Trends-in-Medicine

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by Lynne Peterson

SUMMARY

European doctors were not very concerned about safety questions that have been raised about Boston Scientific's Taxus stent, and doctors predicted overall market share would not change significantly during the rest of 2005, except perhaps in the U.K., where Johnson & Johnson's Cypher stent appears to be gaining ground. ♦ European doctors are aware that Conor Medsystems is developing a drug-eluting stent and they have heard it is interesting, but few knew much about CoStar. ♦ Medtronic's Endeavor stent is likely to gain more market share – and quicker – in Europe than previously thought. ♦ Stereotaxis's Niobe navigation system is catching on, but slowly, in Europe. ♦ Several companies are investigating the use of PFO closure devices to treat migraine headaches. NMT Medical already has a trial fully enrolled in the U.K., but no one has an IDE for a U.S. trial yet.

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PARIS COURSE ON REVASCULARIZATION (PCR)

Paris, France
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There wasn't a lot of critical news released at PCR this year. Boston Scientific's Taxus stent and Johnson & Johnson's Cypher stent battled for market share, while future competitors gave updates on their products.

STENT ISSUES

Drug-eluting stents vs. CABG

The SYNTAX-1 trial is an all-comers study comparing CABG and PCI in patients with three vessel disease and left main disease. As of PCR, 104 sites had entered a total of 12,072 patients.

SYNTAX-1 Demographics

Measurement	CABG n=8,895	PCI n=3,177
3 vessel disease	60.3%	22.3%
Left main	21.0%	8.3%
Lesion success	99.5%	99.5%

Cypher vs. Taxus

Dr. Antonio Colombo of Italy and Dr. David Holmes of the Mayo Clinic debated Taxus vs. Cypher. This was a very popular session, and it appeared to be the only session that required an overflow room. Dr. Colombo argued there is no significant difference between the two stents. He used statistics from SIRIUS, TAXUS-IV, ENDEAVOR-II, REALITY, and his experience at his cath lab to support his position. On REALITY, he said, "This was good data, and it was a prospective trial. J&J wanted to win, but didn't succeed…The subgroups were maybe a little better with Cypher, but that was not statistically significant…We continue to use Taxus and Cypher equally."

Dr. Colombo said he uses Cypher when he is not sure patients will be compliant with Plavix (Sanofi-Aventis, clopidogrel) use, but "for all else, they are the same." He denied there was any significant difference in the two stents in terms of bifurcations, overlapping stents, etc., "That is anecdotal evidence only. Despite SIRTAX, REALITY did not show a difference…Except for the acute MI in SIRTAX, which was 25%, there was no difference in MI. MACE was comparable. How can you have a difference in stent thrombosis and the same MI and death?"

Competitive Drug-Eluting Stent Landscape

Company	Stent	Drug	Key trial	European CE Mark *(approved or expected)*	U.S. launch *(approved or expected)*
Johnson & Johnson	Cypher	Sirolimus	SIRIUS	April 2002	April 2003
Boston Scientific	Taxus	Paclitaxel	TAXUS	January 2003	March 2004
Sorin	Janus	Tacrolimus	JUPITER	October 2004	No U.S. plans
Biosensors	Axxion	Paclitaxel	---	July 2005	N/A
Medtronic	Endeavor	ABT-578	ENDEAVOR	July 31, 2005	1H2007
Boston Scientific	Liberté	Paclitaxel	---	2H05	Mid-2006
Conor Medsystems	CoStar	Paclitaxel	EuroSTAR	4Q05	3Q07
Biosensors	BioMatrix	Biolimus	STEALTH	1H06	2008
Abbott	ZoMaxx	ABT-578	ZOMAXX	3Q06	3Q07
Terumo	Nobori	Biolimus	NOBORI	2006	No U.S. plans
Guidant	Xience V	Everolimus	SPIRIT	3Q07	1Q07
Guidant	Champion (bioerodable)	Everolimus	FUTURE	N/A	N/A
Blue Medical	N/A	Pimecrolimus	---	Too early to predict	Too early to predict
Sahajanand	Infinnium	Paclitaxel	SiMPLE	N/A	N/A

Dr. Holmes spent the first half of his time making friendly jokes about Dr. Colombo – to the point that J&J supporters were starting to get nervous that he was wasting the time allotted to him. When he did get down to numbers, he focused on the SIRTAX and ISAR-DIABETES trials. He called SIRTAX a "good scientific study," saying performance of the two stents was the same, with no advantage to either in terms of device or procedural success, and noting that all subgroups favored Cypher. He concluded, "Saying that all drug-eluting stents are the same makes as much sense as saying that wine from North Dakota is the same as wine from Italy."

Cypher vs. Taxus Statistics Cited by Dr. Colombo to Support Equivalence of Cypher and Taxus

Measurement	Cypher	Taxus	Endeavor
Trial	SIRIUS	TAXUS-II	ENDEAVOR-II
TLR at 9 months	16.6%	11.3%	12.1%
REALITY results			
TLR	9.6%	11.1%	---
Late loss in-lesion	9.6%	11.1%	---
Restenosis	6.2%	10.8%	---
Milan experience			
Number of patients	281	248	---
Prior CABG	24.9%	16.1%	---
Elective IIb/IIIa use	8.2%	18.5%	---
% diameter stenosis	25%	26%	---
Late loss	0.55 mm	0.45 mm	---
Restenosis	13.3%	19.6%	p=0.45
TLR	9.6%	12.1%	p=0.2
TVR	11.8%	14.2%	p=0.2
Late thrombosis	1.4%	1.6%	---
Milan CTO experience			
Number of patients	83	88	---
TLR	14.8%	13.3%	Nss
TVF	17%	16.9%	---
MACE	19.3%	20.5%	---
MI	1.1%	2.4%	---

Cypher vs. Taxus Statistics Cited by Dr. Holmes In Support of Superiority of Cypher over Taxus

Measurement	Cypher	Taxus
SIRTAX trial		
Late loss in-stent	0.13 mm	0.25 mm
Restenosis in-stent	3.2%	7.6%
TLR	4.8%	8.3%
Primary endpoint: MACE	6.2%	10.8%
ISAR-DIABETES trial		
Late loss in-stent	0.43	0.67
TLR	6.4%	12%
REALITY trial		
Late loss in-stent	0.03	0.14
Stent thrombosis: total	0.4% (p=.0195)	1.8%
Subacute stent thrombosis	0.3%	1.2%

Dr. Holmes said he uses Taxus for straightforward lesions, adding, "Both have good outcomes and are deliverable. The data in more complex lesions, long lesions, diabetics, etc., favor Cypher. Late stent thrombosis is a concern, but it is not powerful enough to make (a big issue)."

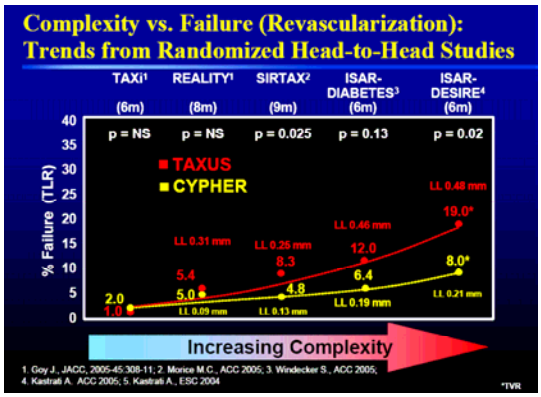
The debate went to Cypher by a hair during the question-and-answer period, but it did not appear to change any minds among the doctors in the audience. Dr. Colombo said, "I admit that whatever direction the pendulum swings, it always is a little more in the direction of Cypher."

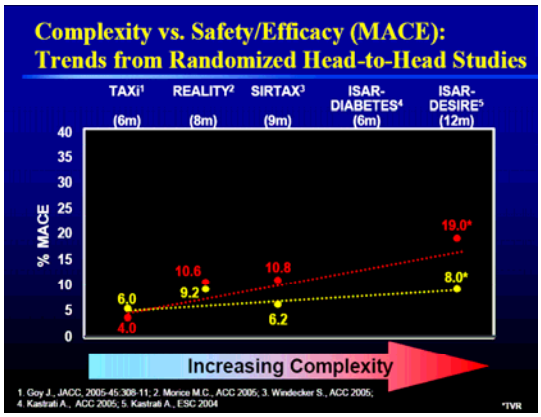
The FDA requested data on stent thrombosis in overlapping stents following the American College of Cardiology meeting in March 2005, where questions about stent thrombosis with Taxus stents was raised. J&J had already started that analysis, and it was presented on the last day of PCR. Is the thrombosis issue with Taxus a class effect? Boston Scientific officials claim it is, but J&J officials firmly believe the problem is

worse with Taxus than Cypher, and their pooled meta-analysis of several Cypher trials – SIRIUS, E-SIRIUS, C-SIRIUS, DIRECT, and SVELTE – showed a clear trend to a greater thrombosis risk with Taxus.

Cypher Meta-Analysis vs. Previously-Published Taxus Data

Measurement	Cypher	Taxus
Non-Q-wave MI in overlapping stents at 6 months	1.2%	7.2%
Non-Q-wave MI in overlapping stents at 9-12 months	1.5% at 12 months	7.5% at 9 months





While these data are not a home run for Cypher, the trend definitely has tipped in J&J's favor. The recent publication in the ***New England Journal of Medicine*** of the ISAR-DIABETES and SIRTAX trials was accompanied by an editorial written by Dr. David Moliterno of the University of Kentucky which concluded: "A higher rate of repeated target-lesion revascularization after placement of paclitaxel-eluting stents is apparent…If a true difference exists between the currently available sirolimus-eluting stents and paclitaxel-eluting stents, it is more likely than not to favor the sirolimus stent…The data overall, from randomized clinical trials and from registries, suggest that the currently available sirolimus-eluting stents provide an angiographic and clinical edge over the currently available paclitaxel-eluting stents. In contrast, the currently available paclitaxel-eluting stent holds an edge on availability, deliverability, and cost."

Market Share Shifts

J&J officials, in particular, continued to claim that Cypher is picking up market share in Europe, but that is not what doctors were saying. They continued to predict that Taxus share would pick up over the rest of this year because of lower pricing, not because of safety concerns with Taxus. A J&J source claimed Cypher market share was up 148% in the U.K. in the first five months of 2005 (from 18% to 40%), and the company expected preferential reimbursement in France to be announced soon after PCR. The French government was expected to provide an extra ~$400 premium for Cypher "because it is better," and the government was expected to allow Cypher a broader use – an additional 35% of the population, where Taxus will not be allowed to be used.

Among the comments that European doctors had to offer on the choice between Taxus and Cypher were:

- *Germany:* "I use 60% Taxus and 40% Cypher. I've started using more Taxus in the last six months because of the cost. By the end of 2005, I will probably be at 70% Taxus, 30% Cypher.
- *Italy:* I use 100% Cypher, but over the next few months I'll probably add some Taxus. Safety and efficacy are not a concern – it's price (that is driving Taxus use). Theoretically, Cypher is better perhaps, but not practically."
- *U.K. #1:* "I use about 80% Taxus and 20% Cypher, and that is unlikely to change this year…I've had no safety problems with Taxus. I'm aware of the issues that have been raised, but unless we see them ourselves, they are not a real concern. There is a risk with all stents…I would only stop using Taxus if a better product came…The new, longer shelf life for Taxus is having no impact; we turn our stock over too quickly for that to matter."
- *U.K. #2:* "Right now, we use about 70% Taxus and 30% Cypher, but Cypher use is increasing as a result of the recent trials. Both safety and efficacy appear better with Cypher. Late loss is better and complications lower with Cypher."
- *U.K. #3:* "I think Taxus safety problems will increase. We are starting to see late stent thrombosis with Taxus. It could be a cluster or my negative attitude, but it feels worse with drug-eluting stents. I think the issue is the polymer, so I am looking forward to biodegradable drug-eluting stents."
- *France #1*: "We are using Taxus and Cypher equally now, but we'll use more Cypher in the future. By the end of the year, we'll be using 30% Taxus and 70% Cypher. We need a stent with a better profile, but sirolimus is better than paclitaxel. Safety isn't the issue; they both have good safety. It is the restenosis rate that is different."

- *France #2:* "I use both Taxus and Cypher, and I haven't changed the proportion of each. I have no concern with the safety of Taxus."
- *France #3:* "We use Taxus and Cypher equally, and we don't expect any change in that this year."
- *U.S.:* "Taxus has a non-Q-wave MI issue. If it is a non-issue, then show us the details of the patients, which they (Boston Scientific officials) haven't done. Boston Scientific is not giving complete data, which is a concern. Use of Taxus is quietly going down. Cypher doesn't show a problem. Stent thrombosis does look worse with Taxus, and Taxus is losing share over it."

Stent thrombosis and aneurysms

European doctors were generally not concerned with stent thrombosis, and they had not switched to more Cypher stents. In fact, the trend is the other way – to more Taxus because of the lower cost of Taxus. The exception was U.K. doctors who appear to be concerned there is a safety problem with Taxus and are moving toward more Cypher stents.

Attendance was low at a session on stent thrombosis and aneurysms with drug-eluting stents, but the doctors who attended were very concerned about how to handle these patients. A speaker suggested that the slow progression of aneurysms might indicate they are inflammatory reactions. In one case that was cited, a patient with a Cypher stent developed an aneurysm nine months post-procedure, and the cardiologist prescribed life-long Plavix. However, at 18 months, the patient presented again with an acute STEMI and was treated with a covered stent, and was reported to be doing fine. Noted pathologist Dr. Renu Virmani commented, "Eighteen months is not long with a drug-eluting stent. The drug preventing healing could cause the aneurysms without a hypersensitivity reaction." A doctor in the audience indicated he was not worried about the aneurysm rupturing, and he also would have used a covered stent.

If the aneurysm increases in size, does the risk of rupture increase? Dr. Virmani said, "That is why covered stents are used, but that is not my answer. A covered graft will eventually occlude, and the patient will go to CABG. I would send the patient to CABG right away…I've had poor experience with stent grafts (covered stents), and I don't believe they stay open." A doctor in the audience said, "There is no risk of rupture. I would use a covered stent and see if the patient is lucky, and it remains open."

A late aneurysm in a stented segment could be due to a hypersensitivity reaction to the polymer, a speaker suggested. Dr. Virmani said she has done autopsies after three deaths from hypersensitivity – two with Cypher stents and one with a Taxus stent. She said, "I think it is a reaction to the polymer." Her recommendation was to try corticosteroids in patients who develop a hypersensitivity reaction to a drug-eluting stent, but other experts noted there is no evidence that this works. One doctor in the audience said he would use a covered stent in these patients, and another said his lab had had two cases, and they re-stented the patients. A speaker suggested IVUS should be done on these patients.

How long should drug-eluting stent patients get Plavix plus aspirin? Speakers urged that, at a minimum, patients with hypersensitivity reactions or aneurysms should be on Plavix plus aspirin for life. A doctor in the audience countered that he only gives Plavix for six months because of the cost. A European doctor said, "We stop Plavix at 3-12 months because we have been ordered to do that."

The wisdom of stopping Plavix and aspirin because a patient needs other surgery also was discussed. Citing a case where a patient got two Cypher stents, stopped his Plavix four months later for a planned prostatectomy and died, a speaker said, "The use of a drug-eluting stent in patients undergoing planned surgery (no matter how large or small) is probably not advisable." Yet, another speaker said doing surgery while the patient is on Plavix+aspirin also doesn't work well, "We tried that, and we had hemorrhagic deaths." Dr. Virmani added, "Can you give generalized instructions? No…but in 80-year-old patients, I wouldn't use a drug-eluting stent."

At another session pathologist Dr. Virmani and Swiss interventional cardiologist Dr. Philip Urban debated whether drug-eluting stents will eventually thrombose and restenose. Dr. Virmani asserted, "It is clear that there will be late thrombosis with drug-eluting stents." Dr. Urban argued that the thrombosis rate for drug-eluting stents is no worse than for bare metal stents. Both doctors agreed that when late thrombosis occurs, it is serious.

> **Dr. Virmani:** She cited 35 autopsies she's completed, 15 of whom died of stent thrombosis, warning, "Absolutely, these stents restenose, but beyond the 12-month period because of the delayed healing. It takes much longer for a vessel with a drug-eluting stent to heal. It's going to take two to three years for these stents to restenose, but you cardiologists don't have the patience to wait that long. Your patients disappear. They die, probably."
>
> **Dr. Urban:** He pointed to long-term studies, including four-year results from the RAVEL trial, which showed no signs of delayed restenosis, no stent thrombosis, and no late stent thrombosis. He said, "It is theoretically possible that a late catch-up will occur, as was also − and wrongly − prophesized for bare metal stents, but we're not seeing that yet."

SPECIFIC STENTS

ABBOTT'S ZoMaxx

The key ZoMaxx trials are ZOMAXX-1 and ZOMAXX-2. Reportedly, only 10 centers are in the ZOMAXX-2 trial. The ZOMAXX-PK trial – a 40-patient, single arm study – also is going on, with a primary endpoint of 30-day MACE.

An Abbott-sponsored symposium reviewed development of this drug-eluting stent as well as the bare TriMaxx.

- A TriMaxx registry done in Brazil with a first-in-man design. The advantages of this stent were describe as: very low profile, good radio-opacity, excellent flexibility and conformability. Bifurcations were excluded in this trial, but the researcher, Dr. Alexandre Abizaid, noted that in 30%-40% of cases, there was a side branch involved, with no "pinch" in bifurcations – "the side branch was wide open" – but there were no data on re-crossing.

- Pathologist Dr. Virmani gave a fairly positive overview of the bioerodable polymer being used on ZoMaxx, and she praised the stent construction. She said, "I was very impressed with the TriMaxx design." In her study of 18 animals comparing the bare TriMaxx, ZoMaxx, Cypher, and Taxus, she found the ZoMaxx better than Cypher in terms of injury and inflammation scores. She also commented, "Most sirolimus-related drugs suppress pro-endothelialization, though maybe they are better than paclitaxel."

- An Abbott official said no name has been given to ABT-578 yet, but he promised one "soon." He emphasized the lipophilicity of ABT-578, saying it is 2.2-fold more lipophilic than sirolimus.

- Dr. Gregg Stone of Columbia University emphasized the importance of elution profiles – and noted that ZoMaxx has a profile very similar to Cypher.

TriMaxx Registry in Brazil

Measurement	TriMaxx (n=50)	
Diabetics	22%	
Unstable angina	24%	
Lesion length	10.7 mm	
RVD	2.82 mm	
Procedure success	100%	
	30-day results	6 month results
Late loss in-stent	.89	---
Late loss in-segment	.56	---
Restenosis in-stent	22%	---
Restenosis in-segment	22%	---
Primary endpoint: MACE	2%	10%
TVR	0	6%
Q-wave MI	0	2%
Non-Q-wave MI	0	0
CABG	0	0
Cardiac death	2%	2%

Key ZoMaxx Trials

Measurement	ZOMAXX-1	ZOMAXX-2
Location	OUS	U.S.
Design	Non-inferiority to Taxus	Non-inferiority to Taxus
Primary endpoint	Late loss in-segment at 9 months (to be equivalent must be within 0.25 mm of Taxus)	TVR at 9 months
Patients enrolled so far	228 of 400	N/A
First patient enrolled	September 2004	N/A
Concomitant heart medications	N/A	Aspirin 325 QD for 12 months Clopidogrel 300-600 mg loading dose Clopidogrel 75 mg QD for 12 months

BIOSENSORS

Biosensors is not expecting a European CE Mark until 1H06 for its biolimus-eluting BioMatrix stent. The company expects to have its automated, pipette-application production system in operation to produce stents for the U.S. trial. The 12-month results with the BioMatrix stent were presented. Biosensors/Occam got a CE Mark for their polymer-free paclitaxel-eluting Calix stent, Axxion, in July 2005.

12-Month Results of STEALTH-1 Trial

Measurement	Bare S-stent	BioMatrix	p-value
Diabetics	22.5%	26.6%	.66
B2 lesions	23.1%	31.6%	---
Class 4 lesions	3.2%	7.0%	.66
6-month MACE	2.5%	3.8%	---
12-month MACE	5.0%	6.3%	---
Other events	7.5%	8.9%	---

BIOTRONIK

Doctors are very interested in Biotronik's absorbable metal (magnesium) stent (AMS), but they continue to have a lot of questions about it. The PROGRESS-1 trial is underway, and by PCR about 65 patients had been enrolled. The company also is starting:

- A 130-patient PROGRESS-2 registry in France and Germany.
- A 300-patient trial in the U.S.
- An SFA trial.
- Eventually, a drug-eluting AMS trial. A speaker said, "We are working to add a drug to further decrease restenosis."

The biggest problem with the AMS stent is deliverability because it is not visible on angiography. Dr. Ron Waksman of the Washington Hospital Center, an investigator,

said, "This stent is not visible, but I don't see that as a negative because of the balloon markers. The only fear is if you lose the stent, but there is security built into the delivery system, so that is very rare. If we get comparable restenosis to drug-eluting stents, this would be attractive to me because we could reduce the Plavix use and could follow patients with non-invasive imaging and avoid late stent thrombosis. But the stent also has to perform on deliverability."

Apparently, there is about 5% recoil with this stent. Dr. Waksman said a pressure of 16 atm should give full apposition, but investigators are still learning what pressure is best.

In terms of absorption time for an absorbable stent, Dr. Waksman suggested it should be less than a year, perhaps two months, "I'd like two months. Health is established by then. It may be determined by recoil in follow-up. So far, there doesn't seem a problem with the current iteration with recoil, but we need more data. Two weeks is too fast." The audience (which was small) was asked their preferred timeframe, and they responded:

- 13% thought 1 week was best.
- 13% said 3 weeks.
- 26.1% said 2 months.
- 34.8% said 6 months.
- 13% said 1 year.

The audience also voted on what indications they thought would be most suitable for this stent:

- Coronaries 11.8%
- Femoral-popiteals 5.9%
- Intracranial 5.9%
- All 76.5%

BLUE MEDICAL

Blue Medical is working on a pimecrolimus-eluting stent. A source said the work is "very, very early." No animal or human results have been presented yet.

BOSTON SCIENTIFIC

Researchers and company officials focused on the positive results of the TAXUS-V and TAXUS-VI trials. The only really new data at PCR were on (1) the results in patients based on glycemic control and (2) slow-release (SR) vs. moderate release (MR) paclitaxel. A meta-analysis found SR was equivalent to MR in restenosis and safety but reduced late loss by 25% and reduced % volume obstruction by 33%. TAXUS principal investigator Dr. Gregg Stone said, "MR had no clear advantage on clinical outcomes but showed a subtle but predictable angiographic difference. There will be no further development of MR. SR is the minimum effective dose in this meta-analysis."

TAXUS-V Results Based on Glycemic Control

Measurement	Control	Taxus
TLR at 9 months		
Good glycemic control	14.8%	8.4%
Poor glycemic control	19.4%	6.9%
Restenosis at 9 months		
Good glycemic control	14.4%	2.3%
Poor glycemic control	14.4%	3.5%

Slow Release vs. Moderate Release Paclitaxel

Measurement	SR	MR	p-value
Amount of drug	1 μg/mm^2	1 μg/mm^2	---
Delivery	Biphasic	Biphasic	---
Release over 30 days	12 μg	33 μg	---
Meta-analysis of TAXUS-II, IV, V, VI			
Number of patients	777	423	---
RVD	2.75	2.81	.0284
Lesion length	19.8	20.6	.08
Stent length	32.9	N/A	---
Multiple stents	21.7	38.7	---
MI at 30 days	6.1%	7.8%	.67
Stent thrombosis	1.3%	0.5%	N/A
Late acquired aneurysms	1.6%	1.5%	Nss
TLR at 9 months	7.4%	7.3%	Nss
Late loss	0.53 mm	0.4 mm	.035
Restenosis	14.2%	N/A	Nss
% net volume obstruction	16.11	10.78	.019

Dr. Virmani criticized the data presentations on TAXUS-V and TAXUS-VI, but a Boston Scientific official defended the data presentation, suggesting Dr. Virmani was "confused." On overlapping stents, he said, "The risk:benefit with Taxus is absolutely on the positive side." He emphasized the ability of Taxus to work in complex lesions and the durability of the effect over time, noting that event-free TLR was 94.2% at one year and 85.1% at two years."

TAXUS-V

The IVUS analysis was presented on 509 patients, including complex lesions and 56 overlapping stents. The speaker said there was no negative edge effect seen.

TAXUS-VI

Two-year follow-up with the moderate-release formulation was presented. There was one additional stent thrombosis in the Taxus arm, but the total number of stent thromboses during the two year period was identical in the two arms. Dr. Eberhard Grube of the Siegburg Heart Center in Germany presented the data, and he concluded that persistent TLR in the

high risk group was decreased at two years. The data looked good, but Dr. Virmani criticized the statistics, saying the numbers don't add up. Another expert questioned about the data thought that might be accurate but didn't feel it changed the overall findings.

Liberté

Liberté has 27% thinner struts than Express and is 11% more flexible. The results of the multicenter, single-arm, non-inferiority ATLAS trial of Liberté vs. an historical review of the TAXUS-IV and -V patients were presented. The primary endpoint is 9-month TVR, which will be presented at ACC 2006. The Liberté post-approval registry reportedly plans to enroll >30,000 patients.

TAXUS-V 9-Month IVUS Results

Measurement	Control n=135	Taxus n=149	p-value	% reduction with Taxus
% net volume obstruction				
Overall	31.78	13.15	<.0001	Down 59%
Diabetics	34.08	13.05	---	Down 62%
Lesions >18 mm	---	---	---	Down 53%
Lesions >26 mm	---	---	---	Down 52%
Overlapping stents	35.38	14.62	---	Down 59%
Incomplete apposition				
Early	3.6%	6.0%	.44	---
Late	11.5%	6.1%	.14	---
Paired data on incomplete appositions				
Resolved	6.1%	0.9%	.05	---
Late acquired	8.7%	4.1%	.27	---

TAXUS-VI 2-Year Follow-up

Measurement	Control n=217	Taxus n=216	p-value
Additional events during Year 2			
Cardiac death	+2	+1	1.00
MI	+2	+3	0.69
TVR	+4	+6	0.54
TLR	+2	+3	0.69
2-year results			
TLR overall	21.0%	9.7%	.0013
TVR non TLR	2.3%	6.0%	.06
TVR	21.9%	13.9%	.0335
Freedom from TLR	79.0%	N/A	---
Q-wave MI	1.4%	1.4%	---
Non-Q-wave MI	5.5%	7.4%	.44
Stent thrombosis			
0-30 days	0.9%	0.5%	1.0
31-180 days	0	0	---
181-365 days	0	0	---
366-630 days	0	0.5%	1.0

30-Day Results of ATLAS Trial of Liberté

Measurement	Liberté n=871	Taxus n=991	p-value
Stent length used	10-28 mm	---	---
Diameter stent used	2.5-4.0 mm	---	---
Stable angina	52.8%	60.0%	.0017
Diabetics	67.4%	76.3%	<.05
RVD	3.14 mm	3.09 mm	.0177
Maximum stent diameter	3.13 mm	3.08 mm	.0258
	Group X	**Group Y**	**p-value**
Stent thrombosis in hospital	0.2%	0	---
Stent thrombosis out of hospital	0.3%	0.2%	---
Total stent thrombosis	0.5%	0.2%	Nss
MACE	3.3%	2.8%	.5
TVR	0.4%	0.2%	.69
MI	3.0%	2.6%	.57
Q-wave MI	0.3%	0.1%	.63
Non-Q-wave MI	2.7%	2.4%	.77
TVR	0.4%	0.2%	.69
TVR remote	0.1%	0.1%	1.0
TLR	0.3%	0.2%	1.0

The Future

Dr. Mary Russell, Senior Vice President of Boston Scientific, has been in charge of the Taxus program and the lead company speaker on Taxus. At PCR she appeared to hand over some of those duties to Joerg Koglin, Senior Medical Director and Vice President. Koglin compared Boston Scientific's drug-eluting stents approach to BMW's and Mercedes' approach to auto development, with "data decision-making, feasibility, proof-of-principle, and expansions." He described the SYNTAX trial as the "test drive." Expect to hear more from him in the future.

Conor Medsystems

Most European doctors questioned have heard of Conor, find it intriguing, but know very little about the company or its stents and, therefore, has no excitement or pent-up demand for the product. Among their comments were:

- *Germany:* "I'm not excited about it."
- *Italy:* "I've heard about Conor, but I don't know anything about it."
- *U.K.:* "Conor will be big, but it is a small player, so it can't push as well (as the larger companies)."

Twelve-month results from Arm 1 of the randomized, dose-ranging EuroSTAR trial of the paclitaxel-eluting cobalt chromium CoStar in de novo single and multi-vessel disease were presented. CoStar is a low profile, high radiopacity stent with a bioresorbable polymer. Dr. Keith Dawkins of the U.K.

and Dr. Antonio Colombo of Italy were the principal investigators.

In Arm 1 10 µg paclitaxel per 17 mm of stent was eluted over about 30 days. The data showed one additional death between six and 12 months. That patient was autopsied, and there was no evidence of stent thrombosis. There was no stent thrombosis between cessation of antiplatelet therapy at six months and 12-month follow-up.

EuroSTAR 12-Month Results

Measurement	Arm 1 n=145	Arm 2 n=125
TLR	2.9%	N/A
MACE	7.6%	N/A

In March 2005, a limited market release of the CoStar stent began in India through Interventional Technologies. CoStar will be marketed in Europe, Latin America, and parts of Asia by Biotronik.

GUIDANT

Vision. The 9-month results from the DaVinci Registry of the bare Guidant Vision stent in 1,344 patients with 1,642 stents showed TVR of 9.7%, 10.8% TVF, and 12.4% MACE, causing pathologist Dr. Virmani to say this compares favorably to drug-eluting stents.

Xience V, a durable polymer-coated cobalt-chromium Vision stent eluting everolimus. The principal investigators in the SPIRIT-III trial of this drug-eluting stent are Dr. Campbell Rogers of Brigham & Women's Hospital in Boston and Dr. Gregg Stone. The principal investigator for the SPIRIT-II trial is Dr. Patrick Serruys of the Thoraxcenter in Rotterdam, the Netherlands. Guidant got an IDE in May 2005 and was due to start the SPIRIT-III trial in 2Q05.

Bioabsorbable everolimus. Guidant's Dr. John Kapek reviewed the company's bioabsorbable everolimus program (the FUTURE trials), which uses a bioabsorbable polymer, Vision balloon delivery, everolimus, and the Champion S-stent. He claimed it: performs like a metallic stent, is non-inflammatory and non-thrombogenic, and is easily processed and sterilized. With the PLA polymer, it is possible to load >50% drug. The stent thickness is 0.0070 inches. The company is still conducting long-term animal studies (which were approaching 15 months at the time of PCR). Full degradation is expected in 18-24 months. First-in-man studies could begin in early 2006.

JOHNSON & JOHNSON

J&J sources offered some interesting perspective on several topics:

- The U.S. Federal Trade Commission (FTC) so far has not appeared to have many problems with the Guidant purchase. Officials were optimistic that not very much would have to be divested.
- J&J may ask the FDA for either (a) a better label for Cypher stents in terms of overlapping stents, or (b) a warning label on Taxus stents about overlapping stents. It is unlikely the FDA will grant either request.
- When the J&J/Guidant merger goes through, it is likely that the Guidant offices in Indianapolis will be closed and all stent operations consolidated either in Miami, where Cordis is now headquartered, or in California.

Neo stent

Development of this stent was on hold, but it has been moved back to active status, though it will not be on the market before at least 2006.

RAVEL

Four-year follow-up on Cypher showed the data are holding up. The secondary endpoint of MACE (death MI, TLR) continued to be statistically significant vs. bare control, but when MACE was defined as death, MI, and clinically-driven TLR, it was not statistically significant due to a higher rate of non-cardiac deaths in the Cypher group. Stent thrombosis and late stent thrombosis remained zero.

4-Year Results on Cypher in RAVEL

Measurement	Cypher n=118	Bare stent n=115
MACE free survival	78.0%	65.2%
TLR	5.9%	25.2%
TLR-free survival	91.8%	73.4%
TVF-free survival	84.6%	65.0%
Death total	1.0%	6.1%
Cardiac death	2.5% *	4.3%
Non-cardiac death	8.5%	1.7%
Q-wave MI	2.5%	0.9%
Non-Q-wave MI	2.5%	2.6%

* All heart failure

MEDTRONIC

On July 31, 2005, Medtronic's Endeavor, a cobalt alloy stent eluting ABT-578, gained a CE Mark. At PCR doctors were wondering when Endeavor would be launched in Europe. At the meeting, Medtronic officials said they had no idea why they hadn't heard about the Endeavor CE Mark approval by PCR. The company submitted an application in February 2005, answered the questions, and then waited a long time with no back-and-forth with regulatory officials. One Medtronic source called it a state of "radio silence." Another source speculated that the European device regulators are probably okay with Endeavor but thought the hold-up was on the drug side, which was what it apparently turned out to be.

European doctors, questioned about the outlook for their use of Endeavor, predicted it would do very well in Europe. By the end of 2005, they predicted it would take an average of 29% market share or more. Among their comments were:

- *Germany:* "I will use it, and it could become No. 1. I'll try 20 (Endeavor) stents, and test it, but the flexibility and practicability look good."
- *Italy:* "Endeavor will be the best drug-eluting stent for deliverability and trackability. By the end of 2005, it will have 20% market share…Endeavor could be the dominant stent if it is priced less than Taxus…I'll probably use Cypher when I need more than one stent, and Taxus for single stent lesions."
- *U.K. #1:* "I will use Endeavor because it is a much better stent on deliverability…Endeavor could take 50% market share in six months, mostly at the expense of Taxus."
- *U.K. #2:* "Endeavor will become the dominant stent eventually, but it won't be a sudden shift…In six months, our use will be one-third for each (Cypher, Taxus, and Endeavor), but in 18 months, we'll be using 70% Endeavor. Endeavor handles better."
- *France #1:* "At first, we'll try Endeavor, but it will probably take 20% market share by the end of 2005, mostly in lieu of Taxus."
- *France #2:* "In a year, we'll be using one-third Endeavor, one-third Taxus, and one-third Cypher. Safety is the same for all of these."

One presentation at PCR played up the purported safety advantages of Endeavor over either Cypher or Taxus, particularly the lack of any stent thrombosis after seven days and a shorter requirement (3 months) for Plavix. Dr. Marty Leon of Columbia University commented, "There are multiple safety 'signals,' suggesting that drug-eluting stents may be associated with an increased frequency of either early and/or late clinical events (stent thrombosis, death, and MI) when compared with bare metal stents. Is late thrombosis an issue? Maybe!" Dr. Leon noted that the Milan experience with Taxus and Cypher showed a stent thrombosis rate of 1.7% with Taxus and 0.9% with Cypher, but the numbers were small and the difference not statistically significant (p=.09).

ENDEAVOR-II

A subset and safety analysis showed consistent results with no surprises. Dr. Richard Kuntz of Brigham & Women's Hospital presented the data, though he noted his personal objection to unspecified subset analyses. He commented that:

- The most recent meta-analysis of drug-eluting stents indicates that there is not a problem with stent thrombosis.
- There have been a total of 10 deaths in the trial, including 4 sudden cardiac deaths – 3 with Endeavor and 1 with bare Driver. If these were added to the stent thrombosis, the difference would still not be a statistically significant difference. But his personal opinion is that sudden cardiac deaths should not be including in the definition of stent thrombosis. He said, "In ENDEAVOR-II, if sudden cardiac death were included in stent thrombosis, they (Medtronic) should have had another 20-30 MIs, and they didn't."
- The stent thrombosis rate was 0.5%. There were no other safety concerns.
- The subset analysis showed consistent benefit vs. bare metal stent.
- There was a higher rate of TLR with longer lesion length, but the results were consistent.

ENDEAVOR-II Subset and Safety Analysis

Measurement	Bare Driver	Endeavor
TLR		
Non-diabetics	10.9%	3.9%
Diabetics	15.2%	7.5%
Diameter <2.5 mm	16.5%	7.2%
Diameter 2.5-3.0 mm	11.5%	3.0%
Diameter >3.0 mm	7.6%	4.0%
Stent thrombosis	0.5%	1.2%

ORBUS MEDICAL TECHNOLOGIES' Endothelial Progenitor Cell (EPC) Seeding Program

Development of this R-stent delivering EPC continues to progress. Final results of the 1-patient first-in-man study are expected at PCR 2006. An interim analysis of the HEALING-2 trial found TLR/TVR only in the low EPC group.

SAHAJANAND MEDICAL TECHNOLOGIES

There were no new data on Sahajanand's paclitaxel-eluting Infinnium stent, but six-month follow-up data from the prospective, multicenter SiMPLE-2 trial are expected at TCT 2005.

SORIN GROUP'S Janus stent

This tacrolimus-eluting Janus CarboStent is a dark horse that could be a come-from-behind surprise. Tacrolimus is sold as Prograf for immunosuppression and as Protopic for atopic dermatitis by Astellas, formerly known as Fujisawa Pharmaceutical Co., so it is a well-known and U.S.-approved drug. The stent has sculptured reservoirs or wells on the external surface of the stent struts, and it does not utilize a polymeric coating. A company official said peak drug release is at one week, then there is a slow release, so that at 30 days about 50% is released and at 90 days about 100% is released.

Janus got a CE Mark in October 2004 and was launched in Europe shortly thereafter, making it the third drug-eluting

stent on the European market. The company claims to have implanted it in >10,000 patients world-wide (non-U.S.), and >500 patients have been enrolled in an international e-Janus electronic post-marketing surveillance registry.

JUPITER-2 Trial of CarboStent

Measurement	Group A-1 n=166	Group B n=166	p-value
Diabetics	20.1%	17.6%	Nss
Bifurcations	0	3.2%	.03
Lesion success	99.5%	99.5%	Nss
Procedural success	95.5%	95.5%	Nss
Lesion length	11.83 mm	12.33 mm	---
30-Day results			
TLR	0	0	Nss
MI	0.6%	0	---
MACE	0.6%	0	---
6-Month results			
TLR	11.8%	4.5%	---
MI	0	0	Nss
MACE	11.8%	5.7% *	---
MACE: stent-related	11.8%	4.5%	---
Death	0	0	Nss
Q-wave MI	0	0	Nss
Subacute thrombosis	0	0	Nss
Late thrombosis	0	0	Nss

* One case of non-cardiac death

Sorin reportedly is looking for a partner for the U.S. and wants a distributor in Japan. A Sorin source said the company has talked with Medtronic and "maybe it is time to talk with them again." A cardiologist said, "Janus is good, but the company is a small player."

The clinical results of the JUPITER-2 trial of Janus vs. a bare Tecnic stent will be presented at the European Society of Cardiology in Stockholm in September 2005, and the angiographic results at TCT in October 2005. This is a randomized, double-blind trial of direct stenting. The principal investigator is Dr. Marie-Claude Morice. Enrollment is completed, but follow-up is not complete. Dr. Morice said she is encouraged by these results but she is reserving judgment until she see the QCA results at ESC and TCT.

TERUMO/ BIOSENSORS

Terumo enrolled the first patient (a live case) during PCR in its 360-patient, prospective, randomized NOBORI-1 trial of the Nobori stent (eluting biolimus A-9 through a poly-lactic acid bioabsorbable polymer) vs. Taxus. (Biolimus A-9 was developed by Biosensors.) The stent is coated with biolimus only on the outside, abluminal surface, in an attempt to reduce the systemic exposure to the drug.

The trial is being conducted in Europe, Australia, and Asia. The primary endpoint is 9-month in-stent late loss. Secondary endpoints include restenosis, TLR, TVR, and TVF at nine months as well as stent thrombosis at 30 days and nine months and MACE at 30 days, four months, nine months, 12 months, and then annually up to five years. The principal investigator is Dr. Bernard Chevalier of France.

NAVIGATION

STEREOTAXIS'S Niobe

Stereotaxis sponsored a breakfast at PCR – a common event at U.S. medical conferences, but not a particularly popular idea in Paris, apparently – to present information on Niobe, a digital magnetic system for navigating catheters and guidewires through the cardiovasculature. Attendance was sparse at the breakfast, but at least one attendee was considering a purchase.

By PCR, three units had been installed in Europe – two in Germany, and one in the Netherlands. Dr. Roderick Meese, whose hospital, Trinity Mother Frances Heart Hospital in Tyler, TX, was the first U.S. site for Stereotaxis (in September 2003) cited several advantages to the system:

- More efficient. And he did report that it shortened procedure time, allowing the hospital to treat more patients.
- Reduction in radiation exposure.
- Change in the physics of wire delivery by improving navigation through tortuous and highly angulated vessels, allow tip alignment in CTOs, and be useful in research.
- Marketing.

In this hospital today, EP and interventional cardiology share one Stereotaxis system, but another is being installed, so interventional cardiology will have its own system. He said, "Right now, about 15% of our (PCI) cases are done with Stereotaxis, and it will be 25%-30% with the new room…I anticipate advances will be approved for EP (e.g., AF ablation), and we are looking at it for the future."

A Stereotaxis system generally means a new fluoroscopy system and a complete upgrade of the existing lab or building a new one – for a total cost of about $2 million. Disposables cost about 10%-20% over the cost of standard products. A source said that, typically, hospitals upgrade their cath labs once every 10 years, and many are planning ahead, a company official said. Dr. Meese explained that there is no separate DRG payment for using Stereotaxis to help recover the costs, but he believes it is still a good investment, "My hospital wants to be on the forefront…Our volume has gone up, and we think there has been an increase in tertiary referrals." A Stereotaxis official said, "The system can pay for itself in two or three years if it adds just two or three cases a week. And the U.S. market is not focused on disposable savings. The

average conventional wire use is 1.62 per case; we are 1.001 guidewires per case."

Reimbursement issues also are different in Europe. There, hospitals provide a fixed reimbursement to cath labs for procedures, so more cases don't increase their revenue. An official explained, "For European hospitals, decreasing disposable costs is huge – and patients not going to CABG are a big savings because CABG is a cost center, not a profit center, for them."

A Stereotaxis official said the company is focused on complex coronary cases, which he estimated make up 20%-25% of procedures. New tools just launched or in development include:

- **Navigant 2005**, which was just launched.
- **Cronus guidewires**, which are on the market in the U.S. and are expected to get a CE Mark in June or July 2005. These reportedly have improved deflection, more lubricity, a Teflon coating, and moderate support (which is popular in the U.S.). These may be more useful in large vessels.
- **Argosy microcatheters**. Conventional wires with ablative devices can go inside these.
- **Titan guidewires**, which were described as the "BMW" of guidewires. These are more trackable than the Cronus guidewires. A design test is due to start in about a month, and U.S. approval is expected by the end of 2005. These are for traditional use or navigation, and they offer more lubricity, a more responsive tip, and a shorter magnet (2 mm instead of the usual 3 mm). These may be more useful in small vessels.
- **Bifurcation capability** was added about a month ago with IC NaviView.
- **Steerable ablative CTO tools** are on the drawing board, and a prototype uses a magnetic RF wire.
- **A drug-eluting stent delivery system** is under consideration but not in firm plans yet. Currently, to deploy drug-eluting stents with Stereotaxis, doctors substitute the wires that come with the DES system with the Stereotaxis wires.

PERIPHERAL ARTERIAL DISEASE

SPECTRANETICS CVX-300
BOSTON SCIENTIFIC'S CryoCath
FOXHOLLOW TECHNOLOGIES' SilverHawk

All of these products are designed to open occluded peripheral arteries. FoxHollow did not have a booth at PCR. A session on these technologies – plus balloon, debulking, and cutting balloons – was well attended. Interesting points that were made about these products include:

- "We don't need procedures that last 10 years, because the typical patient doesn't live that long."
- A speaker said their experience with 279 patients (with 305 affected limbs) showed a complication rate of 11%, which was described as "acceptable," a healing rate ≤1 cm^2/month (considered the minimum), and a 14.8% major amputation rate/year.
- "All these technologies have good initial results, but we need long-term follow-up and level 1 evidence."
- Referrals come mainly from general practitioners, nephrologists, cardiologists, and internal medicine doctors, who refer a lot of diabetic patients. Referrals from nephrologists and internal medicine doctors reportedly are increasing.

There is no clear-cut winner yet in this technology, and the choice of system is often based on personal preferences. One expert said, "For very calcified lesions, especially in diabetics or dialysis patients, I might choose a cutting balloon or Fox-Hollow to debulk. If it is soft tissue or a long lesion, I'd use a balloon or a laser." His experience with CryoCath was not satisfactory, "I did 15-20 SFA patients. It was successful in 12, but the goal is 15 of 15, so the company has work to do. I think Boston Scientific will make it better, but it has to be stand-alone without a stent because it is so expensive."

With the Spectranetics' CVX-300 excimer laser, there are three options, but a company source would not say which is currently the most popular:

1. Lease.
2. Purchase.
3. Pay a per-procedure fee. A source said, "This is becoming less and less legal."

While there are three markets for CVX-300 – vascular surgeons, radiologists, and cardiologists – sources indicated that vascular surgeons are the key buyers now. General practitioners are referring patients to vascular surgeons for laser therapy.

IGAKI MEDICAL

This company is developing the Igaki-Tamai peripheral stent, and a CE Mark is expected "soon." This is a PLLA stent that biodegrades over two to three years. Reportedly, it maintains its radial strength for about six months.

The company also has a coronary stent in trials, and 45 patients reportedly have been done so far in Germany and Japan. In addition, Igaki is working on a tranilast-eluting stent. So far, that is only in animal trials in Japan, but, if successful, it is expected to be marketed in Europe before Japan or the U.S.

JOHNSON & JOHNSON'S Cypher

German researchers presented 6-month data at PCR from CYPHER-BTK, a pilot study on the use of Cypher stents in the treatment of below-the-knee critical limb ischemia (CLI), which occurs when blood flow to a limb is inadequate to maintain reasonable metabolic requirements of the tissues at rest. Pain at rest, in the extremity involved, initially appears only when the limb is elevated and improves in the recumbent position. As the disease advances, rest pain persists in any position and becomes less responsive to conventional pain treatment. Ischemic ulcers are a more advanced stage of CLI and usually appear near bone prominences. Gangrene results from complete tissue death and may be limited to the extremities of the toes or fingers, or it may involve a significant part of the limb.

6-Month Results of CYPHER-BTK Trial

Measurement	Cypher n=30	Bare Sonic n=30
MACE	10.0%	46.6%
Major amputations	0	10%
CABG	0	0
TLR	0	13.3%
In-stent restenosis	0	39.1%
Stent occlusions	0	17.4%

PATENT FORAMEN OVALE (PFO) CLOSURE

Several companies – including NMT Medical, AGA Medical, Cierra, and St. Jude's Velocimed – are investigating the use of PFO closure devices to treat migraine headaches. All of these are believed to be negotiating with the FDA for an IDE.

A PFO is an incomplete closure of the atrial membrane of the heart. It is believed that a PFO allows venous blood, unfiltered by the lungs, to shunt (flow) into the arterial circulation of the brain. This unfiltered venous blood may contain elements (chemicals or microembolisms) that may trigger migraine headaches, strokes, or transient ischemic attacks (TIAs).

About 10% of Americans – 28 million people – reportedly suffer from migraines, and ~20% of these have migraine with aura. Of these, about three million have both an aura with their migraine and a PFO, and these are the people that investigators hope will have their migraine relieved by closure of the PFO. NMT officials emphasized how large this migraine population is – which may, at least in part, explain why the FDA is concerned about over-use of PFO closure devices. However, an investigator estimated that the target patient population for PFO closure devices is about 5% of migraine sufferers – or 1.4 million Americans.

Two companies – NMT Medical and AGA Medical – currently market PFO closure devices in the U.S. under a humanitarian device exemption (HDE). Both companies also have IDEs and are seeking PMA approval of the devices for PFO closure. The NMT trial is CLOSURE-1, and the AGA trial is RESPECT, but enrollment in both trials reportedly has been very slow.

The FDA has been very concerned with the over-use of PFO closure devices, so it is a tough U.S. regulatory environment. So far, the FDA has not approved a protocol for a PFO closure migraine trial in the U.S. As a result, NMT Medical chose to do the first PFO migraine trial in the U.K. In May 2005, Dr. Daniel Schultz, Director of Cardiovascular Devices and Radiologic Health (CDRH) for the FDA, said, "We still have major concerns with regard to use of PFO closure devices. This is a challenge for us from a regulatory standpoint and for you from a scientific standpoint…We want to get them to market in a way that people know what they should and shouldn't be used for."

AGA MEDICAL. A company official said AGA plans a U.S. trial in migraine but offered no timeline. However, it appears the trial will be done only in the U.S., not in Europe.

CIERRA. This private California company started early human trials in Europe in April. This device uses a suction device to hold the tissue in place, and then radio frequency (RF) heat is used to seal the PFO. The advantage of this device is that nothing is left behind in the patient. Reportedly, Cierra is aiming for a CE Mark and launch in mid-2006.

COAPTUS MEDICAL. This private company in Redmond WA, with the help of Boston Scientific, also is investigating an RF-based closure device. It expects to begin human trials by the end of 2005.

JOHNSON & JOHNSON'S NITINOL DEVICES AND COMPONENTS. This company is taking a different approach – using nitinol mesh to promote tissue adhesion and create an immediate barrier to emboli migration plus a sizing device to enable better conformity to the geometry of the PFO and a retrieval device in case of improper placement. There was no information on when human trials are likely to begin.

NMT MEDICAL. NMT Medical announced shortly after PCR that enrollment is complete with 147 patients in the prospective, randomized MIST trial. This study is testing the ability of its STARFlex PFO closure device to reduce migraine headaches. The study, which began in January 2005, is being conducted in the U.K., and the results are expected in 1Q06, possibly at the American College of Cardiology, though an abstract could be presented as early as the American Heart Association meeting in November 2005.

Preliminary demographic information from MIST was presented at PCR. This early look at the whole cohort of patients found that 60% of migraine patients had a right to left shunt, the majority of which were PFOs. This is more shunts

than is typically seen in the general population. Furthermore, >40% of the migraine patients studied had a large shunt – six times the size expected in the general population – and >85% of these large shunts were PFOs. In addition, pulmonary shunts were found in 10% of the migraine patients. In previous studies, PFOs have been found in only ~27% of the general population, and usually only ~7% of these are large.

An expert offered several interesting comments on MIST, including:

- "Patients and doctors are not blinded in MIST."
- "The completeness of PFO closure does not appear to be associated with migraine relief."
- "The control patients get sham, but what is the role of medical therapy in those patients?"
- "Migraine tends to appear in the teens and 20s, not so much later in life."
- "If MIST is positive, it will be a blockbuster, but if it is negative, we will have to go back to the drawing board."

NMT also is in discussions with the FDA about starting a U.S. MIST-like trial of PFO for migraine. ***Medical Device Daily*** reported that the FDA will require a fully blinded sham arm in this trial.

The multicenter BEST trial which also is exploring PFO closure as a treatment for migraines, has started enrolling patients. BEST is testing a new, bioresorbable collagen matrix PFO closure device, BioSTAR.

PROXIMARE. This private company, founded by an interventional cardiologist at the University of Utah, also is working on a device that is believed to promote tissue growth without leaving a foreign body behind. Animal trials are underway, and human clinical trials could begin later this year or in 2006.

ST. JUDE'S VELOCIMED. Velocimed's PFO closure device, Premiere, already has a CE Mark, and marketing was expected to begin this summer. A source said a sham control will be required for any migraine trial in the U.S. but that the FDA has been "very receptive" to the idea of a migraine trial.

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