Trends-in-Medicine

March 2005
by Lynne Peterson

SUMMARY

The concern at ACC wasn't the efficacy of **BOSTON SCIENTIFIC'S Taxus** stent, but questions were raised about safety issues – thrombosis and overlapping stents – with Taxus and perhaps with all drug-eluting stents. In head-to-head studies of Taxus and **JOHNSON & JOHNSON'S Cypher** stent, Taxus also lost its perceived advantages in diabetics and in deliverability when Cypher showed better results in diabetics and comparable deliverability. J&J may be able to use the data to take some market share from Boston Scientific, but how much is limited by J&J's continuing supply issues and Boston Scientific's aggressive defense of Taxus. **MEDTRONIC'S Endeavor** stent is staying alive, and company officials are optimistic that its pivotal trial will succeed and that it will be approvable despite continuing high late loss. The drug-eluting stent programs at **CONOR MEDSYSTEMS** (paclitaxel) and **GUIDANT** (everolimus) are progressing well, and both look, at this point, as if they will succeed.

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AMERICAN COLLEGE OF CARDIOLOGY – DEVICES

Orlando, FL
March 5-10, 2005

Stents dominated this meeting of the American College of Cardiology (ACC). The meeting, as usual, was preceded by a full-day stent symposium sponsored by the Cardiovascular Research Foundation, but there was significant stent news virtually every day of ACC.

DRUG-ELUTING STENTS

HIGHLIGHTS

- **BOSTON SCIENTIFIC** had a tough meeting, and they were doing serious damage control – but they were doing it pretty well. There were several incremental negatives – none enough to result in Taxus being pulled from the market or the FDA calling an advisory committee meeting on Taxus or on overall drug-eluting stent safety. However, the totality of the trial data raised significant questions about stent thrombosis with Taxus, about the ability to overlap Taxus stents, and about the efficacy in diabetics. ISAR-DIABETES, REALITY, TAXUS-V, the Taxus meta-analysis, and SIRTAX were all well-done studies and all suggested an issue with stent thrombosis and Taxus. Boston Scientific officials and experts did their best to minimize this, but the issue has given Johnson & Johnson marketing points, and some doctors are likely to get nervous about Taxus. This issue is not going away; it is going to be talked about for months (perhaps years) to come.

- **JOHNSON & JOHNSON** had a "win" overall at ACC, and it may help the company gain some Cypher market share, but how much share is still unclear. Doctors questioned about their plans said they needed time to study the results of the various trials. REALITY was neutral (which makes it a loss), but the ISAR-DIABETES trial in diabetics took away any advantage Taxus had in diabetics. Other trials found Cypher and Taxus equally deliverable, making it harder for Taxus to continue to claim superior deliverability.

- **MEDTRONIC** officials were happy campers and very upbeat about the ENDEAVOR-II data. Despite an in-stent late loss of 0.62 mm, the restenosis and TVF rates were acceptable. There appears a good chance that ENDEAVOR-III will meet its primary endpoint (late loss within 0.2 mm of the Cypher comparator). However, the regulatory process could take longer than expected, given the safety questions that have been raised about Taxus stents. Medtronic is hoping the FDA will accept 30-day MACE data from an ongoing trial (ENDEAVOR-IV) before that trial is finished, and if the FDA gets skittish about drug-eluting stent safety, the Agency may require more safety data from Medtronic or require Medtronic to complete ENDEAVOR-IV before approval.

ABBOTT'S Zomaxx
No real news yet

There were no data at ACC on Zomaxx, which elutes ABT-578 through a phosphorylcholine coating. A speaker said, "ABT-578 can penetrate into the vessel at a higher concentration than sirolimus (Cypher), but even less is eluted into the bloodstream."

Among the ongoing Zomaxx trials are:

- **ZOMAXX-I.** The first patient in this nine-month, 400-patient, non-inferiority trial (vs. Taxus) was enrolled September 14, 2004, and as of ACC ~10 patients had been enrolled. The primary endpoint is in-segment late loss, and the principal investigator is Dr. Bernard Chevalier of France.
- **ZOMAXX-II.** This pivotal U.S. trial is expected to start "in the near future." It will randomize 1,670 patients to either Zomaxx or Taxus, with a primary endpoint of non-inferiority, using nine-month ischemic TVR. The secondary endpoint is in-segment late loss at nine months.
- A trial is underway in Brazil and Germany in single vessel de novo coronary lesions, with a primary endpoint of MACE at 30 days.

BOSTON SCIENTIFIC'S Taxus
Concerns about safety

Meta-analysis

The safety of Taxus was the big question at the stent symposium and at ACC. At the stent symposium, Dr. Gregg Stone of Columbia University, the principal investigator for the Taxus program, presented the results of a meta-analysis of four Taxus trials which revealed several safety questions. In his introduction to this data, Dr. Stone commented, "I'm brutally honest about data. I show the good and the bad. This is a real, honest-look meta-analysis, which includes TAXUS-V. Boston Scientific has never, ever withheld any data…and we have the main databases from the Taxus trials at the Cardiovascular Research Foundation."

Three concerns with Taxus arose from this meta-analysis.

1. SATs after 500 days: "At about 500 days there is divergence of curves (in in-stent thrombosis)…From that point on there were six late stent thrombosis with Taxus and none with control…This is something we have to keep our eye on. It all begins to occur after 500 days… Everyone will spin this…and think it is awful…But what does it mean?…There is no doubt in my mind that this is, overall, a safe device…There is a questionable increase in late stenosis...We have to watch that…It was six patients (0.4%)…We will track this and see if it increases or decreases with more patients…but it doesn't translate into an increase in cardiac death or MI…Of the six cases, four had clearer precipitating co-morbid conditions, like broken bones or a colonoscopy."

Asked how Cypher stacks up on this issue, Dr. Marty Leon of Columbia University, also a co-director of the stent symposium, said, "We obviously are looking for this… Perhaps we are looking too closely…In the analysis with Cypher so far, we do not see in the patient base or in a meta-analysis an increased frequency with any definition of stent thrombosis from 30 days to three years. So far, I don't have any particular personal concerns. I think all of these devices are more thrombogenic than bare metal stents…Our analysis of Cypher is that it is as safe as bare metal stents, both early and late."

Dr. Stone added, "It is way premature to compare Cypher and Taxus on late stent thrombosis…You need a minimum of 10,000, and probably 30,000-40,000 patients in a trial to sense a difference (between Cypher and Taxus). So, a registry would have to be huge…I think it is premature to say people need to be on dual antiplatelet therapy for life…but I am concerned – not overly concerned…Despite this, patients are doing great overall, and that is what you need to keep your eye on...but you can't bury it."

2. MIs. There was an increase in peri-procedural myocardial necrosis (which if larger would be called an MI) at 30 days. Dr. Stone said, "I think we've figured out what causes this…This may or may not be a relatively minor event… but...there is not a concern about stent thrombosis."

3. Multiple stents increase peri-procedural problems. Dr. Stone predicted that one of the themes of ACC would be single vs. multiple stenting. And there were dramatic differences in the results for single vs. multiple stents in the Taxus meta-analysis.

Pooled Meta-Analysis of Taxus Trials

Measurement	TAXUS-II	TAXUS-IV	TAXUS-V	TAXUS-VI
Formulation	SR/MR	SR	SR	MR
Primary endpoint	6 months	9 months	9 months	9 months
Long-term follow-up	2 years	2 years	9 months	1 year
Angiographic follow-up	97.0%	42.5%	85.6%	93.5%
Geography	Europe	U.S.	U.S.	Europe
Stent platform	NIRx	Express	Express[2]	Express
Diabetics	14.3%	24.2%	30.9%	19.9%
RVD	2.75 mm	2.75 mm	2.69 mm	2.79 mm
Lesion length	10.5 mm	13.3 mm	17.2 mm	20.6 mm
Study stent length	15.4 mm	21.6 mm	28.4 mm	33.1 mm
Multiple stents	4.5%	7.5%	38.8%	32.8%
Stent:lesion ratio	1.71	1.84	1.83	1.72

Meta-analysis of Taxus Trials

Measurement	Control n=1,727	Taxus n=1,718
Overall results		
TLR	14.8%	5.8%
TVR non-TLR	2.8%	3.2%
TVR	16.3%	8.3%
Cardiac death	0.9%	0.7%
Q-wave MI	0.5%	0.6%
Non-Q-wave MI	4.1%	3.7%
MACE	19.7%	11.8%
All death	1.4%	1.3%
Late loss in-stent	0.89 mm	0.41 mm
Late loss in-segment	0.67 mm	0.31 mm
Restenosis in-stent	27.5%	8.4%
Restenosis in-segment	29.9%	12.3%
% volume obstruction by IVUS	26.88 (n=518)	10.32 (n=522)
Freedom from TLR at 200 days	94.2%	85.2%
Stent thrombosis		
Freedom from stent thrombosis at 2 years	99.3%	98.8% (p=.44)
From 6-12 months	Nss difference	
From 500 days to 2 years	0	6 patients (p=.014)
Results out to 2 years		
Freedom from any death	97.6%	97.7%
Freedom from MI	94.3%	94.2% (Nss)
Freedom from TLR	81.6%	92.2%

More Results from the Taxus Meta-analysis

Measurement	Control n=1,727	Taxus n=1,718
TLR		
RVD ≤2.5 mm	20.7%	8.3% (down 60%)
RVD 2.5 mm-3.0 mm	13.1%	5.7% (down 57%)
RVD >3.0 mm	9.8%	3.4% (down 66%)
Lesions <18 mm	13.6%	5.4% (down 60%)
Lesions 18-26 mm	15.7%	5.5% (down 65%)
Lesions >26 mm	22.1%	10.3% (down 53%)
In-stent late loss		
RVD ≤2.5 mm	.63 mm	.30 mm
RVD 2.5 mm-3.0 mm	.64 mm	.33 mm
RVD >3.0 mm	.73 mm	.30 mm
In-segment late loss		
RVD ≤2.5 mm	.64 mm	.31 mm
RVD 2.5 mm-3.0 mm	.67 mm	.31 mm
RVD >3.0 mm	.82 mm	.35 mm
In-stent restenosis		
RVD ≤2.5 mm	42.4%	19.5%
RVD 2.5 mm-3.0 mm	28.3%	10.6%
RVD >3.0 mm	18%	6.3%
In-lesion restenosis		
RVD ≤2.5 mm	24.7%	10.2%
RVD 2.5 mm-3.0 mm	37.1%	17.5%
RVD >3.0 mm	N/A	N/A

Diabetics in the Taxus Meta-analysis

Measurement	Control	Taxus
TLR		
Non-diabetics	13.6%	5.4%
Diabetics on oral medications	19.4%	7.9%
Insulin-dependent diabetics	N/A	5.8%
Late loss		
Non-diabetics	0.66 mm	0.32 mm
Diabetics on oral medications	0.9 mm	0.28 mm
Insulin-dependent diabetics	0.65 mm	0.22 mm
Restenosis		
Non-diabetics	27.6%	12.1%
Diabetics on oral medications	36.9%	12.6%
Insulin-dependent diabetics	41.9%	14.6%

Single vs. Multiple Stents in the Taxus Meta-analysis

Measurement	Single stent n=2,740	Multiple stents n=684	p-value
Average age	62.0	62.9	.052
Type C lesions	21.9%	29.4%	<.0001
MACE overall	3.1%	6.3%	.0002
Cardiac death	0.1%	0.3%	.34
MI	2.8%	0	.0001
Late loss	.61 mm control .29 mm Taxus	.85 control .39 Taxus	---
Restenosis	23.4% control 9.7% Taxus	52.7% control 20.8% Taxus	---
Analysis of multiple stent patients			
Measurement	**Control n=336**	**Taxus n=348**	**p-value**
MACE	4.2%	8.3%	.027
Cardiac death	0.3%	0.3%	Nss
MI	3.9%	8.0%	.024
Q-wave MI	0.9%	0.9%	Nss
Non-Q-wave MI	3.0%	7.2%	N/A
All deaths	1.8%	0.9%	N/A
Stent thrombosis	0.9%	1.1%	N/A
Freedom from MI	92.3%	89.8%	.19
Freedom from TLR	69.9%	90.9%	<.0001
Freedom from MACE	63.5%	76.8%	.0002

Among the other comments Dr. Stone made about these data were:

- "The in-stent late loss creeps up a little with more complex lesions."
- "The stent thrombosis rate out to two years is low in both groups (control and Taxus)."
- "With every drug-eluting stent, you will see a relation-ship between restenosis and lesion length."
- "There is no group based on vessel size and lesion length that doesn't benefit in TLR reduction (with Taxus)."

Dr. Stone concluded the Taxus meta-analysis out to two years shows:

- A marked reduction in TLR and TVF.
- A marked decrease in late loss and restenosis.
- Overall safety.
- An effect at all vessel sizes.
- An effect at all lesion lengths.
- An effect in all diabetic classes and non-diabetics.
- Multiple stents increase peri-procedural problems.

TAXUS-V results

More safety questions – this time about overlapping stents – were raised in the ACC presentation of the 9-month TAXUS-V results. The TAXUS-V discussant – Dr. Steve Ellis of the Cleveland Clinic – described the stent thrombosis with multiple overlapping stents as "disturbing," and noted that it was driven mainly by non-Q-wave MI associated with a significant increase in side branch compromise. He said, "The increased rate of non-Q-wave MI in the overlapping stent group needs further delineation." Dr. Jeff Popma, Director of Interventional Cardiology at Brigham & Women's Hospital, which was the core lab for TAXUS-V, suggested an explanation for the higher than expected incidence of MIs with Taxus: "We believe the MIs were non-Q-wave MIs in overlapped stents. The cardiac death at nine months is comparable…So, the 9-month TLR benefit comes with a 5% increase in the peri-procedure MI rate." He suggested there are several things doctors can do to prevent or minimize this problem:

- Reduction of overlap in the side branch area.
- Opening up larger side branches after implantation of multiple overlapping stents.
- Pre-dilate the side branches.

Boston Scientific's Dr. Mary Russell said the thrombosis problem occurs with all drug-eluting stents, not just Taxus: "The issue that stood out is stent thrombosis…The etiology is unclear. The frequency is so infrequent that it is very difficult to study. And to show statistical significance, you are talking about 100,000 patients…As far as I'm concerned, stent thrombosis is a serious problem. We're very concerned about

9-Month TAXUS-V Trial Results

Measurement	Bare Express n=498	Taxus n=498	p-value
30 day MACE	3.36%	5.1%	---
TVR	17.3%	12.1%	.018
TLR	15.7%	8.6%	---
MACE	21.2%	15.0%	.008
Non-Q-wave MI	4.4%	4.8%	---
Stent thrombosis	0.7% 4 patients	0.7% 4 patients	Nss
Late loss in-stent	.90 mm	.49 mm	<.0001
Late loss in-segment	.60 mm	.54 mm	<.0001
Restenosis in-stent	31.9%	13.7 %	<.0001
Restenosis in-segment	33.9%	18.9%	<.0001
Late loss proximal	.28 mm	.26 mm	---
% in-stent net volume obstruction by IVUS	31.8%	13.1%	<.0001

TAXUS-V Subgroup Analyses

Measurement	Bare Express	Taxus	p-value
2.25 mm vessels (n=203)			
Number of patients	95	108	---
Diabetics	31.6%	47.2%	.0310
MACE	26.9%	18.9%	Nss
Late loss in-stent	.90 mm	.49 mm	<.05
Late loss in-segment	.61 mm	.36 mm	.0036
TLR	21.5%	10.4%	.0332
Restenosis in-stent	44.7%	24.7%	<.05
Restenosis in-segment	49.4%	31.2%	.0147
4.0 mm vessels (n=202)			
Number of patients	103	99	---
Diabetics	22.3%	29.3%	Nss
MACE	14.9%	6.5%	Nss (p=.07)
Late loss in-stent	.87 mm	.42 mm	<.0001
Late loss in-segment	.54 mm	.22 mm	<.0001
TLR	5.0%	0	.06
Restenosis in-stent	14.4%	2.3%	---
Restenosis in-segment	14.4%	3.5%	---
Non-Q-wave MI	5.9%	3.2%	---
Stent thrombosis	0	0	Nss

Multiple Stents in TAXUS-V

Measurement	Bare Express	Taxus	p-value
Multiple stents (n=379)			
Diabetics	33.7%	34.9%	.83
MACE at 30 days	3.3%	8.3%	.047
MACE at 9 months	32.0%	20.4%	.01
MI by FDA definition (CK-MB ≥3xULN)	13.7%	21.9%	.0546
TLR	28.2%	12.6%	---
All death	1.6%	1.1%	---
Restenosis in-stent	57.1%	17.9%	---
Stent thrombosis	0.5%	1.0%	---

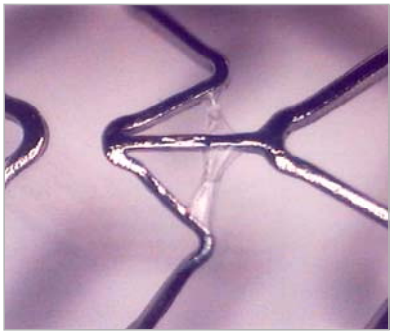
it…I believe there definitely – not maybe – is a late stent thrombosis problem. I think it is an issue in the field…I don't know why it is…There are so many variables that it will take serious work and a lot of patients to figure it out."

Discontinuing clopidogrel (Sanofi-Aventis's Plavix) does not appear to result in stent thrombosis. That was the conclusion of Dr. Ellis.

Principal investigator Dr. Gregg Stone made several points, including:

- There was no stent thrombosis >30 days with Taxus.
- In a complex cohort of patients, Taxus is safe, with a similar rate of death, MI, and stent thrombosis at 30 days and nine months.
- For the smaller 2.25 mm stent, TLR and restenosis were reduced with Taxus.
- With the larger 4.0 mm stents, there was reduced restenosis and a "strong trend" to a reduction in TLR.
- With multiple stents, there was an increase in peri-procedural MACE "due to greater myonecrosis from transient side branch narrowing with decreased (blood) flow…This (stent thrombosis) is a real phenomenon. I have no doubt in my mind that this is a real phenomenon. It could be a spasm from the paclitaxel. Or sometimes, the polymer can form little tiny webs from one strut to another…and sometimes the polymer can clump up a little…This has been shown in Cypher and Taxus…We don't know the reason…My best speculation is that it is the polymer, which does occasionally web or clump. That can happen with all these drug-eluting stents." However, Dr. Marie-Claude Morice, the principal investigator in the REALITY trial, said she has never heard of or seen a case of webbing with Cypher…I think drug-eluting stents will have a low frequency rate of late stent thrombosis…You have to keep your eye on that, and whether it is counterbalanced by the good things happening…And industry needs to find the cause and come up with devices without that (issue)…I will push industry very hard to come up with a solution to these issues."

Here is a photo provided by a source that shows the webbing that he said can occur with the Taxus polymer.



TAXUS-IV

Two-year data from the pivotal TAXUS-IV study that led to FDA approval of Taxus indicate the results seen at 9 months hold up over time. TLR was 3.6% in Taxus vs. 1.6% in control (p=.03).

Other safety and efficacy issues

The REALITY trial, a head-to-head comparison of Taxus and Cypher, sponsored by Johnson & Johnson, also raised thrombosis questions about Taxus. *(See page 7.)*

The independent ISAR-DIABETES trial, another head-to-head comparison of Cypher and Taxus, didn't find any safety issues, but it found Cypher significantly superior to Taxus in diabetics. *(See page 8.)*

BIOSENSORS' A9

No news

There was no news to report from ACC on this biolimus-eluting stent program.

CONOR MEDSYSTEMS' CoStar

Early data looks good

Conor takes a very different approach to drug-eluting stents – a metal stent with more than 580 little, laser cut holes or reservoirs in it that can be filled with one or more different drugs. Ductile hinges were added to handle stent stress, so the holes do not deform from pressure and cause the drug to leave the stent early. Drugs can be layered into the holes with multiple layers of biodegradable/bioresorbable polymers separating them, allowing timed drug delivery and/or multiple drug delivery. Conor stents also can be designed to release two different drugs in two different directions – one to the mural side and one to the luminal side. The initial drug being tested is paclitaxel.

PISCES trial

This was a 191-patient, international, dose-finding trial of Conor's first-generation stainless steel stent eluting paclitaxel. Six different formulations of paclitaxel were evaluated as well as different release rates (slow, medium, fast) and release direction (toward the arterial wall only or toward both the wall and the lumen). All six formulations were found safe and effective, and there was no late stent thrombosis. A speaker at the stent symposium said, "We found that dose and delivery matter, with 10 µg over 30 days and 30 µg over 30 days the best. How quickly and over what time period the drug elutes makes a clinically significant difference. "

12-Month Results of PISCES Trial

Measurement	10 µg paclitaxel dose	Slow release 30 µg paclitaxel dose
Restenosis in-stent	0	5.6%
TLR	0	6.9%
MACE	5.1%	6.9%
Late loss in-segment	.52 mm	.24 mm
Late loss in-stent	.30 mm	.36 mm

EuroSTAR-I trial

Six-month data were presented from one arm of the prospective, multicenter, two-arm, dose-ranging, pivotal EuroSTAR-I registry study. CoStar is a cobalt chromium stent with 30% thinner struts, less polymer, and a lower crossing profile than the stainless steel stent used in the PISCES trial. CoStar elutes 10 µg paclitaxel (per 17 mm stent) over 24-30 days. The trial found that CoStar is likely to be a viable new competitor in the drug-eluting stent market – if Conor can overcome the patent issues it faces with Angiotech over the use of paclitaxel. The trial included single and multiple de novo lesions in native coronary arteries. The other arm of the EuroSTAR-I registry is evaluating a different dose/schedule of paclitaxel: 30 µg released over 30 days. Enrollment completed in this arm two days before ACC. The principal investigators were Dr. Keith Dawkins of the U.K. and Dr. Antonio Colombo of Italy.

Dr. Dawkins concluded: "CoStar is highly deliverable, radiopaque, and safe, with an acceptable rate for complications in both single and multivessel patients." Dr. Marty Leon compared the results to the Cypher RAVEL trial, but Dr. Dawkins preferred to call it "RAVEL-esque."

Patients in EuroSTAR-I got dual antiplatelet therapy (Plavix+aspirin) for six months, but Dr. Dawkins suggested a shorter regimen may prove viable. He said, "I feel confident we could use three months of antiplatelet therapy, but we don't have the data yet to support that."

Less than a week after ACC, Conor announced that it had signed a deal with Novartis to test three Novartis drugs on its drug-eluting stent – Gleevec (imatinib mesylate), which is FDA-approved to treat chronic myeloid leukemia (CML); pimecrolimus, which is FDA-approved as a topical treatment (Elidel) for eczema; and midostaurin, an agent in preclinical development to treat cancer.

EuroSTAR Subgroup Analyses

Measurement	Stent diameter ≤2.5 mm	Stent diameter >2.5 mm
Restenosis in-stent	3.3%	3.4%
Restenosis in-segment	6.6%	3.4%
	Stent length ≤20 mm	**Stent length >20 mm**
Restenosis in-stent	3.2%	0

EuroSTAR-I Trial Results

Measurement	CoStar Arm 1 10 µg eluted over 30 days n=176
Diabetics	16%
Average vessel diameter	2.64 mm
Average number of stents per lesion	1.1
Average number of stents per patient	1.3
Multivessel disease	>50%
Direct stenting	51.7%
Results	
Restenosis in-stent	3.4%
Restenosis in-segment	4.7%
Late loss in-stent	0.26 mm
Late loss in-segment	0.07 mm
TLR	1.7%
MACE	4.8%
Death	1.4%
Q-wave MI	0
Non-Q-wave MI	1.4%
Late thrombosis	0.7%
Restenosis in-stent	3.4%
Restenosis in-segment	4.7%

GUIDANT

Both everolimus programs are progressing

Guidant has two everolimus-eluting stent programs progressing simultaneously. The big question is what happens to these programs once Johnson & Johnson's acquisition of Guidant is complete. Speakers declined to speculate.

➢ **FUTURE program,** with the ML Vision eluting everolimus. Everolimus is an immunosuppressant from Novartis that is approved in Europe and has an approvable letter from the FDA. The elution profile of ML Vision roughly mirrors the elution of Cypher. In fact, an investigator said the elution profile more closely matches Cypher than does Abbott's ABT-578, another sirolimus analog.

➢ **SPIRIT program,** with Xience, an everolimus-eluting stent with a bioabsorbable coating. The six-month results of the SPIRIT-FIRST program were presented last fall and showed:

- In-stent late loss of 0.10 mm vs. 0.84 mm in control ($p<.001$).
- MACE of 7.7% vs. 21% in control.

Guidant Drug-Eluting Stent Clinical Trials

Measurement	SPIRIT-FIRST	FUTURE-I	FUTURE-II
Platform	Xience V	S stent	S stent
Lesion length	10.1 mm	9.2 mm	11.1 mm
Late loss in-stent	0.10 mm	0.11 mm	0.12 mm
Late loss in-segment	0.09 mm	0.19 mm	0.16 mm
Restenosis in-stent	0	0	0
Restenosis in-segment	4.3%	4.0%	4.8%
MACE	7.7%	7.4%	4.7%

Dr. Campbell Rogers of Brigham & Women's Hospital and Dr. Gregg Stone of Columbia University are co-primary investigators in the SPIRIT-III trial. This trial compares 668 Xience patients to 334 Taxus controls. There will also be a non-randomized arm in Japan and three non-randomized arms in the U.S. (80 patients getting a 4.0 mm diameter stent, 105 patients getting a 2.25 mm stent, and ~100 patients getting a stent 38 mm in length). The ~70-patient, nine-month SPIRIT-IV trial is "under construction." This is a non-inferiority comparison with an as-yet-unnamed stent.

No questions have been raised about thrombosis in the Guidant programs, and there is no signal of any thrombosis issue with everolimus. And it appears that Guidant is using a tougher definition of MI than Boston Scientific, Johnson & Johnson, or Medtronic. Guidant's definition is CK-MB ≥2xULN. The other companies use a definition of CK >2xULN with any increase in CK-MB. CK-MB is considered a far more sensitive measure than CK.

JOHNSON & JOHNSON'S Cypher vs. BOSTON SCIENTIFIC'S Taxus

Cypher efficacy and deliverability proven comparable to Taxus, but Cypher better in diabetics, and perhaps safer than Taxus

The key Cypher trials at ACC were head-to-head studies – REALITY, ISAR-DIABETES, SIRTAX, CORPAL, and TAXI. There also were some data on Cypher alone, from ARTS-II and SIRIUS (three-year data). Considered together, these trials may go a long way toward disproving the common conceptions that (a) Taxus is an easier stent to deliver and (b) Taxus is better in diabetics. They also raise questions about the safety of Taxus, which Boston Scientific officials were quick to characterize as marketing tactics, but which are likely to haunt Taxus for some time. However, a Guidant official commented, "I hope J&J doesn't over emphasize the safety issue with Taxus."

REALITY trial – Cypher and Taxus comparable in efficacy but Cypher may be safer

Dr. Marie-Claude Morice of France, the principal investigator, presented the 8-month results of the REALITY trial, a randomized, prospective, head-to-head comparison of Cypher and Taxus, sponsored by Johnson & Johnson. She reported:

- No statistically significant difference in in-lesion restenosis.
- A statistically significant advantage with Cypher on other angiographic measures – late loss, % DS, and MLD.
- No edge effect with either.
- No statistically significant ***difference in safety***, except in a measure that wasn't a pre-specified endpoint: Stent thrombosis <30 days, which was significantly lower with Cypher than Taxus. However, there was no difference in stent thrombosis at eight months.

Dr. David Holmes of the Mayo Clinic, a member of the ACC Board of Trustees, called the data "hypothesis generating." He said, "We have discovered something that may or may not be chance…So far, in clinical trials, there has been a lower stent thrombosis rate with Cypher (than Taxus), but that could be chance alone." Boston Scientific officials and experts dismissed the safety difference since it was not a pre-specified analysis.

8-Month REALITY Results

Measurement	Cypher n=684	Taxus n=669	p-value
Demographics			
Lesions	970	941	---
Angiographic FU	93%	91%	---
Diabetics	27.2%	28.7%	Nss
Number of stents per patient	1.94	1.94	Nss
Number of stents per lesion	1.37	1.39	Nss
Mean stent diameter	2.79 mm	2.80 mm	Nss
Stent max pressures	14.6 atm	14.2 atm	<.001
Lesion success	99.4%	99.4%	Nss
Device success	95.3%	96.6%	Nss
Procedural success	95.0%	94.5%	Nss
Angiographic results			
Primary endpoint: in-lesion restenosis	9.6%	11.1%	Nss (p=0.31)
In-stent restenosis	7.0%	8.3%	Nss
Proximal restenosis	3.5%	4.3%	Nss
Distal restenosis	2.3%	2.8%	Nss
TLR	5.0%	5.4%	Nss
TVR	1.6%	1.2%	Nss
TVF	10.4%	11.5%	Nss (p=.054)
RVD	2.40 mm	2.40 mm	Nss
Lesion length	16.96 mm	17.31 mm	Nss
In-stent late loss	.09 mm	.31 mm	<.001
In-lesion late loss	.04 mm	.16 mm	<.001
In-stent % DS	23.11	26.70	<.001
In-lesion % DS	29.11	31.06	<.001
In-stent MLD	2.00 mm	1.85 mm	<.001
In-lesion MLD	1.79 mm	1.71 mm	<.001

8-Month REALITY Safety Results

Measurement	Cypher n=684	Taxus n=669	p-value
MACE	9.2%	10.6%	Nss (p=0.41)
MI	4.8%	5.5%	Nss (p=0.62)
Non-Q-wave MI	0.15% 1 patient	0.9% 6 patients	Nss
Q-wave MI	4.7% 32 patients	4.6% 31 patients	Nss
SAT <30 days by ITT	0.6% 3 patients	1.6% 12 patients	. Nss (p=0.723)
SAT <30 days in actually treated patients	0.4%	1.8%	.0196
Death	1.8%	1.2%	Nss

ISAR-DIABETES trial – Cypher better than Taxus in diabetics

This independent, investigator-led prospective, randomized, European trial compared Cypher and Taxus in diabetic patients, and found Cypher superior. The investigator said, "Based on this data, the best device for them (diabetics) is Cypher…The Cypher stent attenuates the restenosis process to a greater degree than Taxus…So, statistically speaking, Cypher will give diabetic patients better protection against restenosis than a Taxus stent." Dr. David Holmes, a trustee of ACC, had this comment about the results: "Before this morning, I would have said Taxus is tremendous for diabetics, and all diabetics should have a Taxus stent. This trial says that is not the case."

6-Month Results from ISAR-DIABETES Trial

Measurement	Cypher n=503	Taxus n=509	p-value
Baseline			
Lesions per patient	1.4	1.4	---
Stents per lesion	1.2	1.1	---
Death	3.2%	4.8%	Nss
MI	4.0%	2.4%	Nss
In-segment late loss	0.43 mm	0.67 mm	.002
In-stent late loss	0.19 mm	0.46 mm	.001
Restenosis	6.9%	16.5%	.03
TLR	6.4%	12.0%	.13

SIRTAX trial – Cypher beats Taxus on efficacy and safety

This large, randomized Swiss study, which was funded by the two universities that conducted it without the support of industry, found Cypher significantly superior to Taxus. The discussant, Dr. Marie-Claude Morice of France said, "Both stents are deliverable, effective, and safe. My perception is that the first one (Taxus) is excellent, and the second (Cypher) is even better."

9-Month Results from SIRTAX Trial

Measurement	Cypher n=503	Taxus n=509	p-value
Baseline			
Lesions per patient	1.4	1.4	---
Stents per lesion	1.2	1.1	---
Mean stent length	18.8 mm	18.7 mm	---
Device success	99.0%	98.6%	Nss
Lesion success	99.4%	99.0%	Nss
Results			
Primary endpoint: MACE (cardiac death, MI, or TLR)	6.2%	10.8%	.009
Death	1.0%	2.2%	---
MI	2.8%	3.5%	---
Secondary endpoint #1: TLR	4.8%	8.3%	.025
Secondary endpoint #2: TVR	6.0%	9.2%	---
Secondary endpoint #3: TVF	7.0%	11.6%	---
Primary endpoint for subgroup analysis: MACE in diabetics	HR 1.80 in favor of Cypher		.009
Late loss in-stent	.13 mm	.25 mm	<.001
Late loss in-segment	.19 mm	.32 mm	.001
Restenosis in-stent	3.2%	7.6%	.013
Restenosis in-segment	6.7%	11.9%	.02
Stent thrombosis acute	0.6%	0.4%	---
Stent thrombosis 1-30 days	1.2%	1.0%	---
Stent thrombosis >30 days	2.0%	1.6%	---

CORPAL trial – Comparable safety

This 652-patient trial, conducted in Spain, compared Taxus and Cypher in 652 patients with documented myocardial ischemia secondary to coronary lesions prone to restenosis.

Researchers concluded:

- Cypher and Taxus provided similar safety profiles.
- Restenosis after Cypher is usually focal and mainly due to stent constriction (focal crush); restenosis after Taxus seems mainly related to neointimal proliferation.
- Late follow-up showed minimal differences characterized by:
  - Lower late loss with Cypher.
  - Lower neointimal proliferation (by IVUS) with Cypher.

6-Month CORPAL Trial Results

Measurement	Cypher n=434	Taxus n=410
Number of stents per lesion	1.4	1.4
Average stent diameter	2.84 mm	2.83 mm
Stent length	27 mm	27 mm
Overlapped stents	87	92
Gaps within stents	26	24
IIb/IIIa use	127	102
Results		
Death	0.2%	0.5%
Stent thrombosis	1.0%	N/A
Death	1	1
MI	2	2
Restenosis	12%	18%
TLR	4%	7%
Bifurcated lesions	7%	20%
Late loss by QCA	.36 mm	.54 mm (p=.05)
% residual stenosis	24%	30% (p=.05)
MLD	2.23	2.01 (p=.05)
Focal restenosis	64%	54%
Total occlusions	9%	20%
Stent constriction	2%	7%
Endoproliferative restenosis	78%	91%

TAXI trial

The 6-month results of this head-to-head trial comparing Taxus and Cypher have previously been published, but the 12-month results presented at the stent symposium were new. The principal investigator called this trial a "real-world comparison" of the two stents.

12-Month TAXI Trial Results

Measurement	Taxus n=100	Cypher n=102	p-value
Demographics			
Diabetics	36%	32%	---
Stable angina or silent ischemia	86%	84%	---
Unstable angina	14%	16%	---
RVD	3.2 mm	3.2 mm	---
Number of stents per patient	1.5	1.5	---
Multiple stents	29%	37%	---
Multivessel	18%	25%	---
IIb/IIIa use	4 patients	7 patients	---
Results			
Death	1	0	.9
Non-Q-wave MI	4	3	.6
Q-wave MI	1	1	.7
TLR	1	3	.7
CABG	0	1	.9
Stent thrombosis	0	1	.9
Event-free survival	93%	92%	Nss

ARTS-II trial – Cypher better than CABG

Dr. Patrick Serruys of the Thoraxcenter in Rotterdam, Netherlands, presented the one-year results of the ARTS-II trial comparing Cypher to historical CABG results. He concluded that the Bayesian non-inferiority test was passed, and the Bayesian superiority test was passed. He said, "Based on this analysis at one year, we can conclude that at a 0.05 level of significance patients in ARTS-II treated with a Cypher stent performed better than patients treated with CABG in ARTS-I…The overall MACCE rate was non-inferior to ARTS-I CABG, fulfilling the primary endpoint of the trial."

1-Year Results from ARTS-II Trial

MACCE	Cypher n=607	CABG in ARTS-I historical control n=602	ARTS-I historical control (J&J Crown stent) n=600
Death	1.0%	2.7%	2.7%
CVA	0.8%	1.8%	1.8%
MI	1.2%	3.5%	5.0%
Any MACCE	10.4%	11.6%	26.5%
Adjusted MACCE	8.1%	13.1%	---
Freedom from death, stroke, and MI	96.9%	92.0%	90.7%
Freedom from re-intervention	95.9%	91.5%	78.7%
Freedom from MACCE	89.5%	88.5%	73.7%
Stent thrombosis	2 patients	N/A	N/A

SIRIUS – Cypher efficacy and safety hold up long-term

Three-year follow-up of SIRIUS. Dr. David Holmes of the Mayo Clinic said the nine-month, two-year, and three-year data all look consistent. He added, "Between Year 2 and Year 3, there was one additional stent thrombosis in the Cypher group…so we are not seeing a major increase in problems with that – that is not going to be an issue…These are safe devices out to three years."

MEDTRONIC'S Endeavor

Good news: Late loss high but TVF and TLR acceptable

The 9-month results of ENDEAVOR-II, a prospective, randomized clinical trial conducted in Europe, Asia Pacific, Israel, New Zealand, and Australia, were presented at ACC. It compared Endeavor (an everolimus-eluting Driver stent) to a bare Driver stent. Angiography was performed on the first 600 patients, and IVUS on the first 300 patients plus any patients getting overlapping stents. All patients got dual anti-platelet therapy (aspirin+clopidogrel) for three months. A

speaker said, "Given the excellent deliverability of the Driver stent, coupled with the bioactive effect of the PC (polymer) elution of ABT-578...If the coming trials – ENDEAVOR-III and ENDEAVOR-IV – remain positive, the Endeavor stent will be a welcome addition to the cath lab.

9-Month ENDEAVOR-II Trial Results

Measurement	Endeavor n=598	Driver n=599	p-value	ENDEAVOR-I results
Primary endpoint: TVF	8.1%	15.4%	<.0005	2%
MACE	7.4%	14.7%	<.0001	2%
Death	1.2%	0.5%	Nss	0
All MI	---	---	---	1%
Q-wave MI	0.3%	0.9%	Nss	0
Non-Q-wave MI	2.4%	3.1%	Nss	1%
TLR	4.6%	12.1%	<.0001	1%
TVR	5.7%	12.6%	<.0001	0 (non-TLR)
Late aneurysm	0	0	Nss	N/A
Late incomplete apposition	0	0	Nss	0
Stent thrombosis				
In-hospital	0.3%	0.3%	---	N/A
1-30 days	0.2%	0.9%	---	N/A
Total at 270 days	0.5%	1.2%	Nss	N/A
TLR-free survival	95.4%	87.8%	<.0001	N/A
Restenosis				
In-stent	9.5%	32.7%	<.0001	5.4%
In-segment	13.3%	34.2%	<.0001	5.4%
Proximal edge restenosis	3.5%	4.3%	<.0001	---
Distal edge	1.9%	5.3%	<.0001	---
Late loss				
Late loss in-stent	.62 mm	1.03 mm	<.0001	.61 mm
Late loss in-segment	.36 mm	.71 mm	<.0001	.43 mm
Index	.34 mm	.54 mm	<.0001	---
Other angiographic results				
MLD in-stent	1.99 mm	1.63 mm	<.001	---
MLD in-segment	1.86 mm	1.57 mm	<.0001	---
% DS in-stent	27.9%	42.1%	<.0001	26.8%
% DS in-segment	32.6%	44.3%	<.0001	---
RVD	2.74 mm	2.78 mm	Nss	2.91 mm

The in-stent late loss in ENDEAVOR-II (0.62 mm) was even higher than in ENDEAVOR-I (0.61 mm). The primary endpoint in the pivotal trial for Endeavor is in-segment late loss (which to be successful can be no higher than .20 greater than that for the comparator Cypher arm).

- Dr. William Wijns, one of the principal investigators for ENDEAVOR-II, said, "You shouldn't be concerned. This trial, despite the fact that it establishes the efficacy and safety of Endeavor, also challenges to some extent some assumptions on which other trials are based – that is, late loss and clinical outcome...My point is that clinical outcomes are what matters…Of course, late loss matters …But in deciding which stent to use, there are three issues: (1) ease of use/deliverability, (2) anti-restenosis that can be measured in several ways, including late loss, and (3) safety. To judge between the three is an art. We think we have safety in the ENDEAVOR-II data…We think we have anti-proliferative power, even thought it is not the same late loss you see with Cypher…But who says that the benchmark is zero late loss? The benchmark is clinical outcome. In the high risk subsets we looked at…we did not find any evidence the Endeavor stent didn't work…We did find a uniform treatment effect across the subsets we looked at."
- A speaker said, "The key thing is that there will now be a third stent…The results are as good as for Cypher and Taxus….There is a controversy over how much late loss matters…Some feel very strongly it is an important window…Others think it is not as important, and it matters what happens clinically. When you see studies like this, you scratch your head and wonder if the current thinking is right…There will be spin masters on all sides of this question, and I won't pretend I have the answer…My patients don't care about intimal thickness; they care how often they have to come back to the lab…But from a scientific standpoint, we need more studies."

ENDEAVOR-II Subgroups

Measurement	Endeavor	Driver
TLR by vessel size		
<2.5 mm (n=381)	7.2%	16.6%
2.5-3.0 mm (n=453)	3.0%	12.2%
>3.0 (n=319)	4.0%	7.7%
TLR by lesion length		
<11.1 mm (n=379)	3.2%	7.9%
11.1-16 mm (n=394)	4.6%	14.1%
>16 mm (n=369)	6.6%	14.9%
TLR in diabetics		
Non-diabetics	4.0%	11.2%
Diabetics	7.6%	15.4%
Non-insulin dependent	6.3%	16.3%
Insulin-dependent	11.5%	13.6%

Medtronic officials discussed the ENDEAVOR-II results after the presentation, and they made several interesting comments, including:

- One official said, "We have conditional approval for ENDEAVOR-IV from the FDA…We will start that trial sometime in the next 30 days." However, another reliable source said it will be two or three months before final FDA approval is given, the protocol is distributed, and the IRBs sign off on it.

- ENDEAVOR-IV should be able to enroll in 10-12 months, with enrollment helped by:
  - The ENDEAVOR-II data.
  - The size of the angiographic cohort (~320) patients.
  - The number of centers involved – 20 in the U.S. and 10 in Canada.
- ENDEAVOR-III results will be presented at TCT 2005. This is a randomized, 436-patient trial comparing 327 Endeavors to 109 Cyphers. The principal investigators are Dr. Marty Leon of Columbia University and Dr. David Kandzari of Duke University. A Medtronic official said ENDEAVOR-III "has a high probability of making its primary endpoint."
- Endeavor will be launched in 40 countries outside the U.S. "sometime this spring," but an official could not say when or even if it would be before or after EuroPCR in May 2005. The reason for the uncertainty is the company does not yet have a CE Mark. He said Medtronic has answered all the questions of European regulators, responded to all their issues, and has passed the plant inspection. When Endeavor does launch, an official said, "We will be able to supply more of the market than most analysts have estimated."
- A Medtronic official predicted U.S. approval of Endeavor in "calendar year 2007." For U.S. approval of Endeavor, he said he hopes that ENDEAVOR-I, ENDEAVOR-II, and ENDEAVOR-III, plus 30-day MACE results from ENDEAVOR-IV will be sufficient. He confirmed the FDA wants safety data on 2,000 patients, but only 30-day MACE data, not full 9-month safety data, so he does not believe the FDA will require completion of ENDEAVOR-IV before approval.
- Patients in Endeavor trials are only given clopidogrel for three months, and the unspoken suggestion was that this could be a marketing point.
- With respect to the pending acquisition by Johnson & Johnson of Guidant, he said the biggest issue for Medtronic, and perhaps the Federal Trade Commission (FTC), may be intellectual property (IP). A Medtronic official explained, "The IP environment is a concern. J&J plus Guidant is a concentration of IP. I think the FTC is probably looking at that in its second round (of questions)." A key concern for Medtronic is rapid exchange IP, but he said there are a number of other issues, including peripherals.
- On rapid exchange, an official said, "We will be hurt by lack of rapid exchange, but that patent expires in 2008... The absence of rapid exchange has the potential to mute our market share in the U.S."
- Medtronic is developing its own proprietary polymer internally, and there are plans for a first-in-man trial to begin "sometime this summer, focusing on subpopulations, most probably diabetics and small vessels."
- Officials dismissed the idea that the questions raised about Taxus safety in several trials would have any impact on the FDA's scrutiny of Endeavor data or the Endeavor timeline. However, Dr. Popma of Brigham & Women's Hospital, which is the core lab for ENDEAVOR-III, predicted the Taxus issues are likely to make interventional cardiologists more receptive to a new stent: "All the buzz about late stent thrombosis...will ultimately be concerning to physicians…And the phosphorylcholine (PC) coating on Endeavor is a safe, antithrombotic coating. We also haven't seen any stent thrombosis problem with the Visio stent which has the same coating."
- An ENDEAVOR-III investigator, Dr. Jean Fajadet of France, said, "In France, Driver is the No. 1 bare metal stent, particularly when we have tortuous vessels or difficult anatomy."

Comparison of Drug-Eluting Stent Trials

Measurement	SIRIUS	TAXUS-IV	ENDEAVOR-II
Diabetics	26.4%	24.2%	20.1%
Location	U.S.*	U.S. *	Europe
Clinical Results			
TVF	8.6%	7.6%	***Primary endpoint:*** 8.1%
TVR	7.3%	4.7%	5.7%
TLR	4.1%	3.0%	4.6%
MACE	7.1%	8.5%	7.4%
Late loss			
In-stent with control	1.01 mm	0.9 mm	1.03 mm
In-stent with DES	0.17 mm	0.39 mm	0.62 mm
In-segment with control	0.81 mm	0.61 mm	0.71 mm
In-segment with DES	0.24 mm	0.23 mm	0.36 mm
Restenosis			
In-stent with control	35.4%	24.4%	32.7%
In-stent with DES	3.2%	4.5%	9.5%
In-segment with control	36.3%	26.6%	34.2%
In-segment with DES	8.9%	7.9%	13.3%
TLR			
Control	16.6%	11.3%	12.1%
DES	4.1%	3.1%	4.6%

* Dr. Gregg Stone said TLR tends to be higher in the U.S.

CHOOSING BETWEEN CYPHER AND TAXUS

What does all this new stent data mean for interventional cardiologists? Dr. Steve Ellis of the Cleveland Clinic suggested these are the questions doctors will be wrestling with after TAXUS-V and SIRTAX.

- Are there subgroups of patients that clearly do better with either Cypher or Taxus?

- Is there a difference in long-term risk of stent thrombosis between Cypher and Taxus?
- How do technical issues such as stent length/lesion length ratio, and degree of stent overlap affect choice?

How will the stent data presented at ACC affect the choice of which stent to use? Even Dr. Morice said the REALITY data is not persuasive enough to cause doctors to switch manufacturers, "There are not enough data to select one stent over the other. They are both very deliverable, very efficient to prevent restenosis…The safety (question with Taxus) that is seen there is there, but it is the first time (this has been seen). It is not seen in other trials at the moment…We need to see if it is confirmed…For me, as a doctor, it will not make me change my prescription." Another expert said, "They both work, and they work well."

Experts were asked whether REALITY in conjunction with the ISAR-DIABETES results in diabetic patients, which strongly favored Cypher over Taxus, would influence the choice of stent.

- Dr. Morice said, "The reality is not there…We are seeing small differences, and we need much more data to change practice dramatically…In my opinion, they are both very good, but one is even a little better than the other…You cannot say they are equivalent when you see the superiority of Cypher in diabetics, though that was a small trial…It seems both are excellent, but one is slightly better. You cannot say they are equivalent at the moment."
- Dr. Gregg Stone, the principal investigator for the Taxus program, said, "It (REALITY) was a beautifully done study…What was striking to me was that it shows that even in very complex lesions, there is just ~5% TLR with both stents...I think both devices have made remarkable progress in the fight against symptomatic atherosclerosis …There is no difference in any hard endpoints on safety…The stent thrombosis is an interesting finding…If you look at all the blinded trials of ~5,000 patients, they all have the same stent thrombosis vs. control…If you look at multiple endpoints, you have to have one come up positive now and then."
- Another source: "The way I look at it is there are two very good products in the marketplace, and both work and work well…I think we will…combine these data with the knowledge about a given patient to make a decision about whether there is an important choice of which stent platform to use."

Dr. William O'Neill of William Beaumont Hospital had this interesting exchange with Boston Scientific's Mary Russell:

Dr. O'Neill: "The focus will be on safety after this meeting…Going back to the Vioxx (Merck, rofecoxib) and Celebrex (Pfizer, celecoxib) controversy. How are we going to be able to prove these devices (drug-eluting stents) are safe? There are very low rates of adverse events that occur in the trials, which are primarily powered for efficacy, so when you have a 0.8% or 1.2% event rate and something comes up with p-value, there is a concern that it isn't prospective and needs 10,000 or 100,000 patients to find a true safety connection. On the other hand, the public, the FDA, Sid Wolfe (of the consumer watchdog group Public Citizen), and the malpractice lawyers all focus on safety. How will you handle that?"

Dr. Russell: "When I entered this (Taxus) program, the company made a philosophical decision that, although it is a device company, this was a pharma-like product, so we took a different strategy…and modeled the program along the lines of a pharmaceutical program…You need 20,000 patients, we think, to pick up a low frequency of events...and by the end of this year, we will have 20,000 patients in registries. By getting this large volume of higher quality data we hope we can address these issues."

Other expert comments included:

- "I think it (the stent thrombosis with Taxus) will be a challenge to all of us…We are extremely concerned about safety…I've seen these trials over the years well enough to say that you can't look at one study with a p-value event…You need a multiplicity of events to find out if there is biological plausibility…I think all of us need to be cautious about extrapolating from low frequency events until we see multiple source data…I was surprised that Taxus performed as well as it did in REALITY…I thought it would be clearly inferior, but the primary endpoint (of Cypher superiority) was not met…I'm a little concerned about the way the adverse events were adjudicated because a number of those cases that were called stent thromboses were actually cardiac deaths…so I think there are some ways the data get twisted…But for me, it is a cause of concern."
- "Cypher is a little better than Taxus, but Taxus is cheaper. You can go first-class or business-class…The only thing a little worrisome is the thrombosis, but I think there is a little background noise of thrombosis (with all drug-eluting stents)…If you treat 200-300 patients a year, you don't notice it (the thrombosis rate)."
- "We use Taxus and Cypher equally, and we already use Cypher for diabetic patients, so we don't anticipate a change in our stent usage. The stent thrombosis is concerning, but it won't cause a change in stent usage yet. But we need to watch that, and it will take time for the information to be digested. Ask me again at EuroPCR."
- We use half Taxus and half Cypher, but we will change to 40% Taxus and 60% Cypher. The SAT is a concern, and the diabetic data will definitely cause a change."

Dr. David Holmes of the Mayo Clinic said the ACC wants to get involved in resolving questions about the safety of drug-eluting stents, "The ACC is exploring an initiative to have the ACC enter into a partnership with the FDA to help with long-term surveillance of these terribly important device/drug combinations to document safety and efficacy. The ACC is really interested in that." ACC officials have already met to discuss this initiative, and they plan to make a proposal soon to the FDA.

The Regulatory Perspective of Drug-Eluting Stents

FDA sources indicated that no advisory committee meeting is planned to discuss drug-eluting stent safety, and it does not appear that the Taxus safety issues have made the Agency nervous about the safety of drug-eluting stents in general. A source said, "Problems are to be expected."

However, regulators are following the issue carefully, and, at a minimum, they may give more scrutiny to overlapping stents. A source said, "It is incumbent on doctors and patients to understand the risk:benefit (of drug-eluting stents)…They need to read the label and understand what a particular drug-eluting stent is approved for…Any change in treatment paradigms with drug-eluting stents should be based on data because there are always new things we are learning in this challenging field." A cardiologist involved in drug-eluting stent trials said, "The FDA is starting to be hyper-vigilant about overlapping stents." Another source pointed out that Taxus stents do not have FDA-approval for overlapping, and that could impact Boston Scientific's ability to market Taxus, given the TAXUS-V data.

Miscellaneous Topics of Interest: ICDs

Sources were divided on whether the ICD market is growing rapidly since SCD-HeFT and the CMS national coverage decision. A Delaware electrophysiologist said, "I haven't seen any change in demand." A New York electrophysiologist said, "SCD-HeFT made a big difference. We are getting more non-ischemics now."

Medtronic earlier this year announced that some batteries in its Marquis ICDs are faulty and can lose all power much sooner than expected. No patient injuries have been reported. Electrophysiologists questioned at ACC about the problem said it is a "big deal" for patients, and it is causing scheduling problems, but they were satisfied with how Medtronic has handled the problem so far. One commented, "Medtronic is good at identifying patients and working with us. They released the information (and informed us) before clinical issues made it a serious concern." Another doctor said, "It is an issue. Some patients need the device changed out, and some patients are electing to change it for their peace of mind. A huge number of devices are involved. If the failure rate gets higher than Medtronic is projecting, it could be a real disaster. Right now, it is taking a lot of lab time, impacting scheduling, slowing things down, causing a two- or three-week delay in scheduling new patients for an ICD….But it isn't causing us to change manufacturers. This kind of problem could happen to any manufacturer. What's important is how the company responds, and Medtronic has been fine."

ICD reimbursement continues to be an issue – but for hospitals more than for doctors.

♦