# Trends-in-Medicine

**June 2009**

*by Lynne Peterson*


## SUMMARY

Percutaneous aortic valves was the hot topic at PCR. Experts predicted the European explosion in these procedures will continue. The concern is minimizing off-label use. ♦ A SYNTAVI trial is being discussed to compare percutaneous aortic valves with surgery. ♦ A 51% 1-year mortality rate with transapical implantation of Edwards Lifesciences' Sapien is concerning, but most doctors blamed that on patient selection. However, new data on CoreValve's subclavian approach led some doctors to suggest tiering valve procedures in this order: transfemoral, subclavian, transapical, surgical. ♦ There was little excitement among European cardiologists about Evalve's MitraClip mitral repair, though the data looked good, because the technology is not considered mature yet, the cost is high, and reimbursement remains a problem. ♦ The first data on J&J's new drug-eluting stent, Nevo, looked good – beating Boston Scientific's Taxus on late loss – but experts insisted this was not a surprise, the data are very preliminary, and deliverability could not be determined from the RES-I trial.




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## EUROPCR

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Despite the recession, attendance at PCR in 2009 was fairly comparable to last year, though there appeared to be fewer U.S. doctors at the meeting, and ~500 people from Asia/Pacific and South America canceled at the last minute due to concerns about the H1N1 (swine) flu. For the most part, the news was incremental, but a huge shift in focus was evident – from drug-eluting stents (DES) to percutaneous valves, particularly aortic valves.

There were several new features to the meeting this year, and all of them seemed to be well received.

- **EuroPCR-in-a-box.** More than 500 people around the world were able to watch EuroPCR through direct transmission.
- **Live-in-a-box cases.** Pre-recorded cases were presented with a discussion by a live panel that had not previously screened the video. Organizers said that once a case was chosen for a live-in-a-box presentation, it would be shown, whether it was successful or not, and any postop complications would be recorded as well and included. There were no failed procedures in the live-in-a-box presentations this year, but there was a case that had a couple of complications. The audience appeared to like this style – not to the exclusion of live cases but as an addition to them.
- **Oral abstracts.** There was a large number of submissions, and the sessions were extremely well attended. At this point, there are no plans for poster boards at future PCR meetings.

## PERCUTANEOUS AORTIC VALVES

In 2004, four patients had transcatheter aortic valve implantation (TAVI as it is now being called in Europe), last year it was 4,500 patients, and the forecast for 2009 is 12,500 patients or more. In the U.S., the TAVI ramp is expected to be even faster – unless the FDA and/or the Centers for Medicare and Medicaid Services (CMS) put training or center of excellence roadblocks in the way à la artificial disk, carotid stenting, or LVADs. One way to avoid these regulator-imposed restrictions would be for one of the companies to propose a risk evaluation and mitigation strategy (REMS) to the FDA that limits use, and a Medtronic/CoreValve official said his company is considering doing just that – perhaps limiting training to 75 new sites each year.

*Will this growth trajectory continue?* Experts agreed it will. Dr. Patrick Serruys of the Netherlands said, "We see patients asking for it more and more…There is great enthusiasm among physicians. The less invasive nature is the driving force,

and you can't stop that…There are a lot of candidates. There are still at least 200 hospitals on the waiting list (for training) …There are 600,000 patients waiting, and the surgeons are doing their best with 60,000, so there is a ratio of 1:10 of unmet need."

In France, for example, use is currently limited to 250 patients for the first six months of 2009, then 600 procedures a year will be allowed for three years, Dr. Gerard Fournial, a French cardiac surgeon, explained. Thus, about 5% of French patients will get TAVI and 95% surgery (12,000 surgical valves/year). He said, "European key leaders are worried about TAVI adoption going too fast – that that would kill the therapy."

A speaker at a symposium sponsored by Edwards Lifesciences, estimated that ~40% of aortic valve patients are left alone, and about 15%-20% are the high-risk patients currently being considered for TAVI. Last year, surgical valve replacements increased 20%, and the speaker said, "That is most certainly these patients flooding in and getting surgery." A U.S. doctor said, "We also need to educate the referring doctors…Hopefully, as we evolve this technology, we will not let patients get so far gone – too frail, too old – that I'm not sure any technology will help them." A U.K. cardiologist agreed, "We all seem to receive referrals (specifically) for a TAVI, and the patient is often programmed for that…We have written to our referring physicians asking them not to tell patients they are referring them for TAVI, just for assessment of their valve."

In this environment, valve pricing appears to be holding fairly steady.

Interventional cardiologists and cardiac surgeons joined together at PCR to deliver four messages that were repeated over and over – that TAVI:

1. Needs to be performed by multidisciplinary teams.
2. Ideally should be done in a hybrid cath lab/operating room. Not all cardiologists believe that this is necessary, but many do – and most cardiac surgeons said they do not believe a regular cardiac cath lab is sufficiently sterile. A U.K. doctor said, "As much as we would like a hybrid, we do procedures in our cath lab, and it works well." A Spanish doctor said, "Hybrids are coming, and they will change the organization of the hospital." A French doctor said, "A hybrid is futuristic, but there is only one in France."
3. Requires very careful patient selection. A French cardiac surgeon said, "The most important thing for TAVI is patient selection, and that is not the work of one person. It is a question of a heart team."
4. Should be done ***on-label***, at least for now.

Dr. Serruys has suggested a SYNTAVI trial like the SYNTAX trial, comparing TAVI to surgery. The idea appeals to doctors, but industry reportedly is not enthusiastic. Dr. Serruys said, "We are thinking of that trial…and then you have to introduce a new score (as the Syntax score was developed for that trial)…which includes the eyeballing of patients."

He said a group of 7 surgeons and 7 interventional cardiologists have already met to discuss the idea of a SYNTAVI trial before approaching industry, "That meeting took place in Frankfurt, and a few things emerged. We'll see if we are able to pursue it. There are 2 big contenders – Edwards and CoreValve…We have to…provide health authorities with some serious data on what we can achieve with surgery, medical therapy, and percutaneous treatment. It is really connected to the concept of reimbursement. And the community wants to know exactly what is going on. This explosion of percutaneous treatment, at some point, has to be controlled. Even today the numbers in the registry are without source documentation…In the hospital there is package payment for all we do. Right now there is nothing for percutaneous valves – and the price is ~20,000 euros. Where are you going to find the money? Someone has to say the treatment is justified, and we have to do a trial to do that…We are talking about a randomized trial now…but something serious in Europe will take another 2-3 years to get started."

Medtronic/CoreValve continues to dominate TAVI in Europe, with use driven by interventional cardiologists, while two-thirds of Edwards Lifesciences' valves are used by cardiac surgeons. Both companies offer the transfemoral (TF) systems preferred by interventional cardiologists. Edwards transapical approach (TA) has been favored by cardiac surgeons, but CoreValve has developed a subclavian/axial approach that some experts predicted would challenge TA.

There was nothing in the data at PCR that is likely to change the growth trajectory for TAVI, but there may be a slight shift from Edwards to CoreValve. Cardiac surgeons cited several reasons for a preference for Edwards valves:

- Familiarity with the company's surgical tissue valves.
- The TA approach.
- Fear of a start-up company (CoreValve). This issue may resolve since Medtronic bought CoreValve, and Medtronic is another big surgical tissue valve supplier.
- Concern about fractures and lack of long-term data on the CoreValve system.

The key issues with percutaneous valves remain: mortality, vascular complications, and patient selection. A speaker said, "Mortality is a big issue. Patients need to survive the procedure and to live more than one year if we want to make this a cost-effective procedure." Dr. Fournial added, "There are a lot of differences between the two makers, and at medium follow-up I expect some very bad surprises…The TAVI designs are so different from tissue valves that I'm really not sure of the long-term outcomes, of the durability, so we cannot recommend TAVI for young people."

*How do doctors choose between CoreValve's ReValving System and Edwards Lifesciences' Sapien?* Several factors affect this including:

- **Device availability.**
- **Training availability.**
- **Doctor preferences.**
- **Who is performing the procedure** (surgeon or interventional cardiologist).
- **Annulus size.** The choice of a valve also is determined by the size of the patient's annulus. If the annulus is ≥25 mm, doctors agreed that a CoreValve device is better.
- **Valve delivery system.** The valve delivery systems continue to get smaller. CoreValve has had an 18 Fr catheter, and Edwards showed the first glimpse of performance with its 18 Fr catheter at PCR. Dr. John Webb of Canada, a Sapien investigator, said, "18 and lower Fr will become routine. CoreValve has had it for a while…and it is a superb system. Edwards (now) has the NovaFlex (formerly called the RetroFlex 4) delivery system."

Dr. Carlos Ruiz, director of the Structural and Congenital Heart Disease program at Lenox Hill Hospital in New York, said, "It doesn't matter who does percutaneous valves – just that someone does. Let the center decide who does it best." Dr. Fournial prefers Edwards valves. He explained, "I'm more confident with Edwards because of their experience. Medtronic will give credibility to CoreValve now. Medtronic will be more careful on development. But it is not just an issue of durability; it was a conflict with the surgical community as well. Medtronic is not interested in fighting with surgeons. The principal argument against CoreValve is the design. You have a high pacemaker need because the stent is too heavy and probably pushes too hard on the heart structure, the material is controversial, and so I'm afraid of the durability…Interventional cardiologists prefer CoreValve because it is easier to do…The problem with both of them is that there is no transparency. The registries are not complete. We need randomized clinical trials."

A number of heart centers use both CoreValve and Edwards valves, and that is likely to increase since each device has its advantages and disadvantages. The mortality data on Sapien from PARTNER-EU and SOURCE were in line with expectations for TF, but 50% one-year transapical mortality was making some interventional cardiologists and surgeons skittish. The mortality data on CoreValve's subclavian approach was much better, and some experts at PCR were saying there is likely to be a shift from TA to subclavian. Since Edwards says that two-thirds of its European sales are TA, that could translate to a slowdown in Sapien and give CoreValve some added impetus.

Dr. Webb said TAVI procedure time has come down and is typically <45 minutes. Thirty-day mortality also has fallen, but doctors should expect complications, though the rate is falling, "Complications are going to happen. You might as well admit it…Be prepared for arterial injury."

There was a ***controversy*** at PCR involving valves. The patient chosen for a CoreValve live case from Madrid was deemed "inappropriate" by the panel of experts discussing the case as well as by other experts. Rather, according to experts, the patient clearly should have gone to surgery. The moderator said, "We saw two live cases (in this session)…Technically, they were very successful, but there was…quite a lot of worry among the panel around the fact that the indications to the procedure are moving in a somehow uncontrolled fashion. I think it is important for us and for the good introduction of this technology that the rules of the game are respected and that trials are started to answer the question whether or not such patients should be treated… Maybe we will conclude that patients like the one in the first live case (the CoreValve case) should be treated with TAVI. The fact is we don't know yet, and it is certainly wrong to introduce this as habit." Another expert said, "The case raised ethical questions…EuroPCR stands for credibility. It is clear that TAVI is going to move to patients who today are surgical patients, but we have to do it in a structured way. There is tremendous off-label use of DES, but that technology is mature."

EuroPCR officials were very concerned about this case, and they said it will be discussed at the post-PCR meeting in June. Upon review, if the case did not meet the PCR criteria, what will happen? At a minimum, the case will not appear on the EuroPCR website, and there will be a report at next year's PCR about the outcome with this patient.

### BOSTON SCIENTIFIC

The company doesn't have a percutaneous valve program yet, though it has an investment in Sadra Medical, which is developing a valve. CEO James Tobin said it's too early to get into that market, "My thinking is the cases being done today are refractory cases – patients who will die unless they are treated. So, 70% success means you save 70% of people who were going to die, and the 30% who die may die a few months sooner than they would have. That is a pretty good trade-off, but it isn't a business. It is not a billion dollar market. To be a billion or more market, you need to do other cases, and you need to have more hands involved than the 20 or so people doing it now…For that to happen, you need to have a delivery system that gives you a second chance – repositioning. My belief is that the current products are very good attempts for first generation products…***but*** for this to be a market, you need a repositionable product, so you can treat less sick people with a lot more doctors with less good hands, or you don't have a business…Or, it will cap off way before it should…I'm waiting for a product that will address the product I want to be part of rather than becoming enamored of this refractory market…I'm waiting on Sadra. They have delivery system issues…and we are helping them with it. They were in denial for a long time…and finally they asked for help."

## EDWARDS LIFESCIENCES' Sapien

➢ **PARTNER-EU.** This 130-patient, single-arm, non-randomized study was conducted in 2007, prior to the European launch of Sapien. One-year data have been presented before, but at PCR there were more patients with one-year data. In the latest analysis of TA patients from 7 of 9 sites and TF patients from 4 of 9 sites (none with more than 10 patients in either approach), presented by Dr. Volker Schächinger of Germany, the 1-year mortality rate in transfemoral patients was 22%, which is the lowest 1-year mortality rate seen yet. However, the 1-year mortality rate in transapical patients was 51. At six months, mortality was 45% (later revised to 42%).

*Is 50% mortality so high that TA use may decrease?* Though there is a potential threat from CoreValve's subclavian approach, the mortality rate does not appear to be discouraging doctors already doing TA or doctors considering starting TAVI. Doctors interviewed at PCR insisted that the high mortality is related to patient selection and that comparing TA and TF mortality is not appropriate, but some experts suggested a pause may be needed until the reason for the high mortality is determined.

Comments on TA mortality included:

- *Cardiac surgeon:* "We are operating on rather select patients (with TA)…so the EuroScore is significantly different. TA patients are higher risk…So, at this moment, I think it is an acceptable rate of mortality."
- *Interventional cardiologist:* "I think 50% mortality is unacceptable."
- *Dr. Serruys:* "Fifty percent mortality with TA implies a time of reflection...This is innovative medicine, and if you have a problem, you have to understand why it happened – not to stop prematurely a technology that is certainly going to change medicine, but you have to find out why it happened and then go forward…If you've seen the procedure, it is not a trivial procedure."
- *Dr. P. Kolh, a cardiac surgeon:* "These are registries, so you can't compare one approach to another approach. Usually, the patients with TA were very high-risk patients …but those complications need to be addressed…We need to go into the data and see what can be improved before going forward."
- *German interventional cardiologist:* "I don't believe TA should be diminishing because it is a good procedure. TA can stand up if similar sick patients are included."

➢ **SOURCE** is a post-approval registry of 1,038 consecutive patients in 34 countries. Only 2 sites have implanted <10 valves in this study. SOURCE showed a 30-day mortality rate of 6.3% in TF patients and 10.3% in TA patients (an improvement from 11.6% previously). Dr. Martyn Thomas of Guys Hospital in London said the study found:

- Technical proficiency "can be learned and adapted readily."
- Vascular complications are no longer a predictor of TF mortality.
- The stroke rate is similar for TF and TA.
- TA patients were higher risk patients than TF patients.

**Updated 12-Month Results of PARTNER-EU**

| Measurement | Sapien TF n=61 | Sapien TA n=69 |
|---|---|---|
| **Procedural results** | | |
| Mean deployment time | 30.7 minutes | 11.4 minutes |
| Mean total procedure time | 145.3 minutes | 153.3 minutes |
| Device success | 91% | 91% |
| Time to hospital discharge (median) | 8 days | 11 days |
| Total ICU days | 3.3 | 5.7 |
| Aborted implants | 9.8% | 5.8% |
| Additional intervention required | 3.3% | 4.3% |
| Peri-procedural mortality (Day 0) | 3.2% | 5.8% |
| **30-day outcomes** | | |
| ***Primary endpoint #1:*** 30-day survival | 92.5% | 81% |
| Death | 8.5% | 18.8% |
| Stroke | 3.2% | 2.9% |
| MI | 1.6% | 4.3% |
| Valve embolization | 3.2% | 1.4% |
| New pacemaker | 1.6% | 4.4% |
| Vascular complications | 26.0% | 2.9% |
| Bleeding events | 0 | 8.5% |
| **6-month outcomes** | | |
| ***Primary endpoint #2:*** 6-month survival | 90% | 58% |
| Arrhythmias requiring a pacemaker | 2% | 7% |
| **1-year outcomes** | | |
| ***Secondary endpoinr:*** NYHA improvement at 12 months | 60% | |
| 1-year survival | 78% | 50% |
| 1-year freedom from MI | 96% | 94% |
| 1-year freedom from stroke | 93% | 94% |
| **Deaths** | | |
| Early deaths (≤30 days) | 5 patients | 13 patients |
| Late deaths (>30 days to 1 year) | 10 patients | 22 patients |
| Total deaths | 25% | 51% |

**Comparison of TF and TA Patients in PARTNER-EU**

| Baseline | Sapien TF n=61 | Sapien TA n=69 | p-value |
|---|---|---|---|
| EuroScore | 25.7 | 33.8 | N/A |
| STS score | 11.3 | 11.8 | N/A |
| Coronary artery disease | 54% | 65% | Nss |
| Mitral disease | ~42% | ~65% | 0.02 |
| Peripheral vascular disease | ~20% | ~53% | <0.0001 |
| Prior CABG | ~25% | ~45% | 0.008 |
| Carotid disease | ~15% | ~35% | 0.008 |
| Prior pacemaker | ~10% | ~23% | 0.04 |
| Systemic hypertension | 70% | 77% | Nss |
| Pulmonary disease | 49% | 35% | N/A |
| Renal failure | 36% | 46% | N/A |

Dr. Marty Leon of Columbia University Medical Center in New York, noted, "People tend to minimize post-procedure care. Not an insignificant number of patients required dialysis in SOURCE."

**30-Day Results of SOURCE Registry**

| Measurement | Sapien TF n=463 | Sapien TA n=575 |
|---|---|---|
| **Baseline characteristics** | | |
| EuroScore | 25.7 | 29.2 |
| Peripheral artery disease | 10.9% | 27.5% |
| Carotid artery stenosis >50% | 7.6% | 17.1% |
| Porcelain aorta | 4.6% | 11.5% |
| Prior CABG | 17.6% | 26.9% |
| Mitral valve disease | 16.1% | 32.8% |
| **Procedural results** | | |
| Acute procedure success | 95.6% | 92.9% |
| Valve migration | 0 | 0.5% |
| Valve malposition | 1.7% | 1.4% |
| Device success | 92.4% | 90.8% |
| Time to hospital discharge (median) | 8 days | 11 days |
| **30-day results** | | |
| Freedom from death | 93.7% | 89.6% |
| Freedom from stroke | 97.6% | 97.4% |
| Freedom from MI | 99.8% | 99.3% |
| Perforation or damage to vessels, myocardium, valvular structures | 17.9% | 17.1% |
| Renal failure requiring dialysis | 5.0% | 11.7% |
| Permanent pacemaker | 6.7% | 7.3% |
| Vascular complications | 10.6% | 2.43% |
| **30-day survival by EuroScore** | | |
| EuroScore <20 | 94.6% | 93.4% |
| EuroScore >20 | 93.3% | 88.1% |
| **30-day survival by vascular/access complications** | | |
| No complications | 94.1% | 90.7% |
| Vascular complications | 92.2% | 72.7% * |
| Major vascular complications | 88.6% | 61.1% |

*** 7 of the 14 patients (50%) with vascular/access complications died; while 52 of 561 patients (9%) of patients without complications died.**

➢ **PREVAIL-TA.** This is the next registry to be performed with the latest Edwards device. It will test whether vascular complications and mortality can be reduced through by a combination of training and reduced catheter device size.

➢ **PARTNER-US.** Dr. Leon, the co-principal investigator in this trial, said ~700 patients will be enrolled in Cohort A, with enrollment expected to be completed by the end of this year. Enrollment in Cohort B was completed March 16, 2009. Many of the U.S. sites have implanted >100 patients.

Dr. Leon said, "We are slightly ahead of schedule in terms of enrollment." The PARTNER-US executive committee meets for about a half day every other month.

But this trial may not tell doctors as much as they would like. Dr. Peter de Jaegere, an interventional cardiologist from the Thoraxcenter at Erasmus Medical Center in the Netherlands, commented, "PARTNER-US will be obsolete when it is done." Dr. Serruys agreed, "PARTNER-US is something more or less imposed by the FDA…But it will be very strict and on a specific device, and we are afraid it will quickly be outdated."

After U.S. approval, Dr. Leon noted that there will still be challenges, "This is not for all cath labs." The challenges include:

- Physician training and restricted access considerations. He commented that the Edwards and CoreValve training centers are very comprehensive with very, very intense interdisciplinary training – a "complex training program."
- Milieu considerations (e.g., hybrid cath labs).
- Iterative and next generation devices.
- Staying on-label.
- Managing reimbursement and economics.

Over the next five years Dr. Leon predicted:

- Changes in technology will be incremental and not transformational.
- The transition to a workhorse treatment of choice will be a work in progress.
- Patient preference and cost/availability issues should not have an impact but probably will.
- There will be "roadblocks and surprises."
- Hopefully, there will be surgeon acceptance.

Other information on the Edwards TAVI program included:

➢ **Sapien XT**, the next generation valve. This is expected to be on the European market in 2010. It has a cobalt chromium frame, Perimount-like bovine scallop leaflets and will come in four sizes: 20 mm, 23 mm, 26 mm, and 29 mm – and both a smaller and a larger size. It is being paired with a new delivery system, NovaFlex.

➢ **Training.** Dr. Leon said, "TA has helped us work more closely with our surgical colleagues…In Europe, 125 centers were trained at the end of 1Q09, with at least 2 cardiac surgeons completely trained per site (for >250 surgeons). As of the end of 2008, 950 TF cases and 1,550 TA cases had been done. In the U.S. the interventional cardiologist and the surgical principal investigators are present at every site by FDA requirement. Already 50 cardiac surgeons have been trained, so surgeon involvement is already happening."

➢ **Expanded indications.** Dr. Webb said that Sapien is being used off-label in pulmonary, mitral, and tricuspid procedures, "The company cannot do too much about that, but the data from centers using it in different loca-

tions need to be collected and shared with other users because we are confronted with inoperable patients, and this is a nice solution."

*Asked what the mode of failure of TAVI will be*, a German surgeon said, "I don't think it will be different from other pericardial (tissue) valves…If it deteriorates, that will probably be by becoming stiffer and slowly becoming stenotic …If it fails, repair would be pretty straightforward."

## MEDTRONIC/COREVALVE's ReValving System

Medtronic's acquisition of CoreValve does not appear to have had any negative impact on the adoption of CoreValve's aortic valves. Cardiologists said they haven't seen any changes, but a CoreValve official noted that command and control has become less concentrated. On the other hand, he said Medtronic researchers have been more help than expected.

The news at PCR is the long-term follow-up on the 18 Fr patients from the ongoing, expanded registry. A CoreValve official said the company is talking to a "select group" about what to do post that registry – perhaps a new randomized clinical trial that is tightly controlled to look at very specific parameters.

Dr. Lutz Buellesfeld of Germany reported on safety and performance results using 18 Fr valves. He said CoreValve is now being used in 26 countries at 151 centers, up from 17 countries and 59 centers a year ago. The total number of patients was 3,529 in April 2009, up from 763 last April. A 126-patient, prospective, multicenter, non-randomized, single-arm observational study in patients ≥age 75 found:

- 18 Fr demonstrated both safety and efficacy out to 12 months.
- Acute procedural and short-term results were affected by learning curve bias, so acute results "probably do not reflect the presently achievable outcomes."
- Complications were mainly peri-procedural and in the first 30 days, whereas late mortality appears to be related to comorbidities.

Dr. Jean-Claude Laborde of France reported on 79 cases from 13 countries and 41 centers that used CoreValve's subclavian approach in a registry. He said a lot of patients had porcelain aortas, and procedure time was a little longer than for TF. He called the stroke results a "little disappointing." He concluded, "When the femoral artery is inadequate, there are enough data to consider the subclavian access, which is feasible, safe, and effective…If this encouraging data can be reproduced in a large number, then I think subclavian will probably replace TA and have a major role in the future, even in patients with femoral access available."

**Long-Term Follow-Up on CoreValve Patients**

| Measurement | Hospital discharge | 30 days | 12 months |
|---|---|---|---|
| Death all-cause | 15.2% | 15.2% | 28.6% |
| Cardiac death | 10.7% | 10.7% | 17.0% |
| Stroke | 6.3% | 6.3% | 7.1% |
| MI | --- | 3.6% | 3.6% |
| MACE | --- | 25.0% | 26.8% |
| Permanent pacemaker | --- | 23.2% | 26.9% |
| Freedom from all-cause mortality | --- | 70.9% | ~70% |

➢ The advantage of the subclavian approach are:

- Safety of implantation.
- Less cardiac death.
- Fewer cardiac perforation.
- Less conversion to surgery.
- Fewer valve-in-valve procedures.
- Fewer bleeding complications.

**Registry Data on the Subclavian Approach**

| Measurement | Subclavian |
|---|---|
| **Baseline** | |
| Mean age | 81 |
| EuroScore | 28.2 |
| NYHA Class III-IV | 75.6% |
| LVEF | 49.6% |
| **Results** | |
| Procedural success | 100% |
| Mean procedure time | 168.7 minutes |
| 24-hour survival | 100% |
| Discharged alive and well | 93.0% |

**More Registry Data on the Subclavian Approach**

| Measurement | Subclavian n=79 | TF comparison n=148 |
|---|---|---|
| **24-hour results** | | |
| All-cause mortality | 0 | 2.4% |
| Cardiac death | 0 | 1.8% |
| Aortic dissection | 0 | 0.7% |
| Cardiac tamponade | 1% | 3% |
| Access site bleeding | 1% | 0.6% |
| Major bleeding | 1.3% | 5% |
| Conversion to surgery | 0 | 0.4% |
| MI | 0 | 0.9% |
| Major arrhythmia | 8.9% | 5.6% |
| Pacemaker | 10.1% | 7.2% |
| Stroke | 2.5% | 1.1% |
| **30-day results** | | |
| All-cause mortality | 9.4% | 10.3% |
| Cardiac death | 5.7% | 6.7% |
| Tamponade | 1.9% | 3.6% |
| Access site bleeding | 1.9% | 2.9% |
| Major bleeding | 3.8% | 6.9% |
| Pacemaker | 37.5% | 25.0% |
| Stroke | 3.8% | 2.2% |
| MI | 0 | 0.9% |
| Conversion to surgery | 0 | 0.4% |

- Pacemakers can be implanted at the same time – "treat the valve, place the pacemaker, and close."
- The unknowns are:
  - Access complications, which need to be analyzed in a longer series of patients.
  - Neurological events. However, he believes this will not be a problem.

*What is going on with the FDA?* A CoreValve official said, "We are making an enormous amount of progress."

*Asked about Edwards new 18 Fr delivery system*, an official said, "Our cone is 18 Fr, and the rest is 12 Fr. Edwards entire catheter is 18 Fr, which is more challenging. Our 18 Fr delivery system holds both size valves. Edwards system only holds the smallest valve – and Edwards still requires a cut-down for the large valve."

*What's next for CoreValve?* An official said, "A 31 mm valve delivered with an 18 Fr delivery system."

The need for pacemakers and FDA concern about possible nitinol fractures are the two issues confronting CoreValve. An official said, "We have to live with the pacing rumors until we do a study on where the patients come from. It's a lot of noise. But because our frame is longer, it does increase the possible need for a pacemaker." An Italian cardiologist said, "A 23% rate of pacemakers is a major issue but a minor problem. A VVI pacer is only 1,000 euros. If you wait to implant a pacemaker, patients have to stay in the hospital longer, so in case of uncertainty, it is better to implant the pacemaker…In Italy, 4 centers are doing Edwards, and 21 centers are doing CoreValve."

### TA vs. subclavian

Dr. Serruys called the subclavian approach better than TA at this point, "When TF came, initially the company on top was Edwards, which is a surgical company…I perceived a certain moment of destabilization of that company when it started something percutaneously. I remember some surgeons being irritated that a surgical company was providing interventional cardiologists with a percutaneous instrument. Then, they made a move which is very smart to use the PARTNER word for everything they are doing…and saying they had approaches for both the surgeon and the cardiologist...and the approach for the surgeon was fully justified. There was clearly a case where there is no access in the femoral artery…but it is not simple, and I think maybe the subclavian might be a more elegant and less traumatizing approach. I think you will see more and more subclavian approach because that is very well done…It is not always possible to do subclavian, but personally I think subclavian will be a good alternative. The TA could come back once the introducer is smaller. The (TA) valve is 32 Fr, and that is, for us, a monster. It is ***so*** big. 18 Fr is what we like, and 32 Fr is almost a doubling."

Other doctors – interventional cardiologists and cardiac surgeons – agreed that the choice between TA and subclavian will be made by the multidisciplinary team if both devices are available. And several sources said the availability of subclavian devices may encourage more centers to get trained on both company's devices. Comments included:

- *A cardiac surgeon whose group has done 5 TAs and 3 subclavian valves:* "It is an institutional (team) decision."
- *Dr. de Jaegere, an interventional cardiologist:* "The first preference is TF, and if a patient can't have that, we would go first to subclavian, and then if that is not possible to TA…This is an institutional decision. TF is most the feasible, most technically easy to perform…The reason subclavian would be chosen before TA is the invasive nature of TA…Basically, it is the gradient of invasiveness (that guides the choice)…TF is least, then subclavian, then TA, followed by surgical."
- *Dr. Webb, an Edwards investigator:* "I think (subclavian) has a real future for patients…It is really looking very good. Subclavian is an alternative to TA. It still potentially might turn out to be first-line, but probably not …I'm sure you'll see the two vying, and I can't say which will win out."
- *Dr. Thomas Walther, a German cardiac surgeon:* "I fear that with subclavian sometimes there is a 90 degree angle, and if there is a tear to the subclavian artery, this could be a major problem."
- *Dr. Kolh, a cardiac surgeon:* "(If TA patients didn't get a procedure), 100% would die at 1-2 years…but because we have a new technique doesn't mean we should propose it to everyone."
- *Dr. Philipp Bonhoeffer, U.K.:* "It is not fair to compare TA to subclavian because the patient populations are not the same, and the operators were not the same…Some people prefer subclavian, and there is a trend to move to that even if the contraindications for TF are not really met."
- *Dr. Olaf Franzen of Germany:* "Initially, I thought TA would be better for younger patients, but actually it is more beneficial in elderly patients because of pain control."
- *Germany:* "TA is very elegant, but we do it when we can't do TF. TA is still more invasive than TF."
- *France:* "It's completely wrong to compare the results of one technique to another."

## MITRAL VALVE REPAIR

Mitral regurgitation (MR) is the most common type of heart valve insufficiency in Europe and the U.S., affecting >8 million people, with >600,000 new cases diagnosed each year. Most of these people have functional MR, and only ~20% have a surgical repair.

### EVALVE's MitraClip

A session on MitraClip was very poorly attended; it was clear the focus at PCR was on TAVI, not mitral repair.

On May 14, 2009, Evalve announced that 14 centers in 5 European countries have performed MitraClip procedures, implanting a total of 100 devices with a 93% implant success rate. MitraClip received a C.E. Mark in March 2008, and Evalve began selling the device in September 2008. Enrollment in a pivotal trial, REALISM, is underway in the U.S. and Canada.

However, interventional cardiologists and surgeons questioned at PCR were not enthusiastic about the device or procedure. They insisted the technology is not yet "mature," the device is expensive, and reimbursement is a limiting factor. Among the comments were:

- *Netherlands:* "None of the percutaneous mitral technologies is really mature enough. It is a very evolving field, but we are planning to launch a program…most likely next year rather than this year…to build our infrastructure. Then, by the time it matures, we will be ready. But we aren't going to do MitraClip. The Evalve concept is great, but it has been tested in only 400-500 patients… These technologies still need to be evaluated in academic research centers…My forecast is that mitral valve disease will be accessible by percutaneous techniques, but the technologies are not mature yet, and as time goes on, you will see improvements in the technology."
- *Italy #1:* "MitraClip is expensive, and we have to pay for it out of our research budget. We've done about 10 so far. It won't catch on without reimbursement."
- *Italy #2:* "The technique is still very complex, and there is a long learning curve. It can be done in an hour, but some cases take 2 hours. We did one patient in 35 minutes without general anesthesia. Use will increase. Only two centers in Italy are currently doing MitraClip. Evalve doesn't have any Italian suppliers; they just sell direct. There are economic and logistical issues that prevent our doing more in Italy. The risk with reimbursement is too high to want to do too many. It needs to be reimbursed in a comprehensive program."
- *Greece:* "We aren't doing any MitraClip because we need to learn other things first, because of cath lab capacity, and because the technology is not mature enough yet."
- *Germany:* "Reimbursement is an issue. The government has approved it, but it still has to come out of our budget, and that hasn't been increased."

Dr. Franzen, who was described as being very experienced with MitraClip for heart failure, reported on his results with 37 patients:

- 81% were sicker than the patients in the EVEREST trial: The average age was 70, the average EuroScore was 29, and the average STS score was 15. All were NYHA Class III (45%) or Class IV (55%).
- Most patients had a reduction of 2 grades in heart failure. He said, "To me, this is an indication there is some remodeling going on…On discharge, 70% were NYHA Class 1-2, and at 3 months 82% were Class 1-2…What is very interesting is we have patients who are 'super-responders.' What I see in these patients is they had ischemic cardiomyopathy and had preserved basal contractility. We need to look closely at that in the future."
- 5 had a CRT implant.
- Average device time was 106 minutes.
- Five patients received two clips.
- 91% implant success.
- Complications were minimal, with no in-hospital mortality. Three patients died within 2 months of the procedure, but those were determined not related to the device.

The ACCESS-Europe registry started in April 2009 and is expected to complete enrollment this year. Dr. Franzen said it is mainly health economic data, but clinical data also will be gathered, and the purpose is to enable patient selection decision-making. MitraClip patients will be compared to surgically managed patients with MR. Doctors have to do five procedures before they can enroll patients in this registry.

He said the EVEREST-II trial in 239 patients is fully enrolled and that data will be presented later this year or early in 2010. Dr. Saibal Kar of Cedars-Sinai Medical Center in Los Angeles, probably the most experienced MitraClip user, presented 12-month results from the EVEREST-II High-Risk Registry of 78 patients, showing improved symptomatic status and cardiac function and a reduced rate of hospitalization for congestive heart failure (CHF) in both functional mitral regurgitation (FMR) and degenerative mitral regurgitation (DMR) patients. Implant success was 96%, with 46% of patients getting one clip, 2.6% partial clip detachments, and no clip embolizations.

*Asked how patients are selected for MitraClip*, Dr. Franzen said, "It will be referral from heart failure specialists who tell us they tried everything else. If they say there is nothing they can do medically any more, then we think it over, and, if there is no indication for CRT, then we think of a clip. Then, we discuss if the patient should have surgery or a clip, but for most severe heart failure patients there is no thinking of surgery." Dr. Kar added, "This...is such a safe procedure… The reason I categorize patients into FMR and DMR cate-

gories…is because there is still a concern about what to do for younger patients…This is an extremely safe procedure. It is clearly safer than open-heart surgery."

*Asked if the procedure time is improving*, a speaker said, "It is less of a problem for FMR patients. It is a strong concern for DMR patients, where we know surgery in low-risk patients can be managed with excellent long-term results…For FMR patients, there is still discussion in the surgical community whether replacement or repair should be done…(But) I think main discussion will be to identify the patients who will get reverse remodeling…The bar, the threshold, is going down."

**12-Month Results of EVEREST-II High-Risk Registry of MitraClip**

| Measurement | FMR patients n=46 | DMR patients n=32 |
|---|---|---|
| Baseline NYHA Class 1-2 | 9% | 15% |
| 12-month NYHA Class 1-2 | 74% | 75% |
| CHF hospitalization | 55% * | |
| Predicted mortality | 18.2% | |
| 30-day mortality | 7.7% | |
| MACE | 20% | |
| Stroke | 0 | |
| Renal failure, permanent AF, ventilator | 1 each | |
| Transfusions ≥2 units | 11 patients | |
| Freedom from death at 30 days | 74% | |
| MR ≤2 at 30 days | 82% | |
| MR ≤2 at 12 months | 79% | |

*** Significantly lower than the year prior to therapy.**

### JENAVALVE

The company is developing both transfemoral and transapical approaches for a repositionable and retrievable nitinol valve with a unique clip-based anchoring mechanism. A speaker called this "very, very exciting" and said it is ready to start first-in-man in the next few months.

### New percutaneous aortic valves on the horizon

- **ATS/3f's Enable.** This nitinol, tubular design is a sutureless, surgically implantable valve. A C.E. Mark trial was done in 100 patients, and the results are pending.
- **Cordynamics' 1HT.** A speaker said this monolithic, porcine, sutureless valve with a 21 Fr delivery system, "is a very interesting concept…This has potential."
- **Direct Flow Medical's Percutaneous Aortic Valve (PAV).** This is a conformable, stentless valve with a non-metallic cuff. It is repositionable and retrievable. A first-in-man and prospective, multicenter trial of 50 patients at 4 centers had begun, and 31 patients were enrolled as of May 1, 2009. So far, 4.5% of patients have required a pacemaker, and 4.5% have had a stroke. 18 of 22 patients were discharged alive, with 94.4% 6-month survival.
- **Endoluminal Technology Research's Paniagua.** The first implant of this nitinol, self-centering valve was done in 2003, and none since. The company is "still refining" their valve.
- **Hansen Medical's AorTx.** After an initial 8 cases, the company is "refining" the technology.
- **Heart Leaflet Technology.** This is a nitinol, self-centering valve. Eight first-in-man valves were implanted (2 at 21 mm, 5 at 23 mm, 1 at 25 mm) in Italy.

**Aortic Valves in Development**

| Company | Valve | Characteristics | Status |
|---|---|---|---|
| ATS/3f | Enable | Nitinol, tubal design, sutureless | Trial completed for C.E. Mark with results pending |
| Cordynamics | 1HT | Monolithic, sutureless, porcine valve with 21 Fr delivery system | N/A |
| Direct Flow Medical | PAV | Conformable, stentless valve with non-metallic cuff, repositionable and retrievable | 31 of 50 patients enrolled in prospective trial |
| Endoluminal Technology Research | Paniagua | Nitinol, self-centering | First implant in 2003 and none since |
| Hansen Medical | AorTx | --- | 8 cases done, now being refined |
| Heart Leaflet Technology | --- | Nitinol, self-centering | 8 first-in-man implanted in Italy |
| JenaValve | --- | TA and TF approach, nitinol, clip-based anchoring mechanism, repositionable and retrievable | First-in-man to start in next few months |
| Johnson & Johnson | Bailey-Palmaz | Nitinol cage with nitinol leaflets | Not tested in humans yet, but good animal results at 10 days |
| Lutter | --- | Uses patient's own tissue | --- |
| Medtronic/Ventor | Embracer | Nitinol frame | 11-patient first-in-man trial was 100% successful |
| Sadra Medical | Lotus | Nitinol, self-centering, and retrievable | 10 patients in European feasibility study |
| Sorin | Perceval | Nitinol frame, self-expandable | No humans yet |

- **JenaValve.** The company is developing both transapical and transfemoral approaches for a retrievable and repositionable nitinol valve with a unique clip-based anchoring mechanism. A speaker called this "very, very exciting," and first-in-man studies will start in the next few months.
- **Johnson & Johnson's Bailey-Palmaz.** This nitinol valve cage with nitinol leaflets has not been tested in humans yet. Animal studies showed endothelialization in 10 days.
- **Lutter Tissue Engineering.** A speaker called this valve, which uses a patient's own tissue, "one of the most appealing concepts."
- **Medtronic/Ventor's Embracer.** This has a nitinol frame. A first-in-man trial in 11 patients was reportedly 100% successful, though there were 2 postop deaths (one at 4 days and one at 7 days).
- **Sadra Medical's Lotus.** This is a nitinol, self-centering valve that is repositionable and retrievable. An 18-19 Fr is being launched. A speaker called it "a very creative device." A European feasibility study enrolled 10 patients, and 6 had successful implants, with one patient dying from sudden death. Boston Scientific has invested in this company.
- **Sorin's Perceval.** This has a nitinol panel frame and is self-expandable. It does not appear to have been implanted in any humans yet.

## DRUG-ELUTING STENTS (DES)

European cardiologists said DES is holding fairly steady vs. bare metal stents (BMS), and they expect that to continue over the next 6-12 months. Boston Scientific's Tobin estimated that in Europe Abbott's Xience V currently has >30% market share, Promus ~12%, Taxus ~20%, or a total Boston Scientific share of ~32%. When Taxus Element and Promus Element are launched, Tobin is expecting Taxus Element to keep the Taxus share at ~20% but Promus Element to take the Promus share to 12%-15%, for a total Boston Scientific share of 32%-35%.

Cardiologists said Xience/Promus is still gaining a little market share, mostly at the expense of Taxus.

### Syntax score

The Syntax score – a measure to help decide if patients should undergo CABG or PCI – was formally launched at PCR. Asked how it will be used, Dr. William Wijns of Belgium, past president of EuroPCR, said it is likely to encourage more discussion in situations where there is not a rush (other than AMI and ACS), "I think it is very appropriate that, as the complexity of the disease increases, you step back and discuss the information, and the patient can also digest the information and be exposed to the options…The team needs to come to the bedside and discuss it with the patient…and that is where the Syntax score will be very helpful…My perception was the community was really waiting for this to be available."

*In how many patients is the Syntax score likely to be used?* Dr. Wijns estimated about 25% of patients. Dr. Jean Fajadet, 2009-2011 president of EuroPCR, added, "It depends on the center and the country…The process of new European Society of Cardiology (ESC) guidelines is ongoing, and the first presentation will be at ESC 2010…For the first time the guideline committee will include seven interventional cardiologists, seven non-interventional cardiologists, and seven cardiac surgeons. This guideline will include a chapter dedicated to patient information…For the first time, the Syntax score will be taken into consideration…It will require some time for people to think about this. This is a recommendation …not a rule."

### ABBOTT

- **Xience V.** European cardiologists interviewed at PCR generally said Xience V has become their No. 1 stent, and Abbott claims ~30% market share in major markets. Use is still increasing but more slowly.

- **Xience Prime.** There were no data at PCR on this next-generation Abbott drug-eluting stent. Xience Prime has the same drug at the same dose and the same polymer as the current Xience V, but the stent itself and the delivery system are different. An Abbott official explained, "Where physicians will see this (improved delivery) most is in the longer (stent) lengths (up to 38 mm). Xience V is not available in all sizes and diameters. Xience Prime will have longer lengths and smaller vessel diameters…and in the longer lengths, the delivery will be enhanced…The catheter and the balloon are different, and they taper differently for enhanced deliverability."

Abbott has submitted Xience Prime to European regulators and hopes to launch it in Europe before the end of 2009, leveraging data from the SPIRIT trials of Xience V and without any human clinical data on Xience Prime. There will probably be a post-approval registry.

In the U.S., Abbott will need clinical data on Xience Prime, and the company plans to start a trial before the end of 2009. This will be the first human experience with Xience Prime. Whether the trials will need to be 18 months is not yet clear; Abbott is still discussing that with the FDA.

- **Everolimus-eluting bioabsorbable stent.** There also were no data on this at PCR. So far, 50 patients have had this stent implanted in Phase I, and the Phase II trial which started enrolling at the end of March 2009 in Europe and Asia/Pacific will have 80 patients. An Abbott official said, "The feedback is that it is deliverable and something patients and physicians think – if it works – could revolutionize stenting."

Enhancements were made to the stent between Phase I and Phase II, giving it more radial strength to support the vessel longer. What's next? An Abbott official said, "We will probably finish this trial, look at the data – and we might have data

before the end of the year (most likely the American Heart Association meeting in November 2009)…If all goes well, we could bring it to market in Europe in 2012 or 2013, but we are not even projecting timing in the U.S. yet."

### BOSTON SCIENTIFIC

Boston Scientific's supply agreement with Abbott for Promus ends in November 2009 in Europe and in June 2012 in the U.S., so the status of its follow-on stents is closely watched.

➢ **Taxus Element.** According to CEO Tobin, the Taxus Element trial was fully enrolled in February 2009 and is in follow-up, with data not expected until 2010, perhaps at the American College of Cardiology (ACC) but more likely at EuroPCR. Taxus Element has been launched in some countries, and Boston Scientific is "getting experience" with it.

➢ **Promus Element.** This trial is still accruing patients, but Tobin says enrollment is "going fine" and is expected to finish by October 2009. Follow-up is one year, and the results will not be at TCT 2010, so it will probably be at ACC 2011. Tobin claims Promus Element is more deliverable than Promus, "It is platinum chromium instead of cobalt chromium or stainless steel. The reason you want to use platinum chromium is that (1) It is very strong so you can have very, very thin struts, (2) You can see the stent clearly on imaging (Taxus Liberté you can barely see)…This is like Goldilocks – just right visibility, and (3) It has little recoil (~1%) compared to ~5%-7% with cobalt chromium, and that is noticeable. Today with a coating, a little recoil doesn't matter, but in a next generation product where you are doing just abluminal (drug elution) and a log less drug, it better be up against the vessel wall, or it isn't going to work."

Promus Element is not being sold yet anywhere in the world, and the company doesn't plan to sell it anywhere until it gets approved in Europe. Tobin said, "It's all hands on deck to get it in Europe by November 2009, so we are not messing with Singapore (and elsewhere) right now."

*When Promus Element is on the market, how is it likely to get positioned?* Tobin said, "If you want Element, you will be able to get either flavor (Taxus) or Promus. They will be launched within 30 days of each other. What I think will happen is Promus Element will replace the current Promus, but it may also pick up some share from Xience because the Element stent is noticeably easier to deliver, and you can go further down the (coronary) tree than with any other stent today. As good as Vision is, this is better…We will have Xience available in a better stent…So, we expect some share shift between Xience and Promus Element."

*Will there be bare Element?* Tobin said eventually there will, "The struts are so thin that when you crimp a coated Element on a balloon, there is enough drug to make it soft…But the struts are so thin that it cuts the balloon when you crimp a bare Element…So, we have to toughen up the balloon for a bare Element."

*How will the transition from the current Promus to Element be handled?* Tobin said, "In the Taxus case, we will sweep the shelves and put Taxus Element there…We will sell the Taxus we take back in markets that are behind. Promus is a little different because there are region-specific versions of Promus which has to do with the testing you do on the product at the end. Testing for Promus in the U.S. and testing for Promus in Europe are not the same. So, you can't just take Promus in Europe and move it to the U.S...That we will have to manage. The supply of Promus we get from Abbott is region-specific currently. Promus Element will not be region-specific. We would have to repackage, but the product itself is the same…Our service levels are 99.7% in Europe now with Promus. We will do the same with Promus Element, but Abbott will always have an occasional back order."

*Asked about reports from doctors that Boston Scientific has been very aggressive on its drug-eluting stent prices*, Tobin said, "The leader in pricing stents is Abbott…They have been putting enormous pressure on the field force to take share, and I'm not giving it away. We are responding to them. They are the initiator in this…But it is not a price war. They don't want to cut the price of Xience, so they cut the price of balloons… In our last quarter, we lost some share in balloons, and that is why."

➢ **Taxus Labcoat.** This has been tested in a few patients in Europe. Boston Scientific reportedly will decide in the next 60 days if it will be launched. If Johnson & Johnson/Cordis's Nevo appears to be a threat, the company is likely to push it out in Europe.

### JOHNSON & JOHNSON's Nevo

Six-month data on Nevo showed that it is ***superior*** to Boston Scientific's Taxus Liberté in terms of in-stent late loss, which came as no surprise to almost anyone at PCR. Like Cypher, Nevo elutes sirolimus, and sirolimus is well-recognized as having very low restenosis rates. In fact, that actually has been a criticism of Cypher, with some experts suggesting that too low restenosis leads to poor endothelialization and late stent thrombosis.

The Nevo late loss data came from the randomized, multi-center, single-blind, 394-patient Res-Elution-I (RES-I) trial, which compared Nevo and Taxus Liberté in patients with single *de novo* lesions ≤28 mm (2.5 mm – 3.5 mm diameter) in native coronary arteries.

Nevo is a cobalt-chromium stent with flexible, conformable, thin struts. It utilizes the Conor reservoir technology and a biodegradable PLGA polymer with "Cypher-like" release kinetics. J&J claims Nevo's reservoirs minimize tissue/ polymer contact area by >75%. The polymer is exclusively housed in the reservoirs, completely degrades in 3-4 months, delivering sirolimus over ~3 months. There is no surface coating.

Dr. Christian Spaulding, a principal investigator in RES-I, said researchers concluded that:

- Nevo is superior to Taxus ($p<0.001$ for superiority).
- The same magnitude of benefit vs. Taxus Liberté was seen in diabetic and non-diabetic patients.
- There were no stent thromboses with Nevo while there were 2 with Taxus despite high levels of dual antiplatelet therapy use with both stents.
- While not powered for clinical endpoints, the trial showed lower rates of TLR, TVR, and MACE with Nevo.

*When will the 1-year data on the RES-I trial be presented?* It appears too late for TCT 2009, and J&J has not decided yet where the data will be presented, but perhaps it will be the American Heart Association 2009 meeting.

Dr. Serruys called RES-I a "well-executed trial," adding that it is a proof-of-concept accomplished without a preceding first-in-man trial. Was Taxus a good comparator? Dr. Serruys said, "Critical minds could say that the comparator should have been Xience or (Medtronic's) Resolute, but with a late loss of 0.13 mm in the RES-I trial, I would not be concerned about this."

Dr. Serruys' only criticism of the Nevo data: The use of acronyms like TVF instead of the ARC-recommended longer names (e.g., target vessel failure).

Once the drug is gone, so is the polymer. Over time, Nevo becomes a bare stent – perhaps as soon as 3-4 months. The biodegradation does require more testing for the FDA, but it is not anywhere near the very high hurdle for a totally biodegradable stent, according to J&J sources. J&J's hope is that, eventually, Nevo will be proven to require a shorter course of dual antiplatelet therapy than the 12 months currently recommended for all drug-eluting stents. Dr. Sidney Cohen, vice president, clinical, at J&J/Cordis, said, "That is what the NEVO-IV, -V, and -VI trials will explore."

*Is late loss a good indicator of how the stent will perform clinically?* Dr. Serruys said, "The accuracy of late loss assessment by angiography is far from being perfect… even with the best investigators and the best core lab in the world…The late loss of Nevo has a smaller standard deviation than Taxus, thus showing less variability in this surrogate measure. Less negative late loss is observed with Nevo than Cypher."

Yet, there is still a question whether the late loss benefit will translate into superior clinical benefit. Dr. Renu Virmani, president/medical director of CVPath Institute in the U.S., pointed out that the late loss difference, while statistically significant, was not meaningful, and the MACE, which she believes is more important, was not statistically different from Taxus Liberté.

*Asked about Nevo deliverability*, investigators who participated in the RES-I trial said that they don't know yet – the lesions in RES-I were too simple to provide much information on deliverability. J&J's Dr. Cohen said, "Nevo is world-class deliverable and more conformable (than Taxus). We designed Nevo to be fracture-resistant. The struts with the drug are rigid; it is the connectors that are flexible."

**Results of RES-I Trial of Nevo Stent**

| Measurement | Nevo n=202 | Taxus Liberté n=192 | p-value |
|---|---|---|---|
| ***Primary endpoint:*** In-stent late loss | 0.13 mm | 0.36 mm | <0.001 |
| In-segment late loss | 0.06 mm | 0.20 mm | <0.001 |
| NIH volume | 5.82 $mm^3$ | 19.45 $mm^3$ | 0.004 |
| Procedural success | 97.5% | 97.4% | Nss |
| **Secondary endpoints** | | | |
| ≥50% diameter stenosis | 1.1% | 8.0% | 0.002 |
| MACE | 4.1% | 7.5% | Nss, 0.19 |
| TVF | 5.7% | 7.5% | Nss, 0.54 |
| TLF | 3.6% | 5.3% | Nss, 0.46 |
| **Other results** | | | |
| Death (overall, not just cardiac) | 0.5% | 1.6% | Nss, 0.37 |
| MI | 2.1% | 2.7% | Nss, 0.75 |
| Death or MI | 2.6% | 4.3% | Nss, 0.37 |
| TLR | 1.6% | 3.2% | Nss, 0.33 |
| Out-of-hospital MACE | 1.6% | 4.8% | Nss, 0.08 |
| Out-of-hospital TLR | 1.0% | 2.7% | Nss, 0.33 |
| Patients with ≥0.5 mm late loss | 8.0% | 31.5% | <0.001 |
| Patients with ≥1.0 mm late loss | 1.7% | 9.9% | 0.001 |
| Coronary aneurysms | 1.1% | 3.7% | --- |
| ***Secondary endpoint:*** **Stent thrombosis through 6 months** | | | |
| ARC definite | 0 | 0 | --- |
| ARC probable | 0 | 0.5% | Nss, 0.49 |
| ARC possible | 0 | 0.5% | Nss, 0.49 |
| Any ARC | 0 | 1.1% | Nss, 0.24 |
| **Pre-specified diabetic subgroup analysis (n=65)** | | | |
| In-stent late loss in diabetics | 0.17 mm | 0.42 mm | 0.03 |
| In-stent late loss in non-diabetics | 0.12 mm | 0.34 mm | <0.001 |
| Patients with ≥0.5 mm of late loss | 8.0% | 31.5% | <0.001 |
| Patients with ≥1.0 mm of late loss | 1.7% | 9.9% | 0.001 |
| Coronary aneurysms | 1.1% | 3.7% | --- |
| **In-stent restenosis in individual patients** | | | |
| Overall | --- | --- | Nss, 0.54 |
| IA | 0 | 0 | --- |
| IB | 83.3% | 23.1% | --- |
| IC | 0 | 53.8% | --- |
| ID | 0 | 0 | --- |
| II | 16.7% | 15.4% | --- |
| III | 0 | 7.7% | --- |
| IV | 0 | 0 | --- |

*How is Nevo different from the Conor CoStar stent?* The two stents share the same material – cobalt chromium. Other than that, the design is completely different. Nevo is an open-cell design, "extremely deliverable, and the conformability after expansion is pretty remarkable." There are a variety of ways in which Nevo is changed, "In fact, it is almost unrecognizable (as Conor)….And the delivery system is very different and cutting edge."

*Why did Conor's CoStar fail?* A J&J official said, "They thought they had the elution right, but at the end of the day, they didn't…We went into incredible depth to understand why that failed. We reviewed it in-depth with regulators around the world…and there was unanimous agreement that we had identified the cause: They had reduced the paclitaxel level below the therapeutic threshold." Another official said, "Conor decided to change the manufacturing, staying within the specifications, but we discovered that that slowed the paclitaxel delivery."

*Is the balloon platform the same as Select?* No, and the balloon platform is not the same as anything currently on the market. So, it is a brand new platform and balloon.

The late loss looks very similar to Xience at 6 months in the SPIRIT-II trial. Should it be assumed that Nevo will show late loss catch-up at 1- or 2-year timepoints? Will doctors want 3-4-5 year data before widespread adoption? A J&J official said, "I do not think you will see what we see with Xience and SPIRIT-II…We have not seen that with Cypher… So, we don't think it exists with Cypher as it has been shown with Xience. The specifics on why Xience has shown that over time is beyond the scope of this conversation…That may be a very real finding with that device (Xience), and I don't think it is an issue with this device (Nevo)."

J&J plans to file for a C.E. Mark based on the RES-I data by the end of 2009, so Nevo could be on the European market by March 2010. J&J officials believe familiarity with sirolimus and the extensive Cypher data will help physicians move quickly to Nevo.

*Asked for their opinion of the Nevo data*, European cardiologists said that it is simply too early to tell – that more data are needed, particularly clinical endpoint data. However, Nevo may be available in Europe before there is any additional data, so how do European cardiologists expect to use Nevo? They predicted that Nevo will replace Cypher, probably rather quickly. Whether it can take market share from other stents, particularly Xience, will depend on how it performs in their hands – deliverability. A J&J official said the company has no plans to take Cypher off the market, "Cypher performs very well in large vessels."

Comments on Nevo included:

- "We need clinical data before we'll know how it will do."
- "It isn't just results; it is deliverability that matters. Late loss is not clinical data. Nevo would replace Cypher."
- "Nevo is like Cypher. The delivery is definitely superior. The stent is more flexible than Cypher. The design of Nevo is very similar to the old Cordis Crossflex stent…Nevo will replace Cypher for sure, and it will be a big competitor for Xience/Promus."
- "The deliverability feels good, but we need to test it in more complex lesions to say it is equal or better than Xience."
- "I can't tell about the Nevo deliverability because the cases so far were relatively easy cases….If the NEVO-II trial is all-comers or an enriched population, we will know very quickly, but I expect it to be quite deliverable. The signals have been good – very, very good …We all know sirolimus very well, and the early Conor stent worked well. There is a lot of fundamental work behind the sirolimus elution, and this is about the same elution. It is enough that doctors will use Nevo. The adoption will be very good. In Europe it will just replace Cypher until there are more data."

For U.S. approval, J&J plans two trials, NEVO-II and NEVO-III, and the company expects to combine the results of the RES-I, NEVO-II, and NEVO-III trials to provide the 1,000 patients with 18-month follow-up required by the FDA. J&J plans to file Nevo with the FDA by the end of 2011.

- **NEVO-II** is an OUS trial vs. Abbott's Xience with expanded enrollment to include multiple patient sub-groups in Europe and ***possibly*** other OUS regions. The principal investigators are Dr. Serruys, Dr. Stefan Windecker of Switzerland, and Dr. Manel Sabate of Spain, and the primary endpoint is 12-month **TLF**.
- **NEVO-III** is a non-randomized U.S. IDE trial vs. Cypher to be conducted in Canada and the U.S. The primary endpoint is 12-month **TLF**.

Surprisingly, there will be no trial with randomized U.S. patients for the FDA submission. A J&J official explained that it is speedier to prepare an FDA filing without randomizing patients in the U.S., and the company will end up with comparative data vs. Cypher, vs. Xience, and vs. Taxus. J&J's Dr. Cohen explained, "We could have done a U.S. randomized clinical trial, which is optimal, but the FDA has four companies working on a dual antiplatelet therapy (DAPT) study with >20,000 patients…The FDA agreed we could use the Cypher control patients for the DAPT study and also use them as the control in NEVO-III (for the first 12 months). Then, at 12 months, the patients will be randomized for DAPT for another 21 months." Thus, for FDA purposes, there are two parts to NEVO-III (A and B).

J&J will start enrolling patients in NEVO-III in summer 2009 and expects to complete accrual by October or November 2009. Dr. Cohen said, "The carrot for enrolling patients in the Cypher control is that centers who do that can get in the NEVO part of the trial."

Not unexpectedly, Boston Scientific's Tobin insisted his company isn't worried about Nevo, "It's no surprise that Nevo has less late loss than Taxus…They (Cypher/sirolimus) have had less for seven years now, and it hasn't made much difference in the market. Also, it is early data. Six-month human data aren't even acceptable in the U.S., so it doesn't actually tell you anything. What I hear from people in the (RES-I) study is that the stent (Nevo) is nothing special, not a wonderful stent – better than Cypher, but everything is better than Cypher. It is behind Taxus Element…and it is not as good as Promus/Xience V…People say the acute delivery (of Nevo) doesn't feel as good, that it is not as easy to use…J&J will romance this as a next generation product. In truth, if you think of the biology, there is nothing in the biology that says delivering a drug and polymer in buckets is better than a uniform coating. There is no biology behind it. It is purely an IP (intellectual property) thing…to get around our IP. That's all it is. The other thing is that in those buckets, there is a lot of drug and polymer, so in terms of load, it is about the same as the current stent, but it is in buckets instead of spread across the stent…A true next generation drug-eluting stent will have a log less drug and polymer and be abluminal. What Nevo represents is an alternative generation one presentation. I call it 1B. It is not generation two. This is a classic case of when this is all you have, you romance it a lot. It is ho-hum, a non-event from our point of view."

## PERIPHERAL INTERVENTIONS

Dr. Alberto Cremonesi of Italy said the sentiment at PCR about peripheral interventions:

- **Renal stenting** is not helpful, and the number of procedures is continuing to decrease.
- **Carotid stents** are great – but only in selected patients.
- **Femoropopliteal (fem-pop) stents** are a growing area. He said, "All studies show a benefit of stents over balloon angioplasty, except in lesions <2 cm. Longer lesions are being treated, using longer stents (15-17 cm)…The new generation of self-expanding nitinol stents have fewer fractures…What's new is the role for endovascular therapy as a primary treatment – to provide immediate relief of complaints, immediate improvement in quality of life. The question is whether the gain in quality of life is worth the extra cost of intervention."
- **Superficial femoral artery (SFA)** primary stenting also is growing. However, the longer the lesion, the higher the restenosis is at 12 months. An industry source estimated that 30%-40% of SFAs are stented today, and 30%-40% of these develop restenosis. At PCR, Cook's Zilver PTX showed 5%-6% restenosis at 12 months and 8% at 24 months. Drug-eluting balloons also look promising. Yet, the standard-of-care is plain balloon angioplasty.
- **Behind-the-knee (BTK)** may be the most exciting area. Dr. Cremonesi said, "Many centers are starting to enter the field, treating more, and treating increasingly more challenging lesions.

**Atherectomy devices.** This simply did not get much attention at PCR. Dr. Cremonesi said, "Very honestly there is not enough scientific data to support extensive use of these devices. In very selective cases, we think they can have an advantage, but we have no real hard data telling us that an atherectomy device is better than a balloon at the moment." Dr. Fajadet added, "Percutaneous intervention should be simple and safe, and cheaper is better…If you have a very sophisticated device – such as a laser – it will never work… because it is not simple, not safe, and is very expensive – except for a niche."

**Drug-eluting balloons (DEBs)**. This was a hot topic at PCR in peripheral interventions, and the company getting attention in this space was Invatec, a private Italian company. Dr. Cremonesi said DEBs are a "great novelty" today, "Theoretically, DEBs makes sense, but they still need to prove it." While drug-eluting stents have not worked well in peripheral artery disease (PAD), DEBs look more promising.

*Which peripheral stents are most popular in Europe?* Experts said Bard's LifeStent is No. 1, but EV3 and Abbott's Resolute are also doing well, and people are just starting to test Boston Scientific's newest peripheral stent.

INVATEC claims to be the only company with three different DEBs – all eluting paclitaxel:

1. **In.Pact Admiral** for SFAs. This is the most recent Invatec DEB to receive a C.E. Mark, and it was launched at PCR. A first-in-man case was presented at PCR, using Admiral after laser debulking.
2. **In.Pact Amphirion** for BTK, which was launched in January 2009. Manfred Newrly, global marketing manager, peripheral interventions, at Invatec, said Amphirion is doing well, "It has been spectacular in terms of market feedback, but there is a certain hesitation which I consider healthy because of lack of clinical data. In BTK no dedicated study has been published yet, not even presented, so I think physicians are wise to use that new tool with caution…and we had expected that and are happy with that…so there isn't inappropriate use."
3. **In.Pact Falcon** for coronary arteries, particularly for in-stent restenosis. This DEB was launched a couple of weeks before PCR. Dr. Eberhard Grube of Germany said, "Combining…PTCA balloon catheter technology with local drug administration is a fascinating new concept for the treatment of certain coronary lesions such as in-stent restenosis (ISR), small vessel disease (SVD), bifurcations, and potentially other lesions where conventional balloons, stents, and even drug-eluting stents may not be ideal. A drug-eluting balloon such as the In.Pact Falcon that elutes a known and effective drug (paclitaxel)…holds much promise as an effective treatment option for patients."

Newrly said that what makes the Invatec DEBs different from other DEBs is its proprietary solvent, FreePac, that facilitates paclitaxel absorption into the artery wall, "We think this differentiates us from other people who put the plain drug (paclitaxel) on a balloon. So, a DEB is not a DEB. You need to look at the technology behind the balloon, the adherence of the drug, wiping it off or not, blowing up the balloon… Everyone is under the impression that delivering drug over weeks is necessary…It is surprising to them that a short-term loading dose is effective." Invatec is in the process of filing a patent on its solvent.

There are not a lot of clinical results on Invatec's DEBs yet, but the company plans to invest heavily in clinical research programs to confirm the clinical effectiveness of the In.Pact technology platform and to expand the clinical indications for its DEBs. Newrly said, "The challenge is to bring down the re-intervention rate. Our new device delivers a drug that has the potential to reduce hyperplasia…There were a couple of trials with the prototype balloon, and that gave surprisingly good results, so the TLR dropped from 48% in the plain balloon arm to 17%, which is pretty low…That was only 50 patients in one trial and then 48 in another trial, so the dataset is not huge."

Among the planned trials are:

- A pilot coronary trial of Falcon is planned to start later this year.
- The 375-patient, DEEP trial in BTK will start in July 2009 at nine European centers comparing Amphirion to plain balloon. The first 150 patients will be randomized, and the rest in a registry. Enrollment is expected to take about a year, with 6-month follow-up. The primary endpoint is late loss.
- The randomized THUNDER trial in SFAs will start later this year vs. plain balloon.

*Where will the Admiral fit?* Newrly said, "It will not replace anything. It is an add-on so far. It can replace standard balloons, but so far the data we have suggest that it is adjunctive therapy to prevent restenosis."

*What are the plans for the U.S. market?* Newrly said, "The FDA seems to have stricter rules for approval than Europe, and no one knows what the rules are or what kind of trial…so companies developing drug-eluting balloons are in conversation with the FDA on what to do in terms of getting an IDE submission and what trial to run…We haven't even started talking with the FDA yet…We haven't had any official meeting with the FDA yet…We want to come to the U.S. but we still need to understand the process."

## MISCELLANEOUS

### ABIOMED's Impella

There was no news on Impella at PCR. A few sources asked about it said they are not using it, and one said his center stopped, "We stopped because of lack of efficiency. It doesn't provide the output that CardiacAssist's TandemHeart does, and technically you have a rigid catheter."

### Implantable cardioverter defibrillators (ICDs)

The recall of Medtronic's Fidelis lead is generating opportunities for competitors. And during PCR, Medtronic announced another lead problem, this time with some older pacemakers. In a "Dear Doctor" letter, Medtronic warned that nearly 37,000 Sigma and Kappa pacemakers manufactured primarily between November 2000 and November 2002 may have faulty wiring that could cause them to fail at a higher-than-expected rate. The defect was blamed on "voids" created in the solder joint where the wires are attached to the circuit board, leading to premature battery depletion, loss of rate response, loss of telemetry, or even no output. So far, the company has received two reports of deaths that may be related to the defect.

*Asked about trends in ICD pricing*, Boston Scientific CEO Tobin said, "Hospitals with agreements (contracts) are basically canceling agreements and rebidding (to get a lower price). They never want to let a good crisis go by, and that's what's going on. There is a lot of turmoil in the marketplace from a bidding point of view. But you lose one today, you can win one the next day, so share has not shifted much as all this is going on…There is a lot more foment than usual…We had to put more people into the bidding department because there were so many bids to respond to…We needed more administrative people to keep up with all this."

*Asked about ICD market share*, Tobin said, "We (Boston Scientific) are gaining share at Medtronic's expense… Normally, everyone (every company) gets its own change outs (replacements)…When we were having our recalls, we only got 90% of change outs. Now we are getting more. There is some irritation with (Medtronic's) Fidelis (lead problems)."

Tobin warned that the three major ICD companies – Boston Scientific, Medtronic, and St. Jude – report their ICD numbers differently, which makes tracking market share in ICDs more complicated, "There is ~20% of the market that refills inventory every three months…Medtronic's quarter is off a month from us and so is St. Jude…So, two months out of three, someone is ending the quarter and wants to cram the numbers …We have to compete in that 20% of the market (that refills quarterly) because we won't concede it. When we win, if we put in three months of units, we defer (accounting) on the other two months, and only account for the first month, so we are only 'selling' one month of product, though we are delivering three months. But the other guys don't defer as far as we know, so they can affect numbers by cramming…It makes their numbers look great. Our numbers reflect actual usage."

### LILLY's Effient (prasugrel)

Lilly sponsored a symposium on anticoagulation, and, of course, prasugrel was a key topic. Dr. Bernard Meier of Switzerland said, "Who should get prasugrel? The question should be to whom we don't give it – people <60 kg, a prior stroke, or age >75."

Experts pointed out that AstraZeneca's AZD-0837 – a follow-on for the failed Exanta (ximelagatran) – may have trouble competing with prasugrel because it is BID, while prasugrel is QD.

Prasugrel has been launched already in the U.K. and Germany, but a source said a discussion of prasugrel and cancer hurt the launch in Germany. A German doctor said, 20%-33% of patients at his center are now on prasugrel and that number is low because he is at a tertiary center and because prasugrel is only being used on-label.

### VOLCANO

**Xtract.** Volcano announced a worldwide, exclusive distribution agreement to distribute Lumen Biomedical's Xtract thrombus aspiration catheter in the U.S. and Europe. Xtract has both FDA approval and a C.E. Mark for use in coronary vessels as well as some peripheral vascular applications. The device incorporates three unique design attributes:

1. A single lumen design to maximize cross-sectional area and, in turn, thrombus suction.
2. A circular, right angle tip for close-up access to clots.
3. A curved, directional tip to enable full sweep of the vessel.

Volcano officials said Xtract complements the company's IVUS and virtual histology tools.

**Fractional Flow Reserve (FFR).** Vince Burgess, executive vice president of marketing and business development for Volcano, said FFR grew 82% year-over-year in the last quarter, "People are starting to get the message in a very big way. Given the COURAGE data and that no stent is without possible complications…the evidence really supports confirming the pressure gradient with FFR during the case prior to placing the stent…Since the FAME (trial) came out we have been in the process of upgrading our entire IVUS fleet so they can quickly and easily run FFR so sites don't need to go buy a new FFR box…Instead, it all comes right on the IVUS system…so it is integrated…The vast majority of cath labs have some form of FFR now, typically the old stand-alone system that is cumbersome to use …We are in the process of integrating it into our system that is built right into the room…We thought the FAME data at TCT would drive the business, and it did – and it is a big driver. Europe is picking up FFR even more than the U.S.; they are very cost-conscious."

**Intravascular Ultrasound (IVUS).** Burgess estimated that 15%-16% of PCI uses IVUS today, but the rate is much lower in Europe (6%-7%), and much higher in Japan (~70%). He was reluctant to make any projections about the outlook for IVUS over the next year, but he said he sees no reason that the 2% per year growth won't occur in the U.S. and Europe, "Obviously, growth in Japan has slowed but not plateaued."

*How are hospital budget freezes affecting cath lab build out?* Burgess said 90% of new IVUS is being sold into existing cath labs, and 10% for new rooms, "If that (new room sales) are off 30%-40%, that is a 3%-4% hit for us…Capital equipment into existing rooms has grown year-to-year and quarter-to-quarter even in the downturn…It hasn't been affected (by the recession)…Could we grow faster without the (recession)? Probably but we are growing in spite of it."

**Optical coherence tomography (OCT).** Is OCT a threat to IVUS? Burgess said, "We think it could be cannibalistic partially over the long-term but also complementary…We think it is very early in evolution, and it will take another 3-5 years to work out all the bugs in system, the catheter, the workflow, flushing, etc. We think enough of it that we have acquired two companies in the space…We are very serious about the OCT effort."

Burgess added that OCT has limitations in coronary arteries, "You cannot see through blood, so you have to flush the blood out of the way…and that is a burden on diagnostic imaging… We all need to be very careful that we develop this properly and make sure flushing protocols are safe."

Another limitation to OCT is that it can only see 1-2 mm into tissue. Burgess said, "You can't see full thickness (with OCT), and with IVUS you can see the totality of disease."

**Virtual histology.** *Asked about virtual histology*, Burgess said, "It is very interesting science and technology. After a long period of trying to get comfortable with the level of accuracy and validation, we transitioned to a phase where we understand and characterize what information it is telling us. Now, we are trying to figure out how to use it in clinical practice. Where it seems to get the most use and attention today is not in the traditional sense of finding vulnerable plaque but instead in helping guide more accurate stent placement. People are specifically trying to understand if you look at a lesion in totality, is there an underlying necrotic core in that area where you intend to treat? And if there is, do you want to try to cover it, or do you want to make sure you don't terminate the edge of the stent in a necrotic core? Virtual histology does a very effective job of locating the necrotic areas. We have a number of physicians looking at virtual histology as they plan their stent placement – in addition to the many other factors they take into consideration."

♦