Trends-in-Medicine

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by Lynne Peterson

SUMMARY

Trends-in-Medicine
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TRANSCATHETER CARDIOVASCULAR THERAPEUTICS (TCT)

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During TCT, the U.S. Senate expanded an investigation into how medical device companies promote their products. Republican Sen. Charles Grassley and Democratic Sen. Herb Kohl asked both the non-profit Cardiovascular Research Foundation (CRF), which sponsors TCT, and Columbia University for financial information about outside income for 21 doctors affiliated with the university and CRF, including Dr. Marty Leon, Dr. Gregg Stone, and Dr. Jeff Moses. The investigation appears to focus on financial dealings relating to five companies: Abbott, Medtronic, Medinol, Boston Scientific, and Johnson & Johnson.

In September, Sen. Kohl requested information about the new five-year partnership between the American College of Cardiology (ACC) and CRF. Under that agreement, CRF will sponsor the i2 Summit for interventional cardiologists to be held concurrently with the annual ACC meeting.

The economic turmoil in the financial markets did not seem to be affecting the interventional cardiology market significantly – yet. Cath lab build-outs are going ahead as planned. However, Siemens and GE officials indicated that some cath labs are dragging their feet a bit on projects, not canceling or actually postponing them, just moving a little slower. A Boston Scientific official said, "GE and Siemens say they are continuing, but some decisions are being slowed down. But it is still a fairly strong market." A GE official said, "A month ago, the market felt like it was coming back. DES had bottomed, and volume was slowly increasing, and that frees money for cath lab construction. There had been a freeze on building, and we were seeing the equipment marketing coming back. Now, no one know what's going on. Some people are being more cautious. They aren't canceling things, but they are slowing it down, pushing it out. But the market is healthier than it was this time last year."

Asked about demand for hybrid cath labs that merge interventional cardiology and surgery, a GE official said, "Everyone is starting to think about it."

STENTS

Dr. Marty Leon of Columbia University, chairman emeritus of CRF, reported that drug-eluting stent (DES) use increased 1.3% this year, following a 10% drop in 2007. But he also noted that CABG grew 22% in 2008. Doctors questioned at TCT agreed that DES use is rebounding but very, very slowly.

Xience has taken more than 50% of the U.S. market, and it looks, from interviews with cardiologists and cath lab managers at TCT, that Xience is likely to continue to gain some more share, at the expense of all the other DES. During TCT, Boston Scientific released its figures on market share, putting Promus share at 25% and

Taxus at 19% – a much better showing for Promus and a worse showing for Taxus than expected. If Xience has ~26% share, that leaves 30% for Endeavor and Cypher to split. Doctors did not see Endeavor gaining much share – unless it got rapid exchange, in which case many said they would use much more Endeavor. And shortly after TCT Medtronic said it would launch its stents and catheters on rapid exchange "at risk," counting on prevailing in its patent fight with Abbott.

DES Market Share Among Cardiologists Interviewed at TCT

Measurement	Current use	Usage in 1 year *
Johnson & Johnson's Cypher	35%	19%
Boston Scientific's Taxus	27%	18%
Boston Scientific's Promus	22%	25%
Medtronic's Endeavor	5%	6%
Abbott's Xience	11%	32%

*** Assuming Endeavor doesn't get rapid exchange.**

Physician comments about DES choices and the DES outlook were:

- *Illinois:* "Everything seems to be looking up except in Sweden. DES are back in style in the U.S., including our hospital. We are using DES 85% of the time now. We use them all, but Endeavor is gaining at the expense of Cypher and Taxus. We will use Xience."
- *Louisiana:* "We are still using mostly Taxus because of our relationship with Boston Scientific, but we are starting to use Promus a little, and Xience is available. Cypher hasn't been price competitive, but they are starting to be more competitive. In a year, I think we'll be using mostly Taxus, Promus, and Xience. There seems to be a consistent story that late loss is better with the limus drugs, except Endeavor. If Endeavor had rapid exchange, that would affect our use only slightly. The Endeavor platform and balloon are good, but the drug is not quite as good…(Lilly's) prasugrel might hurt Endeavor because people might be less worried about stent thrombosis."
- *Michigan:* "We are 80% DES and 20% BMS. The DES is our workhorse stent; only a few people (here) use BMS. Cypher historically has the majority, but now we are shifting to Xience and Promus…Rapid exchange is important…We have used Endeavor, and Endeavor and Taxus are not as good as Cypher when it comes to late loss. But choice mainly has to do with ease of delivery. We aren't using much Taxus, but we're starting to use Promus, and the Boston Scientific rep isn't very happy about it. In one year we will see more Xience and Promus, definitely. In a year, I'd say Xience and Promus will be at least 70% of DES, and Cypher will be used in special situations like osteo lesions. I like Xience; it's easy to deliver, and it's user-friendly. Endeavor is easier to deliver than Cypher."
- *New York #1:* "We are using 80% Promus, 15% Taxus, and 5% Endeavor. Endeavor use would go up if it had rapid exchange; it could take 30% share in our lab."
- *New York #2:* "We use 90% DES and 10% BMS. Of the DES, we use about 95% Cypher and 5% Taxus. Next year, Xience will probably take a big bite from Taxus and Cypher, more from Cypher because we use it so much now."
- *North Carolina:* "We used to be a big Taxus user. Now, we are 80% Promus, 15% Taxus, and 5% Cypher. Our DES use is 60% and increasing; in a year it will be 70%. Endeavor is more deliverable than Taxus, but Promus is better than both. Rapid exchange would increase Endeavor use to 30% share."
- *Ohio:* "I use 50% BMS and 50% DES, and DES is 50-50 Cypher and Taxus. The hospital tells us what we can use. We are looking forward to using Xience."
- *Pennsylvania #1:* "We use DES 85% and BMS 15%. Use is fluctuating a lot right now. We use Cypher 80% and Taxus 20%, and we just received Xience stents a few weeks ago. We use mostly Cypher, but that is changing, and Cypher will lose to Xience and possibly to Endeavor. The problem with Endeavor is the delivery system. Our doctors aren't quite comfortable with Endeavor's over-the-wire system."
- *Pennsylvania #2:* "We use 85%-90% DES and 10%-15% BMS. DES use is split between Cypher and Taxus. We just got Xience last week, and we're excited about that. That should take away from both Cypher and Taxus. We don't have Endeavor yet. Ease of use/deliverability is very important, so there may be a little learning curve with Endeavor."
- *Pennsylvania #3:* "We are 80% Xience because the Abbott sales rep is better than the Boston Scientific sales rep, Xience is cheaper, and I like to support the underdog."
- *Tennessee:* "We use Cypher and Taxus 50-50. Both have their pluses and minuses. We don't have Endeavor or Xience yet, and I'm at TCT to learn about them. I see the trend back to DES."
- *Texas:* "We use 85%-90% DES – Endeavor, Xience, Cypher, and Taxus. No major changes are coming."
- *Middle East:* "Cypher is getting cheaper. We use Xience and Taxus, but cost may change that."

DES vs. BMS

The prospective, randomized ODESSA trial used optical coherence tomography (OCT) to compare Johnson & Johnson's Cypher, Boston Scientific's Taxus, and Medtronic's Endeavor stents to bare metal stents (BMS). It found a trend toward a higher incidence of uncovered and malapposed struts with DES than BMS. Cypher had the highest rate of uncovered and malapposed struts and the lowest degree of neointimal hyperplasia. Endeavor had the lowest rate of uncovered and malapposed struts and the highest degree of

neointimal hyperplasia. Taxus had a higher incidence of uncovered and malapposed struts than BMS and an intermediate degree of neointimal hyperplasia.

6-Month Results of ODESSA Trial

Measurement	Cypher n=22	Taxus n=22	Endeavor n=22	Bare Taxus Liberté n=11
Primary endpoint: Stent struts uncovered and/or malapposed	5.4% (Nss, 0.081)			1.8%
Stent struts uncovered and/or malapposed	8.2%	4.3%	0.02% *	0.9%
Struts uncovered	5.9%	2.0%	0.01%	0.8%
Struts malapposed	2.3%	2.3%	0.01%	0.1%
Neointimal obstruction (by OCT and IVUS)	14.1%	25.1%	40.1%	53.8%

* p<0.001 vs. Cypher or Taxus.

Cypher vs. Taxus

In the ISAR-Left Main trial, there was no significant difference between Cypher and Taxus stents in patients with unprotected left main disease (13.6% Taxus, 15.8% Cypher).

SYNTAX – CABG beat PCI

The results of the Boston Scientific-sponsored SYNTAX trial were presented at the European Society of Cardiology (ESC) meeting in Munich in September 2008, showing that stenting (79% Taxus Express, 21% bare metal stents) was ***inferior*** to CABG on MACCE (all-cause death, CVA/stroke, MI, stent thrombosis by ARC, and repeat revascularization). The excess MACCE in the PCI (percutaneous coronary intervention) arm was due primarily to revascularization, and some experts argued that the bleeding risk with CABG outweighed the increase in PCI. However, other experts pointed out that CABG has a durability advantage and that, over time, PCI will compare even less favorably to CABG.

Jeff Lemaster, vice president of stent marketing for Boston Scientific, said, "We were very encouraged by the SYNTAX results…SYNTAX tested the boundaries of PCI…These are highly complex patients who more than likely today are being treated by surgery…This (SYNTAX) is something that should encourage (professional) societies to re-look at PCI guidelines…and say that there are patients that today aren't captured within the guidelines…and interventionalists and cardiac surgeons should look at revising the guidelines."

Subgroup analyses and additional details from SYNTAX were presented at TCT.

- **SYNTAX score – a good way to choose between CABG and PCI.** Dr. Patrick Serruys of the Netherlands, the co-principal investigator of SYNTAX, insisted SYNTAX should not be viewed as a "Taxus failure" as some stent competitors have charged. He emphasized that the trial showed that the delta between CABG and PCI has narrowed and pointed out that the SYNTAX score appears to be a good way to stratify patients for PCI or CABG, "The SYNTAX score has to be combined in an interactive way with diabetes, and then we should be able to see who has to go to surgery and who has to be naturally treated with PCI…The results of the SYNTAX trial suggest that 55% of all patients are still best treated with CABG. However, for the remaining patients, PCI is an excellent alternative to surgery."
  - Patients with a **high** SYNTAX score (≥33) "should remain surgical candidates," he said.
  - Patients with a **low** SYNTAX score (≤22) had comparable outcomes for PCI and CABG, so either is an option.
  - Patients with an **intermediate** SYNTAX score (23-32) had a slightly but not significantly increased risk of MACCE, according to Dr. Serruys.
- **Left main** – equivalent safety for Taxus and CABG. Dr. Serruys said, "For patients with left main disease, revascularization with PCI has comparable safety and efficacy outcomes to CABG. (PCI) is therefore a reasonable treatment alternative in this patient population, in particular when the SYNTAX score is low or intermediate."

12-Month MACCE in Left Main Subgroup of SYNTAX Trial

Measurement	CABG	Taxus	p-value
MACCE			
All-left main (LM)	13.7%	15.8%	Nss, 0.49
Isolated LM	8.5%	7.1%	Nss, 1.0
LM + 1-vessel disease	13.2%	7.5%	Nss, 0.27
LM + 2-vessel disease	14.4%	19.8%	Nss, 0.29
LM + 3-vessel disease	15.4%	19.3%	Nss, 0.42
MACCE by SYNTAX score			
Low SYNTAX score	13.0%	7.7%	Nss, 0.19
Intermediate SYNTAX score	15.5%	12.0%	Nss, 0.54
High SYNTAX score	12.9%	25.3%	0.008
Other findings in left main subgroup			
Stroke	2.7%	0.3%	0.009
Repeat revascularization	12.0%	6.7%	0.02

SYNTAX Score as a Predictor of MACCE in the SYNTAX Trial

Measurement	CABG SYNTAX Score			Taxus SYNTAX Score		
	≤22	23-32	>33	≤22	23-32	>33
12-month MACCE	14.7% (Nss, p=0.38 vs. PCI with SYNTAX ≤22)	12.0%	10.9%	13.6%	16.7%	23.4% (p=0.006 vs. CABG with SYNTAX ≤22)

- **Diabetics** – MACCE higher in diabetics than non-diabetics, driven mostly by revascularization.

12-Month Subgroup Analysis of Diabetics in SYNTAX Trial

Measurement	CABG		Taxus	
	Diabetics	Non-diabetics	Diabetics	Non-diabetics
MACCE	14.2%	11.8%	26.0% (p=0.003)	15.1% (Nss, p=0.08)
Death/CVA/MI	10.3%	6.8%	10.1%	6.8%
Revascularization	6.4%	5.7%	20.3%	11.1%
All-cause death	N/A	N/A	8.4%	3.0%

- **Triple vessel** – better efficacy for CABG.

12-Month MACCE in 3-Vessel Subgroup of SYNTAX Trial

Measurement	CABG	Taxus	p-value
MACCE	11.2%	19.1%	0.001
MI	2.6%	5.2%	0.04
Death	2.9%	4.4%	Nss, 0.18
Repeat revascularization	5.4%	14.7%	<0.001
MACCE by SYNTAX score			
Low SYNTAX score	15.2%	17.3%	Nss, 0.66
Intermediate SYNTAX score	10.1%	18.6%	0.02
High SYNTAX score	8.8%	21.5%	0.002

ABBOTT VASCULAR

Two-year data from 30 patients in the prospective, randomized, open-label, 110-patient ABSORB trial confirm the findings at one year. The trial was conducted in Europe and New Zealand. Dr. John Ormiston of New Zealand, the principal investigator, reported that Abbott's bioabsorbable, everolimus-eluting DES (made out of polylactic acid) worked and was absorbed into the walls of treated arteries. The blood vessels left behind appeared to move and function similarly to unstented arteries. There was no stent thrombosis in the trial and no new MACE from 6-24 months. Dr. Ormiston said, "These are very exciting results that represent a potential major breakthrough in the future treatment of patients with coronary artery disease."

There was a trend that suggested a potential restoration of unstented artery movement to coronary blood vessels after the stent was absorbed, which is not possible with other metal stents.

2-Year Results of ABSORB Trial

Measurement	Stent
MACE at 6 months	3.3%
MACE at 1 year	3.4%
MACE at 2 years	3.6%
Stent thrombosis	0

BIOSENSOR's BioMatrix

Twelve-month follow-up data from the 1,707-patient LEADERS trial, a head-to-head randomized comparison of Cypher and BioMatrix – a biolimus-eluting, biodegradable stent – in a real world, all-comers population showed equivalent safety and efficacy for the two DES.

A predefined optical coherence tomography (OCT) subset analysis of 46 patients from LEADERS showed BioMatrix was more than 10 times more likely to have nearly complete endothelialization (stent/strut coverage) at 9 months than Cypher, though this was not statistically significant. Dr. Carlo Di Mario of Royal Brompton Hospital in London said, "We observed a thin layer of intimal coverage, with an average thickness of approximately 50 microns, on most struts in both stents, explaining the similar efficacy in preventing restenosis, an observation supported by the 12-month results from the main study. The Biosensors stent, however, showed a significantly better level of nearly complete strut coverage, possibly due to the biodegradable polymer. The better intimal coverage achieved by the Biosensors stent at 9 months possibly anticipates a lower risk of late stent thrombosis. This needs to be confirmed by the planned long-term follow-up, lasting for as long as five years after stent implantation."

Dr. Stephan Windecker of University Hospital in Bern, Switzerland, and the principal investigator for the LEADERS trial, said, "Since (BioMatrix) became commercially available earlier this year, we have had significant experience using (it), with excellent clinical outcomes and device success rates, confirming the positive results achieved with the LEADERS study. I believe that these stents represent true next-generation DES technology."

12-Month Results of LEADERS Trial

Measurement	BioMatrix	Cypher	p-value
Primary endpoint: Cardiac death, MI, TVR at 9 months	9.2%	10.5%	0.003
Cardiac death, MI, TVR at 12 months	10.7%	12.2%	---
Repeat revascularization	7.8%	10.1%	---
OCT subset analysis			
>5% uncovered stents	3.6%	39.4%	0.005
>5% malapposition	0.9%	9.7%	Nss, 0.06

BOSTON SCIENTIFIC

Taxus

Part 1 of the HORIZONS-AMI trial showed that Taxus performed better than a bare Express stent in STEMI patients – a conclusion which surprised no one. Taxus was associated with a 41% reduction in the primary endpoint of TLR and a 56% reduction in binary restenosis. Taxus also was non-inferior to a bare Express in all-cause death, reinfarction, stent thrombosis, or stroke at 1 year.

1-Year Results of HORIZONS-AMI Trial

Measurement	Taxus	Express	p-value
Primary endpoint #1: TLR	4.5%	7.5%	0.002
Primary endpoint #2: MACE	8.1%	8.0%	Non-inferior
Stent thrombosis	3.1%	3.4%	Nss, 0.72
ARC definite stent thrombosis	2.6%	3.0%	Nss, 0.55
ARC probable stent thrombosis	0.5%	0.4%	Nss, 0.65
Secondary endpoint: In-segment restenosis at 13 months	10.0%	22.9%	<0.0001

Promus

Asked about any shortage of Promus, Lemaster said there have been shortages of specific sizes due to an inability to make changes to the product mix supplied by Abbott. He explained, "We currently have one Promus product on back order – 1 code out of 60 was back ordered. We anticipate clearing that shortly, and we don't expect any further supply interruptions on Promus."

Why did the shortage occur? Lemaster said, "Our manufacturing forecast for Abbott was fixed for a while. The first time we could adjust that was in October. We were able to reprioritize certain sizes to be built. Abbott has been a great partner. We will clear the backlog and don't anticipate that to be a continuing problem…It is very difficult, given 60 codes, to predict what usage would be with exact science – and not to be able to immediately change manufacturing. We now know the usage (pattern). The biggest difference is we have codes we didn't make before. We didn't make some different lengths. There were 5 codes in a sensitive area."

Taxus Liberté

Shortly before TCT, Boston Scientific received FDA clearance to launch its next-generation drug-eluting stent, Taxus Liberté. Taxus Liberté is a new and somewhat more deliverable version of the paclitaxel-eluting Taxus stent. Taxus Liberté uses the Veriflex design, with the TrakTip catheter tip, mounted on the Maverick2 delivery catheter.

This was the second coronary stent that Boston Scientific got cleared by the FDA since the FDA issued a Corporate Warning Letter nearly three years ago. In late September 2008, the FDA cleared the Taxus Express^2 Atom stent, which is specifically designed to treat small coronary vessels. And shortly after TCT, the FDA cleared a carotid artery stent for high-risk patients, Carotis, which was already approved in Europe.

Taxus Liberté is the only DES specifically approved by the FDA for use in vessels as small as 2.25 mm. The FDA warning letter has held up Boston Scientific's PMA approvals and launches. Lemaster explained that the FDA warning letter does not affect 510(l) clearances, only PMA approvals. The FDA has issued "conditional approval letters" for several PMAs, but Boston Scientific can't launch those products until the warning letter is lifted. Lemaster is hopeful this is a sign that the warning letter will be lifted soon, "It's like the airport has been fogged in, and now the fog is lifting a little, and some planes are starting to take-off."

Taxus Element

PERSEUS-Workhorse, the pivotal trial of Taxus Element, finished enrollment pretty much on time and is now in the data accumulation stage. The 9-month results could be at PCR in May 2009 but are more likely to be presented at ESC 2009 or TCT 2009. PERSEUS-Workhorse, which compares Taxus Element to Taxus Express^2, has enrolled 1,264 patients at 100 sites in the U.S., Australia, New Zealand, and Singapore. The primary endpoint is target lesion failure (TLF) at 12 months. In-segment diameter stenosis at 9 months is the secondary endpoint.

A smaller, 224-patient study, TAXUS-PERSEUS, is comparing Taxus Element in small vessels to a historic control. This study will include 224 patients from 35 U.S. sites with lesions from 2.25-2.7 mm. The primary endpoint is in-stent late loss at nine months, and the secondary endpoint is TLF at 12 months.

Lemaster said, "It is exciting that we have completed enrollment in a third-generation drug-eluting stent, and no one else has even started enrollment on a second-generation DES. I think that is lost on a lot of people. Once, Taxus Liberté is launched, there will be no new DES until late 2011 – which is Taxus Element."

Promus Element

This is Boston Scientific's planned replacement for the current everolimus-eluting Promus stent. Promus Element will elute everolimus from a Taxus Element stent. The agreement with Abbott under which Abbott must supply Boston Scientific with Promus stents ends November 20, 2009, in Europe and on June 30, 2012, in the U.S. Boston Scientific hopes to have Promus Element available in Europe by 4Q09 and in the U.S. by 2011. Lemaster said the company plans to begin enrollment in the pivotal PLATINUM trial in 1Q09, "We are excited to initiate that…We expect to launch it outside the U.S. this time next year, based on other data. We hope to be in Europe in 4Q09…Our goal is to have our own product by then."

Asked on what data the C.E. Mark will be based, Lemaster would say only that "sometimes there are products approved without a first-in-man trial…It could possibly be (based on) U.S. patients in the PLATINUM trial."

Asked if Boston Scientific is holding market share for Taxus by dealing on price or bundling Taxus with other products, Lemaster said, "Certainly, we go to customers and can offer two drugs – with Promus (everolimus) and Taxus (paclitaxel) – as well as balloons, catheters, cutting balloons, and filter

wires. No one can match the total breadth of our product line. But we are not bundling. We deal with customers on a global product basis."

MEDTRONIC's Endeavor – superior safety in one trial then safety and efficacy problems in 2 Danish studies

First, the ENDEAVOR-IV trial showed what appeared to be better safety with Endeavor than Taxus. Then, a day later, two Danish studies – a prospective trial and a registry – raised questions at TCT about both the safety and the efficacy of Endeavor. The SORT-OUT-III trial found Cypher beat Endeavor on safety, and the Western Denmark Heart Registry found Endeavor lost to Cypher on efficacy and did not show any greater safety.

The results of SORT-OUT-IV comparing Abbott's Xience to Cypher are expected next year.

ENDEAVOR-IV trial – Endeavor beats Taxus on safety

The two-year ENDEAVOR-IV data presented at TCT showed no statistically significant difference between Endeavor and Taxus on TVF or TLR but significantly less overall MI and less non-Q-wave MI with Endeavor. ARC definite/probable stent thrombosis was lower with Endeavor. Basically, the trial showed that Endeavor maintained its 1-year benefits at 2 years; there was no "catch-up" or worsening in the second year. Dr. Marty Leon said ENDEAVOR-IV data mirror the findings of a pooled analysis of all Endeavor patients, adding, "If there is anything distinguishing Endeavor from other drug-eluting stents, it is safety…The Endeavor stent looks very much like a bare metal stent and very much unlike the previous generation of DES."

2-Year Results of ENDEAVOR-IV Trial

Measurement	Endeavor n=774	Taxus n=774	p-value
TVF	11.1%	13.1%	Nss, 0.220
TLR	6.0%	4.7%	Nss, 0.255
TLR by angiographic follow-up	9.2%	3.1%	0.045
TLR by clinical follow-up	5.2%	4.9%	Nss, 0.0896
TVR	8.9%	9.2%	Nss, 0.857
Safety			
MACE	9.8%	10.0%	Nss, 0.931
MI	2.0% (15 events)	4.1% (30 events)	0.023
Non-Q-wave MI	1.6%	3.5%	0.022
Cardiac death/MI	3.4%	5.1%	Nss, 0.096
Stent thrombosis			
ARC definite/probable 0-720 days	1.1% (8 patients)	0.9% (6 patients)	Nss, 1.00
ARC definite/probable 360-720 days	0.1% (1 patient *)	0.8% (6 patients **)	Nss, 0.069
Dual antiplatelet therapy for full 2 years	65.5%	71.3%	0.022

* This patient was not on dual antiplatelet therapy.
** 4 patients were on dual antiplatelet therapy; 2 on aspirin only

Asked how his hospital's use of DES breaks down by DES, Dr. Leon said, "75% of the stents in our lab are new-generation DES (Xience, Promus, or Endeavor)…Endeavor penetration in the U.S. may have been hurt slightly by the lack of a rapid-exchange platform, but that may change shortly. The deliverability preferences of non-U.S. physicians is they prefer Endeavor over Xience/Promus…I think these data will impact people's choices."

Dr. Steve Ellis, director of the cardiac cath lab at the Cleveland Clinic, critiqued the ENDEAVOR-IV results. He basically said that the safety claims were overstated because the Endeavor data were from a post hoc analysis. He noted that the trial was not powered for low-frequency events such as stent thrombosis but added, "Endeavor stent thrombosis rates through 6-12 months seem similar to other DES. Endeavor stent thrombosis rates from 12-24 months seem to be less than with other DES…Indirect comparisons of results from different studies should be limited…Uncertainties will remain regarding the comparative safety of Endeavor and other DES at least until the 8,800-patient PROTECT study is completed." However, he agreed that Endeavor should be considered for patients who are not good candidates for long-term dual antiplatelet therapy.

A Boston Scientific official claimed that Endeavor is losing market share, "Why is Endeavor market share going down outside the U.S. and Xience/Promus going up?...Taxus Liberté is still No. 1 outside the U.S. in market share… Xience/Promus is No. 2, Cypher is No. 3, and Endeavor is No. 4….The (ENDEAVOR-IV) data are not a whole lot different from 1 year to 2 years…There was an interesting landmark-type analysis, looking at 1 year and then beyond…but absent was Day 0 to 2 years…As you saw in ENDEAVOR-IV results, there were 6 Endeavor stent thromboses vs. 1 Taxus stent thrombosis, and now you have the inverse of that…If you look at 2 years…they are equal in terms of patient events."

Danish trials

Among the comments about the findings in the 2 Danish studies were:

- Dr. Gregg Stone suggested that it might be a phenomenon peculiar to Denmark.
- Dr. Mary Leon called it a "watch out for the future."
- Moderator Dr. Jeffery Popma of Harvard Medical School said, "It will be a popularly debated study as time goes forward."
- Dr. Alexandra Lansky, director of clinical services at Columbia University Medical Center's Center for Interventional Vascular Therapy, called the results of both studies "sobering." Asked what she will do in her own practice, she said, "When you have choices, (Endeavor) would not be the first choice in my case."

Why did Endeavor perform worse than expected in the Danish studies? Dr. Lansky said, "I think that the early randomized clinical trials (of Endeavor) were done in more simple patients; they always start in simple patients. What we saw from those studies was high late lumen loss of 0.6 mm, and these whole ensuing analyses are trying to justify why late lumen loss would have equivalent TLR rates in a study powered to look at angiographic surrogates and not clinical endpoints. From my perspective, having done the angiographic side, late lumen loss of 0.6 mm for instance is okay in a simple patient population, but when you go into complex patients, you're testing the device, and you're starting to understand the performance of the device, and it transcends restenosis…and goes into safety issues. I guess I'm not completely surprised by these results, and, in fact, I would have expected them a long time ago. So, I think you have to take everything in context. You don't know the final results… until you go to these kinds of studies and look at these complex patients."

Asked what drives selection of DES – the performance of the stent or clinical data, Dr. Marco Valgimigli of the University of Ferrara, Italy, said, "It should be both. But one variable should be kept in mind – late loss is different when comparing Endeavor with Cypher. But for long-term safety, I was impressed with the ENDEAVOR-IV data. A lot of the MI here might be procedure-related." Dr. Mark Turco of Washington Adventist Hospital said, "Some of the data make us more comfortable with DES in thrombus-containing lesions, but we look at some patient-specific variables. With that said, it's very surprising how these particular data differ from the data presented with ENDEAVOR-IV, specifically if you look at the subsets in ENDEAVOR-IV. Those data are very different from these data, so it's very confusing to me. There are practice patterns that are a bit different outside of the U.S. than in the U.S...These national registries can sometimes be a bit confusing, although they sometimes give us good information. This trial seems to support the SCAAR data from a neighboring country (Sweden)."

Dr. Popma said he was struck by how well Cypher performed, "That's a new bar for us in our trials…Have there been technique changes in Europe allowing you to get better results… because they both did very well – a 4% all-comer TLR rate? The loser is still excellent for technical practice."

Asked if blinding affected the trial results, Dr. Stone said, "Blinding is certainly desirable…but I don't think blinding explains all these differences. I am impressed with the differences, but I wonder if these results refer primarily to Denmark? Often in Europe we see much lower TLR rates, so …this is a very important randomized clinical trial."

➢ **SORT-OUT-III trial – Cypher beats Endeavor on safety**. This 9-month, prospective, randomized trial in 2,333 coronary artery disease patients (in 2006 and 2007) found significantly higher rates of TLR, MI, and definite stent thrombosis with Endeavor than Cypher, but there was no significant mortality difference between the two stents. Dr. Jens Lassen, the principal investigator, said that he was surprised by the findings because these patients were taking antiplatelet therapy, "Running through all the minefields of stent thrombosis, it's only speculative, but it's clear that there is restenosis with thrombosis on top of it, so I think we have to reconsider what restenosis is and what is stent thrombosis."

9-Month Results of SORT-OUT-III Trial *

Measurement	Endeavor	Cypher	p-value
All-cause mortality	2.2%	1.5%	Nss, 0.27
Cardiac mortality	1.1%	0.6%	Nss, 0.14
MI	1.4%	0.4%	0.03
ARC definite stent thrombosis	1.3%	0.3%	0.02
Clinically significant restenosis	3.8%	0.9%	0.001

*** All numbers approximated from graphs.**

The study was designed to reflect daily clinical practice, and there was no angiography or study-related patient contact. Dr. Lassen said, "I think that the definite stent thrombosis rate is a quite significant finding. I was surprised that there was that amount of stent thrombosis during antiplatelet therapy in the randomized trial. But that's only half the story. Now, we are able to discuss it a little further because we have the (Western Denmark) registry, and we should be careful about selection bias in the registry. But the signal in the registry is still there. ***It's kind of a warning of a safety problem***."

Although Dr. Lassen said he was surprised by the numbers, he stressed that he hoped SORT-OUT-III wouldn't become as controversial as the Swedish SCAAR study that added to the debate over stent thrombosis with DES. However, he said he sees a possibility of a "catch-up" over time, "If you look into the ENDEAVOR-IV trial, I was amazed to see the presentation – the Endeavor to Taxus comparison. There were seven stent thromboses in the first year, but there was a catch-up after Year 2 in the Taxus group." Dr. Jose de la Torre Hernandez of Spain agreed, "The findings are actually consistent with what we've seen previously in comparisons of DES to DES, although this is the largest trial with significant findings. Endeavor has the reputation of being a very safe stent. That's the way it's often viewed in the U.S., but that's based on reductions after the first year. Perhaps you have to wait longer to see what happens in this study. The other finding also is different than what we have seen previously – more clinically significant restenosis and TLR – and it is important this was found in a routine angiographic follow-up. We've known for many years about what angiographic follow-up introduces into our studies. This is something people have suspected for a long time but never proved."

Asked about the completeness of follow-up, Dr. Lassen said that all but two patients were followed, "Those two emigrated to China and Sweden, but otherwise there was total follow-up. It's easy to track the patients who stay in the country…The results seems overwhelming when you see them. But it's small

numbers, and it's really important in trying to look through these data. In Denmark we have 12 months of antiplatelet therapy, which means that the Cypher group is protected, at least in the other studies we have done, during the first 12 months, and we see quite a lot of stent thrombosis after 12 months in the Cypher group. That is half the story I think."

The selection of stents and patients in SORT-OUT-III was questioned. Dr. Matthias Pfisterer of Switzerland said, "It's a question of baseline risk…When I see that only 6% or 9% of patients (in SORT-OUT-III) have STEMI, that's not what we see in daily practice. It's more like 20%-25% STEMI (in daily practice). So, it makes it difficult to assess, and I see from our data that the baseline drives whether mortality is really different or not." Dr. Lassen responded, "If we compare our study with ENDEAVOR-IV, really, our study is only half the story. We're looking at the first year of Endeavor, and there are a few more disease patients than our patients. I know that 14% diabetics is a low level, but I think that our results are (close to) the first year of ENDEAVOR-IV, so I expect a catch-up which will get us closer to the results in ENDEAVOR-IV…Looking at the literature, Endeavor is a very flexible stent which means it's quite easy to work with, so it can go places where other stents might have difficulties. It could be bias if there's a very calcified lesion. If there's a very calcified lesion, then another stent can't go there...At night, operators will choose the easier stent. Nevertheless, I still think that the definite stent thrombosis rate is quite a significant finding."

Asked why Endeavor may have done so poorly, Dr. Lassen warned, with the caveat that he was purely speculating, "I think Endeavor coverage of the stent struts is too good. It has a high late loss, and what we see here is that it's quite difficult sometimes to differentiate between stent thrombosis and restenosis, and the presentation rate may be similar sometimes. (Perhaps) the acute coronary syndromes we see with the Endeavor stent will be driven by the restenotic problem."

➢ **Western Denmark Heart Registry – Cypher beats Endeavor on efficacy**. This registry followed 6,122 patients (during 2005-2007) for up to 28 months and found that Endeavor is no safer and "seems to be less effective" than Cypher when it comes to the risk of clinically significant restenosis and TLR. Dr. Leif Thuesen of Aarhus University Hospital in Denmark said, "We were surprised by the results. We had expected that the TLR rates or the restenosis would be higher with the Endeavor stent than with Cypher, but we were really surprised that the safety was not better than Cypher. Because it's fair to have a bit higher restenosis rate if the safety is better, but that showed not to be the case here."

Dr. Thuesen said that the results were particularly "scary" because patients had been on antiplatelet therapy for 12 months after stent implantation, "What gives me a little concern is the surprisingly high rate of stent thrombosis despite the antiplatelet therapy. It gives me a safety warning, but I won't say it until we have two-year data. But it's a good indication for the Endeavor stent if you reduce antiplatelet therapy after one year…We took it (Endeavor) off the shelf a year ago."

Asked if the study results support the hypothesis of late lumen loss over-measuring TLR, Dr. Laura Mauri, chief scientific officer of the Harvard Clinical Research Institute, said, "In some ways, TLR is a lower risk group. I noticed the stent diameter was 3.3 mm, which was higher than what it was in ENDEAVOR-IV and most of the other trials done for FDA approval. In terms of…TLR as a measure of efficacy, the most remarkable thing about this study is that on hard endpoints like death there was no significant difference…The most reliable endpoint is mortality…It's reassuring to see in a real-world population that the TLR rates in both arms were low."

Dr. Leon said, "This is an important study. I'm not surprised to see the TLR difference, but I'm very surprised to see TLR rates as low as they are. To see a 1% TLR rate with any therapy in an open enrolled population calls into question the assessment determination of what TLR was…We're used to seeing stent thrombosis occurring within the first 30 days – 70%-80%, but those curves continue to diverge. That suggests a different behavior or pattern of early stent thrombosis – similar to what we saw in ENDEAVOR-IV. I'm curious about that phenomenon and be aware of that – be looking for that in subsequent studies…The numbers are preliminary observations, but it's a watch out for the future."

Dr. Ted Feldman of Northwestern University Medical Center harshly critiqued the Western Denmark Heart Registry, "This registry highlights the tremendous effort it takes to dig into clinical experience and make something useful of it. It illustrates how challenging it is to interpret registry data. The fundamental conclusions/observations are that there is lower mortality, definite stent thrombosis, and TLR for Cypher vs. Endeavor. But we have to be extremely careful in interpreting registry results in general and particularly this registry in terms of selection bias and selection pressure…The time period is 2005 to 2007, a time period where we had a lot of uncertainty about the incidence and importance of stent thrombosis with DES. It is also critical to note that this registry involved a

28-Month Results of Western Denmark Heart Registry *

Measurement	Endeavor	Cypher	p-value
All-cause mortality	8.9%	6.5%	0.02
Cardiac mortality	1.7%	0.9%	Nss, 0.06
MI >28 days	5.5%	4.5%	Nss, 0.87
ARC definite stent thrombosis (patient)	1.4%	0.9%	Nss, 0.15
Clinically significant restenosis (lesion)	1.1%	0.7%	<0.05
TLR (patient)	7%	3.7%	0.0005
TLR (lesion)	5.3%	3.2%	<0.0001
In-segment restenosis (patient)	5.3%	2.6%	0.003
In-segment restenosis (lesion)	3.9%	2.3%	0.0001

*** All numbers approximated from graphs.**

little more than half of the total population of the western Denmark registration, and we have no way to make clear conclusions about why these patients were selected and others were not. There are data in the trial that allow us to make inferences even though there are definite conclusions… (Patients may have been) put into the same bucket, and we see clear indications that this was the case in this registry. There is a population difference. In this trial, you see that Cypher patients are older and on more medical therapy and, in fact, had shorter lesions and longer procedure times. There was a selection as far as different patients and lesions…Very few stent trials are showing very little difference between mortality, and I think we have to make the same conclusion about stent thrombosis. Making an inference in a population where the patient selection is a hugely different variable, is not a fair difference. The study said, 'It is unlikely that we made a complete compensation for selection bias at patient or operator level.' Our challenge is to understand what the population differences are here, not the stent differences."

MEDTRONIC'S Resolute – safety questions raised

Medtronic had been hoping that two features would encourage cardiologists to increase their use of Endeavor: deliverability and a lower stent thrombosis rate than Taxus and Cypher. Endeavor is deliverable, and the ENDEAVOR-IV trial suggested it could be safer, but Danish data raised questions about both efficacy and safety.

Thus, Medtronic's next-generation drug-eluting stent, Resolute, has become more important to the company. However, questions have now been raised about Resolute's safety. Like Endeavor, Resolute elutes zotarolimus. The stent design is the same, the balloon catheter is the same, and the zotarolimus dose (1.6 µg mm^2) is the same for both Endeavor and Resolute, but Resolute elutes zotarolimus at a different rate – faster than Endeavor. The other key difference is the polymer. Endeavor uses a phosphoryl choline-based polymer, and Resolute has a new three-part, proprietary, biostable (not biodegradable) polymer, BioLinx. Medtronic hasn't provided many details about the new polymer, which was developed in-house, except to say that it "is designed to extend the duration of drug exposure in the vessel (over 3 months)." Resolute studies outside the U.S. have shown a lower late loss with Resolute than for Endeavor, giving it a more favorable comparison to Cypher and Xience.

Boston Scientific CEO James Tobin predicted that Resolute will never be approved. He said users are reporting significant malapposition problems with the stent. In addition, a European cardiologist cited a case where a woman got two Resolute stents and both quickly restenosed – and an angiogram showed no other blockages, just inside those 2 stents.

Asked about reports about problems with Resolute, Dr. Renu Virmani, president of CVPath Institute, said, "I have not heard those reports, but I could have predicted it…If it is at all true, it isn't the polymer but the drug dose. The dose is too high. I wouldn't think that it's the polymer."

CELONOVA BIOSCIENCE'S Catania – a new kind of bare metal stent

Catania is a bare metal stent with a new and proprietary nano-coating that the company believes is a new class of stent – not a BMS and not a DES. Catania – a flexible, rapid exchange, cobalt-chromium stent, with a strut thickness 100-300 times thinner than DES and an open cell design – received a C.E. Mark in August 2007 and is available outside the U.S. in 60 sizes, from 8-38 mm, and in diameters from 2.0-4.0 mm. But what makes it really unusual is the coating, Polyzene-F.

Polyzene-F is an inorganic polymer with a high molecular weight. It is:

- **Biostable** and doesn't swell, crack, or degrade into harmful fragments.
- **Biocompatible** and bacterial resistant, preventing platelet adhesion and not triggering the coagulation cascade.
- **Bioinert**, not activating the complement system, preventing immune system response, preventing phagocytosis, preventing inflammatory response, and promoting healthy endothelial cell growth.

A CeloNova-sponsored breakfast had a prestigious panel of cardiologists. Dr. Roxana Mehran of Columbia University Medical Center said, "Our clinicians are starving for the next generation stent, but it must be safe and friendly to the human body."

CeloNova president/CEO Thomas Gordy held up a test tube of Polyzene-F, the material used to cover the Catania stent, and told the audience, "There is enough Polyzene-F in this test tube to cover this entire convention center." The material is a super thin polymer used to "mask the stent so that the body can do its work naturally."

Gordy explained CeloNova's philosophy: "We must transform what we're doing. We have come to a time in the history of medicine where we must go back to making major advances in medicine. We can no longer take incremental steps that marginally prove one difference or another between one medical device and another. This is what medicine is about… We need to reorder medicine and do it effectively."

Dr. Thierry Corcos of France said, "The ideal stent would allow wound healing but inhibit exaggerated neointimal growth. It should be thromboresistant and have high hemodynamic compatibility. Polymers have been used for many years, but the results were disappointing. Most polymers were degrading into fragments that resulted in inflammation, and there was a very high rate of tissue proliferation and thrombosis. Drug-eluting stents have been a major advance. A paradigm shift is occurring that now requires biocompatibility to

be designed into the devices. The concept of biocompatibility is moving from a 'do no harm' mission to one of doing good. The new devices will promote the formation of normal healthy tissue."

Pre-clinical stent studies show that its 40 nm thin surface treatment of Polyzene-F results in endothelial growth. Dr. Corcos said, "It is a second skin, not a fur coat."

Prof. Corrado Tamburino of the University of Catania in Italy, the principal investigator for the early Catania studies, said he was skeptical at first, "When I started using this polymer in patients and having really good results, I switched all BMS to this stent…The patients feel very comfortable. Out of 160 patients, I had only two patients who came back with chest pain…and I treat very complex patients…There are patients with very diffuse complex disease, where it's better to implant DES, but many other patients – 40%-50% in the future – will get Catania…My very best friend received a Catania stent. I asked him, 'Do you want to be on dual antiplatelet therapy, or do you want a good stent with no reaction?'"

Dr. Tamburino presented first-in-man and registry results on Catania. The prospective, single center, non-randomized, single-arm ATLANTA study of 55 patients (76 lesions) tested Catania in patients with symptomatic ischemic heart disease due to *de novo* obstructive lesions of native coronary arteries. Two sizes were used: a small and a large version – strut diameter 65 µm and 74 µm and lengths from 8-38 mm. Balloon diameters ranged from 2.0-4.0 mm, and maximum guidewire was 0.014 in. (0.356 mm). The 6-month data were presented earlier this year.

At 12 months, in an unusually complex first-in-man patient population, the results showed zero stent thrombosis, death, MI, stroke, or CABG. Restenosis was 6.8%. There was no difference between diabetics and non-diabetics in terms of neointimal hyperplasia, late loss, and diameter stenosis. Dr. Tamburino reported full stent healing using IVUS and OCT, and all patients stopped dual antiplatelet therapy after 30 days but continued aspirin (100 mg/d) throughout the 12-month period. The acute angiographic and procedural success rate in the trial was 100%. He said, "The absence of stent thrombosis confirms the strong preclinical evidence that a Polyzene-F surface treatment gives very positive effects."

6- and 12-Month Results of ATLANTA Trial

Measurement	Catania n=55
Primary endpoints at 6 months	
ARC definite/probable stent thrombosis	0
Cardiac death	0
Index vessel-related non-fatal MI	0
TLR	6.8%
TVR (non-TLR)	3.6%
Secondary endpoints at 6 months	
Any death	0
Procedural success	100%
Binary stenosis rate	6.8%
Secondary endpoints up to 12 months	
RVD	2.55 mm
Restenosis	6.8%
Late loss	0.60 mm
Neointimal hyperplasia	27.9 %
Uncovered struts	0.5%

The CATania registry included patients enrolled by the same three first-in-man interventionalists. The registry includes the 55 first-in-man patients and all other patients then eligible for BMS implantation; 269 stents were implanted, and 216 lesions were treated.

Mid-term Outcome of CATania Registry (8.4 months)

Measurement	Catania n=160
Primary endpoints	
Stent thrombosis	0.6%*
Cardiac death	0
MACE	6.9%
Index vessel-related non-fatal MI	0.6%
TLR	5%
Secondary endpoints	
Any death	0
Procedural success	99.4%

*due to inadequate stent expansion and residual dissection, the lesion couldn't be crossed the first time.

Dr. Francesco Prati of Italy presented optical coherence tomography (OCT) and IVUS data, showing a restenosis rate <6%, "We need an additional study to prove that the stent can tackle neointimal restenosis in diabetic patients. Follow-up OCT data in 15 consecutive patients showed that out of 15 stents, only 0.5% of stent struts were found to be uncovered, and only 0.15% of struts were malapposed. In 14 patients, the percentage of non-covered stent struts was <1%, and only one patient was higher than 1% (~4%)."

Dr. Prati said that the REVEAL study showed early vessel healing after Catania stent placement. He looked at IVUS and OCT data in a comparative study with DES and BMS at 7-10 days and at 30 days. Patients with two significant short lesions in remote vessels were treated with two distinct stents – either the Catania stent or a cobalt-chromium DES. The major endpoint was new and relates to OCT technique. It compares the percentage of "healed" stent struts in the Catania stent arm with the DES arm. Healing was defined as stent strut coverage with a linear rim of tissue and without thrombosis.

1-Month Results of REVEAL in 8 Patients

Measurement	Catania stent	BMS	DES	p-value for Catania
Non-covered struts	4.6%	10.9%	18.9%	0.019

Dr. Prati concluded that these findings show moderate neointimal and complete vessel healing, earlier vessel healing than with BMS or DES, and are likely to translate into reduction in acute and subacute in-stent thrombosis.

Asked his opinion of the data, Dr. Antonio Colombo of Milan, Italy, said, "We are concerned about stent thrombosis. When we don't see stent thrombosis, we are interested in other issues. The day it (stent thrombosis) happens, everything changes. Restenosis is definitely controlled, or at least better controlled by DES…but with DES we pay the price with thrombosis, and we know without the stent, we pay the price with restenosis. I would like to be sure that the stent would pay a minimal price or no price in thrombosis. I'm very excited about this data, but we all know that you can have three months without rain, and then there will be a typhoon… There is a subjective point of view, where you make a decision in which the patient is willing to pay the risk of thrombosis and in which patient wants to minimize the risk of restenosis. Sooner or later, we will have to be more thoughtful."

Dr. Renu Virmani said that although she hasn't looked at the data under a microscope – and she would like to see the pathology: "The OCT data are exciting. You get uniform coverage, and you don't get excessive neointimal formulation, but you're only looking at a short time. I think we need to look at the long term, in terms of 18 months. It's exciting that you don't see much thrombus, whereas we definitely see that with DES. Uniform coverage is the most exciting thing. It has more uniform coverage…The numbers are small but look really good." Dr. Virmani said she doesn't have concerns about late loss with this stent and described it as "promising," adding, "I'd prefer no polymer at all. PTFE is not inert. But I'd love to see the pathology (for Catania)."

Dr. George Dangas of New York-Presbyterian Hospital said, "It's exciting; there are issues that happened early regarding late inflammation, but there's also the issue of how fast the stent can be covered early on…I would expect a lot of stent thrombosis with BMS within two weeks…On the other hand, the recognition of cardiologists about late events was pretty high – the risk of late inflammation and late events – so there's also a concern of whether covered stents would get uncovered later on? Or if they are covered early, are they always covered? Is it possible that some of the stent struts early on get uncovered later? It's not impossible although it is a wild thought."

Dr. Julio Palmaz said, "When you have a covered stent, the stent is not metal anymore. It's different from traditional polymers, which would make it more reactive than the PTFE. So, you may have the right balance here. It is a rubber, so it would be an interesting material…PTFE used to be a miracle material for surgeons until they saw that it never got covered by tissue, and they ended up with late thrombosis. In principle, OCT data show something is depositing on the surface. We hope that the data will continue on, and perhaps we have the right polymer."

Dr. Barry Katzen of Baptist Cardiac and Vascular Institute in Miami said, "The preliminary data look very exciting and seem to achieve similar results compared to DES. The thing that's also attractive is that the clinical data we're seeing is in patients on short-term dual antiplatelet therapy. These are relatively high-risk patients. While there is no clinical significance in the legs compared to the coronary, there should be an application for peripheral vascular intervention as well."

Dr. Goetz Richter of the University of Heidelberg in Germany said, "I've been a faithful disciple of Renu (Virmani)…When a stent becomes available and the polymer is less toxic, it covers nicely, and the stent is very thin – it's attractive. I am looking forward to having this available…We never saw thrombosis in all those animals (in preclinical studies). Bare nitinol stents compared to covered nitinol stents in pigs is almost a role model for restenosis. What intrigued me is that I see a similar application for renal, particularly below the knee."

There was some discussion about how much late loss would be acceptable. Dr. Richter said, "We need more data, long term. And we still have to learn about the late loss. 0.6 mm of late loss in diabetics would be okay, but the others?...One of the lessons we have learned is that the thinner the polymer, the better, and that's one of the problems with current DES. The polymer is too thick. The thinner it is…the more even and smooth the surface will be, with fewer cracks, and will result in less corrosion later on."

Asked what's next for CeloNova, Gordy said, "From a business perspective, we always need to continue studies. We have three to four additional studies lined up now, and several are being done concurrently. We want to continue to gather the long-term information…We need to demonstrate how this polymer functions."

Gordy said that they should take another OCT look at 18 months, "It is unlikely that there would be any negative change in the endothelium, but we need to provide more information. There's a fine line here…The challenge is that (it will take) a while before people figure it out. There have been so many studies trying to prove marginal differences between this late loss and binary restenosis, etc., which frankly haven't advanced medicine…The challenge is getting people to understand that if I were a physician and I had a choice for any BMS, I'd clearly choose the Catania."

Gordy added that people who bleed easily are the best candidates for Catania, "We have seen conclusive proof that for anybody with a bleeding risk who can't use antiplatelet therapies, even procedurally (will benefit with Catania)."

The late loss is rather high compared to all the approved DES except Endeavor, but Dr. Tamburino said, "Late loss of 0.6 mm is not so high. In the study, the size of the vessel was very small, and so…0.6 mm late loss in a 3.0 mm vessel…is not a problem." He said a DES is the best solution for a small

vessel (2 mm), but "in almost all other fairly complex lesions, the Catania stent is the solution, in terms of no longer needing long-term dual antiplatelet therapy…So there is a trade off of a small late loss or acceptable late loss with, at the moment, no stent thrombosis. But the preliminary studies in animals and my personal data and the first-in-man control study have shown that there is no thrombosis. We have to consider that the drug-eluting stents give 0.3 mm late loss. How many hemorrhages do you have? How much is the cost? Late stent thrombosis is a very rare event. We are not able to identify which patients are at high risk of late stent thrombosis. We have malapposition, so it's Russian roulette…I am impressed by the OCT data (with Catania); you have complete healing…So, it makes sense, as far as you have healing and endothelial cell coverage…It's very interesting that Catania gets the same results as Endeavor without using long-term dual antiplatelet therapy."

Gordy and Dr. Tamburino stressed that Catania will be especially useful in third world countries where people cannot afford dual antiplatelet therapy. Gordy said he is working to trim costs so that the price can be under 400 euros (at least that was the plan before the euro dropped in relation to the dollar recently). He added, "We can't give it away, but we will come in at a very respectable rate. We will go into France at the BMS rate, and we can make it clear in France that we have a material that is in between DES and BMS."

Asked when the company will try to get FDA approval for Catania, Gordy said, "We could bring Catania to the U.S., and we may do it. If we do, we will have a multiplicity of lawsuits from companies trying to block entry into the U.S. In addition to a few million dollars to the FDA, we'd end up spending three, four, or five million dollars defending ourselves. The question is, we know we have a stent that will heal the world. We have two more coronary stents behind this one, and they are not ordinary stents with ordinary delivery devices. These are new types of materials, new delivery systems, and the question is while we are getting Catania out to the world that wants it and won't block it, do we spend our money trying to get Catania here (in the U.S.) or do we bring our second stent? I'd rather say, 'This is less costly and the patient doesn't have to take antiplatelet therapies.'"

SQUAREONE's BullsEye aorto-ostial stent – a unique bare metal stent

The BullsEye is aimed at a specific subset of aortic stenosis patients who represent 5%-7% of coronary revascularization procedures and 90% of renal artery interventions, supra-aortic, and other abdominal aortic interventions. Dr. Michael Jaff of Massachusetts General Hospital said, "This represents a challenge that includes that fact that the aorto-ostial junction may be difficult to visualize. Often there is inaccurate placement, geographic mismatch, incomplete scaffolding, recross difficulties, stent damage or migration, or guidewire entanglement."

BullsEye features include:

- Flared stent tailored to the unique anatomy of the aorto-ostial junction.
- Delivery system that enables rapid, precise ostial location.
- Double balloon system.
- Tactical positioning that physically stops the stent at the ostium.
- Allows the proximal stent to be scaffolded to improve coverage – like a flower.

The stent is a 316L BMS with a 5mm-6mm diameter and 15 mm length. The system is advanced across the lesion, the locator balloon is inflated, and once the physician is sure that he or she is in the right place, the deployment balloon is inflated to deploy the stent and then the flare is conformed.

The first-in-man studies were BOSS-1 (a renal trial done OUS) and BEAT (a renal and mesenteric trial). BOSS-1 followed 25 patients at three German centers. The primary endpoint was acute procedural success, and the study met that endpoint in 100% of cases. Six-month follow-up is complete, and 12-month follow-up is being collected. There were no procedural complications and no major adverse events. Procedure time was 26 minutes. There were no embolic events, and there was a reasonable and classic reduction in systolic blood pressure. The investigator noted that the non-traditional endpoints may set BullsEye apart from other stent systems and adjunctive devices, and he described this early experience as looking "quite good."

PERCUTANEOUS VALVES

AORTIC VALVES

The data on Sapien, Edwards Lifesciences' femoral aortic valve, from the PARTNER and SOURCE trials were better than expected, but European doctors appear to prefer CoreValve's Revalving System due to ease of use. The two next-generation percutaneous aortic valves to watch are being developed by Direct Flow and Sadra, and their appeal is repositioning.

A key criticism of Sapien is that the device is too large. An 18 Fr device is needed – and is in development – but sources said this won't be available until 2010, though "it should have been ready in 2009."

European doctors – and industry officials – insisted that European governments are not cutting back on reimbursement for percutaneous valves, except in France. A CoreValve official said some European hospitals are paying for percutaneous valves by shifting money to valves from drug-eluting stents (DES) since DES use in 2008 has been below what they had budgeted. Of course, that raises questions about percutaneous valve money for 2009 since it won't be able to come out of money "saved" on DES.

European physician comments included:

- *Austria #1:* "We only use CoreValve because it is a better system. We only do transfemoral, and we do them only in the cath lab, not the OR. We do about 40 a year, and that is holding pretty steady."
- *Austria #2:* "We've done 10 Sapiens, and we need to get permission from the government before we can do more. We expect to do 20 a year. There has been no government pushback; Austria is a comparatively rich country. Sapien is our choice because of their training, and Edwards lets us keep good relations with the surgeons… In Europe, valve use is split pretty equally between CoreValve and Edwards. CoreValve is more accepted in hospitals without heart surgery, but that is not a very good development…The endpoints in the PARTNER trial are good…I'm looking for mortality for both transapical and transfemoral to be <10% in high-risk patients with a EuroSCORE >20 and age >75."
- "Few patients need to be treated transapically."
- *France:* "I am very interested in percutaneous valve replacement. We are not in the trials. We will look at the MitraClip, but I have a problem with it; it all depends where you clip it, and you can't use it for long-term therapy."
- *Spain:* "We are not involved in the trials, but I am keenly interested in percutaneous valves. I understand that there is a big learning curve in using them, and I am anxious to get started."
- *Switzerland:* "The transapical approach is still valid, but the French size must be smaller."

Dr. Marty Leon called percutaneous (transcatheter) aortic valve therapy for aortic stenosis patients a "breakthrough technology." He compared the so-called "inoperable group" as "a lot like a group of patients with cancer. They have a one-year mortality approaching 40%...We had a lot of chaos in the early clinical trials, with small sample sizes and different protocols. Study endpoints were not clarified or standardized. There was inconsistent use of data coordination centers, core labs, and clinical endpoint committees (CECs), and poor long-term follow-up of essential valve-related endpoints…From a clinical perspective, critical aortic stenosis is a horrible disease, and, if untreated, results in 40% one-year mortality. A sense of urgency and sensitivity is required for patients and families. Co-morbidities are associated with a high risk, and the aortic stenosis cohort presents formidable clinical challenges…A high level of physician expertise and commitment is required. Presently, transcatheter aortic valve replacement (TAVR) isn't for everyone, (but) the idea that this will be used off-label in some sort of open way is absurd!"

From an investigational perspective, he said, "This is a complex, untested clinical trial methodology in a difficult patient population with many execution pitfalls, such as endpoint definitions and assumptions. It absolutely requires strong surgical collaboration, and we must consider important secondary quality of life endpoints and not just all-cause mortality. It needs disciplined oversight that is mandatory at every level."

Dr. Leon said what's needed is:

- Expedited approval considerations, especially in the non-operable aortic stenosis cohort.
- Facilitated access to rapidly changing device iterations.
- Sensitivity regarding the secondary endpoint issue.
- Post approval studies clearly defined.
- Enlightened transition approaches to other aortic stenosis study populations.
- CMS endorsement linked to FDA approval.

EDWARD's Sapien

Dr. Thierry Lefevre of the Institut Hospitalier Jacques Cartier in Massy, France, reported 6-month results from the ***transfemoral*** arm of the PARTNER-EU trial and 30-day results of the ***transfemoral*** arm of the SOURCE registry. Data from both studies showed better than expected survival rates with Sapien – <10% in PARTNER-EU at 6 months and <10% in SOURCE at 30 days. Sapien was approved in Europe in 3Q07.

Initial results from the ***transapical*** arms of the Sapien studies showed higher mortality than expected. Overall, transapical mortality in PARTNER-EU was 34% at three months and 45% at six months – above the levels seen in previous studies – but those patients also had higher EuroSCOREs, a mean of 33.5% vs. 23.5% in transfemoral patients. The early results from the SOURCE registry were more encouraging, with 30-day mortality 11.6% in the transapical cohort compared to 17%-18% seen in other trials. Dr. Lefevre said, "Clearly there is a learning curve. This is a rate of success coming from the preliminary study, and now we have a rate of successful implantation of more than 86%...Transcatheter aortic valve replacement addresses an important clinical need in high-risk patients with severe aortic stenosis. Although the technology is still in its infancy, the preliminary outcome of PARNTER-EU shows very encouraging results, with the transfemoral approach showing 90% survival at six months. And, finally, careful attention should be paid to the access site when selecting patients and performing the procedure. Completion of the learning curve and technology downsizing should help solve the vascular issues."

➢ **PARTNER-EU.** This feasibility study done, after Edwards filed for a C.E. Mark, was a prospective, multicenter, non-randomized, observational trial of Sapien. It was conducted in Europe from April 2007 through January 2008, with 67 patients receiving a transapical valve and 54 getting a transfemoral valve. Patients had to have a EuroSCORE >20% and/or an STS score ≥10%. In the transfemoral group, 60 cases were planned, but the procedure was aborted in six patients – three because of vascular access problems, two

because of unsuccessful bicuspid aortic valves, and one due to active endocarditis. Both 23 mm and 26 mm Sapien valves were used.

6-Month Interim Data from PARTNER-EU Trial

Measurement	Femoral arm n=54
Primary safety endpoint #1: Survival at 30 days	93%
Primary safety endpoint #2: Survival at 6 months	90%
Functional improvement (valve gradient, valve area, and NYHA Class)	92%
Device implant success	96.3%
Complications	
MI	1 patient
Cardiogenic shock	1 patient
Arrythmias requiring intervention	6 patients
Valve embolization	2 patients
Stroke	2 patients in first 30 days 1 patient in Months 2-6

➢ **SOURCE.** The European post-C.E. Mark SOURCE registry is a multicenter, observational study of early procedural successes and long-term follow-up of 303 transfemoral patients from November 2007 to September 2008. The 30-day results showed a survival rate of 93%. Dr. Lefevre said that patients in the femoral arm saw improvements in valve gradient, valve area, and NYHA functional class that were sustained over the six months.

In SOURCE, there were two implant failures – one due to ventricular embolization and one due to aortic embolization. There was one procedure-related death due to cardiac arrhythmia; the patient died during balloon insertion. Two patients had MIs at >30 days. There were seven iliac artery dissections, one patient with phlebitis and pulmonary embolism, and one patient with iliac occlusions. The stroke rate was 3.4%.

At the European Association for Cardio-thoracic Surgery meeting in September 2008, the 30-day survival data for the SOURCE transapical patients were reported. The data showed survival was 88.4%, with patients having a mean EuroSCORE of 30%. In contrast, the 30-day transfemoral survival reported at TCT was 93.6%, but the patients had a mean EuroSCORE of 26.4%.

Dr. Mathew Williams of Columbia University made the case for a transfemoral approach vs. a transapical approach, "We have to be careful comparing the outcomes because the current populations are not necessarily similar. This isn't a surgeon vs. an interventional cardiologist battle. We don't need another PCI vs. CABG (fight). There is more experience with the transfemoral approach compared to the transapical (1,183 patients vs. 794 patients), but we are getting increasingly encouraging results. In Edwards' PARTNER-EU trial, the (transfemoral) implant success was 96%. It is a less invasive

30-Day Results of SOURCE Registry

Measurement	Transfemoral n=303
Implant success	>86%
Survival	93.6%
Coronary interventions	0.7%
Valve-in-valve bailout	0.7%
Aborted procedure	2.3%
Malposition	0.3%
Pericardial tamponade	0.7%
MI	1%
Stroke	3.4%
NYHA Class I	39.4%
Complications	7.4%

procedure, and patients have a quicker recovery. What's good about transapical? It is technically simpler – easier to cross the valve and a faster procedure. Theoretically, it may have a lower stroke rate, but most of the hits are when the device is coming across the arch…The main advantage to transapical is that the valve deployment is more predictable. For the REVIVAL-II co-morbidities, it does seem to be a sicker population despite not being captured on the STS score risk assessment. In PARTNER-EU there is a significant difference …Transapical is a good alternative if vascular access is a concern…The correct patients need to be chosen for either procedure."

➢ **PARTNER-US.** As of the end of September, 456 patients had been enrolled. Dr. Leon, a co-principal investigator for the PARTNER-US trial, said that 16 of the 23 sites participating in PARTNER-US are using the Sapien device for the first time. Thus, the trial should provide additional information on the difficulty of the Sapien learning curve. Dr. Leon said, "This is a concern for us…There may be a learning curve that we will look at as we analyze the data. That is something that could turn out to be problematic…This is a difficult study to do. You have to have acknowledged operator and site expertise in both surgical and interventional aortic valve therapy. Site training is comprehensive and laborious. There will be cased screening logs. The screening failure rate is >70% at Columbia. We have trained 20 of 23 sites and are actively enrolling. Our goal is around 60 cases per month. There will be a delayed and staggered roll-in of transapical patients."

The randomized, 1-year PARTNER-US study is actually two trials, but both have the same primary endpoint – all-cause death (superiority):

1. **Cohort A** – transfemoral vs. medical therapy.
2. **Cohort B** – transfemoral or transapical vs. surgical valve replacement.

Asked about the learning curve in patient selection, Dr. Thomas Walther of the University of Leipzig, Germany, said,

"It's proper screening. You need to be aware of the complications. Don't exclude patients with heavy calcification, just be aware of what can happen."

Asked how long it will take before the procedure can be used on lower risk patients, another expert said, "It will take time. We will need a different EuroSCORE. There is a long way to go. Eventually, in 10 years, we may see aortic valve replacement for aortic stenosis. We are already planning PARTNER-II. The most important thing, as technology moves to lower risk patients, is we have to be cautious and wait for data. I think it will move to lower risk patients before we have the data. In 10 years, it will move to lower risk patients, and we will want extremely low mortality of 1%-2%."

Dr. Larry Wood of Edwards Lifesciences insisted that procedural success with Sapien has been better in the commercial release than in trials. The U.S. approval path "has a very high bar for fatigue and durability…There are long test cycles… The FDA wants to see all testing at different cycle rates, and it can take up to a year just to do the non-clinical testing…Every design feature has a trade-off, and priorities must be determined. Repositionable at what price? What if malapposition is <1% and manageable? Would you trade off durability? Today's focus is on procedural success and short-term outcomes, but when does durability come into play? In terms of Edwards' design priorities, we focus first on frame strength. It must be strong to remain concentric post-deployment to achieve a durable result. It must be able to meet FDA requirements for non-clinical testing. As for materials, we leverage from our surgical franchise – our ThermaFix-treated bovine pericardial tissue. For our (Sapien) device, the key focus is durability. In terms of our evolution, we started with untreated, have moved to Sapien 23 mm and 26 mm and then added core technologies. The next-generation Sapien XT THV will be 23 mm, 26 mm, and 29 mm. We like the discreet valve, trying to mimic it just in the annulus, and we've had a low incidence of permanent pacemakers compared to surgery. Reduced profile is also a design consideration, and we're trying to reduce the profile to a 4-5 Fr reduction."

CoreValve's ReValving System

Although CoreValve's aortic valve is doing well in Europe, the company has not yet begun a pivotal trial in the U.S. A CoreValve official said, "There is still no resolution with the FDA for that trial."

Dr. Eberhard Grube of Germany offered some comments at a breakfast sponsored by CoreValve on this percutaneous aortic valve:

- "Four or five years ago, I told CoreValve, 'Let's move forward and not look too closely to the U.S.' At some point, they will follow. The pressure will grow and go up, and the patients will need this, and that is exactly what we are seeing."
- "Calcium is not a good marker to place the device because you don't know where it is in relationship to the leaflets…Calcium can mislead you."
- "Procedural success has been 94.4%-98.2% with the 18 Fr valve."
- 30-day all-cause mortality has been improving and was 3.6% in 3Q08 vs. 5.1% in 2Q08 and 7.7% in 1Q08.
- "There is no aortic regurgitation with this device…That has never been a major problem vs. other (valves)."

Dr. Peter de Jaegere of the Netherlands said 92 centers are now using this valve, with 98% procedural success and an average procedure time of 126 minutes. He described the Rotterdam experience with the ReValving System:

- **Overall.** In 61 patients, the average age was 82, LVEF 46%, mortality 8%, CVA 15%, no TIA, AMI 2%, bleeding/vascular problems 11%, and pacemaker 16%.
- **Five patients died:** 1 tamponade (due to the procedure), 1 sepsis, 1 hypotension during the procedure due to the procedure, 1 heart failure/sepsis in a patient who had been on CardiacAssist's TandemHeart and who he said probably shouldn't have gotten a percutaneous valve, and 1 asystole because the physician didn't watch the patient closely enough and didn't implant an ICD or pacemaker.
- **Stroke rate 9%.** "We did not see a difference in baseline characteristics of the patients who had strokes…We do not see a relationship to the complexity of the procedure and stroke…It is not only embolic that causes stroke, it may also be a watershed stroke…So, what I learned is that if you have to do a balloon valvuloplasty, do it right the first time…I believe the stroke rate will be around 5%."
- **Red flag.** "We saw 11 patients, in retrospect, that we should not have done…We firmly believe that MSCT is the way to measure and define the annulus…You have to use MSCT, but I don't know how to translate the number into stratification of treatment…I believe the implantation guidance will be plain angiography…We have to keep the treatment as simple as possible – angiography and fluoroscopy."
- **Rhythm.** "In our database we found – and changed our practice – that if you implant the valve <6 mm below the AV groove you don't have left bundle branch block (LBBB)…but if you are >10 mm, we always have LBBB."
- **Learning curve.** "The more you do, the better it is…You should do this weekly rather than monthly if that is possible."

Dr. Stephen Brecker described the experience with the ReValving System at St. George's Hospital in London, which has done 20 patients so far. Since December 2007, they've been doing 2 cases a month.

- **Overall.** "We do 280 surgical aortic valve replacements a year with 98.9% mean survival…so we have difficulty convincing surgeons we can do better (percutaneously)."
- **Support.** "The CoreValve support is greater than anything we've seen before and is one reason we went ahead with CoreValve."
- **Pacing.** Of the 20 patients, 9 had pacemakers implanted after the procedure. "We've been very conservative in pacing prophylactically."
- **Mortality.** 30-day mortality/MI/stroke was zero. "One case was complicated by a wire perforation of the left ventricle and tamponade…There have been 4 late deaths – a pulmonary embolism, 1 pancreatitis, 1 progressive heart failure, and 1 chest infection."
- **Procedure.** "We have learned that during the implant there is no need to rush. The implant itself should be done slowly, taking your time to get perfect positioning."
- **Learning curve.** "We really benefited from the proctoring process…We believe there is a steep learning curve. You need to limit the number of operators in your center…Plan, plan, and then plan some more…Involve the surgeons. And get the hospital to own the program. You can't fight the managers in setting this up…I really think you need a minimum of 20-25 procedures a year to get anywhere close to a learning curve…What we experience with the two-a-month is in the first two months we almost had to start again with learning. When you get above that number, you get over the hump of the learning curve, and it is a steep learning curve. You have to do a ***minimum*** of two a month."

DIRECT FLOW MEDICAL'S DFM

Dr. Joachim Schofer of the Hamburg University Cardiovascular Center in Germany described the first-in-human experience with the DFM stentless and retrievable percutaneous aortic valve prosthesis in 21 patients. This European clinical trial was a feasibility and safety study of patients with symptomatic valvular aortic stenosis with an aortic valve area ≤0.8 cm and with a EuroSCORE ≥20%. The valve was delivered femorally.

Dr. Schofer concluded:

- The amount and distribution of aortic leaflet and left ventricular outflow tract calcification impacts procedural outcome.
- The device gives the operator "unprecedented" freedom of handling the device during implantation.
- In the first-in-man experience, permanent implantation was achieved in 65% of patients with good hemodynamic results. "Despite the patients' high surgical risk profile, implantation appears safe, and I think that we could easily increase that rate to 80%."
- Patient selection is crucial.

The DFM valve is a non-metallic tissue valve with bovine pericardial leaflets (encased in a slightly tapered, conformable polyester fabric cuff) that are conformable and flexible, with high deliverability. DFM uses an expandable non-metallic framework that diminishes perivalvular leaks. It is immediately competent upon initial inflation, and implantation does not require rapid pacing or cardiac support. The independently-inflatable balloon rings constitute the upper (aortic) and lower (ventricular) margins of the cuff. It is attached to three small catheters, and the valve, which comes in 23 mm and 25 mm sizes, can be repositioned or retrieved. To expand the valve, the valve's rings are pressured via positioning (fill lumen) with a mixture of contrast agent and saline. Upon expansion of the ventricular ring, the valve is immediately functioning. No rapid pacing is needed during implantation.

The device was implanted in 22 patients (71% of the initial 31 patient intent-to-treat population). Of those 22, there were two surgical conversions. In one patient, the valve was too big, and in the other the valve didn't fully cover the native valve. Dr. Schofer said, "This is part of the learning curve." Leakage was seen in half of the patients, and the other half had trace leakage.

First-in-Man Results with DFM Aortic Valve

Measurement	DFM n=22
NYHA Class change from baseline to 30 days	
Class I	Up 57.2%
Class II	Up 14.3%
Class III	Down 71.4%
Adverse events	
Major adverse events	23%
Death	13% (4 patients)
Major stroke at 12 hours	1 patient
Surgical conversion	2 patients

Dr. Schofer discussed the patients with major adverse events, saying, "One patient died two days after the procedure due to MI. Distal occlusion was found in the autopsy; occlusion was at the site we identified as tight stenosis. We should have fixed this before including the patient. Another death was a patient in whom we failed to implant, and one hour afterwards the patient died of a pulmonary embolism. The third patient died of septal rupture during valvuloplasty. The fourth patient died due to decompensated cardiac heart failure some hours after implantation of the device. He had very bad left ventricular function from the very beginning. There was one major stroke occurring 12 hours after the procedure, and two patients underwent surgical conversion. In addition, we observed total AV block in three patients – one patient after surgical conversion."

Direct Flow will soon have an 18 Fr sheath, Dr. Schofer said. He also predicted that the access site complication rate will be

5%-10% in a larger patient cohort, "This is the reason we did the surgical cutdown in all these patients…This is a unique system. It is very flexible, and you can cross very calcified aortic arches and calcified aortic valve. In addition, it's not a one shot procedure."

Dr. John Webb of St. Paul's Hospital in Vancouver, Canada, critiqued the DFM results, saying, "If there are concerns, they are maybe related to radial strength. The gradients are a little higher than expected…I think these limitations can be overcome by screening and even device modification. It represents one of many new approaches coming along. It is repositionable and retrievable."

SADRA MEDICAL/BOSTON SCIENTIFIC's Lotus

Dr. Jeffrey Moses of Columbia University Medical Center said about 70-80 of these repositionable valves have been implanted at his hospital, "but it still is a high wire act. For percutaneous aortic valve replacement (PAVR) to become a routine procedure, the optimal valve design must have good pre-positioning and control." And he suggested that the Lotus has a unique, second-generation design that addresses all the current challenges, "It's like a long slinky when it's deployed. If you don't like the position, you can lengthen it, reseal it, and then just move it, and ***that is the key point***. You're not in a rush. It is hemodynamically stable and can be placed precisely." The Sadra Lotus Valve procedure is: Valvuloplasty, insert and position, deploy (unsheath), lock, assess, and release.

Why is repositioning important? Dr. Moses said, "Right now 21 Fr (Lotus) devices have excellent flexibility and trackability. Lotus has controlled deployment with a self-centering design. It is easily repositioned and removed and has an adaptive seal to minimize leaks. It also has rapid deployment (the valve begins functioning immediately) with minimal occlusion…However, positioning is critical. With my experience with the Edwards valve (Sapien), I can't emphasize enough that you need a mechanism with precise placement. With the Edwards valve, which has a balloon expandable design, there is opportunity only for placement, and there are challenges in placement and maintenance of position, no matter how experienced you are. With CoreValve's ReValving system, what you see is what you get; the stent shape impacts positioning, and it's also one-shot, with no repositioning."

There are eight patients in the European feasibility study. The mean STS score is 10, with about a 19 mm annula. Five have been implanted with the device, with one cardiac death (not device related). The patients surviving with the valve reportedly showed:

- Significant hemodynamic improvement.
- Pre-positionability and retrievability confirmed.
- Minimal/zero perivalvular leak.
- Excellent visualization.
- Efficient procedure time – 12-25 minutes.
- Excellent placement accuracy.

Dr. Moses said, "The Sadra Lotus system is designed to make PAVR a routine procedure. It improves precision and control in positioning and deployment. It is not as anxiety-inducing as the current procedure, and this shortens the learning curve. And, as the device iterates, it is downsizing and simplifying the mechanics of the elements of the procedure. You will see interesting data over the next several months to a year."

Asked if this is the correct patient population, Dr. Moses said, "Right now it's a nice size…I have to say that the last three procedures were different from the first two. (The device) will be downsized to sub 20 Fr in any iteration in clinical trials."

Other percutaneous aortic valves to watch

➢ **HEART LEAFLET TECHNOLOGIES.** This company is working on at least two valves, including one nitinol support hoop and a 16 Fr catheter-based valve. So far, the valve has only been tested in pigs, juvenile sheep, and eight humans in Italy who were undergoing surgical valve replacement. An investigator said that he found excellent valve expansion, no coronary interference, and no mitral valve contact. Three valves were post-dilated with balloon or backstop to achieve circular expansion. Percutaneous human implants are expected to start in 1Q09.

➢ **VENTOR TECHNOLOGIES' Ventor Embracer.** Dr. Ehud Schwammenthal of Israel said that current risks of aortic valve design include malpositioning and device embolism and coronary artery obstruction. The Ventor Embracer is a self-expandable valve that minimizes pressure loss at inlet, with maximum pressure recovered at outlet. It also has a fluid dynamic shape that avoids oversizing the diameter at the annular-leaflet level. It employs a venture tube principle that allows gradual expansion, streamlines and eliminates flow separation, and prevents turbulence (pressure recovery), producing the hemodynamics of a 23 mm valve. He said, "The shape facilitates implementation of a periannular anchoring system for intuitive and accurate deployment, anatomical positioning, and axial fixation. The native leaflets are embraced between an inlet and a 3-D support frame tracking the shape of the aortic root."

As for durability and fatigue, Dr. Schwammenthal said that the valve has passed 400 million cycles in a durability machine, and that testing is continuing. A first-in-man study was initiated at the Leipzig Heart Center in Germany, and a pilot study is ongoing, with a multicenter, pivotal clinical trial planned for 2009. A percutaneous transfemoral product also is being developed.

MITRAL VALVES

EVALVE's MitraClip

An update on 107 patients from the non-randomized EVEREST trial indicated that 30-day MACE was an encouraging 9%. The High Risk Registry figures also looked good, with mean predicted mortality risk for patients 18.2% and the actual mortality 7.7%.

Dr. Ted Feldman, an investigator, said, "Treating these patients and seeing this happen in the cath lab is one of the most exciting parts of being in the trial. Every operator who starts to learn to do this has that remarkable thrill when it occurs."

Dr. Feldman said that enrollment in the pivotal trial of percutaneous edge-to-edge mitral valve repair, "We have demonstrated proof-of-principle for both degenerative and functional MR. There is an unmet need for poor surgical candidates, and so there will be a high-risk registry. Enrollment is complete in EVEREST-II, which will define the role for MitraClip in patients with a surgical option. Surgical options are preserved, certainly in the first one to two years after the clip is placed. And we'll have the landmark results in a year, including a prospective evaluation of mitral valve surgery."

EVEREST investigator Dr. James Hermiller presented data on eight EVEREST-I patients and 15 EVEREST-II patients – all with functional mitral regurgitation. The patient population was older, with more history of heart failure and larger ventricles. There was a 96% clip implant rate, and only one clip was required in 80% of patients.

Dr. Hermiller said the preliminary results were comparable to the overall EVEREST preliminary cohort. At 30 days:

- 3 patients had adverse events – 1 non-elective cardiac surgery for pericardial effusion and 2 bleeds requiring transfusion of ≥2 units. (1 related to anesthesia and 1 a venous sheath that fell out without being noticed)
- 3 patients had the clip placed but MR was >2+.
- In more than 50% of the patients, the MR was ≤1+.
- In the 12 patients with matched 1-year data, 75% improved, 17% showed no change, and 8% (one patient) worsened without MR >1+.
- Reverse remodeling was seen.
- There was a significant reduction in LV diastolic dimension and volume, but the systolic volume reduction did not reach statistical significance.
- Ejection fraction did not change.
- There were 5 surgeries.

Dr. Patrick Whitlow, director of interventional cardiology at the Cleveland Clinic, described the high-risk registry of 78 (from 25 sites) MitraClip patients in EVEREST-II, which included patients with symptomatic, severe MR. Follow-up is ongoing and 12-month data will be presented at the American College of Cardiology meeting in 2009. The patient population includes older and sicker patients with more diabetes, COPD, and atrial fibrillation. The median EF was 56%. So far, 96% of patients had implants and successful reduction of MR by the investigators' assessment. Mean predicted mortality risk was 18.2%, and the actual mortality was 7.7%. Most of the patients had NYHA Class III-IV heart failure at the beginning of the study, and by 30 days most were NYHA Class I-II. Seventy-six of the patients actually improved." Dr. Whitlow concluded that the MitraClip resulted in improved symptoms in most patients, superior safety compared to the estimated risk for surgery, and addresses a clear unmet need for high-risk patients.

There was a discussion at TCT about whether 2+ MR is meaningful, or if it should be ≤2+. Although several speakers expressed concern about the endpoints in EVEREST, no doctors interviewed at TCT had much concern. Among the comments were:

- *Dr. Feldman:* "In EVEREST we were criticized by surgeons for using the endpoint of MR ≤2+, so the question is: Is functional MR really the right endpoint? Or is 1+ reduction in MR sufficient?...There is justification for choosing the endpoint in the EVEREST trial. Now with data, with the reduction we're achieving, there is some confusion. The goal is to lead people into 2+ MR. Almost three-quarters of patients in the non-randomized EVEREST experience have been left with 1+ MR. We hope as we get better that we will see even better results in the randomized trial."
- "I agree…Those patients are having favorable remodeling going on, and certainly symptomatically they've done substantially better; 80% started out NYHA Class II-IV, and now the majority are down to Class I or II, so that's a reasonable endpoint. If we are willing to allow the device to decrease MR, let's prove that it does decrease MR, and then we'll see the consequences of decreasing MR. It's extremely difficult to evaluate this kind of MR."
- "One of the biggest problems is when you bring patients back for follow-up, you get a different echo in the morning, when the patient is dehydrated, than when you bring him back in the afternoon. The fact that we see favorable remodeling in many of these trials is more important than arguing about the measure of the MR. No matter what we do, the variability in the measurements is going to continue to be a problem. We have to accept that this is the state of the art."
- "No medical therapy has any proven efficacy of any kind in treating MR. None of the trials to date has specified what medical therapy ought to be...We are beating our brains out to try to define medical therapy when we already know it doesn't work; it's not productive."
- "In EVEREST, a large number of patients were excluded because of insufficient MR. We're so used to plain plumbing problems, and this is so multifactorial. We all

have patients with functional MR 3+ or 4+ who are getting along fine, and others with moderate MR…It's a progressive disease, and that's one of the areas we have to get our arms around a little better as well."

Dr. Feldman said that 36 patients had surgery after a clip attempt, "89% of surgical procedures following clip attempts or implants were performed as planned, and 11% were subsequently replaced. There was a MACE rate of 9% at 30 days in this cohort. Most surgical mitral repairs have MACE in excess of 50% and sometimes as high as 70%. Most are reversible adverse events, but it's clear that the percutaneous device we are developing appears to look like a percutaneous device and not a surgical procedure."

Circulatory Assist Devices

Abiomed's Impella

Cardiologists described Impella as a very cool device but for a niche patient population. They generally agreed that it will catch on in interventional cardiology, but uptake will be slow. On average, cath labs will use 1-2 per month for the next year or so. Some sites reported that CMS reimbursement approval takes a couple of months to arrange.

Impella competes with both intra-aortic balloon pump (IABP) and TandemHeart. At an evening symposium sponsored by Abiomed, speakers described Impella as effective at both unloading the ventricle and increasing cardiac output. One said, "It is not just about the heart. It is also about the rest of the organs…Mechanical support in acute MI is still two parts: (1) the heart needs to be recovered, and with this device we are able to unload the heart and reperfuse the deeper layers of the heart; and (2) increase cardiac output."

Dr. William O'Neill, executive dean of clinical affairs at the University of Miami's Miller School of Medicine, pointed out that two IABP trials in the 1980s showed no incremental benefit to IABP – that IABP was used (in PCI) for hemodynamic support, but there was no proven benefit. He called TandemHeart a "wonderful device but technically difficult." He said, "It can be done, but it requires a lot of technical expertise, and it really hasn't taken off…And the sheath is much too large to be of use on a routine basis… Impella is safe and easy to use, provides excellent hemodynamic support in the cath lab. You can put it in and forget about it, basically. Adoption since (FDA clearance) in June 2008 has been phenomenal…People are trying it. I think it will be a widely applied therapy, but we have to get the studies done." He estimated that Impella will be useful in about 1 in 10 cath lab cases, including left main dissections.

Dr. O'Neill is the chair of the executive committee for the ongoing PROTECT-II trial of Impella vs. IABP. This study is enrolling 654 patients with unprotected left main disease or a last patent conduit and EF ≤35% or 3-vessel disease and EF ≤30% – what he called "a very ill patient population." The primary endpoint is a composite of death, MI, stroke/TIA, repeat revascularization, the need for any cardiovascular operation, acute renal dysfunction, and an increase in aortic insufficiency, severe hypotension, or arrhythmia requiring treatment.

As of August 7, 2008, 55 sites had been established and 107 patients enrolled. Dr. O'Neill declined to give any more updated figures on enrollment.

Another Impella trial, RECOVER-II, is expected to start soon in STEMI and non-STEMI patients with cardiogenic shock. This trial will compare Impella 2.5 to IABP in ~834 PCI patients. The primary endpoint is major adverse events at 30 days.

Dr. Raed Aqel of the University of Alabama, Birmingham, the No. 1 enroller so far in the PROTECT-II trial, stressed the importance of having a good relationship with cardiac surgeons, "The patients we are enrolling in the PROTECT-II trial are high-risk patients…Most likely they go to surgeons before they come to you…If you have a good relationship with the surgeons first, that helps a lot."

Dr. Aqel cited two potential clinical applications for Impella:

1. Elective procedures – such as high-risk angioplasty, low EF patients, 3-vessel disease, last patent conduit, unprotected left main stenting, etc.
2. Emergency situations – STEMI, acute MI, cardiogenic shock, acute hemodynamic compromise, etc.

Asked if a patient who crashed on IABP could be crossed over to Impella, Dr. O'Neill said that wasn't allowed in the premarket trials, but now that the device is approved that is possible, "We can't prevent you from doing that because it is available, and you have to figure out what to do most safely to fix that patient…We discourage (crossover), but we don't prohibit it…There is a commercial registry to see if those kinds of cases are being done…We have looked very carefully (at this) in the first four months (since FDA clearance), and we have seen the commercial use in PROTECT-eligible patients. So, we aren't bleeding patients out (of the trial)…It would be a calamity for the trial if all we recruited were low-risk patients…It will be a calamity for you to have the device to use without data…There is some morbidity with the device… Right now it looks like we are recruiting a sick enough population."

Physician comments about Impella included:

- *Arizona:* "We are very excited about it, and we are going to use it in patients who are very high risk. We mailed our letter to Medicare two months ago, and we are still waiting (for reimbursement). We thought we'd get CMS approval weeks ago. We have balloon pumps, but they don't do the same thing; they don't actually move blood as the Impella does. The patients are the sickest, and realistically we would probably only use one a month.

We see people who maybe had a bypass graft 10 years ago, had multiple stents, and now those grafts are blocked. These people are stable, and they are doing fine, but the best thing for them would be to fix it."

- *Austria:* "We don't have Impella yet, but we plan to introduce it. However, a German cardiologist said he has had some difficulties and that it is not as helpful as it looked, but that is not the reason we haven't used it yet. As a bridging device it is not bad, and as a protection for left main, it might be useful – a kind of life insurance."
- *Georgia:* "We don't have it, but we want one. It all depends on the money."
- *Illinois:* "We want an Impella. It costs $50,000, and they said they'd throw another one in for that price. We hope to get one in the next couple of months. It's for the sickest of the sick. There is no waiting list for these patients. We wanted to be part of the trials, but Abiomed said that we would have to buy everything ourselves, and the hospital balked."
- *Louisiana:* "We haven't started using Impella yet. We are just looking at it. The surgeons didn't want to be in the IABP vs. Impella trial. I expect we will use it once a month. The cost is prohibitive. It's $25,000 for a catheter, and we have a really hard time with that; $25,000 is absurd. But it is really cool and probably better than IABP, but IABP still works. I expect we will wait for the cost to come down (before using it much)."
- *Massachusetts:* "We have the device, and we use it about twice a month. That number will slowly increase next year. It is for a small population of very sick patients."
- *New York:* "Impella is a necessity. We use the 2.5 in the cath lab; the 5 is for transplant. IABP is still the work-horse, and we haven't used the Impella for long, but we love it. We use about one a month, but I know use will increase."
- *Pennsylvania:* "We absolutely want an Impella, and we hope to get one in the first part of next year. Although it is for a small, high-risk population, it is a necessity. It will save some lives."
- *South Carolina:* "We use the balloon pump, and we would like the Impella. We'll sort it out in the next few months, and I think we'll get one probably in about five months. It is for a small number of patients. The cost of reimbursement is the main thing right now, and the hospital is pushing back a little. Even though it is for high-risk patients, and for a small number of patients, we are still going to use it."
- *Texas:* "We have Impella. We were part of the trial, and they made us buy the catheters and the machines. We ***maybe*** use it on one patient a month. It is a very expensive toy. But, that said, we like it very much."

THORATEC's HeartMate-II, a left ventricular assist system

A few days after TCT, the FDA warned of problems with HeartMate-II, and Thoratec initiated a "worldwide medical device correction" of all serial numbers of HeartMate-II (Catalog No. 1355 or 102139). At least 27 people have required surgery to replace a HeartMate-II, and five deaths have been linked to the device.

The FDA noted that over time, wear and fatigue of the percutaneous lead connecting the HeartMate-II blood pump with the system controller may result in damage that could interrupt pump function, require reoperation to replace the pump, and potentially result in serious injury or death. The estimated probability of the need for pump replacement due to percutaneous lead damage is 1.3% at 12 months, 6.5% at 24 months, and 11.4% at 36 months.

CIRCULITE's Synergy Pocket Circulatory Assist device

This miniature blood pump, which is designed to be placed superficially like a pacemaker for the long-term treatment of chronic heart failure, merits watching.

PERIPHERAL ARTERY DISEASE (PAD)

Dr. John Laird of the Washington Hospital Center said, "We have no idea about how well nitinol stents for the superficial femoral artery (SFA) work. The only thing for which we have any real data are nitinol stents. Stents do improve the results of femoropopliteal (fem-pop) interventions, and according to some trials – specifically the ABSOLUTE trial – show better patency with the Abbott nitinol stent compared to balloon angioplasty. The more recent RESILIENT trial, looking at second-generation nitinol stents, such as the (Edwards') LifeStent…show better results compared to balloon angio-plasty. The one issue that has been the thorn in the side of nitinol stenting is stent fracture, and with the newer flexible stents there seems to be an increased risk of fracture if stents are stretched during the process."

Dr. Daniel Clair of the Cleveland Clinic said that percutaneous intervention options are increasing regarding tibial bypass. However, he said, "Stents are not helpful in lesions longer than 15 cm, and no reasonable study has looked at this yet, other than covered stents. Restenosis is clearly more difficult to treat, and stent fractures occur in 10%-50% of stents. However, they are excellent for bailout in failed angioplasty."

As for reabsorbable stents, Dr. Clair said, "They won't be clinically relevant for three to five years, but pose a potential highlight for patients."

Dr. Clair said that various bare metal stents such as ev3's EverFlex and Edwards' LifeStent "are used for superficial femoral arteries, not control. We are starting to see drug-coated stents used for below the knee."

EV3

➢ **Protégé EverFlex.** The data from DURABILITY-1 were virtually no different from other SFA stent trials, which is a negative. Protégé EverFlex was supposed to be better. The company spent a long time (too long perhaps) explaining this, but the explanations were somewhat lame. Even an ev3 official said, "We need a breakthrough (in SFA stents)."

The DURABILITY-1 data would probably be approvable by FDA if that is what is seen in DURABILITY-2, sources said, but they warned that it probably would not be sufficient to drive significant market share shifts.

The European, 151-patient, prospective, non-randomized DURABILITY-1 trial of Protégé EverFlex (10-15 cm) in long SFA lesions was the first study to specifically evaluate long stents in long SFA lesions. Protégé EverFlex is a self-expanding nitinol stent that is already available in Europe.

Protégé EverFlex Results in DURABILITY-1 Trial

Measurement	6 months n=129	12 months n=123
Primary Endpoint: Primary patency rate at 12 months	---	72.2%
Secondary Endpoints		
Technical success	100%	100%
Initial arteriographic success	95.4%	---
Follow-up clinical success	94%	---
Primary patency	91%	---
Secondary patency	---	89.1%
Major adverse clinical events		
Stent fracture rate	6.2% (n=129)	8.1% (n=123) (10 fractures)
Mild fracture (single strut fracture)	---	1.6%
Moderate fracture (>1 strut fracture without complete separation)	---	2.4%
Severe (complete separation)	---	4.1%
Number of fractures	6	6
Freedom from TLR	94%	79.1%
Freedom from TVR	---	76.1%
Ankle brachial index	0.89	0.87
Mean Rutherford (baseline 2.89)	0.52	0.50

Dr. Dierk Scheinart of the Leipzig Heart Center in Germany said, "The lessons learned are that:

- Second-generation stent design (flexibility, durability, length) improves fracture and patency results in the SFA.
- Elongation is associated with fracture, and severe fractures are associated with loss of patency and TLR.
- As with any stent, proper deployment is important."

Of the 10 fractures that occurred, 9 happened in stents elongated at deployment. Dr. Lefevre said, "Elongation during deployment should be avoided…As with any stent, proper deployment is important." *Asked if the problem was more of stent design than in operator error*, Dr. Scheinart said, "The first-generation design could not be stretched…It's obvious that you can intentionally stretch the stents. It's not stent design as much as the deployment mechanisms that we have."

The DURABILITY-II IDE study in the U.S. has been enrolling patients for about a year, but company officials would not say how many patients have been enrolled so far. An ev3 official said, "The target is for 40 sites, and we have all 40 identified, and the majority are prepared to enroll. Fracture assessment is out to three years. We are assessing patency at one year as well. Patients with lesion lengths up to 18 cm will be enrolled, and we are including our 20 cm stent. No interim assessments are built into the trial, so it would be a full complement of patients before it is assessed."

➢ **SilverHawk.** ev3 acquired SilverHawk with the purchase of FoxHollow, but ev3 has not done the trials that FoxHollow was so roundly criticized for not doing. Rather, ev3 appears to be continuing the same marketing approach. A European feasibility protocol is in development with a single arm trial planned to start in 1H09 and a randomized controlled trial in 2H09.

Dr. James McKinsey of Columbia University/New York-Presbyterian Hospital described his hospital's experience with SilverHawk. Independent of ev3, his center and Cornell University followed 579 consecutive percutaneous infra-inguinal occlusive arterial lesions (364 interventions) between March 2004 and October 2007 in what he called the "largest dataset in the world."

Patients with claudication and limb-threatening ischemia were enrolled; patients with acute ischemia requiring immediate revascularization and iliac lesions were excluded. Almost two-thirds of the cases were "stand-alone" SilverHawk. He said, "The trial strategy recognizes the likelihood of drug therapy moving into the periphery but accommodates the unique requirements of the SFA by leaving nothing behind. The overall approach is to show that SilverHawk is a cross-cutting

Columbia/Cornell 12-Month Results with SilverHawk

Measurement	SilverHawk
Adverse events	
Hematoma	4.1%
Return to the OR	4.9%
Embolization	1%
30-day mortality	1.8%
Primary patency	
All lesions	62.2%
SFA	61.4%
Popliteal	68.9%
Tibials	62.7%
Limb salvage	
All lesions	89.7%
SFA	95.4%
Popliteal	90.9%
Tibials	83.6%

platform for vessel prep, regardless of the anti-restenosis technology used…I've been using this technology for the past five years because it works for me and my patients. The lower extremity and particularly the SFA remain a very challenging vascular bed for interventional treatment, with no silver bullet yet to the question of long-term patency."

The patient population in the study was skewed towards more advanced disease, and above-the-knee lesions were similar to other published reports, averaging >9 cm lesion length in the SFA and 3.7 cm in the popliteal. Most patients presented with high grade stenosis averaging >85% across the data set. Dr. McKinsey said, "Our tibial lesions, however, were associated with a higher incidence of limb-threatening ischemia. Although lesion length was just under 5 cm, more than half of our patients had chronic total occlusions (CTOs) in their tibial vessels."

About two-thirds of these patients were able to be treated with atherectomy alone. A third had assisted atherectomy, either at end touchup with balloon, or, more commonly, a very small balloon was stretched just a bit to get the device through and opened up. Dr. McKinsey said, "We rarely put a stent in there. We also in some cases did adjunctive atherectomy. We did one of the other procedures, had a complication, and fixed it with the SilverHawk device."

Dr. McKinsey called SilverHawk "an essential tool in the armamentarium of the interventionalists." But he also urged the company to do a randomized clinical trial, "We need a prospective comparison to other endovascular modalities. A randomized trial comparing atherectomy to surgical bypass would be difficult."

PATHWAY MEDICAL TECHNOLOGIES' Pathway PV Atherectomy system

A live case of this device didn't go well at TCT. The doctor apparently got "stuck" trying to clear a site. Dr. Thomas Zeller of Germany said, "I didn't see the live case, but I heard about it…The problem is if you get stuck with the device and continue the activation over two minutes, this can lead to more severe damage of the areas of the lesions which are not so highly calcified. Over time, it goes into the more soft vessel areas, which was obviously the case in the live case…We also observed four cases of perforation in our European multicenter trial…It is not uncommon. It can happen, especially if you simply treat highly calcified lesions…Every mechanical device can cause that."

At a breakfast session sponsored by Pathway, experts discussed the outlook for the Pathway PV Atherectomy device for clearing in-stent restenosis (in the superficial femoral artery). Dr. William Gray of New York-Presbyterian Hospital/Columbia University Medical Center said, "We've done a few cases…I would say it turned out angiographically very well…and we learned a lot about the friction that builds up…We learned that passing the device twice worked well to liberate our last passage…and with a low pressure balloon after that, it worked very well. There aren't a lot of other devices that work well (for in-stent restenosis)…FoxHollow (ev3's SilverHawk) has difficulty in lengthy restenosis because it is side-cutting…How we position this remains to be determined…We have both Pathway and SilverHawk. With SilverHawk, it is harder to do a total occlusion or a large lesion."

Pathway expects to launch a second-generation device next year. Asked what the major changes are with that device, Dr. Zeller said, "The second-generation tip passes more smoothly …and the location of the aspiration holes (is different) – proximal to the cutting place (the first generation is distal). And the embolization rate is clearly reduced with the second generation. In a study in more than 80 patients, we saw fewer embolization…(So, it is an) improvement in safety and handling, which is somewhat easier."

IMAGING

Fractional Flow Reserve (FFR) and Intravascular Ultrasound (IVUS)

FFR: RADI MEDICAL SYSTEMS' PressureWire and VOLCANO's SmartWire

FFR is a method of doing a stress test on a single vessel by measuring pressure during maximal flow. It is a good way to determine if a single stenosis is contributing to a patient's problem. FFR has been widely available for some time, but it is underutilized. Dr. Morton Kern of the University of California, Irvine, estimated that 20% of U.S. cath labs have FFR, and these labs may or may not have IVUS as well.

FFR signal analyzers cost $15,000-$20,000 plus about $600 per patient for wires. CMS reimbursement is low – in the hundreds, not thousands, of dollars.

Dr. Kern explained why he thinks FFR uptake has not been strong, "Physicians can't overcome their training of looking at angiograms…but angiograms are finally showing their weakness. IVUS is an anatomic method of looking at stenosis, but it doesn't measure blood flow…Even a single cross-sectional area may or may not be flow limiting…Flow is affected not only by the cross-sectional area but also the length, entrance angle, exit angle, and the friction – multiple anatomic features that we can't derive from a single cross-sectional picture… FFR should be standard when you don't have evidence of ischemia in intermediate-severe lesions with no strong clinical indicators."

Dr. Kern predicted that FFR use could go up 10%-25% over the next year. He said doctors offer five objections to FFR use:

1. **They can't believe the angiogram is incorrect.** "But angiography is not the tool we want it to be. FFR does away with the guesswork."

2. **The data to support it doesn't exist.** "That argument is now gone with the FAME trial and more than a decade of studies."
3. **It costs too much.** "That is a fallacious argument because the FAME trial found that selecting vessels to treat saved stents, time, contrast, and it took no longer to do. The physician will be paid to do FFR but won't be paid to do stents that are not needed.
4. **They don't want to take extra time.** "That has become overcome by installing the equipment at the bedside."
5. **It is too difficult to use.** "Anyone can learn to use it in a week. All that operators need to learn is to pass the wire, make sure the recordings of the pressure are accurate, turn on the adenosine, record the pressures, get the numbers, and turn off the adenosine. It is very easy to use. Technically, it is unchallenging to an operator who uses guidewires…It is a no-brainer for interventional cardiologists who use guidewires every day."

The FAME trial found that routine measurement of FFR with these devices is better than angiography for guiding PCI in any patient. The presenter, Dr. Nico Pijls of the Netherlands, claimed that FFR should be a routine procedure during stenting. Dr. Roxana Mehran of Columbia University called the data "very compelling," but she warned that this trial is not enough to say guidelines should be changed, "Not every cath lab in the U.S. has this technology...and it would be a big new technology to add…To say you shouldn't be performing angiography without FFR is a far stretch…While the data are compelling, we need more data before we say it should be done in every case…There is definitely a very important role for looking at physiology as well as anatomy…We would need much larger clinical trials to change the guidelines." Dr. Ajay Kirtane, also of Columbia University, said cath labs which don't have FFR should consider getting some technology other than just angiography, "This is a very important trial because it shows that we need to be circumspect in how we treat patients. We should treat lesions that are hemodynamically significant, associated with ischemia, or are symptom-producing lesions and should not treat lesions that don't need to be treated. To make that assessment, you need to go beyond angiography."

1-Year Results of FAME Trial

Measurement	Angiography n=496	FFR n=509	p-value
Procedure time	70 minutes	71 minutes	---
Cost	$6,007	$5,332	<0.001
Length of stay	3.7 days	3.4 days	0.05
Events	18.4%	13.2%	0.02
Death/MI	11.1%	7.3%	0.04
CABG/repeat PCI	9.5%	6.5%	Nss, 0.08
MACE	113 events	76 events	0.02

Asked if FFR will impact IVUS use, Dr. Kern said, "It shouldn't because IVUS should be used for sizing arteries and making anatomic decisions. It will if the operator has been using IVUS to decide if a lesion is physiologically important because IVUS doesn't do that very well. The data that compared IVUS to physiologic impact compared IVUS to FFR, so why use IVUS as surrogate of FFR when you can use FFR directly?"

IVUS: Boston Scientific's iLab and Volcano's VH IVUS

Chris Japp, general manager of imaging products for Boston Scientific, said IVUS is used in about 14%-15% of U.S. cases today and has been growing 1%-2% a year, "We think that will continue, driven by easier-to-use IVUS and more evidence of the need for it."

Asked if decreasing concern with DES safety will cause IVUS use to slow, Japp said, "Maybe, but there also may be more physicians doing implants now that feel a need for IVUS…and with a new stent that may drive IVUS to be sure it is performing as expected."

FFR vs. IVUS

Volcano has an exclusive contract with GE for integration of its IVUS into GE's Innova system, but Radi has the exclusive contract for integration of its FFR into GE's Innova table-site system. Siemens does not have any IVUS or FFR integrated into its system Philips has partnered with both Volcano's IVUS and Radi's FFR but they are not integrated. Cath labs can interface non-integrated IVUS or FFR with any of the systems, but that requires separate units and monitors. A GE official said, "We can sell Volcano's FFR, and now we have a collaboration with Radi to exclusively integrate Radi's FFR into our hemodynamic monitoring system…We chose Radi because it is the market leader in FFR…The FAME trial gave FFR new legs…With FFR you can see inside smaller vessels that IVUS can't reach. Some people say FFR and IVUS compete; others say they are complementary."

Boston Scientific's Lemaster believes IVUS will remain more popular than FFR, "I'm an IVUS fan...I'd want it pre-procedure, during the procedure, and post-procedure if I had a stent …I don't really know that it is driven by DES safety concerns. There are easier to use devices now…We have I-lab (with our IVUS)…and now it is two minutes instead of five minutes to set up…And there is a joy stick table-side to take measurements so doctors can do that themselves instead of relying on a nurse/technician, and that enhances the appeal of IVUS… IVUS is definitely a growing business and that will continue as we see more integrated IVUS systems…That is the trend for both Volcano and Boston Scientific…We now have a partnership with GE; our IVUS system is integrated with GE now." Japp agrees, "FFR is still very much a niche modality …IVUS is so well established that it won't be dislodged any

time soon." However, a Volcano sales rep said, "We've seen a big spike in FFR."

Virtual Histology

Boston Scientific officials believe virtual histology has potential, and their iMAP is waiting for FDA approval. Japp said, "We think it will be used largely in research mode, people interested in researching plaque morphology."

However, during a live case, experts claimed that virtual histology is not yet ready for prime time. One said, "It is not useful yet, but we are all looking to centers to do studies to determine usefulness." Dr. Gregg Stone posed the question: "Would anyone change practice based on virtual histology?" All the participants said not yet.

ANTICOAGULANTS

THE MEDICINES COMPANY's Angiomax (bivalirudin)

Angiomax got a strong push at TCT, but doctors asked about the data were not sure it would give any quick or significant boost to Angiomax use. The company claims that, as of April 2008, Angiomax was being used in 46% of PCI cases, with 22% of STEMI patients getting Angiomax. The drug got a big push at TCT from the results of four trials: NAPLES, PROBI-VIRI, ARNO, and HORIZONS-AMI trials.

- **NAPLES –** found that Angiomax monotherapy is safe and feasible in diabetic patients undergoing elective PCI. There was a significantly better net clinical outcome with Angiomax, but this was driven by non-Q-wave MI. In a post hoc analysis of patients based on risk level, Angiomax performed best in the lower risk patients.

- **ARNO –** Angiomax significantly reduced the composite endpoint of death, MI, TVR vs. unfractionated heparin (UFH) plus protamine – with a better net clinical outcome at 30 days. Minor bleeding was identical in both arms (2.4%) of this 850-patient trial, and there was no significant difference in vascular complications.

- **PROBI-VIRI** – found that prolonged infusions of Angiomax after PCI is a promising option to "reduce myocardial injury and, possibly, prevent stent thrombosis." However, an expert not involved in the trial warned that this study was too small and too short to draw conclusions about stent thrombosis. Dr. David Cohen, director of cardiovascular research for Saint Luke's Mid America Heart Institute,agreed, "It is an extreme stretch from this to say there is any evidence it would reduce stent thrombosis."

- **HORIZONS-AMI –** Angiomax reduces mortality in STEMI patients. Dr. Roxana Mehran of Columbia University Medical Center said, "I hope these data change the way we treat MI…We save 14 lives for every 1,000 patients treated with bivalirudin…This should change the way we treat patients…This is a monumental finding, especially in the high-risk population."

Dr. Ajay Kirtane of Columbia University Medical Center said, "This is really a very large, adequately powered and important study. There was a remarkable reduction in mortality that no one can argue with…The order of magnitude of the benefit surpasses statin therapy…The results are quite striking and define a new standard of care…It has been a long time since anything in a classic heart attack has been shown to reduce

30-Day NAPLES Results

Measurement	UFH + Aggrastat N=168	Angiomax n=167	p-value
Primary endpoint: In-hospital major bleeding	7.7%	1.8%	0.018
Secondary endpoint: Net clinical outcome	20.8%	12.0%	0.038
Death	0	0	---
MI	12.5%	10.2%	Nss, 0.61
Q-wave MI	0	0	---
Non-Q-wave MI	12.5%	10.2%	Nss, 0.61
Unplanned revascularization	0	0	---
Major bleeding	1.8%	0.6%	Nss, 0.623
Minor bleeding	6%	1.2%	0.035
Bleeding in low-risk patients	6.8%	0	0.007
Bleeding in moderate/high-risk patients	9.8%	5.3%	Nss, 0.472

30-Day ARNO Results

Measurement	Angiomax n=425	UFH + protamine n=425	p-value
Primary endpoint: In-hospital major bleeding	0	2.8%	0.043
Secondary endpoint #1: 30-day death, MI, TVR	2.8%	6.4%	0.014
Secondary endpoint #2: 30-day net clinical outcome (death, MI, TVR, or major bleeding)	3.3%	8.0%	0.004
Minor bleeding	2.4%	2.4%	Nss

30-Day PROBI-VIRI Results

Measurement	Short Angiomax (stopped after PCI) n=90	Long Angiomax (4 hour infusion) n=88	p-value
Primary endpoint: Procedure-related MI	16.7%	6.8%	0.041
Secondary endpoint #1: In-hospital bleeding	1.1%	1.1%	Nss, 0.87
Secondary endpoint #2: 30-day MACE	3.3%	1.1%	Nss, 0.43
Secondary endpoint #3: 6-Month MACE	16.7%	10.2%	Nss, 0.18
In-hospital minor bleeding	3.3%	3.4%	Nss, 0.96
Stent thrombosis	0	0	---

mortality…This trial actually showed a reduction in all-cause mortality…There hasn't been any trial in STEMI patients that reduced mortality except TAPAS at 1 year…This is the first trial." Dr. Cohen said, "There is still a little slowness of uptake because physicians tend to be a little more conservative in pharmacology changes…And there was 24-hour stent thrombosis, and we were alarmed by that…But this trial will help move this along…It takes time to change very established habits."

Asked about stent thrombosis, Dr. Mehran said, "At 30 days, there was no difference in ARC definite/probable stent thrombosis. There was a difference in acute stent thrombosis in the first 24 hours – there was a significant increase with bivalirudin monotherapy…At one year, the stent thrombosis rates were no different in the two arms (of the trial)…Perhaps the early stent thrombosis can be dealt with...This was really an unexpected finding…Certainly, I think there are ways to think about that…and (Lilly's) prasugrel may not only take care of the acute stent thrombosis but really reduce the late stent thrombosis from 3.5% to 1.6%."

Dr. David Faxon, who critiqued the trial, said, "There were 12 trials in this area. This is the 13th. There had been contradictory findings about using DES because of the concern of putting a stent in this setting…This trial provides that answer …It is a complicated study, with multiple randomizations, two primary endpoints, and a lot of secondary endpoints. It is fortunate that both primary endpoints were positive…I think the study was well done…I think the findings are real, but you can't over-extrapolate the results."

SCHERING-PLOUGH's Integrilin (eptifibatide)

The 400-patient, open-label 6-month ASSIST trial found that the combination of Integrilin and heparin was equivalent – not superior – to heparin alone in STEMI patients. Integrilin did not improve clinical outcomes, and it was associated with more bleeding.

30-Day and 6-Month ASSIST Trial Results

Measurement	Heparin + Integrilin n=201	Heparin alone n=199	p-value
TIMI major bleeding	22.4%	14.6%	0.04
Minor bleeding	12.9%	9.1%	Nss, 0.21
30-day results			
Primary endpoint: Death, reinfarction, recurrent severe ischemia	6.5%	5.5%	Nss, 0.69
Death	3.5%	2.0%	Nss, 0.54
Re-MI	1.5%	0.5%	Nss, 0.62
Recurrent severe ischemia	3.0%	3.5%	Nss, 0.76
Any revascularization	23.9%	21.1%	Nss, 0.51
6-month results			
Composite of death, reinfarction, recurrent severe ischemia	8.0%	7.1%	Nss, 0.75
Death	4.5%	2.0%	Nss, 0.54
Re-MI	2.0%	1.0%	Nss, 0.62
Recurrent severe ischemia	4.5%	4.6%	Nss, 0.97
Any revascularization	24.4%	22.6%	Nss, 0.68

MERCK's Aggrastat (tirofiban)

The 692-patient FATA trial, found that Aggrastat, though less expensive than Johnson & Johnson's ReoPro (abciximab), was not equivalent to ReoPro in primary PCI. However, Aggrastat also was not shown to be inferior to ReoPro. Dr. Gilles Montalescot of France said, "When you put this (trial) in perspective, the absolute numbers are very similar, so we have two positive studies on one side and two negative studies on the other side…You need to remember that a IIb/IIIa inhibitor works when you deal with high-risk patients…You have to give the drug early…Clearly, all these studies tell us something…We have learned where IIb/IIIas work – early and in high-risk patients. In other situations, it is difficult."

REGULATORY ISSUES

Each year at TCT there is a Town Hall session with regulators, and 2008 was no exception. The hot topic this year was percutaneous (transcatheter) valves. PFO, stroke, and sleep apnea were also discussed but very briefly. FDA officials said they continue to recommend that clinical trials compare best medical therapy to a device plus best medical therapy, with a composite primary efficacy endpoint at two years (due to event rates) of periprocedural all-cause death, late neurological death, and stroke/transient ischemic attack (TIA). FDA officials said that the agency is open to a U.S./OUS pivotal trial.

As for sleep apnea, the FDA said that there is no study showing that PFO closure improves obstructive sleep apnea (OSA), and the effect of a shunt (right to left) related to sleep apnea has not been demonstrated. Proof-of-concept does not yet exist, although it can conceivably come from animal studies.

The FDA perspective

A key priority for the FDA's Center for Devices and Radiological Health (CDRH) in 2009, according to Dr. Jonathan Sackner-Bernstein, associate director for Postmarket Operations in the Office of the Center Director, CDRH, is continuation of the postmarket "transformation," including integration of the FDA's Matrix approach into CDRH daily activities. He said the FDA is using the Matrix as "more than a policeman;" it's also designed to "protect, advance, and inform." He cited two examples where the Matrix helped identify problematic devices so that all devices in the category weren't recalled:

- **Heparin coated devices** contaminated with oversulphated chondroitin sulfate. "We were able to use (an) assay for this contaminant…in order to determine whether the two oxygenators with heparin coating were

a potential risk to subjects. Only one of these two could have had a theoretical risk deemed to be relevant. That manufacturer understood and voluntarily recalled it, whereas the other device did not pose a risk."

- **Artificial organ/combination product in development.** Before the IDE, this company met at least once with the FDA to discuss product design. "With the Matrix approach, not only were the (FDA's) Office of Device Evaluation (ODE) and the Office of Surveillance and Epidemiology (OSE) there…One issue was if the device could be designed from the outset to record events in real time to provide greater reassurance of the safety of the device."

Assessing risks in the postmarket setting requires new science, Dr. Sackner-Bernstein said:

- **The denominator** – "It is not so easy to know this. It is not clear how to find a path to know the denominator for each device."
- **Clinical impact** – What happened to a patient? "There is a perception that HIPAA would prevent us from understanding this. That is under debate…Does HIPAA prevent linking to outcomes? That is a question that will be asked over and over until we get an answer."
- **Causation or association** – "Just because something happened with a device doesn't mean the device caused it."
- **Decision making** – needs to be transparent and clear to all stakeholders.

Dr. Bram Zuckerman, director of the FDA's Division of Cardiovascular Devices in the Office of Device Evaluation, CDRH, repeated two recommendations he has made before:

1. Companies should talk to the FDA earlier.
2. A post-approval study should be designed and submitted with the PMA. "If there are any questions about whether a post-approval study needs to be done for a specific product, utilize the pre-PMA meeting. If the answer is yes, it needs to be seriously considered within your PMA package."

Asked if there is a role for lowering the bar on the pre-market side and significantly raising it on the postmarket side, Dr. Zuckerman said, "We are always interested in thinking about what is a proper pre/postmarket balance…but development of a sound postmarket system is a challenge right now."

The CMS perspective

Dr. Marcel Salive, director of the Division of Medical and Surgical Services at the Centers for Medicare and Medicaid Services (CMS), said his agency works as a matrix as well. He emphasized that CMS "will not pay for items and services that are not reasonable and necessary…That is the crux of coverage."

Among the interesting comments he made were:

- Diagnostic tests have to be used in treatment decisions. "That seems like a no-brainer, but there are some tests that are not used that way."
- New innovations are going on right now at CMS, including value-based purchasing and quality reporting.

PERCUTANEOUS VALVES

Dr. Mitch Krucoff of Duke University Medical Center said, "Aortic stenosis patient suffering is the real deal, and yet it's equally clear that the FDA sees protecting the public as a certain bar whether it is a smart bar or a high bar or a low bar, but my question is: What would it take – what rationale might support on behalf of the American public – for the FDA to begin considering a pre-IDE protocol?…What would it take to think about using some of these devices in the early phases? We see results in Western Europe or Eastern Europe or India or Brazil. What would it take to get them in the hands of American investigators earlier?" Dr. Sackner-Bernstein answered, "We're not necessarily the first at doing something like that when we're talking about the too-sick-for-operation patients, but we are amenable to considering a registry in that group. We would want that in the context of a more rigorous (way).

Don Bobo, Edwards Lifesciences vice president, said, "You have not answered the question. Right now, a medical device that starts in the U.S. is immediately taken out of the U.S. for first-in-man (studies). Does anybody in the FDA believe that that's a fundamental problem with the way we do business? That we can't do it in the U.S.? That there are barriers, so that it can't happen here?" Dr. Sackner-Bernstein responded, "I would respectfully disagree that we're a barrier."

Off-label use

One of the elephants in the room was the potential for off-label use of percutaneous valves if and when they gain FDA approval. Dr. Zuckerman said, "These are first-generation devices, and off-label use is not the major area of concern. The major concern is that the devices demonstrate a reasonable assurance of safety and endpoint efficacy."

However, other officials expressed more concern about off-label use. Dr. Sackner-Bernstein said, "(There is a need to) avoid gaming with overly complex trial designs. We all know that when the device is approved, it will be used in a wide variety of populations, not just necessarily the target population. It is incumbent on the company to make sure that the device isn't used outside the target population." He also said that it is important to define inoperability, and "have it at least adjunctive to a surgical randomized control trial."

CMS's Dr. Salive said, "Whenever someone says that there won't be off-label use, I disagree with that and say, 'Prove it

to me.' There is a lot of off-label use in almost all devices, in varying degrees and amounts, and there are always compelling stories behind that. But let's get good evidence now."

The FDA perspective

Dr. Sackner-Bernstein commented, "With percutaneous valves, it's the concept of effectiveness. In a significant portion of the target population, it has to have clinically significant results. Not (just) statistically significant results, but it has to be clinically significant in the target population. There are challenges with percutaneous valves. They are changing the paradigms of treatment pathology. In the past, if the patient were too well or the benefit wasn't going to be sufficient to justify (a procedure), then there would be a delay in the procedure. Then, there is the high-risk inoperable group, in which the procedure risks outweigh the benefit. Now, we are seeing these devices being proposed for all three of these groups (functional, ischemic, degenerative)…When we start going through the list of mitral disease, it is cumbersome to think about attacking all of these with one device."

Dr. Sackner-Bernstein emphasized the importance of the "totality of the data." Endpoints may include:

- Primary and secondary endpoints, which are especially important when composite endpoints are used.
- Both hard and soft endpoints desirable.
- Survival, ventricular dimensions/mass, exercise testing.
- Quality of life.
- NYHA Class.
- Valvular regurgitation, a "double-edged sword and not necessarily a good surrogate in ischemic MR."

As to the appropriate duration of follow-up, Dr. Sackner-Bernstein said it must assess durability of the safety and efficacy in a population-dependent manner but generally measured in years. And the effect on future established treatment options must be considered.

Asked if the FDA will require a mortality rate around 10%, Dr. Zuckerman said, "You have to have a relevant control to compare. For example, if you're assessing the mortality rate of a 50-year-old who has a 1% mortality rate, that is unacceptable. Dr. Leon said that it would be used in an 80-year-old patient population with 40% mortality rate. If that were the case, then 10% would be reasonable, but you have to have the data (mortality rate data) in the first place."

Asked if the FDA might mandate specialized training for percutaneous valves as it did for carotid stents, Dr. Zuckerman said that decision will be up to Dr. Sackner-Bernstein and CDRH's Office of Device Evaluation.

There was a somewhat heated exchange about the FDA's approach to percutaneous valves.

- *Dr. Bram Zuckerman, director of the FDA's Division of Cardiovascular Devices in the Center for Devices and Radiological Health, to Bobo:* "You asked a question that the agency is always looking for answers, but aren't you involved with a device where the device has been investigated primarily in the U.S.?"
- *Bobo:* "I am involved with only the one, but I'll remind you that the first-in-man was outside the U.S. It was a stroke of luck that we got started here."
- *Dr. Zuckerman:* "When you look at the track record right now in terms of completed trials, I think you were representing the only company who has actually completed their trial, so I don't think that it's a situation where it's hopeless for device development in the U.S. That's the point I want to underline. So, what we would suggest is… if you are going to develop a device in the U.S.…the necessity for pre-IDE communication is essential – especially with the very disruptive transformational technology that we have here, where a lot of answers and developmental pathways are unclear…From our perspective we would also suggest that we need to utilize what we've learned about good clinical trial design over the last 20 years. One of the scenarios that's been talked about is the so-called high-risk inoperable aortic stenosis population. Figures are given as to what the untreated medical mortalities are, and while those are interesting data, those are in reality only guesstimates… My point is that, while this is going to be a very controversial and difficult area to develop, the need to employ good scientific thinking can be lost in the muddle."
- *Dr. Leon:* "We're not talking about some ego-driven way of using these. It almost suggests that (Dr. Zuckerman) was suggesting we do a critical history study. We know these patients die at a very high rate in a very short period of time. This is well understood."
- *Dr. Zuckerman:* "No one is disagreeing with you that these patients have a high mortality. The question is, if it was as obvious as you're making it out to be, then the randomized trial with some kind of group sequential design…the answer will be easily shown. That's a no-brainer. The reality is that I'm not sure, with good medical treatment in this day and age, what the risk:benefit profile is for this patient population. Just show us the data."
- *Dr. Leon:* "There is no medical therapy for aortic stenosis unless you know something I don't. There is no known best medical therapy for aortic stenosis."
- *Dr. Krucoff:* "This is a little different than treating patients with chronic unstable angina. We know that aortic valve replacement saves lives. We are simply trying to parallel a surgical technique that we know is life saving. Of course the science has to be good. But there

should be a kind of collaboration with the agency and CMS that has this sense of sensitivity and urgency to the population. And I don't see that sense of urgency and sensitivity, particularly as we go further down the road and want to start improving these devices."

- *Dr. Zuckerman:* "That sense of urgency is always there because it's mandated by Congress…We also have expedited review pathways. The point that I'm trying to make with the idea of just doing an interim analysis – half the data, two-thirds the data – there are methodologies that are out there which can improve efficiency. The agency doesn't have problems with those methodologies, so it's up to you to be a little bit more creative, as well as the agency recognizing that this is an important area."

The CMS perspective

Dr. Salive said that percutaneous valves would, initially, be a local coverage decision, not a national decision. However, he noted that CMS recently announced that it would not expand coverage of carotid artery stenting, perhaps hinting that CMS will take a conservative approach to percutaneous valves as well. But CMS definitely wants to see more trial data. He said, "I am in favor strongly of clinical trials, and we've seen many of the proposals for those kinds of comparisons with medical treatment or surgical treatment, so that's a good thing…We want to see evidence that includes our (Medicare) patients, so we can know how things will work. Many of our patients won't qualify for a trial. We accept that, but we want to see some enrollment. We also would like to see minorities and women enrolled in the trials. I do think that from the Medicare standpoint we prefer clinical endpoints. I personally have a lot of skepticism for dimensions of the ventricular wall as an endpoint. If you can demonstrate that that is a valid surrogate with evidence from many other studies linked to clinical outcomes, I might be willing to consider that. I do think functional status is important, especially in the context of heart failure. Traditional hard endpoints are important."

MISCELLANEOUS

ACCESSCLOSURE's Mynx vascular closure device

There are several vascular closure devices on the market, but Dr. Charlie Brown, CEO of Piedmont Heart Institute Physicians in Louisiana, said there are several advantages that set this one apart. Mynx is an extravascular placement device that leaves nothing behind; it dissolves in 30 days. It uses a rapidly expanding sealant that fills the tissue, minimizing ooze. It also uses gentle deployment to minimize patient pain. Dr. Brown said, "I've put 150 devices in, and most people don't know you've placed it."

Mynx offers:

- Clinical versatility, including peripheral vascular disease, immediate re-stick, bifurcation sticks, obesity.
- Fast, predictable outcome, regardless of skill level and degree of anticoagulation regimen.
- User friendliness. Dr. Brown said the learning curve is about six or seven cases.
- No intravascular components left behind.
- Minimal trauma to arterial lumen and tissue tract.
- Improved patient comfort and recovery.

At Piedmont Hospital, Mynx use started in October 2007, and there have been 761 Mynx closures through July 2008. Dr. Brown said, "Looking at the experience in a community hospital, in our lab we have 14 Mynx users. There is an early learning curve, a high success rate (98.7%), and a low complication rate (0.6%)."

An audience member, Dr. James Conley, a cardiologist from Buffalo NY, stood up to lavish praise on the device, "I've done more than 2,000 of these procedures…The one thing that's truly remarkable is that it's almost painless. All the other closure devices hurt, and no matter how well one feels, how well the patient is anesthetized, the one thing the patient will remember during the procedure is the closure device and whether it was painless or not. It's that remarkable. You really have to try it. In addition, it has a side port, so you know exactly where you are positioned. When you pull back the balloon you know whether the balloon is situated at the arteriotomy site so the plug can be deployed. It is indispensable and allows perfect positioning. I've used the device in people with peripheral vascular disease. It's not a stitch, and it's not a staple. It is truly excellent. I have also used it for venous closure and femoral vein sticks…and we close the femoral vein with this device, too…The positioning is perfect and it is almost painless…And I don't get paid by the company."

COHEREX MEDICAL's FlatStent

Yes, another device for PFO (patent foramen ovale) closure. This one is a nitinol device designed to fit within the tunnel rather than covering the two sides of the hole. The company is hoping for a C.E. Mark in 2009 and plans to start a randomized clinical trial in the U.S. in 2009 for migraine (yes, migraine).

Asked why this should be different from PFO closure devices that have struggled in the migraine area, a Coherex official said, "We think the definition of chronic vs. episodic is very critical. Other PFO devices targeted episodic, not chronic migraine."

A source said the company is looking at using this device to treat sleep apnea/apoxia. All a company official would say about this is, "We are doing early studies to try to find another indication."

An official said the advantages of FlatStent are:

- The small size and mass exposed in the left atrium.
- Conformability to the anatomy of the PFO.
- Low surface area so maybe there will be fewer arrhythmias, erosions, and clot formation.
- The deployment system with a rapid exchange guidewire approach that doesn't require any assembly.

ZOLL's Reprieve

In the COOL-RCN trial, Reprieve, a systemic hypothermia system (which came from defunct Radiant Medical), was safe and well tolerated but failed to prevent radiocontrast nephropathy. The company is considering whether even to continue an MI trial of Reprieve that had started and had enrolled ~10 patients.

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