



## Percutaneous Mitral Valve Therapy: The Next Decade

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### Executive Summary

After more than a decade, the field of transcatheter mitral valve therapy is still in its infancy, yet it is surprisingly crowded. The first percutaneous mitral valve company was founded in 1999, the same year that the first transcatheter aortic valve implantation (TAVI) company was founded, but while TAVI is now on the market in Europe and in the US, the leading transcatheter mitral valve therapy has only just completed clinical trials. The anatomy of the mitral valve is much more complex than its aortic counterpart, patients with mitral valve disease make up a heterogeneous group, and the anatomical environment for mitral valve implants is much more challenging. Nevertheless, the potential market for transcatheter mitral valve treatments is at least four times that of TAVI, is wide open, and offers a substantial growth opportunity for strategic companies working in the cardiovascular space.

Transcatheter aortic valve implantation has paved part of the way for percutaneous mitral valve therapies, but the latter have their own challenging road to travel. It's worth the journey: transcatheter mitral valve therapy is a market potentially four times the size of TAVI.

- Transcatheter mitral valve treatments are in their second decade of childhood. First-generation companies have come up the learning curve, but only one has completed randomized clinical trials: the Abbott/Evalve *MitraClip*.
- Innovation in mitral valve disease lags behind aortic valve disease because compared to aortic valve disease, the patients are more heterogeneous and the mitral valve anatomy is more complicated. At least five anatomical features are responsible for the normal functioning of the mitral valve, offering many potential points of treatment.
- First-generation percutaneous devices modeled themselves after a surgical predicate based on repairing, rather than replacing, the mitral valve. While open surgeries offer the possibility of combining techniques, early catheter-based companies tended to focus on a single device targeting a single portion of the anatomy. This approach may limit the target populations or require more than one device to treat a broader population.

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- In response to these anatomical challenges, a new crop of companies is developing devices to replace the entire mitral valve percutaneously. Others are offering platforms with a multitude of transcatheter repair and/or replacement options, as well as enabling technologies, such as access and closure devices, as sources of early revenues.
- With such a huge potential patient pool, even niche opportunities can be multi-hundred million dollar opportunities.

The year that just ended witnessed two milestones in structural heart disease: the first US approval of a transcatheter aortic heart valve – the *Sapien* valve from [Edwards Lifesciences Corp.](#) – and the completion of the first ever randomized clinical trial for a percutaneous device for mitral valve disease, the *MitraClip* from [Abbott Laboratories Inc.](#)

These two events are heartening for a cardiovascular industry looking for structural heart disease to provide the next major growth opportunities, particularly because revenues from the largest existing cardiovascular markets are flat: drug-eluting stents have leveled off and cardiac rhythm management is in the doldrums. (See "[Cardiac Rhythm Management Market Faces Continued Challenges Ahead](#)" — *Medtech Insight*, August 2011.) The giant strategies in cardiovascular disease need billion-dollar products to maintain growth, and they're looking to transcatheter heart valve treatments to provide them. Transcatheter aortic valve implantation (TAVI) is already yielding almost \$700 million in revenues (in OUS markets) where some 50,000 patients have undergone the procedure to date. Market estimates place the size of the TAVI market at almost \$2 billion by 2014, including only high risk patients not eligible for open heart surgery. The market for percutaneous mitral valve repair or replacement is much more complex, segmenting into different types of disease and different types of treatments. That market is at a very early stage and estimates are that it will hit \$1.2 billion by 2014, but its ultimate potential is at least four times greater than the aortic valve market.

Both product segments – transcatheter aortic and mitral heart valves – are on the upswing. However, the positive news comes much later than pioneers in the field ever thought it would, going back to the first companies founded in 1999 – aortic valve company Percutaneous Valve Technologies (bought by Edwards in 2003 for \$125 million in cash [\[See Deal\]](#)) and Evalve, developer of the first percutaneous product for mitral valve repair, part of Abbott Laboratories since 2009 when Abbott paid \$320 million to gain Evalve and its MitraClip. [\[See Deal\]](#)

Progress has been particularly slow in the minimally invasive treatment of mitral valve disease, and after almost twelve years, the field is still in its infancy.

## Transcatheter Mitral Valves Enter Into Their Second Childhood

Transcatheter mitral valve repair was originally regarded by many as the more promising, or perhaps more addressable, of the two transcatheter valve markets. That hasn't been the case, but going back to the beginning, because the surgical standard for treating mitral valve disease was repair rather than replacement of the valve (not so for aortic valve disease) that application seemed to offer a procedure that would be more readily amenable to the tools of interventional cardiology than would total valve replacement, which would require the percutaneous delivery of a fairly large device. The mitral valve market was also considered more attractive, because, as noted, it offered probably four times as many patients (4 million people in the US with moderate to severe mitral regurgitation requiring treatment and 50,000 new patients developing significant MR each year versus 1.2 million people with aortic stenosis). (See *Exhibit 1*.)

## EXHIBIT 1

## Types Of Mitral Valve Disease And Statistics

Disease Segment (Patient population)	Description
<p>Mitral Regurgitation</p> <p>Significant mitral valve regurgitation occurs in about 2% of the population. 6.8 million people in the US with mitral regurgitation, 4 million of them with moderate to severe mitral regurgitation.</p>	<p>Leakage of the blood from the left ventricle into the left atrium during systole. It can be caused by structural or functional abnormalities of the mitral apparatus, adjacent myocardium, or both. The most common causes of mitral regurgitation in the US are myxomatous degeneration, chordal rupture, rheumatic heart disease, infective endocarditis, coronary artery disease, and cardiomyopathy.</p>
<p><i>Functional Mitral Regurgitation</i></p> <p>Functional MR is commonly associated with heart failure. 5 million in the US have heart failure, 20 million worldwide. An estimated 2.6 million people in the US have functional MR. 50% of the total mitral regurgitation population.</p>	<p>Incomplete coaptation of the leaflets due to heart disease; the components of the valve apparatus are normal, but the left ventricle may be enlarged or displaced, pulling the valve out of alignment. The left atrium may also be enlarged. These patients account for only a minority of surgical repairs today.</p>
<p><i>Degenerative (Primary or Organic) Mitral Regurgitation</i></p> <p>30% of the mitral regurgitation population.</p>	<p>Presence of an identifiable anatomic mitral valve abnormality such as a flailing leaflet, or a torn chordae tendineae. These patients make up the bulk of open surgical repairs today.</p>
<p>Mitral Valve Prolapse</p> <p>Occurs in 2.4% of the general population.</p>	<p>The billowing of one or both mitral leaflets into the left atrium during systole. It may arise from myxomatous valve disease or in people with normal mitral valve leaflets. Most patients with mitral valve prolapse don't develop severe mitral regurgitation. In most cases, mitral valve prolapse is a benign condition not requiring surgery, so this is not a current target of percutaneous valve therapy.</p>
<p>Mitral stenosis</p> <p>15.6 million people worldwide suffer from rheumatic heart disease with approximately 282,000 new cases each year.</p>	<p>Narrowing of the mitral valve orifice such that the left ventricle doesn't fill properly during diastole. Caused by rheumatic heart disease, calcification of the mitral annulus, infective endocarditis, lupus, or rheumatoid arthritis. (Balloon valvuloplasty is a well-accepted transcatheter treatment.)</p>

SOURCES: Cleveland Clinic; CardiaQ Valve Technologies

An additional driver was the clinical imperative to treat mitral disease because of its link to chronic heart failure. The mitral valve governs the flow of blood between the two chambers of the left side of the heart. The healthy valve allows blood to flow from the left atrium into the left ventricle during diastole (relaxation) and prevents it from flowing back into the left atrium during systole (contraction).

When the mitral valve doesn't close completely (due to degenerative disease or deformation of the valve apparatus because of structural heart changes around the valve) blood regurgitates into the left atrium leading to a decrease in blood flow to the rest of the body. To compensate, the heart tries to pump harder, eventually causing enlargement of the left ventricle and heart failure. Thus mitral regurgitation is both a risk factor for ( and a consequence of ( worsening heart failure, and its presence in heart failure patients increases mortality rates. A health care system interested in decreasing the burden of heart failure is necessarily interested in mitral regurgitation.

## Many False Starts

In pursuit of this goal, dozens of companies have entered the field of mitral valve repair and replacement over the past decade. However, as noted, TAVI has leapfrogged TMVR and TMVI (transcatheter mitral valve repair and transcatheter mitral valve implantation) while transcatheter devices for the mitral valve, including leader MitraClip, are still at very early stages in terms of an understanding of how they should be used in patients. Many that have started the journey have foundered along the way for a variety of reasons, including technical failure, targeting the wrong mechanism, or the lack of sustainable funding. Even a leader in heart valves such as Edwards Lifesciences has dropped its share of projects. Edwards' *Mobius* device, a percutaneous device for the edge-to-edge repair of leaflets that was similar in concept to MitraClip, required suturing and was just too difficult to use. It was resurrected, for a brief time, as a neo-chordal implantation system, but was eventually abandoned. Another early Edwards device, the *Monarc*, fell into the category of percutaneous coronary sinus annuloplasty devices, a development target that has largely fallen out of favor. These devices were placed in the coronary sinus because of its position relative to the mitral annulus in an attempt to reduce the annulus diameter through a reduction in the anterior-posterior distance and bring leaky leaflets together. The approach was initially attractive because it offered clinicians the chance to do a simple interventional procedure: enter through the jugular vein and place a device in the coronary sinus under fluoroscopic guidance.

However, most companies have dropped out of that space (only [Cardiac Dimensions Inc.](#) remains, with its CE-marked *Carillon* products) because it turns out that the anatomic relationship of the coronary sinus to the mitral annulus is variable and unpredictable. In half of the patients, branches of the circumflex artery travel under the coronary sinus, presenting a risk of arterial compression, ischemia, and infarction. Viacor Inc., which was working in this area, shut its doors recently. Another competitor, Mycor Inc., was developing extra-cardiac devices to reduce the annulus diameter, including a surgical version called *Coapsys* and a percutaneous version *iCoapsys*, but it ran out of money and was picked up by Edwards, which hasn't reported any further development on the products. This is to say that the transcatheter mitral challenge has ultimately turned out to be much more difficult than that of the aortic valve.

## TAVI Paves The Way – But Only Part Of The Way

TAVI's early success has at least paved part of the way for mitral valve replacement companies. Transcatheter aortic valve developers demonstrated that percutaneous valve replacement can be done successfully. In the process, they've created some of the tools and concepts that will be useful in mitral valve repair and replacement – access, closure and embolic protection devices – and they've proven that there are initial markets outside the US that are large enough to justify investment, even though the demanding regulatory environment in the

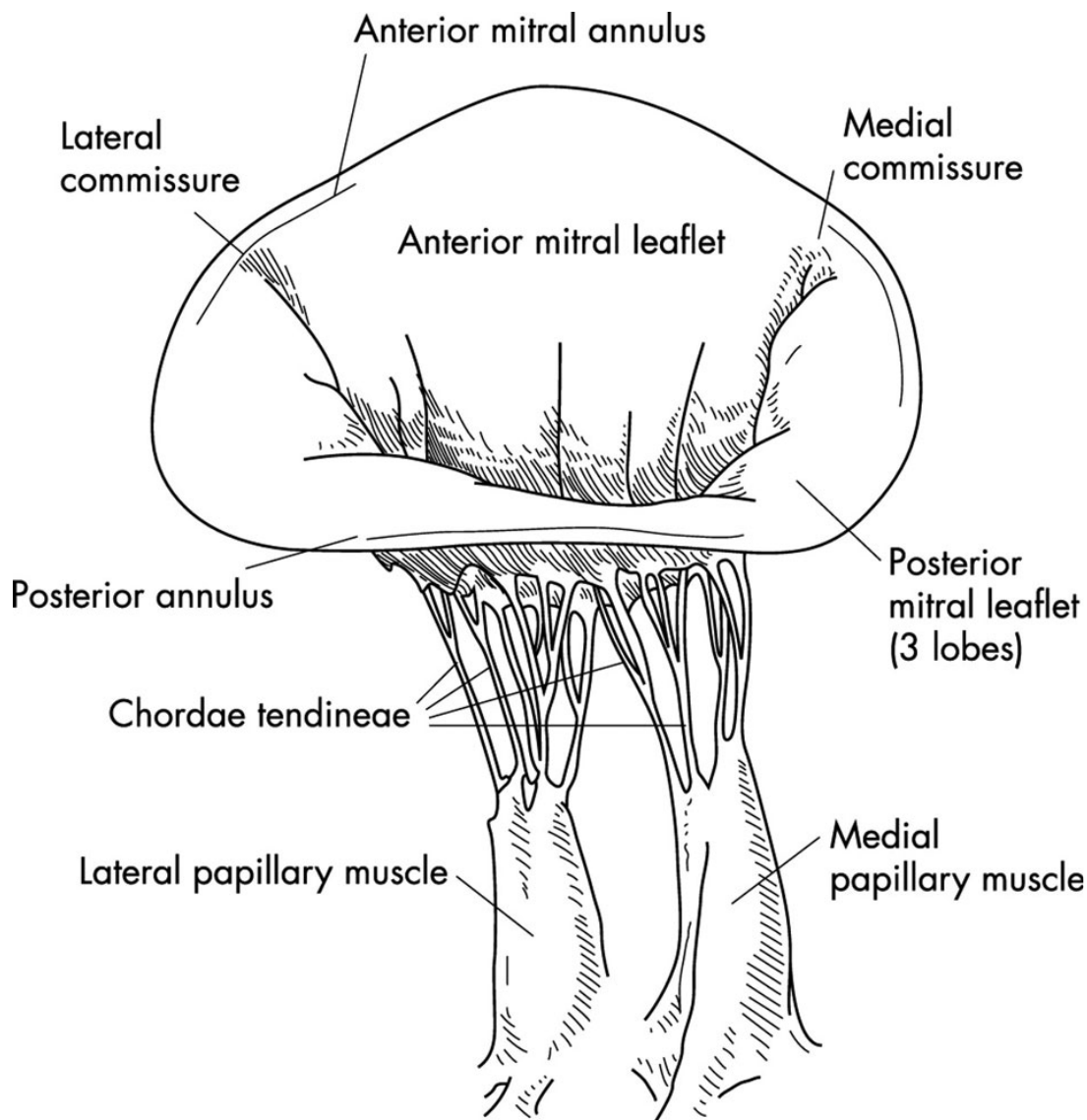
US will delay US revenues for new mitral devices by years. (See "[As TAVI Advances, Adjunctive Devices Multiply](#)" — *Medtech Insight*, December 2011.)

Today, the excitement from TAVI has renewed interest in mitral valve therapy as the next new growth opportunity, and companies that didn't jump into transcatheter aortic valves soon enough see a second chance in an emerging market. Indeed, it is always difficult to be the first company in a new market, but in this case, it can be equally difficult to be the third or fourth company. Alexei Marko, CEO of [Neovasc Inc.](#), which is developing a replacement mitral valve, notes that early companies developing devices for "no option" patients have a certain clinical hurdle to overcome; and once there are already devices on the market, that clinical hurdle gets higher. Companies that entered the TAVI market late are currently facing that challenge, he says. But it's still early days in TMVR and TMVI. "In the mitral valve, there are no proven transcatheter options except MitraClip, so compassionate use cases are still available," he notes. There is in fact keen interest in the space by strategics, many of which have internal programs in mitral valve disease.

However, companies developing devices for the mitral valve have their own long and difficult road to travel. The mitral valve anatomy is complex; it's often described as more of an apparatus than a valve. Several anatomical features influence the operation of the mitral valve; leaflets, papillary muscles, tethers between the papillary muscles and leaflets (called chordae tendineae), the annulus of the valve, and the structure of the left ventricle, which, if dilated as a result of ischemic disease or heart failure, can pull the system out of alignment. (See *Exhibit 2*.)

## EXHIBIT 2

### Components Of The Mitral Valve Apparatus



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While early developers looked at all of these anatomic factors as offering fruitful possibilities for devices with a single point of intervention, the normal functioning of the valve involves a complex interplay of these anatomical features. Surgeons understand this, and over 30 years, surgical repair has become as much an art as a science. In an open procedure, with the benefit of a three-dimensional view and color, surgeons have the ability to see what needs to be done and to operate anywhere on the apparatus, to plicate and cinch the annulus, resect and suture the leaflets, shorten or replace the chordae, in short, tweak it wherever needed. Reducing this surgical predicate to a transcatheter procedure is a far more complicated proposition than developing a transcatheter version of replacing a stenotic aortic valve.

Mitral valve disease, too, is not straightforward. Patients are heterogeneous because they develop mitral valve dysfunction through many different etiologies, and they fall into two distinct classes. Approximately 30% of patients with mitral regurgitation (MR) have the variety of the disease known as degenerative (also known as primary or organic) MR. These patients suffer from anatomic abnormalities in the valve itself: for example, calcified tissue due to underlying disease, ruptured or elongated chordae that cause leaflets to flail rather than meet (coapt) as they should; or they might exhibit a dilated annulus that prevents the coaptation of leaflets. The second category, functional MR, comprises 50%

of patients. In this case, leaflets don't coapt properly because some anatomical feature external to the valve apparatus is abnormal, such as a dilated left ventricle that displaces papillary muscles, chordae, or the annulus of the valve. Patients will have one or both forms of the disease, and the treatments will depend upon which variety they have.

Finally, the mitral valve offers a challenging environment for device implantation. It is that much more difficult to reach than the aortic valve, requiring, in the case of percutaneous devices, femoral venous access, sharp turns, and the necessity of crossing the septum. The mitral valve is also much larger than the aortic valve, leading to additional challenges in terms of the delivery of a large-diameter device. Devices placed in the left ventricle have to contend with movement and dislodgement force, since the left ventricle is a contractile organ. Finally, compared to the aortic valve, there is very little real-estate to which to anchor devices in the mitral valve. The aortic valve resides inside the cylindrical conduit of the aortic root, which is roughly one inch long, and in the presence of heavily calcified leaflets, transcatheter aortic valves can rely on radial force for anchoring; however, there is no such framework for anchoring devices in the mitral valve.

### **The Promise Of Transcatheter Mitral Valves: Opening The Window Of Opportunity**

Despite these challenges, the field is crowded because of the great medical promise of transcatheter mitral valve devices. Such minimally invasive therapies offer the usual benefits as compared to surgery: they avoid a sternotomy, permit procedures to be done on a beating heart and so avoid the negative after-effects of cardiopulmonary bypass, and they offer a shorter time to healing and ambulation. Indeed, MitraClip is fulfilling those goals; clinicians have found that patients who were bedridden before the procedure due to shortness of breath were up and walking around two days after the interventional procedure.

One might say that the clinical opportunity for the transcatheter treatment of mitral regurgitation is even more compelling than aortic valve replacement, because today's standard for mitral valve disease, open heart surgery, leaves many early- and late-stage patients out of the treatment loop. Only 20% of the patients with mitral regurgitation that should be treated because of the severity of their disease undergo surgery. The majority of patients that need some kind of definitive treatment just go without.

Brent Ratz, president and COO of mitral valve replacement company [CardiAQ Valve Technologies Inc.](#), points out that many types of mitral regurgitation are progressive and ultimately fatal, and while there is a large number of patients that need treatment, many of them simply miss the relatively brief window of treatment opportunity.

At the early stages of disease, the symptoms don't outweigh the risks of surgery, so patients endure a period of watchful waiting. Ratz says that eventually patients fall into the zone where they become surgical candidates, but they often pass right through it to the point where they are too sick for surgery. They miss the window of treatment because they don't show up for follow-up visits or the disease progression is more rapid than predicted. Says Ratz, "49% of patients with severe MR don't get referred to surgery because they are already too risky, and that non-referral population increases with age."

CardiAQ commissioned a study to define its market opportunity and learned that the surgical treatment window for mitral regurgitation is roughly five years long. The average patient with mitral regurgitation has a life expectancy of 22 years

from onset of the disease, the study found, and by year 15, the patient is both eligible and healthy enough to undergo surgery. By year 20, the patients are too sick or frail for surgery. CardiAQ's founders believe it's important to address this unmet clinical need. "Many patients could benefit from a definitive treatment, mitral valve repair or replacement, but they end up drifting into some form of heart failure and dying from that," says Ratz. Transcatheter treatments can play a role, not only in the group of patients too sick for surgery, but in potentially treating patients before they become so sick that surgery is required. This is an ideal scenario, particularly since it is known that treating MR can reverse or prevent some of the heart remodeling that accompanies heart failure.

## Replicating A Surgical Gold Standard That's Not Standard

MitraClip has experienced some early success (although it still has a long way to go) precisely because it has followed the conventional paradigm in interventional cardiology. It recreated, with a catheter delivered percutaneously, a specific surgical procedure, the edge-to-edge mitral leaflet repair procedure that was pioneered by Italian surgeon Ottavio Alfieri, MD, in the early 1990s. The Alfieri surgical edge-to-edge procedure stopped mitral regurgitation by suturing the two leaflets in the middle, leaving openings on either side. MitraClip accomplished the same thing by delivering a clip to the leaflets. (See "[Evalue: Leading the Valve Revolution](#)" — *IN VIVO*, September 2006.)

The EVEREST II pivotal trial of MitraClip was, as noted, the first multicenter randomized clinical trial ever completed in the space, and the first ever to use a core lab to validate the results of surgical mitral valve treatments. The trial randomized, on a 2:1 basis, 279 patients with moderate-to-severe or severe mitral regurgitation to either the MitraClip or conventional surgery (repair or replacement of the mitral valve). The primary composite end point for efficacy was freedom from death, from surgery for mitral-valve dysfunction, and from grade 3+ or 4+ mitral regurgitation at 12 months. The primary safety endpoint was a composite of major adverse events within 30 days.

The study concluded that while surgery reduced mitral regurgitation at a superior rate (following the procedures, 4% of the surgery patients had MR in the 3+ to 4+ range as compared to 19% of the MitraClip patients) the two treatments had similar mortality rates, similar beneficial effects on heart remodeling and quality of life, and, at one year, a similar likelihood of being free from the need for a reoperation. As expected, the percutaneous group experienced a lower rate of adverse events at 30 days than the surgery patients.

Looking at subgroups, the clip therapy was most equivalent to surgery in three patient groups: older patients, those with left ventricular dysfunction, and those with functional rather than degenerative MR. In fact, in Europe, where the clip has been approved since 2008, the majority of patients being treated are functional MR patients (rather than degenerative MR patients, the original target group) who are not good surgical candidates. Initially, many believed MitraClip would be best suited to patients with degenerative valve disease where the problems lay in leaflets themselves or the chordae tendineae.

This last finding gets to an issue facing all developers of percutaneous mitral valve technologies: defining the specific patient population that will benefit from a technology. This will require a kind of patient segmentation that never needed to be done for surgery. Surgery divided patients into two groups; those with degenerative MR, (good targets for surgery), and those with functional MR (not so much). As noted, the ability to tailor surgical therapy to individuals obviated the need to segment the population by disease morphology, etiology, or clinical



benefits, issues that the new companies do have to take into consideration, since they tend to fall into different categories according to exactly which part of the valve they're treating.

Companies aiming for the percutaneous repair of the leaflets include, in addition to Abbott/Evalve, start-up **Mitralis** (which will soon be spun-out of the Pavilion Medical Innovations incubator founded by Catalyst Health Ventures and medical device veterans Al Chin, MD, the founder of Origin Medsystems and Mike Glennon, formerly of Medtronic, Guidant, and Stryker). Companies targeting the mitral annulus include **Guided Delivery Systems Inc.**, [MiCardia Corp.](#), [Mitralign Inc.](#), and **QuantumCor Inc.** [NeoChord Inc.](#) is focused on replacing dysfunctional chordae tendineae. A few companies are developing artificial valves for total replacement including CardiAQ Valve Technologies, Neovasc, and EndoValve, now part of [Micro Interventional Devices Inc.](#) Newer companies [Valtech Cardio Ltd.](#) and **TransCardiacTherapeutics LLC** believe they'll serve the goals of the predicate surgeries better with entire platforms that combine all of the above. (See Exhibit 3.)

It does seem risky to try to treat mitral valve disease by addressing only one component of it at a time, but according to Carlos E. Ruiz, MD, PhD, director, structural and congenital heart disease at the Lenox Hill Heart and Vascular Institute (New York), it's difficult to do it any other way. "Start-ups are beginning to combine technologies," he says. "But basically, the problem is how to conduct clinical trials with two experimental devices. That is going to be a major issue."

Ruiz says that surgeons use multiple approaches to the repair of the mitral valve, and that's why the success rate is so high. "If we want to duplicate that with transcatheter technologies, we should also entertain the option of multiple approaches to the repair. We'll need a combination of annuloplasty, chordal shortening, mitral clipping, whatever is needed, but it will have to be in combination."

The single mechanism transcatheter repair device "translates into the number of patients that will qualify for the treatment." In reality, says Ruiz, "There are only small subsets of patients in whom a device that fixes only one item would completely resolve the problem of mitral regurgitation."

Percentage-wise, it sounds like a limited approach. But dollar-wise it's a worthy goal. Rick Geoffrion, CEO of Mitralign, says, "The end user pricing here is such that one doesn't have to sell hundreds of thousands of devices to create a significant market." Indeed, devices for TAVI sell on the order of €17,000 in Europe and \$30,000 in the US. MitraClip is reportedly selling for €20,000 in Europe.

There is a huge pool of patients, Geoffrion says, "but it is incumbent upon every company operating in this space to define their clinical box." Companies need to accurately define the patients who will benefit from their device and they have to define a clinical box that can be accessed, in reasonable volumes, at expert institutions." (According to the model of TAVI, percutaneous valve procedures are performed in centers of excellence, and not by community physicians, a trend that has just been underscored by the recent proposal for a National Coverage Decision for TAVI by the US Centers for Medicare and Medicaid Services [CMS]. TAVI will be reimbursable only as performed by institutions fulfilling criteria that the CMS outlines, some having to do with procedure volumes and training.)

## Mitralign Aims To Be First In Line

Mitralign was founded in 2003 by the Accelerated Technologies Inc. incubator (see ["ATI: Is This the Model for Device Development?" — IN VIVO, February 2005](#)) and is backed by significant funding from an investor group that includes Forbion Capital Partners, Oxford Bioscience Partners, Saints Capital, Triathlon Medical Ventures, [Medtronic Inc.](#), Johnson & Johnson Development Corp., Oakwood Medical Investors, Orchestra Medical Ventures and Palisade Capital Management. GE Capital's Healthcare Financial Services has also provided debt funding. The company is targeting functional mitral regurgitation with an approach to direct annuloplasty that will one day enable interventionalists to create a certain effect depending upon the type and extent of mitral regurgitation. Direct annuloplasty reduces the circumference of the annulus by working directly on it (as opposed to indirect approaches, like the coronary sinus procedure outlined above, or devices that work on the inside or outside wall of the heart to constrain the annulus).

Mitralign's Rick Geoffrion is the former CEO of Accelerated Technologies as well as the former chairman of Impella CardioSystems AG, CircuLite Inc., and FlowMedica Inc. According to Geoffrion, the company is emulating surgical direct annuloplasty with a suture and pledget-based implant that encapsulates into the annulus in a benign manner. Mitralign's approach "does not limit any follow-on interventions or surgical procedures," he says. "Once implanted, you still have all options on the table for future repair or replacement." That advantage makes Mitralign suitable for a first-line therapy, Geoffrion believes, one that not only doesn't preclude future strategies, but may also create a healthier patient with expanded options. "Because our goal is to reduce the size of the annulus toward a normal state it is theoretically possible that we may prepare the annulus better for later valve replacement should it be necessary," says Geoffrion.

Mitralign's current *Bident* system deploys an implant containing two pledgets (folded panels of fibrous material that help anchor sutures) accompanied by a suture and a tiny stainless steel lock. The implant is delivered through a 14F-compatible deflectable guide catheter that provides retrograde femoral access to the left ventricle and directs all subsequent catheters towards the posterior side of the mitral annulus. Under the guidance of fluoro and 3D TEE (transesophageal echocardiography) the operator advances the steerable wire-delivery catheter until the tip of the catheter reaches a target position on the mitral annulus. A small echogenic wire is then advanced through the annulus and into the left atrium. The Bident spacer catheter, which determines the amount of plication and helps in positioning a second wire, is then advanced to the mitral annulus and a second wire is delivered. With the two wires in proper position, the Bident catheter is withdrawn and a catheter pre-loaded with a pledget is advanced over each of the wires. The catheter is pushed over the crossing wire through the annulus to deploy one end of a pledget on the atrial side and then pulled back to deploy the other end of the same pledget on the ventricular side. Two pledgets connected to suture serve as a buttressed anchor for the plication of the annulus. Plication occurs when the two pledgets are pulled together. Once plication is achieved, the plication catheter automatically locks the sutures via a tiny stainless steel lock underneath. The procedure is performed again to deliver a second implant at a second location.

The Mitralign platform may serve the physician's desire for customization, says Geoffrion. "As we learn more about patients and the clinical box within which we work, we may have the opportunity to put in three implants or one implant, depending upon the type of mitral regurgitation or the location of the jet." Geoffrion says it is possible to customize by deciding upon the number of implants and where to place them on the posterior mitral annulus. But for today,

notes Geoffrion, the company is working with two implants in a consistent location on the posterior annulus.

The company expects to initiate a CE Mark study later this year. "We have enhanced and simplified the system to the point where we now believe we can produce repeatable clinical results in the hands of multiple operators. It's going to be an exciting year," Geoffrion says.

## Time For TMVI

The current transcatheter mitral valve industry has grown up around a standard of surgical repair rather than valve replacement. However, given the challenges of catheter-based approaches to mitral valve repair, many newer companies are revisiting the concept of transcatheter mitral valve replacement. As companies wrestle with repairing variable anatomy through a catheter, in many cases, they're developing procedures that require skills that are very different from those of interventional cardiology; they require clinicians to grasp leaflets, suture, deliver energy, plicate and cinch. Looking to a future when techniques might need to be combined to recreate native geometry, transcatheter repairs risk becoming complicated and lengthy. After the success of TAVI, many wonder if it might not be simpler to just drop in a new mitral valve, assuming that some of the lessons learned from surgical replacement are embodied (for example, preservation of the chordae and subvalvular apparatus). Several companies are now attempting to create a new paradigm in transcatheter mitral valve replacement, including Medtronic, Edwards, and at least four start-ups: CardiAQ Valve Technologies, Valtech Cardio, Endovalve, and Neovasc.

Neovasc is a leading supplier of pericardial tissue and related services to the transcatheter valve industry. With well established capabilities for working in tissue valves and catheter development, Neovasc set out to fill a need for a product for transcatheter prosthetic mitral valve replacement. Neovasc is developing *Tiara*, a D-shaped valve that is specifically designed to match the shape of the floor of the left atrium and the mitral annulus. CEO Alexei Marko describes *Tiara* this way, "Looking at the performance requirements for a prosthetic transcatheter mitral valve, a number of critical things needs to be addressed to ensure that the valve functions properly and does not inhibit the functioning of the surrounding native structures." *Tiara* is a pericardial tissue valve within a self-expanding frame. According to Marko, since the *Tiara* valve shape closely matches the native anatomy, it does not project anteriorly to obstruct the left ventricular outflow tract or inhibit the function of the native aortic valve.

As for the challenge of anchoring the prosthetic mitral valve, *Tiara* does not rely on any radial force for securement, Marko says. "It uses an innovative combination of an atrial skirt and anchoring features on the ventricular side to hold it in place without risk of dislodgement. *Tiara* has a very compact design with minimal projection into the atrium and ventricle and has demonstrated excellent durability, hemodynamic performance and minimal paravalvular leak in preclinical testing." *Tiara*'s design also allows flow through the valve to be maintained through the entire deployment process, so the implantation procedure does not require rapid pacing, as do some TAVI procedures.

Marko notes that Neovasc is initially developing the *Tiara* valve for transapical implantation, but it is also expected to be available at a later date for transfemoral implantation. "In animal models, we have found the typical implantation time from the point at which we enter the apex of the heart with the *Tiara* delivery catheter until we are done and closing the access site to be five minutes," says Marko.

Neovasc's valve is currently undergoing chronic testing in animals, and the company aims to be implanting Tiara in humans in approximately 12 months.

## A Fix for Functional Mitral Regurgitation

Rob Michiels, CEO of CardiAQ Valve Technologies, has been part of the transcatheter heart valve industry since its birth, first as an investor in CoreValve Inc. (which ultimately raised \$65 million privately) and later as its president and COO from 2004-2009, leaving his post when Medtronic acquired the TAVI pioneer for \$700 million. [\[See Deal\]](#) Brent Ratz, president, COO, and co-founder of CardiAQ, convinced Michiels to do it one more time, this time with transcatheter mitral valve replacement.

Ratz says that the early transcatheter mitral valve industry went in the direction of percutaneous repair because surgical repair was the gold standard for treating degenerative mitral valve disease. Again, that type of mitral regurgitation is caused by abnormalities in the various components of the mitral valve apparatus, and surgeons wanted the ability to treat the specific morphology of the disease. It also made sense, for reasons of durability, to leave as much of the native anatomy intact as possible. At the same time, surgical valve replacement was less desirable because it bore double-digit mortality rates – in the range of 12%-17% for patients over the age of 70. Surgical repair enjoyed much lower mortality rates and so it became the gold standard. However, under that standard of care, patients with functional MR were – and still are – undertreated; there remains no good solution for them except for annuloplasty rings, which, in the face of ongoing degenerative disease of the ventricle, do not tend to provide lasting freedom from mitral regurgitation and in as many as 20% of cases, result in recurrent mitral regurgitation.

Ratz points out that although surgical repair became the gold standard, it is far from perfect, especially since it does not serve functional MR patients. ACC/AHA guidelines recommend repair over replacement in most instances, but it is only utilized about 60% of the time due to the complexity of the procedures and the recommendation that patients be referred to high-volume, experienced surgical centers.

Over the years, surgical mitral valve replacement has improved. Ongoing clinical studies suggest that when chordae are spared and other such improvements are made, surgical replacement might be as effective as surgical repair. At the same time, replacement mitral valves might also be able to serve a large unmet clinical need: the large percentage of patients with functional mitral regurgitation that don't have any therapeutic options.

## CardiAQ Brings Back Mitral Valve Replacement

CardiAQ Valve Technologies had its beginnings in 2007, when the founders began shopping around a rapid fixation approach for aortic valve replacement developed by its founder and chairman Arshad Quadri, MD, a cardiac surgeon at St. Francis Hospital in Hartford, CT. The field of TAVI was already underway, so the company sought to occupy a middle ground between surgical and transcatheter replacement. At the time, the founders discovered that there was more interest in the technology for mitral valve fixation. The timing was right, says Michiels, because by 2008, the luster started rubbing off of some of the repair technologies that were yielding unimpressive clinical results. CardiAQ's founders began to question whether the surgical gold standard was the right standard for transcatheter devices. Seeing no other replacement mitral valve on the horizon, the company decided to focus 100% of its energies on percutaneous mitral valve replacement. In December 2009, the firm completed a \$6.5 million

Series A funding round [\[See Deal\]](#) led by Michiels and the same group of angel investors who invested in CoreValve in 2002, as well as a follow-on investment from the company's initial backer, Broadview Ventures.

Ratz says "We believe we can eliminate the risks of open heart surgery and provide effective transcatheter treatments for a wider range of mitral regurgitation etiologies. Unlike mitral repair technologies that are limited to just a sliver of the patient population, we believe we can get a much bigger slice with fewer anatomical and morphological restrictions." With a replacement valve, clinicians would not need to concern themselves with leaflet coaptation depth, or, for example, the circumflex artery running underneath the coronary sinus. "Those are not issues for us," Ratz says.

That creates a much bigger opportunity from a market and revenue standpoint, the company believes. "We have a single technology with the potential to address multiple types of MR. It offers simple access, controlled placement, and is more like a true interventional procedure." It will be simple to position and retract a sheath in a manner that is similar to TAVI, Ratz says.

The CardiAQ device is a two-part construct consisting of a bi-level nitinol frame with a tissue valve inside. The dimensions of the valve in its first iteration are 30 mm on the inflow side, and 40 mm on the outflow (anchoring) side. The company will offer multiple sizes at a later stage. Ratz says that the frame is robust and will be stronger than the annulus so the annulus will proximate around the frame to achieve a tight seal.

The valve function will be positioned largely in the left atrium so that it will be protected from the motion and contractility of the left ventricle while also reducing the risk of the leaflets blocking the left ventricular outflow tract. With this approach, even if the annulus is D-shaped rather than circular, it will not impact valve function, because (within design parameters) the frame section containing the tissue valve will resist deformation, Ratz explains.

Anchoring is an enormous challenge for all mitral valve developers. The mitral valve's annulus is an elastic ring; there is no wall on which to anchor the valve. CardiAQ's IP covers a unique anchoring mechanism that makes use of a foreshortening region on the frame. When the valve is compressed, its diamond-shaped struts elongate and the tips of the device anchors are separated. When the device is deployed and expanded in the body, the tips of the anchors come together to provide an axial clamping force around the annulus. (An example of axial clamping is a grommet that provides pressure from above and below.) The anchors help the device to self-position; once one set of anchors contacts the annulus, the other side of the device moves relative to that. "You get a proper deployment plane every time," Ratz says.

CardiAQ may be the only TMVI company that plans to go straightaway to transfemoral access. Others are validating their devices via a transapical approach, which, while offering a straighter shot into the heart, requires an entry into the high pressure side of the valve through the subvalvular structures. CardiAQ faces a tough challenge here because the percutaneous route into the mitral valve is even more difficult than the approach to the aortic valve, in that it requires a bend to get into the left atrium transseptally (through the interatrial wall) and another very tight and tortuous bend toward the mitral annulus. Ratz says the company has overcome a great catheter design challenge to arrive at a delivery mechanism that's strong enough to be controlled and retracted during implantation, but flexible enough to make tight turns. The company is now finishing up its technical feasibility phase and is readying for its first-in-man clinical trials.

At CardiAQ, Michiels plans on adapting the tried and true model of CoreValve, which established its technology and procedures overseas. CardiAQ is probably three to four years away from commercializing in that market. From an investment standpoint, says Michiels, "It probably makes more sense to do a \$25 million venture round to get the CE Mark, then spend the next \$25-\$30 million round to do a market launch in Europe to get to profitability, before wrestling with the FDA around US approval." Michiels says that right out of the gate, the worldwide market for the CardiAQ valve is \$2 billion, \$1 billion if the US is excluded.

Future partnering or exit strategies will depend on how successful large strategics think they will be at advancing their own TMVI programs. Percutaneous aortic valve companies Percutaneous Valve Technologies, Sadra Medical and Ventor Technologies were all acquired after their first data in humans (by Edwards Lifesciences, Boston Scientific Corp. [\[See Deal\]](#) and Medtronic, [\[See Deal\]](#) respectively). But given the current economic climate, companies are obviously going to want to see more progress than that. Michiels notes that CoreValve made it all the way to the revenue stage, which is why it commanded such a large purchase price from Medtronic.

Michiels points out that most of the large strategics have their own internal programs but none have yet reached the clinic. "They all know that if they want to play in the valve space, they have to have a solution for the mitral valve," he says. He also believes there is an opportunity for those strategics that came late to the game on the aortic side. "Rather than spend on a me-too aortic valve project, they might invest in being first to market with a mitral valve," Michiels says.

## Back To The Future

Although still in its infancy, percutaneous mitral valve therapy is already an extremely crowded field, a testament to the widely held belief that it's not an insurmountable problem, just a kind of engineering challenge that will require many solutions and much iteration. After all, that's how mitral valve surgery has grown up over 30 years.

The first long-term definitive treatment of mitral valve regurgitation was introduced in 1960 with the surgical implantation of a Starr-Edwards Silastic Ball Valve. Many iterations followed in valve replacement. By the beginning of the last decade, however, valve repair had taken over as the gold standard, to the benefit of hundreds of thousands of patients across the globe. In the past 12 years, innovators seeing an opportunity to make the repair method less invasive may have inadvertently led the field back to the place where it began: to total valve replacement, this time, through a catheter.

At this stage, there are many unknowns. The MitraClip EVEREST trials provided the field with an excellent proof of concept, and a new set of questions to answer, concerning the durability of devices, the impact on subsequent interventions, the types of patients that are candidates for the device, and what level of clinical benefit justifies the procedure in previously untreated patients. EVEREST II, for example, demonstrated that even when MitraClip didn't do as well as surgery at reducing mitral regurgitation it nevertheless improved measures of heart failure, demonstrating reverse ventricular remodeling and improvements in the severity of disease (as measured by New York Heart Association classification of heart failure). If a procedure is safe, effective, and improves the health of heart failure patients, shouldn't its use extend beyond the group of no-option, non-surgery patients?

Companies operating in transcatheter mitral valve treatment hope so, but it will take many years until they can prove it. These days, risk-averse investors generally don't like a category where there are more questions than answers, but percutaneous mitral valve therapy is still a wide open field, it addresses an important disease, and one that affects millions of patients. Two to three percent of the world's population suffers from mitral regurgitation, and every year large numbers of patients enter the zone where they need definitive treatment. Companies who are first in this market will be rewarded handsomely – as will their investors.

### EXHIBIT 3

#### Selected Start-Ups In Mitral Valve Repair/Replacement

Company	Description/Investors
Cardiac Dimensions (Founded 2001)	Indirect annuloplasty. <i>Carillon Mitral Contour</i> system is annuloplasty device implanted in the coronary sinus to treat functional mitral regurgitation. Implant can be rapidly delivered via the venous system, retrieved and repositioned. Received CE mark in January 2009. Commercial launch of an enhanced version of <i>Carillon</i> to commence in 2012. US clinical trials ongoing.
CardiAQ (Founded 2007)	Valve Replacement. Self-positioning chordae-sparing replacement valve is a two level construct consisting of a tissue valve inside a self-expanding nitinol frame. Device is positioned largely in the left atrium, has unique anchoring system that relies on axial clamping rather than radial force. Company is shooting for transvenous access with its first device. In preclinical phase.
Cardiosolutions Inc. (Founded 2006)	Leaflet space occupier. <i>Percu-ProSystem</i> delivers a proprietary implant (Mitra-Spacer) and a reversible anchoring system that is placed into mitral orifice to occlude the gap that arises when the leaflets fail to close properly. The stem of the device is anchored into tissue near the apex of the left atrium. For the treatment of functional MR, potentially as a long-term implant or a bridge therapy.
Guided Delivery Systems (Founded 2001)	Direct Annuloplasty. <i>Accucinch</i> , delivered via the femoral artery retrograde across the aortic valve uses tensioning cable anchored in the left ventricle wall to reduce annular dilatation. First-in-human studies.
Mardil Inc. (Founded in 2007)	Extracardiac annuloplasty. BACE (Basal Annuloplasty of the Cardia Externally) is a tension band with inflatable silicone chambers that is wrapped around a section of the heart

<p>MiCardia (Founded in 2004)</p>	<p>(promising improved safety over devices that enter the heart). After a surgeon sutures the device to the heart, the chambers are filled with saline via tubing connected to subcutaneous ports. The saline applies pressure at certain points of the heart to coax the mitral valve leaflets within the heart to close properly. The saline levels can be adjusted during or after the surgery to provide the appropriate pressure needed to minimize functional mitral regurgitation.</p> <p>Direct Annuloplasty. <i>Dynaplasty</i> uses RF to adjust annuloplasty ring with shape memory. Ultimate goal is implanted ring that can be adjusted in a period following surgery to eliminate remaining regurgitation. CE mark for first-generation enCor was granted in 2010. Percutaneous version, enCorTC, is three or more years away from market. /HBM Biocapital, Japan Asia Investment Co., Medfocus Funds, Bio-Star Private Equity.</p>
<p>Micro Interventional Devices (Founded in 2010)</p>	<p>Valve Replacement. Acquired Endo valve in April 2011; is valve-sparing (like repair). Also Permaseal, device which provides sutureless transapical access and spontaneous closure for structural heart devices. First product creates access to the left ventricle for devices up to 28F. /Battelle Ventures, New Hope Ventures, Ben Franklin Venture Partners, Lifesciences Greenhouse.</p>
<p>Mitralign (Founded in 2003)</p>	<p>Direct annuloplasty. <i>Bident</i> uses paired pledgets along the posterior wall of the mitral annulus to achieve direct annuloplasty via small plication, which decreases mitral annulus circumference and septal-lateral dimension of the mitral valve. First-in-Human studies completed, soon to begin CE-mark study. / Forbion Capital Partners, Oxford Bioscience Partners, Saints Capital, Triathlon Medical Venture Partners, Medtronic Inc., Johnson &amp; Johnson Development Corp., Oakwood Medical Investors, Orchestra Medical Ventures and Palisades Concentrated Equity Partnership. GE Healthcare Financial Services has also provided debt funding.</p>
<p>Mitralis (Founded 2012)</p>	<p>Focusing on degenerative mitral regurgitation with leaflet restraint concepts invented by Lishan Aklog, MD. About to be spun out of the Pavilion Medical Innovation Incubator, which is</p>



NeoChord (Founded in 2007)	<p>advised by Aklog and Brian deGuzman, MD, both cardiac surgeons at the Heart &amp; Lung Institute at St. Joseph's Hospital and Medical Center.</p> <p>Artificial Chords. Device, licensed from the Mayo Clinic, for the minimally-invasive implantation of artificial chordae through a transapical approach. Treats severe MR due to posterior mitral leaflet prolapse caused by ruptured chordae. /Clarian Health Ventures, Heron Capital, TGap Ventures, Cedar Point Capital, South Metro Investors, Twilight Venture Partners, Two Rivers Angel Investment Network, and 35 individual backers.</p>
NeoVasc (Founded in 2000)	<p>Valve Replacement. <i>Tiara</i> is D-shaped replacement valve incorporating tissue valve inside a nitinol frame that does not impinge on left ventricular outflow tract; uses complex anchoring structures that use the chordae, the force of the atrial portion of the anatomy and other structures. Initially targeting a transapical approach. Preclinical stage. /Frost Group, Gagnon Securities, OPKO Health, Companies directors and management</p>
QuantumCor (Founded in 2001)	<p>Direct Annuloplasty. Radiofrequency system shrinks collagen to remodel the annulus. Electrodes delivered transseptally.</p>
TransCardiac Therapeutics (Founded in 2003)	<p>Artificial chords and Leaflet plication device. Founded by Omar Lattouf, MD, a cardiac surgeon out of Emory University, developing <i>MitraFlex</i>, a mitral valve repair system designed for direct thorascopic approach through the apex of a beating heart. <i>MitraFlex</i> fulfills several functions, including stabilizing and centering the leaflets, automating the capture and connection of the approximate midpoint of the leaflets, implanting artificial chordae tendineae, and reducing the annulus.</p>
Valtech Cardio (Founded in 2006)	<p>Portfolio of sutureless, dynamic devices for fine tuning. <i>Cardioband</i> is sutureless posterior flexible annuloplasty band, <i>Cardinal</i> is semi-rigid adjustable annuloplasty device, <i>VChordal</i> is sutureless device for adjustable chordal repair, <i>Cardiovalve</i>, a replacement valve, is in development. / Oxo Capital Valve Ventures, NGN Biomed, and Peregrine VC.</p>

Note: Other early-stage companies working in this area include Kardium, Millipede LLC, and Tendyne Medical.

*Elsevier's Strategic Transactions; Company interviews; TCTMD.org*

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