Trends-in-Medicine

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By Lynne Peterson

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PARIS COURSE ON REVASCULARIZATION (PCR)

Paris, France
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This was a news-filled PCR, and drug-eluting stents (DES) dominated the meeting. A ream of positive new drug-eluting stent trial data, particularly for Johnson & Johnson's Cypher and Boston Scientific's Taxus stents, was overwhelmed by Guidant's announcement of a delay in its bioerodable drug-eluting stent program and the high in-stent late loss in a key trial of Medtronic's Endeavor drug-eluting stent. In fact, the Endeavor late loss data caused some sources to predict that the whole Endeavor program is now in jeopardy, at least in the U.S. There also could be negative implications for Abbott's ZoMaxx drug-eluting stent program as well.

Cypher is expected to regain a little of the market share it lost to Taxus, and directors of two large U.S. labs said they had recently switched back to Cypher from Taxus – because J&J is under-pricing Boston Scientific. A source said, "Boston doesn't want to go lower." Sources also predicted that pricing will stabilize around the current price they are paying, though they didn't specify what that is.

A New England cardiologist predicted that Endeavor will be the next DES to gain U.S. approval, followed by Guidant's Champion stent, and then Guidant's Spirit stent (durable polymer coated Vision eluting everolimus). However, he doubts that Guidant will commercialize both Champion and Spirit at the same time. In terms of the marketing outlook, he predicted that once all of these stents are on the market, doctors would use:

- 50% Guidant Spirit. He said, "If the data is like the FUTURE-1 and FUTURE-2 trials, it will win by a landslide. It is deliverable, and it would have better anti-restenotic properties. Plus Vision is a good stent."
- 15% Boston Scientific Taxus
- 15% J&J Cypher
- 10% Medtronic Endeavor. This source warned that even if the Endeavor stent gets FDA approval, the late loss issue may dampen use severely.
- 10% Guidant Champion

DRUG-ELUTING STENTS

Measurement	Johnson & Johnson's SIRIUS	Boston Scientific's TAXUS-IV	Boston Scientific's TAXUS-VI	Medtronic's ENDEAVOR-1	Guidant's FUTURE-2
Stent	Cypher	Taxus	Taxus	Endeavor	Champion
Drug-eluting stent patients	533	662	446	100	21
Time period	9 months	9 months	9 months	12 months	6 months
Late loss (in-stent)	0.17 mm	0.39 mm	0.39 mm	0.58 mm	0.12 mm
Restenosis in-segment (drug vs. control)	8.9% vs. 36.3%	7.9% vs. 26.6%	12.4% vs. 35.7%	3.3%	0% vs. 19.4%
Restenosis in-stent (drug vs. control)	3.9% vs. 42.3%	5.5% vs. 24.4%	9.1% vs. 32.9%		0
TLR (drug vs. control)	4.1% vs. 16.6%	3.0% vs. 11.3%	6.8% vs. 18.9%	1.0%	4.8%
TVR (drug vs. control)	6.4% vs. 19.2%	4.7% vs. 12.0%	9.1% vs. 19.4%	N/A	---
MACE	7.1%	8.5%	6.9%	2.0%	4.8%

ABBOTT LABORATORIES

ABT-578

There was no new data on ABT-578 at PCR, but there was new information on the company's ABT-578 program. The drug will be on a new stent platform, TriMaxx. There are four components to stent:

1. **Triplex material** – The stent is a thin layer of titanium (0.0007 mm) sandwiched between two layers of stainless steel, for a total strut thickness of 0.0029 mm). TriMaxx reportedly has the thinnest struts of all current stents. It has good radio-opacity and has shown no signs of delamination in testing. Dr. Marty Leon, of Lenox Hill Hospital in New York, commented, "I do think strut thickness makes a difference…There is still enough surface area to load what we now call a standard (drug) dose…They will load an identical dose to sirolimus and everolimus…If you cut the Cypher dose in half, you still see late loss of 0.1 mm, so we are probably overdosing with sirolimus…And there is very homogenous drug distribution with this stent…The opportunity for the drug to reach the central portion of the stent is greater for this than for many other stents."
2. **A.R.C. technology** – which is the stent geometry and design, which were described as offering excellent scaffolding, flexibility, and trackability. Dr. Leon said, "The crimped stent crossing profile is unparalleled – much less than all other available stents, and the trackability is equivalent to Driver and less than the others."
3. **Catheter** – which is low profile, with minimal balloon overhang.
4. **PhosphoCoat polymer** – a different form of phosphoryl-choline than Medtronic is using on its Endeavor stent.

The first clinical trial of the TriMaxx stent began in mid-May 2004 in Brazil. This is a multicenter, non-randomized, single-arm registry. The company plans to add sites in Germany and Argentina. The primary endpoint is 30-day MACE, with follow-up angiography at six months. Enrollment is expected to be complete in a few months.

The whole Abbott drug-eluting stent program with ABT-578 is called ZoMaxx, and that name includes the drug+stent+polymer. Abbott reportedly toyed with, but rejected, the idea of zolimus as the generic name for ABT-578. ZoMaxx differs from sirolimus by the addition of a tetrazole ring at the 42-position. It is cytostatic and primarily anti-proliferative, but it is also anti-inflammatory. Unlike Endeavor, ZoMaxx has a topcoat of phosphorylcholine to slow elution, and that coating is thicker on the arterial side.

In animal studies, the uptake of ABT-578 was greater than sirolimus and the serum level lower. So the key differences ZoMaxx claims over Cypher are:

- Better uptake in the artery – higher arterial concentration
- Lower serum concentration.

ZoMaxx-1, the first clinical trial, is a 400-patient, randomized, non-inferiority trial comparing ZoMaxx to Taxus at 34 sites in Europe, Australia, and the Middle East. Lesions must be ≥12 mm and ≤30 mm by 2.5-3.5 mm. Predilatation is required. The primary endpoint is nine-month in-segment late loss (delta 0.25 mm). Patients will be given clopidogrel for a minimum of 12 months and preferably 12 months. Follow-up will be at 30 days, six months, nine months (with QCA), 12 months, and then annually out to five years. Enrollment is due to begin in 3Q04.

ZoMaxx-2 will be the North American trial, with Dr. Rick Kuntz and Dr. Alan Yeung the principal investigators. The design is currently under discussion with the FDA, but it reportedly will include 1,000-2,000 patients, will have a so-far unnamed DES comparator, and will use a clinical endpoint, not late loss. It will leverage the ZoMaxx-1 data but will expand the patient base.

Dexamethasone

The news was not encouraging, despite a researcher's attempt to slice, dice, and spin the results of the DESIRE trial, an Italian registry of 332 patients getting 419 dexamethasone stents between July 2003 and May 2004. The trial was sponsored by Abbott and conducted at 20 sites in Italy.

Results of DESIRE Trial

Measurement	Results
Diabetics in trial	22%
IIb/IIIa use	21%
Average stent diameter	3.15 mm
Average stent length	16 mm
30-Day Results (n=298)	
MACE	2%
6-Month Results (n=190)	
Primary endpoint: MACE at 6 months	14.2%
TVR	10%
Death	0.67% (1 SAT with AMI+shock, 1 aortic dissection)
AMI	3.2%
Secondary endpoint #1: MACE at 12 months	Not available yet
Secondary endpoint #2: Restenosis at 12 months MI	Not available yet

Comparative TVR Rates

Trial	8-9-month TVR
TAXUS-IV	4.7%
SIRIUS	4.1%
RESEARCH registry	3.7%
TAXUS-VI	9.1%
DESIRE	10%

The principal investigator tried to explain the high TVR and MACE by comparing these results to other trials. He also argued that the TVF in DESIRE would only be 6.1% if the 56% of patients who were not "trial-type patients" were excluded. He claimed the stent "should have a future," but the doctors in the audience were dubious, and Dr. Marty Leon, a moderator, commented, "I would suggest that sirolimus is a potent anti-inflammatory drug. So is paclitaxel…I think these drugs have multiple actions…and I have to honestly say making intra-trial comparisons can be very misleading. Some of the comparisons to the trials are overly simplistic…None of your patients had angiographic follow-up…If you have a strong feeling this device is equivalent (to other drug-eluting stents), then do a randomized trial against a drug-eluting stent. Right now, I'd say this is inconclusive against drug-eluting stents, even in acute coronary syndromes."

BIOSENSORS/TERUMO

STEALTH-1 is a 120-patient, prospective, randomized, double-blind, multicenter, single-arm study evaluating the Senso system – biolimus A-9 eluted from an S-stent. Patient enrollment in the trial commenced in September 2003 and ended in March 2004, enrolling de novo lesions ≤24 mm in length, with reference vessel diameters between 2.75-4.0 mm. There were no diabetics in STEALTH-1 and no direct stenting (predilatation required). There will be 6-month follow-up data at TCT 2004 and nine-month follow-up at ACC 2005.

First-in-Man Results from STEALTH-1 Trial

Measurement	ARM A	Arm B
Primary endpoint: Late loss at 6 months	N/A yet	N/A yet
Death	0	0
MI	1.5% (spiral dissection during predilatation; patient never got study stent.)	0
MACE	2.9% one MI	0
TLR	1.4% acute stent thrombosis immediately after procedure	0
Death	0	0
CABG	0	0

The agreement between Biosensors and Terumo is only for Europe and Japan. The pivotal European trial (which is not yet named) is due to start in November or December 2004 at 30 centers, enrolling <1,000 patients.

Biosensors plans to leverage the European STEALTH data to go directly to a 2,000-patient pivotal trial in the U.S. – once it finds a U.S. partner. The company has had one meeting with the FDA on the IND and is planning another meeting soon.

BIOTRONIK

Doctors are interested in Biotronik's absorbable metal (magnesium) stent (AMS), but they have a lot of questions, and the data is very early.

A researcher reported on the post-procedure results from a first-in-man BEST BTK trial, in which AMS stents were implanted below the knee. Between December 2003 and January 2004, 63 patients with critical limb ischemia were enrolled just before limb amputation (Rutherford 4-5). Procedure time averaged 56 minutes. At three months, 89% of the stented vessels remained patent. Six-month data from this trial will be available in July 2004, after which the company will look at starting a randomized trial.

Among the issues an expert said the trial helped address were:

- Is the stent safe? He said, "We didn't find any value changes at pre-procedure, one day, 30 days, or beyond." All the limbs were salvaged, but there were several complications, as would be expected in this very sick population, including:
  - 10-hours post-procedure: a hematoma at the groin which required a pacemaker and resolved very well.
  - 24 days post-procedure: a patient died of pneumonia not related to the device.
  - 43 days post-procedure: an occlusion of the left proximal required a fem-fib bypass, surgical removal of the stent area, and replacement by a short venous bypass, then amputation due to continued deterioration. Death was due to pneumonia after amputation surgery.
- Did it provide sufficient support? He concluded it did.
- Is it absorbed as intended? He said it is completely absorbed by 90 days, but that data is not yet available from this trial.
- Does the stent remain patent? He believes it does.
- Is there good imaging with MR-angiography? He said it can be seen with MR-angiography, but it is not visible on fluoroscopy, so placement has to be done very carefully, adding, "You can't see the stent, so you have to be careful not to lose it…We controlled patients with IVUS to be sure the stent was in the right place." Another investigator explained how to place a second AMS stent: "You do have two markers on the balloon…When you do the implantation, if you feel it, you know the position, and then you use it as a roadmap…That helps."

Asked if the Biotronik stent will eventually need to become a drug-eluting stent or whether it will have utility as a bare metal stent, a speaker said, "For sure, it is possible that you can put a medication or drug on this stent. I'm not sure they will start to do that now. One of the observations in pigs is that there is not so much in-stent restenosis…And you already have the effect of this heavy metal…so they work almost like a drug-eluting stent…I'm not sure they have to go that far."

Asked where AMS stents are most likely to be useful, a speaker said, "First we need to demonstrate they work in coronary arteries…Perhaps you should ask this question in two years. Where I think they will be most important is where we need to do multiple stents – bifurcations, re-interventions – but it is probably too early to answer that…First, we need to know how they behave…and if there is good evidence of low restenosis…But the potential is there for a large market."

Deal with CONOR MEDSYSTEM

During PCR, Biotronik announced a distribution and research deal with Conor, which is developing a different approach to drug-eluting stents. The deal applies world-wide except for the U.S. and Japan. Sources described the deal as likely to be good for both companies. Biotronik will market and sell the COSTAR stent, and Conor will manufacture the stent. A Biotronik official said, "Conor plans to sell the Costar in the U.S. itself…The research arrangement was…to create a bioabsorbable drug-eluting stent."

BOSTON SCIENTIFIC

In early May 2004, Boston Scientific announced that it had gotten FDA approval for a small design change to laser welded balloon bond on the Taxus stent, following reports of problems with retraction. A Boston Scientific official insisted that the change has already been made, and stents with the change incorporated already are shipping. He insisted there are no additional changes coming this fall. The change was not intended to address the stickiness issue, for which the company reportedly has not been able to find a solution, and U.S. doctors appear to be learning to live with the stickiness.

There was good news from the company's 446-patient, European, randomized, double-blind TAXUS-VI trial of moderate release paclitaxel in long lesions (≥18 mm and ≤40 mm), small vessels, and diabetics. Multiple stents were allowed. In this trial the same dose (10 $\mu g/mm^2$) was used as is on the commercially-available Taxus stents, but the local drug release was three times higher.

Key 9-month findings:

- Primary endpoint: TVR = 9.1%, a hair higher than expected.
- In-stent restenosis = 9.1%, in the expected range.
- Late loss = 0.39 in-stent, as expected.

Interestingly, the MACE rate in TAXUS-VI was not statistically significantly different from control. There were 14 cases of in-stent restenosis (ISR) in the Taxus arm of TAXUS-VI. A speaker described this ISR as "rare" restenosis that is "totally confined and easy to approach with percutaneous techniques." He claimed:

- The restenotic lesion length was short, making it easy to treat this ISR with percutaneous methods.
- The ISR pattern was focal in 63% of cases.
- The ISR pattern was similar in various high risk subsets, including diabetics, small vessels, longer lesions, and multiple overlapped stents.

Dr. Mary Russell, Vice President for Cardiovascular Affairs at Boston Scientific and the chief of the TAXUS program, presented data on TAXUS-VI subgroups. Dr. Russell also discussed future directions for Boston Scientific's drug-eluting stent program. She said the focus will be on:

- Generating new stent platforms
- Improved deliverability
- Homogenous drug elution

- Small vessel stent
- Large vessel stent
- Expanded indications, such as left main disease, three-vessel disease, bifurcations, and CTOs
- The SYNTAX study comparing Taxus to CABG for three-vessel and left main disease. This multicenter, randomized, population-based, U.S. trial with nested registries will compare Taxus and CABG, with the primary endpoint one-year MACE (including CVA).
- The evolution from Taxus to the new Liberté stent, which will have: thinner struts, continuous cell architecture, short elements (for radial strength), and long elements (for flexibility). Liberté will use the same paclitaxel dose (10 μg/mm^2), same slow release, same polymer, and same stent-to-artery ratio. However, Liberté will use three platforms instead of two and will have a broader matrix and uniform repeating cells.

9-Month TAXUS-VI Subgroup Results

Measurement	Bare Express n=227	Taxus n=219	p-value
Clinical Results in Overlapping Stents			
Number of patients (n=124)	28%		---
TLR	23.0%	1.6%	<.0001
TVR	24.6%	1.6%	<.0001
In-segment restenosis	50.9%	8.1%	<.0001
In-stent restenosis	45.5%	4.8%	<.0001
Late loss	0.86 mm	0.24 mm	<.0001
Clinical Results in Small Vessels (<2.5 mm)			
Patients (n=124)	28%		---
TLR	29.7%	5.0%	<.0003
TVR	31.3%	8.3%	<.0016
In-segment restenosis	45.6%	10.9%	<.0001
In-stent restenosis	40.4%	7.3%	<.0001
In-segment late loss	0.53 mm	0.03 mm	<.0001
Clinical Results in Diabetics			
Patients (n=124)	~20%		---
TLR	22.0%	2.6%	=.0103
TVR	22.0%	7.7%	=.0826
In-segment restenosis	47.6%	10.8%	=.0005
In-stent restenosis	40.5%	8.1%	=.0015
Late loss	0.81 mm	0.19 mm	<.0001

TAXUS-IV Subgroup Results

Measurement	Overall	Diabetics	Overlapping stents	Moderate release paclitaxel	Previous data on slow release
Late loss	0.39	0.39	0.43	65% reduction	74% reduction
TLR	6.8%	2.6%	1.6%	N/A	N/A
Binary Restenosis	9.1%	8.1%	8.1%	58% reduction	57% reduction

9-Month Results of TAXUS-VI (Moderate-Release Paclitaxel)

Measurement	Bare Express n=227	Taxus n=219	p-value
Demographics			
Average stents per patient	1.5	1.5	Nss
Average lesion length	20.32 mm	20.94 mm	Nss
Average stent length	33.2 mm	33.7 mm	Nss
IIb/IIIa use	18.9	21.0	---
Clinical Results			
Primary endpoint: Reduction in TVR	19.4%	9.1%	=.0027
TVR Non-TLR	0.9%	3.2%	=.10
TLR	18.9%	6.8%	=.0001
Freedom from TLR	80.7%	93.1%	=.0001
TLR in long vessels	26.3%	4.4%	=.0097
In-stent MLD	1.58 mm	2.20 mm	<.0001
Safety			
MACE (overall)	22.5%	16.4%	=.1208
Cardiac death	0.9	0	Nss
Q-wave MI	1.3%	1.4%	=1.00
Non-Q-wave MI	4.8%	6.8%	=.42
Stent thrombosis in hospital	0.4%	0	=1.0
Thrombosis from hospital discharge to 30 days	0.9%	0.5%	=1.0
Thrombosis overall to 9 months	1.3%	0.5%	=.6236
Aneurysms	1.0%	1.9%	.45
Late Loss			
In-stent	0.99	.039	<.0002
In-segment	0.66 mm	0.24 mm	<.0001
At proximal edge	0.33	0.16	<.05
At distal edge	0.11	N/A	---
Restenosis			
In-stent	32.9%	9.1%	<.05
In-segment	35.7%	12.4%	<.0001
At proximal edge	3.6	3.5	Nss
% Diameter Stenosis			
In-stent	42.8	22.2	<.0001
In-segment	45.4	30.4	<.0001
At proximal edge	18.3%	12.5%	<.05
At distal edge	11.8%	7.8%	<.05

A U.S. cardiologist involved in many drug-eluting stent clinical trials said:

- He has no concerns with the safety of the Taxus polymer.
- He is concerned with the MACE in the overlapping stents in TAXUS-VI: "It is 7.9%, which is five times the rate for the control…The trend is not in the right direction."
- "Taxus-IV did not expand the drug-eluting stent market."
- His hospital took the Taxus off the shelf for a couple weeks when the retraction issue came up, but it is now available again, though it only

accounts for about 20% of their drug-eluting stent use primarily because of cost (Taxus is more expensive than Cypher at that cath lab), and he does not expect that to change over the next six months.

- He believes that Taxus is better in diabetics.

CONOR MEDSYSTEM

Conor stents have more than 580 little, laser cut holes or reservoirs in them that can be filled with one or more different drugs. Ductile hinges were added to take the stress, so the holes do not deform from pressure and cause the drug to leave the stent early. Drugs are layered into the holes with multiple layers of biodegradable/bioresorbable polymers separating them, allowing timed drug delivery and/or multiple drug delivery. EUROSTAR, a European trial of the Costar stent – a paclitaxel-eluting cobalt chromium stent – is underway.

4-Month Results of PISCES Trial

Measurement	All formulations	10 mcg/17 mm slow release delivered to vessel wall n=39	30 mcg/17 mm slow release delivered to vessel wall n=30
SAT	0.5%	N/A	N/A
Death	0	0	0
Binary Restenosis	N/A	0%	3.7%
In-stent late loss	N/A	0.38 mm	0.30 mm
% volume obstruction by IVUS	N/A	5.1%	5.1%
TLR	N/A	2.6%	3.3%

GUIDANT

Guidant dropped a bombshell during PCR, announcing a delay and possible design change in its FUTURE drug-eluting stent program, which it bought from Biosensors – the stainless steel Champion stent (formerly the S-stent) with a PLA bioabsorbable polymer eluting everolimus. The program delay is due to problems with the stent. Guidant claimed it only found out about these problems when running a test for its IDE filing for the pivotal U.S. FUTURE-4 trial. A source believes that test was a degradation study.

How long it will take to fix the problem(s) is uncertain. Guidant officials were hopeful of fixing the problem quickly but admitted a worst-case scenario is six months. Other sources warned that the fix could take even longer than that.

Just a day before the announcement, Guidant officials had downplayed rumors of manufacturing problems. There had been a report that Guidant had delayed its FUTURE-3 trial in Europe because of an inability to supply the everolimus-eluting Champion stents. A Guidant official said there had been no delay in FUTURE-3, but it was "slow enrolling." He admitted that producing these stents is "a very, very labor intensive process to make them comparable to the hand-made Biosensors stents from FUTURE-1 and FUTURE-2…We are making an automated system for manufacturing…Almost all our output is going to the CE Mark third module and to the IDE."

Before the trial delay was announced, the Guidant official also had said the IDE for FUTURE-4 had been "paused for six to eight weeks to get more data," but he insisted Guidant would file the IDE by the end of June and expected to begin the FUTURE-4 trial in August or September 2004. He also said investigators got a letter postponing the investigators meeting that had been pre-scheduled. FUTURE-4 is a non-inferiority trial, probably against Taxus, with the primary endpoint late loss (which was 0.39 with Taxus). So far, the Guidant FUTURE program has shown a late loss of only 0.11.

What's really wrong and how serious is it? There appears to be more than one problem. Among the issues that have been reported in this program are:

A. **Fractures in the stent itself.** A source said this was due to stent fatigue caused by "poor-quality stainless steel." The source described this as something "eminently fixable" that would not be a program killer, adding that it will take at least a few months (probably three but not six) to fix.

B. **Flaring of the balloon at the stent edge.** A source said there have been reports of the balloon separating from the stent at the edges (flare), and he said this is related to the thickness of the struts and the balloon. When they are mismatched, this can occur, especially in torturous vessels and large vessels. An investigator said, "In recent testing, the stent stuck to the balloon, lifting off the leading edge on large stents…It splays in torturous vessels. It could be a crimping issue. The company knew this a couple of weeks ago…The leading edge lifts off the balloon in the large stents – which means the 4.0 mm and maybe the 3.5 mm stents. The crimping of the balloon on the stent or the fixation of the balloon on the stent may not be adequate…Guidant could drop the 4.0 mm stent because that is the worst problem, but the problem could apply to the 3.5. I'm not sure…I don't know if it is a big issue or a minor issue, but it has happened with stents before – with the old, slotted tube stents."

C. **Flaring of the stent itself at the edges.** An expert said there is "strut flare" of the strut itself – not just the balloon – "when the stent goes around bends." He added, "The securement of the stent to the edges is lost, and the stent flares up at the end, especially the distal end." He said the problem is irrespective of length, but occurs more often at long lengths.

D. **Potential polymer problems.** One expert declared, "The PLA coating is the issue." However, another source disagreed, saying the problem is not with the polymer and

not with the drug – just with the Champion stent itself. A third source said there is "a 70% chance" the durable polymer (the SPIRIT program) will succeed; his 30% negative prediction is because of "all the polymers that litter the battlefield." He said he has more confidence in this bioerodable polymer than the durable polymer (SPIRIT) program.

E. **Manufacturing problems.** Guidant reportedly has found automating the manufacturing process more difficult, and he thinks it is because of the design and balloon changes.

Several issues could have contributed to the stent/balloon problems, sources suggested, including:

- **Stent design.** Biosensors reportedly only sold Guidant the stent design – not the material to make the stent. A Biosensors official said, "It (Champion) is only my design, not my stent." He insisted there is no inherent problem with the S-stent, which has a CE Mark. More than 100,000 S-stents have been sold in Europe and Asia over the past five years. Terumo is collaborating with Biosensors on a biolimus-eluting stent, and Terumo is using an unmodified S-stent and a Biosensors balloon in that program, with Biosensors responsible for manufacturing.

- **Balloon change.** Guidant chose to use its own balloon, not purchase the balloon designed by Biosensor specifically for the S-stent. Guidant reportedly rejected the Biosensors balloon, saying it was too firm/thick to provide the deliverability Guidant wanted. Biosensors officials said they told Guidant they had a thinner balloon in development, but Guidant wanted to use its own balloon instead. Biosensors officials did not describe their balloon as thick, but they admitted it isn't as thin as the balloon used in the bare Vision delivery system, either.

- **Balloon/stent mismatch.** A stent has to match the balloon in stiffness or the integrity is compromised, an expert explained. He suggested there is mismatch between the Champion stent and the Guidant balloon being used, commenting, "Guidant tried to increase the flexibility and deliverability at the expense of stent integrity."

- **Stent modification.** A source said Guidant changed the S-stent design to make the struts thinner, and he believes that is contributing to the current problem. Guidant reportedly needed thinner struts to make the stent more flexible and more deliverable but did not discuss these changes with Biosensors first or seek their input.

- **Stent manufacturing.** Guidant also chose to produce the stent itself, not have it supplied by Biosensors. In FUTURE-1 and FUTURE-2 the Champion stents were manually coated, and automation of the process is proving more difficult than expected, sources generally agreed. A Biosensors official claimed to have automated the process with its other drug (biolimus) using the same polymer on the S-stent, so he argued there is no problem with automation of a drug-eluting S-stent. Sources said the manufacturing ramp-up is proving particularly difficult with long stents and large diameter stents (4.0).

Fixing these problems may take time, sources warned. One expert said he suspects Guidant may have to slightly thicken the struts of the stent and/or use a slightly heavier/thicker balloon. If so, and if the amount of change is within certain tolerances, Guidant may not have to repeat all its bench tests. If not, there could be a long testing process ahead. And the bottom line may be a less deliverable stent than expected – almost certainly less deliverable than Vision.

There was one piece of positive news about FUTURE. There is talk about a possible Japanese arm to the FUTURE-4 trial – a registry arm.

The SPIRIT program

Guidant got a little good news at the meeting from its everolimus-eluting Vision stent with a durable polymer. Most sources believe this program will succeed. However, there are four concerns:

1. **Data.** The data is very preliminary.
2. **Polymer.** Rumors are circulating that there are problems with the polymer. A source said there are concerns with the safety of Guidant's durable polymer, but he has reached enough confidence with it to believe it will be fine. He said, "There is a little risk but not enough to kill it…There is idiosyncratic high inflammation (granulomas), but we saw that in animals with bare stents." He also noted that there were a number of "outliers" in animal studies with the Spirit stent, but he said that occurs with animals, too, adding, "You can't know if it is safe after 30 days, you need angiographic follow-up."
3. **Outlook.** A knowledgeable source continues to warn that what he calls a "Mickey Mouse program" and a "smoke and mirrors" program that will not be commercialized.
4. **Malapposition.** One arm of the pilot program has shown a high (16.7%) incomplete apposition rate, but it is not known yet whether this was the drug or control arm.

Preliminary data was presented from the SPIRIT-FIRST trial, a 60-patient pilot trial designed to assess the safety and efficacy of this drug-eluting stent. The primary endpoint of this prospective, randomized, single-blind, feasibility study is 6-month late loss with the complete data set expected at the AHA meeting in November 2005. The trial, conducted in the Netherlands, Germany, and Denmark, used 3.0 mm x 18 mm stents, with clinical follow-up at one, six, nine, and 12 months plus two, three, four, and five years, as well as angiographic

and IVUS follow-up at six and twelve months. The U.S. pivotal SPIRIT trial has not been designed yet.

Key 30-day findings:

- Incomplete apposition = 16.7% in Group B, which was very high.
- TLR = 3.7%, which was considered good.

30-Day Results of SPIRIT-FIRST Trial

Measurement	Group A n=28	Group B n=32
Primary endpoint: Angiographic in-stent late loss at 6 months	N/A yet	N/A yet
Diabetics	14.3%	12.5%
Lesion length	10.00 mm	11.3 mm
Device success	96.4%	93.8%
Procedure success	100%	100%
Clinical success	96.4%	100%
Incomplete apposition (blood behind stent struts)	0	16.7%
30-day cardiac death	0	0
Non-Q-wave MI	0	0
Q-wave MI	3.6%	0
TLR	3.7%	0

JOHNSON & JOHNSON

J&J presented quite a lot of new and positive data on its Cypher stent, but much of that got buried by the Guidant and Medtronic negative news. J&J is quite simply building a mountain of positive data in support of Cypher, but it is unlikely that this will help the company regain much of the market share taken recently by Boston Scientific, though most sources agreed that J&J is likely to get back some market share.

Despite rumors that both Medtronic and Guidant are having problems with the polymer on their drug-eluting cobalt chromium stents, J&J officials insisted that the future-generation Cypher Neo (formerly Steeplechaser), a sirolimus-eluting cobalt chromium stent, is not having polymer problems. An official said, "The game plan for this stent is an FDA question. With the warning letter we got, we are not sure what the FDA will want from us."

1-Month Results from ARTS-II Trial Comparing Cypher Stent to CABG

Measurement	Cypher n=606	CABG in ARTS-I historical control n=605	J&J Crown stent in ARTS-I historical control n=600
Diabetic patients	26.2%	15.9%	18.7%
Patients with hypertension	67.3%	45.0%	44.7%
Patients with hyperlipidemia	74%	57.6%	58%
MACCE	2.8%	4.1%	8.2%
Death	0	0.5%	1.5%
MI	0.3%	0.5%	1.5%

ARTS II (CYPHER stent vs. coronary bypass graft surgery in multi-vessel disease)

Dr. Patrick Serruys of the Thoraxcenter in the Netherlands reported the preliminary results from the 606-patient, multicenter, European ARTS II trial.

e-CYPHER^{SM} Registry

This post-marketing surveillance study is still enrolling patients, but researchers took a look at six-month data based on clinical follow-up of more than 80% of the patients in the study.

6-Month Results of e-CYPHER^{SM} Registry

Measurement	Cypher
MACE	2.5%
TLR	1%
SAT	0.3%
Diabetics (n=2,716)	
MACE	4.2%
TLR	1.4%
SAT	0.5%
Insulin-dependent Diabetics (n>814)	
MACE	5.9%
TLR	1.5%
SAT	0.4%

SICTO Trial (Cypher for chronic total occlusions)

This was a 25-patient feasibility study in chronic total occlusions. The Israeli researcher said, "When compared to historical data from trials involving the use of bare metal stents, these results suggest that Cypher could be an excellent clinical resource in treating this highly challenging type of blockage."

6-Month Results of SICTO

Measurement	Cypher n=25
TLR	0%
MACE	0%
TVR	8% *
SAT	0%
In-stent late loss	-0.1 mm
RVD	2.6 mm

*** one patient proximal and distal stenosis outside stent and one patient distal dissection at index procedure.**

SVELTE Trial (Cypher for small coronary arteries)

Dr. Eduardo Sousa of the Institute Dante Pazzanese in Sao Paulo, Brazil, presented the results of this multicenter, non-randomized, historically-controlled study in patients with de novo lesion in small vessels (2.25-2.75 mm) with long lesions (15-30 mm).

8-Month Results of SVELTE Trial

Measurement	Cypher n=101
TLR	0%
In-stent restenosis	3.2%
In-segment restenosis	6.3%
MACE	5.0%
In-stent late loss (n=95)	.022 mm
In-stent MLD	1.98
In-lesion MLD	1.67

TROPICAL (Cypher for in-stent restenosis)

Dr. Franz-Josef Neumann, of the University of Munich, Germany, presented the results of this randomized, multi-center, placebo-controlled comparison of Cypher and gamma brachytherapy.

6-Month Results of TROPICAL Trial

Measurement	Cypher n=162	Historical GAMMA-1 and GAMMA-2 results n=221	p-value
Primary endpoint: In-lesion late loss	0.08 mm	0.68 mm	<.0001
Secondary endpoint: Restenosis	9.7%	40.3%	<.001
MACE	4.9%	25.0%	<.001
TLR	2.5%	14.0%	<.001
Late thrombosis at 180 days	0.6%	3.9%	=.080

Future Cypher Trials

- **FREEDOM Trial.** This multicenter, two-arm, randomized trial of Cypher vs. CABG in diabetic patients with multivessel, de novo lesions is funded by NIH and is expected to begin in September or October 2004. Clinical follow-up will be at 30 days, and every year out to five years. The primary endpoint is the composite of all-cause mortality, non-fatal MI, and stroke.
- **REALITY.** Data from this head-to-head trial of Cypher vs. Taxus is expected at either AHA 2004 or ACC 2005.

MEDTRONIC

Prior to PCR, Medtronic's ABT-578-eluting Endeavor stent looked as if it would become the third drug-eluting stent to enter the U.S. market. However, an in-stent late loss of 0.58 mm at 12 months in the ENDEAVOR-1 trial, which was reported for the first time at PCR, raises questions about whether the stent will be approvable in the U.S. Endeavor (a chromium cobalt Driver stent with a phosphorylcholine-coating that elutes 10 μg/mm^2 of ABT-578, a sirolimus analog) must now meet the clinical endpoint in the pivotal European ENDEAVOR-2 trial ***and*** prove late loss non-inferiority to Cypher in the confirmatory U.S. ENDEAVOR-3 trial. Sources do not doubt that ENDEAVOR-2 will succeed, but the concern is that the late loss in ENDEAVOR-3 will not be within equivalency range (a delta of 0.2) of Cypher.

To prove non-inferiority in ENDEAVOR-3, Endeavor must be within a delta of 0.2 mm of the Cypher ***in-segment*** late loss. In prior trials, Cypher has shown a late loss ranging from 0.17-0.24 mm, which would make it appear that Endeavor could be no more than 0.37-0.44 mm. However, the "guru of late loss," Dr. Kuntz said that the delta actually is 0.22 or 0.23 because of the way the trial was powered. That gives Medtronic a little more breathing room.

ENDEAVOR-1 was a 100-patient trial using Endeavor stents from 3.0-3.5 mm in diameter and 18 mm long in lesions <15 mm, with predilatation required. The average stent used in this trial was 10.9 mm.

Key 12-month findings:

- Secondary endpoint: TVF = 2%, which is very low.
- Late loss =.58 in-stent and 0.40 in-segment, both of which are very high.

Results of Phase I ENDEAVOR-1 Trial

Measurement	30 Days	4 Months	12 Months
Safety			
MACE	1% ***Primary endpoint***	2%	2%
Death	0	0	0
All MI	1%	1%	1%
Q-wave MI	0	0	0
Non-Q-wave MI	1%	1%	1%
TLR	0	1%	1%
TVR (non-TLR)	0	0	0
TVF	---	2%	2% ***Secondary endpoint***
Late incomplete apposition	---	0	0
Late Loss			
In-stent	---	0.33	.58
In-segment	---	.21 ***Primary endpoint***	.40
Proximal edge	---	.12	.30
Distal edge	---	.09	.23
%DS	---	21.5%	26.8%
Restenosis			
In-stent	---	2.1%	3.3%
Proximal	---	---	0%
Distal	---	---	0%
In-segment	---	2.1%	3.3%

- Restenosis = 3.3%, which is very low.

Reaction to ENDEAVOR-1 late loss

A debate raged at PCR as to what the 0.58 mm in-stent late loss in the ABT-578-eluting ENDEAVOR-1 means. Most sources were very concerned about it.

- A French cardiologist said, "0.58 is very high. I would not put patients in that trial now…I wouldn't use the (Endeavor) stent when there are other drug-eluting stents available with 0.2 or 0.3 late loss."
- A Canadian doctor said, "We don't know yet what it means. There are still good clinical results and no malapposition. It is not a positive, but not a killer either. Anything less than 0.60 mm late less has no correlation to restenosis."
- A German cardiologist said, "I have been occasionally misquoted saying late loss is a bullshit story…It is very important and the only important measure to know what is going on inside the vessel…But the number of late loss does not immediately convey or transfer to clinical outcome…We do know that 0.6 mm is the cut-off point…Given the variability of core labs in determining late loss, you might argue that a number close to 0.6 might indicate something about clinical outcome, but I think it is too early to say in terms of clinical outcome. It is a very important measure…It is something that developed (in ENDEAVOR-1) over time from four to 12 months with Endeavor…I would be happier with a constant 0.45 mm. It went from .40 to .58, and I don't know what that means."
- An Ohio cardiologist said, "It is a concern."
- An ENDEAVOR-1 investigator said, "At the end of the day, patients don't complain of late loss…You have to keep your eye on clinical endpoints as well…Some late loss is healing…Excessive late loss is a problem, but we do need some healing to prevent thrombotic episodes or dislodgement of the stent."
- A U.S. cardiologist said, "It is very concerning. I'm still not sure what to make of it, but it isn't good."
- Another U.S. cardiologist said, "Late loss is a reasonable endpoint, but you also need (to measure) clinical events…For U.S. regulatory approval, you need both…There will be a future price to pay for an increase in late loss if the late loss is markedly increased…ENDEAVOR-1 can tolerate that (0.58) late loss because they were single, focal lesions in large vessels, but when you get into diabetics, more complex lesions, and smaller vessels, that (level of) late loss may not be tolerated."
- A New York cardiologist said, "In-segment late loss is not an appropriate endpoint for a European trial…In-segment late loss is a contrived measurement…They should keep their fingers crossed…and prayer helps…but I think ENDEAVOR-2 absolutely will meet its primary endpoint. ENDEAVOR-3 is tougher, but I think they will be successful…Deliverability will trump a lot of things, including late loss…People use Taxus for deliverability, and Endeavor is more deliverable."

Sources could not specify exactly how much late loss is acceptable. Dr. Marty Leon commented, "There is no magic number. Up to .40 mm is all right, but beyond that it is unclear what is acceptable." TAXUS-IV principal investigator Dr. Gregg Stone said, "There is no specific number. In TAXUS-IV we found we could tolerate 0.6 mm late loss before TLR went up significantly, but there could be a difference in other studies, other stents, or other patients."

Several sources – and competitors – speculated that the FDA may require additional angiographic data to prove there is no continued late loss progression. Yet, a U.S. expert disagreed, saying, "I don't think the FDA should require more angiography from Medtronic than it did from the other companies as long as the clinical event rates are good." Another source, asked what happens if the results in ENDEAVOR-3 are similar to those in ENDEAVOR-1, said, "I'm not sure the FDA or the market will accept that, but it would be reasonable to approve Endeavor with low event rates."

Pathologist Dr. Renu Virmani dismissed the 0.58 mm ENDEAVOR-1 late loss as inconsequential. She insisted that late loss is not relevant without clinical effects, and ENDEAVOR had remarkably good clinical results. Even a Medtronic competitor cautioned, "The late loss could be a red herring like the malapposition with Cypher. So, I wouldn't read too much into it yet…Doctors care about clinical endpoints – TVR, TVF, and events. They don't cath all the patients, so clinical results are a powerful argument…However, we can raise late loss as a competitive issue – and question where the late loss is going – as a differentiator."

Among the questions that the 0.58 in-stent late loss in ENDEAVOR-1 raised are:

1. **Is the elution too rapid?**
2. **Is the dose too low?** An official said, "We have no plans to change the drug delivery in this product configuration, but that is a possibility for the future."
3. **Is ABT-578 an inferior analog?** A competitor suggested the problem is the drug, "The molecular change could have done something unfortunate. This is the only limus to have nitrogen molecules added."
4. **Is the coating even or does some of the drug rub off during delivery?** An official said, "We have good distribution with the drug. There is no issue with that. There is ionic bonding of the phosphorylcholine to the stent, and there is a topcoat. I don't know if any drug is lost on delivery."

5. **Has the late loss progression stopped?** A source said, "If Medtronic can't demonstrate that the late loss has stopped, why would the FDA accept a 12-month endpoint? The finding is incongruous with Cypher and everolimus late loss, since this is a sirolimus analog. Obviously, Medtronic is not getting the sirolimus results." Another source commented, "Why did late loss go up between four and 12 months? Shouldn't it be over at four months? We have bare metal stent, TAXUS-1, and FUTURE-1 data that it is stable by then…I would have expected the late loss in ENDEAVOR-1 to be stable from four to 12 months…But the late loss in ENDEAVOR-1 could be a fluke."

6. **Is the issue the polymer?** A Medtronic official and most other sources doubted this is the issue. However, an expert on preclinical drug-eluting stent studies said that the drug release seems too fast with Medtronic's phosphorylcholine coating, adding, "It is easy to put a drug in phosphorylcholine, but the release is not well-controlled. They may have needed a top coat. I think the (lack of a top coat) contributed to the late loss."

The Medtronic view

Medtronic officials defended the ENDEAVOR-1 results, emphasizing the good clinical outcome and downplaying the late loss. They insisted there are no plans to change the design of ENDEAVOR-3 – and it may be too late to do this since about half the patients already are enrolled. A Medtronic official said the late loss with a bare Driver stent is about 1.0 mm, adding, "All the late loss theory is based on nine-month follow-up or less. An expert said that, considering clinical outcomes and 12-month follow-up, late loss is acceptable at 0.58 mm…Late loss is not a reasonable binary measure…Late loss is not due to expansion of the stent, and there was no malapposition, so the stent is staying where it should."

Getting doctors to understand this argument will take an education effort, a Medtronic official acknowledged. He said, "Doctors won't understand the concept of healing right away. It will be an issue of education. If 90.3% of the lumen is open at 12 months, and there is 0.40 late loss in the segment, all that says is that we may have some form of clinically insignificant late lumen loss. We know this because of the outcome data."

Clinical Factors Driving DES Product Selection
(from Medtronic survey of 68 European cardiologists)

Issue	Most important to choice of drug-eluting stent
MACE	32%
Restenosis	31%
TVF	9%
TLR	22%
Late loss	4%
% volume obstruction	1%

A Medtronic official said: "Late loss is not a binary measure…but a continuum of healing in the stent. There really is no evidence to support the fact that this late loss correlates to a higher failure rate…To the contrary, we can say it correlates to a good clinical outcome…We believe Endeavor will be very successful, based on two things:

1. We need to make our regulatory approval dates…and we are on track for European approval at the end of 2004, and the U.S. approximately 12 months later.
2. We achieve customer adoption rates when in the marketplace."

Another Medtronic official explained why late loss was chosen as an endpoint in ENDEAVOR-3: "Our pivotal trial is ENDEAVOR-2 which has TVF as the primary endpoint…Given that, we were novel going outside the U.S. with a pivotal trial. The FDA, in discussions with us, wanted us to do a certain patient population in the U.S. to be sure there was no difference in patient demographics…and in discussions with FDA of how to show non-inferiority to another device and how to avoid having to do a 3,000-patient study, we locked in on late lumen loss as a surrogate endpoint …That was the rationale.

Three leading cardiologists defended the late loss in ENDEAVOR-1 for Medtronic. They suggested other reasons for the high late loss in ENDEAVOR-1:

1. **The late loss could be influenced by reference vessel diameter (RVD).** An investigator pointed out that RVD was marginally greater in ENDEAVOR-1 than in SIRIUS or TAXUS-IV. A non-Medtronic expert disagreed, saying, "In our studies, % volume obstruction is not related to RVD."
2. **Late loss could have been influenced by acute gain.** An investigator said it was slightly higher with ABT-578 than with sirolimus or paclitaxel.
3. **Different patient demographics could have been a factor.** Researchers didn't think so, but they raised the issue. They believe the patient demographics are comparable to most other drug-eluting stent trials.
4. **%DS could explain the late loss, when compared to SIRIUS and TAXUS-IV.** An investigator suggested that there is a time-dependent effect:
   a. 4 months: 21.5% DS in ENDEAVOR-1.
   b. 8 months: 23.6% DS in SIRIUS.
   c. 12 months: 26.8% DS in ENDEAVOR-1.

Dr. Richard Kuntz of Brigham & Women's Hospital, the co-principal investigator for ENDEAVOR-2, claimed he is "not unhappy" with the late loss.

- "The bigger vessels get, the bigger the late loss…Is ENDEAVOR-3 in jeopardy here?…My analysis suggests things look okay...I like the low complication rates…I have no reason to spin the data…I'm happy to see more competitors

get into the market, especially on well-deliverable stents…I'm pretty positive about this data, despite the isolated 0.58 late loss in a study not meant to be compared to other studies because of the larger vessels."

- "I don't know that the (advisory) panel or the FDA will split hairs on a statistical difference in late loss if we are in the zone of extreme improvement over the bare metal stent era…The burden of proof will be on the ENDEAVOR-2 data, and the extrapolation says that will be a wildly positive study."

- "I think there is value in late loss, but not the way it is here – not between studies…I will be interested in the ENDEAVOR-3 late loss…It is a measure of how narrow the artery gets…but we are working where we don't know the optimal late loss because that is associated with an increased risk of malapposition or non-coverage…and it is not 0.9 or greater."

- "0.58 late loss should be associated with 10%-12% restenosis…That is well beyond the margins of error. I think the late loss is aberrantly high…It doesn't correlate with the mass of loss…Is this because of the small sample? Probably."

- "The main reason I'm not so concerned about the magnitude of the difference between in-segment and in-stent late loss…is because the case mix has such a powerful fix…It is in the right ballpark…I would adjust down those numbers because they were bigger vessels with bigger gain…I think ENDEAVOR-2 will be in the range and will be fine."

- "The proof is in the pudding – clinical restenosis…I would be very surprised to see this late loss reproduced in the other studies."

Dr. Jeff Popma, Director of Interventional Cardiology at Brigham & Women's Hospital, which is the core lab for ENDEAVOR-3, said:

- "You are probably safe up to 1.0 mm late loss in-stent and up to 0.6 or 0.7 in-segment."
- "I would like to see late loss in ENDEAVOR-2 to be 0.48 or 0.38…We all hope it is lower (than 0.58)."
- "Is progression a concern? It could be to the FDA…Equivalent late loss in ENDEAVOR-2 (0.58 mm) would not have negative implications for ENDEAVOR-3 if the TLR is good in ENDEAVOR-2."

Dr. Peter Fitzgerald, Director of the Cardiovascular Core Analysis Laboratory at Stanford, where the IVUS studies for ENDEAVOR-3 will be done:

- "The issue is flow not late loss."
- "From the majority of what I see inside (the vessel by IVUS), this works. Whether it works as well as we wanted, I can't say. There is wobble room here. Keep your eye on the bare metal. If I saw late loss of 0.5 or 0.6 (with Endeavor), and it was diffuse, that would be a problem."
- Asked how he knows there isn't a problem with late loss progression beyond one year with Endeavor: "You could equal bare metal in 12 years, but who cares if it is 12 years from now."

The outlook for ongoing Endeavor trials

ENDEAVOR-2 is the pivotal, 1,191-patient U.S. and European trial. ENDEAVOR-2 involves single de novo native lesions, stents from 2.25-3.5 mm diameter and 18-30 mm lengths, in lesions from 14-27 mm, with predilatation required. The trial was conducted at 72 sites in Europe, Asia, Israel, New Zealand, and Australia. The primary endpoint is a 40% reduction in TVF (cardiac death, MI, and TVR) at nine months. The final data lock will be in February 2005, with the results to be presented at ACC 2005. The 30-day results of ENDEAVOR-2 were presented at PCR.

30-Day Results of Pivotal ENDEAVOR-2 Trial

Measurement	Group Y n=596	Group Z n=595
Diabetics in trial	17.7%	21.9%
Lesion success	99.6%	100%
Device	99.3	N/A
RVD	2.74	2.78
In-segment MDL	.80	.81
In-segment DS	70.8%	70.8%
Post-procedure in-stent MDL	2.62	2.65
In-segment MDL	2.23	2.28
MACE *	2.9%	3.5%
Death	0.2%	0
MI (all)	2.5%	3.2%
Q-wave MI	0.2%	1.0%
Non-Q-wave MI	2.3%	2.2%
CABG	0%	0%
TLR-PTCA	0.2%	0.3%
TVR (non-TL)	0.3%	0%
Stent thrombosis	0.7%	1.0%

*** Two cardiac tamponades related to stent, one resulting in a death.**

ENDEAVOR-3 is a U.S. confirmatory study in 436 (109 Cypher control stents and 327 Endeavor stents) patients with single de novo native lesions, using stents with a diameter of 2.5-3.5 mm, in lengths from 18-30 mm, with predilatation required. The primary endpoint is **in-segment** late loss (not in-stent) at eight months. Medtronic officials remain firmly positive about the outlook for ENDEAVOR-3, even though they claim not to have seen any early late loss data from either ENDEAVOR-2 or ENDEAVOR-3.

In-segment late loss in ENDEAVOR-1 was 0.40, so Medtronic hopes that this – plus measuring late loss earlier in ENDEAVOR-3 than in ENDEAVOR-1 (9 months instead of 12 months) – will result in a late loss within the mandated 0.2 mm delta (which a statistician said may get stretched to 0.23 mm) from Cypher, which they expect, based on Cypher trials,

to average 0.17-0.24 mm. This means that the drug arm in ENDEAVOR-3 (which already has ~200 patients enrolled) has to come in with an in-segment late loss of 0.40-0.47 mm, and a Medtronic official said the goal is for Endeavor's late loss to be 0.40.

Most sources outside Medtronic view this as an extremely risky strategy for ENDEAVOR-3, with a high probability of failure. They suggested Medtronic change the primary endpoint to a comparison to Taxus late loss or a different primary endpoint – e.g., FFR (fractional flow rate), or TVF. Medtronic officials insisted this will not happen.

Two very knowledgeable sources predicted that ENDEAVOR-3 will fail its primary endpoint, but they still think the stent will get FDA approval – unless the advisory panel digs in its heels about the safety of high late loss or the possibility of continued late loss progression. They both suggested that Medtronic could satisfy the FDA on this issue by doing 18-month angiographic follow-up on at least a reasonable subset of ENDEAVOR-1 patients and show lack of progression beyond 12 months. They said they would be surprised if Medtronic doesn't do this, especially since it would not require a protocol change. They think this information could help the company overcome a missed ENDEAVOR-3 primary endpoint if the TLR/TVF is low.

There have been rumors that the U.S. confirmatory ENDEAVOR-3 trial was stopped, but a Medtronic official denied this. He said there have not been any supply issues with Endeavor stents. He said, "We *paused* (not stopped) enrollment in ENDEAVOR-3 to change to a CRO for randomization and physical distribution of the stents, in order to maximize the blinding issue. Enrollment has already resumed.

Several sources also predicted that there will be little interest in using Endeavor unless late loss comes down. One commented that his large cath lab wouldn't use much Endeavor, and he thinks that will be true in most labs.

A U.S. cardiologist involved in many drug-eluting stent clinical trials said he is concerned with the late loss in ENDEAVOR-1, but he still thinks the stent is approvable, but that approval may take longer than previously expected. Among his comments were:

- "In-stent late loss doesn't change by vessel size, but it does increase by stent length…In-segment late loss decreases by vessel size, but does not change by stent length."
- "The late loss progression in ENDEAVOR-1 is real. There was good angiographic follow-up, and that should have pushed the late loss down and the TVR up, but it did the opposite."
- "The only way the late loss doesn't matter would be if the standard deviation curve is different, and in ENDEAVOR-1 it is a little narrower, but not a lot…I believe very strongly that late loss does matter as long as the curves are comparable."
- He believes that ENDEAVOR-3 will "squeak by," making its primary endpoint, partly because he expects Cypher late loss to be greater than it was in SIRIUS. He said Medtronic told him that the Endeavor late loss will have to be ≤0.44 to prove non-inferiority.
- He thought it was quite coincidental that Medtronic stopped (or paused, as Medtronic prefers to say) the ENDEAVOR-3 trial a week before the ENDEAVOR-1 data came out. Other than that he has heard of no Endeavor stent supply issues.
- Even if the Endeavor stent gets FDA approval, the late loss issue may now dampen use severely. He said doctors will use Endeavor, but not as a No. 1 stent, probably as No. 2, behind Taxus but ahead of Cypher.
- "The late loss issue might make the FDA want some longer-term data – 18 months, 24 months, 36 months – to prove there is no marked progression."
- If ENDEAVOR-3 fails to meet its primary endpoint, he believes it would be an "uphill battle" to get the stent approved based on secondary endpoints, even if they are excellent clinical endpoints. He said, "If you miss the primary endpoint, FDA approval depends on physician testimonials on why patients ***need*** something, and that would be a hard argument for anyone to make about Endeavor."
- His recommendations to Medtronic:
  1. "Finish ENDEAVOR-3, but get FDA permission and consent the patients (now) for longer-term follow-up because the FDA will be concerned with progression, and the company can satisfy that with planned extra clinical follow-up."
  2. "Do an early angiographic look at ENDEAVOR-2, though there could be a statistical penalty for doing that."
  3. "Find another polymer and another drug, but particularly another polymer."

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

Development of this R-stent delivering EPC continues to progress. The HEALING-2 trial is expected to start in late 2004 or early 2005. An official said the company will be meeting with the FDA in 3Q04 to discuss the design of the U.S. pivotal trial. Pricing is expected to be comparable to commercially-available drug-eluting stents.

In a live case using this stent, it was deployed at 18 atm. The operator said there have been no problems with the durability

of the coating with high pressure deployment. The company does not expect much significant data from HEALING-1 because the antibody is mostly killed by wet sterilization. In HEALING-2, the antibody is dried before sterilization, which preserves the antibody function, so positive results are expected from that trial.

EPC Capture R-Stent Program Changes

Item	HEALING-1	HEALING-2
Device	Wet, hand crimped prototype, supplied in sodium azide preservative and required rinsing before use	Dry formulation that preserves the antibody structure and activity; pre-mounted on Evolution 2SDS
Sterilization	Gamma, 15-25 Gy	Gamma, <15 Gy
Bioactivity	Significant reduction in activity with sterilization	Stable with sterilization, comparable to activity as coupled
TVR	9.1%	N/A
Late loss	0.63 vs. bare 0.8-0.85	N/A
Stent thrombosis	0	0
Patients	16, single center, Netherlands	60 at 10 centers in Belgium, Germany, and the Netherlands
Status	Completed	Enrollment started May 2004
Results	***Primary endpoint:*** 30 Day MACE = 0%	Data due at PCR 2005

SAHAJANAND MEDICAL TECHNOLOGIES

This Indian company's Infinnium, a paclitaxel-eluting stent, could become a spoiler for Boston Scientific, at least in Europe. Investigators said they expect it to be priced below currently approved drug-eluting stents. In India, Infinnium sells for $1,300-$1,500, and the same pricing is expected in Europe. Infinnium uses a Millennium (a slotted tube stainless steel) stent, coated with four layers of biodegradable polymer. During a live case at PCR, an investigator commented, "Infinnium has a crossing profile of 1 mm, which is comparable to Taxus and Cypher…So, it is nothing spectacular from that point of view."

The results of the SIMPLE-1 trial were presented at TCT 2003. The nine-month 100-patient SIMPLE-2 is now underway in Europe, Brazil, and India. Dr. Patrick Serruys is the principal investigator. Results are expected at PCR 2005. Sahajanand has filed for a CE Mark based on SIMPLE-1 data.

SORIN BIOMEDICA

First-in-man data from the JUPITER-1 trial of the tacrolimus-eluting Janus Carbostent was reported. This is a two-part trial. The Phase-α was a clinical registry of about 30 patients, which is being followed with a Phase-β that is a 200-patient, randomized, double-blind trial comparing the Carbostent to the Tecnic stent (a bare Carbostent). All patients get clopidogrel (Sanofi's Plavix) for two months post-procedure. Carbostent is a closed cell, mirror-polished stent. As of May 2004, 58 patients had been enrolled, receiving 65 stents.

The TLR looked good – except in diabetic patients. An investigator said, "We were pretty surprised by the dichotomous results. Tacrolimus looks quite effective in non-diabetics, but it lost almost all the effect in diabetic patients… It could be that we need higher doses of the drug in diabetics."

Preliminary Results of the JUPITER-1 Trial

Measurement	Carbostent n=58
Diabetics in trial	22.4%
Clinical success	100%
Procedural success	100%
Thrombosis (in-hospital to 12 months)	0%
30-day MACE	0
Partial 6-Month Results	
MACE	4.9% 1 cancer death, 2 PTCAs
TLR in diabetic patients (10 patients)	18.6%
TLR in non-diabetics (51 patients)	4.2%
Partial 12-Month Results	
TLR (23 patients)	4.2%
MACE	0

MISCELLANEOUS

- There was a rumor at PCR that a company in China is selling a bare metal stent in Europe for $20.

Audience Response Survey on Drug-Eluting Stents

Answer	Response
What is more important in choosing between two similarly efficient drug-eluting stents?	
Deliverability	47.1%
Cost	32.4%
Availability of various sizes/lengths	14.7%
Radio-opacity	5.9%
Personally, how long would you require clopidogrel+ASA if you received a drug-eluting stent?	
3 months	15.6%
6 months	28.9%
1 year	31.1%
Life	24.4%
How important are struts in the design of a drug-eluting stent?	
Very important	59.1%
Important	31.8%
Not important	9.1%
What are the most crucial attributes in the design of a new alloy stent platform?	
Deliverability	58.3%
Conformability	25.0%
Other	15.6%
Thin struts	1.1%

.CLOSURE DEVICES

Nearly three million cardiac catheterizations are done in the United States each year. Doctors use a variety of products and methods of applying compression to close the opening to the femoral artery and achieve hemostasis. Kensey Nash/St. Jude's collagen-plug system, AngioSeal, currently is the market leader, followed by Abbott's Perclose, a suture-based system. Doctors have also tried and rejected many other products. A source said, "StarClose is interesting, but so are others. I need to try them and see the data before we'll consider changing. Our lab currently uses about two-thirds AngioSeal and one-third Perclose." Another doctor said, "About 75% of our patients get AngioSeal…We chose that based on ease of use since all of the devices are now priced about the same now…I think the market has plateaued."

Some interesting new closure devices include:

ABBOTT'S STARCLOSE. Abbott acquired Integrated Vascular Systems in 2003, which was developing the StarClose clip technology. Abbott was showing StarClose it off at PCR and plans to market it along with its other hemostasis products, Perclose, and the topical Chito-Seal. StarClose, a nitinol circumferential clip, received a CE Mark in February 2004 and is being sold in Europe. The pivotal U.S. trial, CLIP, began in March 2004.

The StarClose clip clamps around the artery opening on the outside of the vessel in sort of a looping flower design. It provides a seal without leaving anything in the artery, and it allows re-entry. The metal clip permanently remains in place, but an Abbott official said it doesn't migrate. Sales reps claimed the device is easy to use, with no significant learning curve. Doctors were interested in this, but they noted that there is little data on it yet, and some were concerned about leaving a metal clip in the body. A source said, "I'm not interested in this because going back in would be like a minefield."

ACCCESSCLOSURE'S Matrix. This also got a CE mark recently and will be launched first in Germany and then Italy, followed by Spain. A pivotal trial in the U.S. is due to start in a couple of months. Pricing was not available. This is an extravascular, biodegradable, polyethylgylcol gel that seals the puncture site, then it degrades over 14-28 days. It allows for immediate repuncture. Doctors were very interested in this. A source said, "It works. It's nice. And it is extravascular."

BIOTRONIK'S Neptune. This patch recently got a CE Mark, and the company will start distributing it in June 2004.

BOSTON SCIENTIFIC/THERUS'S SoundSeal. This uses externally applied ultrasound to the arteriotomy site to heat the vessel wall collagen and form a seal. There was no new information about it at PCR, and Boston Scientific was not displaying it at the booth. A source said, "This is very interesting. It hasn't been tested in humans yet in the U.S., but it is a potential game-changer." Another source said, "I have a healthy skepticism about this, but if they get the data, sales would be driven by the ease of use."

CARDIVA MEDICAL'S VasoStasis. This also has a CE Mark, and the company is hoping for FDA approval before the end of this year. To use this device, the doctor deploys a 2F catheter, twists the regulator to expand a membrane at the tip of the catheter, and then pulls back until the arterial puncture is sealed. A clip at the skin surface holds the expanded membrane in place until hemostasis is nearly complete (about 15 minutes), and then the catheter is deflated and removed entirely, and finally, light manual pressure is applied for three to five minutes. VasoStasis is expected to cost about $130 in the U.S., which would price is considerably below Perclose or AngioSeal. VasoStasis also leaves nothing in the artery. A source said, "If you have to apply pressure for 15 minutes, I'm not interested." Another source said, "This is interesting technology. It has some appeal because it doesn't leave anything behind…And a price around $125 would have big appeal."

FUTURE DATA TO WATCH

European Cardiology – August 2004
TAXUS-I – 3-year follow-up

TCT – September 2004
ENDEAVOR-2 – 6-month results of European/U.S. pivotal trial of 1200 patients
STEALTH-1 – 6-month data on Biosensors' Biolimus
MILESTONE-II – Taxus European post-marketing program
ARRIVE-1 – 30-day results of the U.S. Taxus per-approval registry of 2,589 consecutive patients
COSTAR – 4-month data on Conor stent

American Heart Association – November 2004
REALITY Trial – maybe J&J head-to-head trial of Cypher and Taxus
SPIRIT-FIRST – 6-month results of Guidant's durable polymer/everolimus

American College of Cardiology 2005
REALITY Trial – if not at AHA 2004 – J&J head-to-head trial of Cypher and Taxus
STEALTH-1 – 9-month data on Biosensors' Biolimus
ENDEAVOR-2 – final results
TAXUS-V

PCR 2005
HEALING-2 (Orbus's EPC)

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