might consider shorter durations of therapy. Not just everyone gets 12 months, but based on risk and judgment."
- *FDA's Dr. Zuckerman:* "It would be nice if the appropriate drug companies are interested in actually doing RCTs in this area."

3c. Cypher vs. Taxus. If DES thrombosis concerns regarding more complex lesions or patient subsets have been identified, do they apply equally to both of the currently approved DES?

YES, unanimously. There are no data to suggest one is different than the other in the off-label population.

3d. Diabetics. Although diabetic patients were included in the randomized control trials submitted for DES approval, neither of the approved DES have a specific labeled indication for use in diabetics (either insulin-requiring or non-insulin requiring). **Is there a DES thrombosis safety concern for this important high risk cardiovascular subgroup? NO.**

4. Labeling. Given the currently available data and remaining areas of uncertainty, do the risks of stent thrombosis in the broad population of patients currently treated with DES in U.S. clinical practice potentially outweigh the benefits (i.e., reduced repeat revascularization procedures) **compared to the previous standard of care** (e.g., medical therapy, BMS, CABG) **such that the current DES labeling** (indications, contra-indications, warnings, precautions) **should be modified?**

Dr. Zuckerman read the current label for Taxus and asked panel members if they are satisfied with that or if they want death and MI also to be included. The panel asked to have death, MI, and stent thrombosis added to the label.

Yes, the label should be modified to indicate that data outside the on-label indications are limited, and use of the stent outside these indications may be associated with an increased risk of stent thrombosis, MI, and death.

Panel comments included:

- *Chair:* "I think a black box is far too strong for a number of physicians who choose to use this device off-label."

- *Dr. Topol:* "There is something different about these (DES) patients, even though many in the group (panel) don't acknowledge that…Off-label patients are at higher risk…And giving more antiplatelet therapy is a proxy for acknowledging that risk."
- *Dr. Nissen:* "For any label, it is inherent that off-label use is not recommended. That is not saying anything new…I harken back to the Swedish data. I can't rule out a 20% increased risk of death if the device is used off-label vs. BMS. I want to warn people a little more strongly than the current label…I don't want this to be passive. I'm suggesting we be more active. There is enough concern that we might be hurting people by putting DES in these patients off-label."
- *Dr. Kato:* "I want to strengthen the label. The current package insert got us to this point. To leave it alone is a tacit acknowledgment that we didn't change anything and this meeting generally was a waste of time…Black box warnings are designed to highlight safety issues…It sounds like this fits the definition (of a black box)."
- *Dr. Somberg*: "To have a black box, I think we need more consensus and more information. Information is pouring in now. This is just the beginning of the spigot."
- *Dr. Edmunds:* "I can't agree with that (black box) at all, taking into consideration that CABG has better results than DES."
- *Dr. Domanski:* "We've listened to surgery all day…I'm not convinced CABG is better (than DES)."
- *Industry representative:* "There is no precedent for inclusion of off-label data in label, and there are liability issues with that…The FDA needs to take the spirit (of what the committee is saying) and frame it in an appropriate manner…Black boxes and contraindications have very specific meanings. And we need to consider that a lot of companies are already in the pipeline, have finished studies, and are pending approval, so there is impact of some of what we are recommending (on them)."

The final word came from the FDA's Dr. Zuckerman who flatly declared: "The notion of a black box isn't going to happen."

5. Outreach. In addition to current FDA efforts, what patient and/or physician education or other outreach measures (i.e., Public Health Notification) could potentially reduce the risk of stent thrombosis?

The panel did not make many specific recommendations, mostly suggesting increased communications and involvement of professional societies.

Panel comments included:

- *Dr. Nissen:* "We have to get the message out…I'd like to see the letter coming from the FDA because it would have a lot of impact…On the drug side, we have created a patient guide, and I would recommend consideration of that."
- *Dr. Lasky who was the chairman of this advisory committee when Cypher was reviewed:* "I think it is our responsibility to step up...This is our responsibility…We got into this mess in many respects. We need to raise awareness of our colleagues...The professional societies need to be informed in a substantive letter. It is nice to send a letter on letterhead, but this one is on us, and we should all rise to the occasion."

6. Long-term data. What long-term data need to be collected to help further define the risk of thrombosis in DES?

Panel suggestions included: a national registry, genomic testing, trials against CABG, comparators in registries.

Dr. Topol commented, "I think we need to think of a different model for studying DES. There is registry-centric thinking. We've had more registries and that led to uncertainties. It will take 3-5 years for them (new registries) and will lead to more uncertainty. We need a national registry of patients who had late stent thrombosis. That would be incredibly informative. We could look at the genomics of those patients, look at whether there is a predisposition to thrombosis, endothelial cell issues on healing, etc… Patients are calling asking to have stents removed…The problem is now. I think if we collect hundreds of patients who suffered stent thrombosis, we will get a germ line, the genomic underpinnings, of this serious adverse event."

6a. New DES. Should future pre-market studies conducted to support approval of new DES be modified to better assess thrombosis risk?

The panel said pre-marketing approval trials for future stents need to be larger and longer and provide some idea of the thrombosis risk for individual stents, but they didn't say how large or how long.

However, Dr. Zuckerman suggested the FDA is not going to change the requirements for products in the near pipeline. He said, "We (FDA) want to respect the device approval framework...You (the panel) heard about a lack of RCTs to answer important health questions. You heard about Boston Scientific's program, where they initially received limited approval based on RCT data. The sponsor (Boston Scientific) subsequently has almost completed very large trials in AMI and in 3 vessel disease vs. CABG. What else pre-approval are you looking for with DES? The usual paradigm here is different than drugs because of more sequential development." He indicated that death and MI are important endpoints that maybe the Agency should focus on more, but he asked, "What are the fundamental issues that the stent industry is missing in sequential development programs right now?"

Dr. Harrington commented, "I applaud the Endeavor program. That is an 8,000-patient program comparing new therapy to current therapy. We didn't see power calculations (for that), but I suspect it is highly powered. That is the work we need to see…Most of what I've seen (at the panel meeting), I would consider inadequate for approval."

6b. Post-approval studies. Should the long-term follow-up of the pivotal trial cohorts and post-approval studies currently mandated by the FDA be modified?

The panel recommended that pivotal trial patients be followed longer and registries not be allowed to stop after one year, that registries, too, should run longer.

Panel member comments included:

- *Dr. Topol:* "I think the pending FREEDOM and SYNTAX trials (comparing DES to CABG) are terrific… Unfortunately, there has been an unwillingness to do the appropriate trials of conjunctive medical therapy. No trials are pending in that regard."
- *Dr. Somberg:* "We need longer, larger studies, with a randomized control, addressing more complexity that address the increased risk…The noise level is high and the signal low in very low risk patients. But I was very reassured that one major developer is talking about 8,000-10,000 patients in some complex situations…A genomic study is important…and let's look at the dose response of the drug…Registries should always have a comparator and should never be short-term."

7. Plavix. The optimal duration of dual antiplatelet therapy in DES patients is undefined. Indefinite clopidogrel use may not prevent very late stent thrombosis, may expose patients to an unacceptable increased risk of bleeding, and has important economic considerations. **Please comment specifically on the clinical study designs that would be most informative and yet feasible to evaluate this risk given current patterns of DES use and uncertainty regarding the optimal duration of dual antiplatelet therapy.**

The panel recommended that dual antiplatelet therapy be recommended for at least 12 months, but this is an area they also believe needs further study.

Dr. Harrington commented, "There are six million patients with DES. There is a huge imperative to figure this out. I recommend working quickly to get a group of investigators together, look at patients still in the early days of DES and randomize them to various durations of antiplatelet therapy – through 12, 18, and 24 months.

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