Trends-in-Medicine

November 2005
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SUMMARY

In this second of two-part coverage of TCT, PFO closure, percutaneous valves, carotid stenting, SFA treatments, and more are examined.

Trends-in-Medicine
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TRANSCATHETER CARDIOVASCULAR THERAPEUTICS (TCT)
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HIGHLIGHTS

PFO closure. Cardiologists are finally beginning to accept the idea of percutaneous PFO closure for cryptogenic stroke, and they are even considering the possibility that PFO closure may help some migraine headache patients. St. Jude/Velocimed and NMT Medical are in the lead there, but they may get eclipsed by RF technology from Cierra or CoAptus. And the FDA remains very skeptical about PFO closure, and both the FDA and CMS are concerned about off-label use of PFO closure devices. Don't be surprised if this procedure, if ever approved by the FDA, is restricted in some way – perhaps with requirements for training as with carotid stenting, a registry as with ICDs, etc.

Percutaneous valves. After last year's disastrous live case with the Edwards valve, percutaneous valve supporters breathed a sigh of relief when a CoreValve live case went very smoothly. CoreValve is being more restrained about projections for adoption of this technology, admitting it could be 10 years before it is commonly done outside of a limited number of major medical centers. The good news was that the FDA indicated it will loosen just a little the restrictions on who can get a percutaneous valve. Currently, patients have to be nearly dead to get a percutaneous valve, but the FDA appears ready to allow slightly less sick patients to undergo the procedure, though still not relatively healthy 50-year-olds.

Carotid stenting. A CMS official repeatedly cited the difficulties encountered at TCT with live carotid stent cases as a confirmation of their decision to require training and limit use of the procedure. So, don't look for CMS to relent on these restrictions in the near future.

SFA treatments. Use of FoxHollow's SilverHawk atherectomy device is increasing, despite continuing controversy about the company, its officers, and the value of atherectomy of the SFA. Experts want randomized clinical trials, but the company has none planned for at least two or three years. Several different stents are being tested, but these appear to be complementary not competitive, but Pathway Medical's atherectomy device bears watching.

THE REGULATORY PERSPECTIVE

At a Town Hall meeting – and at some other sessions at TCT – FDA, NIH, and CMS officials offered some insights into key interventional cardiology issues before the agencies.

NIH

Two key funding areas for NIH are heart failure and cardiovascular cell therapy research. Cell therapy will get $33.75 million over five years.

FDA

Pediatrics. FDA's CDRH is giving greater emphasis to pediatrics, especially in the cardiovascular area. Dr. Daniel Schultz, Director of CDRH, said, "There have been some interesting discussions on funding of trials of pediatric LVADs. It's a relatively small population, and it is difficult for companies to fund those…We are very interested in working with NIH to get some of those trials done."

Approval timelines. CDRH is ahead of its timetable goals for processing applications so far this year.

Device safety. Dr. Schultz said, "We've all heard concerns about medical devices that are on the market. Some concerns are appropriate…Some (devices) may have been put out there in ways that are perhaps not as appropriate as we would like. We are all sort of obligated to look at what we are doing…that not only are we getting the best and latest technology to market…but that once it gets to market, we have a way to report and monitor performance so the public has confidence that we are looking at this and taking it seriously."

Post-market surveillance. Dr. Schultz said, "Our major focus over the next year (FY2006) will be post-market assessment – getting data, analyzing it, and acting on that data. How to communicate that data is a concern…We are interested in working on that internally, and we want to work with the clinical community…to see what kind of information the clinical community and patient groups need…One thing we would like to do is move to a fully electronic system (of MDR reports), and that is something we are developing and thinking about right now…We are strengthening our control of Condition of Approval studies…This program has been moved to the post-market sector where it will get the attention it should have." He also called for more explanted devices to be returned to companies for root cause analysis.

Surrogate markers. Dr. Schultz said, "(We) are looking at ways to model stent performance long-term by using various types of computer modeling. The goal is…to develop better science that allows us to understand how these things perform and to do it in a cost-efficient way." Dr. Bram Zuckerman, head of Cardiovascular Devices at the FDA's CDRH, said, "Thousands of biomarkers will be discovered over the next decade…It is critical these scientific advances be made…but biological markers are just that…They are not surrogates …There are a lot of biomarkers out there…and <25% are surrogate endpoints…Consideration of a product-specific surrogate rather than a device-specific surrogate may be possible for a minor (drug-eluting stent) device change…The concept of a device-specific surrogate that allows us to look at an iteration of a drug-eluting stent line or minor changes may be a possible, but that needs to be explored further…A surrogate for effectiveness (late loss) will not address key safety questions (e.g., rate of thrombosis)."

Missed endpoints. Dr. Mitchell Krucoff, a member of the FDA's Circulatory System Devices Advisory Committee, said, "We have seen any number of situations come before the panel where the primary efficacy endpoint doesn't look great but a secondary subgroup can be spotted or proposed that looks interesting…I think that (has to be taken) case-by-case …From a statistical point of view, it is never appropriate in a negative trial to take too convincing an approach for a subgroup in that trial. But, depending on the device, you can go back through (history), and see devices approved and others turned down."

Clinical trial issues. Only about 50% of PMA trials are randomized clinical trials. FDA officials said they would like to see improvements in:

- **DSMBs.**
- **Clinical events committee (CEC) adjudication.**
- **Independent core labs.**
- **OUS data.** Dr. Zuckerman said, "We are increasingly looking at OUS data. By statutory mandate OUS clinical studies can be used, but demonstrating the application of the foreign data to the U.S. population and medical practice is of paramount importance."
- **IDE approval letters.** Dr. Zuckerman noted, "When FDA gives approval to start an IDE trial in the U.S., it is just that. The agency may still have concerns with the trial design and may not have complete agreement with the sponsor. Some concerns may be stated explicitly in the IDE letter or may be transmitted to the sponsor in FDA/industry meetings. The bottom line is that an IDE letter is just an IDE letter. At the end of the day, we need to look at the totality of the data. We are very concerned with higher risk products being able to show clinical, as opposed to cosmetic, utility. Often, this results in a complex approval pathway…Even though we approve an IDE, that doesn't mean the data will reach the threshold of approval." Another FDA official said an IDE means a sponsor "can initiate enrollment…Conditional approval means there are still questions the company needs to address, but the FDA no longer has a safety concern that should bar patients from enrolling in the trial."

CMS

Highlights from a talk by Dr. Steve Phurrough, Director of CMS's Coverage and Analysis Group, included:

Carotid stenting. Dr. Phurrough said, "We have become much more concerned about facilities and providers who are providing complex procedures we are being asked to fund…The live case of carotid stent placement yesterday… explains the need to ensure that only approved facilities are performing this."

Coverage with evidence development (CED). Over the last year, CMS introduced this new concept, and Dr. Phurrough suggested it will be used more frequently in the future. He described it this way: "It is a process that we will encourage with either a carrot or a stick…We are saying we will pay if you provide, on a continuing basis, information that allows us to understand the care is appropriate and allows us to develop an understanding of how this (new) technology is diffusing into the community and what happens during the diffusion…History is replete with technology that diffused to the detriment of patients – for example lung reduction surgery. So, there will be more and more cases where we say we will pay but we want (ongoing) information…***We will probably do this about four times a year***."

Registries. CMS wants the way registries are maintained to be modernized. Dr. Phurrough said, "The key issue is that these kinds of processes need to be open processes. We no longer need to have hidden registries, hidden data, maintained for the people collecting it and not available for the public…We think there needs to be some significant work in developing what a registry is, what you can do with it…so that those of us who spend days reviewing evidence understand what the data from a registry means…I'm not sure there is a limit in collecting data on when a particular technology never needs any more data collected There are continuing issues on new technology and how it fits into the community. New technologies today are never very old technologies. We are interested in long-term, simple methods of collecting information that let us analyze how well a technology works." He added that CMS will rarely use registry evidence as the sole evidence of efficacy of a device.

ICD registry. Dr. Phurrough said CMS is looking to replace the initial ICD registry with "another defined registry," but it will be one where the CMS data are available and open to the public.

Other issues

Adverse event reporting. Asked if every pre-market adverse event will end up on a public database somewhere, the FDA's Dr. Schultz said, "Some specific elements of the public and their representatives will be demanding increased transparency from us and from other agencies and companies and from investigators...We are all in this together…and we need to figure out how to do that in a balanced way. We are exploring how to do that internally." CMS's Dr. Phurrough added, "I think this will be a significant emphasis from the agency in the future. We pay for something, then what occurs around that is public information. If there is an adverse event, we expect that to be a public event. How we do that we don't know yet. Short-term, data on healthcare we deliver is public data, and the public needs to understand how the technologies they are paying for do or don't work."

Reimbursement. CMS's Dr. Phurrough said, "We have twice done parallel reviews, and we are developing some joint documents on how we will do that in the future. It will be on a voluntary basis, and it will be such that our timelines will fit into FDA timelines. We have congressionally-mandated timelines, and we don't have the option of not meeting those. So, we don't want to start a CMS process that comes to the congressionally-mandated due date and the FDA is not finished…So, there is still some work to understand technically how we are going to do that." Dr. Schultz added, "In theory it makes a lot of sense (to do simultaneous submissions to FDA and CMS)…We have some limited examples of how that could work."

Global harmonization. Coronary device approvals can lag European approvals by 6-36 months but be ahead of Japanese approvals by 24-40 months, but regulators in the U.S., Europe, and Japan are working to improve global harmonization. A Japanese regulator said, "We are later than the U.S. and Europe – sometimes two generations later. We want to solve this bad situation for our Japanese patients." He said his government is taking steps to improve this, including earlier consultations between industry and the Health Ministry. A French regulator said, "In Europe, we have made a huge improvement in the way the notification body works…So, there is a clear improvement."

However, a U.K. cardiologist said there are new problems in European approvals: "There is a definite perception that the review process is drifting longer in Europe and shortening in the U.S…A real concern to us is at the IRB level. In some countries, one hospital can actually get agreement for the whole country, and in other countries every single hospital has to do a full IRB review. That can make it very hard to get through the paperwork, and they want more and more money. They top slice the money from individual centers so research coordinator money gets shortened. You are talking about a high level harmonization, but I think it is getting more difficult at the grassroots level."

Dr. Zuckerman said, "From our perspective, we do view OUS data very importantly, and it can have a critical role. There are small, simple steps device manufacturers can better employ to make these data more meaningful." Among the steps he suggested were:

- **Registry data from Europe.** "We are interested in better sorting out selection biases in (those registries)…Just as we deal with data here in the U.S., we'd like data independently reviewed by a clinical events committee."
- **Consult the FDA.** And do it early in the process.

ACUTE HEART FAILURE THERAPIES

CHF SOLUTIONS' System 100 Fluid Removal System

A speaker described the multicenter, randomly controlled RAPID trial of this ultrafiltration system, saying it showed:

- Conic ultrafiltration is superior to diuretic strategies in salt and water removal.
- Ultrafiltration is safe.

- No reported adverse events.
- No clinical justification for delay.

An investigator said that the EUPHORIA trial found that "an initial treatment strategy to use ultrafiltration…and evidence of diuretic resistance results in reduced length of stay and improved clinical status." The 200-patient UNLOAD trial, which compared ultrafiltration and diuretic strategies in decompensated heart failure completed enrollment in July 2005. The trial's primary endpoints are weight (water) removal and symptom improvements. Secondary endpoints include effects on electrolytes and renal function, adverse event rates, and days out of hospital alive. The speaker said that there is a small incidence – ~10% – of worsening renal function with ultrafiltration.

FLOWMEDICA'S Benephit Infusion System

This targeted intra-renal treatment was described as a useful therapy for patients with acute heart failure and reno-cardiac syndrome because it widens the renal therapeutic window, delivering drugs with more efficacy. Targeted intra-renal treatment can:

- Improve renal function.
- Improve renal perfusion.
- Suppress renal and adrenal neurohormones.
- Reduce systemic exposure and unwanted side effects.

The Benephit Infusion System is a catheter with side infusion parts. It is a tiny device, using 3.5 Fr infusion branches, which are placed through either a 5 Fr or 8 Fr catheter. The sheath permits simultaneous coronary interventions plus drug infusion via a single femoral artery access site. The 5 Fr sheath permits drug-infusion via the femoral, radial, or brachial artery. The device is available both in Europe and the U.S.

A speaker described a recent comparative pilot trial of the device in 10 heart transplant patients, all with stable renal dysfunction. Four patients received bolus, and six received no bolus. The trial showed that:

- Glomerular Filtration Rate (GFR) goes up with intra-renal (IR) treatment.
- Renal plasma flow is greater with the treatment.

ORQIS Medical's Cancion cardiac recovery system (CRSTM)

Continuous aortic flow augmentation (CAFA) with this device has been shown to normalize flow patterns in the aorta during reduced cardiac output. Cancion CRSTM is a percutaneous cardiac recovery device which uses a femoral approach, with inflow and outflow cannuli. It is hooked up in the middle with an exterior centrifugal flow pump, which preserves flow momentum. A speaker said, "Flow is continuous, and there's a short column of blood. The other mechanism is the vascular biological mechanism…When you turn the CRSTM on, there is normalization of the flow pattern. So, the mechanism of action is continuous aortic flow augmentation…A preclinical investigation with a dog model showed the effect on urinary sodium excretion. Within 2-3 hours of turning on the device, there was a dramatic increase in urinary sodium excretion."

The company's medical director said that the initial feasibility experience with CAFA (12 patients in the U.S. and 12 in Europe) will be published in November 2005. The physician said, "When Orqis is on and the effect is sustained, we see the termination of an adverse viscous cycle…We see the progressive increase of cardiac index over the first 24 hours, then 72 hours, then sustained up to 24 hours after termination of the device."

Device related adverse effects in the initial feasibility experience included:

- Early removal due to bleeding (two patients).
- Under-anticoagulation resulting in early removal due to device thrombosis (two patients).
- Profunda femoris dissection requiring repair (early surgical implant – one patient).
- Iliac artery dissection during sheath exchange post cannula removal (one patient).
- Early removal due to loss of pulse, resolved post cannula removal (one patient).

A randomized controlled pivotal trial (MOMENTUM) is underway with 32 patients with chronic heart failure with acute decompensation who are not adequately responding to IV inotrope/vasodilator and diuretic therapy. The primary endpoint will be change in PCWP, days alive out of hospital, and days off mechanical support.

A speaker said that the company is doing animal tests with an implantable CAFA system, using a pump and motor beneath the skin. He said, "There is a gap between drugs and devices, and one of the things that might fill the gap is continuous aortic flow augmentation. Orqis's Cancion represents a promising opportunity for patients with heart failure refractory to conventional therapy."

ANTIPLATELET AGENTS

Identifying non-responders to Sanofi-Aventis's Plavix (clopidogrel)

Dr. Govinda Weerakkody described a way to identify Plavix non-responders. He studied 111 healthy subjects from three Phase I studies, all receiving 300 mg Plavix, with 91 of these also receiving a 60 mg loading dose of prasugrel, measuring change in maximum platelet aggregation (MPA). His key assumption was that the PD profile of a non-responder is similar to a placebo response. He found:

- Non-responders are individuals with clopidogrel PD responses indistinguishable from placebo.

- Clopidogrel PD non-responders ranged 22%-43%.
- The relationship between non-responder status and clinical outcomes needs to be established by clinical trials.
- The PD non-responder definition is influenced by ADP concentration.
- No PD non-responders were observed in the 91 healthy subjects receiving the prasugrel 60 mg loading dose.

Dr. Weerakkody was asked if there were any data on Plavix 600 mg in his study, and the answer was no. A physician in the audience said, "This analysis is brilliant. We're always arguing about what is non-responsiveness…We agree if you don't take the drug, you're not going to get an effect." A panelist commented, "This study probably under-estimates the variability of patients who take other drugs that interfere with clopidogrel. We also have defined a group of normals who are non-responders and demonstrated that a lot of this is due to the baseline enzyme level…not just drug reactions. For example, we gave some clopidogrel non-responders St. John's Wort for two or three weeks and they all turned into responders."

Three potential competitors to Plavix were discussed at TCT:

1. Lilly's prasugrel (CS-747, LY-640315)

This oral, irreversible, third-generation thienopyridine has some variations on the clopidogrel structure. Dr. Steven Wiviott of Boston's Children's Hospital said, "Thieno-pyridines have to be metabolized, but there are some issues with the metabolism of clopidogrel. About 85% of clopido-grel is inactivated in the blood due to esteraces. This metabolic pathway results in significant loss of the parent drug that is absorbed, and it takes at least two steps of metabolism …Prasugrel, by distinction, is activated in the blood, and there is no loss of the parent drug, so in a single step it is activated."

The JUMBO-TIMI trial followed 900 PCI patients with stenting. The primary endpoint was non-CABG bleeding through Day 30. Secondary endpoint was cardiovascular MACE through 30 days and critical cardiovascular endpoints. Compared to standard dose clopidogrel, Dr. Wiviott said prasugrel had a similar safety profile a non-significantly lower rate of ischemic events.

30-Day JUMBO-TIMI Phase II Update

Measurement	Clopidogrel	Prasugrel	p-value
Primary endpoint Significant non-CABG bleeding	1.2%	1.7%	0.77
TIMI major non-CABG bleeding	0.8%	0	0.62
MACE	9.4%	7.2%	0.26
MI	7.9%	5.7%	0.23
Clinical TVR	2.4%	0.6%	0.03

2. The Medicine Company's cangrelor

The Medicine Company bought this agent from AstraZeneca in late 2003. The drug is rapidly cleared (<10 minutes) by plasma enzymes, with no accumulation. A speaker said, "By the time you turn off the drug, its effect will be gone before you go to the operating room."

A Phase I trial was recently finished in Kentucky, which found complete inhibition of platelet aggregation in two minutes. When the cangrelor infusion was stopped at 60 minutes, at 160 minutes platelet aggregation returned to baseline. A speaker concluded that cangrelor:

- Is safe and well-tolerated at up to 4 mg/kg/min IV.
- Has a short duration of action.
- Has a plasma half-life of 3-5.5 minutes.
- Platelet function recovers within ~60 minutes.

Phase III trials in ACS and PCI patients are scheduled to begin in the next several months.

3. AstraZeneca's AZD-6140

A speaker described the 200-patient, Phase II, dose-escalating (50 mg, 100 mg, 200 mg, and 400 mg BID) DISPERSE trial of oral AZD-6140 vs. clopidogrel. He said, "Looking at Day one, the loading dose shows a much lower level of inhibition with clopidogrel compared to all the other doses of AZD-6140…Clopidogrel somewhat mimics the lowest dose of AZD…There is greater and more consistent inhibition of platelet aggregation with AZD-6140 than with clopidogrel."

The randomized double-blind, 900-patient, DISPERSE-2 trial will assess the safety, tolerability, and preliminary efficacy of AZD-6140 (90 mg or 180 mg BID)+aspirin compared to clopidogrel+aspirin in patients with NSTE-ACS. The primary endpoint is major/minor bleeding. The results will be presented at the American Heart Association meeting in November 2005. A large Phase III trial is planned in an ACS population.

The advantages to AZD-6140 over clopidogrel were described as:

- Faster onset of action.
- Greater and more consistent platelet inhibition.
- More rapid reversibility.

Arterial Closure Devices

One of the most interesting new arterial devices in development is Boston Scientific's SoundSeal, which it got with the acquisition of Therus. SoundSeal uses externally-applied ultrasound to the arteriotomy site to heat the vessel wall collagen and form a seal. Some sources had called it a potential "game changer," but development has moved slowly. However, a clinical trial is expected to start in 2006.

Dr. Eberhard Grube of Germany said the device has been changed quite a bit over the last couple of years. In a single-center, non-randomized trial, complete hemostasis was achieved in 24 of 29 patients. The failures were blamed on inaccurate targeting. Dr. Grube explained how SoundSeal now works: "We rethought the situation, and shifted gears to catheter-based targeting and away from image-guided targeting…A 3F targeting catheter is inserted down the lumen of the existing introducer. Hemostatic compression is achieved by pressing the treatment applicator downward. Blood flow vs. force data is automatically analyzed to establish the hemostasis force range. The applicator display indicates the force range over which adequate hemostatic compression can be maintained. The introducer and targeting catheter are pulled back as a unit. The introducer exits the artery prior to the arrival of the targeting transducer at the arteriotomy. The applicator display indicates the location of the targeting transducer relative to the arteriotomy as it is withdrawn. The display then indicates when the targeting transducer is in the arteriotomy (red means stop pulling). The applicator is maneuvered so that it is targeted at the targeting transducer which is located in the arteriotomy…Treatment depth and dose is automatically calculated and administered after hemostatic compression and arteriotomy targeting are achieved, and the targeting catheter is withdrawn. The applicator displays the treatment time. The applicator is then removed. No coupling gel is required any more."

The steps are:

1. Apply hemostatic compression.
2. Pull back the introducer/targeting catheter to leave the targeting transducer in the arteriotomy.
3. Target focused ultrasound on the targeting transducer.
4. Remove the introducer/targeting catheter.
5. Treatment is automatically administered.

CAROTID STENTING

As many as 200,000 Americans undergo a carotid surgery annually. Due to Medicare reimbursement restrictions, only about 10% of these are done with carotid stents; the rest are surgical procedures – carotid endarterectomies (CEAs). It does not appear that Medicare will loosen these restrictions soon.

Dr. Marcel Salive, Director of the Division of Medical and Surgical Services at CMS, said, "We are looking at the results of post-approval studies to see if they will influence future coverage decisions. CMS advocates enlarging post-approval studies so we get better evidence to understand net health benefits…We felt there was a learning curve and facilities should have oversight at the local level…The approval process takes an average of three business days." He said that, at the time of TCT, 621 facilities in 47 states and the District of Columbia had approval. There were no approved sites in Hawaii, Idaho, or Wyoming.

Currently, there are three groups of patients eligible for Medicare-reimbursed carotid stenting:

- Patients who are high risk with symptomatic stenosis ≥70%.
- Patients with symptomatic stenosis 50%-70% who are in a clinical trial or in a post-approval study.
- Patients with stenosis ≥80% who are asymptomatic but are in a clinical trial or a post-approval study.

The leading carotid stent products are:

- **GUIDANT'S Acculink**, using Guidant's Accunet embolic protection device was the first system approved.
- **JOHNSON & JOHNSON'S Precise,** with J&J's Angioguard embolic protection filter has an approvable letter from the FDA. Final approval is dependent on J&J resolving manufacturing issues with other products.
- **ABBOTT LABORATORIES' Xact,** with its Emboshield embolic protection device, both of which were approved by the FDA in September 2005

A CMS official repeatedly cited the difficulties encountered at TCT with live carotid stent cases as a confirmation of the agency's decision to require training and limit use of the procedure. He said, "If you are watching the live demonstrations, it has been well demonstrated to be a real challenge in some of the live cases."

Asked if there has ever been a case where, after watching training classes for a device, the FDA found them inadequate or the Agency wanted something else done, an FDA official said, "To the best of my knowledge, that has not happened. It is conceivable that we could approve a design for a training program and then, based on evidence from post-marketing sources, that we determine the training program is inadequate. I'm not aware of any examples."

A CMS official clarified that a surgeon has to confirm a patient is high risk before carotid stenting is permitted, but he said the surgeon did not have to actually see the patient physically: "(The rule) doesn't say the patient has to be seen, just that the patient has to be evaluated, and then a surgical opinion written. Our expectation is that as patients are evaluated for carotid stenting, that an assessment is done such that, in the opinion of a surgeon, whether he saw the patient or not, that the patient is at high risk."

CELL THERAPY

Future Interventional Devices and Delivery Vehicles

In the next three to five years, more device-based innovations with enhanced imaging guidance, including echo, are likely. Dr. Warren Sherman of Columbia University Medical Center said that researchers also are looking at hybrid formations. He said, "Preclinical evaluation will be critical in developing therapeutic strategies for both cells and devices. The selection of cell types and products will, expectedly, be disease-

dependent. Delivery device and method will need to be matched up with tissue characteristics and cell properties. Future devices will encompass all approaches presented here today."

Dose deposition, product loss, and product retention will drive the design of interventional devices and delivery vehicles for cell therapy in the future, he predicted, adding that simple changes to existing devices will probably occur, such as:

- **BIOHEART'S Van Tassel needle** – Multiple, variable spaced, with variable positioning and closed end-home.
- **BIOCARDIA'S Helix transendocardial needle** – Offers stable fixation, contrast lumen at base for localization, and, taken to the next generation, has dual injection capabilities. Dr. Sherman said, "Right now we have the most experience in terms of fibrotic tissue, with endoventricular devices such as Biocardia and Bioheart. But we really need to start being quantitative in our evaluation of tissue before we begin to understand whether what we inject into a specific region of the heart is going to stay or not stay."
- **MERCATOR'S Microsyringe** – This device, in the perivascular space, inflates to slide a microneedle through the vessel wall and deliver circumferentially to the perivascular space. A .014 inch guidewire is used. The balloon sheaths the microneedle, and the microneedle penetrates the artery.
- **GUIDANT'S intra-coronary infusion system** – Dr. Sherman said, "We are injecting cells into patients in MRI studies without looking at the clinical value. Guidant has developed a number of innovations in this regard: one in critical study is its balloon coronary infusion catheter, a graded expansion of the balloon to minimize vascular trauma and demonstrate with radioactively inducible particles that, rather than just finding cells along the board zone, as we've come to see in several clinical studies with acute MRI, there is deep penetration."

Among the interesting cell therapy products, Dr. Sherman pointed to V-Kardia's V-Focus Delivery System, which uses a balloon tip with a spreader, coronary sinus catheter, and coronary artery catheters. He said, "This really is a closed system, in which cells or other biologics can be given through the arterial system, taken up by the venous system, pass through an oxygenator, and pass through into circulation."

REVIVAL-2 trial – Stem cell study in AMI patients fails

This was a 6-month, prospective, randomized, double-blind trial of 10 µg/kg granulocyte colony stimulating factor (G-CSF) for five days vs. placebo in 114 patients with acute myocardial infarction (AMI) who had successful reperfusion by PCI within 12 hours of symptom onset and an infarct size of at least 5% of the left ventricle by SPECT. Researchers reported that, although G-CSF therapy is safe and feasible in AMI patients, it does not reduce the risk of restenosis, and it doesn't improve left ventricular recovery.

The principal investigator said, "We think that the stem cell theory is very interesting, but we need more basic data to go further. Nobody knows what the mechanisms of healing are in all these studies." Asked to name the most promising cell-based therapy, he said, "That is difficult to answer since we don't have any randomized studies showing any beneficial effect…The only study that was randomized and placebo-controlled showed no effect, so at the moment I don't know which would be the best. We have to think more about mechanisms."

6-Month REVIVAL-2 Trial Results

Measurement	G-CSF n=56	placebo n=58	p-value
Primary endpoint: Reduction in infarct size vs. baseline	6%	5%	0.45
Secondary endpoint #1: Increase in LVEF from baseline	2.8%	2.8%	0.98
Secondary endpoint #2: Restenosis	35%	31%	0.64
Death/MI	1.8%	1.7%	0.67
TLR	28%	31%	0.94

IMAGING

The use of IVUS is increasing, and one company to watch in this space is Volcano, which has become a bigger player in IVUS since it obtained Jomed's IVUS technology. Volcano and Guidant have a project underway, the 700-patient PROSPECT trial, to try to identify unstable angina (UA), STEMI, and NSTEMI by color (VH) IVUS. So far 272 patients have been enrolled, and the primary endpoints are MACE, cardiac death, cardiac arrest, and re-hospitalization for ACS.

Volcano's newest IVUS product is the Revolution catheter. A first-in-man clinical study was due to start in the U.S. right after TCT. The study, which is also intended to be used for Japanese approval, will enroll ~100 patients.

Volcano already has an IVUS device with an electronic transducer, so this device is expanding the market by targeting doctors who prefer a mechanical device. An official said, "We will ask doctors what they prefer. We have been pushing phased array for more than 10 years, and there are those who don't use that. Now we can say we were trying to sell you phased array, and you haven't bought it. Now, we have this."

Revolution has a higher frequency response transducer – 45 mHz – than either the Boston Scientific IVUS device (~37 mHz) or Volcano's electronic transducer (20 mHz). Officials say this provides higher resolution "so you can actually see more quality images." The crossing profiles of the rotational

and medicinal devices are roughly the same. There are two pieces to Revolution – the catheter and the system, which has an electronic console and pullback. The catheter already has 510K approval, and the full system is expected to have 510K approval by the end of 2005.

The pullback for Revolution, SpinVision, allows a full 15 cm pullback to be performed automatically, though the system may also be operated in manual mode. SpinVision uses an optical encoder to relay precise, absolute position information to the InVision Gold (IVG) console. A Volcano official said it will allow physicians to assess lesion and stent lengths "with simplicity and accuracy." The pullback device is a reusable system, requiring only a single sterile bag for each use.

Volcano introduced a new platform, Meridian, which the company is calling its "platform of the future." Meridian is a joint venture with General Electric (GE). Meridian is a much smaller, lighter, compact, state-of-the-art system than the IVG, which weighs 437 pounds and had 6-7 very complex electrical circuits. Meridian has only 2 electronic circuit boards, both proprietary, and it weighs only 80 pounds. It will come in two forms:

- A stand-up unit that can roll around on wheels (about the size of a desktop computer tower).
- Integrated into a cath lab, specifically into GE's new cath lab. Volcano is pushing this integrated version, but has the roll-around available. "Our intent is to integrate it into the cath lab, so the cath lab has always-on capability as opposed to an island that has to be wheeled in…We think the integrated version will be more popular. We think this will be very appealing to physicians, and then we believe IVUS use may increase."

Meridian will require FDA clearance in the U.S. and elsewhere and will be co-marketed by GE and Volcano. Improvements include a "very, very friendly" user interface that was described as "extremely easy, very intuitive." When it is first released, Meridian will only be in grayscale, but in the first half of 2006, Volcano plans to add VH. A rotational catheter will be implemented on it in 2006 as well.

Volcano also announced a joint agreement with Paieon to jointly develop products allowing in-the-cath-lab combination of x-ray angiography (both 2-D and 3-D) with grayscale IVUS. The Volcano/Paieon system is expected to allow physicians/ staff to quickly assess regions of the coronary tree and simultaneously visual both the patency of the arterial lumen and the presence, quantity, and type of coronary athero-sclerotic plaques. Volcano plans to offer the angio/ IVUS image fusion system as an option for installation and use on its new and existing installed base of IVG IVUS imaging consoles. That is, older units can be retrofitted with this capability. The Volcano/Paieon system has not yet been submitted to the FDA. A Volcano official said, "They (Paieon) have very intriguing 3-D software…Their technology is currently used by GE and Siemens…What is novel that we added is actually integrated IVUS with angiography…so you can see 2-D angiography on the screen, and then scroll down on the same screen and see the IVUS that correlates to what the cursor on the angiography screen is pointing to."

Patent Foramen Ovale (PFO) Closure

Cardiologists are finally beginning to accept the idea of percutaneous PFO closure for cryptogenic stroke, and they are even considering the possibility that PFO closure may help some migraine headache patients, but the FDA remains very skeptical about PFO closure, and both the FDA and CMS are concerned about off-label use of PFO closure devices.

Defending the off-label use of PFO closure devices – and their use beyond the restrictions of a humanitarian device exemption (HDE) – a speaker argued that it is unreasonable for the FDA (1) to expect IRBs to police the off-label use of PFO closure devices (or other devices), and (2) insist on randomized clinical trials of PFO closure devices. He said, "I'm not suggesting this in all areas, but this is one type of area where we need to be innovative…Even if the HDE (for PFO closure devices) were revoked, this issue is not going away." Another speaker countered, "PFO is so prevalent that this is exactly the time randomized clinical trials need to be completed…To me, the challenge is to stop the off-label use or limit off-label use…That falls on IRBs, the FDA, and manufacturers to police off-label use and try to limit it."

Other comments included:

PFO supporter: "I (tell patients) what the acute risks are, I tell them there is 1%-3% risk of something bad happening…and I increase the number because I think when patients hear <1%, it is meaningless…I say we don't know long-term risk…On benefit, I say we don't know."

FDA official: "I appreciate that IRBs are busy…but one of our concerns is how you properly inform a patient who is in the single stroke category of the risk:benefit of the device…If the data aren't there to tell you the potential risk, it is hard to say the patient knows the risk…I would ask where you get the 1%-3%...Based on 50-80 patients, how confident are you that 1%-3% is the right number?"

Cardiologist: "To try to turn the approval process of devices into a police action against the people doing this sort of thing with good intentions (is wrong)."

FDA's Dr. Zuckerman: "From our perspective, the legal route is the one least desirable…The American Academy of Neurology was not swayed (on PFO closures), and the American Heart Association was not swayed by the PFO data. Why should patients be swayed by interventional cardiologists and the Internet?"

Another speaker: "Patients who chose PFO off-label may not have made a wise decision, but they probably were not fully understanding (the risks), including a 10%-15%

chance the PFO will not be fully closed and may not stop a clot."

PFO supporter: "The sponsor of the CLOSURE-1 trial (NMT Medical) has done a very aggressive job (of trial enrollment). They want to have a trial because it is in their best interest. On the other hand, it is not their job or in their purview to restrict physician usage."

CMS's Dr. Phurrough: "There has been no discussion of what is a simple solution – that is for payors not to pay for things with no evidence of benefit. That is a simple solution…No matter how much a patient begs for it, if you (the doctor/ hospital) are not going to get paid, you are not going to do it …But there are problems in enforcing that…We have attempted to limit coverage to a defined indication and outside that only if data are being collected to help define whether this technology has benefit or not…We will continue to push the medical and political community that we should only pay for things that work or if we are collecting the evidence…The coding system is such that you can't determine what is and isn't off-label…So, there is little way for us to determine what is off-label. Even when we make a declaration that we won't pay for off-label use, it is easy to get paid for it – you just lie when submitting the claim. That is known as fraud, but there is no way for us to evaluate it."

Available devices

In the U.S. there are no devices currently approved for PFO closure. NMT's CardioSeal and AGA Medical's Amplatzer both have an HDE, and Amplatzer has FDA approval for ASD treatment. A speaker rated the two devices as fairly comparable, saying, "Every lab has a preference for one or the other…but there aren't much data (for either). The feelings are very strong for one or the other…A lot of times the choice is based on previous training or complications with one device …It reminds me of an argument of the Mets vs. the Yankees …Bottom line, there is no decisive advantage to either device. Both are highly, highly effective, and neither is an optimal design. When people come to my lab and ask me, after 1,200 closures, what is my preference, I say, 'I'm a Mets fan.'"

Comparison of NMT's CardioSeal and AGA's Amplatzer

Company/device	NMT's CardioSeal	AGA's Amplatzer
Secondary stroke prevention	Same	Same
Incidence of residual shunts	---	Slightly better
Ability to handle variable anatomy	Same	Same
Septum secundum thickness	Better	---
Tunnel length	---	Better
Additional fenestrations	Better	---
Retrievability	---	Superior
Migraine headache elimination	Same	Same
Procedural complications	Slightly better	---
Device thrombosis and erosions	---	Better
Perforation	Better	---

Another doctor noted, "PFO closure is an alternative to chronic medical therapy. Very few people would consider this an alternative to surgical therapy because so few patients would consider surgical closure." A Belgian doctor pointed out that some PFO closures result in no benefit, so he said procedures must ensure complete closure, have no complications, and have no mortality. He said he did 175 percutaneous PFO closures between December 1999 and January 2005, with only minor in-hospital complications – 1 pseudoaneurysm, 1 large hematoma, and 1 AV fistula. None of the patients have had stroke recurrence, though three patients had episodes of TIA, and there was asymptomatic thrombosis in four patients who were then treated conservatively. Residual shunting was ≤5%. He said echo is "essential" for diagnosis, as a guide during intervention, and during follow-up to confirm procedural success.

The key concerns with PFO closure devices were:

- Metal and other materials left in patients, especially relatively young patients.
- Residual shunting.
- Ability to adapt to variable anatomy.
- Thrombus formation.
- Arrhythmia. Could stiffness cause rhythm disturbances in the future?

PFO closure debate: *Is interventional PFO closure over-used and abused?*

Dr. Lawrence Wechsler (a neurologist) and Dr. Paul Kramer (a cardiologist) faced off at TCT on the value of interventional PFO closure, including the possibility of extending treatment to migraine sufferers. Dr. Kramer edged out Dr. Wechsler by making a compelling case for PFO closure, saying that current regulations severely restrict its use.

Against PFO closure: Speaking against overuse of PFO closure, Dr. Wechsler pointed to the much hyped EC-IC (extracranial/intracranial) bypass study, reported in 1986, which showed no reduction in stroke, "Just as in the EC-IC bypass example, multiple studies have been published suggesting an association between PFO and stroke, and prevention of recurrent events with PFO. But these are retrospective, non-randomized series, as well as meta-analyses of the same series, which are self-reported, unblinded, and uncontrolled. There are no data that we can hang our hat on and rely on…A beautiful idea can be slain by facts…Just because everyone is doing it doesn't mean it works."

Is PFO an important cause of stroke? Dr. Wechsler argued that no difference has been shown in patients who have PFO vs. those who don't have PFO. He went on to call extending treatment to migraine sufferers "ludicrous." He said, "There is a high prevalence of PFO in migraine with aura, but the more you look, the more you find. The high prevalence of migraine in cryptogenic stroke with PFO is not biologically plausible."

He also doubted whether PFO closure reduces migraine with aura, citing the placebo effect.

Dr. Wechsler concluded by saying that one drug company told him that 200 patients are enrolled in a randomized controlled trial, but 1,000 patients were treated under an HDE (recurrent cryptogenic stroke on oral anticoagulation with therapeutic INR). He said, "That to me as a neurologist is quite stunning. But the real problem is off-label use. There is no way of knowing how many are placed off-label. So the answer is, is there overuse? Absolutely!"

In favor of PFO closure: Dr. Paul Kramer argued that a beautiful idea also "can be killed by the complete absence of facts." He said what is ludicrous is that the only approval is for patients with recurrent cryptogenic stroke, "How do we ask if something is over-abused? There are some problems with the approved indication which are fairly obvious. First, there is no medical evidence base for the use of antithrombotic therapy to prevent recurrent stroke due to presumed paradoxical embolism." He noted what he called obvious exceptions, including:

- First stroke in patient therapeutically anticoagulated for another reason.
- TIA while anticoagulated after first stroke; anticoagulation is absolutely contraindicated.
- No regulatory barrier to open surgical closure of PFO in these patients.

Dr. Kramer said that three PFO closure trials in the U.S. began three years ago, and >120 centers are participating, but enrollment is going very, very slowly, "At the current rate of enrollment, it will be another decade before the most aggressively enrolling trial comes to completion." He explained what he called the "unintended consequences" of the FDA insisting on a randomized trial:

- "The large majority of patients undergoing PFO closure are not being enrolled in a trial. We are learning almost nothing from this experience.
- "Approved devices not designated or studied for PFO closure are being implanted in patients off-label."

Based on company statistics, ~ 200 patients get a PFO closure annually in clinical trials. Another ~1,000 people get PFOs under an HDE. How many patients get a PFO closure device off-label is unknown, but it is estimated to be several times this number.

As for the relationship between migraine and PFO, Dr. Kramer said that about 11% of the U.S. and western European populations suffer from migraines ~1.5 times per month. He said, "Extending PFO closure to migraine suffers isn't ludicrous. It is premature but intriguing."

PFO closure for migraines

NMT Medical was the first company to begin a trial of PFO closure for migraines. That is a European trial, MIST-I, which has completed enrollment, and results are expected in 1Q06. In July 2005, St. Jude/Velocimed was the first company to get permission for a migraine trial in the U.S., but NMT got approval for an ~600-patient, double-blind, randomized, U.S. trial, MIST-II, shortly afterward and expects to start enrollment in that trial in early 2006.

Two live – and successful – PFO closure cases were done during TCT:

- **CIERRA'S PFX Closure System**, which uses RF energy to close the PFO. Cierra is expected a C.E. Mark in mid-2006 and plans a pivotal U.S. migraine trial in 1H06. With the first generation device, the closure rate was only ~52% at 30 days, but an investigator said, "We are working on a modification of the housing and the size of the housing, and we hope the success rate will increase with these modifications. We've learned better imaging techniques, improved placement methods, and found the PFO size limitations with the current device. Four of five PFOs were successfully closed at the most recent 30-day follow-up with the modified device… Right now, we can only do (PFO) diameters >10 mm, but the next generation will allow us to do larger PFOs. Patients will prefer a non-invasive technology, even if the results are less than with devices." A European trial aimed at a C.E. Mark started enrolling just before TCT, and the goal is to enroll ≤60 patients from three sites.

- **ST. JUDE/VELOCIMED'S Premere**, which got a C.E. Mark in December 2004, based on the results of the European CLOSE-UP trial in which the device was implanted in 67 patients. Premere uses a left atrial anchor with a very small amount of metal tethered to the right atrial anchor with a patch, and it is delivered with an 11F catheter. It is designed only for PFO closure, not ASDs.

This device, which St. Jude got with the acquisition of Velocimed, has a C.E. Mark. St. Jude recently received the first FDA approval for a trial of PFO closure in migraine. The ESCAPE trial has already started enrolling patients. It is a prospective, randomized, two-arm, double-blind, multicenter trial. A St. Jude official said a randomized clinical trial of PFO for stroke would be too hard to do in the U.S. He pointed out that NMT Medical's CLOSURE-1 trial has only enrolled about 300 patients in 14-15 months.

St. Jude also plans to start a European migraine trial around the end of 2005, and the company currently is interviewing neurologists for that trial.

St. Jude's ESCAPE migraine trial – a two-arm, prospective, double-blind, randomized, multicenter trial – began in summer 2005, and the principal investigators are New York cardiologist Dr. Robert Sommer and Arizona neurologist Dr. David Dodrick. The primary endpoint is a >50% reduction in migraine frequency at one year.

A user said the learning curve is slightly more difficult than some of the other devices because the technique is different, and there are still problems with sizing, "I believe larger holes are still difficult to close with this device." The ability to reposition the device was described as "debatable," and smaller introducer sheaths and larger devices are needed, but the device is easily retrieved. Another speaker said, "This device is designed for long tunnels…There is no need for transseptal puncture." He said he would not use Premere if the PFO is >18 mm; with PFOs larger than that, he uses AGA's Amplatzer, and he said PFOs larger than 18 mm will not be closed with Premere in the U.S. migraine trial.

A German doctor familiar with Premere said he uses low balloon pressure to help size the device, "It is not our intention to stretch but to get a feeling of the morphology with the balloon." He said a disadvantage to the device is that it is hard to see on echo because of the low metal content. In the patients he's done with Premere, the closure rate has been 26 of 27 at three months, with no device embolizations, no need for surgery, no thrombus formation on the left or right side, and no retrievals, but he said there was one TIA and two rhythm disturbances, one of whom needed pharmacologic therapy.

Following is more information on other PFO closure companies and devices.

➢ **AGA MEDICAL'S Amplatzer.** This self-expanding, nitinol wire mesh device is approved in the U.S. for atrial septal defect (ASD), but it is widely used off-label for PFO closure. The concerns with this device are that it is bulky, stiff, and a large amount of metal, including nickel, is left in patients, but the device is easy to place and retrieve. Another concern with ASD use is reports of cardiac erosion or perforation up to three years post-procedure.

➢ **CARDIA'S Intrasept.** This was described as similar to NMT's StarFlex, but with bigger articulation. Frame fractures and thromboses have been reduced with the fourth generation device made out of nitinol with PTFE on it. Intrasept has a low profile and an articulated configuration for optimal adaptation to the septum. About 6,000 Cardia PFO devices have been implanted worldwide, and 2,000 with Intrasept, mostly in Europe. Last year at TCT residual shunting was reported to be 7.4%; this year the rate was 5%.

Cardia is conducting a small, randomized cryptogenic stroke trial in the U.S. (vs. medical management), and the company is waiting for IDE approval to begin the IMPACT migraine trial. The company also is planning a prospective, open-label, controlled trial in migraine with aura, FORMAT, and the primary endpoint will be frequency of migraine attacks at six months, with the expectation that attacks would be cut by ≥50%.

➢ **COAPTUS MEDICAL.** Like Cierra, CoAptus is developing an RF device.

➢ **GORE'S Helex.** This device is still investigational in the U.S. It comes in sizes from 15 mm-35 mm and is delivered with a 9F catheter.

Gore's Helex Study

Measurement	ASD closure n=248	PFO closure n=468
Success rate	91.5%	100%
Embolization	2.4%	0.8%
Device removed	4.0%	---
Frame fracture	6.4%	1.1%
Significant leakage	2.4%	---
Erosion/perforations	0	0
Atrial fibrillation	---	0.4%
Recurrent event	---	0.6%
Thrombus	---	0
Major adverse events	---	6%

➢ **NMT MEDICAL'S CardioSeal and StarFlex.** Dr. Mark Reisman, the principal investigator in MIST-II, said he is convinced that PFO closure and migraines are associated, but he admitted proving this will be a real challenge. The FDA requires that drug companies show a 50% reduction in migraine headaches, and device companies are being held to the same standard. StarFlex is a double umbrella clamshell-type device, with the arms specially configured for good alignment, but thrombus formation and retrieval problems are a concern. A user said, "Once you have a problem, it is difficult to retrieve."

NMT also is working on BioStar, a device based on the StarFlex platform that largely (90%) disappears over time. BioStar uses a porcine matrix that "melts/fuses" itself to native tissue. It is supported by a low profile, self-centering frame-work, and it has a heparin substrate to reduce protein depositions and the potential for thrombus formation. The idea is for the collagen matrix to be replaced with native tissue over 1-2 years.

Comparison of PFO Devices

Company/device	Closure rate	Mass overall	Mass on left side	Retrievability	Response	Deforming	Can reposition
NMT's CardioSeal	93%	+	+	+	(+)	N/A	N/A
AGA's Amplatzer	96%	--	--	++	++	Yes	Yes
Cardia's Intrasept	N/A	+	+	N/A	N/A	N/A	N/A
Gore's Helex	95%	–/+	–/+	+	+	N/A	N/A
NMT's StarFlex	95%	+	+	+	–	Yes	Difficult
St. Jude's Premere	95%	++	++	+	(+)	No	N/A

BioStar is currently being evaluated in the prospective, multicenter, single-arm, first-in-man BEST study at six sites in the U.K. NMT plans to use BEST to get a C.E. Mark. As of TCT, 42 devices had been implanted, and the principal investigator said the learning curve is "very short," and there has been no MACE or thrombus formation out to 30 days.

- **SUTURA'S HeartStitch.** Sutura announced after TCT that it was spinning off its HeartStitch suturing devices into a new company devoted to their development and commercialization. No name has been announced yet for the new company. HeartStitch is being investigated for treatment of both ASD and PFO closure.

PERCUTANEOUS VALVES

At least 24 percutaneous valves are in development, but development is going slowly. Last year at TCT, a patient died shortly after a percutaneous valve procedure with an Edwards Lifesciences' valve, and some experts were saying that the technology was not ready for live cases. But a percutaneous aortic valve case was done again at TCT this year – this time by Dr. Grube in Germany, using CoreValve's Revalving system – and it went very smoothly. The porcine pericardium valve was delivered with a 21F catheter and took <15 minutes to implant.

CoreValve is being more restrained about projections for adoption of this technology than Edwards officials and investigators have been. The CEO of CoreValve, Dr. Jacques Séguin, said, "For a number of years, (this technology) will be done only in high volume, experienced centers…It will be at least 10 years before this is more commonly done (outside of those centers)."

The best news for valve companies at TCT was that the FDA indicated it will loosen – just a little – the restrictions on who can get a percutaneous valve. Currently, patients have to be near death to get a percutaneous valve, so the mortality tends to be very high.

Dr. Marty Leon complained that the rules are too tough for percutaneous valves, "What is happening now…is that we are applying a level of rigor to the patient population that places the technology at such a disadvantage to even get through Phase I that it is a near impossibility. We enrolled two patients in a (Edwards/PVT) percutaneous valve trial at Columbia. The patient had to be one cut above dead…elderly with so many comorbidities that you can't even assess the safety of the device…We need to talk about an appropriate Phase I (trial)." Another cardiologist said, "There is no margin for error with these patients…Right now, if there is a complication (during a percutaneous valve procedure), there is no fallback mechanism, and that places the patient at great risk."

The FDA's Dr. Zuckerman said, "One size doesn't fit all…It may be easier to get to the pivotal stage in the mitral arena. Dr. Leon pointed out a critical problem in the aortic arena – how to develop a feasibility trial. Certainly in choosing the initial patient population, one of the challenges he and others have had is trying to decipher device problems from the comorbidities that might be associated with these patients and might lead to bad outcomes…Dr. Leon proposed perhaps we should utilize extremely 'low risk' aortic valve patients as our first patients to try out percutaneous aortic valve technology in. From the FDA perspective, we have a fundamental problem with that, given that some of the reported morbidity and mortality results would not justify use of this technology in a 50-year-old man who could get an excellent cardiac surgical valve replacement. On the other hand, I do think you do have a legitimate point that the degree of risk in the initial aortic valve patient and the selection of these patients may need to be refined. You may need to move down a notch or two in risk category to make sure we can decipher what are device-related problems vs. comorbidities. But I'm asking you not to go 180 degrees the other way."

Dr. Leon responded, "It will be interesting to see how this evolved. I agree there is a middle ground…But there are many patients with critical aortic stenosis who are not getting operated on…This is not a referral politics situation. It is a serious clinical effort to do the right thing. There are patients with lower risk who are not getting operated on, who, with proper consent, would consider (a percutaneous valve)…Give us a chance to test some new techniques in a regulated environment, rather than comorbidities being the defining factor, which was the case with the first 65 patients with PVT."

Dr. Zuckerman then added, "This is a good case where common sense is needed. This is a complex area with an established therapy that works extremely well…We believe the current requirements in the U.S. (for percutaneous valves) are not well understood by sponsors. For example, animal studies are quite controversial. It is a mistake for sponsors to undergo chronic heart valve studies in whatever model they choose without consulting with FDA personnel. Even the design of feasibility studies is somewhat challenging, given the new device technology that needs to be developed…These (human studies) are difficult to do, but we can't push major data gathering post-approval…Would we accept lower safety for avoidance of cracking the chest? Maybe."

Dr. Zuckerman made several points:

- **A feasibility trial** will be critical to determine who the patient should be in a pivotal trial. He said, "We are having trouble figuring out what is the optimal control group…Who are patients to treat with this technology?"
- **Key issues with aortic valves** include: evidence base going into the trials is less exact than for coronary stents, there are questions about the valve functioning over time (sustained durability), stroke complications, and infection issues.
- **The FDA defines success** in a mitral valve trial as 1+ MR, not a 2+ repair.

- **DSMBs and CECs** are particularly important since this is an area where there is significant potential morbidity and mortality.
- **A randomized clinical trial** will probably be required for the pivotal trial. He said, "Each site will need cooperation between echocardiography, the cardiac surgeon, and the cardiologist…We want to be able to rule out other potential sources of bias and other reasons we may see positive results, so we can be sure the device is safe and effective. Consider what happens if the surgeons and cardiologists don't have the same level of expertise at a particular site for approaching a mitral valve procedure… And we want the control group to be relevant for the trial. Unfortunately, this rules out certain large databases, such as STS (Society of Thoracic Surgeons), which may not be detailed enough. But, on the other hand, I don't think we have a good handle presently on what an appropriate control group will be for many of these devices."

Dr. Ted Feldman of Evanston Northwestern Medical pointed out that there have been very few patients implanted with these devices. Part of the learning curve for the devices has been figuring out how to use echocardiography for navigation. Dr. Feldman said, "For this completely novel breakthrough technology, the initial procedures are lengthy at first. There is a rapid learning curve, and as each operator has gone to four, five, six procedures, the (procedure) time has gone down dramatically."

Percutaneous Values Used in Humans

Company	Number of patients
Medtronic's "Bonhoeffer" pulmonary valve	100
Edwards Lifesciences' Cribier-Edwards	75
Evalve	55
CoreValve	20

Coronary sinus (CS) approaches to percutaneous valve repair include:

- **EDWARDS LIFESCIENCES' Viking Delivery System.** This utilizes a stent system, using a standard 9F over-the-wire delivery system. An EVOLUTION first-in-man trial is ongoing in Sweden, Canada, and Italy. A speaker said, "This has been attempted in five Canadian patients. In some of those patients, the bridging element was not anticipated based on bench and fatigue testing. Fortunately, there were no clinical adverse effects with those bridge fractures."

- **EVALVE'S MitraClip edge-to-edge repair.** This is a cobalt-chromium clip attached to a 22F delivery system and is rotated into position over the mitral leaflets. The 22F delivery system can be separately steered. A suture is placed in the center to create a figure-eight double orifice. Systolic flow at high pressure drives the leaflets closed, then they open during diastole with low pressure. This system is furthest along in terms of trials, and >600 procedures have been published in peer review journals.

Advantages include:

- No stopping of the heart.
- No cardio bypass.
- No thoractotomy or sternotomy.

Dr. Feldman said, "Among the lessons learned are that a clip can't be successfully placed in all patients for a variety of reasons. However, in all patients, the intended surgery has been performed with no problems."

Dr. Howard Herrmann of the University of Pennsylvania Medical Center said that Phase I results with 27 patients in the EVEREST trial showed 100% edge-to-edge coaptation with the creation of the double orifice. The clip was not implanted in three of the 27 patients (11%), and one device did not function. Partial clip detachment prior to discharge occurred in 1% of patients. He said, "The results showed that this is a feasible technology. It is safe with no major complications, and reduction in the MR achieved was retained in 13 of the 14 patients for six months…This type of repair is very exciting, but there are a number of problems with all of these techniques, including how well they work."

The randomized EVEREST-II trial is underway at ~30 U.S. sites. It is comparing the MitraClip technique to standard surgical mitral valve repair/replacement in patients with functional or degenerative MR.

- **MITRALIGN'S suture bifurcation** utilizing several catheters. Mitralign is trying to perform suture bifurcation using several catheters, including a magnetic catheter placed in the coronary sinus and a guide catheter to the spot on the annulus. Two additional catheters can be placed, and the annulus can be cinched together, then clipped off. The idea is to do suture plication in order to shorten the AP diameter. This is currently being tested in an animal model.

- **MYOCOR**
  - **Coapsys Annuloplasty System.** This is essentially a skewer through the ventricular muscle. It is a robotic surgical approach to MR reduction without cardio-pulmonary bypass (as adjunct to off-pump CABG), and remodels the annulus and ventricle. It is being studied as an adjunct to surgery.
  - **I-Coapsys Implant and Therapy.** This is a percutaneous approach through the cardium, currently being tested in animals. It uses transpericardial access, external implant, and the mechanism of action is annular reduction AP dimension cinching. It includes papillary muscle repositioning and LV stress reduction.

➢ **VIACOR'S Transvenous Mitral Annuloplasty (PTMA) Technology.** This is a separate, diagnostic, reversible procedure using telescoping catheters with no discrete anchor points. It uses nitinol bars and a subclavian implant for later modification/removal.

Other comments about specific valves included:

➢ **CARDIAC DIMENSIONS' Carillon.** A speaker said, "This (mitral valve) device just came into human use. It is anchored to the distal coronary sinus for optimal sizing. A lot of work has been done on this, and there is at least one patient with a very good permanent implant. It is difficult to anchor the distal device, and this will lead to rapid redesign and improvements."

➢ **COREVALVE'S Revalving System.** An expert said that CoreValve has "met some substantial challenges." A CoreValve official said that 21 patients have been done so far, and the company planned to start a 30-40-patient multicenter (5-7 site) European trial right after TCT. In February or March 2006 the company plans to start the pivotal trial for a C.E. Mark, and in 2006 the company will talk with the FDA about a U.S. trial.

➢ **EDWARDS LIFESCIENCES' Cribier-Edwards valve.** A speaker said that this device had "early stunning results after a number of problems were solved. Many early problems with the device were created by delivery – for example, the transseptal wire passage for antegrade aortic valve access. If the wire was removed without covering it with a plastic catheter, the coils were rough and led to some cases of flail of the mitral leaflet. Other challenges included manipulating the catheter, requiring the development of a flexible sheath that pulls the system into the center of the valve orifice. There was also a problem with aortic insufficiency due to leaks. The speaker said, "It appears the use of a 26 mm prosthesis (instead of 23 mm) has obviated the problem."

➢ **MEDTRONIC'S "Bonhoeffer" pulmonary valve.** This is the device with the most use in humans; more than 100 patients have been treated to date. Most patients have had two to three operations before the valve replacement. A speaker said, "One anticipated problem was the initial design of the valve. It was unsupported in the center, and there was a hammock effect in the middle of the valve. This was overcome by suturing the valve in the middle."

Experts at TCT debated the value of percutaneous valves.

CON: Cleveland Clinic surgeon Dr. Patrick McCarthy insisted he wasn't there "just to throw cold water on a hot topic…but to do a reality check…You haven't had embolic events yet…but you will…(These procedures) don't pass the other test – or even the mother-in-law test…But I would continue (investigating these devices). There is definitely a niche of patients."

Dr. McCarthy also commented:

- **Percutaneous Aortic valve replacement (PAVR).** "It is hard to think this is something that will widely sweep the U.S…It is an untested valve…a difficult approach…a bad landing zone…It is a quantum leap to go from (surgery) today to a percutaneous aortic valve replacement."
- **Mitral valves.** "This is a large area that has to be clipped together…If you leave patients with 1-2 MR, they are likely to return for later surgery, and the goal of percutaneous mitral valves is to reduce MR to 2+ or less. In the surgical arena, we wouldn't consider that a good result."
- **Alfiere approach.** "With this you can get fibrosis bridging the valve…and that will diminish the possibility for a later valve repair."
- **Percutaneous edge-to-edge approach.** "It will be technically difficult, and you could embolize or damage the leaflet."
- **Coronary sinus approach.** "If there is MR in these patients, it will affect late mortality."

PRO: Interventional cardiologist Dr. Carlos Ruiz from the University of Illinois at Chicago said, "I can sympathize with the concerns of the surgical community about this new technique – because the results are not comparable to the surgical results." But he noted that the procedures are getting better, "We have not had a mortality in our last 10 consecutive patients…Clearly, it has to be understood that this is a process of technological advance…Initial surgical mortality was >40%. And our surgical colleagues know less invasive surgery is becoming more and more popular – even without clinical trials of its advantages…I think we should view this as new technology that has to be properly studied – and not necessarily do only non-surgical patients."

SUPERFICIAL FEMORAL ARTERY (SFA)

The SFA is a blood vessel in the back of the leg that extends beyond the knee as the popliteal artery. Blockages of the SFA are common and can cause moderate-to-severe pain due to poor blood flow to the leg muscles. Patients customarily have been treated with balloon angioplasty, but restenosis is a problem. Only 59% of ballooned SFAs are patent at one-year, and the patency rate declines to 45% at five years.

Stents are another option, but stent fractures have been a problem. Recoil is transmitted up the SFA, and natural kink points at the hip joint can lead to fractures in the proximal SFA. An expert said, "We have gone away from (stainless) steel and the Wallstent (Boston Scientific), and now more and more we are using nitinol stents and combining them with appropriate antithrombotic therapy."

TCT speakers said that the FDA is poised to make separate rules for stents used in SFAs and in popliteal arteries. The FDA also is expected to set a one-year follow-up timeframe for SFA trials.

SFA stents include:

➢ **W. L. GORE'S Viabahn.** Viabahn is FDA-approved for use in the SFA. An expert said, "Viabahn hasn't shown superiority to angioplasty, but that doesn't mean it isn't a good device."

The first patient in the post-approval VIBRANT trial of the Viabahn stent was treated during a live case at TCT. Viabahn has a durable, reinforced, biocompatible, expanded polytetrafluoroethylene (ePTFE) liner attached to a self-expanding nitinol stent. An investigator said the stent may be particularly useful in treating long stenoses and occlusions of the SFA.

VIBRANT is a 150-patient, randomized, prospective, multicenter, three-year study with duplex ultrasound follow-up by a core lab. The trial is comparing Viabahn to a bare nitinol stent (without any inner lining) and to historical surgical bypass graft in SFA lesions ≥8 cm. Investigators include vascular surgeons, interventional radiologists, and interventional cardiologists.

➢ **EDWARDS LIFESCIENCES' LifeStent.** This FDA-approved, self-expending biliary stent is being tested for SFAs in the RESILIENT trial, a randomized, controlled, 220-patient trial designed to show superiority, not non-inferiority over balloon angioplasty.

➢ **Cook's Zilver PTX.** This paclitaxel-eluting stent is approved as a biliary stent, and it is being tested in the above-the-knee femopopliteal artery in the DESTINY trial

➢ **Vascular Architects' aSpire.** This is a covered stent.

➢ **C.R. Bard's Luminexx.** A 6-month interim analysis of the 12-month, randomized FAST trial found a trend towards improved outcomes after use of this nitinol stent vs. balloon angioplasty in SFAs. Dr. Hans Krankenberg of Hamburg University said that no safety problems have been discovered so far in the trial, though he added, "The deployment of the stent may (sometimes) be difficult."

Dr. Krankenberg said he would be looking for evidence of stent fractures over the next six months. Asked what causes fractures, he said, "We really don't understand what happens in the SFA. There's kinking, compression, and we don't know what happens exactly with different stents. We have a lot to learn. We have to look at stent fractures, of course, and we also see that stent fractures, in some cases, don't impact the outcome. So, we have to learn more about the impact of stent fractures. They will have an impact on restenosis, but we won't say more, especially at this stage of the study."

FAST Trial Results at 6-Months by ITT

Measurement	PTA n=108	Luminexx n=136	p-value
Primary endpoint: Binary Restenosis by ultrasound	38.3% n=94	25.5% (Down 33%) n=94	0.085
Binary restenosis – per protocol	41.5% n=82	24.5% (Down 41%) n=106	0.018

FOXHOLLOW'S SilverHawk

The benefits of this plaque excision (atherectomy) device were nearly overshadowed at TCT by charges and countercharges by supporters and detractors. SilverHawk has FDA approval for use in de novo and restenotic lesion in peripheral arteries. It uses a tiny rotating blade, inserted through the femoral or radial artery, that shaves away plaque from inside the artery, collects the debris, and removes it from the patient. And SilverHawk does remove a remarkable amount of plaque, experts agreed.

Among the allegations were that:

- FoxHollow investigators and consultants were "secret million-dollar investors" in the company.
- FoxHollow opponents were bitter because they had lost money by shorting the FoxHollow stock before it went up in value.
- FoxHollow detractors had demanded unreasonable consulting fees, residuals, and stock options. A FoxHollow supporter said, "We went to them in the beginning, asking for their help, and they wanted consulting fees, residuals, and stock options. We said we wouldn't work that way…We call them the stent mafia: 'You either deal with us, or we take you out.'…They are on a mission to submarine the stock."

Off-label use of SilverHawk – e.g., for in-stent restenosis in the lower extremities – was another topic of debate. A speaker said, "(In-stent restenosis) occurs frequently and usually presents as a diffuse hyperplasia. Short term follow-up results indicate that plaque excision with SilverHawk is safe and feasible for restenosis in the lower extremities…This is an incredibly effective device for this indication, and most experienced operators have been very successful (with it). So if you have a large stent that is totally occluded, this is probably something to consider. If you see a lot of chunks of calcium, and the stent is under-extended, then you should probably stay away." Another expert was less convinced, saying, "This is a bit more than off-label. The (SilverHawk) Instructions for Use (IFU) specifically says it is not indicated. This was taken up by our ethics committee, and you must give informed consent to the patient. The IFU specifically said not to do this."

There also was strong criticism of FoxHollow for not conducting randomized clinical trials of SilverHawk. Asked why Fox Hollow has no current plans for a randomized trial, Dr. Roger Gammon of Austin (TX) Heart Hospital said, "There really is no good gold standard (therapy). And no one wants to randomize (patients)…You might (randomize against) balloon angioplasty, but everyone knows that balloons don't work. The FDA is concerned about stent fractures, and that's an unproven therapy, not a gold standard." Dr. Lawrence Garcia of Beth Israel Deaconness Hospital said, "People say there is no data to support what we do. Well, the data is just now coming out; it's in its infancy, in its first year."

Dr. Gammon predicted the company would do a randomized trial "in a few years," probably compared to the Edwards stent. A FoxHollow official confirmed the company is planning a clinical trial – but said it would not start for two or three years.

Meanwhile, FoxHollow is running a web-based registry, TALON, to track and evaluate acute and long-term outcomes of consecutive patients treated with SilverHawk in the lower extremity peripheral vasculature. Dr. Gammon, a SilverHawk investigator, said, "TALON is the first prospective, non-randomized registry designed to evaluate clinical outcomes following plaque excision in the lower extremities. It captured data on patients without restriction to lesion characteristics or anatomical complexity. Post-procedural outcomes were based on the absence of TLR at six and 12 months…This was the first experience with the device. There were some concerns about how long it (the procedure) would take and how efficient it would be, but the procedure time was 27.5 minutes, on average, and that's remarkable…Complications, including thrombosis, have been quite unusual (rare)…There were some Grade A/B dissections, but no serious dissections, and no perforation…As for procedural complications within 30 days, there was only one patient, who had a retroperitoneal bleed. There were no emergency surgery interventions."

TALON has its critics. One said, "I have trouble with TALON. It is not scientific or really useful. We need a randomized clinical trial…Freedom from TLR is very subjective…I'm impressed with the stability of the SilverHawk results, but it needs a randomized clinical trial before acceptance."

Complications in TALON Registry at 30-Days

Complications	Post SilverHawk	Post adjunctive therapy
Perforations	0.7%	0
Grade A/B dissections	3.2%	7.2%
Grade ≥C dissections	0.9%	0.7%
Aneurysm	0	0.2%
Occlusion/thrombosis	0.3%	0.2%
Embolism	0.1%	0.2%

TALON Registry Results as of April 1, 2005

Measurement	SilverHawk
Patients enrolled	728
Limbs involved	906
Lesions	1,517
Procedures	1,001
Procedures with >1 lesions	40.8%
Above the knee (ATK)	74.2%
Below the knee (BTK)	25.8%
Procedure time (average)	27.5 minutes
Average device insertions per procedure	3.3
Average passes per procedure	17.7
Stenting after SilverHawk	6.1%
Primary endpoint: Freedom from TLR at 1 year	79%

Without a randomized clinical trial to prove the utility of atherectomy in general and SilverHawk in particular, doctors are concerned that, in the future, the technology may be shown to be either useless or harmful. A Florida doctor said, "We use SilverHawk. The real issue relates to atherectomy in general. We saw the same thing with directional atherectomy in the periphery – great results initially and at six months, but the results were not durable. The (SilverHawk) concept may be valid, but there are concerns with the (company's) claims."

When the debates over stock deals and the lack of clinical trials are excluded from the discussion, doctors generally said they like SilverHawk and use is increasing. A surgeon said, "SilverHawk is a good niche product for 5% of SFA patients." Another surgeon said, "Use (of SilverHawk) is high already. It's a reasonably good adjunctive tool and has its role. It works well."

Supporters insisted that SilverHawk is a useful option. Dr. Gammon said, "Current treatments are suboptimal, and so we (FoxHollow) are looking at plaque excision. The (FoxHollow) device is unique compared to other devices. There is no balloon necessary for apposition, there is no balloon trauma to the apposite wall, and there is no heat generation." Dr. Garcia said that plaque excision with SilverHawk is safe and effective, "It is reliable and reproducible, and it is now durable." Another source pointed out that SilverHawk is better than a stent below the knee, "Stents are not recommended in the popliteal area, and below the knee there is too much flexion plus compression. Some people are looking at using drug-eluting stents there, but SilverHawk is better. It leaves nothing behind and can treat multiple avenues in one device."

Asked about thrombosis, Dr. Gammon said, "We did have one vessel that closed. We treated it. It had a nice lumen, slow flow…but once it got to the foot, it ended up thrombosing. It is amazing that you don't thrombose every time with this device…but, for some reason, we see far more thrombosis by putting a foreign body in, like a stent. Vascular surgeons are amazed at this device too, and don't understand it. Thrombosis is a very rare event."

IVUS is not commonly used with SilverHawk. Dr. Gammon said, "The only time I use IVUS is when I'm not sure, when vessels are occluded and I'm not sure it's a lumen that connects to a plaqued artery. Then, I might drop in IVUS because I don't want to put a cutter down a thin wall collateral. I don't need IVUS for plaque analysis because I'm going to cut it. I'm not worried if a lot of calcium is there, so it doesn't enter into the decision-making. I can use IVUS for vessel sizing, but I think you can do that with an angiogram."

A FoxHollow official said the company does plan to add IVUS to SilverHawk, "We're going to put IVUS on the catheter. That part of the plan…We're also considering OCT imaging."

BOSTON SCIENTIFIC/CRYOVASCULAR SYSTEMS' PolarCath

The trademarked name for this thermal (cold) therapy is CryoPlasty. An investigator said, "There is some advantage over balloon angiography because of less dissections. We biopsied some patients with CryoPlasty, and we found they were hypercellular, not hypocellular."

In one study discussed at TCT, researchers reported that survival free from TLR with PolarCath was 83.2% at 300 days and 73.5% at 1,253 days. An investigator said, "These findings are consistent with the IDE registry data. Only three patients required re-interventions during a mean follow-up of 10 months. One additional patient developed clear-cut evidence of stenosis. Primary patency overall was 78% at six months." Below the knee CryoPlasty, referred to as "BTK chill," appears to have reduced dissection and the need for stenting.

PATHWAY MEDICAL'S Pathway PV system

Pathway is developing an atherectomy device that would compete directly with FoxHollow's SilverHawk. It is a rotating, aspirating, expandable catheter that combines aspiration and differential removal of both hard and soft plaque. Pathway PV is still in the engineering stage, but a pivotal trial in Europe is planned to start in early 2006, which would be used to start the U.S. approval pathway.

Asked to compare the Pathway device with SilverHawk, a Pathway official said, "You need to push the nose cone of the SilverHawk through the material (lesion), and cut as you bring the catheter back. Our device cuts as it goes through the lesion…But FoxHollow is doing an amazing job of raising awareness and building referral networks." He added that the Pathway device creates a nice lumen if the doctor wants to put a stent in, "But we think we remove enough plaque that placing a stent isn't necessary."

Pathway also touts the fact that its officials were the folks behind Rotablator (now a Boston Scientific coronary atherectomy device). An official said that the company abandoned coronary applications in favor of SFAs after the negative results last year for two distal protection devices: Medtronic's GuardWire (in the EMERALD trial) and Possis's Angiojet (in the AIMI trial).

VENTRICULAR ASSIST DEVICES (VADS)

Among the key regulatory issues with these devices are:

- Control group.
- Selection bias.
- Positive and negative placebo effects.
- Treatment bias.
- Evaluation bias.
- Lack of blinding.

An FDA official said, "Even though VADs pump blood, that may not be enough for us. You could be comatose and a pump still pumps…Your cognitive function, quality of life, etc., is very important to us, and right now those are concepts we try to require for IDE studies for these VADs." He recommended studying the devices in the type of patient for which a label will be sought. Dr. Zuckerman added, "We are trying to find clinically meaningful endpoints at the same time we are trying to improve devices, and that is tough. From our perspective, we don't want to make the wrong decisions, but at the same time we want to approve appropriate devices…This is a complex question that, unfortunately, needs a lot of thought."

♦