Trends-in-Medicine

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SUMMARY

Interventional cardiologists want both PCI and DES volume to start increasing again, but there were no real signs that this is happening, and the FDA is raising the bar for new DES. ♦ There was more excitement about Abbott's not-yet-approved Xience V than Medtronic's newly-approved Endeavor, and doctors predicted that Endeavor would take <10% market share but Xience could capture "significant" market share, affecting Boston Scientific's Taxus and Johnson & Johnson/Cordis's Cypher almost equally. ♦ Percutaneous valves remain a technically challenging procedure. The regulatory path is almost as challenging, and it doesn't appear to be getting simpler. ♦ European doctors haven't been able to choose between Edwards Lifesciences' Sapien THV and CoreValve's ReValving System percutaneous aortic valves, and use of both is still limited. A new problem has emerged: patients needing a permanent pacemaker post-valve implantation.

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CARDIOVASCULAR REVASCULARIZATION THERAPIES (CRT)

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Medtronic's everolimus-eluting Endeavor stent was approved just days before CRT, and the company's sales reps were excited to be able to talk about it, but Endeavor generated little excitement. Rather, interventional cardiologists have their eye more on Abbott Vascular's zotarolimus-eluting Xience V stent. Yet, it wasn't drug-eluting stents but percutaneous heart valves that were the hot topic at this year's CRT. Percutaneous valves are moving forward, but very slowly, and FDA officials didn't offer much encouragement that the approval process will get any easier.

CRT, sponsored by the Cardiovascular Research Institute at Washington Hospital Center, was attended by many of the experts in interventional cardiology. Industry also was well represented, and quite a few FDA officials both attended and spoke, offering extensive guidance to doctors and companies.

DRUG-ELUTING STENTS (DES)

PCI volume

It was impossible to draw reliable conclusions from these sources. They really are not representative enough, but we should get a good handle on this from the cath lab survey. Overall, the interventional cardiologists at the meeting appeared to be ***hoping*** but ***not expecting*** that the decline in volume has bottomed out and will increase during 2008.

DES volume

DES volume also was difficult to determine from this group of doctors. As expected, interventionalists repeated the usual reasons they think volume should go up, but there was no evidence that DES volume actually will go back up in 2008. One speaker predicted only that the decline appears to be over, with a flattening expected for the near future.

In August 2007, the U.K.'s National Institute for Health and Clinical Excellence (NICE) issued a draft guidance saying that DES were not cost-effective, which probably would have led to the National Health Service (NHS) to stop paying for them. However, in January 2008 NICE said it was not going ahead with that proposal. Instead, NICE is leaving in place its earlier recommendation: that DES be used for lesions <3 mm in diameter and >15 mm in length.

The draft NICE guidance did not appear to be having much impact on other European countries, but sources were well aware of the draft guidelines, and they said they may be used going forward to justify using less DES in some European cath labs.

Dr. Sigmund Silber of Germany commented, "Should everyone get a Porsche or a VW Polo? You might say you cannot afford the Porsche, but if you follow the NICE recommendations, then you have no additional costs because it is more expensive (with DES), but you save money on reduced restenosis." A French doctor said, "NICE has had no impact on our DES use."

Dr. Silber discussed which patients should ***not*** get a DES. He contended that not all DES are created equal, effective DES are a "true medical innovation," DES are superior to BMS in almost all subgroups, and the major limiting factor for DES is prolonged dual antiplatelet therapy. In Germany, he said the practice is to prescribe dual antiplatelet therapy for only 6 months but a year or longer in certain patients. Dr. Silber said, "DES have already passed the point of no return, and we should never go back to BMS." While interventional cardiologists are starting to feel more comfortable that the stent thrombosis issue is not a time bomb that is going to blow up on them, they are still cautiously watching data on stent thrombosis.

The bottom line was that patients:

- ***Should*** get a DES for bypass grafts, long lesions, smaller vessels, large vessels, bifurcations, ostial lesions, and CTO, in-stent restenosis of a bare metal stent, and patients with renal insufficiency, severely decreased LVEF, or diffuse coronary artery disease. Left main is still an undetermined area, he said.
- ***Should not*** get a DES, Dr. Silber argued, if they can't or won't take or comply with dual antiplatelet therapy, have severe co-morbidity and are already taking a high number of pills, have surgery planned for the near future, or have an increased and untreatable high risk of bleeding.

The COURAGE trial – which found that stenting may not be any better than medical therapy for stable angina – definitely had an impact on DES use in the U.S., but European doctors said it has had little impact there. Dr. Silber said, "Our average use (in Germany) of DES is 35%-45%, so COURAGE didn't affect DES use. And, in my personal opinion, it didn't affect overall DES use."

Dr. Gregg Stone of Columbia University and Dr. William Weintraub, chief of cardiology at Jefferson University, debated the ongoing impact of the COURAGE trial:

- **Dr. Stone** argued that PCI is appropriate for everyone with symptoms. He challenged the COURAGE findings, saying they are not representative of the U.S. as a whole, and reminding the audience that only 3% of patients in that trial got a DES. He concluded, "In asymptomatic patients with stable coronary artery disease, PCI with a bare metal stent compared to medical therapy significantly reduces angina and the medication requirement and improves quality of life. The durable relief of symptoms may be further improved with DES and optimal technique. In patients with moderate-to-severe ischemia and stable coronary artery disease, PCI reduced the rate of MI and death….(But) you can't downplay the importance of ischemia…and the resolution of ischemic reduced mortality. COURAGE investigators went out of the way to avoid showing the mortality of PCI vs. medical therapy. Show the data…DES is better than a bare metal stent. I think the story is coming back around…Every study has flaws, and we have to put things in perspective. I do think COURAGE has had an untoward impact. Diagnostic angiography has decreased, which is an unfortunate effect of COURAGE."
- **Dr. Weintraub** argued, "The people with a lot of angina are the ones you can convince me need DES, but (otherwise) it is hard to see the benefit…The COURAGE trial did not show that PCI, as an initial management strategy prevents events. It did show that PCI improves symptoms…COURAGE suggests that, as an initial management strategy, optimal medical therapy is safe and that PCI can be deferred or avoided…In symptomatic patients, we don't disagree much…For patients who are disabled by angina, it is quite reasonable to do PCI… The issue with ischemia is a little complex…We can't really get at that from COURAGE…The idea that the sky is falling and that COURAGE is the end of PCI is not true…None of us want that to happen, and it won't."

Marketing wars

The choice of DES is easier in the U.S., where only three DES are approved. In Europe, the 22nd DES was recently approved. The key takeaways were:

- Good estimates of market share splits between **Johnson & Johnson's Cypher** and **Boston Scientific's Taxus** were not possible.
- Most sources did not yet have **Medtronic's Endeavor** available in their lab, but there wasn't a great deal of excitement about it. Most doctors said they expect Endeavor to comprise <10% of their DES use by the end of 2008.
- Pricing data, again, were not reliable. However, a European doctor said **Abbott's Xience V** is doing better than **Boston Scientific's Promus** in his country because Xience V is cheaper than Promus.
- U.S. doctors are much more excited about Xience V than Endeavor, and several predicted that it would capture "significant" share in their labs.

Physician comments about DES usage trends included:

- *France:* "Right now we are 50% Cypher and 50% Taxus, but by next year we will add Endeavor or Xience, probably Xience." Asked why his center would choose Xience over Promus, he said, "Promus is more expensive than Xience in France."
- *Egypt:* "We are currently 50% Endeavor, 23% Xience, 22% Taxus, and 5% Cypher. By the end of 2008, Xience will go up to about 30% and Taxus down to 15%." Asked why his center is using more Endeavor than Xience, he said, "We've been working with Endeavor longer and

know it better. It has been proven safe. We've had it two years, but Xience use is increasing."

In one interesting session, speakers argued the particular merit of each of the U.S.-approved – or likely to be approved soon – DES.

➢ **Johnson & Johnson's Cypher – *better than Taxus*.** Dr. Sidney Cohen of Cincinnati OH reviewed the findings of a network meta-analysis of 38 randomized clinical trials of 18,023 patients, published in ***The Lancet*** in September 2007, which found that Cypher beat Taxus in terms of MIs, stent thrombosis after 30 days, and target lesion revascularization (TLR).

➢ **Boston Scientific's Taxus – *best in diabetics*.** Dr. Keith Dawkins of the U.K. argued that Taxus is the most effective DES for diabetic patients. He said, "Whichever way you cut the data, you see the (negative) drift with Cypher in terms of TLR at 12 months in insulin-dependent diabetics…Taxus has an impressive dataset (in diabetics)…And it was the first stent to get a C.E. Mark for a diabetic indication (in December 2007)…Data from randomized clinical trials and registries confirm the safety of Taxus in diabetic patients."

➢ **Medtronic's Endeavor – *safest*.** Dr. Leroy LeNarz of Medtronic contended that Endeavor is "the safest stent available in the U.S." He said a pooled analysis of patient-level data for six Endeavor trials shows no evidence of an increase in adverse events for Endeavor vs. (a bare) Driver when comparing death, cardiac death, MI, or stent thrombosis, "By protocol (definition of stent thrombosis), we see nothing that would indicate a signal (for stent thrombosis)…By the ARC definite/probable definition, stent thrombosis was 1.5% with bare vs. 0.8% with Endeavor…There is no evidence of an increased rate of death, cardiac death, or MI in patients treated with Endeavor vs. (a bare) Driver out to 3 years follow-up, and 71% of Endeavor patients were off dual antiplatelet therapy at one year, and 89% were off at two years."

➢ **Abbott's Xience V – *a kinder, friendlier stent*.** Dr. Charles Simonson, chief medical officer at Abbott Vascular, said Xience V has some key differences from the currently approved DES, particularly: a lower drug dose than Cypher or Endeavor and thinner struts. He emphasized that (1) Xience, unlike Endeavor, met all the endpoints in its clinical trials, and (2) Xience beat Taxus in clinical trials, estimated that with Xience (vs. Taxus) there would be 23 fewer patients out of 1,000 patients who will not need a repeat revascularization as well as 17 fewer patients out of 1,000 who will not have an in-hospital MI. Dr. Simonson said XIENCE-V-USA, the Xience post-approval registry, "will kick off this summer if we get the stent launched."

Asked about the possibility of combining drugs on a Xience stent, Dr. Simonson said, "In our preclinical work, the combination of everolimus and dexamethasone has the lowest inflammatory scores on any combination in preclinical study …but from a regulatory pathway, can you build something like that and make it through the regulatory pathway and make it worth development?"

Regulatory issues for DES

The late-stent thrombosis problem with DES was the gorilla in the room whenever devices were discussed, and it was clear that the FDA is setting the bar higher when it comes to pre- and post-market studies, including a demand for long-term follow-up. Dr. Bram Zuckerman, director of the FDA's Division of Cardiovascular Devices, said, "We can't ignore realities. We don't want to put unsafe devices on the market. It doesn't help anyone, including the investigators, and I think the real challenge is figuring out (the answers) to unanswered questions in the DES arena, for example, how long should you take your Plavix (Sanofi-Aventis, clopidogrel)? I would ask industry representatives to consider innovation important but at the same time to be realistic. Don't ask for the sun if we haven't at least taken our baby steps."

Dr. Zuckerman also had another warning: "I think there's an increasing concern with pre-specified game plans, especially with respect to multiple hypothesis testing. This is a key point the industry needs to appreciate. We've become much more concerned with a generation of false positive results, so that pre-specification of some sort of more refined rationale is a key point the industry needs to appreciate."

Dr. Dan Schultz, director of the FDA's Center for Devices and Radiological Health (CDRH), said, "Premarket studies are (now) longer – 12 months vs. 9 months – for the primary endpoint, with a proportion of patients with follow-up beyond one year. Post-market studies are (now) larger, with longer follow-up, and (there is) the new post-market issue of optimal duration of dual antiplatelet therapy…We are responding to events that have occurred later in the post-market arena. We want to know what's going on in the lifetime of the product, and if you want to call it raising the bar, so be it. I call it reacting to science." He added that the FDA is easing some restrictions, including the amount of reporting immediately following approval.

Dr. Schultz also said the FDA is "recognizing the importance of global trials with data collected within and outside the U.S. to support device approval…and encouraging enrollment of broader populations in trials designed to support initial PMA approval, which should speed enrollment." He said that the FDA would consider use of data collected as part of post-market studies to support expanded indications.

FDA officials said new guidance is coming soon that will spell out in more detail the requirements that new DES will have to meet. Dr. Schultz said that the FDA's draft guidance document on DES will include portions on drug substance safety evaluation; non-clinical bench and animal testing; chemistry and manufacturing controls; and clinical trials, including post-approval studies. Time will be available for public comment on the proposed guidance, and the FDA also plans to hold a public workshop for comments and discussion.

Hina Pinto, acting chief of the FDA's Interventional Cardiology Devices Branch, in the Office of Drug Evaluation, CDRH, described how the FDA is raising the bar for new DES programs, including:

- Increasing the amount of clinical information required. Clinical study endpoints are now 12 months vs. 9 months previously.
- A proportion of patients with follow-up beyond one year are now required, and additional follow-up could be required for 18 months or two years.
- Post-market changes include:
  - Larger post-market studies.
  - Monitoring of higher risk patients.
  - Evaluation of the optimal dose of dual antiplatelet therapy (currently considered a class obligation).
  - Evaluation of stent thrombosis up to one year and annually through five years.
- Once the safety concerns related to stent thrombosis have been addressed, the FDA may decrease the requirements in the future for new DES.

New changes in preclinical requirements include performing fatigue testing after simulated cracking, etc. There are also changes to particle testing. The new requirements are in response to the need to more accurately evaluate embolic safety and coating integrity. Other things that could lead to additional new requirements include drug substances and new device iterations. Pinto said, "Second generation DES may have different requirements, depending on changes to stent platform, addition of new stent diameters and lengths, change in elution profile, and change in drug formulation…For novel technology, including degradable polymers, degradable stents, novel stent designs, and DES with biologics, the requirements could be very different than for existing stents. New indications on an existing DES platform would also have different requirements that could include diabetics, bifurcations, small vessels, and long lesions."

Dr. Andrew Farb, an FDA medical officer in CDRH, said that sometimes clinical benefits may outweigh angiographic endpoints, as in an Endeavor trial. He said:

- Individual PMAs stand on their own (with a reasonable assurance of safety and effectiveness required).
- Global trials are acceptable, so companies can leverage OUS studies.
- ARC stent thrombosis definitions are acceptable (probably preferable).
- Pooling of databases provide additional support of DES safety and effectiveness (especially if there are few events between 1-2 years post-implant).
- Post-approval studies are important.
- Clinical endpoints are more important. "(The focus of current DES has) shifted from angiographic or surrogate endpoints to clinical endpoints."

Biodegradable stents present their own unique problems. Dr. Andrew Farb said that biodegradable stents "are just one of the cascade of new devices that have been coming our way. Multiple challenges for the regulatory approach to these devices, and (questions include):

- What are the expected advantages of the biodegradable stent?
- What is the degradation profile?
- What are the degradation products?"

Dr. Farb also pointed out some other biodegradable stent issues:

- For bench testing, standard tests such as stent durability and coating durability "are no longer relevant, but still need to test mechanical properties in a physiologically relevant environment."
- With respect to biocompatibility, the standard tests may need to be altered, keeping in mind extraction conditions and time exposure. And separate testing of the degradation products may be appropriate.
- Design of a pivotal trial is expected to be either a superiority or non-inferiority trial to an approved DES, with the endpoint being target lesion failure (a composite of cardiac death, target vessel revascularization, MI, and target lesion revascularization). The pivotal trial sample size would have to be sufficiently large enough to provide adequate power to test the hypothesis comparing TLF rates between the biodegradable stent and the control, and the duration of patient follow-up would reflect the degradation profile. He said that other clinical endpoints "should include device success, procedure success, and clinical success. If visibility on fluoroscopy is an issue, (there should be) some assessment of frequency of geographic miss and ease of use and some ability to accurately deploy overlapping stents in a bail-out situation." He said that while the number of patients needs to be large enough to detect adverse events, "Not all patients need to be part of a randomized trial, and you can use multiple trials in the U.S. and OUS. Follow-up should go through five years and should assess rates of stent thrombosis."

Asked if there is anything the FDA is looking for in novel DES programs, Dr. Farb said, "It depends on the novelty of the device that you're testing and what potential value that it is."

Stent thrombosis. Dr. John Somberg of Rush University, and the member of the FDA's Circulatory System Devices Advisory Committee who voted against approval for Endeavor and Xience, explained his vote, "The database was never really appropriately constructed by industry to look at serious

adverse side effects, particularly those beyond a year. Therefore, the numbers on long-term follow-up are quite poor. One can say, 'Well, we can build on this.' But the recommendations for approval are based on data presented, not data that might show up in the future. The numbers were disheartening to me. Endeavor had a lot, but Xience had the least follow-up. The reviewer on the panel commented that this was the most data presented on the fewest number of patients…So far the industry has lucked out because, for the most part, the problems have been minor or not materialized, but that may not often be the case. The other aspect I find very problematic is the inadequate explanation of the dual antiplatelet part. You don't just buy the device; you take a whole package – the concomitant medical therapy…We don't know the appropriate dose, the duration of administration, or which agents in particular…The data are very poor…but it's really all we can do right now…We're going to see a number of new antiplatelet agents, but (Lilly's) prasugrel unfortunately – the (bleeding side effect) numbers were atrocious."

Dr. Somberg said that a recent abstract at the European Society of Cardiology showed that the DES stent thrombosis rate may accelerate over time, "We can face a potential new problem, and that would be the press could take up on it, saying that late stent thrombosis is even accelerating…We don't want to see headlines in the ***New York Times*** and the ***Washington Post*** that any new stent increases late deaths."

New DES on the horizon

Even though the pace of approval for new DES appears to have slowed, there are a number of companies with new DES in development. None was attracting significant attention. Interest in bioabsorbable/bioerodable stents may be waning somewhat. Dr. Renu Virmani of CV Pathology commented, "The message is: We need a bioerodable polymer or no polymer. I don't believe in bioerodable stents. Nothing will work well enough." It is difficult to believe that any bioerodable stent will succeed as long as she has this position.

One company with a stent in development that *might* bear watching is **Icon Interventional Systems.** This Georgia-based company claims to be working on a DES using a "new metal" that is stronger than stainless steel or cobalt chromium and thinner than cobalt chromium. It will elute a rapamycin analog (a new limus). But this is still in the discovery stage; preclinical studies have not begun yet.

Other DES in development incorporate new coatings and drugs, such as novel thin and ultra thin strut and absorbable polymer coatings. Among the most interesting were:

- **Medlogics Device Corp.** (MDC), which has a Cobra stent platform, a TEOS (tetra ethyl orthosilicate) mesoporous stent that employs sol-gel composition coatings that function as a bioactive material reservoir. The company plans to start clinical trials in South America.
- **Chameleon Biosurfaces Limited**, which has a novel electropolymerized coating.
- **Bioabsorbable Therapeutics Inc.** (BTI), which is working on a completely absorbable stent.

Keith Robinson PhD of St. Joseph's Research Institute in Atlanta said that while bioabsorbable polymer approaches have dominated the landscape, several new permanent and absorbable polymers and polymer/drug combinations have been developed and show excellent vascular compatibility in early work. Dr. Juan Granada of Columbia University asked, "Why should we move away from polymers? In the best case scenario, polymers are not biologically superior to bare metals. The next frontier is moving towards minimizing the amount of polymer used and decreasing the medication on stents. Drug reservoir is the next frontier; polymeric-based is in the polishing plateau phase, but non-polymeric-based is catching up very quickly."

Dr. Granada said several well-developed non-polymer-based DES platforms have moved from proof-of-concept to extensive preclinical and clinical testing. He noted that, besides drug elution, the surfaces could offer alternative strategies to enhance vascular healing, but these new platforms also pose new technical challenges (e.g., corrosion) that could inhibit the future of these technologies. He reviewed several non-polymer stents:

- **Translumina**'s Stent and Coating System. He called this a "magic box" because the system coats the microporous Yukon stent surface directly. The best data reportedly have been achieved so far with sirolimus and paclitaxel.
- **Setagon**'s Controllable Elution System (CES). The stent's nanoporous surface looks like coral and can absorb and release medication from the metal on its own, and it can release several medications at the same time. So far, results are equivalent to the Cypher stent. There are data with the device that indicate endothelialization can be enhanced.
- **Atrium Medical**'s Alpha 3 Coating (Drug Transference Coating System or DTCS). The pattern of release can be changed – faster or slower – and the results are similar to a BMS.
- **MIV Therapeutics**' Hap Coating. This is a very thin – 0.6 micron – 3-D microporous surface coating that sits like a sponge on top of the stent's surface. The drug is a lipid-based solution, and researchers have been able to load 55 µg of rapamycin into the matrix. A 15-patient study in Brazil is ongoing.

JOHNSON & JOHNSON/CORDIS's pipeline

Dr. Dennis Donohoe, vice president of clinical research at J&J/Cordis, gave a surprisingly detailed overview of what's in their cupboard. The plans he outlined made it appear unlikely

that J&J is shopping for new DES technology to buy. He said the key focuses for J&J right now are:

1. *Two DES programs that are being run almost in parallel.*
   - **Cypher Elite.** This is a sirolimus-based, stainless steel DES but more deliverable than Cypher Select. It has a redesigned platform, a more flexible delivery system, sirolimus at the same dose and delivery rate. Dr. Donohoe said, "On bench top, it is comparable to Endeavor and Xience." A trial is scheduled to start in the next six weeks. The principal investigators are Dr. William O'Neill of the University of Miami and Dr. Lowell Sattler of Washington Hospital Center. The study will be a non-inferiority trial vs. Cypher in single and 2-vessel disease with lesions from 2.25 to 4.0 mm and lesion lengths up to 30 mm. The plan is to enroll 1,770 patients at 94 sites over 12 months, with the primary endpoint target lesion failure (TLF).
   - **Conor SRL ("Conor S").** This is a cobalt chromium Conor stent eluting sirolimus at the same dose and with the same elution profile as Cypher Elite – except that by six months all the polymer (PLGA) is gone. A 338-patient, non-inferiority clinical trial vs. Taxus is expected to start in Europe in the next month. The primary endpoint is in-stent late loss at six months, but secondary endpoints will include clinical measures, and all patients will be followed out to five years. Dr. Donohoe said, "Initially, we are looking at this to minimize restenosis…We see the potential for developing other platforms that potentially can reduce the risk of restenosis, improve outcomes for MI, and specifically for diabetics by looking at biochemical pathways for drugs that could be eluted from this stent to give better outcomes for diabetics…This is a redesigned CoStar – more deliverable, with a slightly lower profile, the same polymer, and a catheter system that should improve deliverability, with an improved, more flexible tip…It has better release control than other DES…We can quickly modify elution rates."
   - **Beyond these.** Dr. Donohoe said J&J is looking at other applications for the Conor stent, particularly for AMI, diabetics, and peripheral DES.
2. *SFA, renal, and carotid peripheral indication trials.* Dr. Donohoe said J&J plans to pursue the SMART stent in SFA and renal indications and will have its first entry into the AAA market – a 12-14F. He said, "We should be first to market with a percutaneous stent graft."
3. *Development of health economics and reimbursement data on a worldwide basis.* Dr. Donohoe said reimbursement is becoming a bigger challenge than getting products approved, and it is becoming more complicated…Now, by region and sometimes by country we need to address local issues and reimbursement…There have been three filters for our products:
   - Can we make it? The technical risk.
   - Can we get it approved by the FDA and Japan? The regulatory risk.
   - What is the market size? The commercial risk.

   Now, there is a fourth issue. Can we get it paid? Reimbursement. This is complicating the design of clinical studies, in some cases leading to larger sample sizes, and the process is constantly challenging. On a yearly basis, a number of countries are re-opening the (reimbursement) decisions and re-evaluating the latest data…There is downward pricing pressure on products. Reimbursement is not a one time deal…It has to be addressed on an annual basis in most major markets."
4. *Physician training and education.* Dr. Donohoe said, "Clearly, these technologies are very complicated…So, the devices not only need to be approved, but training needs to be provided to physicians…which recently was clearly demonstrated with carotid stenting…We have the Cordis Cardiac & Vascular Institute (CCVI)…We generally have supported more than 5,000 education initiatives and made a $30 million investment per year on training and education programs."
5. *Diabetes.*
6. *Structural heart disease.* Dr. Donohoe said, "This is very challenging from a procedural standpoint. We have three programs active in-house in aortic valve replacement and PFO closure."

While it didn't make the focus list, J&J also is working on a vascular closure device, ExoSeal. This is a bioabsorbable PGA plug implant that requires no sheath exchange. Dr. Donohoe said the feedback the company has gotten from physicians is that "the insertion is virtually painless from a patient perspective." Clinical trials in the U.S. and Europe with 6F and 7F sizes have been completed, and the ECLIPSE pivotal trial data will be released at the American College of Cardiology in March 2008 as a late breaker.

PERCUTANEOUS VALVES

AORTIC VALVES

European interventionalists said it was just too early to determine whether **Edwards Lifesciences' Sapien THV** or **CoreValve's ReValving System** is better. Both have a C.E. Mark and are available in Europe, but use of both is still limited. European doctors said they expect the number of centers doing percutaneous valve procedures to increase during 2008, but they still expect the procedure to be uncommon.

PARTNER, the Sapien trial, appears to be enrolling slowly but surely. Doctors did not believe there will be a problem getting the trial enrolled, but it is taking time. One investigator said, "We are enrolling about 1 in 5 of the patients we screen."

During a live case from Germany, Dr. Gerhard Schuler pointed to a problem with both the Edwards and CoreValve valves: patients who need a permanent pacemaker post-valve implantation. Dr. Schuler said 10%-15% of CoreValve patients develop AV block and need a pacemaker. Dr. John Webb, an interventional cardiologist at St. Paul's Hospital in Vancouver, Canada, and an Edwards investigator, said a paper is scheduled to come out soon in the ***Journal of the American College of Cardiology*** which will report a 5.6% rate of permanent pacemakers with the Edwards' valve. However, Dr. Webb added, "It appears CoreValve has a higher rate of pacemaker need, but I'm not sure there really is a difference on pacing need."

Comparison of CoreValve and Edwards Valves

Issue	CoreValve's ReValving	Edwards' Sapien
Ease of implantation	Best	---
Need for permanent pacemaker	10% - 15%	5.6%
Antiplatelet requirements	Aspirin + Plavix	Aspirin only
Closure	Easier: percutaneous	An issue: mostly cut-down, but some operators doing percutaneous

A few days after CRT, Edwards announced it is suing CoreValve for patent infringement, and CoreValve issued a statement defending its technology and insisting it did not infringe on Edwards' patents.

Physician comments on these aortic valves included:

- *France:* "We will probably start sometime in the next 12 months with Edwards because it was a French concept, and there is a bias in France to French products. But we will use it for very few patients, perhaps 50 a year, which compares to 500 surgical valve replacements a year at our center."
- *Germany #1:* "They both have advantages and disadvantages, and I think in the end they will come out pretty equal."
- *Germany #2:* "Use of percutaneous valves is increasing, but neither company has enough proctors and training centers…We use both, but mostly CoreValve because of the access issues with the Edwards valve…I've done 50 CoreValves and haven't needed a permanent pacemaker in any of them. It is an issue, but it shouldn't stymie development."
- *U.S.:* "Using MR (mitral regurgitation) as a primary endpoint is not acceptable. We don't know that reducing it to 2+ is beneficial. That hasn't been shown. MR is a surrogate endpoint, and it is unacceptable."

EDWARDS' Ascendra, a transapical aortic valve implantation system

This alternative to the transfemoral approach involves a small incision between the fifth and sixth ribs of the left chest wall, into which a sheath is placed through the apex of the heart, along with a balloon catheter. Problems include placement and sizing problems, and it requires cooperation between the surgeon and the interventional cardiologist. Advantages include shorter distance, straighter, easier crossing, avoidance of femorals, and avoiding the arch. Disadvantages include thoracotomy, chest tube, and requires general anesthesia (to repair the apex). Dr. Webb said, "The question is whether it will still be around in 10 years…There are problems with positioning that can happen just as easily with apical as with femoral. You can still have the potential risk of late mitral injury…Three cases have been reported, and the patients will require surgery." He said that implant success was very high with the first 50 transapical patients.

SADRA MEDICAL/BOSTON SCIENTIFIC's Lotus Valve System, a self-expanding percutaneous aortic valve

Dr. Eberhard Grube of the Heart Center Siegburg in Germany described this as "a customized solution" to aortic valve replacement, with repositionable and reversible deployment. He said, "This stent has the best of both worlds – low radial strength during the sheathed state and device positioning, and high radial strength when fully deployed." The bioprosthesis is bovine pericardium tissue, so there is no need for anticoagulation therapy. It has:

- Small profile – 21F for first-in-man.
- Excellent flexibility and tracking ability.
- Highly controlled and accurate placement (a self-centering design).
- Minimal occlusion during deployment.
- No perivalvular leakage.
- Locking mechanism and adaptive seal.
- Pre-shaped for easy crossing of native valve.

As of CRT, the device had been implanted in two patients, and Dr. Grube said it demonstrated:

- Ease of delivery around arch and in crossing native leaflets.
- Disruption of normal flow during deployment kept at a safe minimum.
- Safety in repositioning and retrieval.
- No leakage around the lotus valve.
- Excellent hemodynamic results.
- No obstruction of native coronaries.
- Perfect placement.

MITRAL VALVE REPAIR

Mitral valve repair is controversial because of the many unknowns about the approach: What is the value in reducing grades of mitral regurgitation (MR)? How much reduction, if any, is useful? There are many unanswered questions, including that of Dr. Maurice Buchbinder, director of interventional cardiology at Scripps Memorial Hospital in La Jolla CA, who asked, "What is the glimmer of hope here? In my opinion, a lot of efforts around the mitral valve will be if we can demonstrate value in the earlier treatment of the disease, and that's where our hopes should lie."

Among the interesting comments on mitral valves were:

- **On volume.** *Dr. Niv Ad of Inova Heart and Vascular Institute in Falls Church VA:* "There is a steady increase in mitral valve repair for degenerative disease. Mechanical valves are coming down (in use), tissue valves are stable, and the repair rate is steadily going up."
- **On edge-to-edge repairs.** *Dr. Peter Block of Emery University, a member of Evalve's Scientific Advisory Board:* "This is not a competition (between interventional cardiologists and surgeons). There is going to be a lot of work for surgeons and for interventionalists, and I think that we'll complement each other nicely, particularly in the mitral arena."

EVALVE's MitraClip

Dr. Block cautioned, "Keep in mind that this is not perfect technology at all – yet…There are lots of problems. But there is lots of money and smart people in the U.S. being thrown at it, and we usually come up with some kinds of answers." Dr. Carlos Ruiz, director of structural and congenital heart disease at Lenox Hill Hospital in New York, said that he doesn't share Dr. Block's optimism about mitral repair, "It is impossible for me to believe that one single approach – one single device – can ever fix this problem."

EVEREST Trials of MitraClip

Measurement	Experience n=107
One clip	39%
Two clips	61
Deaths	0.9%
Length of hospital stay	3.2 days
Discharged without home health care	97%
Freedom from major adverse events at 30 days	91%
Re-operation for failed surgery	1
Non-elective cardiac surgery	2
Acute procedural success	84%
Less than 2+ MR	74%

MitraClip Trials

Trial	Status
EVEREST-I (Phase I)	Finished
EVEREST-II	Randomized 2:1 vs. surgery 61% enrolled (169 of 280)
EVEREST-II roll in	Randomized to clip 1,126 Randomized to surgery 53

The MitraClip looks somewhat like a clothespin and goes in through the right femoral vein. The EVEREST trial has been ongoing for a few years, and the non-randomized EVEREST-I feasibility trial is fully enrolled. In that trial, one patient on a ventilator died of respirator failure. EVEREST-II is randomizing MitraClip against surgical repair and replacement. A total of 107 patients are enrolled in both. Dr. Block described the downside to the trials: 10 clips have come off. He said, "If it comes off one leaflet, it stays on the other. At least so far – knock on wood – there are no major problems except mitral regurgitation occurs."

On the other hand, Dr. Block called the 84% procedural success "a remarkable improvement," adding, "You might say that a (mitral regurgitation, MR) drop of 2+ isn't good enough and that surgeons can do better, but the answer is that they don't." He pointed out that surgical options are preserved with the device, "If they need surgery, they can have successful mitral valve repair surgery…Successful surgical repair can be performed up to 18 months post-metal clip procedure. For surgery after clip procedure, 66% had successful mitral valve repair surgery."

The high-risk part of the trial is now closed, according to Dr. Block, who said, "If you have patients who are possible candidates, consider them for this trial because it needs to be finished, and with those data we will take a giant leap forward into where we go with percutaneous repair. That is what's leading the pack."

Dr. Block said that some interesting data are coming out of two studies: the Evalve study and the Myocor surgical side concerning negative remodeling, "It turns out, at least in the Evalve data, that if you reduce MR to 1+ or 2+, the ventricle seems to like it. Now, these are small numbers, but the ventricles in the patients at one year from both studies are improving in their function. The Myocor (data are) a little difficult to interpret. You do change the shape of the ventricle. But the dimensions seem to be improving. That's all good news, I think, for those of us thinking about reducing but not obliterating MR. You don't have to reduce it to 0." Dr. Buchbinder said, "I think it was exciting to see the Evalve data with the ventricle improvement, but I think it is hopeful rather than helpful…Not all MR is obviously created equal. The devices that we are trying to do percutaneously have to match or attempt to match pathophysiologically (i.e., whether it is 2+ depends very much on the pathophysiology being ischemic or degenerative, and within those two there are a lot of subsets). Our devices have to be tailored accordingly." Dr. Michael Mack, a cardiac surgeon from Dallas, said, "There are good surgical data out there…I think that the Evalve trial is great, and we will know what core lab results are." Dr. Block added, "We need to not get into the shouting match of who is better and who is not better…If there ever is a place for surgeons and interventionalists to collaborate, this is where it is."

EDWARDS LIFESCIENCES' Monarc System – *an indirect annuloplasty device using the coronary sinus (CS) approach*

Monarc is a passive fixation, two-stent system: a distal stent into the great cardiac vein (GCV) and a proximal stent into the coronary sinus (CS). The three components are a self-expanding distal anchor, a self-expanding proximal anchor, and a bridge connecting the two anchors. It is made of nitinol with biodegradable elements that degrade over weeks, resulting in a shortening of the bridge by one-third. There is acute shortening but also delayed shortening, as it degrades. The implanted device uses a thumb release to withdraw the outer sheath and release the device in the CS.

Dr. Ruiz said that improvement is seen in the first six weeks with this device, with a MR reduction over time, "We see progressive improvement even at 180 days post implant, and the percentage of patients who responded over time a minimum one grade is quite significant…But there are complications. We saw four deaths, including arrhythmia, pulmonary embolism, and multi-organ system failure."

Dr. Webb gave some preliminary results from the prospective, multicenter Phase I EVOLUTION feasibility trial, using the second generation Monarc system. This was a slight update from data presented at TCT 2007. The primary endpoint is safety in treating functional MR in patients with CHF; the secondary endpoint is reduction in MR by one or more grades. Of the 69 patients, 10 could not have the device implanted. In two other patients, the device was implanted incorrectly. The device is implanted through the jugular, and no general anesthetic is required.

Preliminary EVOLUTION Results

Measurement	Findings
30-day safety, including freedom from death, MI, tamponade	91%
90-day safety	87%
30-day MR reduction	45%
MR improvement of 1 grade	40%
MR improvement of 2 grades	20%

So far, 69 patients have been enrolled, 70% of whom have coronary disease. Five patients went on to elective MR surgery for severe MR. One patient had a coronary sinus lead implanted through the device, demonstrating that it could be done. There were two tamponades related to guidewires and two MIs. A core lab analysis of baseline and 90-day angiograms showed issues in 15 patients.

One problem with the device, identified on 9-day fluoroscopy, was that four patients had proximal separation. There were no complications, but new iterations of the device are being developed, according to Dr. Webb. He called the data an incomplete follow-up but said that responder rates improved over time with a reduction in MR of at least one grade, "It appears to be effective, but not everybody is a responder. Responder rates were higher with worse MR at baseline." Most patients in the study had a baseline MR of 2+, and they are the ones who received the most benefit.

Dr. Webb offered very preliminary conclusions from the interim EVOLUTION analysis:

- Implantation is feasible and reasonably safe.
- Efficacy data are encouraging with 60% MR responders at 90 days.
- Safety data are encouraging with 87% event-free survival at 90 days.
- Coronary compression requires risk stratification.
- Anchor separation requires device modifications.
- EVOLUTION-II will test functional outcomes and risk stratifications.

Asked who is the best patient for the device, Dr. Webb said, "You want to exclude patients with organic or degenerative MV disease; they might be candidates for surgical approach, medical therapy, or perhaps edge-to-edge repair. There is some relevance to some relationship between the CS and the mitral valve, so perhaps CT or MR might be the way to screen people."

MITRALIGN's Mitralign Percutaneous Annuloplasty System – *a direct annuloplasty system*

Dr. Grube described the first-in-man results of Mitralign's new retrograde ventricle device. He said that, on a surgical basis, it mimics suture annuloplasty and makes direct annulus repair with five and seven year durability. It is a left ventricle approach using standard imaging. The three-part procedure involves positioning catheters, placing focal anchor/implants, and placating the annulus. The device is delivered through a 12.5F guide in residence within the LV. The device is introduced through the LV, and a steerable catheter is used to guide it through. The wire is a Trident guidewire which can deliver P1 and P3 anchors. Each wire is then exchanged for an anchor, which has an independent suture extending out of the patient. P1 and P3 anchor sutures are tensioned to plicate the annulus, resulting in direct annular reduction. Plication is adjusted to eliminate MR. The lock is then disengaged from the catheter and the sutures are cut. Dr. Grube said that all preclinical cases took less than 90 minutes, skin-to-skin.

A pilot study was done in one German patient in June 2007, followed by a catheter study of 25 patients in Paraguay from July 2007 to January 2008. A week before CRT, there was a successful implant in one patient in Paraguay. A pilot study of up to 20 patients with 2+ to 4+ MR in Germany and the Czech Republic is enrolling.

The first implanted patient presented with dilated cardiomyopathy, an MR grade 3+, and a NYHA score of III. Access was with a single 14F sheath, and placation resulted in a reduction from 3 cm to 1.5 cm. Dr. Grube concluded that:

- Direct repair affected mitral valve geometry as designed.

- Mitralign has achieved a safe, fully percutaneous direct MV repair.
- Patients' MR was reduced from 3+ to 2+ by independent analysis.

Other mitral valve repair systems worth watching include:

➢ **AMPLE MEDICAL's PS3 – *for asymmetric annuloplasty* – used in the CS.** Dr. Ruiz described this device as "very ingenious" because it uses catheters with magnetic tips to connect the GCV with the left atrial (accessed transeptally). Progressive tensioning between the retainer in the GCV and an Amplatzer device placed in the interatrial septum (IAS) by the bridge element modifies the mitral annulus. Once that is done, the doctor can deploy the anchor bridge in the CS and finally put the Amplatzer device in the interior septum, basically constraining and increasing the same asymmetric type construct of the mitral annulus.

➢ **CARDIAC DIMENSIONS' Carillon and Carillon XE – *an indirect annuloplasty device.*** The original device, an active fixation system, has been modified to fix a problem with clippage. The newer Carillon XE has a double loop in the distal part of the device, Dr. Ruiz said it works better. So far, 34 patients have been implanted, with an MR reduction of 80%. The system employs a distal anchor in the GCV and a proximal anchor into the CS, reduces annulus by traction, and is fully retrievable after it is released.

➢ **MICARDIA's Dynamic Ring – *a surgical/hybrid percutaneous approach using electrodes.*** This comes in two sizes: a reshapeable 28 mm - 36 mm C ring or a D ring for ischemic MR. Without activation, the rings function as standard annuloplasty surgical rings. Pre-attached electrodes are used for activation. Each radiofrequency (RF) wire is connected to the MiCardia RF generator. Following implantation, wires are activated as needed to reshape the ring *in vivo*. Echocardiography is used to gauge effectiveness during and after reshaping.

Early *in vivo* experience in 25-30 sheep showed that the A-P distance was shortened by baseline from 0.5-3 mm, intercommissural distance contracted by 1-2.5 mm, and there was no heat damage to surrounding tissue. The implant ring is accessed via a transeptal approach and through a deflectable guide catheter system for optimal positioning. An expandable basket with built in RF electrodes is used to activate the ring upon contact in multiple zones. In a series of sheep and pig models, investigators were able to activate the ring percutaneously and A-P distances were shortened by 0.3 to 2.9 mm. Inter-commissural distance was contracted as well. Dr. Buchbinder said, "One of the ideas behind this technology is that one can go after the recurrent MR that happens in 20%-25% of patients within two years…As one could guess, these coaxial alignments are not always easy to achieve, so other percutaneous techniques are being developed."

➢ **QUANTUM COR's Q-care – *a direct annuloplasty device.*** This device uses a commercially available source to deliver RF energy. Dr. Richard Heuser of St. Luke's Medical Center in Phoenix AZ, a major stockholder in the company, talked about the first nine sheep implanted: "If you look at the septal lateral segment, it was reduced by about 5 mm. If we look at the overall acute results in animals, there was about a 21% reduction…Acute RF treatment of the mitral annulus with the Quantum Cor probe produced no damage to valve leaflets, CS, or coronary arteries."

The probe has been improved and used on 16 animals. Dr. Heuser said, "The acute success rate mean reduction was about 23%. In the chronic animals, the 30-day outcomes showed a reduction of about 21%. Seven animals total maintained at 60 days at about a 4 mm reduction, and at 90 days it was up to 6 mm. At 180 days, we saw a fairly significant reduction and then it seemed to go up a little bit. We think that there is continued collagen formation and reduction, and it appears to level out between 90 and 180 days."

Dr. Heuser said that one challenge is to get the temperatures right. He said, "This is great in sheep, but what about other models?"

➢ **ST. JUDE MEDICAL's *asymmetrical annuloplasty system* – used in the CS.** This devices uses helical anchors into the left ventricle myocardium between P2 – P3 via the CS and in the vicinity of posterior-medial trigone via the right atrium.

➢ **VIACOR's PTMA – *an indirect annuloplasty device.*** Dr. Ruiz called this a "very innovative device." A catheter is placed like a permanent pacemaker implanted through the superior vena cava into the CS. The distal end is at the AIV, nitinol rods are placed, and it reshapes the annulus by reducing the anterior-posterior dimension. Dr. Ruiz said that the implantation success rate is 3 out of 4, or 75%. The three successful patients had an MR reduction of ≥2+. It was impossible to implant the device in the fourth patient.

MITRAL VALVE REPLACEMENT

Dr. Howard Hermann of the University of Pennsylvania suggested that mitral valve replacement might be more effective than repair. He argued that Edge-to-Edge repair uses a large device and is technically demanding. He said that the CS approach to percutaneous annuloplasty, while truly coplanar with the annulus, can pinch the LC artery. Other unknowns include the long-term benefit of a partial circumference ring and risks of erosion or perforation. For these reasons, according to Dr. Hermann, "There is a rationale to developing a percutaneous mitral valve replacement. He said that the Carpentier-Edwards Perimount valve gives freedom from structural deterioration to patients, including those who are ≥60 years old.

Endovalve-Hermann prosthesis. This bioprosthetic valve utilizes a bio-stable structure to allow both folding into a 24F delivery catheter, and then subsequent rigidity. Clinical advantages of the approach include:

- Reduction in MR that reportedly is as effective as surgery.

- Durability of bioprosthetic leaflets.
- Valve-sparing.

A 24F catheter is pushed over a guidewire into the LA, pops open passively, and control cables allow the attachment claws to retract and advance into the native mitral valve and attach, so that the device can function inside the native valve. A more recent prototype has a skirt attached in order to prevent leaks. The device's leaflet design is not finished. The system allows the physician to turn the valve as it is implanted.

Dr. Hermann claimed that percutaneous or minimally invasive surgical insertion of a foldable bioprosthetic mitral valve is feasible, but he said that the device will have to be oriented correctly. Dr. Block added, "When you think about the complexity of a mitral annulus that needs a circular percutaneous replacement, think of all the planes in which it needs to line up correctly, to achieve the kind of result he showed with the ovine (sheep) model is quite remarkable."

Regulatory Issues for Percutaneous Valves

The FDA's Dr. Zuckerman stressed the importance of percutaneous valve post-marketing plans, "Sponsors are not going to get PMA approval without the Agency and the sponsor coming to substantial agreement on the details of a post-market registry plan…Frankly, sponsors need to come to the plate and recognize this…The good news is that we have a body of experience with standard mechanical heart valves, so we could look at relevant objective performance criteria (OPCs) and look at what types of numbers could cause doubling or tripling of significant adverse events…You have a good control standard (surgical valve replacement), and you're trying to introduce new devices through the percutaneous route. It doesn't mean that it can't be done. It can be done. But it really requires careful design analysis and execution at each stage of the way, meaning both in the preclinical and the clinical arena. From the Agency's perspective, we are willing to interact with the industry at multiple time points. One of the problematic features right now is that industry has been somewhat hesitant to show us some of their results. We're not surprised by device failures; we see the whole landscape, and I think that more interaction with the Agency sooner rather than later is going to help move this field forward."

Dr. Zuckerman added that endpoints for the clinical trials "remain somewhat problematic…The literature isn't as good as we ideally would like it to be. However, it doesn't mean that these trials can't be performed and executed. It does mean, though, that you're facing some difficult compromises and balances, and again it's here where the Agency is very interested in interacting with industry to come up with what we feel are appropriate designs." He said that post-market data are crucial to:

- Supplement the understanding about acute device and operator performance.
- Supplement the understanding about chronic device performance.
- Identify chronic device performance.
- Modify premarket expectations for next-generation devices.

Warning that "there are going to be rare but significant malfunctions," Dr. Zuckerman stressed the "need for assessment of longer-term valve results, with a one- to two-year endpoint and five- to 10-year follow-up." Among the unknowns about percutaneous valves right now are:

- Durability in humans.
- Effects of remaining mitral or aortic regurgitation on ventricular reverse remodeling.
- Effects on heart failure progression.
- Effects on the ability to do subsequent mitral valve repair and aortic valve replacements.

"Certainly the Agency is interested in having the right pre- and post-market balance," Dr. Zuckerman said, adding, "For a first-generation device we're looking for a reasonable assurance of safety and effectiveness, and the law doesn't allow us to trade a post-market study that might be 10 times what the Agency might require for showing us at an approval-type decision that we've met a certain bar and that bar is what we need to appreciate the risk:benefit profile of the device and think that it's appropriate. On the other hand, I'd be hopeful, as we are in the DES post-market arena, that if we're clever with the design of our post-market registry experience that we can utilize the data to feed back to subsequent device iterations such that the eventual premarket burden might be reduced based on the data."

Dr. Mack said that, even with surgery, there isn't a robust long-term database of surgical outcomes: "The STS database's shortcoming is that it is 30-day outcomes, and we don't have anything long-term. We're reliant on CMS and state registry data to know long-term outcomes, and for the most part what you glean is death and repeat hospitalization. So those are the best baseline surgery data we have outside of single-center studies." Referring to the DES stent thrombosis problems, Dr. Zuckerman said, "No one has ESP, and we're not going to know every possible complication, but we have to be realistic and learn from recent experiences. Certainly, one of the lessons learned was that no matter how good we think preclinical and limited randomized clinical trial testing look, there's always going to be a need with these life-sustaining, chronic implants to follow products carefully through the total product lifecycle…What I worry about with some of the registry experience, learned from the DES era, is if we don't have standardized definitions or if we aren't sending important case mishaps to independent clinical events committees, the quality of registries and their utility can be significantly hampered…For those in the industry who may be having another stomachache hearing all this, it's really important again to appreciate that the primary endpoint – which will be a

one- to two-year endpoint, will be important at the time of any advisory panel, but having good longer-term follow-up data on your cohorts in Europe and feasibility data from the U.S. are going to be a critical component of any evaluation. Look at the way DES is being evaluated; the same principles will apply for percutaneous heart valve evaluation. So, it's important upfront to be realistic about what this program is going to need."

Cardiologists pointed out that FDA guidance is not available yet for percutaneous valves, even though it was promised two years ago. However, FDA officials kept repeating throughout the conference: "It's coming." They said that the FDA guidance document has been revised but is still going through legal and administrative review, but one FDA official said it would ***not*** cover percutaneous valves.

Matt Hillebrenner, chief of the FDA's Circulatory Support and Prosthetics Branch in the Division of Cardiovascular Devices (CDRH), speaking at a session on regulatory pathways for percutaneous aortic valves, said to expect:

- Endpoint evaluation time to be longer than one year.
- Endpoints such as survival, hemodynamics, echo dimensions, LV mass, function, aortic insufficiency, quality of life.
- A requirement for good quality data.
- Studies to be considered uninterpretable if large amounts of data are missing.

Asked whether there has been a case where the FDA has accepted a quality of life endpoint for approval in very sick patients, Hillebrenner said, "We fall out on the side of the randomized trial. Everyone assumes that the devices are better because they can be used percutaneously. That's not necessarily true. When you go into the medical therapy arm, we don't know that subjecting a patient to medical therapy is worse than putting in the device…We've talked about whether mortality has to be used, and other user endpoints. If you look up surrogate, none will apply in the scientific definition, but we can talk about alternative endpoints, especially with novel devices, we're going to end up relying on them to some extent in the totality of data. I'm looking forward to seeing the Minnesota questionnaire, because when we talk about quality of life, there isn't anything out there using indices as a secondary endpoint. If the data are aligning and support the ultimate conclusion, that is a comforting result and something that will lead to an approvability decision. We realize the limitations, but you can't just do a mortality study. We've discussed using mortality combined with hospitalization. If there's a way to use other endpoints, we'd be open to that, but it would be a struggle because we can't find that validation."

A recurring point of conversation was the role of grades of mitral regurgitation (MR). Should trials enroll patients with MR 2+ or more or is that a nonstarter? Is a device being set up for success if patients with higher grades of MR are enrolled?

Among the other interesting comments on regulatory issues included:

- *Sadra Medical's official:* "How far along do we have to be to have a meaningful discussion with the FDA? The requirement of randomized clinical trials is probably the right thing, but it is difficult to enroll. There's a reason why only one large company is in an IDE at this point… But there's more than Edwards out there. There are a lot of other companies waiting at the doorstep. How does the FDA value the OUS data? If it's high quality, will it reduce the required size of U.S. feasibility? What are the appropriate endpoints, and is mortality required, or are there other primary endpoints?"
- *Dr. Wolf Sapirstein of the FDA* suggested that medical therapy or even no therapy could be a control for percutaneous valves. "If the patient is a non-surgical candidate …I think there is a justification for compare and control to medical therapy or non-therapy. What else is there?... A lot depends on whether bailout procedures are available. With aortic surgery, they aren't really possible, whereas with mitral devices, there is the availability to go back in and treat patients with surgical intervention… When we start talking about going from 2+ MR to 1+ MR, that's not enough. Conversely, if you had a device that could take people from 4+ MR to 0 MR, and one died, I dare say that, after a year, we'd be hard pressed not to give it a pass. Pre-IDE (data are) really important because all these things get flushed out at that level. As we think about mitral regurgitation, there are some things we'd like to know – do you make the patient feel better? At what cost? How many people die, how many live, and for how long? Even the primary endpoint – it is conceivable that it could be a composition of purely object observations, and those can be put together if it's done carefully."
- *Dr. Jeffrey Borer of New York Presbyterian Hospital/Weil Cornell Medical Center* made the case for using quality of life as an endpoint: "What do (patients) want? They want quality of life, and I'm not so sure they're that interested in how long they will live. The analogy is treatment of patients with heart failure; you don't have to make people live longer with heart failure therapy; you have to make them feel better. I think the analogy is appropriate here. Once you get into the population most affected by aortic stenosis, length of life might not be the key issue. For symptomatic patients, I would say you can make people worse by putting the device in. Data now suggest there's an immediate mortality risk of something like 10%. That might be acceptable if the alternative is going on being symptomatic. The question then becomes, with the valve you keep them alive longer, but maybe that's not the key issue…I don't think mortality has to be an endpoint, and the comparison with medical therapy in very sick patients has great value."

- *Dr. Ruiz:* "We know that medical therapy does not work for those patients, and it's not an option to me. Why not include these patients on a registry?"
- *Dr. Mack, a cardiac surgeon:* "You can randomize patients to device vs. surgery, and most patients will agree to it…But randomized vs. medical therapy is the hard part. There's virtually no pushback from patients on that standpoint…When you flip the coin, and they get medical therapy, it's devastating…Patients on medical therapy are desperate…With the Edwards device and CoreValve, you're starting with 10% mortality, so on Day 1 medical therapy is 10% of where the device is."
- *Dr. Block:* "One of the problems that Evalve is going to have – and all of us will have – when the trial is done, if it is at least equivalent or not terribly different than surgery, there will be this constant reminder of the fact that the bar was set so carefully in terms of patient selection that there is only a very small group of patients to which the results of this trial are applicable. Now go forward five years and paint with a broad brush, and say we have five or six devices, yet the number of patients is still relatively small…Is the FDA setting us all up as interventionalists for a time when we have approval of devices in a very limited group of patients? We all have to understand… that in some situations we should expand the indications. But the only way we will be able to do that is off-label use."
- *The FDA's Dr. Sapirstein responded:* "I'm not condoning off-label use, but if a device is approved and is out there and a sponsor wants to expand indication, a subsequent study can be generated, and that isn't as difficult as the initial study, to get specific indications. This happens all the time now with atrial fibrillation…so I don't think FDA is preventing that from occurring."
- *Dr. Mitch Krucoff, a cardiologist from Duke University:* "The key word is balance. We have to step back and realize not just the surgical comparator but medical therapy is a real player in this universe and is a real option for patients. But…we can all get much smarter about using the clinical perspective. What is the comparator? Where is your device likely to work best and is the trial enrollable? Everyone is talking about relief of mitral regurgitation as if that's specifically what we're after, but what we want to do is to optimize the mechanics of the left ventricle and the heart as a whole by relieving the mitral regurgitation. I would submit that we don't have the answer to the question: How does this treatment affect durability of the repair? And did we do it in the best way for this particular population? For patients with 2+ MR, I can understand why it (percutaneous mitral repair) is a non-starter, but we don't know why people with 2+ MR have a mortality deficit. We know they do, but why? Do they rupture chords? Is 2+ enough to cause MI? We don't know that…We need an effort to characterize these patients better. We need to begin to look at natural history rigorously in the area of valve disease."
- *Dr. Borer:* "(Surrogate endpoints) may be accepted, but it may not be right…Seeing less mitral regurgitation is probably a good thing, seeing a smaller heart is probably a good thing, but what does it mean? It's not enough to say it's a good thing. You need to know what the absolute risk of having the abnormality is...We have to look to measure benefits in terms of quality of life, which is what valve disease therapy surgically is supposed to provide. If we did that, we'd begin to see with plausibility some sort of surrogates which may lead to earlier approval of some of these devices."
- *Dr. Laura Mauri, chief scientific officer at the Harvard Clinical Research Institute (HCRI):* "We're talking about a breakthrough technology. This is a first-in-class type intervention, and we don't know what the standards are for medical therapy and surgical therapy and outcomes and what the benchmarks should be. We need to first understand the mechanism of the effect and ultimately look for real clinical benefits, whether quality of life, hospitalization, or mortality."

ATHERECTOMY

CORONARY

In a recent article in the ***New England Journal of Medicine***, Dr. Tone Vilas and colleagues from the Netherlands reported that manual aspiration of thrombus prior to stenting – using Medtronic's 6F Export Aspiration Catheter – resulted in better reperfusion and better clinical outcomes than conventional PCI. In the single-center TAPAS trial, clinical and angiographic characteristics (e.g., TIMI flow or the presence of a visible thrombus) at baseline were not predictive of patients in whom aspiration was effective.

The researchers found that mechanical removal of a thrombus before PCI reduces the existing source of embolism but does not address platelet aggregates, but they said these can be abolished with platelet inhibitors, suggesting that aspiration and GP IIb/IIIa inhibitors may have a synergistic effect.

In an accompanying editorial, Dr. George Vetrovec of Virginia Commonwealth University concluded that thrombus extraction is a "favorable improvement" that is "conceptually sound and appears to reduce the risk among patients undergoing primary PCI" even though other trials of thrombus extraction devices have had mixed results. He commented that the benefits of aspiration appear "related to enhanced distal-bed perfusion," and he suggested that the TAPAS trial may mean that maintaining arterial flow "limits apoptosis and potentially adverse remodeling."

Yet, Dr. Vetrovec pointed out some concerns with the aspiration approach, including:

- Aspiration catheters could dissect or damage the artery, requiring longer stents and increasing the risk of late restenosis.

- The results came from a single-center trial conducted by very experienced interventionalists.
- It is unclear whether other interventional cardiologists would have the same results.
- ACC/AHA/SCAI guidelines would need to be changed.

Most doctors questioned at CRT about coronary aspiration prior to PCI were familiar with these articles, but they did not believe that they would have any immediate impact on the use of coronary thrombus aspiration. A New Jersey doctor said, "Even with 1,000 the findings were not statistically significant on mortality. I don't think many interventional cardiologists will decide to do thrombectomy without checking the size of the thrombus first. You really need to image first, and that will delay the door-to-procedure time. We need more studies before there is widespread adoption of thrombectomy before PCI."

TAPAS Trial Results of Thrombus Aspiration Before PCI

Measurement	Thrombus aspiration + PCI n=535	Conventional PCI n=536	p-value
Myocardial blush grade post-procedure			
Primary endpoint: 0-1 (absent or minimal myocardial reperfusion)	17.1%	26.3%	<0.001
Grade 2	37.1%	41.4%	N/A
Grade 3	45.7%	32.2%	N/A
Resolution of ST-segment elevation (on EKG)			
>70%	56.6%	44.2%	<0.001
30% - 70%	30.8%	37.9%	N/A
<30%	12.6%	17.9%	N/A
Secondary endpoints			
TVR	4.5%	5.8%	Nss, 0.34
Reinfarction	0.8%	1.9%	Nss, 0.11
Death	2.1%	4.0%	Nss, 0.07
30-day MACE	6.8%	9.4%	Nss, 0.12
Death at 30 days by myocardial blush grade			
Grade 0	5.2%	---	---
Grade 1	2.9%	---	---
Grade 2	1.0%	---	0.003
Adverse events by myocardial blush grade			
Grade 0	14.1%	---	---
Grade 1	8.8%	---	---
Grade 2	4.2%	---	<0.001
Other adverse events			
Major bleeding	3.8%	3.4%	Nss, 0.11

PERIPHERAL

Sources said their atherectomy volume increased an average of 3% over the last year, but they predicted it would remain flat through 2008. Other than balloons, doctors insisted that there are not enough data yet to determine which of the atherectomy approaches – lytics, lasers, cutting devices – or stents is best. Most said they are using EV3/Fox Hollow's SilverHawk. A Texas doctor who said he is about to check out Pathway Medical Technologies' Pathway PV Atherectomy System, commented, "All the atherectomy devices have merits for SFA. There is no clear cut technology winner." A speaker said, "There is a paucity of ***good*** data to favor any particular treatment modality…There has been a lot of talk about laser atherectomy but not much data vs. SilverHawk." A European doctor said, "Use is relatively flat because of the lack of proven evidence of the different treatments…I use SilverHawk when I need something, but that is only for a handful of cases. SilverHawk is better than a laser because the laser is bigger (has a bigger footprint)."

Possis was showcasing its new Angiojet Ultra at the meeting. A sales rep said the company is not pushing this device yet to accounts doing <5,000 procedures a year with the old Possis Angiojet. Doctors who have an existing Angiojet and want to upgrade to the Angiojet Ultra have to trade in the old machine (or sell it on the used equipment market); Ultra is not a simple upgrade of the older model. The purported advantages of the Ultra are that it is "easier and faster." Reportedly, a new feature will be added late this year that will only work with Ultra – a 3F coronary peripheral catheter, and after than a pulmonary embolism catheter is expected to be introduced. One doctor commented, "I haven't seen it, but it is not a bad idea. But it has to be quick because it (Angiojet) takes too long now."

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Dr. Nelson Bernardo's Peripheral Device Recommendations

Location	Catheter size	Introducer sheath length with femoral artery access	Balloon catheter length	Best stent
Carotid	6F	90 cm	130 cm	Nitinol self-expanding
Subclavian	7F	90 cm	130 cm	Nitinol self-expanding or PTFE-covered
Iliac (common)	7F	23 cm	80 cm	Nitinol self-expanding
Iliac (external)	---	11 cm ipsilateral 55 contralateral	80 cm ipsilateral 80 contralateral	Nitinol self-expanding
Superficial femoral artery (SFA)	6F	55 cm	130 cm	Nitinol self-expanding
Below the knee (BTK)	---	90 cm contralateral 55 cm antegrade	150 cm contralateral 130 cm antegrade	Nitinol self-expanding or PTFE-covered but avoid stenting if possible