



# Trends-in-Medicine

May 2003

By Lynne Peterson

## SUMMARY

European use of drug-eluting stents is growing about 1% a month, and Boston Scientific's Taxus has captured nearly 40% of the market with pricing about 20% below Johnson & Johnson's Cypher. Taxus is expected to capture most of the U.S. market if the restenosis rate is equal to or lower than for Cypher. ♦ Serious questions about the safety of Taxus were raised: (1) >90% of the drug remains on the stent past 180 days, and (2) peri-stent vessel thickening was observed by IVUS in TAXUS-2 at 12 months. ♦ A new issue also has come up with Cypher – focal lesions, which may be related to the rather stiff stent design.

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## Trends-in-Medicine

Stephen Snyder, Publisher

1879 Avenida Dracaena

Jensen Beach, FL 34957

772-334-8387 Fax 772-334-0856

[www.trends-in-medicine.com](http://www.trends-in-medicine.com)

## Paris Course on Revascularization (EuroPCR)

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European use of drug-eluting stents is increasing slowly but surely. In Germany, however, usage is not expected to grow significantly in the near future because Germany was described as unwilling to accept the higher cost of drug-eluting stents. A speaker said, "We can break down the market price by pushing 'equally effective but less costly' products by 'newcomers'...We should talk with insurance companies and health authorities (about reimbursement), but we should recognize that government reimbursement may condone the fact that the industry already may be making a major profit with this technology."

### European Drug-Eluting Stent Market (in revenue units)

Country	% of EU market	% of market launched	% market penetration	DES market share
<b>As of the end of April 2003</b>				
Total EU	100%	34%	12%	32%
Germany-France	51%	30%	5%	23%
Italy-Spain-Portugal	20%	15%	20%	12%
Rest of EU	29%	58%	18%	51%
<b>As of the end of May 2003</b>				
Total EU	100%	N/A	13%	>40%
Germany-France	N/A	N/A	6%	N/A
Nordic countries	N/A	N/A	N/A	68%

\* Source: Boston Scientific

Sources didn't agree on how much European market share Taxus has in drug-eluting stents. Boston Scientific officials claimed Taxus had 40% share; J&J officials put it closer to 20%. However, there is no question that Taxus is gaining market share in Europe, and that is likely to continue.

### Stent Market Share by Company \*

Measurement	Boston Scientific	Guidant	Johnson & Johnson	Medtronic	Others
1Q2002	27%	25%	25%	8%	15%
1Q2003	36%	21%	20%	7%	16%
Stent sales as % of revenue	32%	72%	62%	57%	N/A
Balloon market share	59%	~33% †	N/A	N/A	N/A

\* Boston Scientific estimate † Guidant estimate

Even Cypher investigators are using more and more Taxus – and the reason is price. A Cypher researcher who currently is using Cypher for 60% -65% of his stent patients, said, “I just got Taxus. I’m not using it much yet, but I will use it...I have been using Taxus for lesions >3.0 mm because, until recently, Cypher was not available in that size, but I use Cyphers for overlapping stents. At the end of the day, price will be the issue, and Boston Scientific is sitting pretty on that...As a clinician, I’m happy for the competition...We benefit from Taxus pricing.”

### Inter-Continental Market for Taxus (in revenue units)

Launches	% of inter-continental market	% of market launched	% of market penetration	DES market share where launched
Total launches	52%	36%	15%	65%
March launches	31%	52%	21%	66%
April launches	21%	14%	7%	61%

\* Source: Boston Scientific

In the U.S. doctors predicted that Taxus would cannibalize the Cypher market if and when it is approved. The general consensus was that Express<sup>2</sup> is a better, more deliverable, more flexible stent than Cypher. Thus, even if Taxus is priced only 5% -10% lower than Cypher. The predictions are:

- 90% -100% market share for Taxus if it has a lower rate of restenosis in TAXUS-4 than Cypher did in SIRIUS.
- ~90% market share if it is equivalent to Cypher.
- 30% minimum market share if it has a higher restenosis rate than Cypher but is still FDA-approved.

A Medtronic official predicted that Boston Scientific would take a majority share of the U.S. market with its Taxus stent if it gets FDA approval – but *not* by significantly undercutting the Cypher price. He doubted that Boston would discount Taxus more than 5% below Cypher in the U.S. despite heavier discounting in Europe. However, he suggested Boston may

offer volume discounts or bundle products using the P3 approach that Guidant successfully used in the past – a strategy that he said J&J could not utilize. The reason he thought Boston would do well is that it has a “very good, very powerful sales force, a much stronger sales force

### The outlook for Medtronic and Guidant.

Sources at Medtronic said the company hopes to keep its sales force until the launch of its drug-eluting stents by having them focus on

balloons and guidewires for now. A Medtronic official said the company has balloons sized for every Cypher stent – which J&J doesn’t have yet – and he predicted this would help Medtronic grow its balloon business over the next couple of years.

Similarly, a Guidant official said his company also plans to do everything it can to retain its sales force. He said sales reps will focus on bare stents, balloons, guidewires and remind customers that Guidant has a drug-eluting stent program underway. He pointed out that if that isn’t enough, and top sales people think of leaving, they could be compensated for directing business to ICDs and sales commissions adjusted accordingly, noting that those sales could be easily tracked. He made it clear that Guidant is not going to lose its top sales people.

These strategies may work. Several doctors said that they plan to boost their purchases of guidewires and balloons from Guidant and/or Medtronic to help support those companies until they have a drug-eluting stent on the market. One said, “Patterns of loyalty and habits are shifting. We will use Medtronic balloons and guidewires in order to keep Medtronic in the game. It will be a small shift away from J&J/Cordis...It is in our interest to have competition around...and we will try to keep them alive with purchases of balloons and guidewires.”

### How do Boston Scientific’s Taxus stent and Johnson & Johnson’s Cypher stent compare?

A Boston Scientific official said, “The marketplace has told us that plus or minus a couple points on TLR or binary restenosis won’t make a difference. If one is 9% and the other 10%, that is equivalent. If there is a two to three point difference, that is still equivalent. More than three or four points, and we probably would have some selling to do.” A doctor who uses both said, “In terms of late loss, Cypher is a better tool, but clinically there is little difference. There is less late loss with Cypher, but whether it matters at the end of the day in terms of clinical issues is not clear.”

REALITY, the head-to-head trial comparing Taxus and Cypher that is underway got mixed reviews at PCR, and there

were indications that even if it is positive, it may not give Cypher much help in overcoming a cheaper Taxus price. A doctor said, "It's a good trial. I like the idea...and if Cypher

#### Boston Scientific Survey of Physician Attitudes about Taxus and Cypher

Type of doctor	Taxus performance better than Cypher	Taxus performance comparable to Cypher	Taxus performance less than Cypher
Aggressive (n=43)	13%	76%	11%
Conservative (n=82)	5%	34%	61%

ends up showing it's a better product, that should influence us – at least for the worst patients." He said the situation then would be similar to what happened in Europe with ReoPro (Lilly, abciximab) – superior efficacy data but a higher price, so use was restricted to high risk patients. A Boston Scientific official said, "Physician feedback on J&J's REALITY trial is that:

- It's unlikely to achieve its endpoint.
- The design assumptions are being questioned.
- The majority of participants I spoke with said they are participating because the stents are free.
- The data will be available in mid-2004."

**PCR Live Cases.** Dr. Jean Fajadet presented 288-day follow-up information on the 60 patients who were live case studies at PCR2002 (92% with clinical follow-up and 37% with angiographic follow-up).

Event	Outcome
Survival	100%
Event-free survival	61.9%
MACE	34%
MI	5%
Repeat revascularization	27.3% (21.8% PCI 5.5% CABG)
<b>MACE</b>	
All patients	34%
Diabetics	30%
Bifurcations	33%
Left main	50%
SVG	40%
Drug-eluting stent revascularizations	22%

One of the most interesting cases was a TAXUS-4 patient who got two Taxus stents (one 3.0 x 24 mm and another 3.0 x 16 mm) for a long, diffuse RCA lesion. She was a smoker who had an MI treated with thrombolysis. Nine months later (February 2003), she presented with recurrent attacks of angina, and angiography revealed edge stenosis, "There was clearly diffuse atheroma on the portion proximal to the stent, with very severe narrowing on the proximal edge...We stented

the restenosis (with a bare Express<sup>2</sup> stent)...The take home message is that with the use of drug-eluting stents, the selection of the stent length is of ultimate importance, and you must consider the full lesion and peri-lesion area coverage...(and) with a very, very long lesion with diffuse vessel disease, it is difficult to make the choice of the stent length. There is no available data yet on the 'Full Metal Jacket' approach."

#### Some of the key topics at this meeting were:

**Drug-eluting stent usage.** Dr. Patrick Serruys suggested that it is unethical not to put a drug-eluting stent in every patient, but other speakers took issue with that position, arguing that it is unethical to put drug-eluting stents in everyone. A speaker said, "I was irritated when Dr. Serruys said it is unethical not to treat all patients with drug-eluting stents. Don't you get irritated? It is unethical not to make choices."

Category	Attitude toward drug-eluting stents
Patients	Everyone should get a drug-eluting stent
Health care system	For patients where the expected clinical benefits are worth the additional costs
Health care insurance	For patients currently receiving CABG.
Hospital administrator	Only for discrete lesions that can be treated with one stent; avoid multi-vessel disease.

**Stents per patient.** Most doctors questioned said their drug-eluting stent use averages about 1.3 per patient. Patients who are high risk with multiple lesions are often staged. That is, they have one or more stents placed during the first procedure and then come back in a month or two and have a second procedure to place additional stents. A J&J official said, "The bolus of patients that we've seen at first tend to be the higher risk patients, to the average number of stents per patient is close to 2.0." An interventional cardiologist said, "In the first three weeks Cypher was available, we used it for 65% of our cases, and we are on the way to 85%-90%. We are averaging 1.7 stents per patient, compared to 1.9 historically. We've used more than 100 with no deliverability issues."

In the drug-eluting stent cost-effectiveness study that Dr. Serruys is running at his hospital in the Netherlands, 1,083 patients had been treated with a drug-eluting stent, getting a total of 2,383 stents (an average of 2.2 stents per patient).

#### Thoraxcenter Interim Report on Drug-Eluting Stent Use

MACE at 9 months	Drug-eluting stents	Bare stent historical control	Risk reduction
Overall	10.1%	14.9%	37%
De novo lesions	8.8%	14.5%	43%

One patient at another European center got eight Cypher stents implanted. A speaker said, "Dr. Renu Virmani reminds us that drug-eluting stents look very similar to brachytherapy, so I feel a little bit nervous about using eight simultaneous drug-eluting stents...Eight stents would require a 40% further decrease in event-free survival to make them cost effective, and that is impossible." Another speaker said, "How do we justify using eight drug-eluting stents?"

**Pricing.** On average, sources estimated that in Europe Taxus prices are an average of \$300-\$500 less than Cypher, but Boston Scientific officials indicated that the differential may not be as steep in the U.S. A Boston Scientific official said, "Our prices in Europe are European-specific...There should be pan-European pricing...Both products (Cypher and Taxus) are priced within a narrow price band. We do not sell on price; it is not a basis of competition for us...Price is something interesting to talk about, but we are getting a significant premium over bare stents, and there is relatively little difference between ourselves and our competitor based on our activity in the market...We will go to school on the (U.S.) marketplace and price appropriately at the time."

- Sources said that the list prices (in euros) for Cypher is 2,300, but it is selling for 2,000. Taxus lists for 1,900 but is selling for 1,600.
- Two U.K. doctors said Taxus has gained 69% market share in their country, with pricing 500E lower than Cypher, and other sources confirmed this differential
- A Swiss doctor said Cypher is about 2,300 euros in his country, with Taxus about 10% below that, but he explained that prices are higher in Switzerland because reimbursement came early. Taxus pricing varies considerably by country, and is especially low in Germany.
- In the U.S., Boston Scientific reportedly plans to offer Taxus at a lower price than Cypher but probably not by as big a discount as in Europe. In setting the European price, a Boston Scientific said the company did a survey with doctors to determine how much doctors would buy at different prices in order to find the highest point on the price/volume curve. The company plans to do the same in the U.S.

Speakers disagreed over how important price is, but most doctors would like to see lower pricing for drug-eluting stents. A speaker said, "This stuff works, and we shouldn't worry about the cost since the price will go down anyway." This speaker urged doctors to pressure manufacturers to lower the price of drug-eluting stents, but he doubted there would be any price harmonization in the near future. However, he did predict there would be aggressive pricing among the companies, which should help lower prices. Another speaker said, "We went and asked (U.S.) patients what they were willing to pay for Cypher stents, and patients going for angiography were willing to pay on average about \$4,000 out of

pocket to avoid surgery." A different perspective came from another expert who said, "A stent thrombosis costs about \$17,400; a procedure with eight drug-eluting stents costs \$18,497."

## BOSTON SCIENTIFIC

Much of the Taxus data was a repeat of information released at the American College of Cardiology meeting in April 2003, but there was new two-year data on TAXUS-1, 30-day results from TAXUS-6, and (preliminary 30-day results), and six-month results on the first 100 patients from the WISDOM registry – and some surprising news about paclitaxel elution rates and vessel thickening. By the end of this year, 3,479 patients will be enrolled in Taxus randomized trials, according to a company official.

### Taxus European Sales to New and Existing Customers (in revenue units)\*

Taxus purchases in Europe by:	February 2003	March 2003	April 2003	May 2003
Existing customers (1,100 cath labs)	6%	16%	29%	33% - 34%
New customers	N/A	N/A	N/A	23%

\* Source: Boston Scientific

**European marketing.** An official said, "Our next area of focus (for Taxus sales) is in Italy, Spain and Portugal. Because of supply constraints we decided to penetrate there second, so we are just getting started there, but we expect it to accelerate quickly...I think we are driving market conversion...About 35% of Taxus customers have been new to drug-eluting stents...23% of Taxus European sales are going to centers that did not use a drug-eluting stent before Taxus...We're gaining incremental customers...Reorder rates (at least three purchase orders) as of April was 72% - 90%, depending on the country."

### Launches expected:

- Australia in June 2003
- Canada in June/July 2003
- Korea in June 2003
- Taiwan before the end of the year

**FDA filing.** A Boston Scientific official indicated the most likely timing for an FDA advisory panel is October 2003. Another official said, "I think our first (FDA) approval will be for single stenting. The FDA mandated data on overlapping stents, and we have TAXUS-6 and TAXUS-5 data, and we expect after the initial filing that we would follow shortly with a supplement to expand the indication to multiple stenting and long lesions. We do have modest data in TAXUS-4, TAXUS-2 and WISDOM...We've also done more than 96 animals in various formats looking at double density of struts and hence

more drug and the total amount given to a single vessel or a single animal, and the safety profile is excellent out to 180 days with both the slow-release and moderate-release.”

**Safety concerns have arisen again with paclitaxel and now raise questions about FDA approval.**

When the TAXUS program first began, many experts predicted that a balance between safety and efficacy could not be achieved, but in the last six months or so, safety concerns had faded, and most sources also believed that the drug would work. The only question remaining seemed to be whether or not the pivotal TAXUS-4 trial would show sufficient reduction in restenosis over the bare Express<sup>2</sup> stent, and the odds appeared about 60% in favor of meeting this primary endpoint.

However, two issues came up at PCR that have serious implications for Boston Scientific and the whole Taxus program.

**1. Elution.** Two experts commented that 90% of the paclitaxel remains on the Taxus stent even after 180 days, and this was confirmed by Boston Scientific officials. One Boston Scientific official explained that the stent stops eluting paclitaxel by Day 10, at which point <5% of the total paclitaxel dose on the Taxus stent has eluted (e.g., a 16 mm stent has 85 µg of paclitaxel, and <4.5% of the paclitaxel is eluted). The remaining ~95% is “locked” into the Translute polymer and remains there forever. This is even more than other speakers and experts suggested.

Several sources seriously doubted that the FDA would accept this level of concentration remaining on the stent without long-term data (two or three year minimum). The drug to polymer concentration is ~8.8% with the slow release, and a Boston Scientific official said doctors are advised not to over-dilate Taxus stents, explaining, “That’s not because of cracking of the coating but because over-inflation affects the metal-to-artery ratio.” Doctors appeared startled and concerned about this revelation. One expert said, “This is something we have to watch. The FDA may require two or three year data before approving Taxus.” Another expert said, “Where there is vessel thickening, there will eventually be stenosis. It indicates inflammation and necrosis.” A source said the **FDA remains concerned about the safety of paclitaxel.**

Conor MedSystem also is working on a paclitaxel eluting stent, the DepoStent. A Conor official commented, “The Boston Scientific system has a fixed matrix left behind...and about 90% of the drug is still left behind.”

**2. Peri-stent vessel thickening.** There was no increase in neointimal volume over time, but IVUS showed *there was a time and dose-dependent peri-stent thickening* in TAXUS-2, and it appears that Boston Scientific was trying to “spin” a negative into a positive. Vice President for Cardiovascular Affairs (and TAXUS chief) Dr. Mary Russell described this vessel thickening as “vascular healing” and said it was “comforting because it indicates vascular thickening as opposed to ‘aneurysmal thinning.’”

However, at least three experts – two of whom are noted for their impartiality and lack of ties to the drug and stent companies -- totally disagreed with her characterization, and all thought it extremely inappropriate, even “stepping over the edge,” for her to characterize this finding as positive.

- One expert described the thickening as “vascular remodeling” and said it “looks like necrosis.”
- At the Late Breaker session on the last day of the meeting, Dr. Serruys presented the IVUS findings from TAXUS-2 again, focusing in particular on the vessel thickening. He didn’t warn that this was dangerous, but he noted that the thickening appears to be growing and certainly cannot be called positive, “Vessel thickening should not be viewed as a positive, and it likely involves inflammation and necrosis. The thickening appears to be dose and time dependent.”
- Another expert who has worked with paclitaxel said there is no mechanistic explanation for this phenomenon other than necrosis and suggested that Boston Scientific officials “stepped over the edge” in offering a positive interpretation. He said, “There is no biological explanation. Necrosis could cause it to look like that, but we won’t know for sure unless there is an autopsy of a patient. It’s an over-simplification to say it is comforting.”
- A fourth expert said the thickening is suspicious of inflammation and necrosis.

**Conor DepoStent vs. Taxus**

Measurement	Conor DepoStent with paclitaxel	Taxus slow-release stent with paclitaxel
% released in Days 0-12	100%	12%
Quantity released in Days 0-12	1 0µg	13 µg
Quantity released in Days 12-180	0	3 µg
Residual paclitaxel	0	92 µg

## TAXUS Trials

Study	Stent diameter	# of stents per patient	Drug elution rate	Lesion length	Stent	Purpose
Taxus-1	3.0-3.5	Single	SR	10-12	Nir	Proof of principle
Taxus-2	3.0-3.5	Singe	SR/MR	10-12	Nir	Proof of principle
Taxus-3	3.0-3.5	Single	Slow	10-12	Nir	N/A
Taxus-4	2.5-3.5	Single	Slow	10-28	Express <sup>2</sup>	High risk expansion
Taxus-5	2.25-4.0	Multiple overlap	Slow	10-46	Express <sup>2</sup>	High risk expansion
Taxus-6	2.5-3.5	Multiple overlap	Moderate	18-40	Express <sup>2</sup>	High risk expansion

June (2003), and you will hear from (an official) that we did that.” Another official said, “We are submitting the fourth module -- chemistry, dosing, stability -- (to the FDA) in the next few days, and the fifth module in June (if TAXUS-4 is positive).” There will be **no** details until TCT, even if the trial is positive but the delta between Taxus and Cypher is significant (a percentage point spread in restenosis of 3 or more points). Even investigators will not get the data until just a couple of hours before it is presented at TCT.

**Update on Taxus trials and research:**

**Preclinical.** An official said a substantial and ongoing pre-clinical program is still underway with Taxus.

## TAXUS-1 Two-Year Results

Endpoint	Bare stent n=30	Nir with paclitaxel n=31
Restenosis	10%	0%
MACE	10%	3.3%
Cardiac death	0	0
Stent thrombosis	0	0
MI	0	0
TVR	10%	3.3%
TLR	10%	3.3%
Adjudicated TLR	10%	0
CABG	3.3%	0

**TAXUS-2.** Between six and 12 months in TAXUS-2 there were no new clinical events, but one TVR was readjudicated to a TLR -- and there were some controversial new CABGs. An official explained, “The TAXUS-2 protocol required TVR to include any PCI within the target vessel, and TLR to include any revascularization involving the stent and 5 mm on either side and then CABG. We did not break them into PCI and CABG TLRs at that time. That was my decision, and I will take the hit on that. It would be pretty unusual to do single-vessel CABG.”

Additional analysis of the TAXUS-2 data is ongoing. An official said, “We are in middle of a blinded, detailed, segmented analysis of the TAXUS-2 data.”

**TAXUS-4.** This pivotal U.S. trial was not unblinded at the time of PCR, and Boston officials and other sources all denied having any idea of the outcome. If the data is negative, Boston officials said they would issue a press release. An official also said, “If the data supports a PMA, we will file in

There were no leaks or gossip about the results from this U.S. pivotal trial. Doctors in the trial said they generally can tell which arm of the trial patients are in once they see the follow-up angiograms, just as doctors could do in SIRIUS, but there have been no investigator anecdotal comments about either arm. The principal investigator for the trial, Dr. Greg Stone of Lenox Hill hospital, will be the only investigator to see the results prior to TCT. Reportedly, Dr. Stone will be advised of the results within 24 hours of unblinding and he -- not Boston Scientific -- will prepare the TCT presentation slides.

**TAXUS-5.** Reportedly, 804 of 1,108 patients are enrolled:

- 64 of the 200 needed with small vessels
- 90 of 200 patients with large vessels (4.0 mm)
- 120 or 300 with long lesions (>26 mm)

## 30-Day TAXUS-6 Results

Measurement	Group A n=227	Group B n=219
Diabetics	21.6%	17.8%
Procedural success	95.2%	92.7%
Technical success	96.6%	98.4%
IIB/IIIa use	18.9%	21.0%
Average stent diameter (range: 2.5-3.75 mm)	3.13 mm	3.13 mm
Average number of stents (average length 33 mm)	1.4	1.4
Average stent length	32 mm	32 mm
Average lesion length	20.3 mm	20.9 mm
Safety		
In-hospital MACE	4.8%	6.8%
Out of hospital MACE	0.9%	0.5%
Cardiac death	0.4%	0
Overall MI	4.0%	6.8%
Q-wave MI	0.9%	0.9%
Total 30-day MACE	5.3%	7.3%

**TAXUS-5-ISR.** This trial was due to start enrolling at the end of May. It is a 448-patient, head-to-head study comparing brachytherapy with Taxus stents (diameters 2.5-4.0 mm, lengths 8-32 mm).

#### Wisdom Registry of Slow Release Taxus

Measurement	Results n=529
<b>Patient Characteristics</b>	
Diabetics	32%
AMI	17%
AMI within 72 hours	10.4%
Unstable angina	32%
Average lesion length	15.01 mm
Reference vessel size	2.93 mm
1 stent	86%
2 stents	13%
≥3 stents	1%
Average stents per patient	1.23
Overall event rate	2.1%
<b>6-Month Results on First 100 Patients</b>	
Cardiac death	2.0%
MI	0
Reinterventions-PCI	3%
Reinterventions-CABG	0
Stent thrombosis	0.2% (1 patient)
Event-free survival	85%
Event-free survival at 6 months	90%

Post-marketing Taxus registries ongoing in Europe include:

- MILESTONE-II
- TRUE (Taxus high risk registry, unique experience)
- Rotterdam registry (all-comers, consecutive)
- WISDOM

#### Other Taxus program topics discussed include:

**Dosages.** Boston Scientific is still exploring the moderate release dose, and an official explained, “It is not clear in high risk lesions if there is an optimal dose. We determined the effect in low risk patients, but maybe one dose shouldn’t be used for all lesions at all times.”

**No edge effect.** An official said, “There is no edge stenosis, and actually a distal edge benefit (with Taxus).”

**Taxus supply:** European doctors and Boston Scientific officials insisted that the Taxus supply problems have been resolved, and all sizes are now available. In the U.S., a Boston Scientific official said the company will do a gradual rollout.

The sizes expected in the U.S. at launch are: diameter 2.5-3.5 mm, length 8-32 mm. An official said, “Our goal is 75% world-wide market capacity and surge capacity incremental to that. We have two vertically integrated facilities with critical redundancies. We can manufacture 40,000 stents a month... and we expect to triple that by the end of the year... We will have an unconstrained international launch... and we expect an unconstrained U.S. launch... (In the U.S.) we will go through a roll-out launch because even though there are no handling issues with Taxus, and there are few things an experienced cardiologist wants to hear about tips, tricks and indications (with Taxus). We will go in measured way, scrub in on cases, provide clinical support and be sure we penetrate. We won’t just drop off a coffee cup and some stents... I would expect the rollout to follow the Express roll out with full penetration in six to eight weeks.”

#### GUIDANT

**Vision stent:** The fix to the Vision stent to crimp the balloon a little harder onto the stent. Guidant officials expect the revised product to be back on the EU market during the summer, and they hope to have FDA approval in the same time frame. An official explained, “The stent struts and the thinness of the Vision profile, given our usual grip securement technology, needed to be modified to conform to the smallness of the Vision. It was a manufacturing issue, not a design change... But the harder you crimp, the less trackability, so it’s a balance.”

**Pixel stent:** New data on the Pixel looked good, too, and suggests that direct stenting – with this stent – is superior to pre-dilatation.

#### Pixel 6-Month Data

Measurement	Pre-dilatation	Direct stenting
Number of patients	174	176
Average lesion length	10.8 mm	10.3 mm
MACE at 180 days	9.1%	6.2%
Death	2.4%	1.4%
MI	0.6%	0.7%
TLR	4.3%	3.4%
TVR	6.1%	4.1%
In-stent restenosis	24.1%	14.2%
In-segment restenosis	25.0%	16.0%
Late loss	0.73	0.73

**FUTURE-1 and FUTURE-2 everolimus program:** The Biosensor’s stent, originally called the Challenger, then the S-stent, is now named the Champion. The FUTURE-1 principal investigator, Dr. Eberhard Grube, said that when the drug is gone, the polymer is gone, too. He reviewed the FUTURE-1 six month results and said the one death that had been seen in the drug arm has now been adjudicated unrelated and is no longer listed as a MACE. FUTURE-2 enrollment is complete

with 10 patients, and the results will be presented at TCT2003. A Biosensor's official was optimistic that Guidant will be able to obtain CE mark on the FUTURE-2 data.

## JOHNSON & JOHNSON

### Average European Cypher Usage

Time	% of All Stent Patients
April 2002	5%
July 2002	6%
December 2002	10%
April 2003	11%

### Focal lesions. The new issue with Cypher is focal lesions.

A speaker showed data suggesting that much of the in-stent restenosis that is occurring with Cypher are focal lesions. Another expert offered an explanation for this, "With a closed cell stent that is fairly stiff in the curvature (like the BX Velocity or Cypher), there may be sites where struts can't oppose the wall or trauma to the polymer during implantation, and then you could see focal failure."

**Supply.** European doctors and J&J officials insisted that the Cypher supply problems have been resolved, and all sizes are now supposed to be available. However, one doctor commented, "We are getting what we want, but sometimes with a rather short shelf life. Sometimes we get stents that have to be used within three months or they are past the validity limit. I'm told that will change." In addition, a major center doing a live case didn't have enough sizes on hand for the live case!

A J&J official said the problem is that the company had to discard a lot of the inventory it made for the planned November/December 2002 launch because the shelf life expired. J&J didn't want to rebuild inventory fully until they knew when the launch would actually occur, so inventory was not where the company would like to have had it at launch. He said, "When we have full supply depends on demand, but probably in the next three to five months."

**Diabetics.** Some competitors suggested that Cypher doesn't work in diabetics, but J&J officials and other experts disputed this. One speaker said, "Spin artists suggest that Cypher stents don't work very well in diabetics, especially those on insulin ...but clearly they work in diabetics."

**Interim ECypher results.** Data was presented from the E-CYPHER registry, which is similar to Boston Scientific's WISDOM registry but larger. The goal of this registry is 15,000 patients, with more than 6,000 enrolled now. Of these patients, 9% got multiple (mostly overlapping) Cypher stents.

## E-Cypher Registry Interim Results

Measurement	Results
<b>Patient Characteristics</b>	
Number	5,766 patients with 7,357 lesions getting 8,215 stents
Male	77%
Prior PCI	32%
Diabetics	29%
De novo lesions	86.0%
Average number of stents per patient	1.3
Average number of stents per lesion	1.04
Restenosis (mostly ISR)	14.0%
CTO	9.7%
Bifurcations	9.5%
Treated with only one stent	81.7%
Bare stent or balloon	9.0%
Most common stent	18 mm x 3.0
Clopidogrel ≤3 months	61.5%
<b>Safety at 6 months</b>	
MACE	7.8% at 201 days
Death	2.1%
Q-AMI	0.9
Non-Q AMI	1.7
PCI-TLR	2.5
CABG	.7
Non-TLR PCI	~6.3
Event-free survival at 6 months	92%

**Cypher failures.** Some experienced Cypher users said the rate of failure (inability to deploy, non-crossability) is about 10%, but others claimed it doesn't occur at all. When a Cypher is tried and can't be deployed, they either substitute a bare stent or a Taxus stent, and they may have to eat the cost. J&J has no standard U.S. or European policy on reimbursements or returns. In Europe it appears to be a country-by-country, and perhaps site-by-site policy. A French doctor said there is no reimbursement in that country.

**Japanese launch.** A J&J official said the company hopes to launch Cypher in Japan next year, perhaps in April, but the Japanese regulatory timetable is difficult to predict.

## JOMED

Officials confirmed the company is being broken up and the parts sold, with an announcement expected *this week* or early next week. They would not specify who is buying what, but sources said Abbott is buying the stent business and Volcano Therapeutics is buying the IVUS business. As to Jomed's drug-eluting stent program, an official said the company has decided that the problem with its tacrolimus-eluting stents is the coating. Jomed currently is doing a Phase I study of tacrolimus sprayed on bare stents (à la DELIVER), but no trial is yet underway with tacrolimus via a **SurModics** coating – because the SurModics deal fell through. A source said

SurModics got more and more difficult to deal with, and the agreement was never finalized.

### MEDTRONIC AND ABBOTT LABORATORIES

Abbott cross-licensed ABT-578 to Medtronic, and Medtronic cross-licensed its over-the-wire and rapid exchange balloon delivery system to ABT. Both companies are using the same BiodivYsio phosphorylcholine coating, but each is putting it on its own stents. An Australian ABT-578 researcher said, "The coating has been FDA approved for around six years...The drug elutes away from the stent rather rapidly; 60% is gone in 24 hours, and the vast majority within eight days. It's totally gone within 14 days. About 30% of the drug is off-loaded within 24 hours."

An Abbott official said the two companies are closely collaborating on their ABT-578 programs, and Abbott and Medtronic did a joint presentation of early ABT-578 data. The numbers were small, but the drug appears to work and there were no serious safety issues.

- In the ENDEAVER porcine studies, ABT-578 was found to be safe at 28 and 90 days, with a treatment effect at both time periods. There were no aneurysms, medial necrosis or AMI.
- The ENDEAVER-1 human study recently finished enrollment with 101 patients in Australia and New Zealand, using Medtronic's Driver stent, a cobalt chromium alloy.
- Abbott's PREFER-IVUS trial is the first-in-man data for ABT-578, using the BiodivYsio stent. This study was supposed to enroll 50 patients, but was stopped after 11 patients because of irregularities in the early Abbot animal data and, a researcher said, "The desire for a new stent platform."

#### 90-Day PREFER-IVUS Results

Location	Late Loss	Binary Restenosis
In-stent	0.2%	0
Proximal margin	0.2%	0
Distal margin	0	0
In-segment	0.1%	0

#### PREFER Results

Endpoint	In hospital	30 days
Death	0	0
MI	9.1%	9.1%
TLR	0	0
Event-free survival	90.9%	90.9%

### OTHER DRUG-ELUTING STENT PROGRAMS

#### Conor MedSystem

Conor's DepoStent continues to get prime time attention at every major cardiology meeting. A Conor official report on the results of the first 53 patients of the DepoStent eluting paclitaxel, commenting, "It is not the world's greatest platform, but it is equivalent to other systems. The first generation balloon was not quite right...but it has been changed and it has a much more tapered, appropriate-sized balloons with a better delivery system going forward...There is good opacity...The cell size appears good enough for kissing balloons...I wouldn't expect this stent to have more or less restenosis than other trials."

#### Conor First-in-Man 30-Day Results

Measurement	Results
Average lesion length	11.38 mm
Average number of stents	1.3
MLD final	2.67
%DS	13.2
Technical success	94%
Procedural success	94%
MACE	0

Conor also has started two other trials of the paclitaxel-eluting DepoStent.

- PISCES. This 120-patient feasibility study is looking at four formulations, with four and 12 month angiographic follow-up. The principal investigator is Dr. Serruys.
- SCEPTER. This CE-mark approval trial is ongoing now, and will enroll 260 patients.

The Conor official said, "We believe paclitaxel is a very potent drug...but we believe the toxic-to-therapeutic window is very small and not completely understood." Unlike the Taxus stents, the DepoStent elutes all of the paclitaxel loaded on it, a Conor official insisted.

#### GOODMAN/AVENTEC

The company's first-in-man IMPACT trial of mycophenolic acid (MPA), the active metabolite of the immunosuppressant mycophenolate mofetil (Roche's CellCept), on a Duraflex stent was not positive. The company has confidence in its coating and "plans to continue looking at...different (MPA) doses, multi-phase release and combinations with other drugs...(as well as) new cytostatic drugs. We will continue with our Opticoat polymer technology. The next feasibility study will begin in late summer 2003."

**IMPACT Trial 6-Month Results**

Measurement	Moderate MPA	Slow MPA	Bare Duraflex
Number of patients	50	55	50
Average lesion length (mm)	11.59	13.87	11.80
In-stent restenosis	12%*	12%*	25%
In-lesion restenosis	18%	16%	25%
<b>Primary endpoint:</b> Late loss	1.04	0.95	0.91
TLR	1 patient	0	0
Death	0	3.6%	0
Non-Q-wave MI	4%	0	6%
CABG	0	1 patient	0
Total MACE	~16%	16.1%	18%

\*nss from bare stent

However, **LIGHTLAB**, which was bought by Goodman last year has a pretty nifty OCT cardiac catheter in development. The view it provides from a small, very light fiber appears far superior to IVUS. The company is expecting CE Mark this fall for this product.

**GORE/MEDINOL**

Medinol's Nirflex – a bare stent with a folded balloon – already is sold in Europe. The company filed a PMA with the FDA for the Nirflex and an approvable letter was granted in March 2003, pending manufacturing approval. A Medinol official said the delay in approval was due to the Iraq war interfering with manufacturing site inspections in Israel. Those are now being scheduled, and he expects that to be complete in the next month or two.

Medinol and Gore are collaborating on the NOA system, a NirTop stent – a high pressure, closed-cell stent – on the Aptera delivery system from Gore. NOA already has a CE

**NIRTOP 9-Month Results**

Measurement	NOA	BX Velocity	Cypher	Guidant Vision
Average vessel diameter	2.74	---	---	---
In-stent restenosis in vessels >3.0 mm	6.3%	25%	3.6%	---
TLR at 180 days	4.4%	--	---	---
TLR at 210 days	7.0%	---	---	---
TLR at 270 days	8.9%	16.6%	4.1%	---
SAT	0	---	---	---
Late thrombosis	0	---	---	---
Late Loss	0.65	1.10	---	0.83
MACE	10.1%	18.9%	7.1%	---

\*Source: Medinol

Mark, but sales have been limited to live case centers so far. In June Medinol plans to increase the number of sizes and sizes available.

The PMA for NOA won't be filed until the end of 2003, with FDA approval expected in early 2004. NOA has a very, very slick balloon, and doctors who saw it were impressed. The balloon is not folded, and it expands and contracts elastically, so it can be re-used. A Medinol official claimed there will be less dislodgement with this system, better trackability and deliverability, a smoother finish than all of the current stents except Medtronic's S-7, and a comparable profile. He said, "It will be good for direct stenting." Pricing is expected to be competitive, not a discount.

The results of the international, prospective, randomized NIRTOP trial of 305 patients getting a bare NirTop were presented at PCR. Dr. Antonio Colombo of Italy was the principal investigator.

**India**

A company in India is working on a paclitaxel-eluting stent to compete with Taxus – at a significantly lower price – and sources said it appears to be a quality product. Dr D. S. Gambhir of the Kailash Heart Institute in Noida, India, presented results from the 80-patient SIMPLE-1 trial on the safety and efficacy of the Infinium stent. This stent has four layers of a biodegradable polymer, with three loaded with paclitaxel, each of which has different elution kinetics. A larger, randomized trial is scheduled to start in July 2003.

**6-Month SIMPLE-1 Results**

Measurement	Results
Stent lengths	16-18 mm
Mean reference vessel diameter	2.45 mm
Event-free survival	93.7%
MLD*	2.17 mm
Late Loss*	0.22 mm
%DS	19.5%
Binary restenosis	4.4%

\*39 evaluable patients

**NMT MEDICAL**

PFO closures weren't center stage at PCR, but they did draw some interest. NMT sponsored a live symposium that linked cardiologists at PCR and neurologists at the European Stroke Conference, which was going on at the same time in Valencia. As a part of the symposium, a live PFO closure case was performed at the Thoraxcenter in Rotterdam, the Netherlands, using NMT's Starflex Septa Closure System – the first device to receive European approval for this application. Last fall, an FDA Advisory Panel recommended against approval of

Starflex for the treatment of cryptogenic stroke, but the company hasn't given up. CLOSURE-1, a randomized, controlled, superiority trial was designed to compare PFO closure to traditional medical therapy in 1,600 patients who have suffered a TIA or stroke.

### ORBUS MEDICAL TECHNOLOGIES

First-in-Man data from Endothelium Progenitor Cell (EPC) Seeding program, the Phase I HEALING study of the EPC-R stent, was presented. A speaker said, "The applications are many-fold. It may be a good synergistic approach to drug-eluting stents. It won't require such cytotoxic drugs...If it holds true, and really prevents subacute thromboses, then it may reduce the need for antiplatelet agents other than aspirin." The moderator said, "This may be the next generation stent coating."

### SORIN BIOMEDICAL

The Janus Carbostent is a closed-cell stent with a coating that elutes Fujisawa's tacrolimus directionally and in a controlled manner. The company claims no drug can be detected in the drug at any release point, and that the stent is suitable for direct stenting. In the future, this stent could be modified to elute more than one drug or with different release kinetics along the stent. The JUPITER-1 study is currently underway, with 32 patients enrolled so far and zero MACE so far.

- PK studies were done by Dr. Virmani. One month after implantation, about 50% of the drug has been released. The drug concentration in the blood was always below the HPLC sensitivity threshold, confirming no drug was released into the blood stream.
- A pig study in Italy compared the Janus stent to a bare Carbostent, and found a 39% reduction in neointimal area at 28 days, and a statistically significant 50% reduction in neointimal hyperplasia at 30 days."
- Based on these results, the JUPITER-1 registry of 30 patients was conducted. Since the 30-day safety was good in that (30-day MACE in 20 patients was 0), the trial is being expanded to a randomized beta phase with 200 patients, followed at six, 12 and 24 months.

### TRANSLUMINA

This privately-held company attracted some attention at PCR with its "Magic Box" that allows European cath labs to create drug-eluting stents right in the cath lab. Using the Magic Box, the labs can coat Translumina's Yukon<sup>DES</sup> stents with any drug they choose, from paclitaxel to statins, rapamycin or estradiol. The stent's non-polymer surface is sand-blasted to create small cavities that become a carrier for drugs. A company official would not give the pricing except to say that it is lower than either Cypher or Taxus but a premium to a bare stent.

### TERUMO

This very large Japanese medical products company has less than 2% of the Japanese stent market. It was working on a simvastatin-eluting stent but has stopped that program due to lack of efficacy, though safety was reportedly acceptable. However, the company has not given up on statins – it just wants to find a different statin to use.

### MISCELLANEOUS ISSUES AND TOPICS

**Aneurysms.** This was a big worry at last year's PCR, particularly with Taxus stents, but that concern appears to have evaporated. An expert said, "I don't think you should worry about aneurysms. The percentage is very low...and there are no clinical events associated with them."

**Antiplatelet usage.** There is no risk of adding Sanofi's Plavix (clopidogrel) to a IIb/IIIa inhibitor in high risk patients, a speaker said. However, debate continues over how long to give Plavix. Some experts variously recommend one, two, three, six, or 12 months, and a few think patients should be on Plavix for life. One speaker said, "There is absolutely no evidence that we should give clopidogrel more than one year."

**Bifurcations.** Dr. Colombo reported on six month clinical outcomes in bifurcations treated with drug-eluting stents, placed with the crushing technique, at his hospital in Milan, Italy. There were 25 patients with 54 lesions treated.

#### 6-Month Bifurcation Results with Drug-Eluting Stents

Measurement	Rate
Death	4%
MI	0
TLR	16%
CABG	4%
Repeat PCI	12%

**Clinical guidelines.** More than one speaker commented that doctors are not following clinical guidelines, and they said there is a gap between clinical trials and clinical practice. One said, "Physicians are not always doing what they are supposed to do."

**Direct stenting.** Several sources suggested that direct stenting may be safer with Cypher than with Taxus because Cypher is less flexible, but this remains an unresolved issue.

**Drug combinations.** There is increasing interest in putting more than one drug on a stent – a chemotherapy-type approach. A speaker said, “The first work was done by a German group combining Hirudin and iloprost, using a bioerodable polymer. The drugs were mixed and released as the polymer eroded...Drugs also can be layers or combined chemically.” He cited the combination of triamcinolone (Bristol-Myers Squibb’s Kenalog) and 5-FU, which have different elution rates, “It made an NME, and the results were startling. There were incredible results in neointimal thickening.”

**Edge Effect.** Several speakers emphasized that they do not believe there is an edge effect with drug-eluting stents. Rather, they urged doctors to use cover lesions fully with longer stents, avoid gaps between stents, maintain optimal deployment, avoid injury beyond the stent, and use optimal anticoagulation therapy.

**The future of interventional cardiology.** During the Highlights Session at the close of the meeting, a speaker pointed to these areas for future advances:

- Revival of dead myocardium through angiogenesis (PDGF, VEGF, TGF, EPO) and/or cell transplantation (EPC, bone marrow cells, etc.).
- Non-invasive coronary imaging.
- Increased cardiologist participating in multivessel disease, peripheral interventions, PFOs, ASDs, TASH, valve repair and replacement, and closure of left atrial appendages.

**In-stent restenosis.** Dr. Colombo also reported on his experience with using drug-eluting stents for in-stent restenosis in 322 patients: “The average stent length was 27.7 mm. This is a total departure from our policy of limiting stent length. Spot stenting does not exist any more with drug-eluting stents.”

#### 6-Month ISR Results with Drug-Eluting Stents

Measurement	Rate
MACE	5.1%
TVF	17.9%
Repeat revascularization	12.1%
TLR by Lesion	Type
Left main	12.5%
Bifurcation	6.6%
CTO	4.2%
Reference vessel diameter ≤2.5 mm	3.3%
SVG	7.7%

**IVUS.** A speaker urged that IVUS be used more frequently. However, other experts said cost is likely to keep this a niche product, useful mostly in clinical trials.

**Oral therapies.** Data was on systemic liposomal bisphosphonates to prevent restenosis. A single injection of a liposomal bisphosphonate – alendronate – at the time of PCI may aid in healing and prevent restenosis. A speaker said this approach, which has been shown effective in animals:

- Targets the critical cells – monocytes.
- Does not interfere with vascular healing.
- Involves a single systemic administration.
- Is not limited to diffusion from struts.
- Offers a sustained effect with a transient drug release.
- Can use a single administration for multiple devices in the same patient.

**Overlapping stents.** Doctors said they consider it safer to overlap Cypher stent than Taxus stents, and sources do not believe TAXUS-4 has enough overlapping stents to reassure people. Boston Scientific officials indicated they expect the FDA to limit approval to non-overlapping stents.

**Statins.** The value of statins was reiterated. A speaker said patients can and should take a statin – any statin. He dismissed a study which found that combining Pfizer’s Lipitor (atorvastatin) and Sanofi’s Plavix (clopidogrel) decreased the efficacy of clopidogrel, saying, “There is no evidence of an interaction (difference in hazard ratio) between statins (products metabolized by the CYP3A4 pathway) and the efficacy of clopidogrel.”

**Stent design.** Experts still don’t fully agree as to how important stent design is, but it has become an issue in analyzing drug-eluting stents. An expert said, “How struts interact and stent design matters...the design of the stent and where the struts lie on the vessel wall determine where the drug is deposited...Stents generally expand asymmetrically.”

**Thrombosis.** There are some cases of thrombosis with drug-eluting stents, but they occur 0.5%-1% with bare stents, and the rate with drug-eluting stents does not appear higher than for bare stents, so experts said the thromboses are background noise and not a concern – except to competitors.

**Vascular brachytherapy.** Several speakers warned against using drug-eluting stents after brachytherapy, saying too many questions have been raised and there is no data yet. A speaker also warned that there may be long-term safety concerns with vascular brachytherapy, “There is late catch up – as the pathologists have been warning – and late thrombosis is still an issue....A late catch-up phenomenon or late thrombosis

will ultimately minimize the benefit of radiation...The initial global use enthusiasm for VBT has diminished...Industry (and physician) 'spin' has exaggerated the short- and medium-term data."

**Vulnerable plaque.** Interest in this concept – and improvements in imaging modalities – continue to increase. Dr. Valentin Fuster said, "The best antithrombotic is high HDL...it prevents the factors that lead to blood clots...HDL prevents a clot by preventing a monocyte from committing suicide." Dr. Fuster is initiating a three-arm study comparing (1) statin, (2) statin+PPAR, and (3) fibrate.

Dr. Fuster also is a big believer in coronary and myocardial imaging to identify vulnerable plaque, and he said the technology is improving. He does not recommend imaging everyone, instead recommending its use for people with two or more risk factors, especially elevated CRP or tissue factor activity. "With this technology you will see a lot of 40% (stenosed) lesions that might be missed angiographically," he said.

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#### **Future data to watch:**

##### **TCT 2003:**

- ENDEAVER-1 30-day subset and 30 day MACE on ABT-578 on Medtronic's Driver stent.
- More results from E-CYPHER.
- TAXUS-4 results.
- FUTURE-2 results.

##### **European Society of Cardiology 2003**

- Probably more E-CYPHER results.

##### **American Heart Association 2003**

- Possibly more E-CYPHER results.

##### **American College of Cardiology 2004**

- ENDEAVER-1 4-month data on ABT-578 on Medtronic's Driver stent.

##### **PCR 2004:**

- TAXUS-6 nine-month angiographic and IVUS results.