Trends-in-Medicine

November 2005

by Lynne Peterson and D. Woods

SUMMARY

TCT has gotten so large, so popular, and so comprehensive that it is difficult to cover everything. This is the first of a two-part series on the meeting. The first part will deal only with drug-eluting stents. Topics to be covered in Part II include regulatory issues, carotid stents, PFO closure, percutaneous valves, and SFA therapies.

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Trends-in-Medicine
Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

TRANSCATHETER CARDIOVASCULAR THERAPEUTICS (TCT)

Part I – Drug-Eluting Stents

Washington, DC
October 16-21, 2005

HIGHLIGHTS

Drug-eluting stent competition. Medtronic's Endeavor failed to meet its primary endpoint in a confirmatory trial, but this may not be a game killer for Medtronic. Sorin's Janus stent also failed to meet its primary endpoint, and the outlook for this tacrolimus-eluting stent which already is on the market in Europe, is less certain, though Sorin remains committed to it. Boston Scientific's Taxus has lost market share to Johnson & Johnson's Cypher worldwide, but that may stabilize after TCT, at least for a while.

Investigational drug-eluting stents. Conor Medsystems' CoStar was a star at TCT, and doctors are very excited about it – provided the patent issues don't prove fatal. Abbott's ZoMaxx is starting to be considered a real contender. Bioabsorbable programs by Guidant and Biosensors also got a lot of attention, and experts were starting to describe bioabsorbable stents as the stent technology of the future.

Stent thrombosis. Concerns that Boston Scientific's Taxus stent may have a worse risk of stent thrombosis were pretty much dismissed, but now the question appears to be whether all polymer-based drug-eluting stents have a higher stent thrombosis risk than bare metal stents. Experts repeatedly called for development of drug-eluting stents without durable polymers. This is likely to give a boost to Conor Medsystems.

Approved and Investigational Drug-Eluting and Bioabsorbable Stents

Approved	On the near horizon	Farther away
U.S.	Medtronic's Endeavor	Ethos' Xcell
Johnson & Johnson's Cypher	Abbott's ZoMaxx	Devas' Access Plus
Boston Scientific's Taxus	Conor Medsystems' CoStar	Goodman/Avantec
Europe	Guidant Xience-V	Advanced Technology Ventures' Xtent
Johnson & Johnson's Cypher	Cook V-Flex	Terumo's Nobori
Boston Scientific's Taxus	Neich/Orbus's Genous	Biotronik's AMS
Sorin's Janus		
Biosensors' Axxion		
Only available in Asia		
Biosensors' BioMatrix		
Sahajanand's Infinnium		

Several issues have come up that are likely to help determine which new drug-eluting stents are successful – and which also are giving increased attention to bioabsorbable stents and polymers and to non-polymer drug-eluting stents – including:

- **Late stent thrombosis (LaST).**
- **Patients who stop antiplatelet therapy, have resistance to clopidogrel** (Sanofi-Aventis's Plavix), or experience increased bleeding with antiplatelet therapy. A speaker commented, "We are just beginning to understand that there are patients who do not respond properly to clopidogrel...There are hyper- and hypo-responders." Dr. Patrick Serruys of the Thoraxcenter in Rotterdam, Netherlands, said, "We are really in the infancy of this concept." Dr. Marty Leon of Columbia University said, "We use dual antiplatelet therapy routinely at Columbia for a year. And if it is a really complex lesion, we are now out to two years." Potential causes for clopidogrel non-responsiveness include: genetic variables, patient non-compliance, inadequate dose, DES-drug interaction, etc.
- **Concerns with durable polymers.**

Stent thrombosis

"All stent thromboses are catastrophes," Dr. Rob Schwartz of Minneapolis Heart declared. He explained that 100% of these patients suffer an MI, with 35% mortality. He estimated that an additional 800 deaths a year may be caused by drug-eluting stents. He said the incidence of late stent thrombosis is at least 0.35% in drug-eluting stent patients, and it may also occur when patients are stable on antiplatelet monotherapy, "Globally, there is a drug-eluting stent thrombosis increase of about 0.5%. That is small but significant...Drug-eluting stents are more thrombogenic (than bare stents)…We can't ignore the problem any longer. For the most part these devices are safe, but not safe enough. We must improve our technology to make this device safer."

Is Taxus more thrombogenic than Cypher? Despite the SIRTAX results and a recent ***New England Journal of Medicine*** editorial which suggested it is, experts at TCT generally dismissed this idea. Dr. Marty Leon said, "There are soft signals of an increased stent thrombosis with Cypher, and I think the same thing is true with Taxus…We are seeing an increased risk with either Cypher or Taxus."

A consensus appears to be forming that polymers should not be permanent. Interventional cardiologists speculated that one of the explanations for stent thrombosis with drug-eluting stents is the polymer. A speaker speculated, "Whether bioabsorbable will be the norm or a niche is still unclear." Dr. Marty Leon said, "The sirolimus family of drugs is fundamentally less toxic than paclitaxel. Paclitaxel is a very, very edgy drug. The drug itself (paclitaxel) has biologic effects that can precipitate thrombosis…But, equally, very important is the drug carrier issue. Other people will say let's do without a drug carrier – for example, Biosensors and Conor. Getting rid of the polymer is one way…but I think there are ways to develop truly stable polymers…I think phosphorylcholine is one of these."

Among the non-polymer options that got a lot of attention at TCT were:

- Biodegradable polymers – e.g., Guidant's Xience-V.
- Biodegradable stents – e.g., Biotronik's AMS (magnesium) or Igaki-Tamai's PLLA stent.
- Non-polymer stents – e.g., Conor's CoStar, Sorin's Janus, or Translumina's Yukon.
- Microdroplet polymers – e.g., LabCoat's Precision.

Late restenosis – A catch-up effect?

Contrary to bare metal stents, there is a delay in neointimal formation with drug-eluting stents by IVUS, though not much difference in late TLR. A speaker said, "I agree there is some catch-up on neointimal hyperplasia by IVUS, but <7% which compares favorably to bare metal stents…Drug-eluting stents can afford to have some late catch-up without causing ischemic obstruction." Another expert said, "I don't know if the Cypher rebound contributes to a late effect. The polymer itself has been shown to cause inflammation. You can't use the polymer alone because of the inflammatory effect. Phosphorylcholine is non-inflammatory."

The stent marketing war – Cypher takes back some market from Taxus

During TCT, Boston Scientific announced it had lost some market share to Cypher in 3Q05 compared to 2Q05.

Drug-Eluting Stent Market Share

Time period	Johnson & Johnson's Cypher	Boston Scientific's Taxus	Medtronic's Endeavor
2Q05	$210 million	$202 million	0
3Q05 OUS except Japan	$194 million (48.5%)	$198 million (49.5%)	$8 million (2%)
3Q05 U.S.	$347 million (46%)	$403 million (54%)	0
3Q05 Japan	$115 million	0	0
3Q05 Worldwide	$656 million (51.9%)	$601 million (47.5%)	$8 million (0.6%)

*Source: Boston Scientific

Throughout TCT, doctors debated the merits of Cypher vs. Taxus, and there were proponents and detractors for each. These comments at a TCT debate on the topic pretty well summed up the positions:

- **Dr. David Holmes – Cypher better:** "A meta-analysis shows that Cypher is better than Taxus. There is no difference in overall stent thrombosis in this meta-analysis; we need more data. Head-to-head trials show a concordance in an advantage for Cypher."

- **Dr. Eberhard Grube – No difference:** "Pivotal trials and the REALITY trial show similar clinical outcomes (to Taxus and Cypher), and there are comparable event rates and comparable stent thrombosis in the real world."
- **Dr. Gregg Stone – Mega trial needed:** "We need a mega-trial to resolve this issue…We need an all-comer, real world study. I think it is imperative to conduct such a study."
- **Dr. Stephen Windecker – Cypher better:** "Our meta-analysis found sirolimus more effectively reduced TLR and restenosis (than paclitaxel). There was no difference in death, MI, and stent thrombosis...The benefits of sirolimus in reducing the risk of TLR was observed in all classes of patients and all lesion characteristics."

Dr. Windecker's conclusions were based on SIRPACT, a new, independent meta-analysis presented for the first time at TCT. He looked at seven published (or soon to be published) randomized clinical trials with 4,214 patients – BASKET, CORPAL, REALITY, SIRTAX, ISAR-DESIRE, ISAR-DIABETES, and TAXI.

SIRPACT Compared to Historic Controls

Measurement	Relative risk reduction (RRR)	Statistical significance
TLR		
BMS vs. PTCA	36% in favor of BMS	Yes
DES vs. BMS	70% in favor of DES	No
Cypher vs. Taxus	In favor of Cypher	Yes
Number needed to treat to avoid 1 TLR per year		
BMS vs. PTCA	14 patients	---
DES vs. BMS	10 patients	---
Cypher vs. Taxus	35 patients	---

SIRPACT Meta-analysis

Overall measurement	Relative risk reduction (RRR)	Statistical significance
TLR	36% in favor of Cypher	Yes
Restenosis	30% in favor of Cypher	Yes
Mortality	9% in favor of Cypher	No
Stent thrombosis	15% in favor of Cypher	No

STENT, the first U.S. head-to-head registry comparison of Cypher and Taxus, found no difference in either the efficacy or the safety of the two drug-eluting stents. STENT is a large, 8-center registry started in May 2003. Researchers reported on the results through September 2004:

- Taxus stents tended to be used in slightly more complex patients – more older patients, patients with more ACS, patients with slightly lower pre-procedure TIMI grade flow, slightly smaller vessel diameters, and higher ACC lesion risk score.

STENT Registry 9-Month Comparison of Cypher and Taxus

Measurement	Cypher	Taxus	p-value
Patients enrolled	2,394	1,563	---
Share of use *	59.5%	38.8%	---
Completed 9-month follow-up	2,282	1,476	---
Subacute stent thrombosis	0.7% 16 cases	0.5% 7 cases	0.38
TVR	4.2%	3.4%	0.23 HR 1.18 in favor of Taxus
MACE	7.9%	6.8%	0.20 HR 1.2 in favor of Taxus
MI	2.2%	1.8%	0.44
Death	2.7%	2.1%	0.26
CABG target vessel	0.5%	0.7%	0.40
Re-PCI target vessel	3.7%	2.8%	0.13

*** More Cypher used because Taxus was not available when registry started.**

- There was no statistically significant difference between Cypher and Taxus on death, MI, TVR, MACE, or SAT.
- In the "real world" Cypher and Taxus have comparable clinical and safety outcomes.

Asked how these centers choose between Taxus and Cypher today, Dr. Charles Simonton of Carolinas Heart Institute said, "Three centers have contracts with Boston Scientific for Taxus, so they use a high percentage of Taxus – at least 80%. The other sites are more evenly balanced (between the two). For the whole registry, there is about a 50/50 split right now…The take-home message is that both stents are safe and have similar clinical outcomes. Most likely, these results will allow a little more ability to the two companies to stay in the (cath) lab. It (the choice in the future) may come down more to price and other features…The race will be to have the slickest, most deliverable stent…It will be more like the bare metal stent world, when the easiest to deliver stent won out…Most operators probably would say Taxus is easier to deliver than Cypher. Most would say the deliverability of Taxus is better, and that may be why we see it being used in slightly more complex lesions."

The EVENT registry, which was funded by two ***drug*** companies – Millennium and Schering-Plough – is recruiting three waves of 2,500 patients each. A researcher presented data on the first wave of 2,500, which was collected by 31

9-Month Results of First Wave of EVENT Registry

Measurement	30-day results	6-month results
Death	0.3%	1.6%
MI	6.3%	9.4%
TLR	---	2.5%
Urgent-PCI	0.5%	---
Urgent-CABG	0.4%	---
Stent thrombosis	0.4%	1.0%
Death/MI/TLR	---	12.4%

sites. Drug-eluting stents were used in 92% of these procedures, with the mean average of 1.6 drug-eluting stents per procedure. Cypher stents were used in 52.5% of patients and Taxus in 47.5%. Researchers had not yet analyzed differences between Cypher and Taxus stents.

Regulatory issues relating to stents

A speaker explained that the timeline for approval of a new drug-eluting stent will depend on where in this chart the stent falls.

FDA Approach to Drug-Eluting Stent Approvals

Measurement	DES A	DES B	DES C
Drug name	NME	Approved systemic	Paclitaxel, sirolimus
Drug formulation	Novel	Similar drug release profile (local/systemic)	Same drug formulation as approved DES
Stent	New stent material	3176L, cobalt chromium, nitinol	Approved stent platform
Trial design	RCT with n≥2,000	RCT with n<1,000	Single arm registry and n<1,000
Overall product	Entirely new product	New and old technology	Serial iteration of existing DES
Approval time	Slow	Faster	Fastest

An FDA official said, "For any drug-eluting stent – new or not – there are several options. You can run one pivotal trial, and we recommend to not solely power it with an angiographic endpoint but to power it on a clinical endpoint or a combination of a clinical and an angiographic-type endpoint…Simply powering a trial will not get to the answers you need on safety; we are cognizant of that. You need a significant number of patients for safety."

ABBOTT LABORATORIES

ZoMaxx

There were no new data at TCT on this TriMaxx stent which elutes zotarolimus (ABT-578). A speaker said there may be "some hint" from the ZOMAXX-I trial early in 2006. The pivotal ZOMAXX-II trial vs. Taxus began enrolling patients in May 2005, with a goal of 1,670 patients.

ZoMaxx was described as having the lowest strut thickness (.0029 inches) of all cobalt chromium stents. A speaker commented that the crossing profile of ZoMaxx is "a little worse than Taxus Liberté, but they are fairly comparable." The elution curve is very similar to Cypher, but the elution is slightly less than Cypher for the first 13 days and then slightly faster. The inflammatory score with ZoMaxx decreases steadily from Day 1 to Day 180, while Cypher decreases for 30 days and then rebounds.

Zodiac

Experts at TCT discussed this next-generation combination drug-eluting stent. It is a dual-drug stent, with 10 μg/m^2 zotarolimus and 10 μg/m^2 dexamethasone mixed together and then applied to the stent in a layered fashion, using the phosphorylcholine coating that is used with ZoMaxx. The two drugs have different mechanisms of action: Zotarolimus is more potent than dexamethasone in inhibition of smooth muscle cells, and zotarolimus potently inhibits MCP-1, while dexamethasone inhibits IL-6 and TNF-α.

The two drugs are synergistic when combined on a drug-eluting stent. Both drugs are completely gone in 30 days, with a similar elution profile to Cypher. Zotarolimus elutes very quickly from the PC coating, and dexamethasone releases even faster, but when they are combined, there is some "interaction" between the two drugs, and the dexamethasone is released more slowly – closer to the elution profile of zotarolimus. An investigator said, "It's possible the combination will take TLR <3%, and perhaps it might be good for high risk patients."

Only animal studies have been done to date. A proof of principle study has been completed in an animal model, and a "large number" of porcine experiments have been done. These studies found a complimentary activity at the cellular level, both anti-proliferative and anti-inflammatory mechanisms. A PK study in 40 patients is planned in the U.K., and it reportedly will be used to obtain an IDE in the U.S. The PK study is intended to show there is no systemic leakage of drug.

BIOSENSORS INTERNATIONAL

Biosensors has three different stent programs underway, plus numerous programs with other companies.

BioMatrix

Dr. Alexandre Abizaid of Brazil reported on new BioMatrix data from a 90-patient study in Brazil and another study in Thailand. The Thai study looked at 160 patients in an all-comers setting, and Dr. Abizaid said nearly 100 patients have completed six-month follow-up. The Thai MACE rate was 2.5%, death 1.8%, TLR 0, TVF 1.2%, and no stent thrombosis. The ongoing, web-based BEACON registry, which started early this year in Asia, has enrolled 800 patients from nine sites so far.

Brazil Experience with BioMatrix

Measurement	BioMatrix n=30	Bare S-stent n=30	RAVEL (historical control)	
			Sirolimus n=30	Bare stent n=15
Late loss	0.24 mm (p<.0001)	0.71 mm	0.15 mm (p<.001)	0.77 mm
Neointimal volume index	0.19	2.71	0.18	2.02
% stent obstruction	2.23%	19.92%	3.3%	33.5%

Axxion

The principle investigator of the 140-patient, 3-center, EAGLE trial of Axxion is Thomas Ishinger of Germany, and the primary endpoint is late loss. EAGLE is a small pilot trial for a bigger study.

Other studies

Biosensors is planning two new stents – a stainless steel stent platform, which improves on the S-stent, and a cobalt chromium stent. Other BioMatrix studies underway or planned include:

- An all-comers registry underway in Thailand looking at biolimus in a "real-world" setting.
- BioMatrix vs. Cypher.
- STEALTH-II. This is a 1,584-patient prospective, randomized trial of BioMatrix vs. Taxus at ~70 sites, looking at TVF at 9 months, etc.
- Studies to assess small vessels (2.25 mm) and long lesions

Biosensor Drug-Eluting Stent Programs

Description	BioMatrix	Excel	Axxion
Drug	Biolimus A-9	Sirolimus	Paclitaxel
Stent	S-stent	---	---
Stent delivery system	Gazelle	---	Nexus-2
Polymer	Proprietary bioresorbable	Bioresorbable	Glycocalix coating (similar to phosphorylcholine) in a very thin base over which paclitaxel is laid
Trial program	STEALTH-II in U.S. BEACON registry in Asia LEADERS-EU in Europe	In China	EAGLE in Europe
Where manufactured	Singapore	China	Netherlands
Commercial date	C.E. Mark expected in 1H06; U.S. approval expected in 2H08	Will only be sold in China	C.E. Mark received in July 2005. There are no plans to bring it to the U.S.

BOSTON SCIENTIFIC'S Taxus
Results holding up longer-term

Dr. Gregg Stone of Columbia University presented long-term data from the TAXUS-II, IV, V, and VI trials which indicate that there is no "late catch-up" in Taxus safety between two and three years. He reported no increased risk of early stent thrombosis in that period, with stent thrombosis rates at three years comparable to control. The one-year results were also positive for Taxus from the web-based, all-comers ARRIVE registry.

Taxus safety

Questions about Taxus safety have plagued Boston Scientific since just before the recall of the Taxus stent in 2004. Opinion leaders continued to defend the safety of Taxus, but doctors appear to be voting on this issue with their feet since Taxus has been losing market share to Cypher. However, Taxus may have bottomed out, at least until a new drug-eluting stent enters the U.S. market. Both Cypher and Taxus may be at risk from non-polymer-based stents, when they become available or from a stent (Endeavor ?) that requires a shorter regimen of antiplatelet therapy.

Longer-term Results in Taxus Trials

Measurement	TAXUS-II at 3 years		TAXUS-IV at 3 years		TAXUS-V at 1 year		Meta-analysis of TAXUS II-IV-V-VI	
	Control	Taxus	Control	Taxus	Control	Taxus	Control	Taxus
Formulation	---	SR/MR	---	SR	---	SR	---	Varied
Stent platform	NIR	NIRx	Express	Express	Express[2]	Express[2]	Varied	Varied
Results								
TVR	23.8%	12.4%	23.8%	13.4%	21.8%	15.8%	---	----
TVF	N/A	N/A	26.7%	17.4%	---	---	---	---
TLR	21.4%	12.3%	19.1%	6.9%	19.0%	11.2%	19.8%	9.3%
TLR in insulin-dependent diabetics	---	---	21.6%	6.3%	19.6%	10.9%	23.4%	9.2%
MACE	26.1%	15.4% SR 15.1% MR	28.3%	18.2%	25.9%	18.9%	---	---
All death	12%	11.7%	---	---	---	---	Freedom from 95.7%	any death 95.4%
Cardiac death	1.1%	1.6% SR 1.6% MR	2.5%	2.5%	1.1%	1.1%	Freedom from 98.0%	cardiac death 97.9%
MI	---	---	6.3%	5.7%	---	---	Freedom 93.6%	from MI 93.4%
Q-wave MI	1.9%	0.8%	---	---	0.2%	0.5%	---	---
Non-Q-wave MI	4.5%	3.1%	---	---	4.4%	4.9%	---	---
Stent thrombosis	1.2%	0.8%	0.8%	1.2%	0.7%	0.7%	Freedom from 99.2%	stent thrombosis 98.7%

1-Year Results of Taxus ARRIVE Registry

Measurement	Taxus n=2,585
Diabetics	31%
Direct stenting	36%
Average stent length	30.6 mm
Single vessel	34%
Bifurcations	8%
Results	
Cardiac death	1.1%
MI	1.8%
Re-intervention rate	5.4%
Key measurement: Overall Taxus-related cardiac events (MACE-like rate)	6.9%
Stent thrombosis in low risk patients	0.2%
Stent thrombosis in high risk patients	0.5%
Cardiac events in diabetics	1.9%
Non-diabetic cardiac events	0.8%
Taxus-related re-interventions in patients with multiple stents	
Overall	7.5%
Long lesions	6.6%
AMI	5.4%
Bifurcations	7.1%
SVG	4.3%

Stent thrombosis. Experts have shifted from a focus on whether Taxus has more stent thrombosis than Cypher to a concern that all drug-eluting stents with a durable polymer increase the risk of stent thrombosis. The messages were:

- Let's get rid of the polymer.
- The future is bioabsorbable stents.

Competitors

A Boston Scientific official said, "Our position is clear…We chose paclitaxel because we thought it was the best drug for a drug-eluting stent. We have a very strong licensing arrangement with Angiotech that we will aggressively protect. You can ask Guidant what it is like to be on the opposite end of that…It will not be easy for another paclitaxel to enter the U.S. market. We will protect our patent position to the fullest extent."

A Boston Scientific official said, "For the next 12-24 months, the landscape is what it is (Cypher and Taxus)…Certainly, as more competitors come into the market, there will be shifts…but we are confident of keeping our leadership share…When Endeavor or ZoMaxx launch in 2007 or 2008, we will be on the third or fourth generation Taxus – so their competition doesn't stand still. By the time Guidant gets on the market with (a drug-eluting) Vision, Vision will be a decade old, and we believe our superior deliverability will maintain."

Pricing

A Boston Scientific official said, "In the U.S. (drug-eluting stent prices) are fairly stable. In Europe, I think ASPs (average sales prices) are pretty stable…When we launched Taxus Liberté…there was no reason to lower the price…We will compete, and price is a component. Local people (sales reps) handle that at the local level. Pan-Europe and pan-international, we don't have a strategy to undercut prices. There are local situations, but pricing is pretty stable globally."

Stent guarantee program

In January 2006, Boston Scientific is launching the one-year ASSURANCE program in the U.S. Hospitals that sign up for the program will be entitled to a free Taxus stent if a patient comes back for in-stent restenosis in a Taxus stent during 2006. An official said, "We wanted to make a bold, confident statement…so we are telling hospitals we want to stand behind them in the best way we know how."

CONOR MEDSYSTEMS' CoStar

Paclitaxel

Experts are convinced that this cobalt chromium stent works, is deliverable, and will be a serious contender. The big question is whether the first drug chosen infringes on patents held by Angiotech and Boston Scientific. A Conor official insisted the company will launch "at risk," and he was confident Conor will prevail in a patent dispute.

Conor hopes to have a C.E. Mark by the end of 2005. An official said the company "is in discussion with European regulators," which suggests that regulators have had questions that Conor is trying to address. Once Conor gets a C.E. Mark, an official said it intends to launch immediately.

The 1,700-patient U.S. pivotal trial, COSTAR-II, will use 10 µg/30 days. The primary endpoints are 8-month MACE and in-segment late loss vs. Taxus in 2.5-3.5 mm vessels with single or multivessel disease. In the U.S., Conor plans to build its own sales force of 80-90 sales reps. It is hoping to lure experienced sales reps from other stent companies.

Other drugs

Conor has a deal with Novartis to test three of Novartis's drugs, and Conor expects to have animal data on all three by the end of 2005, plus some human data on one (pimecrolimus). The deal is for only one of the three drugs, and it is a non-exclusive license. Once one is chosen, a clinical trial will begin next year in Europe. The three drugs are:

1. **Gleevec** (imatinib mesylate), which is FDA-approved to treat chronic myeloid leukemia (CML).
2. **Midostaurin**, an agent in preclinical development by Novartis to treat cancer.

3. **Pimecrolimus** (Elidel), which is FDA-approved as a topical treatment for eczema. Pimecrolimus is not an mTOR inhibitor, but it is anti-inflammatory, and it has a different mechanism of action and different kinetics than Sorin's tacrolimus. If pimecrolimus is the choice, the European trial will be designed for a C.E. Mark filing, and it will have three arms – pimecrolimus, pimecrolimus +paclitaxel, and control. The pimecrolimus+paclitaxel has pimecrolimus in one well of the stent, and then paclitaxel in the next well, alternating them – not mixing them. Pimecrolimus has a fast burst action compared to the slower release of paclitaxel. A speaker said the elution rate is 60% in the first few days, and then 60% in one month, with the drug completely gone in 2-3 months. Elution is slightly slower with a polymer like the one used on the paclitaxel-eluting CoStar.

COSTAR-I trial in India

The final results of this trial were presented by the principal investigator. In this trial, CoStar was evaluated in a high risk patient population and three doses were tested. Researchers established that the 10 µg dose for 30 days was the lowest effective delivered dose; the 3 µg formulation for 30 days was ineffective, and a high dose (30 µg) for 10 days showed the most rebound clinically from 4-12 months.

Final COSTAR-I Results

Measurement	Paclitaxel 30 µg for 10 days n=10	Paclitaxel 10 µg for 30 days n=40	Paclitaxel 3 µg for 30 days n=37
30-day results			
Death	0	0	2.7%
MACE	0	5.0%	8.1%
Q-wave MI	10.0%	0	2.7%
Stent thrombosis	1 patient	0	2 patients
TLR	0	0	0
4-month QCA results			
Primary endpoint: Late loss in-stent	0.51 mm	0.43 mm	1.07 mm
Late loss in-segment	0.28 mm	0.23 mm	0.55 mm
Restenosis in-stent	14.3%	1.9%	32.6%
6-month results			
Death	0	0	5.4%
MACE	10.0%	7.5%	21.6%
Q-wave MI	10.0%	0	2.7%
Stent thrombosis (30 days to 6 months)	0	0	0
TLR	0	1.8%	5.9%
TVR	0	1.9%	6.5%
12-month results			
TLR	7.1%	1.9%	6.5%
TVR	7.1%	1.9%	6.5%
MACE	10.0%	7.5%	21.6%
Stent thrombosis (30 days-12 months)	0	0	0
Late loss in-stent	0.90 mm	0.55 mm	0.74 mm
Late loss in-segment	0.76 mm	0.25 mm	0.46 mm
Restenosis	27.3%	N/A	14.3%

GUIDANT

Xience-V

This everolimus-eluting stent uses Guidant's proprietary durable polymer, the cobalt chromium Vision stent, and the Vision delivery system. Dr. Campbell Rogers of Brigham & Women's Hospital said, the polymer has good adhesion to the stent and is a non-tacky, durable coating that survives stent expansion "with great robustness." He also indicated that Guidant has found a way to manufacture the stent with "remarkable reproducibility."

Guidant insists it can get a C.E. Mark based on the SPIRIT-I data, but Dr. Patrick Serruys, the principal investigator, said he believes European regulators will insist on at least some of the data from SPIRIT-II, which will complete enrollment in early November, 2005. Even if Guidant gets a C.E. Mark this fall for the Xience-V stent based on the SPIRIT-I trial, an official said the company will not launch the stent this year. A Guidant official said the company wants to wait for at least some data from SPIRIT-II first to have a "better characterization" of the stent, but the company also may:

a. Be waiting for J&J acquisition to be completed – if it is.
b. Know there are issues that will hold up the C.E. Mark for a few months.
c. Have or get a C.E. Mark but not announce it.
d. Want reassurance from a larger trial so they don't repeat the Sorin mistake of launching a product based on early data only to have a larger trial fail.

The 300-patient SPIRIT-II trial is expected to be fully enrolled by mid-November, so there could be early data by the end of 2005 or early 2006.

SPIRIT-III, the 1,002-patient pivotal U.S. trial may finish enrollment as early as January or February 2006. As of October 19, 2005, there were 50 active sites enrolling patients, and 256 patients had been enrolled. The number of sites is being increased to 72. There could be data, at least from an angiographic subset, at TCT 2006. The primary endpoint in this trial is late loss at 8 months. A non-randomized Japanese arm of this trial, with 88 patients, will start enrolling in November 2005. Guidant plans to seek simultaneous approval in the U.S. and Japan.

Everolimus-eluting Vision stent

A cobalt chromium Vision stent that elutes everolimus (the FUTURE trials program) will not move forward until the deal with J&J is complete. It is a most promising product, but J&J reportedly wants to see more internal Guidant data before making a final commitment to it.

Bioabsorbable BVS stent

Guidant also has a bioabsorbable stent (BVS) program in development. This has a thin (<5 μm), bioabsorbable PLA matrix polymer coating (with a top coat) on a BVS stent platform, eluting everolimus, and using the ML Vision balloon delivery system. The coating is very thin, with high drug-loading capability. It maintains its strength for six months, but degrades and is gone in 12-18 months. Everolimus is not yet approved in the U.S., though Novartis has an approvable letter from the FDA, and a speaker at TCT predicted that full approval will come "literally any day now."

The BVS stent has a similar elution curve to Cypher and Xience. A source said, "One advantage of coating over the top is it smoothes it out. Uncoated, the stent is rather rough...But the PLA on the surface makes it very smooth." The radial strength of the BVS stent is "slightly less" than ML Vision, but it is stronger than the MultiLink. BVS can't be seen on fluoroscopy, but there are gold marks that give it visibility.

Currently, the manufacturing processes are being refined, and the company is working on manufacturing scale-up. Animal studies are being finalized to support a first-in-man study.

JOHNSON & JOHNSON'S Cypher

J&J's path forward in drug-eluting stents is not clear and won't be clear until and unless the acquisition of Guidant is complete. J&J doesn't want to start down one DES path only to switch to another path right after the merger. However, J&J does still have an internal program – with Cypher Select and Neo – and both those programs are continuing.

Neo

Development of Neo was halted for a while, but earlier this year J&J resumed work on Neo (formerly Steeplechaser), and the Neo Advisory Board met during TCT. Trials of Neo are again in the planning stage – but for post-merger and only after J&J reviews the whole stent portfolio post-merger. One of the problems J&J is facing is that different countries want a different comparator in the Neo trial: The U.K. wants Neo compared to Cypher; the U.S. wants Neo compared to Cypher Select, etc. A J&J source said the different comparators are more for reimbursement than regulatory purposes.

Cypher Select

Cypher Select is already on the market in Europe, based on the results of the DOMINO trial. Cypher Select is not available in France because it hasn't been granted reimbursement there yet. The outlook for Cypher Select in the U.S. reportedly has not been decided.

PRISON-II Trial – Cypher more effective than a bare stent in CTOs

The prospective, randomized, single-blind, two-center PRISON-II study found the Cypher stent was superior to a bare BX Velocity in chronic total occlusions (CTOs). PRISON-II was a 200-patient study conducted in the Netherlands. In the study, Cypher significantly reduced both in-stent and in-segment restenosis, TLR, and TVR compared to the bare stent. A low rate of subacute and late stent thrombosis was seen with both stents.

Asked about the prevalence of bare metal stents in Europe, an investigator said, "There is still a lot of use. Drug-eluting stents are used for 20%-100% of patients. In my hospital, we are using 40-60% drug-eluting stents. The biggest issue is the cost, so we always have to deal with hospital management and try to get drug-eluting stents, and that's the real issue. A study like this, in my opinion, is evidence that you should use drug-eluting stents for those kind of patients."

6-Month PRISON-II Trial Results

Measurement	Bare BX Velocity n=100	Cypher n=100	p-value
Primary endpoints			
Restenosis in-segment	41%	11%	<.0001
Restenosis in-stent	36%	7%	<.001
Secondary endpoints			
TVF	24%	8%	0.003
MACE	20%	4%	<.001
MLD	1.47 mm	2.48 mm	<.001
% Diameter stenosis	48.75%	22.01%	<.001
Late loss in-stent	1.09 mm	0.05 mm	0.0001
Late loss index	0.45 mm	-0.02 mm	<.001
Other results			
Death	0	0	Nss
MI	3%	2%	Nss
TLR	19%	4%	0.001
TVR	22%	8%	0.009
Re-occlusions	13%	4%	<.04

SISR Trial – The last nail in the coffin for vascular brachytherapy?

Cypher beat out vascular brachytherapy (VBT) for the treatment of patients with in-stent restenosis in the SISR trial, a nine-month, 384-patient, multicenter, randomized study. The study met the primary endpoint of TVF (a composite of cardiac death, MI, or TVR), and it showed lower MACE with Cypher, due to a decrease in TLR.

Principal investigator Dr. David Holmes of the Mayo Clinic said, "We finished this trial…just as brachytherapy was fading away." He said that device, lesion, and procedural success were excellent, with no difference between the two groups, and there was less late loss in Cypher patients than those with

VBT. He said, "There was dramatic improvement in the patients treated with SES (Cypher)."

Other points Dr. Holmes made included:

- Asked how much of a problem in-stent restenosis is, he answered, "This issue is still with us; not everyone gets a drug-eluting stent."
- "What price did patients pay for this improvement in clinical outcome? Stent thrombosis at nine-month follow-up occurred in two patients. The numbers are very small for this catastrophic late event…Both treatments were effective in reducing neointimal hyperplasia within the treated lesion…(but Cypher) resulted in significantly less TLR than VBT…The final bottom line for this trial is that (Cypher) was superior to VBT in reducing the primary endpoint of TVF."
- Asked about the future for VBT, he said, "The most appropriate term is in the past tense…It may be the last of these kind of trials because…while we have heard about some non-inferior trials, this is a non-non-non-inferiority trial. It is unambiguous in terms of the findings…The bottom line is that (Cypher) was superior to VBT in TVF."

Dr. David Williams of Rhode Island Hospital commented on the SISR results at the formal presentation. He called the results "quite pronounced and convincing." He said the size of the trial was too small to find out the actual rate of stent thrombosis in patients who receive a stent, "The association of a particular combination with stent thrombosis became quite clear to us in our earlier investigations, and, accordingly, requires additional attention and surveillance as we adopt the strategy of using SES (Cypher). Now we have this information, what do we do with it? It's odd when a clinical trial is completed, comparing two strategies, and the results are vetted, that the usual care arm of the trial no longer exists…We don't have the option of VBT. Our options are using balloon, bare metal stent, or drug-eluting stent…SISR doesn't contribute substantially to the more current problem of in-stent restenosis of drug-eluting stents. This should be pursued. And finally, while this is preferred strategy today, it's by no means a perfect strategy."

9-Month SISR Trial Results

Measurement	Cypher n=259	Brachytherapy n=125	p-value
Primary endpoint: Target vessel failure	12.4%	21.8%	0.023
TVF in various subgroups			
Non-diabetics	12.8%	21.6%	0.074
Diabetics	11.6%	21.6%	0.170
Insulin-dependent diabetics	16.7%	36.4%	0.226
Females	14.6%	25.6%	0.150
Males	11.4%	19.5%	0.085
Small vessels	16.7% (Mean baseline lesion length 9.38 mm)	18.9% (Mean baseline lesion length 9.15 mm)	0.0799
Medium vessels	7.8% (Mean baseline lesion length 15.83 mm)	27.5% (Mean baseline lesion length 15.13 mm)	0.005
Large vessel	12.2% (Mean baseline lesion length 26.19 mm)	16.2% (Mean baseline lesion length 26.53 mm)	0.573
Safety results			
Secondary endpoint: MACE	10%	19.2%	0.015
TVR	10.8%	21.6%	0.008
TLR	8.5%	19.2%	0.004
Non-Q-wave MI	2.3%	0	0.183
Death	0	0	Nss

Small and large vessels

The 100-patient trial of Cypher in small vessels (2.0-2.25 mm) was designed for U.S. regulatory approval, as was the 100-patient SIRIUS-4.0 trial. The comparator in the small vessel study was the balloon angiograph arms of the STRESS and BENESTENT-I and -II trials. The 4.0 Cyphers were compared to bare stents.

6-Month SIRIUS-2.25 Results

Measurement	Cypher	
MACE	7.4%	
Subacute thrombosis	1.1%	
LaST	1.1%	
Late loss in-segment	0.23 mm	
Late loss in-stent	0.36 mm	
Restenosis in-segment	16.9%	
	Diabetics	**Non-diabetics**
Restenosis	26.5%	9.3%
TLR	0.5%	1.9%
TVR	10.0%	5.7%
MACE	10.1%	5.7%

6-Month SIRIUS-4.0 Results

Measurement	Cypher	Bare Venus/ Crossflex
Mean length	24.5 mm	---
Late loss at 6 months	0.08 mm	0.61 mm
Restenosis in-stent	1.1%	13.3%
Restenosis in-segment	2.2%	17.8%
MACE	5%	N/A
Death	2%	N/A

Meta-analysis

A meta-analysis of four Cypher trials (SIRIUS, E-SIRIUS, C-SIRIUS, and DIRECT) found that high risk patients with long lesions had better results with Cypher – even with multiple stents or overlapping stents – than bare metal stents. Dr. Campbell Rogers reported that lesions treated with multiple long Cypher stents had significantly fewer side branch occlusions than patients treated with multiple long bare metal stents.

Cypher Meta-analysis

Measurement	Cypher	Bare metal stent
30-day results		
Non-Q-wave MI	0 (p=.028)	3.6%
MACE	1.3%	3.6%
9-month results		
Death and MI	7.6%	37.8%
Thrombosis	0.6%	0.9%
TLR	5.7%	35.1%
TVR	13.3%	36.0%

Overlapping stents

Preliminary results from the MATRIX study have been submitted to the FDA. Dr. Roxana Mehran of Columbia University presented the results at TCT. MATRIX will include 3,500 consecutive Cypher patients, using both on-label and off-label indications. It is an all-comers, real-world cohort including high risk patients. Numerous substudies were pre-specified, including, bifurcations, CTOs, AMI, multivessel, and SVGs.

Preliminary MATRIX Results

Measurement	30-day results n=747	6-month results	Overlapping stents at 6 months n=135	Diabetics
Death	0.4%	0.5%	0	0.5%
MI	2.7%	---	5.2%	3.6%
Non-Q-wave MI	2.7%	3.3%	5.2%	3.6%
TLR	0.1%	3.0%	---	2.0%
TVR	0.1%	4.4%	---	---
Stent thrombosis	0.1%	0.2%	---	---
Late stent thrombosis	---	0.4%	---	---
TVF	3.6%	---	---	---
MACE	---	7.9%	---	---

MEDTRONIC'S Endeavor
Failed primary endpoint but may still be approvable

ENDEAVOR-III results

The primary endpoint was missed in ENDEAVOR-III, but Endeavor officials insisted the company will still file Endeavor with the FDA by summer 2006. 30-day safety data on 2,000 patients are required, and Medtronic will have that 30 days after ENDEAVOR-IV is fully enrolled, which the company now expects in "spring 2006." Scott Ward, President of Medtronic Vascular, insisted the FDA will overlook the missed primary endpoint in ENDEAVOR-III and, instead, consider the totality of the data on Endeavor. He is still predicting U.S. approval and launch in 2007.

Ward said, "The results today reflect the combined results now of the ENDEAVOR-II and ENDEAVOR-III programs. Those two studies combined have about 1,297 patients included…The efficacy profile of this product is very well characterized. We will need to complete safety on 2,000 patients – MACE – and that will be done on the conclusion of patient enrollment in ENDEAVOR-IV. We anticipate completing enrollment in ENDEAVOR-IV next spring and submitting late next summer, which should leave us on track for approval in calendar year 2007. So, the program is very much on track."

In-segment late loss was the primary endpoint, and the difference between Endeavor and Cypher was just 0.21 mm, and experts had predicted that a difference in the range of .20-.23 would be acceptable. The co-principal investigator, Dr. David Kandzari, said the problem "wasn't that Endeavor fared worse than expected but that Cypher did better than expected – better than it has ever done." A Medtronic official explained that the problem was the standard deviation – that the "tails" in the standard deviation – made Endeavor miss the primary endpoint.

Dr. Patrick Serruys discussed the results, and he was pretty negative about what this means for Endeavor in general. His key concern was that the failure of ENDEAVOR-III to meet the non-inferiority endpoint of in-segment late loss may indicate the stent would do even worse in high risk patients, though that remains to be proven.

The key findings in ENDEAVOR-III, according to Dr. Serruys were:

- No difference (between Endeavor and Cypher) in MACE. "That is almost identical."
- In-stent late loss was 0.60 mm for Endeavor vs. 0.15 mm for Cypher.
- In-segment restenosis was 11.7% vs. 4.3%.

His other points included:

- In-segment late loss may be a "hybrid endpoint," mixing edge restenosis and/or tapering of the vessels.
- In-segment late loss will "hide" in-stent late loss.
- In-segment late loss incorporates the edge effect, therefore artificially masking in-stent late loss, which accurately reflects intrastent neointimal inhibition of the drug-eluting stent.
- There are too many unknowns in the way TLR is currently measured.
- In higher risk cohorts, the differences in late loss are more strongly associated with a risk of TLR.

Approvability of Endeavor

ENDEAVOR-III was only a confirmatory trial; ENDEAVOR-II was the pivotal trial, and it met the primary endpoint of TVF. A big question is whether the FDA will look beyond the

missed primary endpoint in ENDEAVOR-III to the other findings in the trial. Medtronic already needs 30-day MACE data from ENDEAVOR-IV for approval, but will it also need longer-term data from that trial to make up for the problem in ENDEAVOR-III? Maybe not.

ENDEAVOR-III 8/9-Month Results

Measurement	Endeavor n=327	Cypher n=109	p-value
QCA results at 8 months			
Angiographic FU	282	94	---
Primary endpoint: In-segment late loss by QCA at 8 months	.34 mm	.13 mm	<.001
In-stent late loss	.60 mm	.15 mm	<.001
MLD in-stent	2.08 mm	2.52 mm	<.001
MLD in-segment	1.92 mm	2.15 mm	<.001
% DS in-stent	24.3%	11.0%	<.001
% DS in-segment	29.9%	23.9%	<.001
Secondary endpoint: Restenosis in-stent	9.2%	2.1%	0.02
Restenosis in-segment	11.7%	4.3%	0.04
% volume obstruction	16.1%	2.7%	<.001
Other secondary endpoints			
TLR at 9 months	6.3%	3.5%	0.34
TVR at 9 months	6.0%	5.3%	1.00
TVF at 9 months	12.0%	11.5%	1.00

Safety Findings in ENDEAVOR-III

Measurement	Endeavor n=327	Cypher n=109	p-value
Additional results			
Death	0.6%	0	1.00
Q-wave MI	0	0	Nss
Non-Q-wave MI	0.6%	N/A	0.04
CABG	0	0	Nss
PCI	5.4%	3.5%	0.61
Stent thrombosis	0	0	1.00
MACE	7.6%	7.1%	1.00

ENDEAVOR-III Compared to ENDEAVOR-II Results

Measurement	ENDEAVOR-III n=282	ENDEAVOR-II n=264	p-value
Angiographic results at 8 months			
Angiographic follow-up	87.3%	88.6%	0.71
Late loss in-segment	.34 mm	.36 mm	0.75
Late loss in-stent	.60 mm	.61 mm	0.78
Clinical results at 9 months			
TLR	6.3%	5.8%	0.87
MACE	7.6%	8.8%	0.66
TVF	12.0%	9.5%	0.36

To overcome a missed primary endpoint that is a surrogate endpoint (as in ENDEAVOR-II), an FDA official said Medtronic will need to:

1. **Explain why it happened.** "Dig in the data and find out why it happened." Medtronic has two explanations it can offer: (1) late loss is higher with Endeavor than with other drug-eluting stents, and (2) Cypher had lower than usual late loss in the trial.

2. **Show consistent findings.** Medtronic will need to compare the other (secondary) endpoints in the confirmatory trial, and if the findings are similar to the pivotal trial, that may be acceptable. If the comparison varies, then another trial would almost certainly be required. The consistency across the other endpoints is very important to FDA in this situation.

Yet, even with strong showings on both these points, approval is not a shoe-in. Another FDA official pointed out that it is ***very*** hard to overcome a missed primary endpoint in a device trial, just as it is in a drug trial. He noted that the FDA will look at the totality of the evidence, as Medtronic wants, but he insisted it is very, very rare when the Agency accepts a failed primary endpoint, "When you miss a primary endpoint, it is much more difficult to understand the trial. You need to look at the totality of the data very carefully...and remember that it is not just one trial (that is submitted)."

In addition, Medtronic also has to navigate through the drug side of the FDA (CDER), which both Johnson & Johnson and Boston Scientific found a more lengthy process than expected. Add to this that zotarolimus is a new molecular entity (NME), and the task becomes even more difficult – or perhaps just lengthier.

The FDA also could decide to wait for the full results of ENDEAVOR-IV, especially after Dr. Serruys suggested that Endeavor may do worse in high risk patients. The FDA will have little data on high risk patients, which could make labeling a problem without the ENDEAVOR-IV results. However, enrollment in ENDEAVOR-IV also is starting to pick up. The number of sites is being increased from 39 to 80, and the angiographic subset is completed. The key will be how fast ENDEAVOR-IV gets to the 80 sites.

Medtronic officials were optimistic about approval. Ward said, "The efficacy profile has been well characterized, and we are very pleased with that…We think the FDA will take ENDEAVOR-III in the context of the full (Endeavor) portfolio. They will look at the preponderance of evidence."

The outlook for Endeavor use after ENDEAVOR-III

European doctors were more conservative in their predictions about how much market share Endeavor will take after the results of ENDEAVOR-III. Medtronic officials were claiming to already have >15% market share in Europe, but Boston

Scientific's estimate was closer to 2% OUS except Japan. *(See page 2)*

An Endeavor investigator from the U.K. was more optimistic: "We have had Endeavor in our lab for two months, and physician preference already favors Endeavor. We are finding Endeavor easier to deliver, even over Taxus Liberté and Cypher Select…They are selecting smaller stents because they can get them further down in the vessel…we are probably expanding our stenting because we can get the (Endeavor) stents in. Does the data support that? No, but we are doing it…I use Endeavor in patients where I want a drug-eluting stent but where I want to get rid of or decrease the antiplatelet therapy…and that is occurring more frequently."

Poll: Endeavor efficacy less than Cypher but similar safety

CRT Online (**www.crtonline.com**) conducted a survey during TCT, asking doctors to vote on how they view Endeavor vs. Cypher after the ENDEAVOR-III trial results were announced. As of October 24, 2005, 267 doctors had voted, and the results were:

- 2% – Endeavor is safer than Cypher.
- 6% – Endeavor has similar safety and efficacy to Cypher.
- 75% – Endeavor has a similar safety profile but is less effective.

Endeavor-CR

Medtronic also is working on a zotarolimus-eluting stent with a different polymer developed by Medtronic in-house. The dose of zotarolimus is similar but not identical to Endeavor. The principal investigator is Dr. Ian Meredith in Australia. The approximately 150-patient RESOLUTE trial was scheduled to start in November 2005. The trial design is the same as for ENDEAVOR-II except that there will not be any 2.25 mm diameter stents in RESOLUTE.

Dr. Marty Leon said, "The clinical outcomes were pretty good with Endeavor, but the angiographic and IVUS data were not quite as good as with other sirolimus analogues. (The question was) do you take a chance to improve efficacy that could sacrifice safety? The polymer (Medtronic is using) is one-quarter the thickness of the Taxus Translute polymer. It is very thin, and the least inflammatory polymer we've seen. Dr. Renu Virmani hasn't seen a biostable polymer other than phosphorylcholine that is as non-inflammatory as this, at least in porcine arteries. And that is good…And the release is extended more than Cypher, perhaps by a factor of two… Early animal data with this new polymer suggest that there does not appear to be late catch-up with this new polymer… This is a calculated risk (by Medtronic) and well-thought out."

ENDEAVOR-IV

This ongoing trial will have ~2,100 patients when fully enrolled. Medtronic needs the 30-day MACE data from this trial for the Endeavor FDA submission. A Medtronic official said the trial would complete enrollment in spring 2006, and the company plans to submit its PMA in late summer 2006.

ENDEAVOR-V

This is an 8,000-patient registry in Europe and OUS, with MACE at 12 months the primary endpoint. The trial will be used to further characterize Endeavor, not for regulatory submission. There are 3 principal investigators:

1. Dr. Martin Rothman, U.K.
2. Dr. Chaim Lotan, Israel
3. Dr. Ian Meredith, Australia

Dual drug therapy

Medtronic also is working on a drug-eluting stent that combines more than one drug, but no further details were available.

SORIN'S Janus
Trial failed but company not giving up

The tacrolimus-eluting Janus stent failed to meet its primary endpoint in the JUPITER-II trial, but experts said the stent and the drug (tacrolimus) should not be abandoned – that the elution kinetics may need to be adjusted. The principal investigator, Dr. Marie-Claude Morice, said the Janus late loss met expectations, but, as in ENDEAVOR-III, the bare stent did better than expected. She added, "This program must not be abandoned. The carbofilm coating is very original. I think the drug is a very good one. There is probably room for more work to increase the profile of the drug-release."

JUPITER-II Results

Measurement	Bare Tecnic n=166	Janus n=166	p-value
Number of stents per patient	1.18	1.23	---
Number of stents per lesion	1.04	1.09	---
6-month efficacy results			
Primary endpoint: Late loss in-segment	0.44	0.40	Nss
Late loss in-stent	0.63	0.67	Nss
Late loss proximal edge	0.24	0.25	Nss
% DS	36.4%	33.0%	0.053
Restenosis	15.8%	9.4%	Nss
TLR (stent-related)	10.6%	5.7%	Nss
6-month safety results *(updated from ESC results)*			
MACE	11.3%	7.6%	Nss
Stent-related MACE	11.3%	6.4%	Nss
Acute thrombosis	0.6%	0	---
Subacute thrombosis	0	0	---
Late thrombosis	0	0	---

The discussant, Dr. Stephen Ellis, noted that the JUPITER-II trial was in a lower-risk cohort of patients than in the major Cypher and Taxus trials. Dr. Ellis agreed that the program should not be abandoned, "This is a promising stent and a promising drug. Perhaps the release kinetics need to be revised – and it needs to be studied in more high risk patients." He also wondered whether the early angiography (at 6 months instead of the more common 8-9 months) could have either helped or hurt the Janus performance.

Other Drug-Eluting Stents

Cook's V-Flex

This polymer-free stent with a lipid coating has paclitaxel spray-coated on the abluminal surface. New data were presented at TCT from the prospective, multicenter, 117-patient ELUTES-II trial. The ELUTES-III trial was a dose-escalation study, testing 2.7 µg/m^2, 3.5 µg/m^2, and 4.0 µg/m^2. The primary endpoint was late loss at six months. Researchers concluded that ELUTES-II confirmed the usefulness of increasing the paclitaxel dose on this platform, but both ELUTES-II and ELUTES-III failed to reproduce the biological efficacy (in-stent late loss) observed in ELUTES-I.

9-Month ELUTES-II Results

Measurement	PBOA and/or cutting balloon n=38	V-Flex with 0.9 µg/m^2 paclitaxel n=41	V-Flex with 2.7 µg/m^2 paclitaxel n=38
TLR	39%	29%	10.8%
MACE	44%	29%	22%
Event-free survival	56%	71%	78%
Stent thrombosis	0	0	1 patient
In-stent late loss	1.00 mm	1.14 mm	0.80 mm
% DS	59.7%	44.9%	40.4%
Restenosis	57.6%	40.0%	33.3%

6-Month ELUTES-III Results

Measurement	V-Flex with 2.7 µg/m^2 paclitaxel	V-Flex with 3.5 µg/m^2 paclitaxel n=41	V-Flex with 4.0 µg/m^2 paclitaxel n=38
TLR	8.9%	6.7%	6.7%
Death	0	2.2%	2.3%
Non-Q-wave MI	2.2%	4.4%	0
Primary endpoint: Late loss in-stent	0.72 mm	0.63 mm	0.65 mm
% DS	29.8%	27.3%	25.7%
Restenosis	12.8%	10.5%	10.5%

Goodman/Avantec

This company also has a license to pimecrolimus from Novartis. An official said a first-in-man study would start in Europe and OUS in the next couple of months, using a different dose and a different polymer than Conor. A Japanese trial also is planned.

LabCoat's Precision

Precise amounts of polymer are applied to stents with microdroplet deposition technology. How thick it is put on determines the speed of drug release, and the droplets can be put on specific stent surfaces – e.g., just the luminal or just the abluminal side.

Microport's Firebird

This stainless steel, sirolimus-eluting, rapid-exchange stent is manufactured in Shanghai and is the No. 1 drug-eluting stent in China, and sales have begun in Latin America. It is priced comparable to Taxus and Cypher. There are no plans to bring it to markets where patents would be an issue.

Neich Medical/Orbus Medical's Genous

This is a bioengineered R-stent designed to capture endothelial progenitor cells (EPCs), which then flatten out and mature into endothelial cells, forming a functional layer over the stent and intrastrut. Preliminary results from the multicenter, non-randomized HEALING-II trial looked promising. There was no clear correlation based on gender, hypertension, family history, smoking, or age with EPC number, but there was a correlation with diabetes and statin therapy (with simvastatin). A speaker said, "Statin therapy was associated with a 2-3-fold increase in EPC number, so we gathered that statin therapy may improve EPC number and even the outcome of EPC capture stenting."

The HEALING-III trial is due to start in 1Q06. This is a multicenter, randomized, prospective trial of 450 patients from 20 European sites, with in-stent late loss at 9 months the primary endpoint. It will compare Genous to a bare stent. Results from an interim analysis are expected in 1Q07. There will be three arms:

- Bare stent + 80 mg atorvastatin QD (Pfizer's Lipitor)
- Genous + 10 mg atorvastatin QD
- Genous + 80 mg atorvastatin QD

Sahajanand/MIV Therapeutics

Sahajanand, an Indian company, and MIV Therapeutics, a Canadian company, are merging. The combined company will be headquartered in Canada and be a Canadian company, but the stents will continue to be manufactured in India, and there will be an Indian office. Sahajanand has two current drug-eluting stents:

- **Infinnium**, a stainless steel paclitaxel-eluting stent with a 2-3 layer biodegradable polymer on a rapid exchange delivery system. It has three polymer layers – fast, medium, and slow release.
- **Supralimus**, a stainless steel sirolimus-eluting stent with a 2-3 layer biodegradable polymer on a rapid exchange delivery system.

MIV brings coating technology to the table. It is a passive, biocompatible, hydroxyapetite coating – which is a different coating than currently used on Infinnium or Supralimus stents. It is a bioceramic coating, layered to provide controlled release, that will be used with both a new drug (not named) and for multi-drug release. This program is thought to be in advanced research, with human clinical trials expected to start this year, but sources would not say where.

Sahajanand drug-eluting stents are currently sold in India, South America, the Middle East, and the Philippines. They are not sold in Europe, but there are plans to enter the European market within a year. Sahajanand does not currently sell in Japan, but it is considering entering that market.

Two trials of the Infinnium are completed and one is ongoing:

- SIMPLE-I – a real-world study of 3.0 $\mu g/m^2$.
- SIMPLE-II – using 1.4 $\mu g/m^2$ in single de novo lesions.
- SIMPLE-III – a 120-patient, ongoing study in multivessel stenting, using the 1.4 $\mu g/m^2$ dose.

A cobalt chromium program is starting:

- **Infinnium-Core** – with paclitaxel, a biodegradable polymer, and rapid exchange.
- **Supralimus-Core** – with sirolimus, a biodegradable polymer, and rapid exchange.

SIMPLE Trials

Measurement	SIMPLE-I	SIMPLE-II
Number of patients	282	103
Location	India	India, Brazil, and Netherlands
MACE to 30 days	---	***Primary endpoint #1*** 1.0%
6-month results		
MACE	5.0%	1.9%
Late loss in-stent	0.20 mm	0.38 mm
Late loss in-segment	0.11 mm	0.17 mm
Stent thrombosis	2.1%	0
Restenosis in-stent	5.9%	***Primary endpoint #2*** 7.4%
Restenosis in-segment	8.9%	8.5%

TERUMO'S Nobori

Terumo has licensed biolimus worldwide, except for the U.S., from Biosensors. Terumo is developing Nobori, a biolimus-eluting stainless steel S-stent with a thin biodegradable poly-lactic acid (PLA) polymer. The drug/polymer matrix is coated exclusively on the outside, abluminal surface of the stent, targeting vessel wall tissue. About 70% of the drug is gone in seven days, but 90% of the polymer is still there at 90 days. At two minutes, there is a blood concentration of 0.0522 ng/mL of biolimus, but at three months, there is no detectable drug in tissue. Terumo is expecting a C.E. Mark in 2006, but there are no plans to bring Nobori to the U.S.

The prospective, randomized (2:1), 360-patient NOBORI-1 trial started enrolling patients in May 2005 (with a live case at EuroPCR, and enrollment is expected to be completed by the end of 2005. The trial, which is being conducted in Europe, Australia, and Asia, is an equivalency study comparing Nobori to Taxus Express[2]. The primary endpoint is in-stent late loss at nine months, and the principal investigator is Dr. Bernard Chevalier of France.

Other Nobori trials include:

- A NOBORI-PK registry which began this year.
- The NOBORI SV/LL registry, which is expected to begin in 2006.
- The NOBORI-2 registry, which is expected to begin in July 2006.
- A Japanese randomized trial that is planned for 2006.

The bare stent platform is the S-stent, a corrugated ring stent, which combines repeating S symmetry and very short segment lengths to provide flexibility and high vessel wall support in both straight and curved vessels. It is a flexible, conformable stent designed to provide uniform drug distribution to the vessel wall. The drug carrier is (PLA) a biodegradable polymer that degrades primarily by hydrolysis and the degradation product is water soluble lactic acid. It gets absorbed by tissue and is eventually converted to water and carbon dioxide.

TRANSLUMINA'S Yukon

Custom coating a stent with a drug right in the cath lab just before use is an idea that has appeal, and Translumina got attention at TCT by showing it can work. In the ISAR-TEST trial, Yukon, a non-polymer-based, rapamycin-coated stent, was shown to be as effective as a Taxus stent in treating in-stent restenosis.

Using its proprietary stent coating machine, the Magic Box, Translumina coated a bare Yukon stent with sirolimus. Yukon uses a new porous, non-polymeric surface finishing technology – PEARL – with which the drug bonds.

ISAR-TEST was a prospective, randomized, non-inferiority trial of 450 patients with angina or a positive stress test and in-stent restenosis. The trial was powered to show less than a 0.13 mm difference in late loss between a sirolimus-coated Yukon and a Taxus, and this primary endpoint was met, with a difference of only .002 mm between the two stents. The investigator said, "We concluded that (Yukon) is not inferior to (Taxus). We may have the first successful non-polymer approach to drug-eluting stent technology in interventional cardiology...The release is faster, (but)…there is no difference in efficacy, and there are hypothetical advantages without the

use of a polymer. The late stent events (thrombosis) are associated with the presence of polymer. It's clear what we need from a drug-eluting stent is to have the drug released in a period of time in which the process of restenosis is active. The best value would be the stent releasing the drug within that time and, after that, no polymer."

Dr. Sheldon Goldberg, commenting at the formal presentation of the ISAR-TEST results, was not completely convinced by the ISAR-TEST results. He said, "The question is: What is the optimal rate of drug release? There is a time period for thrombosis, inflammation, and proliferation. That is the importance of the polymer…If there's no polymer carrier, up to 40% of drug loss occurs on expansion. The polymer provides consistent dosing and control…However, polymers have notable problems. The continuity of polymer continues to curve in, deployment separates the struts of the stent and draws the incontinuity polymer out to form webs. The webbed polymer breaks and recoils, leaving an area bare of polymer…Then, there is the issue of side branch loss, which is an important point with multiple overlapping stents…Potential problems with polymer include balloon stickiness, side branch compromise, inflammation, restenosis, and thrombosis." However, he said he had questions about the polymer-free Yukon, wondering if there would have been similar efficacy if the patients had been in a higher risk subgroup.

ISAR-TEST Results

Measurement	Yukon n=225	Taxus Express n=225	p-value
Stent occlusion rate	0.4%	0.9%	Nss
Death or MI	4.4%	4%	Nss
Primary endpoint: Late loss in-stent	0.48 mm	0.48 mm	.98
Late loss in-segment	0.34 mm	0.24 mm	.09
Secondary endpoint: Restenosis	14.2%	15.5%	.73

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