Trends-in-Medicine

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by Lynne Peterson

SUMMARY

DES penetration and overall stent volume are holding fairly steady in Europe. DES use in Europe and Japan were largely unaffected by the COURAGE trial results.

♦ Abbott's Xience is picking up market share in Europe faster than Medtronic's Endeavor, but both are gaining slowly.

♦ Johnson & Johnson/Conor's CoStar was a disaster almost across the board, but J&J is not giving up on the reservoir program.

♦ Experts and competitors expect Medtronic's ENDEAVOR-IV trial to be positive, but the FDA wants to see that data and take it to a panel, probably in the fall, before approving Endeavor.

♦ Percutaneous valves were the hot topic at PCR, but training and adoption – and perhaps enrollment in the surgical arms of U.S. trials – are likely to move slowly. Experts believe the procedure should be restricted to Centers of Excellence for the foreseeable future, with 30-100 procedures a year done at each center. Both CoreValve and Edwards LifeSciences are expected to succeed.

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EUROPCR

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EuroPCR moved to Barcelona this year, but that was not the only change. In previous years, drug-eluting stents dominated the meeting, but this year percutaneous valves got nearly equal attention. The four-year-old Transcatheter Valve Symposium (TVS), formerly held only in the U.S., was integrated into EuroPCR this year. A record 11,347 people attended PCR this year, with more than 100 live cases presented from 16 international centers and 131 companies exhibiting.

The "Novelty Award" went to Abbott and Biotronik for their efforts in bioabsorbable drug-eluting stents (DES). The winners of the "Best Three Clinical Case Presentations" were:

- 1st Dr. Edo Kaluski of the University of Medicine & Dentistry of New Jersey for "Protruding partially deployed stent."
- 2nd Helene Routledge of France for "Use of deflectable tip catheter for complex interventions beyond insertion of bypass grafts."
- 3rd Dr. Manjeet Juneja of Australia for "Percutaneous closure of an ascending aorta pseudo-aneurysm with an Amplatzer septal occluder."

EuroPCR's view of the highlights of the meeting included:

➢ **Surgery.** Dr. Vicente Riambau of Spain said:

- A team approach is needed, with cardiologists and surgeons working together on percutaneous valve repair and replacement. Dr. Jean Marco of France promised that EuroPCR 2008 would focus on consensus between surgery and interventional cardiology rather than controversies between the two specialties.
- Training remains a key issue for carotid stenting, but additional trials (including a best medical treatment arm) and cost-effective analyses are needed.
- Current endografts are better than first-generation devices, and endovascular abdominal repair (EVAR) can be offered to fit and young patients with suitable anatomy by an experienced team, but EVAR is not cost-effective.
- Nitinol stents are better than other stents for lower limb revascularization, but more developments are needed in this field – "perhaps DES."

➢ **Percutaneous peripheral interventions.** Dr. Alberto Cremonesi of Italy said the next step will be to move beyond technical aspects toward clinical

treatment strategies. He also emphasized the importance of physician training and credentialing for endovascular procedures.

- **Percutaneous valves.** Dr. Philipp Bonhoeffer of the U.K. noted that percutaneous valves are moving into the mainstream of cardiology. He said there currently are 16 mitral programs, 14 aortic programs, 4 pulmonary programs, and 15 less invasive programs, with 35 companies involved and 17 transcatheter programs in clinical trials. A live pulmonary and three live aortic valve replacement cases were presented – a CoreValve transfemoral case, an Edwards LifeSciences transfemoral case, and an Edwards transapical case – and all were successful. Dr. Bonhoeffer cited a comment by Dr. Valentin Fuster (of Mt. Sinai Medical Center) that biologic aortic valves should be used in even younger patients because follow-up procedures could be done with a percutaneous valve later. He also highlighted one completely new area: mitral valve replacement, saying, "How this is going to work, I wouldn't want to predict, but the research is interesting." He did not mention Endovalve by name.

- **PCI.** Dr. Marie-Claude Morice of France called magnetic navigation "incredible," and she urged that late stent thrombosis be considered "in perspective." She said, "The current results of DES are the best they have ever been…Safety issues with first-generation DES have been thoroughly analyzed...Even though stent thromboses are very limited in absolute numbers, they have generated a loss of confidence affecting the use of DES, which is increasing in many countries and centers at the moment …The second-generation DES are here. Could this be the beginning of a new step forward?" She was enthusiastic about the third-generation stents that are coming, including bioabsorbable stents, AlchiMedical's coating technology, and the Genie catheter for liquid local drug delivery just after use of a BMS.

DRUG-ELUTING STENTS

PCR was supposed to open with a debate about the choice of percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), or medical management, and the huge auditorium was packed. Clinical cardiologist Dr. Steven Nissen of the Cleveland Clinic was expected to argue that the COURAGE trial found that medical therapy is no better than stenting as an initial management strategy in patients with stable coronary disease, and Dr. Keith Dawkins of the U.K. was to defend PCI.

However, at the last minute Dr. Nissen cancelled. Instead, Dr. Dawkins gave his pro-PCI argument, speaking, of course, to the choir. He took quite a few personal shots at Dr. Nissen, but didn't really add anything new to the debate. The audience only heard the message they wanted to hear: "DES-assisted PCI should still be the treatment for suitable symptomatic coronary artery disease (CAD)." Dr. Dawkins emphasized, "Do patients like medications? They don't. When you start adding in multiple meds, compliance drops… In Europe, and certainly in my practice, the majority of patients we treat are unstable patients. The majority of patients we are treating appropriately, according to the guidelines…In COURAGE…9% of patients had multivessel disease, but only 41% (of these patients) got more than one stent. How can you treat multivessel disease with one stent?...COURAGE was not a blockbuster trial. It just confirms what we knew already…In terms of DES efficacy, a patient-level meta-analysis by Dr. Gregg Stone of Columbia University Medical Center, published in the ***New England Journal of Medicine*** earlier this year… showed a very impressive reduction in TLR (target lesion revascularization). So these do work."

Dr. Dawkins had some strong criticism of Dr. Nissen, "He is …messianic, thinking everything he does is correct…I can't figure out why Steve Nissen has it in for us (interventional cardiologists)…In the last few months, a succession of trials for which he has been the principal investigator have not worked."

Dr. Ran Kornowki of Israel commented, "It is my impression that the (DES) field is moving in the proper scientific direction…We still need to improve our clinical results when treating diabetics, multivessel disease, and diffuse coronary disease…We should all look forward to seeing whether those challenges are met with the new generation of drug-eluting stents."

U.S. market trends

Boston Scientific COO Paul LaViolette said, "Market conditions are challenging but improvements are expected. Penetration has been flat for the past 5 weeks." He indicated U.S. DES penetration was 71% in January, 69% in February, 67% in March, and 65% in April. He said, "Following ACC (the American College of Cardiology in March 2007), we mapped a step down in DES penetration…We (now) have a degree of stability that did not exist since the beginning of the stent thrombosis controversy…May month-to-date is a slight increase…We do see, at least in early May, a recovery in bell-wether product sales…It may be too early to signal a rebound in DES volume…but at least we see stabilization and perhaps a rebound."

LaViolette also indicated there appears to be a bolus of deferred patients building up. He said, "Following the (FDA) DES panel (in December 2006), there was a drop-off in procedures unrelated to seasonality…Then, after ACC we see for the first time a separation between diagnostic procedures and interventional procedures…So, we are seeing diagnoses in the lab not being converted to interventional procedures… Patients who are diagnosed and not moved on to a interventional procedure are aggregating in a pool of deferred procedures. Those patients will ultimately move back into PCI volume…So, we are seeing a pool of patients who need therapy and have not received it." Dr. Donald Baim, chief

medical officer of Boston Scientific, predicted that we would see an up tick from this within a year.

What is the outlook for Endeavor and Xience/Promus in the U.S.? A Boston Scientific official predicted, "If Endeavor loses a substantial time advantage over Xience, I'd question if there will be any uptake in the U.S. at all…The FDA has no incentive to move forward faster...If Endeavor launches after Xience, it may not be used at all. There is no safety advantage, and it would be dead on arrival…If doctors know Xience/ Promus is coming, and Endeavor is out only 1-2 months before that, they may not try Endeavor."

U.S. doctors were more optimistic about both Endeavor and Xience, though they wouldn't predict market shares. A Midwest doctor said, "The choice will depend on price. Endeavor and Xience are comparable to Cypher and Taxus, so it will come down to cost and supply…The CoStar failure is making it hard for all new technology, not just DES."

Japan

In Japan the COURAGE trial appears to have had little or no effect on DES use in Europe. A Boston Scientific official said DES penetration in Japan is in the 72% range and stable, with a value of ~$500 million. He claimed there is pent-up demand for Taxus in Japan and predicted its market share will be 60%+ within a year, with market leadership by the end of 2007. But he warned the launch will take time because of training requirements. He said, "Unlike the U.S. roll-out, we are unlikely to get overnight conversion in that market (Japan)." The selling price in Japan is $2,600.

European market trends

Perhaps surprisingly, the COURAGE trial appears to have had little or no effect on DES use in Europe. Doctors from nine different European countries agreed that overall stent volume did not go down in the past few months as it did in the U.S.

J&J officials disputed reports that the overall stent market has contracted sharply in the past few months. Rick Anderson**,** company group chairman at J&J/Cordis said, "We don't see that market impact…Market shares have been relatively stable over the last year, even with the introduction of multiple new products." A Boston Scientific official said, "The (DES) market is beginning to stabilize and will continue to stabilize." Another Boston Scientific official pointed to some small share loss in Europe, saying, "There is evidence of a 3%-4% Cypher (Johnson & Johnson) share drop in Europe, a clear erosion. But the product (Cypher) has some legs. People sare not in a rush to give it up."

However, DES use stopped its slow but gradual increase in Europe when the stent thrombosis controversy first started last fall. DES penetration is remaining relatively stable, with doctors predicting the balance between DES and BMS will hold steady at least for the next 6-12 months. J&J's Anderson said, "It has been a pretty noisy marketplace since the ESC (the European Society of Cardiology) meeting last year (September 2006). Some of the stability we've seen in share …relates to physicians sorting out the information and data. There is a lot of data…and I think we are still learning a lot… There is a sense of security with what they know vs. what they don't know." However, the audience at one interactive PCR session predicted DES use will go up in the coming year: 78.3% said increase, 13.0% decline, and 8.7% flat.

The stent thrombosis issue has had another effect, though: DES market shares have become harder to change in Europe. Medtronic's Endeavor, Abbott's Xience V, and Boston Scientific's Promus are picking up customers, but slowly. Doctors cited three reasons for this:

- **Data and experience.** The thinking appears to be: The "devils" they know – Johnson & Johnson's Cypher and Boston Scientific's Taxus – are better than the ones they don't. Doctors appear nervous about possible future surprises. Endeavor just hasn't been able to convince most doctors that it is safer; many think it may be and hope it will be, but they want to see more data. Xience/Promus also needs long-term data. An Italian doctor said, "Xience has only one study, and there is no long-term safety data."
- **Contracting.** Many European hospitals use an annual or every-two-year bid system, and new DES have to both wait for the bidding cycle and win the bid.
- **Reimbursement.** This does not appear to be a major problem. Most countries reimburse, to one degree or another, for DES, and the reimbursement applies to whichever DES is used. However, a source said that hospitals used to be able to buy 10%-20% of their DES supply outside of the bidding arrangement, and new stents could count on this for a base until bids came in, but the source said it has gotten tougher to get any traction in this area.

European doctors at PCR were questioned about their current use, and though their market shares don't match the shares the companies are reporting, it is indicative of trends going forward: both Taxus and Cypher losing market share fairly equally to Endeavor and Xience/Promus, but Xience/Promus making bigger gains than Endeavor. Not enough doctors who had been using Conor's CoStar could be identified to determine what DES was being substituted for CoStar. A Boston Scientific official said Taxus share OUS differs by country, but ranges from 38%-45%. He added, "Endeavor came out, peaked in the high teens, and is showing some

European Market Share (*from doctor interviews*)

DES	Current share	Share in 6-12 months
Boston Scientific's Taxus	47%	42%
Johnson & Johnson's Cypher	34%	29%
Medtronic's Endeavor	8%	11%
Abbott's Xience/ Boston Scientific's Promus	11%	18%

erosion from that peak, certainly no gains. Xience/Promus captured ~10% (more Xience than Promus, based primarily on their head start)." Another Boston Scientific official said, "When you ask people, confidence in Endeavor is waning."

Other comments on market share projections included:

- *France:* "We'll probably be using 30% Xience within a year. It's a true second-generation stent."
- *Italy #1:* "I'd like to use some Xience, but we are in a two-year contract with Taxus and Cypher."
- *Italy #2:* "More than half of our stents are Xience/ Promus, and we are splitting our (zotarolimus) use equally between Xience and Promus."
- *Germany:* "If Xience or Promus were priced comparable to Taxus, I would use it – once there are clinical data. Xience got its C.E. Mark on 27 patients, and there wasn't a clinical endpoint in SPIRIT-II or -III. The Xience trials were too small, and there was no primary clinical endpoint…Why don't I use Endeavor? I have experience with Taxus, and if it works, don't fix it. CoStar's late loss was ~0.6 mm, and Endeavor's late loss was ~0.6 mm, so why is CoStar off the market and not Endeavor?...Cypher and Taxus have set a standard that is hard for the others to reach…I'm a very early adopter in clinical trials, but in general use I'm more conservative."
- *Greece:* "We use Cypher, Endeavor, and Xience – no Taxus. Our use of Endeavor will go down a little, and Xience will go up a little."
- *Finland:* "We'll be using less Endeavor and more Xience."

Pricing. According to a Boston Scientific official, the annual DES pricing decline in Europe remains about 3%, but the gap between Cypher and Taxus is now $100, "so not only are we seeing stability (in pricing) but also a premium price for Taxus." A Medtronic official said there is still some erosion in European DES prices but pricing "seems to be stabilizing, perhaps because of Xience…Boston Scientific has sold Taxus on price to select accounts, but customers want Promus at the same price, and that is a problem for them." An industry source said that where Abbott is selling Xience, they appear to be holding their premium pricing, but he said Abbott is giving away a lot of product. For example, he suggested that in Italy, the Xience share has increased, but he thinks that is with "no-charge" product.

Regulatory issues

Boston Scientific's LaViolette predicted there would be no new, competitive DES platforms in the U.S. until 2011 or 2012. He said the FDA now wants:

- More bench and animal data for a longer duration.
- More clinical data for a longer duration (12 months instead of 9 months).
- A significant quantity of 24-month clinical follow-up at the time of PMA submission.
- 5-year follow-up.
- Post-marketing: more clinical data for a longer duration, data in more complex patients, and more complex postmarking programs.

ABBOTT VASCULAR

For the first time Abbott had a high profile at PCR, and its booth was packed most of the time, though this was due in part to the large number of Abbott staff attending the meeting. There was a high degree of excitement and enthusiasm among the Abbott sales reps.

Xience V

No supply problems with Xience V, an everolimus-eluting Vision stent, were reported by European doctors.

During PCR, Abbott issued a statement that it remains "highly confident" in the performance of its everolimus-eluting Xience V in both diabetic and non-diabetic patients: "The clinical data from more than 1,300 patients that has been presented to date show that Xience V is superior to Taxus on reducing major adverse cardiac events (MACE), reducing retreatments and reducing vessel renarrowing (restenosis). In fact, MACE was approximately 2-3 times lower with Xience V than with Taxus across all our SPIRIT trials." Abbott said it remains on track to submit Xience to the FDA this quarter.

Dr. Stone presented both the 3-year SPIRIT-First results and a meta-analysis of the SPIRIT-II and -III trials of Xience. He concluded that, compared to Taxus, Xience results in reduced late loss and restenosis; reduced TLR; similar death, MI, and stent thrombosis; and fewer MACE. The discussant said, "The SPIRIT-First and -II results are somewhat reassuring. This stent seems to be ready for prime time."

3-Year SPIRIT-First Results

Measurement	Bare Vision n=28	Xience n=266
MI	0	7.7%
Death	0	0
Clinically-driven TLR	25.0%	7.7%
MACE	25.0%	15.4%
Clinically-driven TVR	32.0%	7.7% (p=0.04)

SPIRIT Trials

Measurement	SPIRIT-First	SPIRIT-II	SPIRIT-III
Location	Europe	Europe, India, New Zealand	U.S.
Length of follow-up	3 years	1 year	9 months
Number of patients	295	300	1,002
Design	Xience vs. Vision	Xience vs. Taxus	Xience vs. Taxus
New data	Yes	Pooled meta-analysis	

The diabetic subset analysis will be presented at TCT 2007, and SPIRIT-IV comparing Xience V and Taxus in >3,600 complex patients (including ~30% diabetics) is currently enrolling patients.

Meta-Analysis of SPIRIT-II and -III Trials

Measurement	Taxus	Xience	p-value
Diabetics	27.1%	27.9%	---
Late loss in-stent	0.33 mm	0.14 mm	<.001
Late loss in-segment	0.22 mm	0.11 mm	0.0004
Restenosis in-stent	4.9%	1.9%	0.02
Restenosis in-segment	7.8%	4.1%	---
Ischemic TLR at 9 months	5.1%	2.4%	---
Stent thrombosis	0.45%	0.25%	Nss, 0.59
MI	2.7%	1.7%	---
Cardiac death or MI at 9 months	3.2%	2.1%	Nss
MACE	8.0%	4.1%	0.004

BVS

Nine-month clinical results were presented from the first cohort of ABSORB, the first-in-man evaluation of this bioabsorbable stent, which elutes everolimus from a PLA-matrix coating on a PLA stent backbone. The elution profile looks very similar to Cypher. ABSORB was a prospective, open-label trial conducted at 6 sites in Europe and New Zealand. There was no additional MACE from 6-9 months. The investigator concluded, "ABSORB demonstrated continued safety, acceptable in-stent late loss, possibly driven by bioactive remodeling or mechanical late recoil, which is being addressed by a modification of the stent design…We are starting cohort B now for another 30 patients." The modified stent has the same material and the same strut thickness, but more uniform strut distribution, for more even support of the arterial wall, etc.

9-Month Results of ABSORB Trial

Measurement	BVS n=25 evaluable
MACE	4.0%
Cardiac death	0
Non-Q-wave MI	4.0%
Stent thrombosis (ARC definition)	0
Stent thrombosis (by per protocol definition)	0

BIOSENSORS' BioMatrix

The two-year results of the STEALTH-1 first-in-man trial of BioMatrix (eluting biolimus A9) were presented by Dr. Alexandre Abizaid of Brazil. He said, "Biolimus is very similar to siro-limus…Currently, the platform has abluminal release only and a bioabsorbable polymer…These 2 features can theoretically increase safety." MACE was 5.1% at 1 year and 6.5% at 2 years (both Nss vs. control). There was 1 additional TLR in the biolimus arm and 1 additional Q-wave MI in control between Year 1 and Year 2. STEALTH-II will be the pivotal trial for U.S. approval.

Biosensors officials wouldn't comment directly on the regulatory status of BioMatrix or biolimus in Europe, but they said they expect a C.E. Mark by fall 2007. One official said, "Regulators everywhere have gotten more difficult since the DES controversy ignited last fall."

Another official said that in the U.S., the biolimus drug master file has been filed, but the FDA is asking for more data on their tests and larger and longer trials (two years and >2,000 patients). Biosensors plans to start a U.S. pivotal trial later this year.

BOSTON SCIENTIFIC

During PCR Boston Scientific announced it had gotten a C.E. Mark for the Taxus Liberté Long (38 mm) stent, which is now the longest DES on the market. It will be sold in four diameters: 2.75 mm, 3.0 mm, 3.5 mm, and 4.0 mm.

Quality systems update

Third party verification audits were started in May, and Boston Scientific hopes to complete these by the end of 3Q07. There will be a mid-way meeting with the FDA in mid-July. LaViolette predicted that the FDA will want to audit 25% of the 24 sites Boston Scientific is auditing. He also suggested that Taxus Liberté "may not be gated by this timeframe." He said the first sites being inspected are Galway, Maple Grove, and Quincy – where Liberté is made. So, when those are done, Boston Scientific plans to meet with the FDA (in September or October) and try to get Liberté approved. He said, "We are not modeling Liberté by the end of the year. That would be optimistic but not impossible."

Asked how long the third party audits will take, LaViolette said, "We will go to >24 locations and spend about a week more or less in each, but we will do some simultaneously…The caveat is that it remains to be seen whether any quality system emerges needing a change…If one needs a change, then dealing with the audits through the summer…By the end of August we should be complete with the internal assessment and ready to see if there is a red or green light to bring the FDA in. Then, FDA timing is up to them…Unless we are derailed by a new discovery, all should be done in 3Q07."

Taxus

The Boston Scientific message at PCR was the maturity of the Taxus data. Officials were emphasizing the length and breadth of the Taxus program, saying, "Maturity separates the different drug-eluting stent programs." Dr. Baim also claimed

Taxus has an advantage in diabetics (*See page 10*). Dr. Baim stressed that there had been an "incorrect and over-emphasis" on stent thrombosis and COURAGE trial data. Any increased mortality with DES is due predominantly to Cypher, Dr. Baim said.

New labeling is being finalized for Taxus with the FDA, and target availability is June 2007. This includes more data and new, easy-to-read, user friendly reference tables.

Among the new data on Taxus at PCR were:

- **4-year results of the TAXUS-VI trial**, using the moderate-release formulation of paclitaxel (which has not been commercialized). TAXUS-VI was a randomized, double-blind, controlled, international study of 44 patients. At both 3- and 4-years, follow-up was 98.1%. Dr. Eberhard Grube of Germany reported a sustained TLR benefit, a safety profile comparable to a BMS, with low MI, low stent thrombosis, and low death rates. There were no new stent thromboses after two years, and the TLR benefit was durable in this high-risk population.

4-Year TAXUS-VI Results

Measurement	Taxus MR	Control	p-value
TLR	12.9%	21.4%	0.0082
Cardiac death	2.4%	N/A	---
Stent thrombosis	No new ST after 2 years	---	---

- **2-year results of the ARRIVE registry.** The ARRIVE-1 and -2 registries included >7,000 "real-world" patients. A researcher reported that discontinuation of clopidogrel before 6 months is a significant predictor of stent thrombosis at both 1 and 2 years. Information available from 13 of 16 very late stent thrombosis patients (VLST) – stent thrombosis between 12 and 24 months – indicated that 30.8% had discontinued dual antiplatelet therapy within seven days of a VLST event, but failed brachytherapy, chronic total occlusions, prior MI, and age also were factors in VLST. Other statistically significant predictors of stent thrombosis up to one year included long lesions, multiple stents, calcified lesions, small vessels, smoking, and congestive heart failure.

Updated ARRIVE Registry Results

Measurement	ARRIVE-1	All ARRIVE patients (-1 and -2)
On aspirin at 2 years	92.2%	---
On Plavix at 2 years	58.5%	N/A
Stent thrombosis (by ARC definition)	0.7% from 12-24 months	1.0% at 30 days 0.3% from 31-180 days 0.4% from 6-12 months

Boston Scientific is seeking new label indications from the FDA for Taxus in:

- **Small vessels** – already submitted, based on TAXUS-V.
- **In-stent restenosis (ISR)** – already submitted, based on TAXUS-V.
- **Diabetics** – Currently, the diabetes message is directed at markets outside the U.S., but Boston Scientific will seek a U.S. label in diabetics, though officials couldn't predict timing on this. The company also believes there is evidence that paclitaxel "may be a better anti-restenotic than sirolimus in insulin-resistant conditions." Dr. Baim explained, "Smooth muscle cell migration is an indication of anti-restenotic effect…Paclitaxel inhibits migration in normal and in high glucose conditions. Sirolimus does not inhibit smooth muscle cell migration to the same extent in a diabetic-like state (high glucose). At the same time, sirolimus inhibits growth of endothelial cells under high glucose."
- **Acute myocardial infarction (AMI)** – to be submitted based on the HORIZON-AMI trial, the results of which may be reported at TCT 2008. A Boston Scientific official said, "AMI is an area where doctors have backed away from DES, so approval in AMI would increase with positive HORIZON data and possibly a label…We hope to get a label based on the one-year data, which was our original understanding with the FDA."

Promus/Xience

Boston Scientific's goal is to minimalize cannibalization of Taxus and maximize aggregate (Taxus+Promus) sales. LaViolette commented, "Nowhere will you see us maximizing Promus sales." The company appears happy with Promus sales so far, and LaViolette said Promus has convinced them of the value of a two-drug strategy, and they are committed to continuing a two-drug program.

LaViolette said the operating margin for Promus is 30% (compared to 50%+ for Taxus) and vowed to "make it ourselves if there are supply issues," though he said Boston Scientific doesn't want to make Promus itself unless there is no other option.

Future stents

- **Taxus-Petal**, a new dedicated bifurcation stent. First-in-man studies are to start in 3Q07.
- **Taxus-Element**, a new platinum chromium stent that is more radiopaque, using Apex delivery system and having a strut measurement of 0.0032. The pivotal clinical trial (1,200 patients) is to begin "in the next several months." Dr. Baim said, "The IDE is approved and the trial sites selected. We will have an initiation meeting in early July. We will recruit quickly. The design is non-inferiority vs. Taxus Express. The polymer and the drug are the same, just the underlying stent platform is different. Our discussions with the FDA went very smoothly. It is well powered to show all safety endpoints."

- **Promus-Element**, an everolimus-eluting Taxus with an Apex polymer. Boston Scientific officials said this is not expected to be available until 2012, and that they are waiting for FDA guidance for trial requirements. LaViolette said Boston Scientific will be building production lines for Promus-Element, and those could be used to produce Promus if Promus-Element is not ready (approved) by the time the Promus supply deal with Abbott ends. LaViolette also said that Boston Scientific already has one line that could be converted to Promus-Element, and Boston Scientific will have Promus to sell until Promus-Element is available – there will be no off-market time.

  Abbott's requirement to supply Boston Scientific with Promus ends:

  - **U.S.** – on December 31, 2010.
  - **Japan** – one year after marketing approval is granted or on December 31, 2010, whichever is later, but in no event later than June 30, 2012.
  - **Europe** – three years after Boston Scientific got its first commercial shipment of Promus from Abbott (which was about December 2006), so about December 2009, unless Boston Scientific gets a C.E. Mark for Promus before then. If Boston Scientific submits Promus-Element for a C.E. Mark before December 2009, but the company does not yet have the C.E. Mark, it can apply for an extension. LaViolette said he believes European regulators may be open to extending this by another two years (to December 2011), but no later than June 30, 2012.
  - **Rest of the world** – December 31, 2010.

Other programs/products

- **PFO devices.** All officials would say is they have "a couple of investments."
- **Percutaneous valves.** Boston Scientific's biggest investment in this space is in Sadra Medical, but there was no news on that at PCR.

JOHNSON & JOHNSON

The negative news: Before PCR, J&J announced that the pivotal COSTAR-II trial failed to meet its primary endpoint of non-inferiority to Taxus, and, as a result all CoStar development and sales were halted. The data presented at PCR from COSTAR-II explained why J&J abandoned the program; the data were nothing less than a disaster by almost every measure.

However, J&J plans to use the Conor reservoir platform to develop a sirolimus-eluting stent. J&J/Cordis Chief Technology Officer Dr. Campbell Rogers said the company is already making progress with the Conor/sirolimus platform merger, insisting the Conor reservoir system has "unbelievable potential" to deliver sirolimus. He said, "There is more bang for the buck with drug delivery with the reservoir-based platform than with Cypher…We anticipate a first-in-man trial will start early next year, potentially sooner than that." J&J's Anderson added, "We will accelerate efforts in first-in-man and move as quickly as we can, especially based on the early animal data we have…Some of the things we are looking at are not possible in the surface-coated world, as compared to the reservoir world. That is why we are so excited about reservoir technology, because of the possibilities."

Six different Conor/sirolimus formulations have been tested *in vivo*, though Dr. Rogers did not show results from all of these. In the three formulations he did show, there was greater efficiency and programmability with the reservoir-based delivery than with the Cypher comparison.

J&J also has an "active program" underway to develop reservoir-based approaches in the periphery and for orthopedics, ophthalmology, neurovascular, and oncology.

The positive news: Perhaps to take some of the edge off the bad CoStar news, J&J highlighted several new programs:

1. **Percutaneous valve.** Dr. Rogers said this is "an area of tremendous interest," and J&J has an internal program both in aorta replacement and in mitral repair underway, but it also is pursing external partnership opportunities. Asked about challenges in this area, Dr. Rogers said, "IP (intellectual property) and engineering are both issues. Our eyes are wide open…Both are important."
2. **Patent foramen ovale (PFO) closure device.** First-in-man studies have been completed with an over-the-wire (OTW) device, and a C.E. Mark trial will begin in 1H08. It was described as having an extremely small footprint, using left atrial anchors, a tantalum coil for radiopacity, nitinol mesh to promote issue adhesion and to provide an initial barrier to emboli, and will come in a wide range of pocket lengths. Dr. Rogers said the device "lies primarily in the tunnel and promotes healing," with 100% closure at six months. He added, "PFO is waiting for the big shoe to fall on migraine, and we will learn from other (competitor) trials what link may exist, and then we will be well-poised to enter that market."
3. **Inter-J&J cooperative efforts.** J&J/Cordis is trying to leverage expertise in other areas of J&J, especially Ethicon Endosurgery, which makes flexible tubes that Dr. Rogers suggested could be adapted to catheter technology, and BioSense Webster, with its imaging and navigation technology. Anderson said atrial fibrillation (AF) ablation is a big growth marketplace, and BioSense Webster technology can shorten procedures and make the procedures more electrophysiologist-friendly, "We see tremendous opportunities, but there is a lot of clinical work to be done…We'll continue to push forward in this space, which is a clinical unmet need…We think in the future of the EP lab, robotics will very much have a role."

4. **Vascular closure.** The ExoSeal device uses a synthetic, bioabsorbable, polymer (PGA) plug implant, with no sheath exchange. ECLIPSE, the 400-patient, multicenter, non-blinded, randomized, pivotal trial of ExoSeal vs. manual compression, began in April 2007, and >200 patients have been enrolled already. What differentiates it from the many other vascular closure devices? Dr. Rogers said, ExoSeal is "a simple, fast, painless procedure."

5. **Medinol.** J&J has signed an agreement to be the exclusive global distributor for Medinol's latest generation bare metal (stainless steel and cobalt chromium) coronary stents. J&J said the two companies will work together on regulatory approvals, with a C.E. Mark submission for a cobalt chromium stent in 2H07 and a U.S. PMA supplement submission in 1H08. However, Dr. Rogers said there is no ongoing research program with Medinol at this time.

Dr. Rogers also provided an update on other J&J coronary stent programs, including:

- **Cypher Elite** – a sirolimus-eluting Cypher with a new stent design and a new delivery system but the same SurModics polymer. Elite uses a Cypher Select platform with ~130-140 micron struts, which was described as "dramatically thinner than stainless steel by a good chunk." Based on current FDA guidelines, J&J expects an IDE in 2H07 to begin a ~1,750-patient pivotal trial, with a PMA submission in 2H09.
- **Cypher Neo**. J&J is "not moving forward at this time" on Neo. No clinical trials are planned at this time.
- **Cypher NxT**. This has been abandoned completely.
- **Bioabsorbable stent**. J&J officials didn't mention this, and there was no news on this program.

Cypher

Boston Scientific's LaViolette said fractures with Cypher stents are "on the FDA radar screen. It is a growing issue."

Conor's CoStar

Before doctors saw the details of COSTAR-II trial at PCR, there had been some criticism of J&J for abandoning CoStar, but once the results were presented, there was no longer any doubt why J&J took that action. CoStar was simply a disaster in that trial.

COSTAR-II compared the paclitaxel-eluting, cobalt chromium CoStar to Taxus. In that trial, CoStar wasn't a small miss; it missed on almost every measurement, making CoStar look like a bare stent in comparison to Taxus. All three of the global co-principal investigators presented pieces of the data, which showed:

- CoStar had significantly higher 8-month MACE and 9-month late loss than Taxus.
- The differences in 8-month MACE were largely driven by clinically-driven TLR.
- Death, Q-wave MI, and protocol-defined late stent thrombosis were comparable.
- HbA_{1c} <6.5 in the absence of diabetes was ***not*** associated with adverse clinical outcomes.
- In diabetics, outcomes are worse in patients requiring insulin.
- ***A lack of efficacy but not safety*** determined the differential outcome between CoStar and Taxus.

8-Month COSTAR-II Clinical Results

Measurement	CoStar n=972	Taxus n=670	p-value
Primary endpoint: MACE (cardiac death, MI, clinically-driven TVR)	11.0%	6.9%	0.005
Cardiac death	0.5%	0.7%	Nss, 0.541
MI	3.4%	2.4%	Nss, 0.242
Clinically-driven TVR	8.1%	4.3%	0.002
Clinically-driven TLR	6.6%	3.1%	0.002
Secondary endpoint #1: MACE in single vessel	9.7%	6.0%	0.015
Secondary endpoint #2: MACE in multivessel disease	16.6%	9.9%	Nss, 0.085

9-Month COSTAR-II Angiographic Results

Measurement	CoStar	Taxus	p-value
Freedom from MACE to 270 days	91.2%	94.4%	---
Clinically-driven TLR to 270 days	92.2%	96.3%	HR .468
Late loss in-stent	0.64 mm	0.26 mm	<.0001
Late loss in-segment	0.49 mm	0.18 mm	<.001
% DS in-stent	25.3%	12.8%	<.001
% DS in-segment	31.9%	24.0%	<.001
Restenosis in-stent	17.9%	4.1%	<.0001
Restenosis in-segment	18.7%	6.7%	0.0002
Stent thrombosis (protocol defined) at 9 months	0.6%	0.1%	Nss, 0.252

Diabetics in COSTAR-II at 8 Months (32.5% of all patients)

Measurement	CoStar	Taxus	p-value
MACE in all diabetics	14.4%	10.9%	Nss, 0.271
MACE in insulin-dependent diabetics (IDDM)	18.9%	22.5%	Nss, 0.649
MACE in non-insulin-dependent diabetics (NIDDM)	12.7%	7.9%	Nss, 0.157
MI in all diabetics	3.8%	5.2%	Nss, 0.470
MI in IDDM	6.4%	10.0%	Nss, 0.448
MI in NIDDM	3.2%	4.0%	Nss, 0.692
TVR in all diabetics	10.6%	6.3%	N/A
TVR in IDDM	13.5%	15.0%	N/A
TVR in NIDDM	9.5%	4.0%	N/A
In-segment late loss in all diabetics	0.52 mm	0.20 mm	N/A
Restenosis in-stent in all diabetics	16.1%	3.9%	N/A
Restenosis in-segment in all diabetics	16.9%	6.7%	N/A

What went wrong? Among the possible explanations were:

- **Patients.** The difference with CoStar could have been driven by complex patients with multivessel disease and patients undergoing angiographic follow-up. There were more real-world patients in COSTAR-II than other pivotal DES trials.
- **Taxus performance.** Taxus performed better than expected, with a late loss of 0.24 mm, which "is very low."
- **Drug kinetics.** The dose of paclitaxel and the early-release kinetics obviously were not appropriate. J&J's Dr. Rogers pointed out that paclitaxel has a narrow therapeutic index, and only nanograms of the drug were delivered per day with the CoStar formulation. Boston Scientific's Dr. Baim also suggested that the release kinetics were a factor in the failure of the CoStar stent. He said a Boston Scientific study found that the amount of paclitaxel released by CoStar is halfway between that released by Taxus SR and Taxus MR, "But that release curve was obtained in DENA (an organic solvent), and when we try to duplicate that in PBS (saline), we get a very different (faster) elution profile (with CoStar), so it is not really a surprise the results didn't match Taxus."
- **Stent design.** While J&J and most experts believe the reservoir design is not to blame, one source suggested the naked stent between the wells could have been a factor.
- **Manufacturing variability.** This could have been a factor, and a Conor official said they are looking into that, but noted, "Manufacturing variability has steadily improved over the last three years, so the variations and tolerances we started with tightened considerably."

There were also rumors at PCR that there have been fractures in the CoStar. J&J officials would neither confirm nor deny this. All they would say is they still need to look at the data.

Despite the findings of COSTAR-II, there is still interest in the results of the EUROSTAR-II trial. That trial comparing CoStar to BMS has been completed but not reported yet. A German doctor said, "There was no reason to withdraw CoStar from the market. I've had several patients who could get a CoStar when a Taxus didn't work. I still expect CoStar to outperform a BMS."

MEDTRONIC'S Endeavor

The zotarolimus-eluting Endeavor stent was submitted to the FDA in November 2006, and Medtronic is waiting for a date for the Advisory Committee meeting and for approval. At this point, a panel is unlikely before September or October 2007. Part of the delay was due to internal FDA review delays caused by the stent thrombosis panel in December 2006. The FDA had some questions for Medtronic, and the company has answered them.

However, the FDA now is ***requiring*** the full ENDEAVOR-IV dataset. ENDEAVOR-IV is finished but not unblinded, and Medtronic expects to give that data to the FDA in July 2007. A Medtronic official said, "The FDA would like to see it and be sure it met the primary endpoint." The official said that, at the request of the FDA, the ENDEAVOR-IV data will ***not*** be made public before the Advisory Committee meeting. That is, it won't be presented at a meeting or announced by press release, "The FDA does not want investigators to know the results until Endeavor goes to panel." A final FDA decision is expected 30-45 days after the advisory committee meeting, which should translate into approval in late 4Q07.

Boston Scientific's Dr. Baim challenged the competitiveness of Endeavor, saying the release kinetics "would seem to be too rapid, which is why Medtronic is working on Endeavor Resolute." He also disputed Medtronic's claim that there is little or no stent thrombosis with Endeavor, pointing out that "7 events in the first 30 days is 'unusual,' and 6 stent thromboses per 1,300 lesions (which translates to 0.5%, which is very comparable to Cypher and Taxus) is expected…but 8 stent thrombosis per 55 patients (1.4%) for BMS seems high…In Year 2 with <1,000 patients followed, what can we say about 1 per 1,000? This is not robust evidence. We need more data, especially comparing Endeavor to Cypher to tell us if there is a difference in stent thrombosis."

Medtronic officials were very upbeat about the outlook for the ENDEAVOR-IV trial, but an official commented that even if the trial were to fail, Medtronic wouldn't abandon the Endeavor program. Even some competitors were predicting that trial will meet its primary endpoint (TVF measured post-angiography). Dr. Baim said Taxus consistently demonstrates a TVR of 4%-5% and a TVF of 7%-8% in trials, and that is what he expects in ENDEAVOR-IV. Dr. Baim commented, "I wouldn't bet on ENDEAVOR-IV…I wouldn't bet against Taxus either." Boston Scientific's LaViolette added, "Endeavor is a very deliverable stent, and it is perceived by the marketplace more positively for deliverability than any other clinical attribute…Highly deliverable stents tend to find their way into very challenging cases in the real world…The most important piece of information the marketplace is looking for is how Endeavor performs in the real world…I think that will dwarf any outcome in a controlled trial…I would focus on what you are hearing about real-world performance."

Long-term data

Dr. Andreas Zeiher of Germany presented long-term data on two Endeavor trials, concluding, "Endeavor is associated with sustained and low clinical event rates in both trials. It is associated with an excellent safety profile and no late stent thrombosis in either study, which is quite remarkable. Driver, as a bare comparator, was also associated with stable long-term clinical results…These data...are extremely encouraging."

- **4-year data was presented from ENDEAVOR-I.** There were no additional MIs, no additional stent thrombosis (after the one case at 10 days), no additional TLR or TVR after Year 3. TLR event-free survival at 4 years was 96.9%.
- **3-year data were presented on ENDEAVOR-II.** The TLR and event-free survival curves plateau at about 1 year, but MACE and event-free survival curves separate early and continue to diverge over 3 years. TVF curves separate early and continue to diverge.

3-Year Results of ENDEAVOR-II Trial

Measurement	Endeavor	Bare Driver	p-value
Follow-up	96.5%	96.7%	Nss
Cardiac death	3.3%	4.5%	Nss
MI	3.3%	4.3%	Nss
Q-wave MI	0.3%	1.0%	Nss
Non-Q-wave MI	2.9%	3.3%	Nss
Stent thrombosis	0.5%	1.2%	Nss
TLR	7.3%	14.7%	<.001
TVR (not TL)	2.9%	4.8%	Nss
MACE	12.0%	20.7%	<.001
TVF	12.8%	21.4%	<.001

Endeavor Resolute

Endeavor Resolute is a zotarolimus-eluting Driver stent with a new BioLinx polymer. Nine-month angiographic and IVUS results of the 130-patient RESOLUTE trial were presented at PCR, and the trial found low 30-day and 9-month procedure-related MACE, with no stent thrombosis. The company said the findings justify continued development, and Resolute is aimed at: small vessels, long lesions, and diabetics. A Medtronic official said the company has already filed for a C.E. Mark for Resolute.

9-Month Results of RESOLUTE Trial

Measurement	Resolute
Diabetics	17.7%
Current smokers	22.3%
Device success	99.2%
Procedure success	96.2%
Average lesion length	15.49 mm
Primary endpoint: In-stent late loss	0.22 mm
In-segment late loss	0.12 mm
Secondary endpoint: 9-month MACE	7.0%
Non-Q-wave MI	4%
TVR	0
Stent thrombosis	0
Incomplete apposition (IA)	7 persistent 4 resolved 2 late

XTENT'S Custom NX Bifurcation Stent

Six-month results of the 100-patient CUSTOM-II trial of this biolimus-eluting stent were presented at PCR. The MACE and restenosis rates looked good, considering the complex nature of these patients. The discussant commented, "Whether this approach offers an advantage is yet to be seen."

A source said the FDA wants 12-month TVF data, with angiography after the clinical TVF follow-up, 2,000 patients, and 24-month follow-up on a subset of patients (~100-200).

Asked about this potential competitor to the Boston Scientific bifurcation program (Taxus-Petal), LaViolette said all the Xtent stents (in Europe) are being placed on consignment. He called them "not a big deal," adding, "They sound nice, but I can't get there."

6-Month Results of CUSTOM-II Trial

Measurement	Custom NX in long lesions (<20 mm) n=69	Custom NX in 2 lesions n=31
MI	4 patients	0
TLR	1 patient	3 patients
MACE (cardiac-related death, any MI, clinically-driven TLR)	6 patients	3 patients
% DS	14.9%	2.6%
MACE	9%	
Late loss in-stent	0.31 mm	
Late loss in-segment	0.22 mm	
Restenosis	7.5%	

DIABETICS

Boston Scientific was claiming that data show its Taxus stent is superior to other DES in diabetics, and it was a strong marketing message, supported somewhat by a U.S. meta-analysis. But competitors weren't conceding the diabetics to Taxus.

Abbott took exception to the Taxus claims, issuing a statement pointing out that in the SPIRIT-II diabetic subset analysis Xience V was shown "to be more effective than Taxus in diabetics, with in-stent late loss at 6 months of 0.15 mm for Xience vs. 0.39 mm for Taxus."

Johnson & Johnson also got some ammunition for its Cypher counter-marketing efforts from a Swiss meta-analysis and an analysis of diabetic patients in the ARTS-II trial.

- **UCSD meta-analysis.** A meta-analysis by Dr. Ehtisham Mahumud of the University of California, San Diego, which examined diabetics in 11 randomized clinical trials and 16 registries with >11,000 patients found:
  - Single digit revascularization rates in diabetics treated with DES, which an expert called "surprisingly good."
  - No significant difference in stent thrombosis between Cypher and Taxus.

- Similar TLR/TVR and MACE with Taxus and Cypher in randomized clinical trials (RCTs) and all analyzed registries.
- A non-significant trend to lower TVR and MACE with Taxus in registries reporting use of both Cypher and Taxus.

Meta-Analysis of DES in Diabetics

Measurement	Taxus	Cypher
All diabetics n RCTs		
TLR	9%	7.8%
MACE	15.5%	12.9%
Stent thrombosis	0.64%	0.39%
Diabetics treated with DES in RCTs		
TLR	8.0%	8.9%
MACE	16.2%	13.8%
Stent thrombosis	0.6%	0.78%
Diabetics treated with DES in registries		
TVR	5.8%	7.2%
MACE	10.1%	11.9%
8 registries with >5,000 patients		
TVR	Odds ratio in favor of Taxus 0.77 (Nss, p=0.15)	---
MACE	Odds ratio in favor of Taxus 0.83 (Nss, p=0.056)	---

➢ **ARTS-II.** 3-year follow-up in a 159-patient diabetic subset of ARTS-II found stent thrombosis rates were not related to diabetic status – there was no difference in stent thrombosis in diabetic and non-diabetic patients. ARTS-II, sponsored by Johnson & Johnson, was a randomized, multicenter, single-arm trial in 1,205 patients with multivessel disease, comparing Cypher to the results of CABG and BMS in the ARTS-I trial. Researchers also reported that, despite a higher risk profile, the overall MACCE rate for diabetic patients in ARTS-II was lower with Cypher than with BMS patients in ARTS-I and not significantly different from CABG patients in ARTS-I.

ARTS Trial Results

Measurement	Cypher in ARTS-II at 3 years n=159	ARTS-I CABG n=96	ARTS-I PCI n=112
Overall			
Diabetics	26%	16%	19%
3-vessel disease	54%	30%	27%
Stented lesions	3.2	3.8	2.5
Average stent length	72 mm	---	48 mm
Diabetics			
Number of patients	159 patients	96 patients	112 patients
MACCE at 3 years	***Secondary endpoint:*** 27.7% (Nss vs. ARTS-I CABG, p=0.10) (p<.001 vs. ARTS-I PCI)	17.7%	47.3%

Other ARTS-II Results

Measurement	Cypher	CABG	ARTS-I BMS
Freedom from MACCE at 3 years	80.6% (p<.001 vs. ARTS-I BMS)	83.8%	66.0%
Definite stent thrombosis at 30 days	1.3% (p=0.018 vs. ARTS-I BMS)	---	7.1%
Stent thrombosis at 3 years (ARC definitions)	3.3% definite 5.3% definite/probable 6.4% definite/probable/possible	---	Not tracked

➢ **Swiss meta-analysis.** Dr. Bernard Meier of Switzerland presented his independent meta-analysis of 18,023 patients in 38 trials, comparing Cypher, Taxus, and bare metal stents. The study found Cypher was better than Taxus in diabetics, death, MI, and stent thrombosis.

Swiss DES Meta-Analysis

Measurement	Cypher vs. BMS	Taxus vs. BMS	Cypher vs. Taxus
MI	HR 0.81	HR 1.00	HR 0.83
Early stent thrombosis	HR 0.95	HR 1.01	HR 0.98
Late stent thrombosis	HR 1.09	HR 2.84	HR 0.37
TLR	HR 0.30	HR 0.42	HR 0.70
Probability of being best			
	Cypher	**Taxus**	**BMS**
Death overall	46.0%	28.7%	25.3%
Cardiac death	25.7%	30.7%	43.6%
MI	96.6%	~0.5%	~1.0%
Death or MI	75.7%	11.1%	13.2%
Early stent thrombosis	49.7%	24%	26.3%
Late stent thrombosis	45.9%	0	54.1%
TLR	99.9%	0	0

PERCUTANEOUS VALVES

AORTIC VALVES

There are many points on which surgeons and interventional cardiologists disagree with respect to percutaneous valves, but one thing on which they appear to agree: ***percutaneous valves are the future***. Sources agreed that adoption may initially be very slow and limited to Centers of Excellence, first in Europe, and then in the U.S. Several U.S. sources predicted that the FDA would put training requirements on its approval, similar to what it requires for carotid stenting. They also predicted that CMS may further limit reimbursement to a limited number of sites, along the lines of what it does with left ventricular assist devices (LVADs).

Yet, sources also believe that a slow, limited, and controlled roll-out of this technology is important to its success. Comments included:

- *Spain:* "I don't plan to get involved yet. It's too early. It requires experienced teams."

- *Germany:* "We have a waiting list of 60 patients. Patient acceptance of this technology is unbelievable. Now it is up to reimbursement – and taking a measured approach."
- *Switzerland:* "I think only a few Centers of Excellence should be established in Europe. We don't have the volume to justify a center in Switzerland yet. I'd like to refer patients to a center in Paris."
- *Canada:* "There is no doubt in my mind that AVR will be a percutaneous procedure within three years…It will be standard-of-care because it is easier to do."
- *U.S.:* "I hope use is limited to Centers of Excellence because everyone is opening a cath lab today."

The two companies in the lead in aortic valve replacement are CoreValve and Edwards LifeSciences, and sources all agreed that both are likely to succeed, that they are not, at this time, really competitive, but there are at least 12 other companies with aortic valves in development. However, most sources agreed that a hospital will probably choose one brand or the other, not offer both CoreValve and Edwards valves. An expert said, "They are both very good devices. It is not that one is better than the other. I can't say one is better than the other. I just don't see a significant difference between the two." A U.S. doctor said, "CoreValve is more deliverable. If it were up to me, I'd use the CoreValve."

Outside of clinical trials, experts estimated that a typical European center, once trained, should be able to do 30-50 procedures a year. This was a pretty consistent estimate. U.S. investigators estimated 50-100 patients a year, depending on the size of the facility.

CoreValve's ReValving System. This is ahead in Europe since it was the first percutaneous aortic valve to get a C.E. Mark – and that came just days before PCR. CoreValve is charging €15,000 for its valve, and an official claimed to be "halfway through reimbursement in Europe." The company has said it will not immediately market the ReValving System, but will do an expanded clinical evaluation at a small number of select international sites. At PCR, company officials insisted they will do a "slow market release, in certain countries and with certain operators, to be sure it is used correctly…We want the experienced people to start…It is really for the very skilled operator." In one year, they expect to have trained operators in more than a dozen countries and are projecting sales of 1,000 valves. All patients will be put in a mandatory registry that the company hopes to use in support of its U.S. application.

CoreValve has the smallest delivery system (18F). It currently offers only a transfemoral approach and is focusing on interventional cardiologists. Yet, the company is developing a transapical approach, though that is still in animal testing, but it is ready to start human testing with a 21F size. An expert explained, "Now, it has to pass through the valve, and you have to push instead of pulling, so they wouldn't do an 18F yet…But I'm happy with a 21F or even a 23F transapically."

A CoreValve official said the company is about to submit an IDE for a U.S. feasibility study in 20 patients at three sites (La Jolla, New York, and Chicago) with 6-month follow-up. An expert said, "CoreValve needs to get 'Big Company' support for its clinical program…That hasn't happened yet because the big companies don't want to make a mistake. They are willing to pay more to buy after there are more data."

CoreValve also is planning for its U.S. pivotal trial, and Dr. Maurice Buchbinder of La Jolla CA will be the principal investigator. The FDA is expected to allow 15-20 sites to participate in the pivotal trial, "The problem is 57 sites want to be in the trial, so we will be in a difficult position choosing sites." The CoreValve official said the company would like the design of the pivotal trial to be: randomizing patients either to ReValving or surgery, with patients in the surgical arm who don't quality for surgery getting balloon valvulo-plasty (with the possibility of crossover to ReValving), followed by medical therapy (also with the possibility of crossover to ReValving). He doubts the FDA will approve that design. More likely, he admitted, the FDA will require a trial design similar to the one Edwards is using. Dr. Buchbinder said the FDA wants an STS score of 12 or 13 (which he said was equivalent to a EuroScore of ~20) as an entry criteria, not just a EuroScore. He said, that worries him "because if you

Results with 3rd Generation CoreValve Aortic Valve

Measurement	CoreValve	
Age	81.9	
EuroScore	21.4	
Procedure time	129 minutes	
30-day mortality	14.7% overall 19.6% for first 51 patients 9.8% for next 51 patients	
Peri-procedure MACE	15 patients: 4 tamponade 4 tamponade + valve misplacement 3 valve misplacement 2 coronary impairment 2 abdominal hemorrhage	
Per-procedure mortality	1 tamponade, 1 MI	
In-hospital major complications	14.7% 30-day mortality 3% conversion to surgery 8% stroke/TIA	
Comparison of on- and off-pump patients at 30 days		
	On-pump n=23	**Off-pump n=79**
EuroScore	24.1	20.5
Mortality	22%	11%
Conversion to surgery	9%	1%
Stroke/TIA	13%	6%
6-month follow-up (n=88 discharged without complications)		
Death	3 patients (none device-related)	
MI, stroke, MACE	0	

include near-death patients, the outcome won't be as good." He said another detail with the FDA is the technical data on the nitinol stent used in the ReValving System. He added, "We hope to get started by the end of the year."

CoreValve has a third-generation device in development, and the C.E. Mark trial is complete for that. Dr. Raoul Bonan of Canada, a CoreValve investigator, reported on the results with 102 patients. Most post-procedure paravalvular leaks were Grade 0-I: 33% 0, 47% I, 17% II, and 2% III/IV.

EDWARDS' Sapien THV valve. Edwards is hoping for a C.E. Mark this year for this valve, and it is ahead in the U.S., where a pivotal trial is due to begin next month. Edwards has two active aortic programs underway, both using the same Sapien valve:

- **Transfemoral placement** with the RetroFlex delivery system.
- **Transapical placement** with the Ascendra delivery system. Dr. Pieter Kappetein, a surgeon from the Netherlands, said his most recent transapical Sapien procedure took just 45 minutes. He said the advantages to this approach are: no vascular trauma, no crossing the aortic arch, no plaque disruption, and short catheters. The disadvantages are that some general anesthesia is still needed, though some experts are suggesting it might be able to be done under local anesthesia.

  Dr. Thomas Walther, a German surgeon, said, "Since February 2006, we've done 61 transapicals. On average, patients had a EuroScore of 27.8, an STS score of 15.9, and were NYHA Class III/IV. Thirty-day mortality was 0.6%, and mortality at follow-up was 15.3% (only one a valve-related cause)…There were 3 surgical conversions, and 1 re-operation during follow-up. There were no strokes, which is impressive…Our current practice is to do them off-pump…We've had one valve dislocation. Overall survival at 30 days was 93%, while the EuroScore predicted 27.8%."

Both approaches are likely to find usage. An expert said, "We have two procedures (transapical and transfemoral), which give us more options for patients. We should keep in mind there is no competition between the two…The transfemoral approach provides interventional cardiologists with a technique for high risk patients, and the transapical approach provides surgeons with a technique for high risk patients." Another said, "It is too early to compare transapical and transfemoral. Superiority of one over the other is very, very, very premature." A third expert said, "There is a tiny indication of an increased risk of neurological complications with the transfemoral approach, just a slight indication." However, while some surgeons are learning to do both approaches, interventional cardiologists are limited to the transfemoral approach.

So far, Edwards percutaneous valves have been implanted in ~400 patients worldwide. An Edwards official said, "This is no longer a procedure that can be done only by Dr. Alain Cribier or Dr. John Webb." Dr. Webb said more than 120 patients have gotten percutaneous valves at his center in Vancouver, Canada, including 35 with the transfemoral approach, and he offered data on 84 of these patients:

- 9.5% failures overall, a little over half (5%) due to failure to cross, but procedure rates improved with experience.
- 11% mortality at 30 days.
- 4% clinical stroke.

Edwards pivotal aortic trials

- **PARTNER-EU.** This European, multicenter, single arm, prospective registry of 125 consecutive patients, is expected to take about 18 months to enroll.
- **PARTNER-US.** This 18-site, U.S., multicenter trial will enroll 600 high risk, symptomatic AS patients. The Retro-Flex delivery system for the Sapien will be incorporated into the trial over the next few months. The trial has started enrollment, and Edwards expects to have 3 U.S. sites actively enrolling initially. The trial is expected to take 18 months to enroll and is divided into two parts, each with two arms, each reportedly powered so that FDA approval could be based on either part alone; both parts are not required to be finished or successful for approval.
  - **Part 1: Non-operable candidates**, who will be randomized to either medical management (which can include balloon valvuloplasty) or a Sapien valve. This is a non-inferiority trial of 350 patients. The primary endpoint is all-cause mortality at one year. The decision on whether or not a patient is a surgical candidate is up to the surgeon.
  - **Part 2: Operable candidates**, who will be randomized to either surgical AVR or a Sapien valve. This is a superiority trial of 250 patients. The primary endpoint is all-cause mortality at one year. Dr. Michael Mack, a cardio-thoracic surgeon from Dallas TX, predicted that this trial will have trouble enrolling patients. He said his hospital had 65 patients referred for participation in a percutaneous aortic valve trial between August 2006 and March 2007, and of the 52 who have completed evaluation: 7 were eligible for randomization, 8 got a transapical valve, 8 had conventional surgery, 8 died, 8 were turned down or excluded for some reason, 9 declined participation, and 4 had a transfemoral procedure performed. Dr. Mack said, "I think this is a significant problem… The FDA is aware of the problem. I think the bar is too high right now (for surgery). The higher the bar, the more problems with patient co-morbidity. The bar needs to be lowered. Using an STS score of 15 is only 4% of all valve patients." He said he is backlogged with patients wanting to get in the trial, but they don't qualify.

An Edwards official said the company is still working with the FDA on if and how it can incorporate transapical procedures into the PARTNER trials. He said they thought they could do that without changing the size of the trial, but that has not been worked out yet with the FDA.

Training

Both companies also plan a low, systematic roll-out of their valve, and they are establishing training sites. Yet, this may take time. And there may be adjustment issues for interventional cardiologists who are not accustomed to having their patients die during a procedure – and mortality is not insubstantial with valve patients.

➢ **CoreValve.** Officials estimated that interventional cardiologists will need 15 procedures to be sufficiently trained, with a maximum of three cases a day. Their estimate is that they can get 13 doctors trained in the next six months, but they explained that they always train two doctors from each site – a team: one to position and one to release. Right now, CoreValve has two European trainers: Dr. Jean-Claude LaBorde in Toulouse, France, who has committed to doing training every other week, and Dr. Ulrich Gerckens in Germany, who will be doing training "a few days a month." The company is looking for more trainers, but it will take time to get them up to speed.

A CoreValve investigator who has done >20 procedures said he doesn't yet feel comfortable to be a trainer. He wants to do at least another 20 procedures and another six months first. He also stressed the difficulty of patient selection, saying that even once the technical aspects are mastered, choosing patients takes practice.

➢ **Edwards.** Officials estimated that a doctor will be sufficiently trained with 8 procedures, which is surprising since the CoreValve device is considered less technically challenging, and CoreValve believes doctors need almost twice that much training. Edwards has more investigative sites in Europe than CoreValve, but it is not clear how many are sufficiently experienced and willing to be trainers. Edwards' training starts with didactic lectures and video cases, followed by simulator practice, and then live patients with a proctor. An Edwards official said that, at least for the foreseeable future, there will be a company person in every operating room or cath lab for every procedure. Edwards' goal is to have 15 sites up and running in Europe by the time it gets its C.E. Mark, and then those sites would become the training sites for other doctors. Edwards officials would not estimate how many patients they think will be done in the first year after approval.

Issues

Experts emphasized factors that are necessary for successful percutaneous valve implantation:

- **Technique.**
- **Experience.** A speaker said, "This is not an easy procedure with pretty tough visualization. Our device (Edwards' Sapien valve) is pretty small and elegant, but that makes it more difficult to see."
- **Good valves.** Most experts agree that CoreValve's smaller sheaths (18F) are better. Although Edwards' valve is larger, users reported success with their 23F approach, and the company said it is working on a 21F design. An official said, "Our view is that it is a strong stent and frame that will lead to a long-term durable device…We also want to reduce the profile but not without maintaining the effect…We believe we can reduce the profile …but we are happy with the current device."
- **Patient selection.** Dr. Kappetein said the typical transapical valve patient today is 85-years-old with severe aortic stenosis, prior CABG, a EuroScore of 44, and an STS score of 21. Another expert said, "We tell transfemoral patients that if it doesn't work, they will die. We don't take them (percutaneous failures) to surgery any more." Dr. Buchbinder said candidates for an 18F transfemoral CoreValve should have a EuroScore ≥15 age ≥65, no excessive tortuosity, mild-to-moderate calcification, no stenotic lesions, an iliac/femoral diameter >6.0 mm, a 20-23 mm annulus, and careful aortic arch assessment."

Among the questions doctors had about percutaneous valves were:

- *How many patients are considered inoperable, thus candidates for percutaneous valves?* Surgeons generally claim they don't deny surgery to anyone, while interventional cardiologists believe there are a lot of patients, particularly older patients with comorbidities, who are denied surgery and would benefit from percutaneous valves.
- *What is the 2-year survival without aortic valve replacement?* A speaker suggested it is ~30%.
- *How accurate are echocardiography measures of the annulus?* Not very, according to Dr. Carlos Ruiz of New York, a CoreValve investigator. He said, "Echocardiographers will jump on me, but we found as much as a 3 mm - 4 mm difference between echo measurements and CT measurements. At present, we are conducting a study with Dr. Grube on CT imaging pre-implantation of the CoreValve. The data are not finalized yet, but I think you will be surprised how much variability there is in the measurement of the annulus. And I think we should get the size of annulus before doing valvuloplasty. We don't like to oversize by more than 10%, so I would be very careful oversizing more than 10%." A surgeon warned, "Many of you (interventional cardiologists) are no longer trained in echo...We need echo-guided cardiologists."
- *Is there any risk of damaging the leaflets of the percutaneous valve if you post-dilate?* Dr. Ruiz said, "Theoretically, I think so...But so far the Edwards data (with post-implantation dilatation) doesn't seem to have

an impact on the relatively short longevity of experience we have with their valve. For CoreValve, I think the same applied…Time will tell if it is safe or not."

- *What should be done if the percutaneous valve is misplaced? Should it be retrieved or implanted into the descending aorta?* Dr. Ruiz said, "I would be very concerned leaving the extra valve outside of where it was supposed to be deployed. If you can safely retrieve it, that would be my first choice. But…it may be very hard to try to retrieve, and you may not be able to retrieve it. Then, there is no choice but to leave it…In one case, I put it too low, and we had no option, and we put a second valve within the first prosthesis."

- *Should cardiac assistance or rapid pacing be used to decrease cardiac output during post-dilatation?* Dr. Ruiz said neither is usually necessary with CoreValve's third-generation, 18F device, "It is incredibly flexible, very friendly, and if you have experience, you can deploy it safely without any cardiac assist or pacing. But I think there is still some room for cardiac assist devices like the (CardiacAssist) TandemHeart in patients with very depressed LVEF…So, no, you don't need it except perhaps in a very few cases."

- *What is the stroke rate with percutaneous valves?* Speakers agreed that the stroke risk with a transapical approach is zero but 8%-10% with the transfemoral approach.

- *What antiplatelet therapy is needed?* Generally, Plavix (Sanofi-Aventis, clopidogrel) is started the day before the procedure, with no loading dose, and continued for one year post-procedure.

- *What should be done about concomitant coronary artery disease?* Experts said they would recommend stenting in a separate procedure a couple of weeks before the percutaneous valve procedure, but Dr. Grube said he has done a case where he stented first and then put in a valve during the same procedure, though he doesn't recommend that.

- *Should balloon dilatation be done post-surgery to reduce regurgitation?* Dr. Bonan said balloon dilation is only done to ease deployment of the prosthesis, not to prevent regurgitation, "When you have a paravalvular leak, we do it to expand the prosthesis more rapidly rather than waiting on temperature to expand the nitinol. We saw that paravalvular leaks may almost disappear in a day or two, so we have a tendency not to re-dilate."

- *How durable are the devices?* Dr. Webb said, "Most of the time, stent fractures are not clinically important, but over time that may be more important in terms of restenosis…We haven't seen any stent fractures, but long-term follow-up is an issue, especially with self-expanding nitinol valves (CoreValve), which may have a slightly greater risk of fractures."

Among the progress that has been made with percutaneous aortic valves is:

- Cardio-pulmonary support is usually not needed any longer.
- Procedure time has improved.
- Patients and doctors both like the results. Dr. Grube, who has done quite a few percutaneous valves, said, "If you are present when this technique is applied and see how fast and smooth it goes, you are impressed, and it is a very gratifying procedure."

Dr. Mack urged interventional cardiologists and surgeons to work together in hybrid operating rooms. He said that, for a surgeon doing <22 aortic valve replacements a year, the average mortality is 8.7%, "so there is an opportunity to improve these results by taking higher risk patients and treating them with catheter-based approaches."

Dr. Mack also offered several predictions, including:

- A hybrid specialty would develop – the surgeon-interventionalist. Surgeons are increasingly getting cross-trained in catheter-based procedures.
- Surgical valve volumes actually will go up initially with the approval of percutaneous valves.
- At least 4-5 of the 14 aortic valves in development will make it to clinical reality.
- The patient age for tissue valve replacements will go down because percutaneous valves will be able to be used for a second procedure in these patients.

Aortic Valve Comparison

Feature	JenaValve	CoreValve's ReValving	Edwards' Sapien
Valve type	Self-expanding nitinol	Self-expanding nitinol	Balloon expanding
Anchor	To the original valve	In the aorta ascendens	By pressure within the original valve
Advantages	Relatively short stent Repositionable High flexibility	Ease of implantation Small sheath	Simple system High flexibility
Disadvantages	Unknown	Incorrect positioning possible Passively anchored Little flexibility Lack of long-term results	Incorrect positional possible Passively anchored Not suitable in case of aortic insufficiency
Status	Starting human trials in late 2007	C.E. Mark	Submitted for C.E. Mark Enrollment has started in U.S. pivotal trial
Catheter size	20F	18F	23F

*** Source: JenaValve and PCR speakers**

- There will be a shift away from mechanical to tissue valves.
- The smaller the valve delivery systems, the more likely they are to be done transfemorally. "If they stay large, they will mandate a higher degree of surgical involvement."
- Percutaneous valves have to last a significant amount of time – close to the 12+ years with tissue valves. Dr. Friedrich Mohr of Germany agreed, "Edwards is guaranteeing only 5 years (with its percutaneous aortic valve), so I don't think it is ethical to put that in a 65-year-old patient and consider it a lifetime valve."
- Percutaneous valve safety doesn't need to be as effective as surgical replacement, but it has to be close to it, and paravalvular leak needs to be minimal, and an appropriate patient population needs to be defined – and continuously redefined.

SORIN. A surgeon said Sorin's percutaneous aortic valve looks very good and bears watching, but there was no news about it at PCR. A Sorin official said the animal research is finished, and one patient has been done transapically.

JENAVALVE. The one new aortic valve that was getting some attention at PCR was the JenaValve by a private company called JenaValve. The JenaValve has three features: a nitinol stent, a biological valve, and a delivery system that features an interesting repositioning and fixation mechanism. A JenaValve official said the valve can be implanted by either a transapical or transfemoral approach. He said the key feature differentiating it from Edwards and CoreValve is the 3-feeler tip. So far, this has been tested only in animals.

MITRAL VALVES

There were sessions on mitral valves as well at PCR, but they are not included in this report. However, Edwards announced that it has discontinued its Mobius mitral repair program. Edwards is continuing its Monarc mitral program, and it is transferring resources from Mobius to Monarc, which an official described as "promising."

MISCELLANEOUS

Intravascular ultrasound (IVUS). Sources generally agreed that there isn't likely to be an up tick in IVUS use. A source said, "Those who do use IVUS are using it more, but the average guy isn't interested in it." Another source said, "The average doctor finds it hard to link this with their procedures. People are either established IVUS users or not." A third doctor cited four reasons IVUS is not growing, in this order:

1. **Lack of being convinced.** Doctors see images they don't understand.
2. **Convenience.** IVUS takes time, and it is an extra step.
3. **Outcomes.** There is no evidence that using IVUS affects patient outcomes.
4. **Cost.**

PFO Closure. NMT Medical said its MIST-II trial in migraine patients has started enrolling patients, but none had yet been implanted. More than a year after the key findings from MIST-I were presented (at ACC 2006), the details still have not been presented anywhere, but an investigator said they are being reviewed for publication.

FUTURE DATA

European Society of Cardiology 2008:

- SYNTAX trial of CABG vs. Taxus primary endpoint data. Enrollment finished in April 2007.

TCT 2007:

- The ENDEAVOR-IV data will *not* be presented as was expected unless the FDA advisory panel has already been held.
- 12-month data from "every single" patient in the RESILIENT-I and -II trials of Edwards LifeStent in peripheral arteries (SFA) will be presented.
- Data from the BEACON trial, an all-comers trial with Biosensors' BioMatrix DES.

American College of Cardiology 2008:

- Biosensors' LEADER European trial of the BioMatrix, which is fully enrolled with ~1,700 patients.

TCT 2008:

- HORIZON-AMI one-year data on Taxus in acute MI.

2008 (meeting unknown):

- NMT Medical should report the results of MIST-III, which is a 148-patient, two-year follow-up of the MIST-I trial of PFO closure for migraines.

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