Trends-in-Medicine

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by Lynne Peterson

SUMMARY

Percutaneous valve use is continuing to ramp up in Europe, but governments/insurers are starting to balk at the cost, and more countries are expected to follow France's example and cap the number of procedures, perhaps as early as later this year. ♦ Percutaneous aortic valves are being used mostly on-label in high-risk patients, not migrating downward to healthier patients. ♦ European doctors are splitting their use almost equally between Medtronic/CoreValve and Edwards, and that is likely to continue for the near future. ♦ Edwards 18 Fr should be available in late 2009 or early 2010. ♦ Subclavian access won't eliminate use of the transapical approach, but it may decrease TA volume as a percent of total procedures. ♦ Medtronic/CoreValve is expected to start its pivotal U.S. trial in June 2010; details on trial design and the nitinol fracture risk continue to delay the start of that trial. ♦ The need for a permanent pacemaker continues to be more of a problem with CoreValve than Edwards, but cardiologists stressed that there are inexpensive pacemakers and length-of-stay is reduced, so the pacemaker cost is not a big issue. ♦ Mitral repair is still considered too difficult and too expensive, with not as much value as hoped.

Trends-in-Medicine
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TRANSCATHETER VALVE THERAPIES (TVT)

Seattle, WA
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This is only the second year for TVT, and it is a small meeting, but it is quickly becoming an important and useful meeting to the field. All of the key companies in the field were represented, and the faculty were key opinion leaders from across the globe. The meeting was more a sharing of information opportunity than an effort to educate doctors not yet involved in the field.

TRANSCATHETER AORTIC VALVE IMPLANTATION (TAVI)

What *is not* controversial: Aortic stenosis (AS) patients have a long asymptomatic period, a short symptomatic period, then death.

What *is* controversial includes:

- **What to do with asymptomatic severe AS patients.** Should these patients be treated? Dr. Allan Schwartz of Columbia University Medical Center argued not all asymptomatic AS patients should go to surgery, "Does operating early (in asymptomatic patients) lower the risk rather than operating at the onset of symptoms? I would argue that the data say no." He pointed out that Medicare database information puts the hospital mortality with asymptomatic aortic valve replacement at 8.8% (13.0% at low volume centers and 6.0% at high volume centers), but the STS (Society of Thoracic Surgeons) database is 4%.
- **What to do with low gradient, low EF and CHF.** This is 5%-6% of AS patients. Dr. Schwartz contended that patients with low gradient AS probably don't benefit from surgery.
- **Whether to treat the oldest old (age >80).** At least 30% of patients with Class I AS do not get aortic valve replacement (AVR) because they are too frail, too old, or have comorbidities. Dr. Schwartz said, "I think patients of any age should be considered for aortic valve replacement, particularly percutaneous AVR. Appropriately chosen patients have acceptable operative risk, improved survival, functional status, and quality of life after AVR."
- **The type of valve to use (tissue vs. mechanical).** Dr. Schwartz described tissue valves as a reasonable option for people age >55 and superior for those age >65.
- **The impact of comorbidities.**

Asked how the decision is made in Italy on when to do TAVI and when to do surgical AVI, Dr. Franceso Maisano of Italy said, "I think that patients should enter the selection process with no pre-selection bias…(In an 82-year-old, mildly frail patient) I would start with TAVI if I find the patient has nice anatomy…I

would really consider TAVI for any patient over age 80." Dr. Alec Vahanian of France added, "Before the results of trials, we cannot and should not offer this treatment to patients at low risk."

The learning curve for TAVI cannot be minimized. Dr. Marty Leon of Columbia University Medical Center emphasized, "This procedure is not for everyone." Dr. Gerhard Schuler of Germany said, "85% of patients can be implanted easily with no problems, but in 10%-15% of patients it is difficult. You need all the help you can get, and in 5% you have to deal with very severe complications, and if you are not prepared for these complications, the patient will very likely not survive."

Asked how many cases he has had to convert to surgery, Dr. Schuler said, "That was limited to the early learning curve, and I had to convert a number of patients, and not all of them survived, but that was years ago…We have not converted any patients in the last three years."

The European experience

European cardiologists said use of percutaneous aortic valves is continuing to ramp up, and new centers are opening. A U.K. cardiologist said, "Neither company can meet all the demand yet…It will take at least two years to absorb all the high-risk patients."

However, use in France remains capped by the government, and an industry source said that Switzerland is starting to copy German reimbursement, and some countries besides France are starting to limit the number of procedures, though he did not say which countries. A German doctor said, "There may be attempts to limit reimbursement (in Germany). The insurance resistance (to TAVI) is gathering speed. I expect they will limit the numbers (in Germany). We will have some limitations this year."

The U.S. outlook

Experts agreed that much of the TAVI field in the U.S. will depend on the outcome of Edwards' ongoing PARTNER-US trial. Was there too much of a rush to get PARTNER underway? Dr. Leon said, "That's what keeps me up at night…This is a large, randomized trial with the sickest of sick patients. It has been well conducted…I suspect if we did PARTNER two years from now, we would get better results…Hopefully, the results will be good enough to demonstrate the value of this therapy…I hope we embedded enough secondary endpoints and non-morality-related assessments of the benefit of this therapy that if we don't hit our expected primary endpoints that we will be able to fall back on the other well conceived and powered secondary endpoints. The FDA was categorical on the one-year all-cause mortality endpoint, and they haven't backed off of that."

Take-away messages on aortic valves

At the end of the meeting, Dr. Leon summed up what he considered "consensus impressions" on aortic valves, which included:

- The rapid penetration in Europe demonstrates the unmet treatment need for elderly and comorbid patients.
- Industry has been very disciplined in the commercial release of their valves – with "meticulous" physician training and mostly on-label use. "So far, this has been a very, very careful release."
- After a "chaotic" learning phase, TAVI has matured and clinical outcomes have stabilized.
- Mortality at 30 days and 1 year – 7%-8% with Edwards – is still very high for an interventional procedure. "There is no other interventional procedure where 7% mortality at 30 days is good. That is something as interventionalists we are still trying to understand and come to grips with."
- Comparing transapical (TA), transfemoral (TF), and subclavian approaches is difficult because the patient populations are so different.
- The complications need meticulous attention and careful problem-solving.
- TAVI is very milieu sensitive and requires a significant multidisciplinary institutional commitment. "It is not for everyone."
- Rigorous evidence-based medicine is lacking. "We need thoughtful randomized trials to expand indications and convince doubting 'comparative efficacy' healthcare economists."
- Unexpected problems are likely to crop up. "As with most new breakthrough therapies, I expect some 'speed bumps' in the future…maybe durability issues. I think we should expect it won't always be so easy, and we will need to confront some unexpected issues…We need a longer timeframe to assess these patients." What will these be? The most likely is a durability issue, but paravalvular leaks are also a concern. And it may be something not expected.
- So-called next-generation devices may offer some advantages, but they are largely incremental changes, not transforming technology.
- More time and attention should be given to improving accessory devices – sheaths, wires, balloons, positioning, access closure, etc.
- Advanced imaging (especially CT angiography) will be essential to optimize outcomes.

THE GOOD

The good: *TAVI can be performed safely in high-risk patients and in an acceptable timeframe.* So far, about 8,000 TAVI cases have been done, split almost equally between Edwards Lifesciences' Sapien and Medtronic/CoreValve's ReValving System. Dr. Leon commented, "It is striking how well the survivors do. In terms of symptom benefit, (TAVI) is absolutely dramatic in the survivors."

Mortality appears acceptable, but it is higher than interventional cardiologists are used to. How low can it get? Experts on a panel at TVT suggested it can come down to 3%-5% with careful patient screening, and they said this is reasonable in high-risk patients, but it will have to come down even lower for TAVI to be adopted for younger, healthier patients. Dr. Michael Mack, a surgeon from Dallas TX, said mortality of 1%-2% is possible, "We are over the steep part of the learning curve…Surgical mortality is 1%, and this (TAVI) has to achieve that – and it is achievable."

Yet, Dr. Mack warned that TAVI has to move into younger, healthier patients because insurance companies and the government may not pay for too many of the very, very elderly, "Healthcare economists probably will not allow us to treat some of the patients we are treating today. Although we get a lot of patients in their late 80s and 90s, it will be tough to justify to healthcare economists that it is reasonable to treat these patients…The ultimate barometer on this will be regulatory and more so reimbursement."

However, Dr. Leon said there is a serious learning curve, and there have been several problems with TAVI studies, including:

- "Chaotic" early clinical trials.
- Study endpoints have not been clarified or standardized.
- Inconsistent use of core labs and clinical event committees (CECs).
- Poor long-term follow-up on many essential valve-related endpoints, like follow-up echo.
- All problems are exaggerated due to the complexity and acuity of the patient population.
- The rigor of post-approval studies has tended to decline appreciably.

THE BAD

The bad: *Conduction abnormalities result in a need for permanent pacemakers in 5%-33% of patients, valve migration during deployment is not predictable, and paravalvular aortic regurgitation remains a concern.* There also is just one chance to get it right; there are no simple bailout options.

Permanent pacemaker use – This is particularly a problem with CoreValve devices. Dr. Jean-Claude LaBorde of the U.K. – a CoreValve user – said that, on average, 23.4% of CoreValve patients and 6.3% of Edwards patients have required a permanent pacemaker, "It is quite true there is a significant number of pacemaker implants…Despite this, we have tremendous implantation in the last two years. (Current use in Europe) is 50% Edwards and 50% CoreValve despite this complication. Why? Either it is not viewed as a complication, or there is a tremendous advantage with CoreValve… Probably the answer is in between." In Siegburg, Germany, 33% of patients reportedly end up with a new pacemaker. Dr. Leon noted that at other centers 15%-35% of CoreValve patients require a permanent pacemaker.

Dr. LaBorde cited several predictors or suspected factors to the need for a pacemaker:

- Pre-existing conduction disorders.
- Anatomy and the self-expandable nature of CoreValve – mismatch between the annulus and the frame diameter, aortic root angulation, or low implantation of the valve.
- Timing of the pacemaker decision.

A pacemaker isn't entirely a negative, according to Dr. LaBorde, who reported shorter hospital stays for CoreValve pacemaker patients, "We have increased the number of patients going home at Day 5…Whatever you do – Edwards or CoreValve – every time you face a pacemaker requirement." He said there are two approaches doctors can take:

1. ***Conservative attitude*** – making a late decision on pacemaker use, though this results in a prolonged hospital stay for the patient.
2. ***Innovative attitude*** – making an early decision for a pacemaker. "Put the valve in and immediately the pacemaker, and the patient is ready to go home…The next step is a biodegradable temporary pacemaker lead, and then a decision at one month. Medtronic is working on this. The patient comes back at one month and either you need a pacemaker and give them a date for the pacemaker and they do it 1-2 weeks later, or there is no need, and you send them home."

Interventional cardiologists at TVT didn't just complain about the pacemaker issue; they offered a potential solution, at least with the CoreValve device: placing it higher. Dr. Nicola Piazza of the Netherlands reported on a recent analysis of 91 patients which also suggested that implanting the CoreValve device slightly higher will cut down on the need for permanent pacemakers, "We found that the mean depth of implantation was 10.3 mm in patients who developed new onset LBBB (left bundle branch block) acquired during or after valve implantation vs. 5.5 mm in patients who did not develop LBBB ($p<0.001$). The depth of implantation was an independent predictor of LBBB and the need for a permanent pacemaker. If we implant the CoreValve device slightly higher (2-3 mm higher), we may reduce the need for a permanent pacemaker."

Asked which is more dangerous – a pacemaker or embolization of the frame, Dr. Schuler said, "The depth of implantation may account for the increased rate. We also know that occurrence of LBBB is not only connected to implantation of the frame but may occur early during balloon angioplasty in 30% of cases…I was surprised (at the 30% of patients who had heart block at the time of ballooning). I don't know what the explanation is. These are data from Rotterdam…But users know that there is continuous movement of the prosthesis during implantation…And if you are aiming too high, this may result in embolization of the prosthesis into the aortic root."

Asked how difficult it is to adjust the CoreValve by 1-2 mm, Dr. Piazza said, "Edwards is implanted 4-6 mm in depth, and they don't see these conduction abnormalities…If we implanted CoreValve similar to an Edwards valve we might reduce abnormalities…So, positioning of the valve will be a major important factor in the future on pacemaker use."

Paravalvular aortic regurgitation (AR) – The bad news is that AR occurs ~11% with TAVI vs. 0 for surgical valves. Dr. Leon said, "To a certain extent, some degree of this is the rule …Over time, it didn't change much – not worse or very much better…In the early analyses, there is no indication of increasing left ventricular size (in these patients)…So, at least so far there have been no important consequences of these leaks…I do think there is less leak with CoreValve than Edwards." Dr. Piazza said, Grade 3-4 aortic regurgitation was 3% with CoreValve and 5% with Edwards, "Typically these patients don't do well."

Asked what this issue means long-term, Dr. Peter Block of Emory University said, "Once we start to dip into surgical candidates, then we really need to address this issue…If you have 50-year-old patients and talk them into TF valves and they have 2+ AR, I'm not sure you did that patient any favor…For the older patients, it is moot. Most of the folks we implant are age >72, and many are ~87. For younger patients it is a big problem."

Left main coronary obstruction – This appears to be procedure-related. It is rare (<1%) but when it occurs "it is quite dramatic." Dr. E. Murat Tuzcu said that at the Cleveland Clinic they always have cardiopulmonary bypass (CPB) ready in case this happens. He and other experts said they occasionally use CardiacAssist's TandemHeart, but CPB is generally preferred. Only one expert at the session would use Abiomed's Impella (5.0) in these situations.

Valve embolization – This also is rare 0.4%-0.6%. Dr. Piazza said this occurs because of undersizing of the prosthesis, too high/too low implantation, rapid pacing terminated too early, incomplete release of leading hooks (CoreValve), etc.

THE UGLY

The ugly: *Vascular complications remain a concern, and mortality is increased three-fold when a vascular complication occurs. Embolic events (stroke) continue to occur. Embolic protection is likely to be needed in the future.*

Vascular complications – such as iliac perforation. Dr. Leon said, "In the early (Edwards) REVIVE/REVIVAL experience, it was 15.5% and three-fold in-hospital mortality if the patient had vascular complications...In the (CoreValve) SOURCE registry, major complications were 10.6%, which at least is encouraging…And if a patient had a major complication, mortality was not as great as in REVIVAL…which indicates to me that we are learning to manage these complications better. TA complications are more access site-related and more infrequent, but when they occur, they are serious, and the patients don't do well."

THE FUTURE OF THE TRANSAPICAL (TA) APPROACH

Experts at TVT appeared to suggest that, going forward, the transapical approach is likely to have little utility. Dr. Leon said, "Clearly, the sicker patients are gravitating to the transapical procedure, which has been demonstrated in multiple series, including PARTNER…which makes comparison of the (transfemoral and transapical) data difficult…TA is associated with an increased patient risk profile and worse 30-day and 1-year outcomes – perhaps due to increased patient risk factors and/or physician training issues."

Currently Edwards valve can be put in either TF or TA, and CoreValve is put in TF, though CoreValve has had a good early experience with a subclavian approach. Dr. Schuler said subclavian is more difficult and time consuming, and TA is faster.

Dr. Leon wondered if there is a future at all for TA. He asked, "If you could put an 18 Fr in subclavian…why would you do TA?" Another expert responded, "In patients who require a combined aortic and mitral valve, TA might be a reasonable approach…and as we go to younger patients, the issue of paravalvular leak becomes a bigger issue…and (bigger skirts) may be needed, and the only way to get that may be TA… From a patient standpoint either TF or subclavian is feasible …But we have other patients where TA might be better or a good option." Dr. Mack said, "Subclavian will not kill TA. Ultimately, subclavian may be less invasive than TA, but percutaneous TA is coming, and that may be a big deal. It may mean you can eliminate the thoracotomy. You always need a surgeon for a subclavian…Percutaneous TA is better than subclavian because it is straight and short."

Several experts called for a head-to-head trial of TF vs. TA, but they would also like to see head-to-head trials of different devices (e.g., CoreValve vs. Edwards).

Comparison of the transfemoral (TF) and transapical (TA) approaches

The mortality in the Edward's PARTNER-EU trial is 8.1% with TF but close to double that – 18.8% – with TA. Vascular complications are higher with TF than TA (26% vs. 2.9%), but there are more bleeding complications with TA. Mortality at 30 days is also higher with the CoreValve device in TA than TF: 6.3% TF and 10.3% TA in the European post-approval SOURCE registry. The 30-day SOURCE results, which were presented at EuroPCR in May 2009, were reviewed.

Dr. Francis Duhay, a cardiothoracic surgeon from Pennsylvania, said, "The superior outcomes from TF appear to be more in the first three months…and mortality appears to be attributable to patient selection, learning curve, and the technology gap."

What are patients dying of in the first 30 days? Dr. Duhay said two-thirds die from complications related to the procedure: ~30% to major bleeding, with stroke No. 2, "Stroke prevalence is equal between TA and TF, but it tends to be embolic with TF and survivable with TA. The TF strokes are associated with watershed events and often fatal. Coronary obstruction is rare, but we see mortality related to that as well."

30-Day Results of SOURCE Registry

Measurement	Sapien TF n=463	Sapien TA n=575
Baseline characteristics		
EuroScore	25.7	29.2
Procedural results		
Acute procedure success	95.6%	92.9%
Valve migration	0	0.5%
Valve malposition	1.7%	1.4%
Device success	92.4%	90.8%
30-day results		
30-day mortality	6.3%	7.3%
Freedom from death	93.7%	89.6%
Freedom from stroke	97.6%	97.4%
Freedom from MI	99.8%	99.3%
Complications		
Perforation or damage to vessels, myocardium, valvular structures	17.9%	17.1%
Renal failure requiring dialysis	5.0%	11.7%
Permanent pacemaker	6.7%	7.3%
Vascular complications	10.6%	2.43%
Stroke	2.4%	2.6%

Mortality with Sapien by TA

Trial	Number of patients	30 days	6 months
U.S. feasibility study	38	17.5%	58.7%
TRAVERCE	168	14.9%	70%
PARTNER-EU	130	18.8%	50%

Which patients should not get TA? Dr. Duhay said, "Patients with severe end stage lung disease do not tolerate this procedure very well…or patients with severe RV dysfunction."

Asked how he chooses between Edwards and CoreValve since he does both, Dr. Jan Kovac of the U.K. said, "Primarily on size. Edwards is limited on size. If that is equal, then at the moment we do CoreValve." Dr. Schuler said, "There is no firm algorithm to determine which to use. If patients are referred to a surgeon, they get TA. If they are referred to a cardiologist, they get TF – which I think is correct at the present time."

Why are there more patients in the SOURCE TA group than the TF group? Dr. Alec Vahanian of France said, "Most had a contra-indication for TF…We have no evidence to say one approach is better than another." Dr. Alain Cribier of France said, "My personal view is that TA and TF should be around 50% each, maybe a little more TF than TA…(But) I have seen some centers in Germany where they just decided to do TA and that's it."

Why isn't there more off-label use? Dr. Vahanian said, "We strongly repeat that we should not do that. There is a very strong pressure, mostly from the patient to be treated, and it is difficult to resist…We do that (resist), but there is a strong pressure. We know off-label is there and will probably increase, but we should not embrace this attitude right now. Our role is to run the trials and answer the questions…but the patients are pushing us…The team helps sometimes. And if you have a strong surgeon, it can help to prevent that."

Future TAVI Devices and Indications

The key features expected to be in newer valves are:

- **Lower profile devices.** Dr. Leon predicted 18 Fr will be standard and perhaps even lower.
- **Expanded range of valve sizes** – from 17 mm to 29 mm.
- **Dedicated delivery systems** that are user-friendly, sheath-based, with soft, tapered noses and perhaps tip deflection.
- **Improved circumferential annulus.**
- **Optimal positioning** before and during deployment (improved placement). Many of the newer valves in development are repositionable. Dr. Block predicted, "No valve we will be using five years from now will not have the option (of repositioning and retrievability)."
- **Embolic protection devices.** Whether these are really needed is not entirely clear, but they would prevent embolic debris during procedures. Embrella Cardiovascular's Embrella Embolic Deflector, which guards right and left carotid inflow from embolization, is perhaps the closest to clinical practice.
- **Closure devices**, such as Abbott's Prostar 10 Fr device.

- **Long-term durability** of valve and platform. Dr. Leon said that valves with a 10- to 15-year life are needed.
- **Dedicated accessories devices** – sheaths, guidewires, valvulopathy balloon, etc.
- **Transaxillary** (subclavian) AVR.

Evolving indications for TAVI:

1. **Lower risk AS patients** – and the field is already moving toward this.
2. **Managing mixed AS and coronary artery disease patients**.
3. **Bicuspid valves.**
4. **Aortic regurgitation.**
5. **Valve-in-valve.** The idea of putting a TAVI in a patient who previously had a surgical tissue valve is a new idea, and the experience so far is limited, but experts said the concept is justified and can be done with either an Edwards or a CoreValve. However, valve-in-valve cannot be done if the original valve was a mechanical valve. Dr. Leon said, "What I take away…is this is a procedure that will have some (value) …but there is work to be done in understanding the designs for this indication…and it may involve some (coordination) with our surgical colleagues."

One concern is that the current TAVI devices are too big to do a valve-in-valve procedure with 19 mm surgical tissue valves. Dr. Mack said more than half of U.S. surgical tissue valves today are 21 mm, with ~25% 23 mm, and another 15%-20% 19 mm, "With the current transcatheter designs, that is problematic. It leaves us 25% (in which we can do valve-in-valve). This will be an issue down the line. There is a concept of solving this with a two-tiered stent in which the valve sits in the upper part of the stent, supervalvular, while the smaller part sits in the annulus. Some concepts like that may solve the smaller valve issue."

Specific Aortic Devices

Only Edwards' Sapien and Medtronic/CoreValve's ReValving System have European approval, and no percutaneous valves have FDA approval. Speakers at TVT named numerous devices in development, hesitating to call them next-generation devices. However, the data on these are either very early, very limited, or very poor. Dr. Leon cautioned, "Edwards and CoreValve had a great head start, and I don't think they will just sit and wait for others to overtake the market. They are rapidly iterating…I'm certain they will successfully compete with the 'next-generation' technology."

Percutaneous Aortic Valves in Development

Company	Valve	Type	Size	Notes	Key advantage	Issues
ABPS Percutaneous Valve	Bailey-Palmaz PercValve	Nanotechnology, nitinol frame	10-12 Fr	In animals	Quick endothelialization	---
Direct Flow Medical	---	Bovine pericardial, rapid pacing not required, conformable, non-metallic	22 Fr but 18 Fr soon. First-in-man underway.	European trial underway	Repositionable, retrievable, minimizes paravalvular leaks	Opening process and frame durability
Edwards	Sapien XT	Porcine pericardial leaflets	24, 22, and soon 18 Fr	Transfemoral, transapical. Has CE Mark	Good hemodynamics, open frame, short covered area	User friendliness, size
Hansen Medical/ AorTx	---	Low profile folded metallic frame, tissue valve	---	---	Retrievable, repositionable	---
Heart Leaflet Technologies/Bracco	---	Porcine pericardial, self-expanding, nitinol	16.4 Fr with 23 mm valve	About to start first-in-man	Very low profile, repositionable	---
JenaValve Technology	JenaValve	Self-expanding, nitinol, commercially available biologic valve, clip-based anchoring	---	Transfemoral, transapical	Repositionable, low profile	---
Medtronic/CoreValve	ReValving System	Self-expanding, nitinol	18 Fr	Transfemoral, or subclavian. Has CE Mark	Ease of deployment, less paravalvular aortic leak	Permanent pacemaker need
Medtronic/Ventor	Embracer	Bovine pericardial leaflets, self-expanding, self-seating, Venturi shape	18 Fr TA, and soon 14 Fr TF	Transapical now but transfemoral coming. CE Mark study being planned.	Axial fixation may reduce native leaflet displacement, may have less aortic regurgitation	Commissural alignment in diseased valves, anchoring barbs, long-term hemodynamic stability, outlook for transfemoral design
Sadra Medical/ Boston Scientific	Lotus	Bovine pericardial tri-leaflet, self-expanding nitinol woven platform, self-centering	21 Fr, but soon 18-19 Fr	Redesigned to be simpler. CE Mark study to start in late 2009 or 2010.	Repositionable bidirectionally, very flexible, retrievable, can be re-elongated	Too complex, too many moving parts, accurate positioning and opening force
Symetis	---	Self-expanding, annular fixation	---	Transapical. First-in-man starts 3Q09.	---	---

DIRECT FLOW MEDICAL

Dr. Joachim Schoffer of Germany reported on the 25-patient, prospective, European feasibility trial. The average age was 82, and 71% were NYHA Class III. Implant success was 71%; failures were due to: iliac access probes, excessive calcification, etc. Of the 22 who actually got an implant, 2 had to undergo surgical conversion (one for sizing and one for placement), and 65% required a permanent pacemaker. Two additional patients died, and only 18 were discharged from the hospital.

In the 18 patients with 30-day follow-up, NYHA Class improved, mortality was 12.9%. There were 3 procedure-related deaths, and 1 device-related death. Two patients required a permanent pacemaker.

An 18 Fr device is coming, and Dr. Schoffer said, "This should increase the safety and ease of use because of the low profile and simpler positioning…There are some drawbacks (to the current system) that are being addressed, and the new device should lead to improved positioning, better sizing, and enhanced delivery and deployment."

One question about this device is its radial strength since it is non-metallic, and it may not be appropriate for all patients. Dr. Schoffer said, "The radial force of this prosthesis does not compare to stent-based valves…There is still room for improvement in the radial force with this device, and that has been done with the 18 Fr device, but patients are doing well with this valve…and they have almost no paravalvular leakage." Direct Flow CEO Dr. Bernard Lyons said, "I think there will be (selected) patients…but I am pleased with the stability of the device."

EDWARDS LIFESCIENCES' Sapien XT

The PARTNER-US trial has enrolled more than 900 of the planned 1,040 patients, though Dr. Leon, the co-principal investigator, wouldn't say exactly how many patients are enrolled so far, but he said enrollment is "moving rapidly." The primary endpoint is all-cause mortality (non-inferiority vs. surgical valve) in Cohort A and freedom from death at 1 year (superiority vs. medical therapy) in Cohort B.

Cohort B – (vs. medical therapy) completed enrollment in February 2009, and it is possible the results will be at the American College of Cardiology (ACC) meeting in mid-March 2010, but that would mean a very quick turnaround on the data. If Edwards misses ACC, it is uncertain where the data would be presented because the preference would be for an American meeting, but that would mean holding off until fall 2010 for TCT or the American Heart Association meeting, and if the news is good, the company likely won't want to wait that long. It is possible Edwards may file for FDA approval based only on Cohort B.

One criticism of Sapien has been the size, but Edwards devices are getting smaller. Dr. John Webb of Canada said, "Now, there is 24 Fr, 22 Fr, and 18 Fr – the same as CoreValve, which really required a conceptual change. With the NovaFlex (formerly the RetroFlex 4) system…the balloon and valve are inserted sequentially…Failure to cross is no longer a problem (with this)." Another expert said, "I think it will expand the pool of patients – significantly. I think there are a lot of patients with small femoral and small iliacs that we are not including in trials now. I think we will have more patients to treat."

The PREVAIL TA and PREVAIL TF trials of the 18 Fr are both underway.

A big question is whether the 18 Fr Sapien XT will be able to be delivered through the subclavian artery. Experts who use Sapien said that, theoretically, it will be small enough to deliver subclavian, but until it is tried – and it hasn't been yet – they won't know for sure. One potential issue is whether there is room in the subclavian space to work with the stacked design of the 18 Fr catheter.

For patients not amenable to the 18 Fr device, Edwards has the Ascendra transapical delivery system. Dr. Webb said the new Ascendra 2 has a delivery catheter that flexes better. In fact, several speakers praised the user-friendliness of the Ascendra 2.

MEDTRONIC/COREVALVE's ReValving system

In Siegburg, Germany, 30-day clinical outcomes were reported to be: 40% with 25 mm, 8.3% with 21 mm, and 10.8% with 18 mm.

Are the CoreValve patients lower risk patients? Dr. Leon doesn't think so. Without comparing the CoreValve patients to the Edwards patients, Dr. Leon said, "Some said the patients are not quite as high risk…I don't agree…These are high-risk patients as well."

MEDTRONIC/VENTOR's Embracer

There was a lot of interest at TVT in this device. Asked which device intrigues him the most, Dr. Mack said Embracer, "I've had the opportunity of firing (this) on the bench, and I'm very intrigued with that…I very much like the design and deliverability. It is only TA now, but ultimately it will go to TF."

Dr. Thomas Armitage of Medtronic described the results on 21 of the 27 patients enrolled so far in a one-year, 30-patient, feasibility study of Embracer. Among these patients, 86% were female, 76% NYHA Class III, and EuroScore averaged 24.4. There were 10 deaths – 6 within 30 days and 4 later; none were deemed valve-related. Three serious adverse events occurred: an aortic dissection requiring conversion to surgery, a circulatory collapse, and a ventricular apex bleed. After surgery, the patient's gradient went from 59 to 13. Dr. Armitage said, "It is a small study, and mortality was high, but it is a first-in-man experience. The data suggest there is a learning

curve which may improve with greater experience. A C.E. Mark study is being designed."

SADRA MEDICAL/BOSTON SCIENTIFIC's Lotus

So far, only 10 patients have been treated. The mean age of patients was 84.2, mean EuroScore 17.3. Of these 10, only six were actually implanted; the other four patients had problems relating to the complexity of the first version of the device and access problems. One patient died, so only 5 patients still have a device. The one patient with one-year follow-up reportedly showed maintenance of benefit on echo.

Dr. Leon said, "The current system is ***not*** user friendly. It is large and complex and takes too many steps, the release is too stiff, and there are erratic system malfunctions (too many moving parts)."

A second version has reduced the number of attachments from 15 to 3 and the profile from 21 Fr to 18-19 Fr. Clinical trials are expected to start by the end of 2009.

MITRAL VALVES

Attendance at the mitral sessions was much lighter than for aortic valves, and there appeared to be far less interest in mitral valves, though they had prominent positions in the TVT program. Dr. Greg Stone of Columbia University Medical Center commented, "Struck with how different the field of mitral is from TAVI. The disease is different, surgical and medical options are different, the devices are different, and mitral is further behind (TAVI), with the gap growing."

Mitral surgery was described as "a wonderful surgical procedure, usually minimally invasive and usually in young people," which makes it hard for percutaneous procedures to compete. Dr. Stone said, "I have trouble even consenting people for a percutaneous procedure when surgical outcomes are so terrific." He wondered if mitral surgery will ever become as common as stenting. Dr. Ted Feldman of Evanston Hospital, a MitraClip investigator, said, "I think we are beginning to figure out when we do screenings for Evalve referrals who these patients are…The success rates for mitral repair are very, very good at many centers, but I would be a little surprised if it is 100% anywhere."

Functional mitral regurgitation (FMR)

There is a high incidence of FMR. In the U.S., about 620,000 people per year have mitral regurgitation (MR), and ~380,000 of these have moderate-to-severe MR. However, only about 10% of these moderate-to-severe MR patients get a repair procedure each year, and only about 10%-20% of mitral valve repairs are for FMR.

FMR is a difficult disease to treat and is associated with increased morbidity and mortality. As a result, patients are under-treated, with few referrals and a lack of adequate treatment options. Dr. Leon said these patients are generally not referred for surgery but are treated with medical therapy. Yet, the presence of moderate or severe MR is an independent predictor of poor peri-procedural and late clinical outcomes. For example, significant MR double or triples mortality in CABG patients.

With FMR, there is increased mortality, increased tricuspid regurgitation, abnormal hemodynamic parameters, increased left ventricular (LV) and left atrial (LA) chamber size, reduced exercise performance, and worse NYHA Class. FMR also worsens with exercise.

Is there really a pool of patients with moderate-to-severe FMR that is under-treated? A 2007 EuroHeart survey found that 52% of operable candidates with symptoms had no surgery. Dr. Leon said, "This disease is underappreciated. It is often

Mitral Devices

Company	Device	Type	Status	Notes	Key advantage
Cardiac Dimensions	Carillon	Coronary sinus	66 patients so far	Fixed length device for immediate cinching	Retrievable, repositionable
Edwards	Mobius Stitch	Edge-to-edge	---	17 Fr, low profile, flexible, built-in nitinol clip	--
Edwards	Monarc	Coronary sinus	IDE trial to start by end of 2009, 59 patients so far	Self-expanding nitinol stents with a bridge	Variable length for gradual cinching
Evalve	MitraClip	Edge-to-edge	C.E. Mark, pivotal U.S. data 3/2010, >1,000 patients so far	---	---
Guided Delivery System	Accucinch	---	Proof-of-concept in 2 patients, first-in-man in Germany to start in 4-6 weeks	14 Fr, simple – if it works. Reversible, removable, adjustable. Eliminates MR completely at 6 and 12 months	---
Johnson & Johnson	---	Retrograde direct plication annuloplasty system	---	---	---
Mitralign	Trident and Bident	Direct annuloplasty	First-in-man in Germany and Brazil in next month	---	---
Viacor	PTMA	Coronary sinus	9 patients so far	Immediate P2 S-L shortening	Adjustable nitinol rods, re-accessible late

included together with organic MR. It is often unrecognized. We struggle with heart failure doctors that this is a disease… There are few referrals for FMR unless the patient needs CABG as well."

So, how do interventional cardiologists go about introducing a percutaneous treatment for FMR? Dr. Leon said:

1. It has to be **clinically relevant**. "It can't be blue sky or a 50-patient registry. It has to be true evidence-based medicine demonstrating improvement in clinical parameters – symptoms, exercise performance, re-admission for congestive heart failure (CHF), mortality. That will be the FDA standard."
2. The **pathology** has to justify the procedure.
3. Operator **usability** is a factor. "The device has to be easy to use. You have to be able to train physicians, and the procedure has to be generalizable to a broad international population. The boundaries for this have to be simpler than for aortic stenosis."
4. The **cost** has to be manageable. "This has to be in the range of what people can afford at a time when procedural medicine is going to be attacked."

Experts estimated that in one year, perhaps 7% of mitral patients will get a percutaneous repair, and in two years, 10% might be treated percutaneously. One said, "Some functional MR may get repairs, and I think surgery will do better (than MitraClip), but that doesn't mean Evalve won't meet the endpoint (in EVEREST).

TVT message about mitral valves

Dr. Stone summed up the mitral message at TVT. Among the points he made were:

- There are so many different causes and so many different ways the mitral valve can be repaired, that it is "naïve to think there is one fix."
- Mitral valve surgery is more difficult for the patient to go through than aortic surgery. Most patients accept and recover from aortic surgery much faster.
- There are very little data on mitral valve *surgery*.
- The EVEREST trial of MitraClip is likely to be critical to U.S. and broader European adoption of MitraClip. Dr. Stone said, "I personally expect this trial to be positive and to show non-inferiority…If this trial is positive, we will have entered an era of structural heart health…It will lead to a radical shift in how we approach patients, and referral patterns will significantly change."
- Next-generation devices are not that far behind MitraClip. Within the next several weeks, Cardiac Dimensions is expected to get permission from the FDA to start its pivotal U.S. trial. Dr. Stone said, "If that is a positive trial, then we will have the next device, which presumably is even simpler…Who wins is not the issue but establishing a role for interventional therapy."

EVALVE's MitraClip, an edge-to-edge device

MitraClip received a C.E. Mark in March 2008, and Evalve began selling it in September 2008. European use reportedly is 70% for FMR. Dr. Feldman said, "The European experience with MitraClip is surgeons referring poor patients or high-risk candidates for surgery to cardiologists for MR therapy...That is a clear pattern. And this is what we saw in the U.S. trials of Evalve…where the mean age of patients brought into the trial by cardiologists and surgical referrals is substantially older than the mean age for MR repair patients. For now I think it is a selection bias issue more than anything."

European cardiologists at TVT said Evalve's MitraClip is catching on ***slowly*** in Europe for three reasons:

1. **It's too expensive.** Even though the cost is not higher than aortic valves, doctors said it is too much for a mitral procedure. A German doctor said, "Our MitraClip use is minimal because there is no reimbursement, and it is very expensive." A U.S. surgeon said, "MitraClip is more complex than I thought."
2. **It's difficult to do.** Dr. Stone said, "This is not the easiest of devices to use…It is not an easy technique, and it requires new skills – from transseptal puncture to echo. My prediction is this will be done in specialized centers (in the U.S.)."
3. **The results are not good enough.**

The results of the pivotal EVEREST trial are expected at the ACC meeting in March 2010. If the EVEREST trial does meet the primary endpoint, how will that impact U.S. usage? Dr. Stone said, "Some referral doctors won't even want to hear about it, but other patients will be demanding it…On the functional side, people right now appear to be applying Evalve more for FMR…The results (of EVEREST) will be game changing no matter what it shows."

Some surgeons indicated they won't mind giving up FMR patients to cardiologists. One said, "Before I operate on someone with FMR, I need to be pushed. I don't think it is likely to improve their survival. If they are highly symptomatic, I make some of them feel better, but I can't tell at the beginning which ones those are, so I step away."

However, Dr. Stone pointed out that the number of FMR patients in EVEREST is relatively small. A surgeon added, "I'm unwilling to concede FMR patients…We will see what the randomized trial shows, but I'll bet MACE will be higher in the surgical arm, especially stroke…It may be better to do a clip in younger patients. If the results aren't good, you can go on and do surgery…sort of like stents and CABG."

If MitraClip gets FDA approval, what percent of MR patients are likely to get it and how fast will it be adopted? The consensus appeared to be 10%. An expert said, "There are two problems. One is reimbursement…I think we will have the same problem with aortic valves…And second, it is not like I can do 5 Evalves in a day like I can stent 5 patients." Another

expert said, "I'm not 100% sure we know what the perfect Evalve case is…There are nuances to these valves…I think that we still have some learning to go." Dr. Howard Herrmann of the University of Pennsylvania said, "My concern is we will let the genie out of the bottle with Evalve approval…I don't think adoption will be robust like TAVI, which will be 30%-50% of valve replacements in the next 5-10 years. I don't think mitral will be anywhere near that…I think we will see centers of excellence, but it won't grow as fast." Dr. Feldman said, "We are already seeing a usage pattern in Europe… Referrals are virtually all high risk and mostly functional MR. I think it is clear that is what we will see…What comes over my desk are referrals with late stage, primary FMR, most of whom are anatomically not suitable for the clip. That will be what people think the indication is."

Is MitraClip likely to see widespread off-label use? Dr. Feldman said, "No, and I don't think CMS will give us anything close to (a broad use approval)…I think it will be clearly-defined reimbursement…I wouldn't be surprised if one indication out of the FDA/CMS process is 'high-risk patients with an STS score ≥12. That is a clearly defined population where this is a clear benefit." Dr. Leon added, "That is reasonable but a sliver of the population." Dr. Stone questioned whether MitraClip could get a broad label on just 78 high-risk patients."

CARDIAC DIMENSION's Carillon XE, a coronary sinus approach

Dr. Schofer, the principal investigator for the AMADEUS trial, said the results will be published soon in ***Circulation***. AMADEUS is a prospective, single-arm, 30-patient, multicenter trial with Carillon XE. TITAN was a 36-patient, multicenter trial with Carillon XE2. In both trials, MR was significantly reduced at both 1 and 6 months. However, he said there is "a significant learning curve."

Carillon XE and XE2 Results

Measurement	AMADEUS trial n=48	TITAN trial n=53
Baseline		
Age	64.4	62.0
Ejection fraction	29.2	28.4
NYHA Class III	77%	94%
Complications		
Primary endpoint: 30-day MACE	13.0%	1.9%
Death	2.2%	1.9%
MI	6.5%	0
Cardiac perforation	6.5%	0
Device embolization	0	0
Surgery or PCI related to the device	0	0
Efficacy		
MR reduction	<0.05	N/A
NYHA Class II at 6 months	80%	N/A
6MWT	<0.05	N/A
Quality of life	<0.05	N/A

OTHER MITRAL DEVICES IN DEVELOPMENT

Coronary sinus. All three leading coronary sinus devices were described as "capable of modest reduction in MR (1-2 reduction) which has resulted in improved functional status, improved 6 minute walk test (6MWT), and better quality of life. But the trials so far have all been non-randomized trials, and the benefit is best in patients with baseline MR of 3-4+. The results have been duration out to 2 years with Monarc. The downside is that there can be compression of the LCX (left circumflex) in 20%-30% of patients, requiring careful pre-screening.

Indirect annuloplasty. All devices in this category have failed so far.

Direct annuloplasty. Mitralign's Trident device offered good cinching, with 1x3 plication. This was tested in humans in Paraguay, with significant safety and efficacy issues.

Now, the company is working on the Bident system, a 2x2 plication device, which offers more cinching and greater reduction of MR. It has significant changes from Trident.

Surgical annuloplasty. Surgeons have not been standing still. Among the surgical approaches in development are:

- MitralSolutions – being tested in the 45-patient MARS trial in Europe at 5 centers. In the first 32 patients with 6-month follow-up, there has been no residual MR.
- Micardia's Dynaplasty – uses RF energy-activated, nitinol-based system to variably change the configuration of an annuloplasty ring. There is also a subcutaneous port access system for making adjustments. Potentially, this also could be done percutaneously.
- QuantumCor – an RF energy device at subablative temperatures. In sheep and pigs it shrank collagen without a thermal effect. So far, it has been tested in a lot of animals but no humans. The company's goal is to try to move to a percutaneous, transseptal device.

Percutaneous mitral valve replacement

This field is moving slower than percutaneous aortic technology. Percutaneous mitral devices in development include:

- **Endovalve** – has a repositional, transseptal approach.
- **CardiAQ Valve Technologies** – has an immediately functional, repositionable device described as having "some very, very neat designs."

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