Transcatheter Mitral Valve Technologies: The Heart of Cardiovascular Device Innovation

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Executive Summary

The current atmosphere in medical device investment is one of caution: Over the last five years, about two-thirds of high-impact medical device M&A deals have occurred following U.S. commercialization¹, that is, after targets had already generated the robust clinical data needed for U.S. marketing approval, payment and reimbursement. Many large companies, it seems, want earnings today more than they want tomorrow's potential. This trend aligns with other technical product-based industries where incremental innovation tends to slowly evolve markets, versus dramatic evolutionary shifts.

Next-generation mitral valve repair and replacement are another story. The companies developing these technologies are commanding strategic valuations at the earliest stages of development. At the combined apex of clinical, technical, economic and market trends, Transcatheter Mitral Valve Replacement (TMVR) and Repair (TMVr) technologies are among the last steps in the cardio-strategic roadmap. For large companies with more money than risk, they offer the tantalizing promise of massive value-creation.

These technologies are generating high valuations based on a paradigm shift and the hope that surgeons and interventional cardiologists can repair or replace even the heart's interior valves without cracking open the chest. Recognizing their potential, many large medical device companies are vying with each other for the firms that have been developing these technologies: Edwards Life Sciences acquired Harpoon for $100 million; Medtronic acquired Twelve for $408 million at closing and $50 million more at CE marking, and others have made substantial investments as well—but there are still targets for acquisition.
What is the attraction of these early TMVR and TMVr technologies?

**BACK BAY LIFE SCIENCE ADVISORS ANALYZED THE MARKET AND SEE FOUR ELEMENTS DRIVING THIS FRENZY:**

1: **Companies learned a lesson from TMVR/r’s older cousin, Transcatheter Aortic Valve Replacement (TAVR)** — Before physicians started thinking about replacing the mitral valve via catheter, several companies demonstrated the ability to replace the relatively simpler aortic valve with TAVR, but only a few companies invested early in this technology. Those few now command a market worth more than $1 billion in worldwide annual sales. Having missed out once, large manufacturers do not want to pass up the even larger value-creation opportunity of mitral valve repair and replacement.

2: **The population in need of this technology is much larger than TAVR’s and their options are few** — In the U.S. alone, there are more than four million people with moderate to severe Mitral Regurgitation (MR) and only 2% of them are treated surgically, leaving more than a million patients who could benefit from a minimally-invasive transcatheter intervention. As medical device companies have seen TAVR hit the billion-dollar mark, with an annual U.S. procedure volume of ~25,000, they are watching this addressable patient pool with even greater interest.

3: **One size does not fit all here, and it is not clear which solution will prevail** — There is a broad pipeline of both repair and replacement devices but no consensus on which solution should be used and when. This leads us to:

4: **Device manufacturers need to place bets right now to build the Mitral Valve ‘toolbox’ of the future** — Some replacement valves may preclude revisions if the replacement fails. While early repair device experience suggests this may be a more flexible option than replacement, it is not known now which repair option(s) will be best for this complex and varied disease among a dense pipeline of unique approaches. In fact, patients may need multiple options in their lifetime and to be successful, companies should look to build a diverse and comprehensive valve ‘toolbox’ to meet this need.
TAVR: Lessons Learned

Before discussing the mitral valve, which allows blood to flow from the left atrium to the left ventricle of the heart, let’s consider the aortic valve, which is both more accessible and more circular. As people age, calcium builds up on the aortic valve; this can interfere with the heart’s ability to pump blood into the aorta. As the valve degenerates, the heart compensates by remodeling its chambers, which can eventually lead to severe symptoms such as breathlessness, fatigue, and fainting. Medical treatment for this condition, aortic stenosis, is generally inadequate, and often the only option for symptomatic patients is surgery—involving a sternotomy and cardiopulmonary bypass, an approach which may not be tolerable for older, sicker patients.

Around the turn of the millennium, European physicians worked with Israeli engineers to design a transcatheter heart valve (THV) for inoperable patients that let surgeons implant a replacement valve through a patient’s groin with a catheter. In 2004, Edwards Lifesciences acquired Percutaneous Valve Technologies’ (PVT) preclinical device and went on to develop the SAPIEN valve for inoperable and high-risk aortic stenosis patients, revolutionizing and expanding the treatment of aortic valve diseases.

Enabled by transformational technology, the initial Indications for Use (IFUs) for transcatheter valve replacement centered on inoperable patients, but physician comfort with the technology, new clinical trials and iterative generations of safer and easier-to-use devices have helped TAVR to expand to lower-risk populations, sustaining growth in an initially small market.

Today, more than 300,000 severe aortic stenosis patients have been treated with this approach, and what was once reserved for only the sickest patients is now gaining use in lower-risk patients as well.

TAVR is now a greater than $1 billion market, with relatively few competitors. Soon after Edwards bought PVT, Medtronic acquired CoreValve Inc. (after CE-mark and feasibility milestones had been reached). St. Jude Medical, meanwhile, has developed the Portico Transcatheter Aortic Heart Valve, and Boston Scientific also worked their way into the mix with several large acquisitions.

Although many companies may have “missed out” on this market, there are lessons to be learned from the TAVR experience for researchers, doctors, and investors:

• First and foremost, it is possible to replace a human heart valve using transcatheter techniques.

• Second, gaining a foothold in the market with patients who have no surgical options enables both doctors and regulators to become more comfortable with the technology, and opens a path to wider adoption among those who are less in need, but can still benefit from minimally invasive techniques.
Third, do not be late! By the time TAVR proved itself a commercial success, Edwards and Medtronic had gained significant durability and safety data\(^9\) and had achieved a dominant market position, leaving would-be competitors playing catch-up.

**Now for Something Even Bigger: TMVR/r**

**A LARGE POPULATION IN CRITICAL NEED**

As TAVR proved itself in the U.S. and Europe, clinicians and industry researchers set their sights on the more complicated mitral valve, which separates the left atrium and ventricle. This part of the heart, however, poses daunting challenges: the mitral valve's anatomy and orientation make it significantly more difficult than the aortic valve to repair and replace. In addition to the anatomical challenges, the causes and manifestations of mitral valve disease are more varied and complex than aortic valve degeneration. While the difficulties of the
problem abound, the need for a solution is greater as well: there are many more people with mitral valve disease than aortic valve disease and their treatment options are nowhere near as efficacious.

One form of the disease, Mitral Valve Regurgitation (MVR), occurs when the valve starts to fail and blood flows backward from the ventricle to the atrium. MVR is diagnosed in around 250,000 new people every year and affects almost 7 million people in the U.S. and 9 million Europeans. Compared to the ~50,000 annual U.S. aortic valve replacements performed each year, ~1.7 million U.S. MVR patients have disease that is severe enough to require surgical treatment.

WHEN SURGERY IS NOT AN OPTION

Like most valve diseases, MVR is primarily a disease of the aged, and while age is the most significant factor, the disease is further classified by its other contributory causes. In some cases, it is accelerated by an intrinsic defect in valve structure either from prolapse or rupture of a leaflet or chord. These patients have Degenerative or Primary Mitral Regurgitation (DMR), and represent 20–30% of the MVR population. On the other hand, 50–70% of patients have Functional Mitral Regurgitation (FMR), usually caused by ischemic injury to the left ventricle that prevents the valve from closing effectively (i.e., coapting). FMR is particularly complex because the valve malfunctions due to a ischemia and ventricular dilation, which itself can lead to rhythm problems and heart failure.

Without treatment, up to 5% of patients with severe disease are expected to die annually. The statistics are even more dismal in older patients. Surgically implanting an annuloplasty ring that restores valve leaflet coaptation works relatively well in the low-risk DMR patients. Unfortunately for FMR patients, annuloplasty is not ideal because the left ventricle is usually distorted, rendering the solution ineffective. For these patients, MVR recurs 40% of the time after surgical repair.

Regardless of the cause of MVR, these patients are sometimes elderly and frequently present with other cardiac conditions. This makes surgical repair too risky, and only 2% (~30K) of MVP patients can safely undergo surgical treatment. Within the MVP patient population, those who have cardiomyopathy (inadequate pumping ability), remodeling of the ventricle, or age over 75 are considered high-risk patients. Almost half of these high-risk patients are not surgical candidates.

Back Bay Life Science Advisors spoke with a cardiac surgeon who indicated that because mitral regurgitation disease is dynamic, it is very hard to tease out the exact symptomology and to convince the community at large—patients and physicians—to try surgery.
How do You Heal a Broken Heart?

MITRACLIP (EDGE TO EDGE REPAIR)

When it comes to the aortic valve, the solution space is fairly straightforward. There are several notable differences among Medtronic, Edwards, Boston Scientific, and Abbott’s TAVR solutions, but they all fundamentally do the same thing—replace the patient’s faulty valve with a prosthetic valve. However, with the mitral valve, there are many potential ways to improve MVR symptoms. Unlike the more reliably circular aortic valve, the mitral valve is anatomically complex, making the design of mitral valve therapeutic devices more difficult.

Abbott’s MitraClip is currently the only FDA-approved transcatheter approach to repair a faulty valve. MitraClip is a transcatheter application of a surgical technique called the edge-to-edge Alfieri technique—it ‘clips’ faulty leaflets together to reduce the backflow of blood into the atrium. Like the mitral valve anatomy itself, the approval process had twists and turns and required multiple approaches. MitraClip’s pivotal study, the EVEREST II trial, was designed to evaluate treatment with the MitraClip device compared with surgical mitral valve repair/replacement among patients with severe mitral regurgitation. On the heels of its registration, the EVEREST II trial showed better patient safety, improvement in symptoms, and fewer major adverse events compared to open-heart surgery; the MitraClip received approval in 2013 for percutaneous treatment of DMR.

However, MitraClip approval is not the end of the story; the questions and complications from MitraClip indicate that this solution will not be appropriate in all cases. Among EVEREST II participants, 21% of the MitraClip patient cohort underwent surgical revision within one year. In addition, MitraClip efficacy in the larger FMR population was unclear, an issue that is being explored in the current COAPT trial. Finally, surgeons have limited ability to revise a clipped valve as a patient’s MVR disease progresses. Patients may safely undergo surgical reintervention if the clip fails, but further transcatheter approaches may not be an option.

In short, Back Bay learned that the limitation of MitraClip is that it does not completely eliminate MVR, and there is no way to identify if the ventricle will remodel.

Despite these issues, MitraClip has been used in 50,000 patients worldwide and generated annual sales more than $250 million. Even with so many questions, the MitraClip device has gained high utilization—pointing to the unmet needs of MVR patients.

Pipeline

Both the positive and the negative lessons from MitraClip highlight the need for additional treatment options—and the financial opportunity that these other options will present—as well as unanswered questions that need to
be addressed. These questions present themselves clinically, as doctors and patients confront individual cases and select a treatment strategy, but researchers also deal with these same questions as they aim to develop different solutions to the problem, and decide where to allocate resources not for treatment but for research.

The first question is one of overall strategy: whether to repair or replace the mitral valve. As is often the case with medical innovation, identifying patient disease characteristics and matching them to the appropriate technique is an ongoing debate. In many cases, experts believe that it may be good to start with repair and save the replacement option for future intervention.23

But simply deciding to repair or replace is only the beginning. At the close of 2017, at least twenty-six companies focused on TMVr (repair), each offering different approaches to the mitral valve, including direct annuloplasty, coronary sinus contraction, and chordal repair:

**Adjustable Annuloplasty Rings** – Various pipeline transcatheter approaches to mitral valve repair have been modeled after surgical annuloplasty, which reduces the size of the valve annulus to improve valve coaptation. Multiple annuloplasty designs have been developed and introduced: Carillon (by Cardiac Dimensions (Carillon))

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<td>Edwards - Valtech (Cardioband)</td>
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<td>Mitralign (MPAS)</td>
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<td>CHORDAL REPAIR EDGE TO EDGE</td>
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<td>Medtronic - Twelve (Twelve TMVR System)</td>
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Dimensions, Inc), Cardioband (Valtech Cardio – now Edwards Lifesciences) and Bident (MPAS).

**Chordal Repair Devices** – The mitral valve leaflets are tethered to the ventricle by chords, and when chord rupture is the cause of MVR, chordal repair devices are indicated. DS1000 (NeoChord) and the Harpoon System (Harpoon Medical – now Edwards Lifesciences) have developed devices to replace ruptured chords.

**Replacement Valves** - On the more aggressive side, there are currently at least twenty-eight companies developing mitral valve replacement devices to address MVR patients where repair may not be adequate or appropriate. Replacement requires delivering a bulkier implant to the mitral valve location and lifelong anti-coagulation for the patient, making it less attractive for some surgeons and patients.\(^\text{24}\)

Given the bulkiness of the implant and the anatomy of the mitral valve, MV replacement is acknowledged to be more difficult than TAVR. This point is sometimes overlooked when analysts breathlessly extrapolate the potential of the TMVR market from the TAVR market. The most direct route to the mitral and aortic valve is transapical, which requires a mini-thoracotomy—not a small procedure—and runs the risk of ventricular injury and bleeding complications. Although TAVR was pioneered with a transapical approach, a transfemoral approach (deploying the valve through the groin) quickly became more common as lower profile devices were introduced.

But more so than the aortic valve, navigating the journey from the groin to the mitral valve requires considerable technical acumen, especially the final step traversing the septum separating the right and left atrium (transseptal route). Once the replacement device penetrates the septum, the delivery system must make a sharp turn to access the mitral valve.
Despite these challenges, the CardiAQ device (CardiAQ Valve Technologies—now Edwards Lifesciences) valve has demonstrated that transfemoral replacement is feasible\(^2\) and many others are following in their footsteps.

In addition, there are some patients for whom repair or replacement of the mitral valve does not improve regurgitation symptoms due to concurrent tricuspid valve disease.\(^2\) It is estimated that nearly 50% of patients with mitral regurgitation have moderate to severe tricuspid regurgitation,\(^2\) and some companies, such as Mitralign, have designed annuloplasty repair technology to accommodate transcatheter approaches to the mitral and tricuspid valves together. Whether transcatheter applications to the tricuspid valve follow a similar trajectory as mitral valve repair and replacement remains to be seen.

No one expects “one size to fit all” in the complex mitral valve space. It is possible that patients may need several interventions, performed either in combination or in series, over the course of their lifetime.

**Place Your Bets, Everyone**

M&A activity over time reflects the interplay of these factors, including a large addressable patient population, the emergence of new techniques, lessons learned from TAVR, and ongoing questions of repair versus replace.
• In 2012, the Sorin Group (now LivaNova) made a $5.4 million minority investment with an option-to-buy in the TMVR company HighLife SAS\textsuperscript{28} whose founder was TAVR pioneer Georg Börtlein, the co-founder of CoreValve (now Medtronic).

• Three years later, Edwards, Medtronic, and Boston Scientific each paid upfront fees ranging from $200 to $428 million to acquire their own TMVR company (CardiAQ Valve Technologies, Twelve, and MValve, respectively—the last being in the form of an investment option). Abbott expanded their portfolio with two TMVR companies (Tendyne and Cephea Valve Technologies).

At the time of acquisition, most of these targets had performed only feasibility studies and lacked robust clinical data. It was not a coincidence that TAVR sales hit $1 billion worldwide this same year.

While 2015 was the year of TMVR acquisition, 2017 showed a resurgence of interest—and investment—in the more conservative approach of valve repair:

• After being courted and successfully fending off a $900 million acquisition offer from HeartWare,\textsuperscript{29} Valtech's Cardioband annuloplasty device was acquired by Edwards Lifesciences in 2017 for an upfront payment of $340 million, with a total deal value of $690 million.\textsuperscript{30}

• Edwards further solidified their position in the mitral valve space by acquiring the DMR-focused chordal surgical mitral valve repair startup Harpoon Medical for ~$100M upfront.\textsuperscript{31}
Boston Scientific, who has also declared strong intentions to enter and lead the TAVR market, made a $90 million equity investment in Millipede for their TMVr technology. With an option to acquire the company after completion of FIM study, the total deal value came to $540 million.32

What’s Next: Building a Toolbox for the Long Term

Mitral valve disease is a tough problem. Many interventional cardiologists and cardiac surgeons believe that the key to better outcomes is defining the appropriate transcatheter therapies for a patient’s specific disease and anatomy.

The acquisitions of the past three years, especially by Edwards, show that forward-looking companies are answering the call and building a “toolbox” approach for treating MVR. One cardiac surgeon noted to Back Bay that European centers have already tried a combined approach—with MitraClip and Cardioband, MitraClip and NeoChord, MitraClip and Carillon. From the perspective of both companies and patients, combined solutions that are designed to work together would be preferable.

We expect other large manufacturers to similarly diversify their portfolio to offer multiple treatment options to the physician, creating further acquisition opportunities for the remaining pipeline companies.

Companies also need to consider that this is a long game. Head-to-head trials comparing standard surgical and medical management with TMVR/r are needed.
needed to expand the addressable patient population to lower-risk patients and increase market size. In addition, these solutions do not come inexpensively and combination therapy will only drive up prices. In the current reimbursement climate, this means companies must demonstrate superior outcomes and therefore should carefully plan which patients will be studied with which combinatorial approach.

**Conclusion**

Will transcatheter mitral valve technologies continue to fire up medtech and drive unprecedented early-stage acquisition and high valuation? Some medical device companies are betting on it and the industry is on alert.

Despite knowledge gaps in efficacy, durability, safety and usability, these new technologies continue to drive a new paradigm in medical device transactions. Large clinical trials are needed to build knowledge and answer questions—questions which in the past would have been answered before heat was generated. Still, we have largely reached consensus that a transfemoral approach is the preferred mechanism. Back Bay expects most of existing technologies using a transapical approach to convert to transfemoral.

Further, we believe that device manufacturers will broaden their view moving forward to building a "toolbox" of various TMVR/r technologies with different approaches (e.g., annuloplasty, chordal repair etc.) to address the needs of the heterogenous mitral valve population.

All of this should continue to shape and drive large device manufacturers to continue to place bets on pipeline companies. As additional data becomes available and the field matures, valuations will likely rise, as will expectations for clinical success. And looking even further down the road, tricuspid valves will likely be the natural extension of additional deal activity in the heart-valve space, though given the much smaller tricuspid valve disease population and need, mitral valve technologies will remain the "poster child" for cardiovascular medical devices.

“**In the future, careful patient selection will play a fundamental role in identifying specific patients most likely to benefit from TMVI vs. TMVR vs. mitral valve surgeries.**

. . . Is some procedures may become complementary (i.e. surgical mitral annuloplasty and subsequent TMVI, or a combination of different TMVR approaches in the same patients with staged procedures). . . However, timing, indications and sequence of procedures is speculative at the moment.”

Maisano, et al. 2015

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“For the next wave of acquisitions, the bar is going to be higher for reducing more risk before somebody says, okay, this is one that’s worth adding to my portfolio, unless the company is interested in picking a really early stage company that can be then included in the R&D pool internally.”

TMVR Company Executive

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Maisano, et al. 2015

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Maisano, et al. 2015
About

Back Bay Life Science Advisors

EXPERTS IN CARDIOVASCULAR INNOVATION

Back Bay Life Science Advisors provides strategy consulting and transaction advisory services to the life science industry. Our expertise spans the continuum of stage, sector, and geography, across every therapeutic class. Back Bay works with local and global biopharmaceutical and medical technology sectors on both the buy and sell side of transaction execution, from gleam-in-the-eye preclinical technology platforms to $2 billion established brands. We have deep knowledge of the cardiovascular and vascular disease continuum and have carried out assignment for both large and small companies.

Some of the assignments for our major device and biopharma companies include developing structural heart and heart failure innovation strategies; developing vision and strategy for hospital-based vascular and cardiovascular care franchises; and leading diligence efforts for major cardiovascular acquisitions.

We also have a strong roster of entrepreneurial, venture-backed clients who are developing cutting-edge therapies and diagnostics in areas such as ventricular and chronic limb ischemia, venous thromboembolism, valve disease, heart failure, myocardial ischemia, cerebrovascular and peripheral vascular aneurysms, hypertension, and rhythm disorders.

Meet our life science experts at bblsa.com.

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