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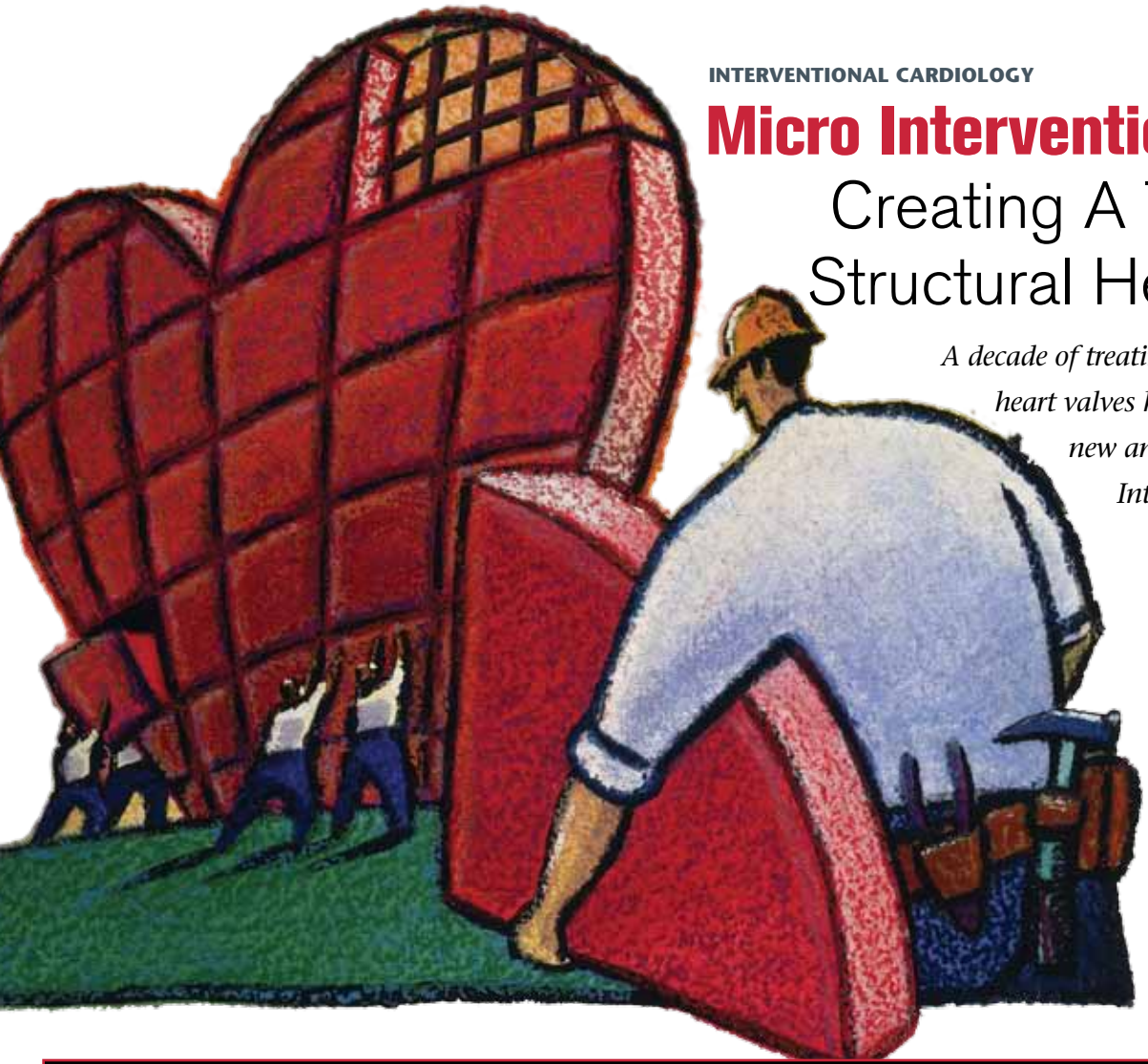

INTERVENTIONAL CARDIOLOGY

Micro Interventional Devices: Creating A Tool Box For Structural Heart Disease

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BY MARY STUART

The Renal Denervation Buzz • Have Pharma's Option-Based Deals Peaked?

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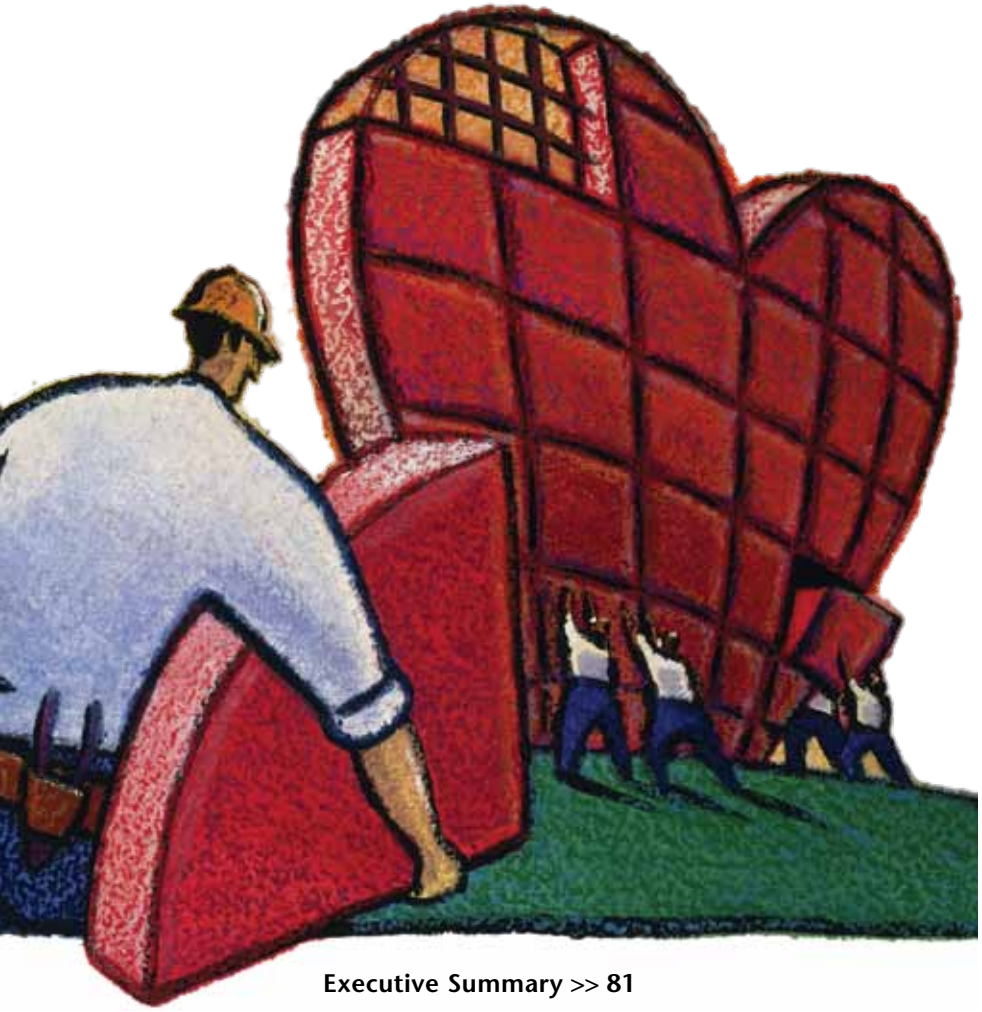

- Founded by Michael Whitman, the founder of Power Medical Interventions, which advanced minimally invasive general surgery with computer and power assisted surgical instruments, MID intends to do the same for structural heart disease.
- In Europe, which has seen the bulk of transcatheter valve procedures, transapical (rather than transfemoral) aortic valve delivery is occurring in an increasing number of cases, and to address that approach, MID has developed Permaseal, a transapical access and closure device.
- Mitral valves are the next large opportunity in transcatheter valve repair, but there transfemoral access is harder because the valves are larger and delivery is more difficult, making the transapical approach – and products that enable it – more attractive.
- In addition to having enabling technology, MID also has its own mitral valve replacement device, through the acquisition of Endovalve.
- MID's long-term goal: build a platform of products to treat all aspects of structural heart disease – LVAD implantation, PFO/LAA closure, cardiac ablation – and the growing transapical opportunity is only the company's first step.

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In his 30-year medical device career, Michael Whitman has been involved with several disruptive technologies that have changed the practice of medicine. In 1995 Whitman was working at **Johnson & Johnson Interventional Systems Co.**, the developer and manufacturer of the first coronary stent, when J&J acquired **Cordis Corp.** and became the market leader in percutaneous coronary intervention. He subsequently founded Power Medical Interventions (PMI), to help advance the evolution of minimally invasive general surgery by developing intelligent surgical instruments to make it easier to do laparoscopic surgeries, including single-port laparoscopy and NOTES (natural orifice transluminal endoscopy). According to Whitman, "Whenever there is a disruptive or transformative technology, there is often a need to create peripheral devices around it to support it." He points out that when stents were launched, stent delivery systems had to be improved, and ultimately the stents themselves improved, transforming into drug-eluting stents. Whitman has spent his career working to fill these kinds of gaps. In 2009, after **Covidien Ltd.** bought Power Medical Interventions, he was looking for the next disruptive opportunity and decided the time was right to create an enabling platform around structural heart disease.

Two years earlier, the first transcatheter aortic valve, *Sapien* (from **Edwards Lifesciences Corp.**), had been launched in Europe, and it was closely followed by the *CoreValve* from **Medtronic Inc.** These new devices, which can be implanted without open heart surgery, help patients with aortic stenosis that are too frail or too sick for surgery to benefit from a replacement heart valve. Now the field has accumulated some ten years of experience in Europe (including clinical trials begun by Edwards in 2002), time enough to identify some of the opportunities that accompany these breakthrough technologies and make them easier to perform. Such improvements may even expand the potential patient population for these new devices. It is these new opportunities in structural heart disease upon which Whitman's new company, **Micro Interventional Devices Inc.** (MID), has set its sights.

Transcatheter aortic valve implantation (TAVI) is an extension of the reach of interventional cardiology from revascularization strategies to the treatment of structural heart disease. Whitman notes that the latter brings some challenges that are unique to both interventional cardiology and cardiothoracic surgery.

He points out that stents are relatively simple devices that are easily delivered through the femoral arteries with small (3 French) delivery catheters. Bioprosthetic heart valves, on the other hand, are more complex devices that range from 18- to 29 Fr. in diameter. "Here we are talking about larger devices and larger delivery sheaths," Whitman says. "The heart valve is a functional organ, and the procedure is not a simple dilatation and implantation. It is not clear who the future provider will be; a new discipline is emerging combining interventional and surgical skills."

Two opportunities that Whitman has initially identified are a transcatheter valve for the replacement of the mitral valve, and an easy and effective transapical access and closure method. The latter would ideally enable access to the heart in the large number of patients for whom advancing large delivery devices and valves through the femoral arteries or over the aortic arch is not feasible, and represents MID's initial product offering. (*See Exhibit 1.*)

That first product is *Permaseal*, a device that will help clinicians create a less traumatic access point through the chest and apex of the heart, reduce bleeding complications during the procedure, and result in rapid puncture closure. One of the reasons the company is focusing initially on an access and closure device is that it can be validated in a short timeframe; as a wound closure product, the regulatory bodies require only 90-day clinical endpoints. Yet the product may have structural heart applications beyond TAVI and transcatheter mitral valve implantation and repair, including left atrial appendage closure procedures and even cardiac ablation. The core technology that underpins this first product – tissue anchors that can be delivered remotely – also forms the basis of several other products in the company's future pipeline, most notably a prosthetic mitral valve and a closure device for septal defects of the heart, like PFO or atrial septal defects.

At MID, Whitman has pulled together several people with whom he's worked before at J&J and PMI, including Bill Hennemann, PhD, MID's chief scientific officer, in the hopes of repeating their previous successes. About his team Whitman says, "Our long suit is the identification of gaps in an emerging technology field, and applying engineering and innovation to create the new tool box required by new procedures."

Exhibit 1

MID's Initial Target Markets

Aortic Stenosis

- The prevalence of aortic stenosis exceeds 830,000 people in the US and 1.75 million in the EU.
- Approximately 30% of patients receiving valve replacement for aortic stenosis in the EU are currently receiving transcatheter valves, with as many as 50% of these patients being treated from the transapical approach.
- It is estimated that the transapical closure device market will exceed $400 million by 2016.

Mitral Valve Disease

- 56% of the 5.2 million people with heart failure in the United States have mitral regurgitation (MR).
- There are approximately 850,000 patients with severe MR in the US, with severe MR a contributing factor in an estimated 100,000 patient deaths per year.
- There is a $2 billion market opportunity for heart surgeries related to mitral valve disease.

SOURCE: Micro Interventional Devices

LESSONS FROM POWER MEDICAL

In starting MID, Whitman is looking to emulate some of the lessons he learned from Power Medical, a company he founded in 1999 with the goal of helping minimally invasive surgery reach its full potential. Specifically, the company set out to create a family of computer-assisted, power-actuated endomechanical instruments to overcome the challenges of remotely (that is, via laparoscopic access) cutting, closing wounds, and reconnecting tubular anatomical structures. Whitman says he started the company because the manual devices used in endoscopic procedures were prone to malfunction. "We thought we could improve outcomes in that space by using computers and minimally invasive micro-engineering." PMI targeted

Talk to cardiologists or surgeons and they'll now generally agree that the decision on transapical or transfemoral access should be based on a pre-operative review of the patient and his or her individual risk factors.

high-volume procedures performed on critically ill patients, including colectomies for colorectal cancer, lung-volume reduction for lung cancer and emphysema, stomach stapling for morbid obesity, and esophageal reconstruction for gastroesophageal reflux disease. "These are critical disease states, they are not elective, and because you are working on large viscera, devices need to be robust in order to compress tissue effectively during surgery," he points out.

Power Medical enjoyed many successes. In 2007, the company went public, raising $42 million. A year later, it signed a collaboration agreement with **Intuitive Surgical Inc.** to develop a robotic cutting and stapling tool for Intuitive's *da Vinci* system. PMI's devices were used in thousands of procedures in more than 350 hospitals worldwide before Covidien acquired the company in 2009.

In many respects, two-year-old Micro Interventional Devices shares the mission of Power Medical, albeit in a different clinical specialty. In fact, MID could use the competitive factors listed in the prospectus for the Power Medical IPO, which said that Power Medical aimed to offer "efficacy and consistency of wound closure and hemostasis; the ability to provide access to difficult-to-reach anatomy; ease of use, visibility for the surgeon and control over the device, innovation and a number and variety of addressable surgical applications."

However, in some respects, Whitman hopes MID will not follow in PMI's footsteps, saying that the new company has instead "learned to sidestep some of the potholes" of its predecessor.

One such misstep that MID is looking to avoid regards financing. Power Medical Interventions raised $107 million privately before its IPO. Unfortunately, by 2009 the stock market collapse of 2008 had done its damage. PMI's stock price had lost 81% of its IPO value, forcing NASDAQ to temporarily delist the company for failing to meet minimum equity requirements. At the time of the collapse, cash on hand was $4.7 million. In Covidien's $64 million purchase price was the assumption of $28.3 million in debt.

Power Medical was running a costly enterprise; the company brought in an experienced management team and set out to develop a global distribution footprint. In 2008, PMI had 177 employees, including a direct sales force of 36 in the US in addition to sales offices in Europe. The company's R&D organization consisted of 19 people.

To be fair, the company was founded when highly liquid capital was available, i.e., before the financial collapse, and many of Power Medical's peers suffered similarly. According to a review of medical device IPOs conducted by *START-UP* magazine in 2009, the 40 medical device companies that went public from 2005 to 2006 all lost significant value, with the best performance belonging to the 11 companies that went public in 2005, which, at the time, had only lost 36% of their value. Meanwhile, the companies that followed with IPOs in 2006, 2007, and 2008 saw their stock prices drop by two-thirds. (*See "Have Device VCs Bet Too Big?"* — IN VIVO, *September 2009*.)

Whitman says Micro Interventional Devices has learned from that experience and is structured for lean times. The company is maintaining an extremely low burn rate and is focused on getting its products to the clinic. "We will reserve our decisions on distribution and business structure for the appropriate time," he says. MID's Series A round occurred in conjunction with the acquisition of mitral valve company Endovalve Inc., which was seeded by Battelle Ventures, such that the combined entity had $450,000 on the balance sheet. A supplemental financing by regional venture fund Ben Franklin Technology Venture Partners brought in an additional $100,000 and space in the Ben Franklin incubator in Bethlehem, PA. In May 2012, seed investors participated in a $500,000 bridge financing, along with the Life Sciences Greenhouse of Central Pennsylvania.

MID is about to begin the European clinical trial of its Permaseal device, called STASIS (Sutureless Transapical Access and Closure Study). The trial will enroll 40 patients at five sites. MID is seeking a $5 million to $8 million Series B round that it intends to close by September, by which time much of its clinical risk, it believes, will be reduced. At the same time, it appears that market risk for a transapical closure device is going down as adoption of this approach increases.

TRANSAPICAL ACCESS: EVOLVING RAPIDLY

There are two methods of implanting transcatheter heart valves. The first, known as a transfemoral approach, involves a groin cutdown, placing a sheath in the femoral artery, and delivering the prosthetic valve over the aortic arch. The second is the transapical approach, in which the chest space is accessed by an anterolateral thoracotomy (an incision below the breast and between two ribs). A needle puncture is made in the apex of the heart, and the puncture is dilated to allow the valve to pass into the ventricular cavity.

The use of one access method over another had been somewhat controversial in the early days of TAVI, with the two pioneers using different approaches: Edwards – the only TAVI device currently available in the US – relied first on transapical (TA) delivery but has since developed a transfemoral system, while CoreValve focused on the transfemoral (TF) approach.

The respective merits and disadvantages of each method can be broken down along the lines of the respective skill sets of the clinical specialty performing the procedure, with surgeons relying largely on TA delivery and interventionalists using the TF approach.

Those who have argued for the transfemoral approach point to it as the least invasive method, avoiding the costs, bleeding complications, chest and ventricle wall trauma and hospital recovery time of a thoracotomy.

Those who argue for the transapical method find it risky to navigate large devices through frail anatomy in older patients (the average age being 84 to 85 in the Edwards PARTNER clinical trial). In many cases, the TA proponents argue, the advantages of less invasiveness are overcome by vascular complications caused by the large devices. Transapical delivery theoretically reduces these risks because it avoids scraping plaque and calcifications in vessels or thrombus on the aortic arch. Transapical delivery also permits for the delivery of larger devices. Finally, since TA provides a straight shot in from the apex (six inches to the heart valve as opposed to the 4 ½ foot distance the device has to travel to reach its destination via the femoral artery) many feel that positioning the valve this way is faster and easier.

No matter what approach is employed, the one thing all clinicians agree upon is that these are high-risk procedures, notes Vinod Thourani, MD, a cardiothoracic surgeon at the **Emory University School of Medicine** and a co-founder of rival transapical closure company **Apica Cardiovascular Ltd.** In his view, to best optimize outcomes, "TAVI procedures should involve an interventional cardiologist because they are adept at inserting things by way of the catheters in the femoral artery, and we need surgeons, because they are familiar with the surgical treatment of the aortic valve, have experience with large-bore catheters in the femoral artery (which may require a surgical femoral artery cutdown), and can do thoracotomies or sternotomies when needed, all of which may require suturing of the heart."

Thourani points out that, while transfemoral access is often the preferred choice, the larger, early-generation sheaths that are commercially available in the US for the patients in the high risk population (who are the initial recipients of these devices) require the surgeon to perform a femoral artery cutdown, cannulation, and repair of the artery after removal of the sheath. Could he, as a surgeon, do this without an interventional cardiologist, or could an interventional cardiologist do it without him? "Most likely," he says.

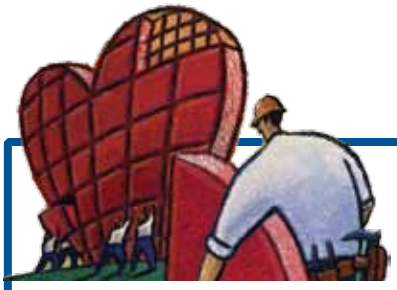
But today, in the US at least, that issue is largely moot since FDA approval of the Edwards valve in November 2011 and subsequent reimbursement by the Centers for Medicare and Medicaid Services, finalized in May 2012 (*see "National Medicare Coverage Established For Transcatheter Valve Procedure"* — Health News Daily, *May 2, 2012*) mandate a "heart team" approach that requires formalized collaborations between surgeons, interventional cardiologists and other specialties.

PATIENT-DRIVEN, NOT DOCTOR-DRIVEN

The heart team approach looks to shift the decision on which delivery approach will be used away from being a physician-driven turf battle to one that is focused on what is best for the particular patient. (In practice, however, this remains a gray area because, despite the "heart team" approach, interventional cardiologists often control the patients.) In Europe, where physicians have some ten years of experience, TAVI is done via transapical access almost as often as it is done transfemorally – in 30 to 50% of cases, depending upon the center, even though transfemoral is often the first choice. The US experience, which is much more limited, is much the same. Initially, the US waters were muddied based on unfavorable early clinical reports. One, for example, was presented at the TCT (Transcatheter Cardiovascular Therapeutics) conference in November 2011. An analysis of 104 TAVI patients that were treated via transapical access in Cohort A (PARTNER trial group supporting PMA approval of the Edwards Sapien valve) showed that, according to several clinical endpoints, TF delivery appeared superior to TA. However, surgeons pointed out that the there was a learning-curve issue; treating physicians had only four to five procedures in their experience, and that the trial cohort was quite small. (*See "Transcatheter Valves: Tough Love For Transapical Placement Method At TCT"* — "The Gray Sheet," *November 14, 2011*.)

Subsequent clinical data has presented a different picture. An analysis of the Continued Access Cohort of PARTNER as reported by Todd M. Dewey, MD, at the Society for Thoracic Surgery conference in January 2012, found that, based on 822 patients who underwent transapical heart valve procedures after the PARTNER randomization period was over, transapical and transfemoral patients experienced comparable outcomes, including a similar stroke rate. In fact, stroke rates were lower for the transapical group than for the surgical group. Studies done by groups in Europe also suggest that clinical outcomes are similar for both access methods at four years of patient follow-up data, but a head-to-head comparison of the two has never been done.

Talk to cardiologists or surgeons and they'll now generally agree that the decision on transapical or transfemoral access should be based on a pre-operative review of the patient and his or her individual risk factors. Howard Herrmann, MD, an interventional cardiologist at the Perelman School of Medicine at the **University of Pennsylvania**, the inventor of Micro Interventional Devices' Endovalve and an advisor to the company, says, "I think people generally feel that if femoral access is good that should be the first approach. But if the patient has small vessels and some potential vascular complications, or the transverse aorta is particularly atherosclerotic or has large thrombi or mobile masses on it, you want to avoid crossing them, even if the iliac and femoral vessels are large enough." Herrmann says it all boils down to risk-benefit: "If femoral or iliac vessels are marginal and you could potentially avoid the risk of stroke by avoiding an atherosclerotic aorta, those things start to favor transapical."



The reality is that anywhere from one-third to half of all TAVI patients are treated via transapical access, largely because many patients are not candidates for the transfemoral procedures.

From the surgeon's perspective, Emory's Vinod Thourani identifies similar considerations, and adds that vascular compli-

Exhibit 2

Companies Pursing Transapical Access Closure

Company	Approach/Funding
Suture-Based	
Entourage Medical Technologies	CardioClose delivers sutures in a helical path to provide circumferential closure of the dilated access site./Highland Capital Partners, Sofinnova Ventures.
SpiRx Closure	A-Stitch delivers two perpendicular mattress stitches.
VasoStitch	Pre-placement of a running suture that also creates a working channel for large bore device./Private investors.
Sutureless	
Apica Cardiovascular	Coil and plug technology developed at Georgia Tech and Emory University. Large sealing coil that engages and stabilizes the access site has a reaccessible closure cap that seals the site after the procedure./Seroba Kernel Life Sciences and Triventures.
Micro Interventional Devices	Permaseal delivers soft tissue anchors and elastomer that expands to accommodate instruments of different sizes while maintaining tension around the puncture to achieve hemostasis. Easy and rapid one-handed delivery by pulling the trigger on a "gun." Mass of entire implant is less than half a gram. Clinical trials in Europe in the summer of 2012./Ben Franklin Technology Venture Partners, Life Sciences Greenhouse, Battelle Ventures, Life Sciences Greenhouse of Central PA.
Novogate Medical	Trocar-based access device and closure system; company says that the implant left behind potentially offers reaccess (and serves as a pointer for the re-entry site)./BDB Technology Investments.

SOURCE: Elsevier's *Strategic Transactions*

cations lead to higher mortality rates in heart valve patients, many of whom are in their late 80s and early 90s. Thourani says, "The best and safest option for the patient is not to force something down his throat. We should not be comparing transapical and transfemoral in a vacuum; we should be tailoring the approach to the patient's needs."

PULLING THE TRIGGER ON TRANSAPICAL ACCESS

The reality is that anywhere from one-third to half of all TAVI patients are treated via transapical access, largely because many patients are not candidates for the transfemoral procedures. This significant level of adoption is occurring even though no transapical access closure devices are currently available. Today, transapical access and closure require that surgeons laboriously suture a purse string in a ring, that is, a series of running stitches that can be drawn up tight to control the opening, like pulling the drawstring on a bag of marbles.

The need for new technologies for the transapical delivery route has been recognized by at least six companies, including (besides MID and Apica) **Entourage Medical Technologies Inc.**, **VasoStitch Inc.**, **SpiRx Closure LLC**, and **Novogate Medical Ltd.** Apica, which is in its first-in-man studies in Europe, and MID, which will soon begin, appear to be the early leaders and will likely be the first two companies to market. (*See Exhibit 2*.) According to Whitman, "We could have chosen any problem to work on, but we picked this, because it is the second most critical aspect of a heart valve procedure, the first being proper implantation and orientation of the valve in the native annulus. If you don't position it properly or you embolize something that is life threatening. So is closure. If you fail to close the myocardium, the patient can exsanguinate, experience a cardiac tamponade post-operatively, and go into congestive heart failure."

The team at Micro Interventional Devices made a long list of desired design attributes before going to the drawing board and coming up with Permaseal. According to their initial assessment, the ideal transapical access and closure device would be: deployed single-handedly, spontaneously self-sealing, compliant with the beating heart in a way that doesn't cause it to migrate, the apical opening must comply with the diameter of various instruments successively placed through the opening (the dilator, the sheath and the valve itself), the implant should have little mass, result in reproducible results, be adaptable to femoral aortic and atrial approaches, and be minimally invasive. To this last requirement, the company's first-generation version of Permaseal will be advanced through a thoracotomy, but after the proof-of-concept phase, the company will miniaturize components so that they can be delivered either percutaneously or a through a very small muscle incision.

Permaseal does not use sutures. The implant is a biocompatible elastomer web, or rather a series of what the company calls "V stays" that run from soft tissue anchors that attach to the wall of the ventricle. (*See Exhibit 3*.) A puncture is made through the webbing to access the apex, and the heart tissue will expand to accommodate the instruments. At the same time, the stretchy but strong webbing will keep tension over the wound to keep it closed or else approximated around the instrument.

When the instruments are withdrawn, the puncture site spontaneously heals. Very little mass is left in the body, less, says Whitman, than the amount of material left behind after suturing, since sutures are buttressed by pledgets to keep them from pulling all the way through the muscle tissue. Purse string sutures also strangle tissue and result in an akinetic section of the heart wall, according to Whitman. "If your suture ring is 20 mm and you draw it down to 4 mm, you have defunctionalized a 16 mm portion of the muscle, and that can affect the wall motion of the heart."

The implant's delivery device looks like a gun with a long, slender snout. The nose of the gun is placed up against the heart muscle, the operator pulls the trigger, and six anchors through which the elastomer is threaded enter the tissue. The process is as easy as using a staple gun.

Micro Interventional Devices is betting that Permaseal is superior to its competing transapical closure devices in terms of speed, ease-of-use and the amount of material it leaves in the body. The mass of the Permaseal implant is less than half a gram.

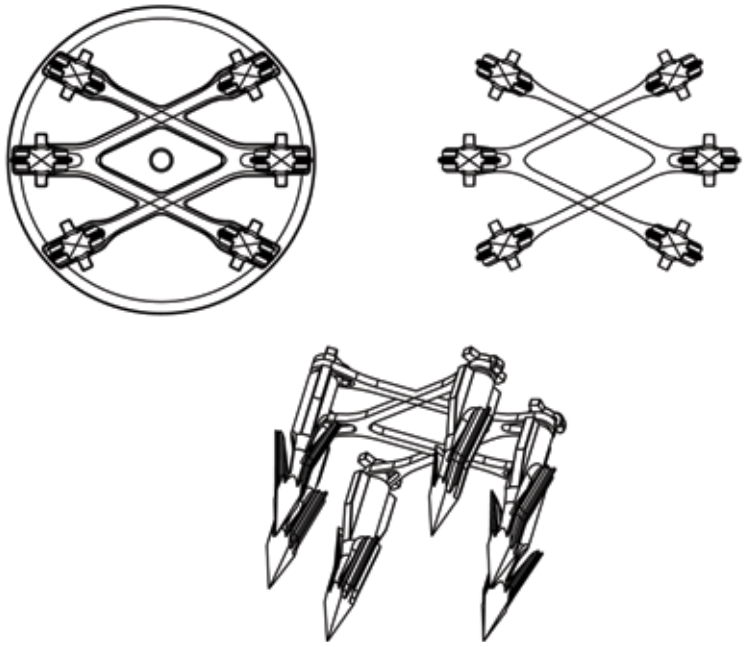
The company has completed its preclinical work on a beating heart, and found that the myocardium expanded nicely to accommodate a valve, a sheath, a dilator, and a guidewire, successively, showing that it could close from 18 Fr. to 10 Fr. to 5 Fr. to 0.35 Fr. CSO Bill Hennemann says histological and functional outcomes have been excellent. The company is preparing for its clinical trial in Europe, led by principal investigator Rüdiger Lange, MD, Director of the Department of Cardiovascular Surgery of The German Heart Center in Munich, Germany.

Ultimately, Permaseal has the potential to create shorter and easier approaches for many cardiac procedures, including minimally invasive mitral valve replacement, where the transapical approach is even more compelling than it is for TAVI because prosthetic mitral valves in development are large (29 Fr. or so) and if delivered via the femoral artery, have to cross the septum and take a sharp right-hand turn. Doing this at the end of a 135 cm catheter would be extremely challenging, Whitman notes. Indeed, for TAVI, it's hard to tell whether in the future, transapical access will hold a greater, or lesser, share of procedures. Next-generation companies are developing smaller aortic valves, which lend themselves ideally to TF delivery; **Colibri Heart Valve LLC**, for example, is developing a valve that can be folded into a 12 Fr. catheter. In any case, it seems Accertain that there will always be a large percentage of patients who are not good candidates for transfemoral TAVI, and the up and coming mitral valve market, four times as large as the TAVI indication, will certainly be looking for technologies that improve transapical procedures.

Finally, MID executives suggest that the proprietary soft tissue anchors used in Permaseal will themselves enable new procedures. In patent foramen ovale or atrial septal defect closure, in the future, the anchors might be delivered to hold in place a patch of bovine pericardium, creating an implant with a lower profile and much less mass than PFO closure devices on the market today. The anchors also solve a problem for Endovalve, a transcatheter prosthetic mitral valve developed initially by Dr. Herrmann at the University of Pennsylvania.

Exhibit 3

Permaseal For Transapical Access And Closure



SOURCE: Micro Interventional Devices

MITRAL: THE NEXT BLOCKBUSTER VALVE OPPORTUNITY

In choosing which of its first two potential products to focus on, MID decided that it could get an access and closure device to market much quicker than a new mitral valve. So while developing Permaseal, the company is continuing to work on its mitral valve product. Unlike the aortic valve market, which is crowded with next-generation competitors hoping to follow Edwards and CoreValve/Medtronic, the mitral valve space remains fairly wide open. Apart from the *MitraClip* from **Abbott Laboratories Inc.**, a transcatheter device for the repair of the leaflets of the mitral valve, there are no minimally invasive mitral valve products on the market and the market opportunity is huge, potentially exceeding aortic valves. In the US, there are 4 million people with moderate to severe mitral regurgitation (MR) requiring treatment and 50,000 new patients develop significant MR each year. In contrast, there are 1.2 million people with aortic stenosis.

For 12 years, however, companies have come and gone in this field because mitral valve regurgitation is a much more challenging problem than aortic stenosis. For one thing, mitral valve devices have a fixation challenge. The transcatheter aortic valve can be seated in a tube-shaped anatomic structure and radial strength holds it in place. Mitral valves must be actively attached to a D-shaped annulus without impinging on the aortic outflow tract or other nearby structures. (In open

procedures, surgeons suture devices to the native annulus).

In a minimally invasive approach, it is also difficult to replicate the surgical standard for repair, since the mitral valve relies on several inter-related components for its functioning. The chordae, the papillary muscles, the annulus and the leaflets of the mitral valve can all malfunction to upset the fine balance of how the mitral valve works. The University of Pennsylvania's Howard Herrmann says he was spurred to invent a solution to mitral regurgitation after working with MitraClip and some of the coronary sinus devices developed by Viacor Inc. (now defunct), Edwards and **Cardiac Dimensions Inc.** (*See "Percutaneous Mitral Valve Therapy: The Next Decade"* — Medtech Insight, *March 2012*.) "If you do only one thing, like appose leaflets with the MitraClip or push a little bit on the posterior annulus with a coronary sinus device, you are not likely to be as successful as a surgeon going in and repairing the leaflets, cutting out some of the chords, cutting the leaflets and then adding a ring," he explains. Those fixes for a single portion of the mitral valve anatomy are usually unacceptable compromises. "It was attractive to be able to do something for patients, but I realized that none of these devices was going to be as effective for patients as surgery. We just didn't have the toolbox that a surgeon has under direct vision to repair what is a much more complex structure than the aortic valve," he points out.

Herrmann reasoned that a less invasive replacement of the entire mitral valve might solve the problem, and set out to develop a foldable mitral valve prosthesis, so he founded Endovalve in 2005 with seed funding from Battelle Ventures LP and Innovation Valley Partners LP. (*See "Endovalve Inc."* — START-UP, *July 2006*.) Endovalve had to overcome a number of design challenges, according to Herrmann: "First, we had to fold it small enough to insert it into a catheter-based system. Then we had to find a way to affix it to the mitral annulus. Third, we needed a good seal between the edges of the device and the native heart wall so there is no leak around it, without interfering with the outflow tract of the left ventricle." Hermann's device had skirt technology to help seal it and prevent paravalvular leaks and some unique methods for attaching it to the mitral annulus.

However, in preclinical studies, there were some problems with the permanent fixation. "We were working on that when MID approached me about Permaseal, asking me to be on their advisory board. When I saw their technologies, I realized that they could improve the fixation of the Endovalve prosthesis," he notes. Specifically, the solution lay in MID's soft tissue anchors and the ability to remotely deliver them through catheter-based technology. "It reminded me of what surgeons are doing in open valve replacement with suturing," Herrmann says, pointing out that TAVI with a balloon expandable stent achieves passive fixation. "You blow up the stent against the calcified aortic valve and friction and the radial strength of the cage holds it in place," he explains. It's a different situation in the mitral position, there is no calcium to attach to, and the annulus is deformable.

There was a natural fit between the two companies developing complementary technologies. They also just happened to be in geographic proximity to one another in southeastern Pennsylvania. As noted, MID acquired Endovalve at the time of its Series A round and engineered some solutions around the mitral valve. "Fixation, proper seating and anchoring are key," says Whitman. "It was obviously a great combination of the technologies of the two groups." In the transaction, MID also gained Endovalve's methods patents on implanting the mitral valve, which are very broad, according to Whitman.

It's a complex project, says Herrmann. "That's the reason there is no mitral valve replacement device in clinical trials or on the market." It's obviously a product with a long development cycle ahead of it, which is why Whitman says, "We would like to see a strategic partner here because of the complexity of the application and because it is an important emerging technology."

A NEW SPECIALTY CALLS FOR NEW TECHNOLOGIES

Shifts of this sort present opportunities for technology developers, and early-stage Micro Interventional Devices is preparing to serve an emerging structural heart disease specialty. Just as Power Medical Interventions created enabling tools for minimally invasive surgery, so too is MID looking to do the same with TAVI and other structural heart procedures. MID is in business, Whitman says, to remove the limitations that exclude patients from treatment, a worthwhile goal for a device start-up and a strategy for building a valuable product line.

There are still some big unknowns for the company. Will the tissue anchors work in all types of human tissue, even infarcted tissue? In the TAVI existing market, will surgeons, famously proud of their suturing skills and generally initially resistant to new wound closure devices, find the need for a transapical closure device compelling? Will such an easy and consistent device cause interventional cardiologists, who, some say, tend to push the envelope on transfemoral access in TAVI, to consider transapical as a first option more often? The first-in-man tests beginning soon in Germany will begin to answer these questions.

Whitman says that in two short years, "We have greatly reduced the material risk of executing this business; we have known materials, known processes, we have done preclinical work and we are very happy with our histological and functional outcomes in a porcine model. We know we can make Permaseal in quantity at a very attractive price, and we believe our quality will be very high. When we used this device in the porcine model, it worked very effectively." The next step is to reduce the clinical risk.

The team at Micro Interventional Devices hopes its first product will broadly enable the field. Whitman rhetorically asks, "If you had good access and closure, why wouldn't you want to adapt instruments to a shorter and easier approach for all cardiac procedures?" The company believes that's its opportunity. IV

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