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SUMMARY

U.S. DES usage is likely to go down – and perhaps substantially. Cardiac surgeons, medical cardiologists, and reporters are not going to drop the late stent thrombosis issue, personal injury attorneys are starting to discover it, and patients are concerned.

♦ The FDA may consider DES label changes, but no recall of drug-eluting stents is likely. The Circulatory Systems Advisory Committee meeting on December 7-8, 2006, will focus on labeling, post-marketing studies, and the definition of stent thrombosis. But it will also give DES critics a forum and increase publicity about patient deaths. ♦ Experts believe the cause of stent thrombosis is multifactorial, but in the longer term the issue may drive interest in, and acceptance of, bioabsorbable stents.

♦ The everolimus-eluting Vision stent (Abbott's Xience V/Boston Scientific's Promus) is expected to capture significant market share quickly when approved in the U.S., but will hospitals buy it from Abbott or Boston Scientific? The decision is likely to be up to hospital purchasing agents, not cardiologists.

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TRANSCATHETER CARDIOVASCULAR THERAPEUTICS (TCT)

Part I – Drug-Eluting Stents

Washington, DC
October 22-27, 2006

The safety of drug-eluting stents dominated TCT this year. The conference began with a strong defense of the safety of drug-eluting stents (DES), but it may have been preaching to the choir. By the end of the meeting it was clear that U.S. DES usage will go down – whether interventional cardiologists want it to or not.

In his opening comments, Dr. Gregg Stone of Columbia University Medical Center, vice chairman of the Cardiovascular Research Foundation (CRF) which sponsors TCT, said, "The field has, of late, been characterized by hyperbole and inaccuracies…Drug-eluting stents have led to symptom-free survival for literally hundreds of patients since their introduction." He cited his own practice at Columbia University in New York as an example: "In a six-month period right before drug-eluting stents were introduced, we saw 292 patients with 311 ISR (in-stent restenosis) lesions. After DES, in the same six-month period, we saw an 86% reduction in ISR cases – to 44 ISR lesions." However, he added that he has seen "infrequent...cases of late stent thrombosis after three years that we didn't see with bare metal stents."

Dr. Stone blamed the media for "a lot of hype and hysteria" that fueled what he called the "ESC firestorm" over DES and late stent thrombosis, adding "We were not prepared for the ESC (European Society of Cardiology) firestorm." He said the media live by the motto: "If it bleeds, it leads." And he wasn't the only person at TCT to blame the messenger (the media).

The studies presented at the World Congress of Cardiology (WCC) in Barcelona in September 2006 – a joint meeting of ESC and the World Heart Federation (WHF) – really ignited the firestorm over stent thrombosis. Those studies found an increase in late stent thrombosis with DES. They included:

1. A **Swiss/Dutch analysis** of their Taxus and Cypher registries, covering a total of 8,146 consecutive patients from April 2002 to December 2005, found a stent thrombosis rate of 2.9% at three years. Even more concerning was the almost linear increase between 30 days and 3 years, with incident density of 1.3 per 100 patient-years. The stent thrombosis rate with DES appears to be 0.6% per year – each and every year, with no plateauing. There was no significant difference in stent thrombosis between Cypher and Taxus.
2. A **meta-analysis** by Dr. Edoardo Camenzind et al which found a statistically significant increase in stent thrombosis with Cypher and a non-significant increase with Taxus. This analysis looked at death and Q-wave MI as surrogates of stent thrombosis during long-term follow-up. At TCT, Dr. Camenzind said his WCC meta-analysis was done without all the Cypher trial

data because he couldn't get it all, and said that, as of TCT, he still did not have all the data he wants. However, Johnson & Johnson officials disputed this, insisting they sent his team all their data prior to WCC.

Meta-Analysis: Incidence of Death and Q-wave MI

At 3 years	Bare metal stent	DES	p-value	Relative difference
Death or MI in **Cypher** trials	3.9%	6.3%	**0.03**	+38% (absolute increase 2.4%)
Death or MI in **Taxus** trials	2.3%	2.6%	0.68	+12% (absolute increase 0.3%)

Bern/Rotterdam Study of Stent Thrombosis with Drug-Eluting Stents

Location	Cypher	Taxus	p-value
Bern patients	2,775	1,336	---
Rotterdam patients	1,100	2,905	---
Measurement	**Stent thrombosis**	**No stent thrombosis**	**p-value**
Age	60	63	0.007
ACS at time of index procedures	71%	59%	0.03
Average stent diameter per patient	2.8 mm	2.9 mm	0.46
Bifurcations	28%	17%	0.0005
Average stent length per patient	43.4 mm	35.8 mm	<.05
Stent thrombosis at 3 years	2.9%		---

Experts generally agreed that there is some "signal" of an increase in stent thrombosis with DES, but interventional cardiologists repeatedly stressed that the risk is minimal, and many were very critical of the WCC presentations. Dr. Stone said, "There is no increase in cardiac mortality, though there is some concern about non-cardiac mortality." He suggested that DES may slightly increase late stent thrombosis, but pointed out that bare metal stents also increase restenosis, "At one year, you see differences, a one-year prevention of restenosis that actually reduces death and MI – potentially – with DES." Another expert said, "What happened at WCC was irresponsible. The overall hysteria was irresponsible."

Dr. Stone concluded, "There is a clear signal that late stent thrombosis occurs more frequently with current DES than BMS – a 0.2% to 0.4% increase per year in the first four years." He also noted:

- Based on available patient-level meta-analysis, the cumulative frequency of cardiac death and MI are not significantly increased with DES, though more data are needed.
- Undoubtedly, safer DES are needed.
- The breakthrough success of DES in reducing restenosis and improving the quality of life for patients with CAD should not be foreshadowed by DES failures.
- There are no convincing data to suggest important differences in early or late stent thrombosis when comparing Cypher and Taxus.
- BMS should be preferable to DES if extended dual antiplatelet therapy is problematic.
- The causes of late stent thrombosis require care and attention. The majority of events are probably due to biological DES responses (drug/polymer).
- For the time being, we recommend extended dual antiplatelet therapy for one year in all DES patients and possibly longer in select high risk situations.

FDA officials as well as other experts now appear to agree that the cause of any stent thrombosis problem, if there is one, is multifactorial, not due simply to durable polymers.

Other comments on stent thrombosis included:

- "How can you extrapolate from five low risk patient trials to real world patients?...I don't think it is one factor. I think it is multifactorial."
- "We all have 1 or 2 stent thromboses, and we didn't have them with bare metal stents."
- "Stent thrombosis is real. It is there. I'm glad the FDA is having a panel."
- *FDA official:* "We take stent thrombosis very seriously, but I don't feel we have all the information necessary yet." Asked if DES trials should be larger or longer, he replied, "We could make them two-, three-, or four-times the size of the per-market trials, and there would still be adverse events in the real world."

DATA ANALYSES

TCT was full of analyses and re-analyses of the data – so many analyses that it had some heads spinning. One of the problems in comparing past analyses has been the difference in the definition of stent thrombosis. Different companies and different trials used different definitions. That may be ending.

Academic Research Consortium (ARC)

After WCC, interventional cardiologists, representatives of major stent manufacturers, academic CROs (Cardiovascular Research Foundation, Duke Clinical Research Institute, Cardialysis, HCRI, DCRI), several academic medical centers and hospitals, and FDA officials all got together to set a common definition for stent thrombosis. ARC, which was co-chaired by Dr. Patrick Serruys and Dr. Donald Cutlip of Harvard, agreed on a definition, originally called the "Dublin definition," and now called the ARC definition. It was endorsed by the British Cardiovascular Intervention Society.

- **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.

The randomized clinical trial data for Cypher and Endeavor were analyzed using the ARC definition. The Taxus data had not yet been done by ARC, but that was planned.

In addition, there were new analyses from Johnson & Johnson on Cypher, from Boston Scientific on Taxus, from Medtronic on Endeavor, and from the Cardiovascular Research Foundation on both Cypher and Taxus data. And additional analyses can be expected in the future. Some used the ARC definitions, and some didn't. The main argument with the ARC definition appears to be over the inclusion of "possible" stent thromboses. Johnson & Johnson and Medtronic officials said they are willing to accept the ARC definitions – all of them. Boston Scientific and some key interventional cardiologists, on the other hand, dispute the inclusion of "possible" stent thrombosis.

Cardiovascular Research Foundation (CRF)

Dr. Stone described the CRF study of 5,200 patients in nine prospective, double-blind, randomized trials, saying that he had gotten permission from Johnson & Johnson and Boston Scientific to obtain the databases from 4 Cypher trials (1,848 patients) and five Taxus trials (3,506 patients) for an ***independent academic*** analysis. This is what CRF found:

- Up to one year there is no difference in stent thrombosis between Cypher and Taxus.
- After one year, it appears the stents are associated with an increased incidence of stent thrombosis. Together, there were 14 stent thromboses with DES vs. 2 with BMS, which he said, "is definitely an increase in stent thrombosis with DES."

The question, however, is: Does this translate into increased death and MI? And Dr. Stone said it does not appear to do so, "Overall, it doesn't seem that there is an increase in death or MI. There is no statistically significant difference…In non-cardiac death, the meta-analysis showed no difference in cardiac death between Cypher and Taxus, (p=0.40)." But there was a positive difference in freedom from ischemic TLR – in favor of DES.

Dr. Stone continued, "Overall, there is little doubt that late stent thrombosis is increased with DES, although the frequency is low – approximately 1.5 per 1,000 patients per year…But if you look at freedom from all-cause death, there is no difference between DES and BMS." On TLR up to four years, in every type of lesion, there was a 50%-70% reduction in TLR revascularization with DES. He asked, "If stent thrombosis is slightly increased with DES compared to BMS, why are the rates of death and MI similar? Is it possible that DES have some other benefits?...One of the things that must be appreciated that we have learned in the last few years is that restenosis isn't as benign a process as we thought…About 10% of patients with restenosis actually present with MI...So, is it possible that the increase in stent thrombosis is offset by a reduction in death and MI by prevention of restenosis? This is an interesting hypothesis that needed testing. We went back to look at the incidences of death or MI in seven days, in a blinded fashion, independent of one device. There were 14 stent thromboses in control and 20 in Taxus, leading to 12 deaths or MI with control and 19 with Taxus. However, there were 290 ischemic-driven TLR in control compared to 20 in Taxus…But you see both devices have 23 patients with death or MI, so it does seem the benefits and small frequency of death or MIs exactly balance the risk from stent thrombosis. Nonetheless, stent thrombosis is a concern and we'd like to prevent it."

At a Conor-sponsored symposium, Dr. Roxana Mehran and Dr. Marty Leon of Columbia University Medical Center discussed the CRF analysis. Dr. Mehran said, "It is inappropriate to compare Cypher and Taxus because the definitions (they used) were so different...In our own analysis, there is no question that if you look at it (stent thrombosis) after one year, there is a separation of curves...The causes are multifactorial ...but the majority of events are probably due to biologic DES response (drug/polymer)."

At the symposium, Dr. Mehran and Dr. Leon got into a somewhat heated debate with noted pathologist, Dr. Renu Virmani, of the non-profit CV Pathology.

- *Dr. Virmani:* "I would like to know if you have a 0.5% increase in MI (from stent thrombosis with DES), and yet the bleeding rate with Plavix is 1%-2%, why would you give them Plavix for 12 months? Plavix has its own complications. Why give them more antiplatelet therapy if you have no problems?"
- *Dr. Mehran:* "I didn't say there is no problem. I said there is a signal."
- *Dr. Leon:* "I don't think we are denying a biologic event …In these nine randomized clinical trials (of Taxus and Cypher)…the incremental increase in late stent thrombosis at Year 1 was 0.5% or 0.6% over the course of three years – from Year 1 to Year 4 – and that was statistically significant. There is an increase in late stent thrombosis (LaST). I'm not arguing that…But when you look at the cumulative death/MI over four years, it is not statistically significant. Why? There is a dramatic reduction in restenosis…And death/MI with DES is lower in these trials."

Comparison of Safety of Cypher and Taxus vs. Bare Metal Stents

Measurement	Cypher trials (n=1,748)			Taxus trials (n=3,506)		
	Bare stent	Cypher	p-value	Bare stent	Taxus	p-value
Freedom from stent thrombosis at 1 year	99.4%	98.8%	Nss, 0.20	99.1%	98.7%	---
Stent thrombosis at 5 years	5 patients	0 patients	Nss, 0.25	9 patients	2 patients	Nss, 0.33
Freedom from ischemic TLR	76.4%	92.2%	<.0001	80.0%	N/A	N/A

- *Dr. Virmani:* "You excluded TLR…They were adjudicated as not included."
- *Dr. Leon:* "They were not excluded in the ARC analysis."
- *Dr. Virmani:* "This is data from the companies."
- *Dr. Leon:* "No, this is HCRI data...I didn't get it from the companies…It is the same data sent to the FDA…You could argue someone is not sending the right data…but this is patient-based data shared with the FDA."
- *Dr. Virmani:* "Bioerodable polymers are likely to be less inflammatory as they degrade…I won't have a DES in my artery…Some patients on Plavix also get thrombosis, and some patients are resistant to Plavix."

Boston Scientific analysis

Boston Scientific officials were not ready to accept the ARC definition of stent thrombosis. They questioned, in particular, the "possible" category. Dr. Donald Baim, Chief Medical and Scientific Officer at Boston Scientific said, "There has been a lot of talk of 'Dublin' or ARC definitions – which have yet to be peer reviewed or published. They talk of definite thrombosis, probable thrombosis, and a new category of possible stent thrombosis – any unexplained death for 30 days and beyond. That is an intriguing definition. Unexplained death happens in people with coronary artery disease."

Asked why the Taxus data had not yet been re-adjudicated under the ARC definition, Baim said, "The main reason is our protocols, from the beginning, included definitions of definite and probable almost identical to Dublin – and our events were adjudicated by Dr. Cutlip – so, looking at those data, we felt little need to have them re-adjudicate what was already adjudicated. In contrast, Cypher has an interesting history. Initially, they only used definite stent thrombosis, then re-adjudicated it and included probable, and now they are attempting to cling to a double definition and add 'possible' to the list…There are a couple of issues: whether patients who have an intervening TLR and have another intervention like DES or brachytherapy and then develop stent thrombosis are still scored (under ARC) as DES stent thrombosis. And in the possible category, there are issues with patients dying at a rate of 1.5% per year just from coronary artery disease at an equal rate in both arms. So, does the inclusion of possible stent thrombosis help or obscure any differences in late stent thrombosis? Our position going into the FDA meeting is that 'definite' and 'probable' are really things we should look at."

Dr. Baim said Taxus trial data from >3,500 patients in five trials were examined by CRF just before TCT, according to the protocol definition (definite and probable), "with essentially equivalent findings to the Boston Scientific analysis." Now, an HCRI analysis will be done before the FDA panel meeting and will include possibles. Dr. Baim added, "The confusion that is going to come is the application of the Dublin (ARC) definitions in their fullest extent, which includes the category of possible."

Dr. Stone, who was the principal investigator for the Taxus trials, said the detailed patient reports in the Taxus database were blinded, and the impact of stent thrombosis, clinical restenosis, death, and MI examined. He concluded, "Overall, the risk of stent thrombosis and associated death is 2.1% in control and 1.5% with Taxus."

Dr. Stuart Pocock of the London School of Hygiene and Tropical Medicine looked at the pooled Taxus trial data and concluded, "In 3,500 patients out to four years, it is very apparent the two curves (bare and Taxus) follow each other. There is a constant (stent thrombosis) hazard after six months of 2.3%/year, death 1.5%/year, and MI 0.8%/year – exactly the same as the natural history of the disease…The possible definition includes natural history deaths in both arms and dilutes out any signal for a difference in stent thrombosis…For Taxus, there is no evidence there is any increase in death and MI…People always thought restenosis was just a nuisance, but a Cleveland Clinic study of 1,186 (restenosis) patients found 9.5% presented with MI and 0.7% died in the hospital. So, if you prevent 100 restenoses/year and 10% of those prevented restenoses would have resulted in a restenosis-related MI, that would be ample benefit to offset 4-5 per thousand increase in very late stent thrombosis…There is a slight increase in late stent thrombosis after six months, but, given the TLR reduction by 50%, the probable reduction in TLR-related MI and death, Taxus is comparable or lower than a bare metal stent."

A Boston Scientific speaker added, "The Taxus reality is that Taxus is as effective as Cypher in complex lesions. Taxus and Cypher have the same low 0.5% incidence of stent thrombosis after one year. Taxus reported lower death (0.4% vs. 7.0% BMS), lower death Q-wave MI (7.6% vs. 8.1% BMS) through Year 4. Taxus has a favorable benefit:risk...We can't go backwards toward BMS; it is unacceptable to have that percentage coming back for repeat procedures."

Johnson & Johnson analysis

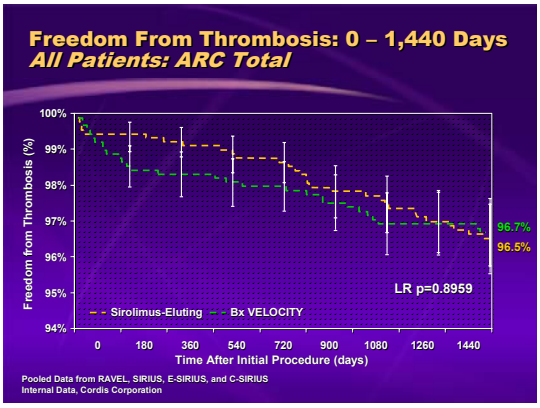
J&J had its own independent analysis done by HCRI of four Cypher trials (1,748 patients), using the ARC definition, and they said it found no statistically significant difference in the rate of thrombosis, death, or MI between Cypher and a bare Bx Velocity at four years. While the freedom from thrombosis does decline with Cypher over the four years, the same pattern occurs with the bare stent.

J&J Analysis of Adverse Events with Cypher

Complications to 1,440 days	Cypher (n=878)	Bx Velocity (n=870)	p-value
Death	6.5%	5.1%	0.2190
MI (Q-wave and non-Q-wave)	6.3%	6.1%	0.9210
Q-wave MI	2.1%	1.3%	0.2611
Non-Q-wave MI	4.3%	4.9%	0.5706
Any death and any non-fatal MI	11.4%	10.1%	0.3968
Any death and any non-fatal Q-wave MI	8.0%	6.1%	0.1348
Cardiac death and any non-fatal MI	8.2%	7.6%	0.658
Stent thrombosis (ARC total definition)	3.5%	3.4%	Nss

Dr. Brian Firth, Worldwide Vice President for Medical Affairs and Health Economics at J&J/Cordis, said the J&J analysis doesn't match the Camenzind meta-analysis, but it does include all four studies (SIRIUS, E-SIRIUS, C-SIRIUS, and RAVEL) over four years, with a patient-level analysis. He concluded, "There is an ongoing risk (of stent thrombosis) with both Cypher and a bare metal stent, but the risk is small. Using the new ARC definition, we see no difference in the rate of thrombosis at four years. We see a few more with a bare metal stent early, and a few more with Cypher late. But at the end of four years, the count is virtually identical."

J&J officials also argued that stent thrombosis is ***not*** a class issue. Dr. Campbell Rogers, Chief Technology Officer at J&J/ Cordis, said, "We need to revisit the conventional wisdom that all DES are the same…All DES are not the same in terms of clinical considerations of early and late clinical outcomes…In the DES world it is naïve to assume that there is some class effect of DES. They are not a class in the sense that BMS are a class…ARC is a definition (determined) with everyone sitting at the table…I think it is high time to stop nibbling around the edges (of the ARC definition), accept this, and move forward …Stop arguing about it and start showing and sharing data."



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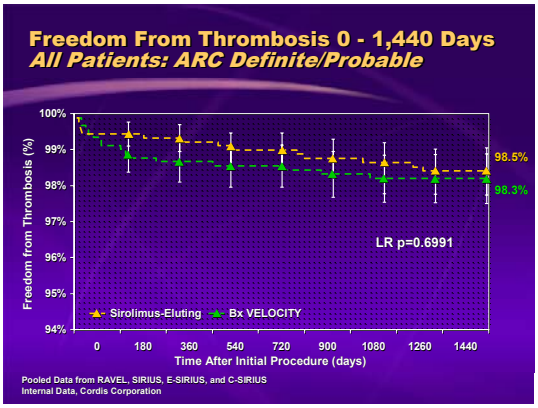

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THE DES DEBATES

DES debate #1

Dr. David Faxon of Brigham & Women's Hospital and Prof. Sigmund Silber of Germany faced off in the hot debate of the day: ***Should DES use be curtailed in the milieu of mounting safety concerns?***

DES use should be curtailed

Dr. Faxon, arguing on the side of caution (and of curtailing DES use), started the debate by asking – and answering – three questions:

- ***Is late and very late stent thrombosis increased with DES?*** Dr. Faxon said that late and very late stent thrombosis "could be a real phenomenon" and cited trials that showed after one year there is a very small but statistically significant increased risk of stent thrombosis in the range of 0.5% to 0.6%, adding, "And in a higher risk population the percentage is probably substantially higher."

- ***If we accept that there is an increased risk of late stent thrombosis with DES, does it matter?*** He said, "If we accept that there is a small increase in stent thrombosis, does it matter? I think the answer is, it must matter…I think the sum of those studies show that there is something going on here."

- ***Is prolonged antiplatelet therapy the answer?*** He said, "I'd argue that it's not for all patients – not all can take dual therapy indefinitely, and many patients – one in seven in the PREMIER registry – stop prematurely. Major and minor bleeding is increased two-fold, and the cost is about $2,800 a year…And there is also nothing wrong with BMS."

He concluded, "Late and very late stent thrombosis is increased with DES by 0.2%-0.5% per year and is likely underestimated and higher in high risk lesions…So is it reasonable to restrict (DES use) until the safety issues are resolved? That's a no brainer."

DES use should not be curtailed

Dr. Silber said that his patients have been calling him post-ESC: "Previously, they were not happy because they didn't get a DES. Now, they're unhappy because they have a DES."

The issue is dual antiplatelet therapy, not the safety of DES, he contended, saying, "The reality is that we have good data, despite a significant increase in late stent thrombosis. But I'm surprised that people are surprised…We need to give clopidogrel longer. I was surprised that patients received clopidogrel for such a short period of time because you should have given it longer. The question is: How long do you give clopidogrel to avoid these events? In Europe, the guidelines recommend clopidogrel for at least six and up to 12 months or longer. These are ESC guidelines. The American guidelines say three months for sirolimus and six months for paclitaxel. I think the Americans now have to rewrite them. Yes, we see an increase in the rate of late stent thrombosis, but according to what we know, it is unethical to withdraw patients after six

months of clopidogrel. I'd never do this…Clopidogrel is the key answer to this problem it seems."

Dr. Silber also warned, "Don't throw the baby out with the bath water." He argued that DES have proven their efficacy and noted that there are some safety concerns but that BMS also show late and very late thrombosis, "We need more data. And new and better DES are mandatory."

DES debate #2

This was really more of a not-quite-a-debate for the media about the DES controversy.

DES are safe

Dr. Leon made several points, including:

- "Much of what has been said over the last two days, we would characterize as an effort to help restore the balance, but there certainly is a feeling…that there has been an hysterical over-reaction to some recent data that was not published but presented."

- "A deliberate effort has been made to analyze a more complete data set to validate or contradict some of the conclusions that were derived from those (European reports)…The data that created such interest largely related to the meta-analysis of a series of clinical trials…with Taxus and Cypher…The total number of patients…was about 5,200 patients. These are data the FDA has access to – submitted to the FDA on an annual basis – and it was almost an implication that we were asleep at the switch. These data have been carefully examined on an annual basis…highly scrutinized, and nothing sudden or different was discovered."

- "Unfortunately, the results reported at the (European meeting) represented an incomplete data set, representing an amalgam of published reports – data from different studies from different journals, without access to all of the data. We have requested and received all of the data, including the entire data set for four years – and an independent patient-based meta-analysis was performed and results...directly contradict the findings of (what was) reported or discussed at the (European meeting)."

- "We believe that there is a process called late stent thrombosis that occurs with greater frequency with these two DES (Cypher and Taxus). It begins to emerge after one year, so it's a late event, and we've seen events that occurred as late as three years. The rate event is 0.5% – the incremental increase in the event rate. That's about one in 200 patients."

- "This (late stent thrombosis) is a biologic event. Does it cause a clinical consequence? We've known for 20 years that stent thrombosis can cause adverse clinical consequences – heart attacks and death. So, we looked at the clinical events to see if patients are being harmed. Are they having more heart attacks and more deaths? The patient base in the meta-analysis did not indicate that there was an increase in the cumulative heart attack and death rate up to four years for either of these devices, analyzed any way you could possibly analyze the data."

- "Our conclusion is that patients are not being harmed with the use of DES, and any small increase that may occur in heart attacks and death after one year is offset by a reduction of those similar events for one year associated with the dramatic decrease in the frequency of restenosis. We have a different opinion (from the European presenters), and it's important…to understand that. We are in no way suggesting that this signal of late stent thrombosis isn't there; we're simply arguing that the consequences from these studies have not harmed our patients, and the reduction in restenosis more than counter-balances the concerns."

Asked if late stent thrombosis could cause an event but we're not seeing it yet, Dr. Leon said, "When you get an event from LaST it is immediate. Is the function linear and will it continue? We don't know."

Asked how he accounts for a signal without events, Dr. Leon answered, "We are seeing events associated with late stent thrombosis." Dr. Stephen Ellis of the Cleveland Clinic said, "Some of the answer appears to be that the process of restenosis is not benign. Sometimes treatment of restenosis leads to heart attack, so there appears to be an evening out."

Asked how long it will take to get answers, Dr. William O'Neill of the University of Miami said, "The registries are okay, but they won't be definitive. The trials aren't getting to the mechanistic question of why they occur. Late stent thrombosis occurs, but why does it develop? My own hypothesis is we've changed the way we implanted from BMS to DES. With BMS we used high pressure balloon inflations – fully apposed against the wall – and IVUS. Now, with DES, people are becoming somewhat lackadaisical – not routinely using IVUS. Very often, stents are inadequately deployed, and when clopidogrel is stopped, there's a risk. I urge companies for trials that will give us a mechanistic understanding of why it occurs. It's not a random event, and there has to be an explanation. There is some ultrasound data from Cypher that people with subacute thrombosis had inadequate expansion of the Cypher stent."

DES do have safety concerns

Dr. Spencer King of Fuqua Heart Center in Atlanta countered with his own points:

- "After a year there seems to be this excess signal confusing people about how long they can take Plavix and aspirin. This is creating a concern. The incidence is fairly low, but it is clearly higher in DES than BMS. But this is data generated from the trials where the lesions weren't difficult, and we've heard the rates of LaST are higher in more complex lesions, which is our impression."

- "Most clinicians have seen this (late stent thrombosis), so from a patient perspective right now, in the selection of a stent, my position has been that we ought to be selective and

perhaps not universally use DES but use them where we think they are most critically needed to reduce restenosis."

- "The patients are so different. In patients who have an increased risk of bleeding, the risk of restenosis may be trivial in that patient. In a patient with a high risk of restenosis and no bleeding risk, DES make great sense. We have lost a little bit of the risk:benefit cognitive discussion of this with such excitement about a new technique."

- "I think that all this discussion is about rather small, rather infrequent late events…The magnitude of the problem isn't huge at all, but the concern has created a big problem for physicians and their patients regarding how to deal with this. Permanent Plavix and aspirin is not the solution."

- "There is more to what we don't know than to what we know. What about patients who are not in these randomized trials…From my perspective, we don't know what that risk is. The Rotterdam study suggested they were at higher risk, two yesterday said no."

In the middle

Asked about the explanation that there would be a reduction of deaths with a reduction of restenosis – the counterbalancing argument, Dr. O'Neill said, "For an individual patient, if he has one of those events, there's about a 40% chance he'll die and a 60% chance of a heart attack, so for each individual patient it's a big problem. Now, it's an uncommon problem, and you aren't going to see a significant difference in events. The real problem – why we're so concerned – is that it has potentially catastrophic consequences. That's the conundrum we have right now – sudden death or large heart attack."

Dr. Barry Uretsky of the University of Texas, Galveston, said, "I wasn't involved in these analyses, and I am quite confused as to the real risk. But what we know is that the number of patients that were studied in these trials wasn't very large relatively speaking because the percentage of risk is quite low in either arm…I checked our own experience at our institution, and it was about the same as the trials. We reported some data some years ago, and there was late stent thrombosis, and the latest was 211 days. I checked on the 2,000 stents we put in since 2003, and our latest stent thrombosis was about 33 days, and it only means that our sample size is so low that we can't have a high level of confidence about differences between BMS and DES. That is some of the issues with the analyses we've heard. You need more data to get to a more comfortable conclusion."

Other comments included:

- *Dr. Jeff Moses of Columbia University:* "We need larger studies to see what the safety issue is. But my question is whether restenosis is a benign condition and (if it has a) counterbalancing effect."

- *Dr. King:* "It's relatively benign but not completely benign. It costs money and hospital time. Any procedure you do creates in some patients an enzyme leak classified as an MI. If you add all the MI that occur as a result, you will show effect. But I would submit that an MI occurring subsequent to redilitation of a stent is not to be equated with a spontaneously occurring MI due to stent thrombosis, so we have to be careful about how that was analyzed."

- *Dr. Moses:* "The proof is in the pudding. We have a reduction in restenosis, and we saw a trend in non-Q-wave MI even in the first nine months which did show us patients presenting with infarction and unstable angina."

- *Dr. Ellis:* "I'll cite a study from my own center. We looked at 1,200 with restenosis; 9% presented with MI of one sort or another. That was done and came out prior to this major controversy."

- *Dr. Leon:* "It depends on what you mean by benign. We spent more than 20 years trying to eradicate restenosis. I don't think we did it because it was a benign process."

- *Dr. Moses:* "Some of these late stent thromboses are not from clots. Some are late restenoses that turn into heart attacks. We believe delayed healing plays a predominant role."

ANTIPLATELET THERAPY

At the WCC, the reaction to the stent thrombosis issue was a call for longer dual antiplatelet therapy – Sanofi-Aventis's Plavix (clopidogrel) + aspirin – for a year or longer. Most interventional cardiologists commenting at TCT on dual antiplatelet therapy said they are now recommending patients take it for at least a year, perhaps for life – or at least until more is known about long-term safety of DES.

When is it time to stop clopidogrel? Dr. Faxon said, "I think we need a lot more data, so I don't know. My concern is that since we don't know, the safest thing is to prescribe clopidogrel as long as we can. I share your concern. We (Americans) should have been more careful. Currently, I keep people on it indefinitely, but it does influence my choice of a stent. If someone is going to be unreliable – or plans surgery – then I think twice about DES based on the data." Dr. Silber of Germany said, "One year is not enough. I stick with six months and in more complex cases give it for three years." An Indiana cardiologist said, "At least a year is our practice… Will prolonged Plavix prevent the very late stent thrombosis? That is undetermined. There are not enough data."

Both Dr. Faxon and Dr. Silber said they try to make surgeons operate on patients while on Plavix. Dr. Faxon said, "I try to make the surgeon operate on the drugs. Surgeons sometimes don't like that. If they don't want to, I tell them that the patient has a one in 10 chance of having a heart attack during the operation, and they usually change their mind." Another expert said, "I tell the surgeon that if you don't operate on the drugs, there's a nine in 10 chance I'm going to find another surgeon."

Yet, Dr. Stone warned against long-term Plavix use, calling it a "knee-jerk reaction," noting that it isn't clear whether a long-term Plavix strategy is efficacious. He said that results presented at TCT by Dr. Antonio Colombo of Italy of a study of 2,160 consecutive DES patients "doesn't show that long-term use of clopidogrel is efficacious. Clopidogrel also has side effects. It is usually associated with a 1% increase in major bleeding every year you're on it."

He concluded, "Can we restore a balance in the field of DES and interventional cardiology in general? With DES we have reduced the need for PCI and CABG and have improved the quality of life for millions of patients. DES have side effects; there is a higher incidence of late stent thrombosis…However, a knee-jerk response of long-term clopidogrel prescription in all DES patients should be avoided because of uncertain necessity and efficacy, major bleeding with chronic use (of Plavix), as well as the high societal cost. Mega-trials are being initiated to characterize the underlying causes of stent thrombosis – to determine if stent thrombosis rates are different between different DES, and whether long-term dual antiplatelet therapy is protective."

Other comments on Plavix use included:

- *Dr. Leon:* "We don't have data that taking Plavix makes a difference, except for an anecdotal association…We do know from the CHARISMA trial that there is a 1% increase per year in major bleeds when you give clopidogrel on top of aspirin…We don't know if continuing the double antiplatelet therapy would prevent these events. That's the great dilemma right now – what the bleeding hazard is. There are data suggesting that by adding the second drug (Plavix), you may increase the risk of major bleeding 1% per year. It becomes a balancing act…You have to think about patients, capacity, risks, and make (the decision) on an individual basis. But we have expanded the (dual antiplatelet therapy) policy at Columbia to a year…We'd always assumed that 90% of the events would be over in a month, and now we see a change in the pattern, and that needs to be discussed with the patients."
- *Dr. Uretsky:* "I'd take it indefinitely. We talk about how long patients are able to pay for their drugs. I may put in BMS until the data are in. The risk of the problem is quite low, but on an individual basis it's quite severe. When I have to talk to my individual patients, I keep them on dual antiplatelet therapy."
- *Dr. King:* "A lot of patients on chronic Plavix and aspirin are at risk for significant bleeding…The question is: Do you assign everyone to permanent aspirin and Plavix, given the incidence is fairly low?"

Future Stent Thrombosis Studies

Several studies are being planned to try to settle the question about stent thrombosis and DES. These include:

- The multicenter **STENT** thrombosis registry, starting later this year, will enroll 10,000 consecutive "real world" patients receiving DES at up to 12 sites. These patients, on aspirin and clopidogrel, will be followed for 2-5 years.
- Johnson & Johnson is sponsoring **E-SELECT**, a 30,000-patient global registry, and **INSIGHT**, a U.S. randomized trial of standard vs. long duration Plavix.
- Medtronic is helping to sponsor the **PROTECT** trial, an 8,000-patient open label comparison of Endeavor vs. Cypher over three years. There will be earlier analyses to see if the trial should be stopped sooner.

The FDA Perspective

Dr. Bram Zuckerman, head of cardiovascular devices at the FDA, said, "We need to take a step back and see what we learned today...I think we made a significant step forward today in that we do have the first patient-level meta-analyses, and they are more reassuring in certain aspects, especially with regard to how these important products affect the individual patient. On the other hand, I would point out that:

- The patient-level meta-analyses are done in lower risk (on-label) patients. The ability to expand to the real world still is quite limited.
- The number of patients followed up more than three years still looks rather limited.
- We also are still dealing with a limited number of trials."

Dr. Zuckerman continued, "(This discussion) certainly made a step forward…but there are many important questions that remain. The FDA will continue to dynamically follow this situation because we do think there is a signal there. The exact nature of the signal and how to frame the risk:benefit situation for an individual patient still remains somewhat unclear, but I do think the data…are consistent with the FDA's recent web statement that these devices, as far as we know, continue to be safe and effective for the FDA labeled indications…But because there are many broader issues that require intensive ongoing analysis of these data and others, the Agency is having an open advisory panel…where we hope to be able to discuss these important issues in great detail and to also discuss the need and design of new trials that need to be conducted to better optimize the use of these products."

The FDA Circulatory Systems Advisory Committee will meet on December 7 and 8, 2006, to discuss stent thrombosis and the new ARC definition. Stent manufacturers have been asked to provide an analysis of their clinical trial and registry data using the ARC definition.

Industry and other sources offered comments on what is likely to happen at the FDA panel:

- "I'm not sure…I think there will be a full discussion of all the trials…The FDA asked the (DES) companies to adjudicate the registries as well as the randomized clinical trials (for the panel meeting)… What we saw (at TCT) is information similar to what we will see at that meeting: There is a small signal (in the two approved DES). The frequency is low, but it is consistent enough to be a real finding. I don't know how the FDA will react. I think they will see it as a risk to the procedure and leave it to physicians to decide the risk to a given patient."
- *Boston Scientific:* "Our position going into the FDA meeting is the ARC 'definite' and 'probable' stent thrombosis are really things we should look at…Our data have already been independently reviewed, and it puts us in very good stead. We already gave the FDA our data this summer. We expect our data to be endorsed. No surprises are expected."

An FDA official said the panel will focus on what the FDA should do about stent thrombosis – a new label, more post-marketing studies, a large, all-industry study, etc. There will be pharmacologists who understand drugs and statisticians, and it will be relatively balanced between interventional cardiologists and medical cardiologists. The official said, "The advisory committee is not expected to change the requirements for approval of new DES in the near term."

DES USAGE OUTLOOK

Prior to TCT, there was an impact on DES usage from the stent thrombosis issue in general and from the WCC data in particular. Dr. Stone estimated that in the few months before TCT, there was a 5.4% decrease in DES implantations and a 2.2% decrease since WCC. He noted that U.S. penetration of DES stabilized at about 87% in 2005.

In the first days of TCT, interventional cardiologists were generally predicting that they would go home and hold DES usage steady. However, by the end of TCT, most sources were admitting that usage is likely to go down in their cath lab, and in some cases substantially. Pressure from medical cardiologists, cardiac surgeons, and personal injury attorneys, along with continuing media coverage and growing patient concerns, are all expected to be factors.

In this environment, doctors were enthusiastic about Abbott's Xience/Boston Scientific's Promus, undecided about Medtronic's Endeavor, and cool to Conor's CoStar. Comments about usage if all of these stents were available now included:

- *New York #1:* "We are half Cypher and half Taxus now, and I think we could go to a third Taxus, a third Cypher, and a third Xience. Conor? Why use it?"
- *New England:* "The limuses may be different, but Conor and Endeavor won't benefit from the stent thrombosis with Cypher and Taxus…I have no use or interest in Conor, but Xience looks like Cypher by IVUS. People like Driver (bare Endeavor) better than Vision but Driver is not rapid exchange (RX). Xience has a better chance than Endeavor because of the RX issue, and everolimus is seen as more potent. Xience is comparable to Cypher with better deliverability, so it is like a next-generation Cypher. With Endeavor, the only claim to fame is no or low stent thrombosis, but the ZoMaxx failure will hurt it. Zotarolimus will be seen as a weak limus, an under-powered limus."
- *Canada:* "I am a bit of a conservative, so I'll be very careful trying a new stent. I'm most interested in Biotronik's bioabsorbable magnesium stent and the estradiol-eluting stent…But I would use Endeavor because I used it in trials."
- *New York #2:* "I've become a little more selective in the last 2-3 months. Our use of DES has dropped from about 85% to 70%-75%, and after TCT it may go down to 65%...I absolutely will try Endeavor. It seems to have a lower stent thrombosis rate, but it is not as effective on restenosis…Now we are 75% Taxus and 25% Cypher. In six months, we could be 25% Cypher, 35% Taxus, 13% Endeavor, 13% Xience, and 13% Conor."
- *Arizona:* "I'm chief of cardiology, so the medical cardiology attitude (about DES use) won't affect our usage. I'm happy with Cypher (20%) and Taxus (80%), but in six months we might be 50% Taxus, 20% Endeavor, 15% Xience, 10% Cypher, and 5% Conor."
- *New York #3:* "We will probably see DES usage go down a little after TCT. We are currently 98% Cypher. I don't see us starting with Taxus; it's like a middle child, and we probably wouldn't get Xience. Conor really depends on the data. Endeavor – why?"
- *Midwest:* "The data (on stent thrombosis) at TCT were reassuring, and I think Camenzind was wrong, but our DES usage will probably go down a little after TCT. When Endeavor, Xience, and CoStar are available, we'll try each of them and see what we think. Xience is a limus, so it will be good on restenosis, and it has a more flexible platform than Cypher. If we try Xience and it performs like the bare Vision, then it will take a lot of share (in our lab)…What I'm looking for is a bioabsorb-able stent…Bundling is a hospital decision." Asked whether this hospital is more likely to buy Xience or Promus, the response was, "Abbott can bundle Xience with its wires, which are the best, but Boston Scientific can bundle Promus with its balloons."

Paul LaViolette, COO of Boston Scientific, admitted that the stent thrombosis issue has affected DES use in general and Taxus in particular, but he was more optimistic than the doctors questioned about the DES outlook. He predicted the

market will now stabilize: "We can (now) turn our sights back to the marketing battle…I'm not saying the market is entirely quieted, but resolution has been introduced. But the (stent thrombosis) story has had an impact on the marketplace. Penetration rates were 85%-88% in the U.S., Japan had reached 72%, and international had reached 53%...The impact through the first half of 2006 showed a reduction of 1%-2% in the U.S., no impact in Japan, and a market slowing in Europe…There is no question U.S. penetration dropped post-ESC (WCC) after 6-8 quarters of slow growth that was a reversal of fortunes, but Japan and Europe are now stable. As we look to the fourth quarter, we expect – as a function of TCT and the upcoming FDA meeting – that U.S. penetration will stabilize at 83% for 4Q06, which is lower than the 3Q06, but no change from the end of 3Q06 to the end of 4Q06. We expect Europe will also remain quiet…The late stent thrombosis issue is understood by physicians. They are not spooked by it or afraid of it. They understand we introduced an anti-proliferative process, and there may be a biological cost of that…and that may be an inherent therapeutic trade-off…There is no question they would like to see that improved over time, but it also may be acceptable risk."

LaViolette predicted the FDA advisory committee meeting would lead to DES "adoption restoration," but he also expects a "quiet period" for some months, "We expect restoration of expansion in 2007. We expect 83% DES penetration (in the U.S.) at the end of 2006, 84.5% for the first half of 2007, 87% the second half of 2007, and 88% at the end of 2007." He also predicted global market growth in 2007, with Japan remaining stable.

In this environment, where should and shouldn't DES be used? Dr. Stone said, "What we can't say is if they should be used routinely in more complex and unapproved indications." He offered his own recommendations on DES usage. Situations where he indicated DES are not recommended:

- Two stents in a bifurcation.
- Full-metal jacket (ultra long lesions).
- Unprotected left main.
- Multivessel disease.
- Acute myocardial infarction.
- ISR after failed brachytherapy.

Dr. Stone's Recommendations for DES Use

Condition	Level of evidence	Comments
Chronic total occlusion	Ia-B	---
Bifurcations	IIa-B	---
Aorto-ostial lesions	IIa	---
Multivessel disease	IIa	---
Saphenous vein grafts	IIa	---
Bifurcation with 2 DES	IIa-C	We do not recommend routine treatment of bifurcations with 2 DES regardless of technique.
DES for ISR of DES	IIa-C	---
Unprotected left main	IIb-B	This should be restricted to research or situations where patients are at high risk for surgery.
Acute MI	IIb-B	We cannot routinely recommend DES in AMI.

A speaker noted that, using evidence-based medicine, there is Level Ia evidence for DES use in approved indications, adding, "What we can't say is if they should be used routinely in more complex and unapproved indications…We do not recommend routine treatment of bifurcations with two DES regardless of the technique…In unprotected left main, our recommendation is DES should be restricted to research or situations where the patient is at high risk for surgery…We cannot routinely recommend DES in AMI…For in-stent restenosis of a DES, use with a note of caution."

Specific Drug-Eluting Stents and DES Companies

Abbott

Abbott officials said they plan a new DES or DES iteration every two years. John Capek, formerly of Guidant and now President of Cardiac Therapies at Abbott (responsible for drug-eluting stents) said, "In BMS we were producing a new stent or iteration every year. That won't happen with DES. But we do think it is possible to do it every 2 years…We continue to make metallic stents better, and we see that happening in DES as well. DES will have the same dynamics as bare, but at a different rate."

On the appropriate use of DES vs. BMS, Capek said, "We are uniquely positioned to participate in both sides of this debate. We expect a modest movement from DES to BMS of 3%-4% (recently). Some of that may be in particular patient populations where BMS may be better. But that doesn't detract from a significant opportunity to grow into a still fairly large and unpenetrated market with Abbott products."

Richard Gonzalez, President and COO of Abbott, said:

- "When we looked at this market, we were attracted because it is large, highly attractive from a profitability standpoint, and is innovation-driven. None of that has changed. If there is a minor change in DES penetration based on thrombosis, we need to look at each company specifically. That doesn't bother me. It is still $5.6 billion, where we can take share…and where innovative products can take share quickly and effectively."
- "We are excited about what Xience can do. This is a market where there are still opportunities to bring new innovative products to the marketplace."
- "There is a debate on the right balance of late stent thrombosis and reinterventions and restenosis. Clearly physicians don't want to step back to a 15%-25% restenosis rate. They want a better balance between low level thrombosis and low levels of restenosis, and that is the opportunity here. We will see how Xience fares there. We feel very good."

- "And this is a market where there are a lot of opportunities to have an impact – the carotid market, which is looking to expand to the asymptomatic population. With the right reimbursement, that could be a significant opportunity… In the peripheral space, there is significant opportunity to bring DES into that space…This is a highly attractive market." Capek added, "We are not the first DES nor the first into the metallic stent market. But once we (Guidant) entered the metallic stent market, for 35 of 36 quarters were the market leader…I think Xience will take market leadership as we did with (Guidant) Multi-Link."

ENDEAVOR-III two-year data are expected at ACC 2007.

BVS

BVS is a bioabsorbable stent with everolimus (same dose as Xience) with a PLA polymer, a Vision delivery system, and a new stent design. The design goal is to deliver the drug in a manner consistent with a metal stent.

The first data on BVS were presented at TCT, and it looked both safe and deployable, with a high procedural success rate and no MACE at 30 days. The first-in-human ABSORB trial compared BVS and Vision in 30 patients at six sites in Europe and New Zealand with single de novo coronary artery disease. BVS uses a PLA polymer that breaks down to lactic acid and is metabolized through the Krebs cycle. Thus, neither the drug nor the polymer is left behind. The everolimus release kinetics of BVS are the same as for the Xience V stent and similar to Cypher. Abbott intends to follow these patients out to five years.

Dr. John Ormiston of New Zealand, the principal investigator, said, "The results couldn't be better, really." Asked if the stent might eliminate the late stent thrombosis issue, he said, "We don't know, but there is a hope…The strut goes away, so (it isn't) exposed to the bloodstream. Also, the polymer coating goes away, whereas in DES the polymer is permanent and doesn't go away. I think the patients like the idea of a device that goes away."

The typical antiplatelet regimen is six months of Plavix and aspirin for life. As far as the stent's radial strength, he said, "We don't know everything about it. We'll know more at six months." He also said that he has heard that Abbott is working to make the stent's struts even thinner, to about the same thickness as metal stents.

ABSORB 30-Day Clinical Results

Per protocol population	BVS n=26
Diabetics	3%
Smokers	20%
Mean age	62
Clinical device success	93.3%
Clinical procedural success	100%
Safety	
Cardiac death	0
MI (Q-wave and non-Q-wave)	0
Ischemia driven TLR (CABG and PCI)	0
MACE	0
Stent thrombosis (acute and subacute)	0

BVS Recoil

BVS stent expansion	BVS post-stent deployment	BVS absolute stent recoil	BVS relative stent recoil	Recoil for Xience V
2.86 mm	2.67 mm	0.20 mm	6.85%	4.2%

ZoMaxx

Before TCT, Abbott announced it was discontinuing the ZoMaxx program, so it came as no surprise that the ZOMAXX-I trial missed its primary endpoint. The primary endpoint was 9-month in-segment late loss, and that exceeded the non-inferiority confidence interval by 0.02 mm. ZOMAXX-I was a prospective, randomized, single-blind trial of the zotarolimus-eluting ZoMaxx (a TriMaxx stent eluting zotarolimus from a phosphorylcholine coating) vs. the paclitaxel-eluting Taxus. Dr. Bernard Chevalier of France presented the results.

Abbott officials stressed that the ZoMaxx ***program*** has been discontinued, but they are ***not*** dropping zotarolimus. Perhaps they will try it on another stent – or wait to see what happens with Medtronic's Endeavor (a Driver stent eluting zotarolimus from a phosphorylcholine coating).

9-Month ZOMAXX-I Results

Measurement	ZoMaxx n=199	Taxus n=197	p-value
Angiographic and IVUS results			
Late loss in-stent	0.67 mm	0.45 mm	<.001
Primary endpoint: Late loss in-segment	0.43 mm	0.25 mm	0.003
Restenosis in-segment	16.5%	6.9%	0.007
Restenosis in-stent	12.9%	5.7%	0.03
Volume obstruction	14.6%	11.3%	0.02
9-month clinical results			
MACE	12.5%	9.6%	0.43
Cardiac death	5.5%	4.5%	N/A
MI	5.5%	4.6%	0.82
TLR	8.0%	4.1%	0.14
Stent thrombosis	0.5%	0.5%	1.00

Protocol Specified Parametric Analysis

Primary endpoint	ZoMaxx	Taxus	Mean difference	Upper 1-sided confidence interval
In-segment late loss	0.43 mm	0.25 mm	0.17	0.27

Dr. Serruys said that the ZoMaxx decision "was driven by a number of factors; in our view, the product would not be competitive when coming to market. Capek said, "ZOMAXX-I not only didn't meet the primary endpoint but also, as you can appreciate, the performance was in a fairly simple patient population, while the data would be heading in a more complex patient population. So, we made the decision the product was not commercially viable for us. We are now re-deploying and integrating the ZoMaxx organization into our mainstream cardiac organization. In terms of manufacturing, we are re-directing manufacturing capacity dedicated to ZoMaxx to bring up additional capacity for Xience V going forward."

There was a fair amount of speculation on why ZoMaxx failed while Endeavor appears to be succeeding. The expectation was that ZoMaxx would do better than Endeavor because the stent had a polymer top-coat and release kinetics very similar to Cypher. Capek said it was a combination of factors, "It is the drug, the polymer, the release rate, and the stent beneath …It is not all drug. We made the decision that it was not commercially viable. I wouldn't jump to a conclusion on class or on someone else's use of the drug." Gonzalez added, "At the end of day, we had access to both products (ZoMaxx and Xience)…We looked at the data in a lot of detail…We spent a lot of time analyzing it…ZoMaxx is just not a competitive product for us. I don't think you can equate higher late loss to a safer product…We looked carefully at that. That would be a leap of faith that the data doesn't support."

Dr. David Cohen of St. Luke's Mid America Heart Institute in Missouri gave the critical assessment of the trial. He said, "The bottom line is that sometimes we learn a lot more from a negative trial than a positive one. I don't know if we'll remember the ZoMaxx stent in 10 years, but hopefully we won't forget (its) fundamental lessons." He said there were three insights from this trial:

- **DES design remains a very inexact science.** There are limitations to preclinical testing for DES design using similar drugs and similar elution kinetics but resulting in very different inhibition of neointimal proliferation and very different in-stent late loss.
- **In-segment late loss is not a good endpoint for DES vs. DES trials.** He said the concept of using in-segment late loss as an endpoint is really problematic, "I think the ZOMAXX-I trial really exemplifies this…Therefore, in-segment late loss fails to reflect the initial 0.2 mm to 0.3 mm of neointimal proliferation…and better continuous endpoints are needed."
- **There is a curvilinear relationship between late loss and restenosis.** He said this is the first trial to show this relationship and said that it has important implications.

The moderator at the session where the ZOMAXX-I data were presented said that two zotarolimus trials have shown "greater late loss than the control stents – the Cypher and Taxus stents. Zotarolimus looks similar to sirolimus, yet we're seeing greater late loss. What's going on here?" The investigator had no answer. Another expert commented, "We have to step back and understand that as a drug delivery system, there are differences between two different shapes of platform and how they expand in the tissue – the uniformity of drug delivery within the tissue. (All this shows that) this is a very complex difference, and what we're seeing is the clinical result of that. What we think are two very comparable platforms, in real human application may be different."

Dr. Laura Mauri of Brigham & Women's Hospital said that the trial design may have been a problem, "Whenever you design a non-inferiority trial, you're most interested in how that translates to clinical practice. So, you need to have an angiographic surrogate delta and standardize for a certain amount of TLR. It may no longer be appropriate to use the same size delta. The choice of a delta and a comparator are critically important."

Another expert said, "I think the key points have been made – designing non-inferiority trials is clearly very tricky, and it's necessary to pay tremendous attention in design to what you try to accomplish – what the real clinical questions are. If what you are interested in is stent diameter stenosis, then that should be your primary endpoint. In choosing non-inferiority, we have to be very careful about the delta, that it meets the criteria roughly agreed to, and is also clinically meaningful. If we don't, then the trials will be a disaster – so attention to design is important."

Xience V

Xience was launched in October 2006 in the majority of European countries, and Abbott is submitting it for reimbursement in France and Belgium. Officials insisted the company is on track for an FDA submission in 1H08, with approval "approximately a year later." Japan reportedly is on track for approval in 2009.

An official said Abbott has "a large European sales force, fully trained, with a priority focus on premier accounts." Capek said, "We've had positive feedback from physicians. We haven't had one customer comment that it doesn't perform at the level of Vision or better…Remember when you model that we lose one month of the three-month rollout this quarter."

Xience is currently manufactured in California for the international market. Over time, Abbott expects to get all its facilities approved for manufacturing Xience. Asked about Xience manufacturing capacity, Capek said, "We are expanding our existing capacity. We have state-of-the-art facilities…one in California and two in Ireland. There is sufficient capacity to meet commercial demand into 2007… We will exit 2007 with the ability to supply >50% of the international DES market while simultaneously building inventory for a U.S. launch…There will be sufficient capacity in 1H08 to supply >50% of the total global DES market (U.S., Europe, Japan)."

Capek said, "For us, (with Xience) it is about penetrating the DES market and competing in the DES market…Our basis of competition is in four categories:

1. **Clinical outcomes:** Though we measure late loss, it is not clinical. Those are TLR, TVF, MACE, and SATs.
2. **Acute product performance:** Deliverability, procedural success, ease of use, RX, and OTW. You have to have a system to allow the stent to be delivered to the target site. It is absolutely essential to have a platform that allows deliverability and deployment.
3. **Operational execution:** Sales and service, training and education, inventory, shelf-life. You cannot exist as a market leader without this as well.
4. **Product pipeline:** Predictable workhouse iterations, lesion-specific stents, next-generation technologies."

Speaking at an Abbott meeting, Dr. Virmani, talking about the preclinical Xience data, said, "Cypher induces a lot of inflammation. There is a lot more with Cypher than any other stent…That we see less with Xience should give us confidence that it will do well in humans – and better than Cypher." Dr. James Hermiller of the Care Group in Indianapolis said, "Xience really behaves like the Vision did, which is a very deliverable stent…There is no design compromise with Xience."

Ongoing Xience trials include:

- **SPIRIT-V** has been initiated. This is a real world, international and includes a diabetic registry.
- **SPIRIT-III** is completing enrollment. Enrollment had been suspended but it has started recruiting again. Data from this trial are expected at the American College of Cardiology 2007 or, more likely, at EuroPCR 2007.
- **SPIRIT-First** two year data will be available in 1H07.

Dr. Serruys gave the results of a subset analysis of diabetic patients in the SPIRIT-II trial of the Xience V stent, saying it showed nearly identical rates of in-stent late loss at six months in diabetic patients to those in the general population. He concluded, "At six months, SPIRIT-II met its primary endpoint. Not only is Xience V non-inferior to Taxus…but it even shows superiority…Xience V showed a low observed MACE and ST rate (MACE 2.7% and stent thrombosis 0.5%). SPIRIT-II clinical and angiographic results confirm the results of the first-in-man study…I'm sure that this is going to be a very important DES in the future."

6-Month SPIRIT-II Subset Results

Primary endpoint: in-stent late loss	Xience V n=201	Taxus n=72	p-value
General population	0.11 mm	0.36 mm	<0.0001
Diabetic subset	0.15 mm	0.39 mm	---

Asked why Abbott didn't compare Xience to Cypher, Dr. Serruys said, "It was a strategic decision. It's clear that Cypher, in terms of inhibition, is No. 1, but we said, 'Let's compare to Taxus, and we can always go for non-inferiority with Cypher.' Today, it is no longer necessary because of the late loss difference. We are in good shape and don't have to do further comparisons."

Other next generation stents

- Fluoro polymer (same coating as with Xience) but new delivery system.
- Bifurcation stent with same drug, dose, and polymer but on a stent specifically designed for bifurcations.
- Possibly a new coating and a new drug in an advanced coating configuration.

BOSTON SCIENTIFIC'S Taxus

Paul LaViolette, COO of Boston Scientific, claimed that worldwide Taxus is No. 2 in DES, and Boston Scientific is No. 1 in balloon catheters, IVUS, and embolic protection; No. 2 in bare metal stents, guidewires, and guided catheters. In the U.S., he said Taxus had 54% market share in 3Q06, with pricing down 3%, but he predicted pricing would remain relatively stable going forward. In Europe, he noted that Medtronic's Endeavor has taken market share mainly from the limus DES – due to stent thrombosis and efficacy perceptions, but he didn't appear worried about the Endeavor threat to Taxus, saying, "Endeavor has yet to really meet, in a clinical trial, the primary endpoint. That is a question that will be weighed by regulators going forward. And it has never been tested in a randomized fashion in 'real world' challenging situations."

Promus

Boston Scientific officials said they expect to have Promus on the market about two months after Abbott launches Xience V, and supply is not expected to be an issue. LaViolette said, "We think Abbott is a great company and a fine partner…We expect to launch in December with a limited launch. Then, on a supply-related basis, we will expand and launch in 1Q07, and we expect to reach a full launch in 2Q07 or mid-2007…We are protected in the distribution segment such that 50% of the supply is available to us if supply is constrained…And we are cloning the technology, not for the purpose of a backup supply but to accelerate our self-sufficient vertical integration and subsequent development and leadership in 'verolimus (everolimus) technology."

Asked how Promus will launch and how it will affect Taxus, LaViolette said, "We expect the majority of Promus users to be Cypher users…There is a lot of customer segmentation in this market…and we will follow a very clear segmentation strategy that allows us to concentrate our effort. We will reinforce Taxus with our massive database, and we are going

to emphasize Promus as what it is – a promising next generation DES that we think, based on late loss and early clinical evidence, has the right to be competitive to Cypher with superior deliverability to Cypher and reinforces Boston Scientific as the deliverability leader. But Promus still has a ways to go to take the lead position…Promus is a new and emerging program with scant data. We have a long way to go to begin to understand exactly what advantage or disadvantage Promus may have over Taxus Liberté. We need a smartly designed head-to-head trial that we would look to engineering." Executive Vice President and CFO Larry Best added, "We are aggressively building and pursuing the 'verolimus program, and the quicker we do that, the quicker we will have all the profit and no sharing. So, our goal is to get there sooner rather than later."

Taxus beneficial in AMI

The HAAMU-STENT trial found Taxus has significantly lower late loss at one year than bare metal stents in acute MI (AMI). This was a randomized, single center, 145-patient study done entirely in Helsinki, Finland. Researchers also reported:

- Taxus resulted in wider luminal diameter and less late loss at follow-up than a BMS.
- The rate of stent thrombosis was ***not*** higher with Taxus under the influence of dual antiplatelet therapy.
- There was a trend toward less TVR with Taxus, but the study was not powered for clinical events.
- The strategy of using Taxus in STEMI-PCI appears safe and feasible in the short term, but more data are needed on long-term effects.

1-Year HAAMU-STENT Results

Measurement	BMS n=75	Taxus n=70	p-value
Angiographic results			
In-stent MLD	2.0 mm	2.5 mm	<0.001
In stent % DS	34%	24%	<0.001
Primary endpoint: Late loss	0.73 mm	0.26 mm	<0.001
Clinical results			
Restenosis	24%	14%	N/A
MACE	14 events	11 events	Nss
Death	4.9%	9.8%	0.23
TVR	11%	3.7%	0.072

Taxus in diabetics

The 1-year results of the multicenter, retrospective TC-WYRE study in 1,558 consecutive patients at 19 U.S. sites found that Taxus was equivalent to Cypher overall but beat Cypher in diabetic patients.

1-Year TC-WYRE Results

Measurement	Cypher	Taxus	p-value
Primary endpoint: TVR	4.4%	2.3%	0.23
TVR in diabetic patients	8.5%	2.8%	0.004
MACE	7.3%	7.2%	Nss
Stent thrombosis	0.8%	0.9%	Nss
Late stent thrombosis	0.1%	0.1%	Nss

Taxus Liberté

Follow-up data from the global, multicenter, single-arm, 871-patient TAXUS-ATLAS pivotal trial indicated that the safety and efficacy benefits seen with Liberté at 9 months were maintained at 12 months in "workhorse" lesions.

1-Year TAXUS-ATLAS Results

Measurement	Taxus	Bare Express	p-value
Primary endpoint: TVR non-inferiority	9.2%	8.9%	0.83
Cardiac death rate	0.8%	1.0%	0.62
MI	4.0%	3.9%	0.89
Stent thrombosis	0.9%	0.7%	0.63

The global TAXUS-OLYMPIA registry found that Taxus Liberté is safe and effective in complex patients and lesions. The presentation included 12-month data from the 529 patients in Phase I of the multi-phased registry and preliminary 6-month data from the first 2,066 patients in Phase III.

TAXUS-OLYMPIA Registry Results

Measurement	Phase I 12-month results	Phase III 6-month results
Diabetics	49%	59%
Small vessels	40%	40%
Complex lesions	60%	60%
Cardiac event rate	3.7%	3.0%
MI	1.4%	0.9%
TVR	1.9%	1.8%
Cardiac death	1.5%	0.9%
Stent thrombosis >1 year	1.7% (1 additional)	---

CONOR CoStar

Johnson & Johnson plans to buy Conor for $1.4 billion in cash. The boards of both companies have approved the deal, which is expected to close in 1Q07.

At TCT, Dr. Mitchell Krucoff of Duke University reviewed the Conor trial data at a Conor-sponsored symposium, saying a meta-analysis of all CoStar data indicated:

- Safety and efficacy are maintained out to 12 months.

- One stent thrombosis occurred at less than 6 months and none beyond six months.
- The U.S. pivotal trial – a 1,675-patient, single-blind, non-inferiority comparison to Taxus – is underway and is the "first real-world randomized DES trial." In this trial, HbA1c will be evaluated as well in all the patients.

Dr. Krucoff said Study CI-CMS-005, the CoStar study in Japan, is expected to start enrollment by the end of November 2006.

A CoStar investigator said the balloon on Xience is better than the one on CoStar, but he also indicated Conor is putting a new, improved balloon on CoStar soon.

The single-blind COSTAR-II trial is still ongoing and fully enrolled, and some data from that trial were presented at TCT. This is a non-inferiority trial comparing CoStar to Taxus.

COSTAR-II Trial

Measurement	Taxus n=686	CoStar n=989
Primary endpoint: 8-month MACE (cardiac death, new MI, TVR)	Assumes <10%	Assumes Δ5% for equivalence
Single vessels	75%	
Multivessel	25%	
Blinded 30-day pooled results		
MACE	2.8%	
Cardiac death	0	
Stent thrombosis	0.2%	

Conor also is developing a dual drug combination of paclitaxel and pimecrolimus (licensed from Novartis). Dr. Keith Dawkins of the U.K. said pimecrolimus does not inhibit endothelial progenitor cells the way sirolimus and other mTORs do, adding, "Sirolimus causes greater oxidative stress and endothelial apoptosis than pimecrolimus…The next generation DES will be a 'gentler' drug, and pimecrolimus may be this gentler drug. It has a broad therapeutic window, is conducive to endothelial salvage, and the diffuse characteristics may be better."

The Genesis program includes:

1. **Corio stent** – a CoStar loaded with 325 µg pimecrolimus on a 3.0 mm x 16 mm stent. Dr. Dawkins said the potential advantages of this stent are that the pimecrolimus acts to prevent restenosis without delaying vessel healing, the dual drug delivery is designed to be a more potent solution to restenosis, and it may be more efficacious in complex lesions, ostial locations, bifurcations, diabetics, small vessels, and saphenous veins.
2. **SymBio stent** – which compares release of pimecrolimus 165.5 µg + paclitaxel 10 µg on a 3.0 mm x 16 mm stent.

So far, two patients have been enrolled in a first-in-man GENESIS trial comparing, in one arm, CoStar and Corio, and in the other arm, CoStar and SymBio.

JOHNSON & JOHNSON'S Cypher

Effective in long lesions

Dr. Seung-Jung Park of Korea presented the results of a 500-patient LONG-DES-II trial comparing the efficacy of Cypher and Taxus in native long coronary lesions. The primary endpoint was the rate of restenosis at 6 months. This study showed:

- Cypher appears to be more effective in inhibiting neointimal hyperplasia and resulted in a reduced risk of the restenosis and reduced need for repeat revascularization in patients.
- Cypher consistently reduced late loss, restenosis, and TLR vs. Taxus.
- The focal restenosis pattern more common in Cypher patients may be an additional benefit due to its ability to predict benign clinical prognosis.
- Incidents of death, MI, or stent thrombosis were similarly low for both groups.
- Although angiographic and clinical stent thrombosis occurred in 2 Cypher patients, the incidence of these events was not found to significantly differ between the two groups.

The moderator noted that there was higher late loss in longer stents and more complex lesions, even in the Cypher group.

LONG-DES-II Results

Measurement	Cypher	Taxus	p-value
Primary endpoint: **Restenosis at 6 months**			
In-segment	3.3%	14.6%	<0.001
Proximal edge	1.4%	4.3%	0.157
In-stent	2.9%	11.8%	0.001
Distal edge	0.0%	2.2%	0.041
Clinical outcome at 9 months			
Death	0.8%	0	0.499
MI	8.8%	10.8%	0.452
TLR	2.4%	7.2%	0.012
TVR	3.2%	7.6%	0.030
Stent thrombosis	0.8%	0	0.071
Composite of death, MI, TLR	11.2%	16.8%	0.071
Composite of death, MI, TVR	12.0%	17.2%	0.100

Dr. Jeffrey Popma of Brigham & Women's Hospital, who critiqued the trial, called it "an important and complex trial" and noted that it compared favorably to previous studies. He said, "It had a very high angiographic follow-up rate, and we can believe the numbers…It is important to put into perspective that it is unlikely that we are going back to BMS …This is a very, very important contribution to our understanding of DES in long lesions. Importantly, it's safe…There were no differences between the stents when it came to peri-procedural complications, and MACE was not different at six months."

Noting the "substantial superiority of Cypher to Taxus" in long lesions, the moderator asked if doctors should be using Cypher in long or complex lesions. Another expert said, "This particular study is very impressive and is probably the strongest weight of evidence that one stent has significant benefit over another for long lesions." However, he said he was puzzled by some things – for example, that the restenosis and TLR rates are lower than those in pivotal trials of short lesions, "I guess the longer the lesion the higher restenosis? Maybe with sirolimus there is no difference by how long the lesion is, and that would be very important information to know." Another expert said, "There is no question that this is an important trial to all human beings who face coronary stenting with long lesions."

Cypher in bifurcations

NORDIC BIFURCATION was an 8-month, 413-patient, randomized trial in five Nordic countries (12 centers) comparing two stenting strategies for Cypher use in de novo bifurcation lesions: (a) the main vessel with optional stenting of the side branch (MV), (b) main vessel plus side branch (MV + SB). An investigator said it is optimal to use only one stent because it is cheaper and takes less time, but stenting of side vessels and other complex bifurcation stenting strategies are also efficacious, "The study shows we can use (a stent) in the main vessel, but in some cases we need to use two stents. But if it is possible, it's better to use one stent."

The researchers also concluded:

- In both groups, procedural success rates were high, MACE rates were low, and angiographic stenosis >50% was low.
- MV is recommended for routine bifurcations.
- The study did not contradict the use of a complex bifurcation stenting strategy in special cases.

Dr. Barry Rutherford of Kansas City MO, who critiqued the study, said, "This is quite a conservative approach, and there are some questions that come up. First, what is the anatomy of the bifurcation? We haven't seen any classification of the bifurcations, and some classification of the bifurcation anatomy would be very helpful." He added that he was sure the authors wouldn't want the study translated to bifurcation of the left main, which he said would be a different strategy. Overall, he said, "The results are staggering, and the follow-up is remarkable. The TLR rates are remarkably low, and perhaps most striking are the low SAT rates that were reported. In most other studies that look at bifurcation stenting, the stent thrombosis rates can be as high as 4.7%-5%, and the results here are almost too good to believe…Overall, it's a remarkable study, and it lets us off the hook a bit in terms of treating these complex bifurcation lesions."

NORDIC BIFURCATION Trial Results

Measurement	MV	MV + SB	p-value
1 stent	206 patients (13% diabetic)		---
2 stents	207 patients (11% diabetic)		---
Results			
Entire bifurcation lesion diameter stenosis >50%	22.5%	16.0%	Nss, 0.15
Main vessel diameter stenosis >50%	4.6%	5.2%	Nss
Side branch diameter stenosis >50%	19.2%	11.5%	0.062

Cypher vs. Taxus

There is no significant differences between Cypher and Taxus in terms of death, MI, or TVR. That was the finding at one year in the DEScover registry, a prospective observational study of 6,906 patients at 151 U.S. sites enrolled from December 2004 to June 2005. DEScover compared BMS and DES, and then broke the results down further to compare Cypher and Taxus. Dr. David Williams of Rhode Island, an investigator, said that, overall, DES had a lower rate of death (3.1%) compared to BMS (5.9%), "Death or MI was not significantly different…but tended to favor DES…The cumulative rates of death and MI in-hospital at one year were similar between Cypher and Taxus…TVR was similar."

DEScover Registry One-Year Results

Measurement	BMS n=397	DES n=6,509	p-value	Cypher n=3,873	Taxus n=2,536	p-value
In-hospital results						
Death	1.0%	0.2%	0.007	0.2%	0.08%	0.22
MI	1.5%	0.6%	0.04	0.6%	0.5%	0.40
Stent thrombosis	0.3%	0.06%	0.26	0.03%	0.1%	0.31
Repeat PCI: any	0.5%	0.4%	0.65	0.4%	0.3%	0.67
CABG	0.5%	0.09%	0.07	0.1%	0.04%	0.41
TVR (PCI/CABG)	1.0%	0.3%	0.04	0.3%	0.3%	0.49
Death/MI	2.5%	0.7%	0.001	0.8%	0.5%	0.18
1-year results						
Death	5.9%	3.1%	0.005	3.3%	2.8%	0.45
MI	3.5%	2.4%	0.19	2.2%	2.6%	0.20
Stent thrombosis	0.8%	0.6%	0.67	0.5%	0.8%	0.06
Repeat PCI: any	9.3%	8.4%	0.62	8.7%	7.9%	0.37
CABG	3.5%	1.4%	0.0007	1.3%	1.5%	0.20
TVR (PCI/CABG)	9.5%	6.0%	0.007	6.3%	5.5%	0.20
Death/MI	9.0%	5.2%	0.002	5.2%	5.3%	0.64

JW MEDICAL'S Excel a lower priced Chinese DES

The MEDISTRA study looked at this new sirolimus-eluting, bioabsorbable stent that was placed in patients at Medistra Hospital in Indonesia from January 30, 2004, to February 28, 2006. Other DES (Taxus, Cypher) or BMS were used if the Excel was not appropriate. In the study, 277 patients received a total of 771 stents. Of those, 470 were Excel stents, which

uses an S-stent platform and a biodegradable carrier of poly-lactic acid polymer. The primary endpoint was TLR at six and 12 months. The secondary endpoints were six-month in-segment restenosis, in-segment late loss, and MACE.

An investigator said, "The study did not have a sponsor. The platform is good, the drug (sirolimus) is good, and the polymer is very good. We are very confident…Despite the inclusion of challenging real world cases (such as diabetes, multivessel disease, small vessels, complex lesions, etc.), the preliminary Excel rates are encouraging, with low MACE rates and a 'clean' angiographic appearance of the stent."

Asked what advantages this stent may have, the investigator said, "It's cheaper because it's made in China. The technology is from Biosensors, but the factory is in China." He said the cost of an Excel is about $1,200. It is expected to be launched in a few other Asian countries, including Thailand. Asked why there was no late stent thrombosis at 12 months, he said, "It's probably the polymer. Polymers may cause hypersensitive, inflammatory reactions, etc., so there are various causes, but among them is the polymer, and this stent has a biodegradable polymer, so after six months you don't have any more polymer." The stent does have a primer that remains on the stent.

MEDISTRA Results with Excel Stent

Measurement	30 days n=232	6 months n=210	12 months n=54
Cardiac death	0.9%	1.0%	1.3%
Non-cardiac death	0%	0%	0%
Non-fatal Q-wave MI, non-fatal non-Q-wave MI, any non-fatal MI, CABG	0%	0%	0%
TVR/TLR	0.4%	1.9% *(Primary endpoint)*	3.9%
Late stent thrombosis	0%	0%	0%

6-Month Angiographic Results in MEDISTRA

Measurement	Cypher	Taxus	Excel	BMS
Pre-procedural				
RVD	2.60 mm	2.57 mm	2.53 mm	3.20 mm
MLD	0.93 mm	0.95 mm	0.97 mm	1.09 mm
% DS	57.3%	62.2%	60.0%	66.0%
Post procedural				
RVD	2.61 mm	2.61 mm	2.53 mm	3.17 mm
MLD	2.13 mm	2.11 mm	2.08 mm	2.73 mm
% DS	17.7%	18.8%	17.7%	12.8%
Stent MLD	2.28 mm	2.29 mm	2.33 mm	2.76 mm
In-stent % DS	12.1%	11.5%	7.23%	12.2%
Results at 6 months				
RVD	2.67 mm	2.60 mm	2.64 mm	3.22 mm
MLD	1.89 mm	1.78 mm	2.07 mm	2.06 mm
% DS	29.2%	31.7%	21.6%	35.9%
Stent MLD	2.03 mm	1.92 mm	2.26 mm	2.06 mm
In-stent % DS	24.0%	26.3%	14.2%	35.9%
Late loss in-segment	0.24 mm (p=0.055)	0.31 mm (p=0.03)	0.01 mm	0.55 mm (p=0.003)
Late loss in-stent	0.25 mm (p=0.055)	0.35 mm (p=0.004)	0.07 mm	0.59 mm (p<.001)
Restenosis in-segment	18.2% (p=0.013)	10% (Nss)	5.2%	16.7% (Nss)

Dr. Philip Urban, who critiqued the presentation, said that the Excel stent "appears to be a promising device…In-stent late loss is an important parameter, and the data from the MEDISTRA trial fit very nicely within the target zone that one would expect. It was bang on target and compares well with the Cypher stent." He mentioned some of the study's limitations, including 34% successful angiographic follow-up. However, he found the late loss figures "remarkable" and "impressive" but added that the p-values "are of little value."

As far as safety, Dr. Urban said he was confused with the data, adding that he may have read the figures wrong, "There were two reported subacute stent thromboses – 0.9% at 30 days. But then we're told there were two early deaths at less than 30 days which were possible stent thrombosis, which equals 1.8% overall stent thrombosis." He also said that there was no late stent thrombosis because of inconclusive follow-up data. Dr. Urban said he'd like to see the full clinical follow-up at 12 months with independently adjudicated events and a randomized comparison to an established DES in order to define its place as a credible competitor, but, in conclusion: "It is very encouraging, preliminary, and (some of the procedures) are very complex, with an average of 2.8 stents per patient."

MEDTRONIC

Like Johnson & Johnson, Medtronic gave its blessing to the new ARC definition of stent thrombosis. Medtronic had been proud of the fact that there have been no stent thrombosis reported with Endeavor in its clinical trials – yet. However, by the new ARC definition, Medtronic can no longer say that. However, the rate is still below BMS. By the ARC overall definition, incidence-free survival was 99.0% with Endeavor and 96.7% with the bare Driver. By the pre-specified HCRI stent thrombosis definition, incidence-free survival was 99.6% with Endeavor and 98.8% with a bare Driver.

Dr. Cutlip, who worked on the ARC definitions, explained, "(By ARC definition), there are 3 stent thrombosis cases with Endeavor:

1. **Definite** – one MI with death within a few hours.
2. **Definite** – a proximal RCA TLR and distal new stent. Both BMS. Same day MI.
3. **Probable** – a Q-wave MI. Occlusion to distal stent, no thrombus.

CEO Art Collins said that Medtronic agrees with J&J that there is ***not*** a class effect in terms of stent thrombosis, "I can't remember a cardiology meeting so dominated by one topic (stent thrombosis)…J&J took a

strong position that there is not what has been referred to as a class effect of DES…and I confirm what we said previously: We agree with J&J 100% in this regard." Sean Salmon, Vice President and General Manager of Medtronic's Vascular Business agreed, adding, "Boston Scientific said they had a higher (stent thrombosis) risk, and they claimed it is a class effect...We bristled a little at that…They also said they had no difference in hard endpoints – death and MI…We know that late stent thrombosis can, has, and will occur in the Endeavor program…but we don't think it is at a rate greater than BMS."

Medtronic officials emphasized that even though this definition means Endeavor has some stent thrombosis, the rate is still lower than BMS. Scott Ward, President of Medtronic's Vascular Business, said, "By now we are all spinning on which definition (of stent thrombosis), adjudication, re-adjudication, prescribed data, or not…A fog of war has developed a bit…Endeavor is a safe and effective choice for physicians…At this point it is critically important that all companies follow their clinical data…We have been and are fully transparent…We have complied with every data analysis request and participated in the recent re-adjudication of our data that was conducted by an independent third party panel… As we look at this data, by any metric – mortality, Q-wave MI, all-cause mortality, ARC definitions – pre-specified protocol – Endeavor is a safe choice and safer than BMS or Cypher or Taxus…(With the ARC definitions) we still have zero thrombosis in 1,300 patients…As Dr. Gregg Stone said – there is no better metric today than to look at CEC pre-specified protocol definitions for ST – and for Medtronic that is still zero… Pre-specified stent thrombosis by HCRI definition is zero late stent thrombosis in pooled clinical trials. By the re-adjudicated ARC definition of stent thrombosis, Endeavor is 99.5% ST-free and no different from BMS. In fact, Endeavor trends better than BMS."

Salmon claimed that the Endeavor stent thrombosis rate "is significantly lower than Taxus or Cypher." He added, "We have a theory (stent thrombosis) has to do with inflammation…Maybe it is not the polymer but the drug itself…(But) the inflammatory scores are no different with Endeavor than (a bare) Driver in animals."

Stent Thrombosis Comparison

Stent thrombosis	Endeavor	Cypher	Taxus	Bare Driver
Definite by ARC	0.5%	1.6%	---	---
ARC definite, probable, and possible	1.0%	1.0%	---	---
HRCI definition at 2 years	0.3%	2.5%	3.2%	1.2%

Endeavor

Endeavor received a C.E. Mark in Europe in July 2005, and a Medtronic official claimed that it now has "20% market share in addressable markets, and >25% share in more than a dozen countries worldwide. Regulatory and reimbursement approval in China, Australia, Korea, and Taiwan will drive growth."

Medtronic submitted Endeavor to the FDA on November 16, 2006, and is hoping for approval in mid-2007 – based on 30-day safety data from ENDEAVOR-IV. And officials said they reconfirmed with the FDA prior to the submission that this is all they will need for approval. Ward said, "The U.S. launch is on track for approval in summer 2007. We have the largest safety data set ever submitted to the FDA for a DES – 2,100 patients with >1,000 followed >2 years. We don't anticipate any change in dossier requirements…As early as last week, we confirmed the FDA requirements for submission…We went back and asked and got confirmation that the FDA will stay with the current submission plan. We are submitting in November (2006)…The overriding factor in our regulatory strategy is that zotarolimus is an NME…They (FDA) said they want 2,000 patient exposures to support the safety of that…So, we have known we need minimum 30-day data on 2,000 patients prior to submission. That has been critical to the design of our programs…The efficacy of Endeavor is well characterized and published…We believe there is adequate evidence of efficacy to support approval. On safety, we need to hit the 2,000 patient threshold…We will be submitting the Endeavor PMA on 2,000 patients for 30-days – and you can take that as something that the FDA has agreed is what is required to support approval."

However, Medtronic officials expect there will have to be an FDA advisory panel on Endeavor, probably in March or April 2007. Ward explained, "We are assuming a panel. I think we will go to panel. There always is a chance we won't…I expect, in particular, in this environment that we will go to panel, but possibly we won't."

There appear to be no Endeavor manufacturing issues, so Medtronic should be able to provide all the Endeavors the market needs. Ward said, "We produced >375,000 Endeavors, gained the experience necessary to have great confidence as we bring the product to the U.S. We have no back orders and no quality issues…At the time of (European) launch, we had 80,000 units, and we launched simultaneously in 40 countries …and we had a flawless launch. Now we are in more than 105 countries, and it is easier to say where we are not: Canada, U.S., or Japan."

The lack of rapid exchange ***is*** an issue, but Medtronic officials believe it is surmountable – and a non-issue in the long-term. Ward said, "We will launch in the U.S. as OTW and multiple exchange. It will be difficult…to figure market share for several reasons: 50% of accounts in the U.S. are mixed accounts – currently using OTW, multiple exchange, or a mix. These accounts are responsible for >55% of DES units sold. We already have tremendous access to the vast majority of this marketplace. There is 75% OTW overlap with high volume CRDM accounts. They will switch to Endeavor and use Multiple Exchange and OTW. Since we are in accounts already, we will leverage CRM so accounts have the opportunity to try it (Endeavor) and then use it…I think we will do better (in terms of market share) than you expect…We will eventually get access to RX…The patents expire in

2008…They could be extended 2-3 years…But when we get that (RX), it will be a secondary bolus for this (Endeavor), especially in the U.S. We will launch it (RX) the day the patents expire."

Nine-month data from ENDEAVOR-IV will be at EuroPCR 2007.

Endeavor Resolute

Even before Medtronic has the Endeavor stent approved by the FDA, it is reporting clinical data from a newer generation drug-eluting stent, Endeavor Resolute, which uses a different polymer (BioLinx) than the original Endeavor. BioLinx is a blend of hydrophilic and hydrophobic polymers and is programmable. It elutes the same dose of zotarolimus as Endeavor but over 180 days (though most of it is gone at 90 days). A Medtronic official claimed deliverability is "exactly the same as Driver."

Dr. Ian Meredith of Australia, an Endeavor and Endeavor Resolute investigator, said that the new stent has an improved inflammatory score over the original Endeavor. Four-month data on the initial 30 patients in the first-in-man RESOLUTE registry with Endeavor Resolute showed low late loss, average MACE, minimal neointimal hyperplasia in-growth, and low adverse clinical events. The study's aim was to improve clinical outcomes in more complex lesion subsets while maintaining the current safety profile seen with the original Endeavor.

In RESOLUTE, 130 patients were enrolled at 12 sites in Australia and New Zealand. Data on 30 patients were available at four-month follow-up. Primary endpoints were in-stent late lumen loss at 9 months by QCA. Secondary endpoints were MACE at 30 days, 6, 9, and 12 months, and IVUS and angiographic parameters at nine months. The 30 patient subset was studied at 4 months for MACE, angiographic and IVUS parameters, and nine-month results will be compared to an Endeavor II DES cohort.

Early RESOLUTE Trial Results

Measurement	Endeavor Resolute n=30
30-days	
Device success	99.2%
Procedure success	96.2%
MACE	3.8%
Death	0
TVR (non-TLR)	0
Stent thrombosis	0
4-month subset results	
MACE	3.3%
Non-Q-wave MI	1 patient

There is likely to be more RESOLUTE data at EuroPCR 2007, and Medtronic is expecting to start a pivotal trial of Resolute in summer 2007.

Terumo's Nobori

A Phase I study presented at TCT found that Terumo's Nobori was non-inferior to Taxus. Nobori is a biolimus-eluting stainless steel S-stent with a bioabsorbable PLA polymer. Dr. Bernard Chevalier of France presented the 9-month clinical and angiographic results of the 120-patient NOBORI-1 trial in de novo lesions. The primary endpoint was met (a non-inferiority margin of ≥20 mm in late loss), with Nobori late loss 0.15 mm and Taxus late loss 0.32 mm. Dr. Chevalier concluded, "The Nobori stent, in this cohort of patients, is both safe and effective, with no acute, subacute, nor late stent thrombosis, no angiographic restenosis, and no clinically driven TLR up to nine months."

X-Cell Medical's Ethos

Two different formulations – moderate release (SR) and fast release (FR) – of this estradiol-eluting DES failed to show any clinical advantage over a bare stent in the randomized, triple-blinded, 90-patient ETHOS-I trial. In-stent late loss was almost identical in the three groups, so there was no benefit to Ethos, and there also was no difference in terms of in-stent volume obstruction. An investigator, Dr. Alexandre Abizaid of Brazil, concluded, "There was no evidence of incremental benefit associated with the estradiol-eluting stents. However, pre-clinical work confirmed that the dose of estradiol has to be lower – much lower than the one we used – so ETHOS-III will use a much lower dose and a smaller amount of bioabsorbable polymer…This was a negative study; there was no clinical advantage of Ethos over control in either group…But in such a small trial, you can't conclude (it is ineffective) in terms of clinical endpoints."

6-Month Angiographic Results of ETHOS-I Trial

Measurement	Ethos-SR n=30	Ethos-FR n=28	Bare stent n=32	p-value
Primary endpoint: Late loss in-stent	0.82 mm	0.86 mm	0.86 mm	0.950
In-stent MLD	1.91 mm	1.97 mm	1.91 mm	0.903
In-stent % DS	30.3%	31.8%	34.0%	0.735
In-stent restenosis	10%	13.3%	13.3%	0.872
In-lesion MLD	1.81 mm	1.90 mm	1.85 mm	0.836
In-lesion % DS	33.9%	34.4%	35.7%	0.905
In-lesion late loss	0.51 mm	0.50 mm	0.57 mm	0.785
In-lesion restenosis	13.3%	14.3%	12.9%	0.987
MACE Results				
	Ethos-SR n=32	**Ethos-FR n=31**	**Bare stent n=32**	**p-value**
Secondary endpoint: Overall MACE	18.8%	10.3%	9.4%	0.473
Death	3.1%	0	0	0.381
MI	3.1%	0	0	0.381
Emergency CABG	0	0	0	---
TLR	12.5%	6.9%	6.2%	0.621
TVR	12.5%	10.3%	9.4%	0.918
TVF	18.6%	10.3%	9.4%	0.473
Stent thrombosis	0	0	0	---

MISCELLANEOUS

- **BARD'S Luminex stent.** The 12-month results of the FAST trial failed to demonstrate the superiority of the Luminex nitinol stent over stand-alone balloon angioplasty in patients with SFA lesions 1-10 cm in length.

- **BIOTEGRA** is working on a stent with only 10%-20% of the total polymer that Cypher and Taxus use. It is coated with a modified heparin coating instead of a polymer. Human trials have not begun yet. Asked why this heparin-coated stent should succeed where J&J's heparin-coated stent did not, an investigator said, "J&J's heparin was covalent, and this is a heparin coating that has been used in heart-lung machines." The investigator said the company will need a partner to commercialize this.

- **DEVAX Axxess stent.** This biolimus-eluting stent has been submitted for a C.E. Mark in Europe, and an OUS trial is ongoing. An official said the company has reached agreement on a trial protocol with the FDA and started the trial outside the U.S. while waiting for Biosensors to clear the drug with the FDA. The company hopes to begin enrolling U.S. patients in late 1Q07 or 2Q07. The lead indication will be bifurcations.

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