Trends-in-Medicine

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By Lynne Peterson

SUMMARY

More positive news for J&J Cypher stent, and the delay in FDA approval didn't dampen enthusiasm. Boston Scientific is poised to be the No. 2 entry, and its TAXUS data is holding up, though questions/worries abound. Guidant continues to stumble with a recall of its new Vision stent in Europe, an undetermined problem with its own everolimus program, and regulatory hurdles that may make it difficult to bring Biosensor's everolimus-eluting stent to the U.S. Medtronic is quietly working on its ABT-578 program and may start a U.S. pivotal trial in September 2003. Drug-eluting stents appear cost-effective in the long-term, and cath labs are prepared to bite the bullet in the short term, but pricing may be a significant factor when multiple drug-eluting stents become available.

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AMERICAN COLLEGE OF CARDIOLOGY:
DRUG-ELUTING STENTS
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Doctors questioned at the meeting about the outlook for drug-eluting stent use estimated that, on average, they would use them in 86% of patients within six months. An Indiana doctor said, "We will use 90%-95% drug-eluting stents because of the medico-legal environment. We hate J&J, but they have a better product (Cypher) now." A New Jersey doctor said, "We'll use drug-eluting stents for 100% of patients. We're afraid not to for legal reasons." An Illinois doctor said, "We'll use drug-eluting stents for 100% of patients. We have to because of the liability if we don't." Another Midwest doctor said, "We will use drug-eluting stents for 40%-60% of patients – in all cases with a great expectation of restenosis. The legal threat is absurd. You don't get sued for not using a stent now and just doing a balloon."

Drug-eluting stents are expected to decrease bypass procedures, but initially there may not be as dramatic a drop in CABG as some experts have predicted. A doctor said, "CABG may not go down because the average interventional cardiologist may not want to do complicated cases and may still refer them within his hospital for bypass." Another doctor said, "Procedure volume will go up, and CABG will go down about 25%. Re-interventions will go down, but not right away. With drug-eluting stents, we may stage surgery: do one vessel now and tell the patient to come back."

Doctors also believe patients may demand drug-eluting stents. One expert commented, "A TVR rate of 11%-12% is where drug-eluting stents get cost effective…(But) I think most patients would prefer a drug-eluting stent for every lesion, and who can blame them?"

For doctors and hospitals looking to find the most cost-effective categories for Cypher and other drug-eluting stents, several suggestions were offered:

- **Diabetics**. A speaker said, "There should be no controversy in diabetics… It is a safety concern for our patients to use drug-eluting stents in these patients. In diabetics, there is a dramatic risk of restenosis that is dramatically reduced with Cypher – a 17% restenosis rate with Cypher compared to 50.5% with a bare stent." Another speaker said, "The patients most likely to benefit from drug-eluting stents are diabetics, and I strongly urge you to use them predominantly in diabetic patients."

- **Small vessels** (≤2.5 mm diameter). A speaker said, "With a restenosis rates of 40% in small vessels, you will have a significant benefit with drug-eluting stents. The problem will be that many of the drug-eluting stents are not available in 2.5 and 2.25 mm diameters. We need smaller size drug-eluting stents."

- **Long lesions** (3.5 mm x 20-30 mm). An expert said, "With bare stents, the longer the lesion, the higher the rate of restenosis, but that is not true in drug-eluting stents. You are not penalized with drug-eluting stents, so you can use longer stents. We should start shifting to using longer stents…In our institution, we looked at last year's stent usage, and we used 1.43 stents per patient. In about 50% of patients we used one stent: 1,978 patients got one stent, 719 got two stents, and 319 got three or more stents. We all should try to find ways to limit the number of stents -- and one way may be to use longer stents." Another expert said, "Long lesions with long drug-eluting stents are the way to go."

Perspective	Preference for drug-eluting stents
Patient	DES for every lesion
Hospital	DES for discretion lesions that can be treated with one stent. Avoid DES for multivessel disease.
CMS/insurers	Use them for patients currently receiving CABG
Society and the health care system	DES should be used for patients where the expected clinical benefits are worth the additional cost

The ACC and AHA are working on guidelines for drug-eluting stent usage. A speaker suggested:

- Class 1: Diabetics; lesions 15-30 mm x 2.5-3.5 and 50%-99% obstruction.
- Class IIa: Ostial RCA, LAD, LC or protected left main lesions, parent vessel bifurcation lesion balloon of the side branch.
- Class IIb: Recanalized CTO; lesions >30 mm in length x 2.5-3.5 mm diameter; in-stent restenosis (ISR with a focal pattern).
- Class III: SVBG disease; ISR with diffuse disease; unprotected left main.

ABBOTT LABORATORIES

In addition to estrogen, dexamethasone and ABT-578, Abbott is working on an angiopeptin-eluting BiodivYsio stent with a phosphorylcholine "sponge" coating that absorbs the drug onto the stent struts. The drug elutes over a period of two weeks. First-in-Man data using a 22 µg dose from a researcher in Hong Kong found zero restenosis in 12 consecutive patients, a late loss of .48 and a %DS of 18.9%. The researcher said, "There is some suggestion that this cytostatic analog of somatostatin, an inhibitor of growth hormone with anti-proliferative effect, could promote re-endothelialization…An intermediate dose of 126 µg is the target dose and appears to be more promising."

BOSTON SCIENTIFIC

Boston Scientific had good additional TAXUS-2 data at this meeting, and there was a hint that the TAXUS-4 safety data may be better than expected, but it looks as if Boston Scientific may have slightly poorer data overall than J&J and the company already is trying to sell its paclitaxel-eluting stent on price (making it cheaper than Cypher).

The Boston Scientific Express-2 delivery problems are real, and a Boston Scientific official admitted this and said the stent is being modified. He explained, "They can't fall off. The problem occurs in only 1 in 1,500 stents. The majority of cases occurred in failed procedures where the stent was being withdrawn. We are responding by making a minor change to the crimping process *(NOTE: This change is believed to be related to the crimping pressure).* We've found that if (doctors) withdraw the stent and the guidewire simultaneously, this doesn't occur, but we want to decrease the need for doctors to learn a new technique." There also was a report that the texture of the balloon is being changed, but the Boston Scientific official did not confirm this. Boston reportedly is about to or just did submit a PMA supplement to modify the Express. Sources did not believe this change would apply to the Taxus (drug-eluting Express-2) stent.

An FDA official indicated that the Agency is unlikely to take action following non-fatal Medical Device Reports about the Express-2 if: (a) the events occurred at a similar rate in the clinical trials, (b) they are in a cluster, or (c) the company is taking action to correct the problem that the Agency feels is sufficient to warn doctors/patients or to change the product. Thus, it would appear that the FDA is unlikely to issue a warning letter at this point – unless the number of incidents increases, a patient dies as a result, or Boston Scientific moves too slowly on correcting it.

TAXUS Trials

Study	Stent diameter	# of stents per patient	Drug elution rate	Lesion length (mm)
Taxus-1	3.0-3.5	Single	SR	10 - 12
Taxus-2	3.0-3.5	Single	SR/MR	10 - 12
Taxus-3	3.0-3.5	Single	Slow	10 - 12
Taxus-4	2.5-3.5	Single	Slow	10 - 28
Taxus-5	2.25-4.0	Multiple overlap	Slow	10 - 46
Taxus-6	2.5-3.5	Multiple overlap	Moderate	18- 40

Interventional cardiologists who use the Express-2 said they still like the stent. Some have seen this problem quite frequently, and others have not seen it at all. Even those who haven't seen it, described the perceived loss of control of a device during a procedure as a huge and very scary problem. A New Jersey doctor said, "All you need is one event, and you may never use the stent again." He also described Express as "not as good as the Nir in terms of delivery."

Taxus may do better than expected, even as second-to-market. J&J's Cypher stent will capture all of the drug-eluting stent market when it first comes out, but Boston Scientific – if it is second to market – may not have a hard time convincing cath labs to switch to the Taxus stent. In fact, several sources, asked what they would do when Taxus becomes available, said they would switch to Taxus. Obviously, cath labs have not forgotten their ire over J&J's pricing of the Palmaz-Schatz stent and ReoPro (abciximab). An Illinois cath lab director said, "We'll switch 100% from Cypher to Taxus because of the history with J&J." However, not all cath lab directors felt that way. Another said, "We would stay with Cypher because it has longer data, was first on the market and has shown good safety. But Express (Taxus) is a really good stent – flexible and low profile."

TAXUS-2

Two especially interesting points were made about the TAXUS-2 data.

1. The TVF rate in TAXUS-2 may be higher than announced. The numbers do not appear to add up, unless some or all the CABG is excluded – and sources said it shouldn't be.

2. The TVR rate in TAXUS-2 may predict a 15% binary restenosis rate in TAXUS-4 because, an expert explained, the TVR is usually about two-thirds of the binary restenosis rate.

A post-hoc analysis of the six-month results of TAXUS-2 (using a Nir stent with a Translute coating) found consistent efficacy in all subgroups: diabetics, small vessels, longer lesions, females, IIb/IIIa users, multiple stenting, and direct stenting. A speaker said, "The lessons learned are that paclitaxel may be as efficient in standard risk lesions as in more complicated lesions…and it might be more effective in some high risk patient populations, such as diabetics...Why was TAXUS-2 different from DELIVER? We really think it was the polymer. When there is no polymer, you find up to 40% drug loss on expansion in bench testing, so we think a polymer carrier provides structural integrity, release control, etc."

The 12-month follow-up on TAXUS-2 showed an increase in MACE-free survival from six to 12 months, which an investigator said suggests "TAXUS prevents rather than delays in-stent restenosis." Discontinuation of clopidogrel (Sanofi's Plavix) did not affect in-stent restenosis. There was one additional TLR in the drug group, reportedly due to a readjudication of a TVR."

6-Month TAXUS-II Results

Measurement	Control	TAXUS-II
TLR	15.2%	6.3%
In-segment restenosis	25.6%	2.5%
Late loss in vessels <2.5 mm diameter	0.84	0.3
TLR in lesions ≥10 mm	15.6%	4.6%
TLR in lesions <10 mm	10.7%	1.6%
Late loss in lesions ≥10 mm	0.83	0.27
Late loss in lesions <10 mm	0.72	N/A
Females		
Restenosis	19%	0
Late loss	0.87	0.33
Restenosis in males		
Restenosis	11.8%	4.3%
Late Loss	0.75	0.26
With IIb/IIIa		
TLR	10.4%	2.5%
Restenosis	19.6%	0%
Late Loss	0.87	0.25
Without IIb/IIIa		
TLR	14.0%	3.3%
Restenosis	18.5%	1.4%

12 Month TAXUS-II Results

Measurement	Control n=270	TAXUS-2 SR	TAXUS-2 MR
Lesion length (mm)	10.6	10.5	10.2
Primary endpoint: % DS	21.89	7.85	7.85
Restenosis at 6 months	19.0%	2.3%	4.7%
MACE			
6 months	19.8%	8.5%	7.8%
12 months	21.7%	10.9%	9.9%
Stent thrombosis	0	0.8%	0.7%
Death	0.8%	0	0
Q-wave MI	1.15	0.8%	1.5%
Non-Q wave MI	4.2%	1.6%	N/A
TVR overall	17.5%	10.1% (nss)	6.9% (p=.003)
TLR	14.4%	4.7%	3.8%
TVR remote	3.0%	3.1%	1.5%
CABG	1.1%	3.1%	1.5%
MACE-free survival	10.5%	8.8%	

TAXUS-4

This data will be presented at 2 pm on September 15, 2003, at TCT. However, a speaker warned: "Pay attention to the MIs at 30-day in TAXUS-4. There may be something to distal

vessel passivation that may be an issue." A source explained that he was hinting that paclitaxel may prove somewhat MI-protective.

TAXUS-4 Patient Characteristics

Measurement	Group A	Group B
LAD	40.5%	40.8%
# stents	1.07	1.05
2.5 mm	20.7%	21.1%
3.5 mm	29.6%	31.9%
16 mm length	62.8%	N/A

Comparison of TAXUS-4 and SIRIUS

Measurement	TAXUS	SIRIUS
16 mm length	62.8%	N/A
Reference vessel diameter	2.75	2.8
Average lesion length (mm)	13.4	14.4
Average sent length (mm)	21.6	21.4
1 stent only	91.2%	65%

TAXUS-5

This trial has enrolled 271 patients, and the FDA recently opened it up for the full enrollment of 1,108 patients. A researcher said, "Garden variety cases will be closed soon, and then we mostly will be enrolling complex lesions." The second phase of TAXUS-5 will look at in-stent restenosis in 528 patients, comparing the Express-2 to beta brachytherapy. The trial design has been submitted to the FDA, and investigators hope to get approval soon to start this.

MISCELLANEOUS

New data shown on rhodamine-labeled paclitaxel showed uniform distribution of the drug on the stent.

GUIDANT

Guidant has several problems that were the topic of discussions at this meeting, including:

1. Guidant announced the recall of its bare Vision stent in Europe. There was quite a buzz about this. Asked how long Vision would be off the market, a Guidant official indicated the company does not know yet exactly what is wrong with the stent, "There is no timeline yet. We first need to find out what went wrong."
2. Reliable sources confirmed that Guidant has a problem with the polymer it was using for its own everolimus-eluting stent program.
3. Sources suggested that Biosensors and Guidant probably are underestimating the regulatory hurdle of getting a biodegradable stent approved in the U.S., and Biosensors officials were, not surprisingly, unaware of the key role that CDER plays in the approval process.

EVEROLIMUS

Sources agreed that there is no problem with everolimus, though there is some problem with the Vision/everolimus stent program (not the Biosensor program). The cause of the Vision/everolimus problem has not yet been definitively determined, but sources all agreed there is not a problem with everolimus. Biosensor has studied its everolimus-eluting stent in more than 100 pigs, and officials insisted there have been no safety questions raised. A Biosensor's official said, "Right now more (animal) trials are ongoing for FDA filings on production validation products." Sources outside Guidant and Biosensors agreed that everolimus safety is not an issue.

There were several theories about the Vision/everolimus problem, and the predominant one was contamination. An expert said, "A foreign body response was observed in a small subset of animals. Possible causes have been identified, and studies are in progress to validate these findings."

In the Vision/everolimus program, three doses are being tested: 90 $\mu g/cm^2$, 190 $\mu g/cm^2$, and 380 $\mu g/cm^2$. In a pig study, Biosensor's everolimus stent shows a low % stenosis in all groups, evidence of a drug effect and no necrosis. A speaker said, "(Biosensor's) everolimus is equivalent to Cypher in inhibition of neointimal hyperplasia (% stenosis) in the low injury porcine model." Dosing of everolimus is comparable to sirolimus but not identical. J&J has tested sirolimus up to a dose of 1200 µg, but Biosensor has only tested everolimus to about 600 µg.

Several interesting things came out at the ACC about Guidant's drug-eluting stent efforts, including:

- Guidant reportedly has not tested Biosensor's coating and everolimus on the Vision stent. A Biosensor official said, "That would be worth trying…But they (Guidant) are leaning toward our polymer."
- Biosensor's does not plan to bring the S-stent to the U.S. without a drug partner – and that could be someone other than Guidant. However, officials insisted the S-stent will not come to the U.S. as a bare stent.
- The stability of sirolimus on the Biosensor's stent is different from Cypher because of the difference in the two polymers, sources explained. But Biosensor officials pointed out that their everolimus stent does not need to be frozen; rather, it can be stored at room temperature.

FUTURE TRIALS

The FUTURE-1 data on everolimus eluted by Biosensor's bioabsorbable S-stent (this is the Challenge stent, but Guidant wants Bisosensors to refer to it as the S-stent from now on) looked very good, and it compares favorably with RAVEL and TAXUS-1. A researcher said, "In theory and in the animal data, it is very promising because it has some unique

capabilities, including drug loading and release patterns and it is asymmetrically coated, so more drug is released to tissue and less to the bloodstream." However, other experts warned it is a very small trial and very preliminary.

FUTURE-1 Results

Measurement	Everolimus n=26	Control n=15	p-value
MACE at 30 days (primary endpoint)	0	0	Nss
6-Month Safety			
MACE composite	7.7%	8.3%	---
Death	3.8 (COPD)	0	Nss
MI	0	0	Nss
TLR	3.8%	8.3%	---
TVR	1 at 184 days	1 at 194 days	---
6-Month In-Stent			
% DS	2.73%	27.2%	p<0.0009
MLD	2.98	2.11	p<0.0001
Late loss	0.1	0.83	p<.001
Restenosis (secondary endpoint)	0	9.1%	Nss
Acute gain	1.95	1.82	Nss
6-Month In-Segment			
MLD	2.45	1.93	---
% DS	20.7%	33.9%	---
Late loss	.17	.26	---
Restenosis	4.0%	9.1%	---

In FUTURE-1, 2.5-4.0 stents 14-18 mm in length were available, and up to two stents could be used. Diabetic patients were excluded. The drug was undetectable in the bloodstream at 30 days follow-up in a two-patient PK study (the drug falls below the limit of detectability – <0.2ng/ml -- within days).

DELIVER Trial

The DELIVER failure was reviewed, and speakers emphasized that the drug appears to work -- just not at the dose and with the delivery system tried. One expert said, "The drug works but the magnitude is not at the level of some other drug-eluting platforms."

Guidant researchers tried to put a positive spin on the failure of the DELIVER trial, comparing the Achieve stent (a Penta stent eluting paclitaxel) to a bare Penta stent. There was no statistically significant difference in the demographics of the two groups. A researcher said, "There was definite evidence of a decrease in late loss and restenosis with Achieve…There was a significant decrease in neointimal hyperplasia but the magnitude of the effect was insufficient to meet the pre-specified endpoints. A drug-drug interaction with IIb/IIIa use is suggested but needs further study. There was a modest effect, an excellent safety profile, and a higher dose might have had better efficacy results…The formulation and the delivery system are very safe."

DELIVER 270-Day Results

Measurement	Achieve stent	Bare Penta stent	p-value
RVD	2.85	2.77	p<.05
Lesion length	11.7	1.1	p<.05
In stent late loss	.82	.98	p<.05
MLD at 240 days	2.08	1.86	p<.001
Restenosis	16.7%	22.4	Nss
Death at 270 days	1.0%	1.0%	Nss
MI	1.2%	1.0%	Nss
TLR	8.1%	11.3%	---
TVF	11.9%	14.5%	---
Safety at 30 Days			
MACE	1%	N/A	---
Thrombosis	0.4%	N/A	---
Aneurysm	0.9%	N/A	---

Measure	FUTURE-1	First-in-Man Cypher	RAVEL	TAXUS-1
MLD	2.98	4 months: 0.3% 12 months: 2.2%-2.3%	2.43	2.97
Late loss	0.1	0.09 - 0.1 at 4 months 0.08 - 0.11 at 12 months	0.001	0.35
% DS at 6 months	2.73%	Fast release: 4.0 at 12 months	15%	13.3%
Binary restenosis	4.0%	0	0%	0%
Clinical events at 6 months	1 COPD death, 1 TLR, 1 TVR at 184 days	N/A	2 Q-MI, 1 CABG, 2 non-Q MI	0
MACE	7.7%	3.3%	3.3%	0%

DELIVER 30-Day Safety Results

Measurement	DELIVER-II
Death	0.72%
Total MACE	3.6%
TLR (PCI)	0.59%
Q-wave MI	0.79%
Non-Q wave MI	1.44%

Comparison of Demographics of DELIVER-II and SIRIUS Trials

Measurement	DELIVER-II	SIRIUS
Diabetics	28.1%	25%
CTO	0	21%
Bifurcations	0	35.4%
Restenotic	0	34.5%
Multivessel disease	40%	50.6%
Stents per patient	1.4	1.48
IIb/IIIa use	60%	20.6%

Miscellaneous

- Guidant and Biosensors will work jointly to develop a everolimus-eluting stent for the Asian market.
- Several speakers said Novartis is working closely with Guidant on development of an everolimus-eluting stent. One commented, "There is a real cooperation between Novartis and Guidant."

JOHNSON & JOHNSON

The news was mostly positive for Cypher at ACC:

- 90.1% three-year event-free survival in the First-in-Man Cypher trial.
- More than one speaker commented that you can improve the results with Cypher by using one longer stent instead of two overlapping stents.
- The C-SIRUS, E-SIRIUS, SECURE and long-term RAVEL data all looked good.
- The delay in Cypher approval by the FDA has not dampened enthusiasm for this drug-eluting stent.

J&J plans to start REALITY, a head-to-head trial of Cypher and Taxus (Boston Scientific's paclitaxel-eluting Express-2 stent) in Europe in May 2003.

- At least 1,000 patients will be enrolled in Europe, the U.S. and Asia, starting in May 2003. The trial is powered to show superiority of Cypher, with the assumption of a restenosis rate of 15% with Taxus and 8% with Cypher. The primary endpoint is binary restenosis at 8 months, not late loss or TVR.
- Stent diameters from 2.25-3.5 will be used. Most Taxus data has been on a 3.0 stent, and J&J reportedly feels it can win in small vessels and that's why the very small sizes are included and will be emphasized.
- Data is expected to be available at TCT 2004.
- JNJ is confident of winning, but they also may have been forced into the study because they wanted a controlled study and reportedly a European researcher was going to do it on his own trial and present it if J&J didn't sponsor the study, sort of forcing J&J into the study.

The drug-eluting stent cost-effectiveness study that Dr. Patrick Serruys is conducting in Rotterdam will not be analyzed in time for the EuroPCR meeting in May 2003, but a preliminary, partial analysis will be presented there. The final analysis may not even be ready for the European Society of Cardiology meeting in August 2003.

RAVEL

Two-year follow-up data from the RAVEL trial shows that Cypher continues to have an effect long-term in these select patients.

RAVEL Results at Two Years

Measurement	Sirolimus n=120	Control n=118
Restenosis	0	26%
Late loss	-.01	0.8
%DS	15%	37%
MLD	2.42	2.54
Death	5%	2.5%
Event-free MACE	90.0%	80.5%
Q-wave MI	1.7%	0
Non-Q wave MI	0.8%	3.4%
TL-CABG	1.7%	0
TL-RPTCA	0.8%	13.6%

Cost Effectiveness

The cost effectiveness study of the Cypher stent concluded that Cypher is "highly cost effective for the target population of the SIRIUS trial." The intent-to-treat analysis assumed a bare stent price of $1,000 and a Cypher price of $3,000. A subgroup analysis also found every subgroup below the U.S. threshold for cost-effectiveness. A speaker said, "For patients who require three or four stents for single vessel disease, then there are issues with cost and you need to be careful…but with 1.4 stents on average, across the board it looks pretty reasonable…The only area with questions about cost-effectiveness are patients with two or three focal lesions where you get pretty good results with a bare stent…and I'm not sure if, for them, we will get the same the cost-effectiveness."

Cost Effectiveness of Cypher Stent in SIRIUS Trial

Measurement	Sirolimus n=533	Placebo n=525	Delta	p-value
Stents implanted	1.4	1.4	0	Nss
Cost	$7,252	$4,395	$2,856	p<.001
Initial hospital costs	$11,345	$8,464	$2,880	p<.001
6 mo FU	N/A	N/A	($1,106)	N/A
Primary endpoint: Follow-up costs from discharge to 12 mo.	$5,468	$8,040	($2,571)	p<.001
12 month total	$16,813	$16,504	$309	Nss

Subgroup Analysis of Cypher Cost-Effectiveness

Measurement	Change in One-Year Cost
Diabetics	$411
No diabetes	$369
LAD	$483
No LAD	($76)
RVD >3.0	$993
RVD <2.5	($1,256)
Length <15 mm	$772
Length >20 mm	($1,055)

Measurement	Cost Difference	Cost per repeat revascularization avoided	Cost per QALY gained
U.S. threshold	---	<$10,000	<$50,000
Primary analysis	+$309	$1,650	$27,500
Longer stents available	+$136	$727	$12,116
Longer stents + no additional clopidogrel	-$96	Dominant – improved outcome and reduced costs	Dominant – improved outcome and reduced costs

E-SIRIUS

The real-world, European E-Sirius trial showed dramatically better results with Cypher than a bare BX Velocity. The primary endpoint of MLD was 2.2 with Cypher and 1.32 with bare stent, the in-stent restenosis was 3.9% vs. 42.3%, and the in-lesion restenosis as 5.9% vs. 42.9%.

E-SIRIUS 8-Month Angiographic Efficacy Results

Measurement	Cypher	Control	p-value
Number	175	177	---
Average lesion length	14.9 mm	15.1 mm	---
Overlapping stents	34.3%	30.5%	---
Device success	100%	99.4%	---
# of stents per patient	1.6	1.5	Nss
MLD (primary endpoint)	2.2	1.32	N/A
Mean late loss	0.2	1.05	p<0.001, a treatment effect of 81%
In lesion MLD	0.19	N/A	---
%DS	24.3	48.7	p<0.001
In-stent binary restenosis	3.9%	42.3%	p<0.001, a 91% decrease
In-lesion binary restenosis	5.9%	42.9%	p<0.001, an 86% decrease
Proximal margin restenosis	2.1%	8.8%	---
Distal margin restenosis	2.0%	11.0%	---
Safety			
MACE	8.0%	22%	---
Stent thrombosis	1.1%	0	Nss. Both subacute thrombosis.
Major bleeding	3.4%	2.3%	Nss
Death	1.1%	0.6%	Nss
MI	4.6%	2.3%	Nss
Emergent CABG	0	0	---
TLR	4.0%	20.9%	p<0.001, an 81% decrease
9-month survival free from MACE	91.9%	71%	---
9-month survival free from TLR	95.9%	78.3%	---

C-SIRIUS

The eight-month angiographic and nine-month clinical results of the 100-patient Canadian C-SIRIUS trial showed that Cypher works very well in long lesions (15-32 mm) in small vessels (2.5-3.0 mm). C-SIRIUS treated patients with an average lesion length of 14.5 mm and 2.65 reference vessel diameter (RVD). Up to two stents per patient were permitted by the trial protocol, and 24% of patients in the trial were diabetics.

C-SIRIUS Results at 8 Months

Outcome	Bare Stent	Cypher	Change	p-value
In-stent MLD	1.5	2.46	Up 64%	p<0.001
In-stent LL	1.09	0.09	Down 91%	p<0.001
In-stent binary restenosis	41.9%	0	Down 100%	p<0.001
In-lesion MLD	1.41	2.16	Up 53%	p<0.001
In-lesion LL	0.76	0.1	Down 87%	p<0.001
In-lesion binary restenosis	44.2 %	2.3%	Down 95%	p<0.001
TLR	9 patients	2 patients	---	N/A
Non-Q wave MI	2 patients	1 patient	---	N/A
Q-wave MI	0	0	---	Nss
Death	0	0	---	Nss
Late thrombosis	1 patient	0	---	N/A
MACE-free survival	82%	96%	Down 15%	p=.027

Other Cypher Data

In the SECURE Compassionate Use Registry, Cypher worked very well in brachytherapy failures, and the results in RESEARCH, a registry of Cyphers used to treat in-stent restenosis (ISR), showed better results with Cypher than a bare stent. RESEARCH was conducted in the Netherlands, and the Cypher patients were complex.

SECURE: Compassionate Use Registry

Measurement	Brachytherapy failures n=62	No radiation failures n=15	P-value
TLR	21.5%	8.8%	p=0.13
TVR	25.3%	11.8%	p=0.1
Non TVR	8.4%	8.8%	Nss
Stent thrombosis <30 days	1.2% (1 patient)	5.9 % (1 patient with multiple events)	p=0.2
Stent thrombosis >30 days	0	0	Nss

Bifurcations

This was a sour note for J&J and Cypher. The SIRIUS Bifurcation study found that Cypher "reduced restenosis in the main vessel to 6.1% and nearly eliminated in-stent restenosis." However, the 22.7% restenosis rate in the side branch with Cypher was described as "disturbing." A speaker said he thinks it was due to incomplete stent coverage, but said the results do not justify routine Cypher double-stenting in bifurcations, "I don't think we can answer whether we need two stents or a stent plus a balloon. The lack of an advantage in the group receiving two stents suggests that if a successful result can be achieved with a balloon alone, there is no advantage to routinely implanting a Cypher in the side branch."

6-Month Angiographic Results of the SIRIUS Bifurcation Study

Measurement	Stent+Stent n=63	Stent+PTCA n=22
MACE		
Q-wave	1.6	4.5
Non-1	9.5	4.5
TLR	9.5	4.5
Death	1.6	0
Late loss (in lesion, main vessel)	.27	.14 (p=nss)
Late loss (in-lesion, side branch)	.52	.27 (p=nss)
In lesion restenosis (main vessel)	6.0	6.2
In lesion restenosis (side branch)	24.0 (p=.74)	18.7

RESEARCH Registry: Cypher Use for In-Stent Restenosis

Measurement	Control n=66 consecutive patients	Cypher n=57 consecutive patients
Demographic differences		
Previous brachytherapy	6%	25%
Mehran Type II-IV (lesion complexity)	22%	46%
Results		
Preliminary (65%): Survival free of re-intervention	90.9%	87.7% (p=.4)
Re-intervention in previously irradiated vessels	N/A	21.4%

There was an Italian poster on Cypher that was getting some attention. It was a study at Dr. Antonio Colombo's hospital in Milan, Italy, looking at 322 consecutive Cypher patients. The results were not nearly as good as in SIRIUS, but the presenter said these were very complex patients. There were four thromboses, all during the procedure.

Italian Cypher Study

Measurement	Cypher
30 day MACE	5.1%
In-hospital TVF	3.7%
6 month out-of-hospital TVF	17.9%
Total 6-month TVF	21.6%

MEDTRONIC

Medtronic reportedly will begin its pivotal drug-eluting stent trial in September. It will be an international trial and is expected to enroll about 1,800 patients, with about 500 from the U.S. It is a superiority trial, comparing an ABT-578-eluting S-8 stent to a bare sent. FDA officials have indicated that a bare stent comparator trial probably would not be accepted after the first drug-eluting stent is approved, so it is not clear how Medtronic will be able to do this. It makes sense that the FDA would approve the protocol now since there is no approved drug-eluting stent, but once Cypher is approved, it is possible that Medtronic will have to change this trial design.

JOMED

Jomed is continuing to work on a tacrolimus-eluting stent. Given the high MACE rate (>30%) with its ceramic coating, Jomed is now putting tacrolimus on a FlexMaster stent without a carrier matrix, using a 230 µg dose, in the PRESENT-2 trial. Ninety-five patients have enrolled in this 250-patient trial. A speaker said, "So far, no patients have come back – and that is good news given the sobering (MACE) news from the first two trials."

MISCELLANEOUS STENT INFORMATION

➢ The U.K.'s NICE Committee met this week to discuss drug-eluting stents. A cardiologist who presented to the committee said they were impressed with the level of detail presented, which they often don't see from other specialties. The source said the presentation was helped by the fact that restenosis is so high with a bare BX Velocity, because it helped make the case for cost-effectiveness, which he thought would have been harder to make if some other bare stents had been the comparator. Overall, he thought the meeting went fairly well, but he is convinced that NICE will not approve drug-eluting stents for all patients.

➢ The President of the ACC said the ACC, in conjunction with the American Heart Association, is currently updating the guidelines for interventional cardiology, and those guidelines are expected to be completed before the end of this year. They will include a section devoted to drug-eluting stents. He said, "This is very rapidly evolving technology and procedure and you have to figure out when you are closest to the truth while the technology evolves. The guidelines help inform, but ultimately the decision is up to the physician and the patient."

➢ An IVUS expert said that in 88% of cases, malapposition occurs on the ***normal*** wall, not the plaque wall."

Other drugs being explored for use on a stent:

- **Nitrous oxide** by Blue Medical (the Noblesse trial).
- **Estradiol** by Abbott/BiodivYsio (the EASTER trial)
- **Dexamethasone** by Abbott/BiodivYsio (STRIDE trial).
- **Mycophenolic acid** (MPA) by Aventec (IMPACT trial).
- **Epothilones**. Kosan is trying to shop its epothilone-D for use on drug-eluting stents. In cancer, the drug is still in Phase I trials (Phase II are supposed to start this year), so the company appears to be a little aggressive here. At the AACR meeting last year, we learned that (a) Kosan was in discussions with a stent company for use of Kosan's FK-506 and (b) Kosan has a rapamycin analog that it was looking at for use on a drug-eluting stent.
- **Statins**. Terumo is working on simvastatin, but there was no data about that at this meeting.

Comparison of Different "Limus" Analogs

	Everolimus	Sirolimus	ABT-578
Intended pharma indication	Chronic & acute rejection of heart, kidney, lung	Chronic & acute rejection of heart and kidney	None
Receptor binding	2.0	0.6	N/A
Smooth muscle cell inhibition	0.9-3.6	0.4-3.5	N/A

STENT COATINGS AND POLYMERS

A cautionary note on polymer was sounded by pathologist Dr. Renu Virmani. She warned, "No polymer is truly benign… and bio-erodable stents are not as benign as you might want to think…At 28 days they may be healed, but at 90 days when they are degrading, there is inflammation. I believe no

polymer is truly benign…In man, you need 18 months to two years for (wound) healing."

Among the coatings being investigated:

- The polymer on **Abbott's** BiodivYsio stent isn't evenly distributed; it is 1 micron thicker on the vessel side of the stent.
- **Blue Medical** is using a PEA/polyester amide coating on its Noblesse stent (an SS Gendyl stent) which elutes nitrous oxide. Blue Medical also has a kind of biodegradable stent, with the drug embedded in the polymer. There is an uncontrolled bolus first and then a controlled release of conjugated drug as each polymer layer is uncovered.
- **Biosensor** uses a biodegradable PLA coating for its polymer. It is an ultra-thin coating, typically one-third the weight of a durable coating. The coating and the drug are co-released, with 90% release in four weeks. The polymer reportedly has high drug carrying capacity, high bioavailability of the drug on ablumenal surfaces, and when drug is gone, the coating also is gone.
- **GCIB direct drug deposition** – a spray coated process using a carbon matrix. This might reduce local reactions seen with polymers.
- **Igaki-Tamai** is still working on a poly-l-lactic acid (PLLA) degradable stent.
- **Jomed** has abandoned the use of a ceramic coating for drug-eluting stents after cracks were found in some coated stents.
- Surmodix' second polymer customer reportedly is Jomed.
- The **Sorin** stent had deep drug reservoirs.

CONOR MEDSYSTEM continues to get attention and may have the technology of the future for drug-eluting stents. In the Conor drug-eluting stents, there are more than 580 little, laser cut holes or reservoirs in these stents that can be filled with one or more different drugs. Ductile hinges were added to take the stress, so the holes do not deform from pressure causing the drug to leave the stent early. Drugs are layered into the holes with multiple layers of biodegradable/ bioresorbable polymers separating them, allowing timed drug delivery and/or multiple drug delivery.

These stents can be designed to release two different drugs in two different directions -- one to the mural side and one to the luminal side. There also are burst and slow (10-12 day) release forms. The Conor Dose 1 is similar to the moderate-low dose paclitaxel used by Boston Scientific, and the Conor Dose 2 is similar to the slow release paclitaxel used in TAXUS-2. A researcher said, "The key difference between this and (Boston Scientifics' program) is the residual drug on the stent. After 10, days there will be no more drug on the Conor stent."

- PISCES is the 120-patient, first-in-man trial of four doses of paclitaxel on this stent, evaluating less burst release and more slow release (linear release).
- SCEPTER is the European pivotal trial.

Other restenosis approaches:

1. **Tissue engineering** -- the covering of a stent with endothelial cells.
2. Orbus is working on endothelial progenitor cell (**EPC**) **capture** technology, using a gelatin coating with a CD34 monoclonal antibody. A speaker said, "This is the first demonstration of a successful technique for passivation of an intravascular device by in vivo autoseeding…Maybe today we are starting another new era -- the auto-seeding technology vs. the drug-eluting stent…If it works, we can eliminate the drugs and enter a new era."
3. **Hyperbaric oxygen therapy** to reduce restenosis. A small study had some very interesting results: a TVF of 1% vs. 10% with placebo (p=.023).
4. **Oral rapamycin**. This concept is still alive, if not well.

THE REGULATORY PERSPECTIVE

A brief presentation by an FDA official revealed that once the first drug-eluting stent is approved:

- The FDA will review the appropriateness of granting expedited approval for other drug-eluting stents. Thus, it appears Boston Scientific was able to get expedited review because J&J hadn't yet been approved when Boston submitted Taxus.
- New drug-eluting stents may be able to do equivalence trials using a surrogate endpoint, but they must prove the drug provides an additional benefit over and above the stent.
- Data gathered as part of post-marketing surveillance cannot be used for expand indications.
- Superiority trials would have to be huge, so future drug-eluting stent trials probably will need to take one of the following approaches, and a speaker suggested the key is adopting the angiogram as a surrogate for clinical outcomes.

  1. **Strategy I**: U.S. dominant
     - U.S. *non-inferiority* trial with 1,800-2,000 patients, PLUS
     - European *superiority* study of 500-8,800 patients, angiography-based.

2. **Strategy II**: European dominant
   - European *superiority* trial of 1,200 patients
   - U.S. *non-inferiority* trial of 500-800 patients, angiography-based.

The differences in the way CDER approves drugs and CDRH approves devices was highlighted at another ACC session. Ray Lipicki, former director of the FDA's Division of Cardio-Renal Drug Products said:

- Approvals of NMEs have been "perking along pretty constantly" for the last 15 years.
- CDER generally does not accept biomarkers or surrogate endpoints. Anti-hypertensives are one exception. Blood pressure and cholesterol have been accepted as surrogates, but their acceptability is decreasing.
- Instructions for use (dose and dosing interval) are increasingly important to the FDA.
- Morbidity and mortality also are increasingly important. He called them an "audible rumble," but warned they may increase to thunderstorm or even hurricane proportions.
- Two trials are required with a p-value ≤.05 – or one trial with a p-value ≤.00125.
- The burden is on the sponsor to prove safety, not the FDA to prove something is unsafe.
- The QT focus at the FDA is getting a little "extreme."
- Combination products are considered by the FDA to be a "convenience," so they face some additional hurdles:
  - All ingredients need to show they contribute to the clinical effect. A+B must be better than A or B.
  - The product should not change the practice of medicine. That is, convenience shouldn't make doctors prescribe the wrong dose or wrong combination of doses. Thus, all doses and all combinations need to be available.

Dr. Bram Zuckerman, Director of CDRH's Division of Cardiovascular Drugs said his division uses different endpoints than CDER. He commented, "While we (at CDRH), in philosophy, are moving toward a drug standard, we are not there yet, and it was not Congress' intent for us to be there for all products." Among the comments he made were:

- Devices must have adequate manufacturing controls and appropriate labeling, points that he felt are sometimes forgotten but can be just as important as proper clinical trials.
- A one-size fits all approach does not work in device approvals.
- CDRH uses a more risk-based strategy that allows other clinical trial design paradigms, and CDRH doesn't necessarily reach the same conclusions as CDER.
- Over the next decade, CDRH expects to require more randomized clinical trials "as next generation technology becomes more complex and difficult to evaluate."
- On drug-eluting stents:
  - The measures of restenosis are highly case-mix sensitive (measured and unmeasured variables).
  - Large scale meta-analytical databases may help in approved new balloon-expandable stainless steel stents but are likely too crude for anti-restenosis therapies.
  - An even more challenging (approval) than Cypher will be an NME on a stainless steel stent…Drug-eluting stents are moving toward additional NMEs, and there are important safety questions that will need to be resolved pre-approval rather than post-approval.

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