Trends-in-Medicine

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by Lynne Peterson

SUMMARY

Drug-eluting stent (DES) penetration has dropped to ~70% of procedures, and interventional cardiologists expect it to drop further before bottoming and bouncing back a little. ♦ The COURAGE trial, to be released soon, is expected to show that PCI is no better than medical management, and that may affect use of stents as well. ♦ **Medtronic's Endeavor** and **Abbott's Xience** stents are likely to face little or no delay in FDA approval because of the stent thrombosis issue, but other new DES may experience delays. The FDA is preparing new guidance on requirements for DES approvals, and this is expected to mandate: longer and larger trials, more "real-world" patients, and clinical endpoints. ♦ Despite pleas from interventional cardiologists to loosen approval requirements, the FDA remains adamant that randomized clinical trials are required for approval of PFO closure devices and percutaneous heart valves. ♦ Doctors were speculating about possible future CMS restrictions on reimbursement for PFO closure devices and off-label DES use.

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CARDIOVASCULAR REVASCULARIZATION THERAPIES (CRT)

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Percutaneous heart valves and patent foramen ovale (PFO) closure were hot topics at CRT this year, but the meeting was dominated by discussions of the safety of drug-eluting stents, including a full-day *Workshop with the FDA*. CRT, sponsored by the Cardiovascular Research Institute at Washington Hospital Center, was attended by many of the leading experts in each field as well as FDA officials. This was the first public discussion of drug-eluting stents since the FDA Circulatory Devices advisory committee meeting in December 2006 and came less than a week after the same panel discussed PFO closure.

DRUG-ELUTING STENTS (DES)

The safety of drug-eluting stents was clearly on the minds of industry and interventional cardiologists at CRT. In addition, "The High Road Going Forward," a DES "think-tank," will be held in Washington DC on May 3-4, 2007, with the FDA, European regulators, etc. participating.

The outlook

According to interventional cardiologists questioned at CRT, DES use now is ~70% of patients nationally, though this varies from cath lab to cath lab. Doctors generally agreed that DES use will decline more over the next six months, perhaps down to an average of ~50%-60%, before rebounding and perhaps settling at the end of this year at around 65%. In addition, several doctors noted that the number of stents being used per case is declining.

Patients who are not getting a DES now who would have gotten one before are mostly getting a bare metal stent (BMS), but some are getting coronary artery bypass (CABG). Sources predicted this should stop the decline in CABG rather than increase CABG procedures (flatten the curve).

The release of the COURAGE trial – percutaneous coronary intervention (PCI) vs. medical therapy – at the American College of Cardiology (ACC) later this month is also likely to depress DES use. Sources believe the trial will show no advantage to PCI, and perhaps even a slight advantage to medical therapy. While most of the stents used in COURAGE were BMS, sources predicted that use of all stents, including DES, will be negatively impacted, at least initially. COURAGE is a prospective trial of 3,260 patients followed for 3-6 years at 38 sites (12 VA, 13 U.S. non-VA, and 13 Canadian). It is funded by the U.S. and Canadian governments as well as multiple sponsors from industry. This trial is also evaluating the cost-effectiveness of PCI, but those data are ***not*** expected at ACC.

Stable patients with angina, prior myocardial infarction (MI), or silent ischemia were randomized to PCI plus maximal medical and lipid-lowering therapy (simvastatin) vs. no PCI but with equal medical and lipid management. Medical therapy is aggressive, including aspirin, Plavix (Sanofi-Aventis, clopidogrel), simvastatin (with an LDL target of 60-85 mg/dL), long-acting metoprolol and/or amlodipine, long-acting nitrates, lisinopril, and tirofiban (Merck's Aggrastat) and/or low molecular weight heparin (LMWH), if needed. The primary endpoint is a composite of all-cause mortality, MI, or hospitalized biomarker-positive (abnormal troponin and/or creatine kinase) acute coronary syndrome. COURAGE is powered to detect an absolute 4% (relative 21%) difference in the primary endpoint, with the main hypothesis that PCI plus aggressive medical therapy (projected event rate 15%) will be superior to medical therapy alone (projected event rate 19%).

Among the experts who spoke on DES were:

➢ ***Dr. Marty Leon*** of Columbia Presbyterian Hospital in New York said, "DES penetration is ~70% (nationally), and this may go down further…The message to the FDA is: Preclinical study of these devices has to be tighter and more rigorous…I bristle at the notion that we have been cavalier about this (DES)…There is no subject in medicine that has been studied with this degree of exhaustive completeness over a short period of time…Perhaps the focus – efficacy – was wrong. Today, safety is clearly the prime consideration with new devices." He described DES penetration as on a downward slope but likely to rebound.

➢ ***Dr. Jeffrey Popma,*** Director of Interventional Cardiology at Brigham & Women's Hospital, said that what is needed next in DES is:

- More patients and longer follow-up for new molecular entities (NMEs).
- Less rigorous pathways for iterative stent designs for approved indications.
- Acceptance that treating "complex disease" will result in higher complication rates.
- Longer term outcome studies in complex patients.
- Differentiation of the dual antiplatelet effects on stent thrombosis vs. non-target lesion MIs.

➢ ***Dr. Renu Virmani,*** a pathologist with CV Pathology, argued:

- Randomized clinical trials (RCTs) must be performed on a large number of patients with a disease that affects the majority of real-world patients following observational and safety studies.
- Data should be collected at a non-company facility.
- During follow-up, every effort must be made to collect data on cause and circumstance of death.
- Autopsies should be requested on the consent form, including limited autopsy options (e.g., heart only).
- Follow-up should be for three to five years.
- Hearts should be sent to a central lab that has the knowledge and methods needed for examination of the heart and stents.
- A panel of experts (including a pathologist) should decide on the cause and manner of death when autopsies are not performed.
- She called the ARC definitions of stent thrombosis "absurd." She called it a "skewed definition to hide deaths related to DES."

➢ ***Dr. Ron Waxman*** of Washington Hospital Center, Course Director of CRT, said a recent poll on CRTonline asked what interventional cardiologists would like to see in the revised FDA requirement for DES approval:

- 8.33% said longer follow-up for premarket studies.
- 14.58% said longer follow-up for post-market studies.
- 8.33% said broader inclusion criteria for premarket studies.
- 54.17% said all of the above.
- 14.59% said none of the above.

Dr. Waxman said that what needs to be done now is:

- To take a more responsible approach – and not follow in the footsteps of the airline industry.
- FDA to reassure patients and physicians that DES are safe and effective. He said, "They (FDA) made one statement, but probably they are not communicating well."
- FDA needs to work with industry and academia to simplify the approval process.
- Industry should stop the DES war and Dear Colleague letters that their product is better than bare metal stents or another DES and continue to invest in new DES technology.
- Academia needs to invest in the education of physicians and patients, design and conduct trials, and refrain from publishing incomplete data.
- The media needs to stop the attack on PCI and DES and stop scaring patients.

The industry perspective

Officials of both **JOHNSON & JOHNSON** and **BOSTON SCIENTIFIC** said they supported the FDA's draft guidance on DES. Dr. Donald Baim of Boston Scientific added:

- "The FDA decision that these devices are safe and effective should stand…No matter how we look at the Taxus data, we can't find a 0.5% excess mortality…What puzzles me is how we can have the best and most rigorous trial science mixed in with impressions and media opinions in this complex stew that is still confusing the safety and effectiveness of these devices on-label."

- "There are slightly higher event rates with off-label use. I think that result is still in the range of what we expect for the treatment alternative – bypass – over the two years of follow-up. But our job, as industry, is to provide that in randomized trials."
- "New devices really should be required to show safety and efficacy to the same level of rigor as these devices (Taxus and Cypher)…but I agree that the hurdle for minor changes in stent geometry – with the same polymer and drug – should take somewhat less in terms of a clinical trial burden or else the pace of development will slow down or stop."

JOHNSON & JOHNSON/CONOR'S CoStar

Results from the pivotal COSTAR-II trial of CoStar will ***not*** be at ACC but ***will*** be at EuroPCR in May. An expert said this makes him think the data will be neutral to negative, but he admitted he hasn't seen the data yet. There is a rumor that there is an issue – restenosis or stent thrombosis – at the well sites in patients with a CoStar, but that rumor could not be confirmed.

REGULATORY ISSUES

The FDA can't approve new iterations of approved DES, percutaneous heart valves, and PFO closure for stroke any faster, according to Dr. Bram Zuckerman, Director of the FDA's Division of Cardiovascular Devices in the Center for Devices and Radiological Health (CDRH). He explained, "We need reasonable assurance of safety and efficacy. That is a common theme with all these transforming technologies… We really don't have the data right now." He suggested that pooling data for any of these devices is an option that sponsors could consider. Ashley Boam, Chief of the FDA's Interventional Cardiology Devices Branch at CDRH, said, "The time to scale back the recommendations…is really when you have a good understanding of the technology and how it works. What is interesting about DES is that it is much more difficult to say you have a broad understanding of the stents. We have two stents with drugs studied (Cypher and Taxus)…We have stents coming with drugs never studied before…and polymers never studied in vascular indications…So, while we know a lot about Cypher and Taxus, we can't always take that information and take it forward…For that reason, the recommendation for 2,000 patients revolves around new drugs – those never studied before. If someone comes up with new limus never studied before in humans, there will be a need to study low-rate toxicity." (***Translation:*** longer and bigger trials).

On the drug side of the FDA, the Center for Drug Evaluation and Research (CDER) is "very interested in the dual antiplatelet side of the DES stent thrombosis issue." Dr. Andrew Farb of the FDA said that, following the FDA Advisory Committee meeting in December on DES, the FDA needs to determine several things about dual antiplatelet use with DES:

- The profile of patient compliance with dual antiplatelet therapy.
- Definite rate of significant bleeding complications with dual antiplatelet therapy.
- Identify what, if any, bridging strategies are used during dual antiplatelet interruption.
- Determine actual Plavix prescription patterns.
- Whether invasive/surgical procedures are being deferred due to prescribed dual antiplatelet therapy.

The DES outlook

New DES are expected to go before an advisory panel for the next couple of years at least, and panel meetings may be scheduled with just 6-8 weeks notice. The posted Cardiovascular Devices advisory committee schedule does not mean there won't be additional panels added, an FDA official noted.

The FDA (CDRH in conjunction with CDER) plans to issue "later this season" a **guidance document** on the design of DES trials. When the guidance document is completed, there will be a public workshop to discuss it. No DES investigational device exemptions (IDEs) or premarket approvals (PMAs) are being held up pending completion of this guidance document, an FDA official insisted. Right now, the guidance document is still being developed, but it is likely to require:

- More diabetic patients.
- More 2 vessel patients.
- Continued emphasis on post-marketing registries.
- Perhaps restricting IVUS and angiographic follow-up until after the clinical endpoint time has been reached so as not to confound that endpoint. Collection of IVUS and angiographic data will probably be done in a separate study or after the clinical endpoint data are collected.
- That late loss not be the primary endpoint. An FDA official said, "Late loss as a stand-alone primary endpoint for a brand new stent is not appropriate any more."
- 2-year follow-up.
- Perhaps tougher preclinical data (bench and/or animal), which is what Dr. Marty Leon was recommending the FDA require.
- At least 2,000 patients for safety for a new drug.

The FDA ***is*** approving IDEs for DES, and IDEs are not being delayed because of the stent thrombosis issue or to wait for the new DES guidance document. In fact, an FDA official said, "I've had plenty of meetings in the last 60 days (about IDEs) that would indicate people are going ahead without a (FDA) guidance document."

MEDTRONIC'S Endeavor and **ABBOTT'S Xience** are likely to face little or no delay in FDA approval because of the stent thrombosis issue, but other new DES, especially if an NME is involved, are expected to be delayed, though an FDA official said the Agency's goal is not to make it a significant delay. The official said, "Obviously, there is no intention to put the brakes on, but we don't have blinders on either…For companies (with DES) in progress, there are serious issues that we do feel need to be addressed, but we also recognize that these programs went forward based on best guidance at the time, so we have been sitting down with the companies and starting to talk about the best way to address our concerns without throwing the blocks (brakes) on ongoing programs."

The official said the FDA doesn't want to change the rules of the game on companies that are nearly finished, but the Agency ***is*** changing them for companies that are not as far along. However, new iterations of existing stents still can't be approved in the simplified way that new BMS are approved.

Reimbursement

An expert said, "CMS is in active discussions on a national coverage decision on both DES and PFO closure, but no decision has been made whether to do that or not. It is an important issue, and I hope they do it – at least with PFO closure." Other opinion leaders were not aware of any CMS plans for a national coverage decision on either PFO devices or DES.

Percutaneous heart valves

FDA officials indicated the Agency will ***not*** retreat from the requirement for RCTs for approval and will not grant a humanitarian device exemption (HDE) for mitral valves. Several experts were urging the agency to allow a registry instead or historical controls and to grant HDEs for mitral valves, but FDA officials remained adamant that RCTs are required and showed no interest in HDEs for that indication. In additional, for mitral valves the FDA will require that patients demonstrate ***functional improvement***, not just an improvement on echocardiography.

Cardiologists have also failed to convince the National Institutes of Health (NIH) to sponsor a trial comparing percutaneous mitral valves and surgery. An NIH official stated flatly that NIH is not interested in doing that type of trial, "Comparing one device to another or one procedure to another is less interesting (to NIH)…than the question of repair (vs. replacement)…For us to compare one device to another, where devices are evolving, is not our most effective mission."

PERCUTANEOUS HEART VALVES

This is estimated to be a very large market. In 2002, for example, there were $870 million in valve repairs and replacements, using $305 million worth of prosthetic tissue valves. Currently, at least 33 companies have percutaneous valve programs underway, including 16 mitral valve programs, 13 aortic programs, 4 pulmonic programs, 4 trans-apical programs, and 16 less-invasive programs. A cardio-thoracic surgeon said, "There is a huge population of patients that even when we see them as surgeons we do not feel are candidates for surgery." Dr. Marty Leon said, "There is clearly an unmet clinical need that has been underestimated and oversimplified in the past."

Aortic valves

Trial design is still controversial. Experts and regulators have not agreed on:

- **Inclusion/exclusion criteria.**
- **Relevant endpoints** for PMA trials.
- **Indications for use and labeling.**
- **The appropriate control groups.** For aortic valves, surgical controls have several issues:
  - *Surgical controls might include all patients with symptomatic severe aortic stenosis (AS).* An expert said, "Many experienced surgeons have publicly stated that 'there is no such thing as an inoperable aortic stenosis patient, especially the octogenarians'…Or surgeons who say, 'I cannot remember the last time I turned down an AS case.'"
  - *They could include selected patients with AS and significant comorbidities with logistic EuroScore of ≤15 or STS score <10 (8-10).* An expert said, "This is a so-called 'higher risk surgical group' yet still operable with relatively acceptable surgical outcome."
  - *They should not include patients in the "poor operative" condition with critical AS and EuroScore >20 or STS ≥15.* In those patients randomization to surgical treatment may be impossible.
  - *Balloon valvuloplasty patients might be useful.*
  - *Historical controls have hazards.* A statistician said, "Historical control data may not be a very good option for approval (of percutaneous valves) currently, though it might be valuable in determining new designs (e.g., future iterations of an approved valve)." Problems with historical controls include:
    - **a.** Validation.
    - **b.** Replication of the same inclusion/exclusion criteria.
    - **c.** Replication of the same definitions of safety and efficacy endpoints.
    - **d.** Blinding.
    - **e.** Confounding by time.

- **The definition of the high risk patients** (e.g., STS score vs. logistic EuroScore). An expert joked, "It's like pornography. You know it when you see it." Dr. Julie Swain, a cardiothoracic surgeon with the FDA, suggested that surgeons, in collaboration with cardiologists, decide which patients are eligible for percutaneous valves using the STS score, adding, "Using the EuroScore is not validated and is probably invalid…What is high risk? You won't find surgeons agreeing, so I don't use that term any more. Maybe we can say 'elevated risk.' And surgeons in one state may view it very differently than someone else…The definition of high risk is a moving target that is generally not agreed on by the surgical community."

Even bench testing of these devices has not been perfected. An industry speaker said, "In addition to standard benchtop testing and animal testing, developers should perform:

- Cadaveric studies on AS hearts.
- Acute implants prior to aortic valve replacement.
- First-in-man testing on non-surgical patients with severe AS under very controlled conditions and in collaboration with surgeons."

Issues which bench testing do not address but which are important include:

- Ability to exclude the native aortic valve.
- Valve retention forces.
- *In vivo* durability of valve leaflets.
- Durability of novel stent designs. An industry speaker commented, "We don't even know how to do finite element analysis (FEA) on a lot of these new stent designs."
- Paravalvular leak risk.
- Delivery system performance in tortuous and diseased anatomy.

Dr. Michael Mack, a cardiothoracic surgeon from Dallas, argued that the STS score is the best measure of a patient's level of risk. He compared STS with two other common scoring methods, but he noted that many risk variables are not included, such as chest radiation, advanced liver disease, number of previous sternotomies, oxygen dependence, etc. And he said that all risk algorithms are based on operated patients and don't factor in inoperable patients.

Dr. Mack said that, of 52 patients screened for transcatheter aortic valve replacement (AVR) trials in Dallas since August 2006: 5 were transplanted, 4 are scheduled for valve transplant, 7 are awaiting entry into a pivotal trial, 9 didn't participate because they or their family turned down the trial, 8 were turned down by surgeons, 8 are still under evaluation, 4 died during the evaluation process, and 7 were candidates for conventional surgery. He said, "There is a large pool of patients who are not candidates for conventional AVR or who can be defined as very high risk – which is best defined by the STS risk algorithm, supplemented by clinical judgment."

Dr. Rob Michaels, president and COO of **CoreValve**, said there are also post-marketing challenges that need to be considered, "Everyone is convinced that getting market clearance is an uphill battle, but a lot of people forget, ignore, or miscalculate the slippery slope that is the post-clearance challenge. We need to clearly define who are the first people who get to use a novel device, well define the training, and there has to be post-surveillance. And then there is the business consideration of iteration, operations perspectives, and something that is as important as clearance – reimbursement."

Dr. Michaels recommended that the early adopters of percutaneous valves be Centers of Excellence with:

- Related and extensive experience with balloon valvuloplasty.
- Real interdisciplinary cooperation.
- Sufficient patients to get through the learning curve and become the teachers for the next generation of users. And, he pointed out, it isn't just physicians who need training: company personnel and proctors, cath lab staff, and pre-procedural data providers all will need training.

The aortic valves used by surgeons did not gain FDA approval through randomized clinical trials, and several experts urged the FDA to allow objective performance criteria (OPC) for percutaneous valve approvals. Dr. Swain said, "We will consider virtually any type of trial design…You can propose anything …(But) this is absolutely new technology, first-in-kind with an unknown risk:benefit profile, and the objective performance criteria for implantable surgical valves were developed over a decade of literature after a couple of decades of clinical experience. So using valve OPCs, I don't see how beneficial or relevant that would be." Dr. Zuckerman added, "You have posed a difficult question. We have a transforming technology, and you want to

Comparison of Valve Patient Scoring Systems

Measurement	STS	EuroScore	Ambler
Number of relevant variables	26	17	9
Risk prediction	Slightly under predicted	Over predicted by 2-3x	N/A
Data to be presented at AATS* meeting on 538 AVR patients			
Highest 10% of risk	36.02%	13%	17.2%
Mean predicted mortality for the highest 10%	13.4%	54.1%	45.5%
Observed early mortality	19.0%	15.5%	12.8%
% of observed overall mortality	65.5%	51.7%	38.5%
All mortality odds ratio	1.24	1.04	1.05

* American Association for Thoracic Surgery (AATS) meeting is May 5-9, 2007, in Washington DC.

find the least burdensome way to get it to market. We are required by our regulations to consider the least burdensome way to market, but we also have to establish reasonable assurance of safety and efficacy pre-approval, not post-approval."

Other comments on percutaneous valve trial designs included:

- *Dr. Marty Leon urged a registry for patients not eligible for randomization in a clinical trial:* "It is painful to see the foot-dragging…We screened >200 patients, and it is painful…The delays and interruptions in a study are very difficult…I think it (the trial) has to be randomized and has to be the subset of elevated risk patients. We are still struggling with the non-operable patients…We have patients with a known risk of 25%-40% mortality at one year if they are randomized to best medical therapy, and that is a difficult experience…It is very difficult to randomize these patients…There are ethical and emotional considerations that sometimes override the rigors of the clinical trial process."
- *Dr. Peter Block of Emroy also argued in favor of a registry for non-randomizable patients:* "I don't think any of us are against a randomized trial. Most investigators, I think, are in favor of an RCT…but from the outside it seems there is foot-dragging…and that needs to be overcome, and we need to get on with it! We started looking at randomized trials months ago…and now we are still sitting here in March 2007 saying maybe we need a few more of this and that. When will we get to the end of this?...The bottom line is that we are all dealing with patients who essentially have a death sentence within a year…To randomize them to medical therapy is very difficult when we have a technology (like percutaneous valves)…We are saying please let me have an option for the 90-year-old lady who I can't send to surgery."
- *Dr. Mitchell Krucoff, an interventional cardiologist from Duke, suggested one trial design does not fit all devices:* "I look at it as not so much foot-dragging, but we are in danger of combining too many issues into one clinical trial design rather than thinking more systematically about technical features…A lot of technical progress has already been made to simplify the procedure…These devices are very different in their design…How much do we know about durability...and, ultimately, the…clinical outcomes…To think we can develop one trial design to cover moving technical issues, moving design features… is why the discussions have been so slow to move forward…Another approach is to randomize centers – include centers with no percutaneous valve program…I think it has been pretty clear that this is an area that needs creativity, statistical soundness, and clarity of objectives."
- *Another speaker urged the FDA to allow surrogate endpoints in valve trials:* "One needs to show safety and efficacy, but it is also important not to make the regulatory hurdle so high that it is impossible, and the place that could happen is with valves. I think some surrogate for clinical outcomes needs to be developed. I'm not a big enthusiast for surrogates, but there may be places where we can define the parameters…Valves, especially aortic valves, may deserve thinking along these lines."

The FDA's Dr. Zuckerman responded, "Certainly, we don't claim to have all the answers…But we also need to appreciate certain realities. We are talking about a really new design (percutaneous valves)…We want to reach a point where we have an OPC structure…but just the basic engineering (of percutaneous valves) is not as well understood as we would all want…We need to know they are safe long-term…One thing that has limited the pathway in the U.S. is the lack of recognition that this is an extremely high risk procedure, and there needs to be good, independent data safety monitoring. If we look in aggregate at some of the results, they are not all rosy. There is a learning curve, and that is the reality. As to where the Agency can go…We are just looking for ways to minimize bias, confounding, and chance, so that, at the end of the day, both industry and the Agency have a clear idea of what the data say…We've heard in aortic and mitral situations that there is a critical lack of data for good, precise risk stratification. Our goal in designing aortic trials for surgical risk in higher risk patients who are given med treatment or a percutaneous valve is to come up with datasets at the end of the day that both industry and FDA can interpret such that we agree on the results. That is a big challenge, and we think the RCT design is the cleanest, most effective way to get there. Certainly, there will be controversy. Can we define this really, really high risk aortic population that should unquestionably get a valve? You are thinking of some HDE population. I would encourage you to think further about it…Do careful enrollment logs at your institutions…and we are always willing to reconsider…***But*** one of the central points is we are just now starting to get the type of data that show the limitations of STS, and especially EuroScore, in defining appropriate populations."

Sadra Medical is one of the 13 companies with aortic valves in development. Dr. Donald Baim, Chief Medical Officer of Boston Scientific, which has an interest in Sadra, described **SADRA'S Lotus** valve. He said, "This is designed to address some of the remaining shortcomings – delivery (with a retrograde approach and large delivery sheath profile), positioning (lack of precision and reversibility), peri-prosthetic leaks (which have come down but still exist in some patients).

The Lotus valve is trackable, with a reduced profile, and has:

- Streamlined delivery, with a self-expanding nitinol stent with pericardial valve sewn in the distal end.
- Accurate position and secure placement. It is self-expanding and self-centering during passive shortening. Radial force and retention are optimized.
- Non-occlusive during deployment. The valve begins to function almost immediately during unsheathing.
- A seal minimizing peri-valvular leakage.

- Repositionable. It can be elongated, recaptured, and repositioned as needed at any time prior to final release."

The Lotus valve has gone through preclinical testing, including acute porcine studies, diseased cadaver hearts, percutaneous cadaver studies, and some surgical procedures. The first-in-man is expected to start by mid-2007, initially using a 21F device, but in late 2007 switching to a 19F device that is now in bench testing. The valve comes pre-assembled from the factory, and – unlike the CoreValve or Edwards valves – the valve does not have to be crimped on the delivery catheter.

Mitral valves

Dr. Howard Herrmann of the Hospital of the University of Pennsylvania in Philadelphia said surgery remains the gold standard for mitral regurgitation (MR), but he said surgical risks are higher than most people think, and the results are not as good as people assume. He pointed out that repair is generally preferable to replacement, and he said the key roadblocks to percutaneous mitral valves are: folding, deployment, alignment, attachment, anchoring, durability, and sealing. He cited four myths related to percutaneous mitral valve replacement (MVR).

- **Myth #1:** ***Repair is always better than replacement due to improved survival.*** He said, "Most of the (repair) data are…old data. The reason for the difference in repair vs. replacement is likely due to severance of chords. When chords are preserved during mitral valve replacement, the results are likely to be similar to repair. There has never been a randomized trial comparing these, but there are a number of non-randomized comparisons. Repair is better than replacement only in lower risk patients…And bioprostheses are getting much, much better."

- **Myth #2:** ***Surgery has a very low risk and very, very low morbidity.*** He said, "Overall complications are 24.7% with replacement, and hospital readmission rates are not trivial – 22.2% in all comers in a Medicare database."

- **Myth #3:** ***Repair valves have no leakage in long-term follow-up.*** He said, "Data show 40% of patients in five years have MR 2+ or greater."

- **Myth #4:** ***Percutaneous repair mimics surgical repair techniques.*** He said, "It is unlikely we will achieve perfect results with all patients with a percutaneous approach. There is a subset of patients who will respond to (percutaneous valves), but we don't know how to select them yet…This is not yet quite as perfect as surgery."

A cardiothoracic surgeon raised an interesting point. He asked what happens to the atrial fibrillation (AFib) patients who get both their mitral valve and their AFib treated in one surgical procedure if patients get their mitral valve fixed percutaneously. He said, "About a third of patients presenting for mitral valve surgery have AFib, and we know the combination of mitral valve disease and AFib is not a good outlook…The first step in mitral valve disease is to push surgeons to do more repairs (rather than replacements), to move from mid-sternotomy to minimally invasive (procedures)…I think ~50% can be done minimally invasively. And then look into percutaneous approaches to supplement mid-sternotomy patients, not the replacement patients."

The role of an RCT in mitral valves was described not just as a way to determine if a product should be approved but also to illustrate for practicing physicians what the choices and trade-offs might be for individual patients who would qualify for either therapy. Logistical challenges to a randomized mitral valve trial include:

- **Enrollment.** This can be strongly influenced by referral patterns, making participation of key stakeholders necessary. Strong patient/physician preferences (for one type of procedure or another) must be overcome to allow randomization.

- **Bias.** Blinding is not reliable for patients and sometimes not for assessments of efficacy.

- **Generalizability.** Can what one operator does be duplicated by other operators. What is the device learning curve?

- **Hypothesis testing can be quite complex.** EVALVE "jumped two feet in the river" with its EVEREST trial to try to show safety superiority vs. surgery and non-inferiority on efficacy.

Other percutaneous mitral valve development challenges include:

- **Technology.**

- **Clinical.**

- **Regulatory.** Ferolyn Powell, president and CEO of Evalve, said, "We've been working on Phase I for four years. By the time we get to (an FDA) panel, it will be almost seven years. Eventually, we will come to a consensus on what the clinical trial design should look like. A company entering (this field), must put a stake in the ground and choose a design…So, there is a risk – Did we choose the right design? Maybe that's why we chose an RCT because it was the most clear-cut way to ensure that trial designs wouldn't change before we got to a panel."

- **Reimbursement.** Powell said, "It is great if a device works, but if people don't get paid to use it, it won't get used."

- **Time.** Powell said, "We are looking at three years before U.S. approval (if all goes well)."

Other comments on percutaneous mitral valves included:

- *Cardiothoracic surgeon:* "Mitral valves are much more difficult to sort out on operative risk because there are so many different diseases captured in mitral valve repair/

replacement…If you look at single-center (percutaneous valve) series, the problem is that you have surgical excellence there that is not reflective of the real world…It is very difficult to define a high risk population or risk vs. surgery for mitrals…One of the issues is the applicability of the (percutaneous) results."

- *Interventional cardiologist:* "In the long run, mitral devices will be very different from aortic valves. This is not like DES, where use went off-label. I don't think it will be easy to go off-label in mitral valves, and I don't think we should initially…I urge caution getting outside of trial guidelines…And I think all the endpoints will be soft endpoints, like, 'Do you feel better?' The FDA will have to ask investigators to define endpoints carefully and then go for it, but it won't be body counts."
- *FDA's Dr. Zuckerman:* "The trials are moderate in size but designed to measure both echo parameters and actually how the patient is feeling and doing (NYHA class)…The FDA is obliged to look at the totality of the data, consider the patient as a unit of analysis, and that is the key point…Even if you win on echo criteria, if we can't establish that the patient is doing better, we have a problem here. This underlines the need for good trial execution and careful gathering of secondary endpoints …We want to find an appropriate control to compare (percutaneous mitral valve) against in an equitable fashion."

Asked why a registry is possible with mitral valves but not with aortic valves, an FDA official pointed out that balloon valvuloplasty is available for aortic patients but no such treatment is available for mitral patients, which is why the difference in the registry approach. Dr. Leon responded, "Valvuloplasty is tantamount to no therapy in aortic. (Valvuloplasty) is no option…It is palliative for short periods of time only."

PATENT FORAMEN OVALE (PFO) CLOSURE

Dr. William Maisel of Beth Israel Deaconess Medical Center in Boston, the chairman of the FDA panel which discussed PFO closure for stroke on March 2, 2007, reviewed the panel discussion at CRT, suggesting there "may be a lesson or two to learn from the history of PFO for percutaneous valves" – in terms of HDEs, high risk patients, lack of currently approved devices, FDA advisory panel requirements for RCTs, etc.

Dr. Maisel pointed out:

- Randomized clinical trials are necessary, and the panel expects the companies to complete the ones that are ongoing. He predicted those ongoing trials could be completed in another two or three years.
- The slow enrollment in ongoing clinical trials has been due to off-label device use and patient/physician bias.
- Medical therapy is the standard of care for first cryptogenic stroke; PFO closure is ***not*** the standard of care.
- For patients with a first cryptogenic stroke, any of the following would be acceptable:
  - A longer enrollment window.
  - Broadening enrollment criteria – transient ischemic attack (TIA), age, etc.
  - Other randomization schemes (e.g., 2:1).
  - Pooling of control data from different trials as long as patients are relatively comparable. However, there appears to be little interest by industry in doing this.
- Professional medical societies should conduct physician and patient education campaigns to get physicians to enroll patients in ongoing trials.
- The FDA made the right decision to allow patients at perceived higher risk, who fell under the previous HDE definition, to be entered into a registry that collects data on those patients but which may not lead to device approval.
- The panel does not approve of reducing the number of patients needed to complete the ongoing trials.
- The sample size in a trial varies by what the trial is designed to show.

Sample Size Needed Based on Risk of Stroke

Risk of stroke		Sample size
Control	Treatment arm	
4%	1%	396 patients
4%	2%	1,130 patients
6%	2%	358 patients
6%	3%	741 patients
8%	4%	552 patients
10%	5%	432 patients
12%	6%	351 patients

Dr. Horst Sievert, formerly of Germany and a new member of the Washington Hospital Center staff, thinks the question of PFO closure and stroke has already been answered, declaring, "There is no question that a PFO may cause stroke." He posed several questions and offered answers to those questions:

- *Do patients with stroke due to a PFO have a risk of recurrence?* This has been shown in a number of different trials. The annual risk for stroke or TIA after a first event is 2%-14%/year, so these patients are at, I think, quite a high risk of recurrence.
- *Is the annual stroke risk of 1%-10%/year something which needs treatment?* In (one) trial, there was a 3.5% annual stroke risk for PFO + aneurysm vs. 0.8% with PFO only. The risk for the average 45-year-old person is 0.02% per year. So, therefore, I think a risk of 1%-7% is something that needs treatment.

- *What are the treatment options? Is medical treatment an option?* Medical treatment has never been tested in an RCT, and it is dangerous, with a 0.5%-5% bleeding risk per year. Obviously, it is not very effective because the 1%-10% annual stroke risk is in patients on medical therapy.
- *Is surgery an option?* It is probably effective, but it has never been tested in an RCT…and there's a 1%-2% risk with that.
- *What about catheter closure?* Procedural success is near 100%, safely.
- *Is PFO closure effective?* Our common sense tells us that if there is no PFO, there is no paroxysmal embolism. That is quite straightforward. RCTs will take another 5-10 years.
- *Do we need RCTs?* Yes, always.
- *Will we get RCTs – with enough patients, with new and appropriate technology, with sufficient follow-up, and within a reasonable time?* No.

PFO and migraine headaches

Dr. Sievert also argued that PFO closure is likely to work for at least a subset of migraine patients. NMT Medical's MIST-I trial of PFO closure for migraine failed to meet its primary endpoint (elimination of headaches), but it met a secondary endpoint of ≥50% reduction in headaches. Dr. Sievert said, "Should we close PFO for migraines? No, not at this time. We should enroll patients in randomized trials." Those are:

- AGA Medical's PRIMA trial of the Amplatzer.
- NMT Medical's MIST-II trial of the BioStar.
- St. Jude's ESCAPE trial of the Premere, which is approved in Europe. ESCAPE is a ~492-patient trial at ~80 U.S. sites (65 neurologists and 15 cardiologists). The primary endpoints are (1) the percent of patients who experience ≥50% reduction in monthly migraine attack frequency from baseline at months 4-12 of follow-up, and (2) major complications through 12 months.

Other PFO devices in development include:

- Carag Medical Technology's Solysafe septal occluder, which is an over-the-wire system.
- Occlutech's Figulla PFO occluder.
- SeptRx, another over-the-wire device.
- Cierra PFX, a radiofrequency (RF) closure system.

IMAGING

New imaging guidance technologies that were reviewed at CRT included:

- **OCT imaging**. In the future this may incorporate flow assessment, macrophage imaging, polarization imaging, etc.
- **Cardiac CT** is emerging technology that has achieved significant mileage over the last few years. 64-slice cardiac CT angiography (CTA) provides high quality imaging for coronary atherosclerosis assessment and distinguishing between "soft" and "calcified" or "mixed" plaques.
- **Coronary physiology pressure and flow measurements** are an important cath lab tool. It can determine when to defer intervention – in patients with fractional flow reserve (FFR) >0.75.
- **TOPSPIN intravascular MRI (IVMRI)**, a miniature magnet, has been validated *ex vivo* and *in vivo*.
- **BioScan LightWire technology** is all integrated into a conventional 0.014 inch guidewire. This has been validated in animals, and the first-in-man study is being planned.
- **NIR infrared spectroscopy.**
- **Raman spectroscopy.**
- **Optical low coherence interferometry (LCI).**
- **Intravascular ultrasound (IVUS)** has gained an important place in interventional practice and will become even more important in the DES era. It can improve BMS expansion and probably total vessel revascularization outcomes, and it can improve DES sizing and/or expansion and ***may*** avoid later DES-related complications. However, it does not have the resolution to visualize a thin fibrous cap. A speaker urged the companies working on this technology to develop similar and competitive products or agree to an open platform, "This is most interesting to me and probably least interesting to companies."
  - **Gray scale IVUS** is "exquisitely accurate" for making measurements but limited in terms of plaque characterization with the extent of calcification.
  - **Integrated backscatter IVUS (IB-IVUS)** is being developed in Japan, but the clinical utility still needs to be demonstrated.
  - **Co-registration of IVUS and angiographic images.** Volcano and Paieon are working on this, but it is not yet a clinical reality. However, a speaker predicted this will be very helpful technology.
  - **MediGuide (Israel) is working on a medical positional system (MPS),** which is similar to GPS positioning.

- **IVUS virtual histology (VH)** calculates amplitude as well as the frequencies of the echo, enabling identification of different types of plaque. One of the main applications of VH is identification of "vulnerable plaque" or "thin cap fibro-atheroma (TCFA)." The clinical utility still needs to be demonstrated.

Dr. Gary Mintz of the Cardiovascular Research Foundation (CRF) in New York said IVUS is getting more and more integrated into the cath lab, making it easier for staff and less hassle for physicians. The two leading companies in this area are **BOSTON SCIENTIFIC** and **VOLCANO**, and both companies are developing laptop or PC-based access so doctors can review images from home or anywhere else.

CORINDUS' CorPath, a remote control cath system compatible with current workflow routine, was discussed by Dr. Ron Waxman. He said it improves operator safety and comfort. He said a key reason for moving to robotics in the cath lab is to ease the workload on the interventional cardiologist, "There is about a 60% chance of a spine problem if you (an interventional cardiologist) are near retirement. A 2004 study found 42% of physicians indicated they had orthopedic problems (resulting from cath lab work). Interventional cardiologists also have higher DNA damage from radiation and a higher rate of cataract formation…Robotics should be installed in every cath lab, and everyone should use it…but it has to be simple. The change in culture is not dramatic, but it is still a change. It does have a chance, though it requires a change in culture. Time will tell if in five years we do procedures in a robotic way or in the conventional way." The CORRECT trial in support of a 510K application for CorPath is reportedly nearly ready to start and will include 100 patients at six U.S. and European sites.

DRUGS

LILLY'S prasugrel

There were two posters at CRT with ***new*** data on prasugrel, an antiplatelet drug that will compete with Sanofi-Aventis's Plavix (clopidogrel) if and when it is approved by the FDA.

1. Prasugrel 60 mg loading dose vs. both 300 mg Plavix and 600 mg Plavix loading doses. The ongoing, 13,614-patient pivotal Phase III trial of prasugrel enrolled the final patient in January 2007, and Lilly hopes to have the data at the American Heart Association meeting in November 2007 but may not be a able to complete the data analysis by that time.

This pivotal trial compares a prasugrel 60 mg loading dose (LD) to only a 300 mg Plavix LD but many cath labs use a 600 mg LD dose.

Thus, another smaller (41-patient) and shorter, crossover trial was done to look at a 600 mg Plavix LD. Each patient got one dose for a week, followed by a 2-week washout period, then a different dose for a week, another 2-week washout period, and then another dosing option. The key measures were platelet aggregation and vasodilator-stimulated phosphoprotein (VASP), a measure of the P2Y2 receptor effect. The study found that at 24 hours a LD of 600 mg Plavix is better than a 300 mg Plavix LD, but 60 mg prasugrel is better than either Plavix dose, and the curves separated early and remained separated during the entire 24 hours. This trial also looked at non-responders using four different measurement scales and found no prasugrel non-responders with any of the scales. There were no major or minor bleeds with prasugrel.

2. Study of switching from Plavix to prasugrel. This 40-patient study was done to provide guidance on the use of prasugrel when and if it is FDA-approved in patients already on Plavix. All patients were on background aspirin (81 mg) throughout the study. After a loading dose of 600 mg Plavix and a 75 mg Plavix maintenance dose for 10 days, patients were randomized to either prasugrel 60 mg LD + 10 mg prasugrel maintenance for 10 days or prasugrel 10 mg for 11 days with no loading dose.

The study found no washout is needed when switching patients from Plavix to prasugrel:

- Withdrawal: 4 in patients on Plavix, all considered related to aspirin use, not Plavix. There were no withdrawals when patients were on prasugrel.
- No washout is needed when switching a patient from Plavix to prasugrel, whether a prasugrel loading dose is used or not.
- In patients switched from Plavix to prasugrel, inhibition of platelet aggregation (IPA) increased from 51% to 81% by 30 minutes and to 90% by 1 hour.
- A steady state IPA is reached in ~70% of prasugrel maintenance patients within 4 days.
- There is higher inhibition of platelet aggregation with either prasugrel approach (LD or no LD), and that is maintained out to the end of the study.
- There were no bleeds or other adverse events.
- After switching from Plavix to prasugrel, a new and higher steady state was achieved. This takes about 3-4 days to achieve.

♦

Prasugrel vs. Plavix

Measurement	Prasugrel 60 mg LD + 10 mg maintenance x 7 days	Plavix 300 mg LD + 75 mg maintenance x 7 days	Plavix 600 mg LD + 75 mg maintenance x 7 days
Platelet aggregation at 24 hours	~10% (p<.001 vs. both Plavix LD)	~45%	~30% (p<.001 vs. Plavix 300 mg LD)
VASP at 24 hours	~2% (p<.001 vs. both Plavix LD)	~57%	~40% (p<.001 vs. Plavix 300 mg LD)
Non-responders	0	11.1%-33.3%	0-11.4%