Medical Technology

A Toolbox Will Be Needed to Treat Mitral Valve Disease: Repair and Replacement

**Bottom Line:** In September 2015 we wrote a deep dive report on transcatheter mitral valve replacement therapies and, while we continue to be enthusiastic about the mitral valve replacement market, it is clear to us that treatment will require a toolbox, including replacement and repair products (see Exhibit 1). Edwards Lifesciences’ acquisition of Valtech for $340 mm, plus $350 mm in additional milestone payments, underscores the investments that are being made in bringing to market new technologies for patients. This is an enormous market, with 4.1 million people with moderate to severe mitral regurgitation in the U.S. alone. While EW is furthest along with its investment, ABT, BSX, and MDT are not far behind, along with multiple private companies. We expect 2017 to be a significant year in device development and in building clinical data support. Thus, in this deep-dive report we provide investors the roadmap to the next medical technology wave.

**Key Points**

- In September 2015 we wrote a transcatheter mitral valve replacement (TMVR) deep-dive report entitled “TMVR, It’s Gonna Be Big.” A little more than a year later and we are still excited about the TMVR market potential, which we update in this report, but we also turn our attention to mitral valve repair.

- We have learned some things along the way that make the timing of this report important: 1) given the complexity of mitral valve disease, one size and approach will not fit all; 2) this is a big, big market, with 4.1 million people with moderate to severe mitral regurgitation in the U.S. alone; 3) given the complexity of the disease it will take time for minimally invasive surgical approaches to reach the commercial market, probably longer than we thought a year ago; and 4) Edwards Lifesciences’ November 28, 2016 acquisition of Valtech for $340 million, plus $350 million in additional milestone payments, underscores the investments that are being made in bringing to market new technologies for patients.

- We are just at the very beginning, with many of these companies in the early stages of development. In the U.S., Abbott’s MitraClip is the only mitral valve repair device with FDA approval (October 2013), but there are several companies with CE Mark approval including NeoChord, Mitralign, Valtech, and Cardiac Dimensions. Even in its infancy, we are encouraged by the industry’s progress. (See Exhibit 1.)

- One of the things that became apparent to us is that minimally invasive treatment of mitral valve disease is not a one-size-fits-all approach. EW is likely furthest along with its investment, but followed closely by ABT, BSX, and MDT. One thing is clear: 2017 will be a significant year in device development and building clinical data support.

Please refer to pages 27 to 30 for Important Disclosures, including Analyst’s Certification.
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A Tool Box Will Be Needed to Treat Mitral Valve Disease: Repair and Replacement

In September 2015 we wrote a transcatheter mitral valve replacement (TMVR) deep-dive report entitled “TMVR, It’s Gonna Be Big.” A little over a year later and we are still excited about the TMVR market potential, which we update in this report, but we also turn our attention to mitral valve repair. We have learned some things along the way that make the timing of this report important: 1) given the complexity of mitral valve disease, one size and approach will not fit all; 2) this is a big, big market, with 4.1 million people with moderate to severe mitral regurgitation in the U.S. alone; 3) given the complexity of the disease it will take time for minimally invasive surgical approaches to reach the commercial market, probably longer than we thought a year ago; and 4) Edwards Lifesciences’ November 28, 2016 acquisition of Valtech for $340 million, plus $350 million in additional milestone payments, underscores the investments that are being made to bring to market new technologies for patients. What has been suggested throughout the literature is that repair has a lower perioperative mortality rate while replacement seems to demonstrate longer-term effectiveness, including a decreased risk in mitral regurgitation (MR) recurrence. Companies will need both in their toolbox to address mitral valve disease.

We are just at the very beginning, with many of these companies in the early stages of development. To start to paint the picture, traditional mitral valve repair is performed through an open procedure by a combination of surgical leaflet repair, chordal repair, and annuloplasty ring implantation. This procedure is extremely complex, but the shifting landscape to a minimally invasive approach has the potential to be a safer alternative by eliminating the need for cardiopulmonary bypass, allowing for less blood loss and faster time to ambulation, and expanding the market to candidates that were previously excluded from surgical treatment options.

In comparing mitral valve repair to replacement, the reasons for choosing repair over replacement include lower operative mortality, and improved left ventricular function without left ventricle obstruction (LVOT). Further, by making repair the first line of treatment, new minimally invasive devices that preserve the anatomy for additional procedures (e.g., replacement) will allow surgeons to address problems earlier in the disease continuum. As the influx of MR devices improve in safety and efficacy, they are crossing barriers between surgical approaches, disease classification, and intended use.

Below is a detailed list of the myriad of devices that are creating traction on both an academic and commercial level and the dynamics of an overly complicated disease that will shape the mitral valve repair industry. In the U.S., Abbott’s MitraClip is the only mitral valve repair device with FDA approval (October 2013), but several companies have CE Mark approval, including NeoChord, Mitralign, Valtech, and Cardiac Dimensions. Even in its infancy, we are encouraged by the industry’s progress.
Exhibit 1: Mitral Valve Repair Devices

<table>
<thead>
<tr>
<th>Company</th>
<th>Device</th>
<th>Regurgitation</th>
<th>Intended Treatment</th>
<th>Surgical / Percutaneous Approach</th>
<th>FDA</th>
<th>CE Mark</th>
<th>Clinical Pathway</th>
<th>No. of Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott</td>
<td>MitraClip</td>
<td>DMR / FRMR</td>
<td>Edge-to-Edge Repair</td>
<td>Transapical</td>
<td>10/2013</td>
<td>03/2008</td>
<td>MitraClip is currently used for the treatment of DMR patients, and management is looking to expand the indication to include FMR patients with its COAPT trial (n=110). As of 10/24/16, the trial has enrolled 482 patients and enrollment is expected to be completed mid-2017, with 1-year data expected to be submitted to the FDA in 2018E.</td>
<td>40,000+</td>
</tr>
<tr>
<td>Edwards Lifesciences</td>
<td>PASCAL</td>
<td>DMR / FRMR</td>
<td>Edge-to-Edge Repair</td>
<td>Transapical</td>
<td>--</td>
<td>--</td>
<td>An EU first-in-human early feasibility study is expected to begin 2017E, with data from this study used to support CE Mark study</td>
<td>Multiple (early stages)</td>
</tr>
<tr>
<td>NeoChord</td>
<td>DST1000</td>
<td>DMR</td>
<td>Chordae Replacement</td>
<td>Transapical</td>
<td>12/2012</td>
<td>--</td>
<td>The RECHORD trial (n=385) is planned for enrolment in 4Q16, with 1-year follow-up data expected 2018E.</td>
<td>550+</td>
</tr>
<tr>
<td>Haspion Medical (Edwards Lifesciences)</td>
<td>Haspion</td>
<td>DMR</td>
<td>Chordae Replacement</td>
<td>Transapical</td>
<td>--</td>
<td>--</td>
<td>The EU study (n=27) is in progress with expected CE Mark approval in 2017E</td>
<td>40+</td>
</tr>
<tr>
<td>Mitril</td>
<td>MPAS</td>
<td>FRMR</td>
<td>Direct Annuloplasty</td>
<td>Transapical</td>
<td>02/2016</td>
<td>--</td>
<td>Although its Mitril MPAS Percutaneous Annuloplasty System (MPAS) is CE Mark approved, in the U.S. management has shifted resources towards a tricuspid repair product.</td>
<td>NA</td>
</tr>
<tr>
<td>Valtech (Edwards Lifesciences)</td>
<td>CardioBand</td>
<td>FRMR</td>
<td>Direct Annuloplasty</td>
<td>Transapical</td>
<td>09/2015</td>
<td>--</td>
<td>U.S. pivotal trial is expected to begin enrolment in 2017E</td>
<td>125+</td>
</tr>
<tr>
<td>Valvare</td>
<td>Amend</td>
<td>FRMR</td>
<td>Direct Annuloplasty</td>
<td>Transapical</td>
<td>--</td>
<td>--</td>
<td>Initial clinical experience (n=5) will be used to support proposal for AMENDTM early feasibility study, which is expected to begin enrolment 2017E</td>
<td>6</td>
</tr>
<tr>
<td>Millipede</td>
<td>IRIS</td>
<td>FRMR</td>
<td>Direct Annuloplasty</td>
<td>Transapical</td>
<td>--</td>
<td>--</td>
<td>Initial clinical experience (n=9) is expected to have 1-year data in 2017E (note: all patients implanted through open surgery)</td>
<td>9</td>
</tr>
<tr>
<td>Ancora Heart</td>
<td>AccuCinch</td>
<td>FRMR</td>
<td>Direct Annuloplasty</td>
<td>Transapical</td>
<td>--</td>
<td>--</td>
<td>CRICH 2+ feasibility study (n=4) with the redesigned device and protocol began April 2016, which is expected to be followed by an IDE early feasibility study in mid-2017E</td>
<td>7</td>
</tr>
<tr>
<td>MVRx</td>
<td>AIRTO</td>
<td>FRMR</td>
<td>Indirect Annuloplasty</td>
<td>Transapical &amp; Tranapigage</td>
<td>--</td>
<td>--</td>
<td>Data for Phase II of the MAVERIC trial (n=115) is scheduled to be presented in May 2017E (EuroPCR). Phase I data (n=11) showed 85% of patients had MRI grade &lt; 3 at 1-year, an improvement from baseline 9%.</td>
<td>19</td>
</tr>
<tr>
<td>Cardiac Dimensions</td>
<td>Cardin</td>
<td>FRMR</td>
<td>Indirect Annuloplasty</td>
<td>Tranapigage</td>
<td>09/2011</td>
<td>--</td>
<td>U.S. pivotal trial (n=400) is expected to begin 3-year enrolment process in 1H17E, with 1-year follow-up data expected in 2021E</td>
<td>700+</td>
</tr>
<tr>
<td>Mardil Medical</td>
<td>VenTouch</td>
<td>FRMR</td>
<td>Ventricular Remodeling</td>
<td>Minithoracotomy</td>
<td>--</td>
<td>--</td>
<td>Enrollment in the first-in-human clinical trial (n=15) is expected to be completed by mid-2017E</td>
<td>17</td>
</tr>
</tbody>
</table>

Source: Company reports, TCT 2016, ClinicalTrials.gov, and BMO Capital Markets.

Exhibit 2: Indications for Mitral Valve Repair, Replacement, and Medical Therapy

<table>
<thead>
<tr>
<th>Indications</th>
<th>Clinical Presentation</th>
<th>Causes</th>
<th>Current Treatment</th>
<th>Population Effected</th>
<th>Target For Transcatheter Mitral Valve Replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral Regurgitation</td>
<td>Leakage of the blood from the left ventricle into the left atrium during systole.</td>
<td>Mithromatos Degeneration; Chordal Rupture; RHEUMATIC HEART DISEASE; Infective Endocarditis; Coronary Artery Disease; Cardiomyopathy.</td>
<td>Mitrval Valve Repair; Mitrval Valve Replacement.</td>
<td>United States: 6.6 million, including 4 million with moderate to severe mitral regurgitation.</td>
<td>Yes</td>
</tr>
<tr>
<td>Functional Mitral Regurgitation</td>
<td>Incomplete coaptation of the leaflets due to heart disease, resulting from left ventricle being enlarged or displaced, pulling the valve out of alignment.</td>
<td>Ischemic dilated cardiomyopathy (Atrial enlargement secondary to left ventricular dilation); Papillary muscle displacement due to left ventricular remodeling, which results in tethering and excess tenting of the leaflet.</td>
<td>Mitrval annuloplasty [MAP] combined with subvalvular procedures.</td>
<td>United States: 5 million with heart failure, including 2.6 million with functional MR (or 50% of total mitral regurgitation population).</td>
<td>Yes</td>
</tr>
<tr>
<td>Degenerative Mitral Regurgitation</td>
<td>Flailing leaflet or torn chordal tendinace.</td>
<td>These patients make up the majority of surgical patients, totalling 30% of mitral regurgitation population.</td>
<td>--</td>
<td>Worldwide: 20 million worldwide.</td>
<td>Yes</td>
</tr>
<tr>
<td>Mitral Valve Prolapse</td>
<td>Billowing of one or both mitral leaflets into the left atrium during systole.</td>
<td>Mithromatos Valve Disease; Normal Mitrval Valve Leafle.</td>
<td>Non-Surgical Treatment Options.</td>
<td>--</td>
<td>No</td>
</tr>
<tr>
<td>Mitral Stenosis</td>
<td>Narrowing of the mitral valve orifice, not allowing for the left ventricle to fill properly during diastole.</td>
<td>Rheumatic Disease; Calcification of mitral annulus; infective endocarditis; Sepsis; Rheumatoid Arthritis.</td>
<td>Valveplasty.</td>
<td>Worldwide: 15.6 million people with rheumatic heart disease, including 282,000 new cases per year.</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Mitral Regurgitation is a Large Market Opportunity

Mitral regurgitation affects nearly 7 million people in the U.S., or 2% of the population, with roughly the same number in Europe, including 4.1 million suffering from moderate to severe MR and 250,000 new patients added each year. This creates a sizeable patient pool, or one that affects nearly 4.5x more elderly U.S. patients (9.3%) than aortic valve disease (2.0%).

Exhibit 3: The U.S. Mitral Valve Market Opportunity

Despite the incidence rate of heart valve disease, the penetration rate of heart valve surgery is remarkably low. Of the 4.1 million patients with moderate to severe mitral regurgitation in the U.S., only about 20%, or 1.67 million, are eligible for treatment. However, 49% of the eligible population are at high risk for surgery, 49% have the appropriate indications, but are not referred, and only 2% actually undergo a surgical intervention, or about 34,000 individuals.

Exhibit 4: Mix of Mitral Valve Patients—Treated, Not Referred

There are two primary types of MR: 1) degenerative MR or DMR, considered to be structural or degenerative in nature, is typified by a diseased valve that ceases to close properly; and 2) functional MR or FMR, considered to be a ventricular disease, exists when the valve is basically normal, but the surrounding structures are prohibiting it from functioning normally (e.g., the left ventricle may be displaced or enlarged, throwing off the alignment of the valve, or there may be problems with the
papillary muscles or mitral annulus). In either case, the disease leads to chronic heart failure, stroke, and death.

- While the majority of mitral regurgitation patients that walk into a physician’s office have functional mitral regurgitation (FMR; ~75%) versus degenerative mitral regurgitation (DMR; ~25%), very few FMR patients are treated surgically. Of the surgical MR procedures that are performed each year (or 2% of the patient pool), 85% of them are for patients with DMR and 15% for FMR.

- The surgical repair procedure is actually very successful in DMR patients. For example, in the EVEREST II clinical trial which evaluated Abbott’s MitraClip versus surgery, at five years 86% of DMR surgical patients were event free, as defined as freedom from mortality and reintervention, while only 55% of FMR surgical patients were event free. This creates a real need for therapeutic solutions for the FMR population, and today the first line of treatment for FMR patients is to treat the coronary artery disease (CAD) or heart failure, with the possible consideration for CRT therapy. Thus given the size of the FMR patient pool (1.6-2.8 million people in the U.S.) and the associated doubling of mortality in patients with mild to severe mitral regurgitation following a myocardial infarction, it is not surprising that most of the new repair and replacement technology efforts target the FMR population.

- In thinking about repair versus replacement, and the benefits of a toolbox approach, a study published in The New England Journal of Medicine comparing FMR repair and replacement patients (n=251) demonstrated no significant difference in left ventricular reverse remodeling or survival at 12 months (hazard ratio of 0.79, p-value=0.45), but repair procedures demonstrated a 30% higher rate of recurrent mitral valve regurgitation versus replacement (32.6% versus 2.3%, p<0.001)\(^1\). This too provides food for thought as the therapy evolves.

- Many of the early designs appear to be predicated on finding the easiest and fastest way to the mitral valve, with different access routes (similar to TAVR). For patients with degenerative mitral regurgitation (DMR), a disease of the valve, a transapical (TA) approach makes sense, as the left ventricle might just be healthy enough to withstand the trauma. For patients with functional mitral regurgitation (FMR), where the disease is not a valve problem but more of a LV remodeling issue and the left ventricle is already compromised, there are several approaches, including: 1) a transseptal approach; 2) a transjugular approach, which can be used for procedures when the transapical approach is considered dangerous due to poor left ventricular functionality; and 3) a mini-thoracotomy, which provides a compromise between surgical and transcatheter procedures; the incision below the armpit prevents the need to split the breast bone as in normal surgical procedure without needing to rely on transcatheter devices.

We briefly review the current surgical treatments for MR, which provide the groundwork for minimally invasive techniques, including: 1) leaflet resection; 2) chordal replacement; and 3) annuloplasty. In accordance to damaged or deteriorated valve leaflets, surgeons will trim, shape, and rebuild the leaflets using traditional suturing techniques. The same holds true for chordal replacement with sutures that place tension on the leaflet to prevent prolapse during systole. This practice can be challenging since it is hard to measure and judge the exact length of a chord as well as anchoring it to limited access sites. It should be noted that for any of these techniques, the arduous process is performed as an open procedure where the heart must be placed on cardiopulmonary bypass or a heart-lung machine and an incision is made in the left atrium.

Thus, annuloplasty ring implantation has become the gold standard to repair the mitral valve surgically because it is used to reshape and minimize the annulus by supporting the valve. Annuloplasty procedures are used to treat the mitral valve for long-term preservation of LV function, demonstrating low post-operative mortality, improvement in heart failure symptoms, and improvement in ventricular size and ejection fraction\(^2\).

Although annuloplasty rings differ based on geometry and rigidity, the market-leading ring is the Carpentier-Edwards Physio II (FDA approved September 2008) from Edwards Lifesciences. The ring was co-invented by Dr. Carpentier, who pioneered the first annuloplasty ring in 1968 and has since evolved the geometry, material, and surgical technique to eliminate mitral regurgitation. Other major annuloplasty ring manufacturers include Medtronic and St. Jude Medical.

While annuloplasty procedures are effective, the procedure is cumbersome, with the anchoring procedure using interrupted sutures (stitches that are not connected to each other), and one of the major hurdles is correctly sizing the ring to the annulus, frequently resulting in an undersized ring. They can be used in both DMR and FMR patients, with varying degrees of success. In DMR patients, they show some degree of dilation and therefore can be associated with better durability than ringless repair. In FMR patients, reshaping the annulus does not directly address the fact that the LV is aberrant and it has actually been shown that 25-30% of severe MR patients have recurrent MR post-procedure.

There is much debate on the pros and cons of the rigidity of the ring but we do want to make one point clear: it is not that all annuloplasty devices do not work; that is not what we are trying to say. Instead, they likely will need to be supplemented by the development of additional techniques.

Exhibit 5: Carpentier-Edwards Physio II Annuloplasty Ring

Source: Image courtesy of Edwards Lifesciences.

Mitral valve prolapse, a disease that displaces a mitral valve leaflet, is the most common finding in patients with degenerative valve disease and is not a target for minimally invasive techniques. It is defined by a spectrum of lesions that ranges from simple chordal rupture (likely the prolapse of an isolated segment, also known as fibroelastic deficiency) to a more severe form, or multi-segment prolapse (likely involving one or both leaflets caused by significant excess tissue and large annular size, also known as Barlow’s Disease).\(^3\) Depending on the severity of the mitral valve prolapse it results in varying degrees of mitral regurgitation, which can either be treated with medical management or more advanced surgical techniques, but is likely not a target for transcatheter mitral valve technologies.

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\(^2\) Audrey H. Wu, MD, MPH, Keith D. Aaronson, MD, MS, Steven F. Bolling, MD, FACC, Francis D. Pagani, MD, PhD, FACC, Kathy Welch, MS, MPH, Todd M. Koelling, MD, FACC. “Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction”. JACC. 2005: 45 (3), 381-387.

Mitrail stenosis is a valvular disease that narrows the opening of the valve; similar to aortic stenosis, it may benefit from TMVR devices. It is defined as a narrowing of the mitral valve opening that does not allow for the left ventricle to fill properly during diastole. It can be caused by rheumatic disease, calcification of the mitral annulus, infective endocarditis, lupus, and rheumatic arthritis. The current treatment of choice is valvuloplasty, in which a very small, narrow catheter is placed in the valve and is opened, such that the balloon at the tip of the catheter is inflated until the leaflets (flaps) of the valve are opened. This too is an application for TMVR technologies, but with a smaller patient population: 2.8% of patients 75+ in the U.S. have aortic stenosis, versus 0.2% with mitral stenosis.

Repair Is the First Line Treatment Over Replacement

One of the things that became very apparent to us in writing this report is that minimally invasive treatment of mitral valve disease is not a one-size-fits-all approach. Walking out of Edwards Lifesciences’ 2016 analyst meeting it hits us that even this company, which is the preeminent valve manufacturer, has multiple shots on goal to address the disease. Not only do physicians have the opportunity to treat several anatomical abnormalities at the same time (e.g., to combine leaflet and annulus repair in the same procedure), but also to choose the approach (e.g., transseptal versus transapical) and the treatment modality (e.g., repair versus replacement). What follows is a brief description of the devices as we understand them today, but one thing is clear: 2017 will be a significant year in device development and building clinical data support.

Abbott’s MitraClip was the first FDA approved (October 2013) device for percutaneous mitral valve repair to treat high-risk DMR. The device is implanted through a transseptal approach and mimics an edge-to-edge repair by clipping the anterior and posterior leaflets together, forming a double orifice. FDA approval was based on the EVEREST II study (n=279), which randomized 2:1 MitraClip versus conventional surgery. The study demonstrated favorable LV remodeling at one year, as well as a reduction in re-hospitalizations for heart failure at one year of 73% (p<0.0001). The limitations of the device are that it seems to be less effective than conventional surgery at reducing mitral regurgitation, resulting in a higher level of residual MR. This is likely the reason for the FDA to compose very specific language in the MitraClip indications for use:

“The MitraClip Clip Delivery System is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR ≥ 3+) due to primary abnormality of the mitral apparatus [degenerative MR] in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation.”

Improvements have been made to the next generation device, the MitraClip NT; with leaflet grasping and engagement that is improved with larger grip angle and enhanced steering control. This new device eases medial movements and grasping efficacy, leading to better tension especially in DMR with prolapse.
While the approval is for DMR, some data in the EVEREST II study for FMR patients demonstrate a reduction in MR in 82% of the patients (n=48) to ≤2+ at three years (on a scale of 0-4, with 3 and 4 considered to be severe regurgitation), whereas in the surgical FMR cohort 100% of the patients reached ≤2+ at three years. In an effort to expand utilization of the MitraClip device to FMR patients, Abbott is running the COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation). The trial began enrollment in August 2012 (n=610) and as of October, 2016, 482 patients have been enrolled in the clinical trial; while the process has been slow it has been steady and we expect full enrollment to be completed mid-2017 followed by FDA approval 2019E. The purpose of the COAPT trial is to confirm that MitraClip is a safe and effective mode of treatment for FMR in symptomatic heart failure subjects who are not considered appropriate candidates for mitral valve surgery. The primary endpoint of the study is recurrent hospitalization for heart failure at two years. At TCT 2016 in Washington D.C., data was presented on the first COAPT patients (n=50) demonstrating a 94% implant success rate and with 38% of patients requiring two MitraClip devices. At one-year follow-up, 29% of patients had 26 heart failure events that required hospitalization and two patients required non-elective surgery for device-related complications. Mitral regurgitation severity was reduced, demonstrating an MR score of ≤2 (on a scale of 0-4) in 83.3% of the patients versus 0% before treatment.

Clinical data continues to build for using MitraClip to treat FMR, and there are currently five clinical trials in-progress to help support utilizing the device to treat mitral valve disease.

### Exhibit 7: MitraClip In-Progress FMR Clinical Trials

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Enrolled as of 10/24/16</th>
<th>Total Expected Enrollment</th>
<th>Primary Efficacy Endpoint</th>
<th>Primary Safety Endpoint</th>
<th>Primary Endpoint Timeline</th>
<th>Expected Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>COAPT</td>
<td>482</td>
<td>610</td>
<td>Recurrent heart failure hospitalization</td>
<td>Device detachment, embolization, non-elective surgery, LVAD</td>
<td>2 years</td>
<td>2018E</td>
</tr>
<tr>
<td>MITRA-FR</td>
<td>231</td>
<td>288</td>
<td>Death or recurrent heart failure hospitalization</td>
<td>--</td>
<td>1 year</td>
<td>2017E</td>
</tr>
<tr>
<td>RESHAPE-HF-2</td>
<td>132</td>
<td>380</td>
<td>Death or recurrent heart failure hospitalization</td>
<td>Mortality, stroke, MI, non-elective surgery</td>
<td>1 year</td>
<td>TBD</td>
</tr>
<tr>
<td>MATTERHORN</td>
<td>31</td>
<td>210</td>
<td>Death, heart failure hospitalization, reintervention, or stroke</td>
<td>Major adverse events at 30 days</td>
<td>1 year</td>
<td>2017E</td>
</tr>
<tr>
<td>EVOLVE-HF</td>
<td>0</td>
<td>168</td>
<td>Improvement in 6-minute walk test</td>
<td>--</td>
<td>6 months</td>
<td>TBD</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>876</strong></td>
<td><strong>1656</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: TCT 2016, Clinicaltrials.gov.
As the MitraClip’s edge-to-edge repair only addresses one aspect of MR, we are starting to see the device used in conjunction with other repair devices (e.g., annuloplasty rings) as well as multiple MitraClip devices used in one procedure (e.g., improving the functional outcome by treating leaflet perforation and stabilizing the first clip). Looking forward, if repair is seen as a step before replacement, the MitraClip may have a disadvantage. Although the frequency of reintervention is low, surgeons can face difficulties opening the clip, causing further damage to the leaflets. Ultimately, surgical replacement may be the only available remedy to the damaged leaflets as the clip itself prevents transcatheter replacement from being a viable option.

The DS1000 from NeoChord is an implantable artificial chordae used to replace existing degenerated and damaged chordae. These chords are sutures that are referred to as neochords and are suspended in tension by anchoring to the prolapsed leaflet and apex of the left ventricle. Chordae replacement is not a new technique as surgeons have been repairing MR through an open heart approach for years but the novelty of the DS1000 is driven by a minimally invasive approach that eliminates the need to place the patient on bypass. The device utilizes a transapical approach, meaning a small incision is made between the ribs and the DS1000 penetrates the heart wall through its left ventricle, minimizing trauma to the heart while it remains in a beating state. Additional benefits of this approach include the preservation of anatomy by eliminating the need for leaflet resection, which is traditionally done in other mitral valve repair techniques. NeoChord received CE Mark approval December 2012 and published data March 2014 from the TACT trial (N=68) reporting that off-pump transapical implantation of the artificial chordae to treat MR is technically safe and feasible (90% of patients reported MR grade ≤ 2 at one-year follow-up). Looking forward, NeoChord kicked off its U.S. pivotal study called ReChord by enrolling its first patient on November 9, 2016. The study is approved to enroll up to 585 subjects at up to 20 U.S. centers. The study’s primary endpoint will be to evaluate major adverse events for traditional open heart mitral repair versus off pump NeoChord use and serve as the basis for receiving FDA approval and expanding its footprint to the U.S.

Exhibit 8: NeoChord DS1000

Source: Image Courtesy of NeoChord, Inc. All rights reserved.

The Harpoon Mitral Valve Repair System from Harpoon Medical is another artificial chordae system used to treat DMR and severe prolapse. A 3mm-diameter shaft is inserted into the left ventricle through a transapical approach and once the device is in the desired position against the prolapsed leaflet, the surgeon pulls a trigger and a small needle will pierce the leaflet, releasing a self-forming anchor attached to an artificial chordae. The device is retracted and a second knot is tied with a Teflon pledget on the epicardium of the insertion site. The artificial chordae can be tightened to increase tension or additional cords can be deployed to optimize coaptation of the leaflets. At the TCT Conference in October

2016, Harpoon presented one-year data for its early feasibility study, with 13 patients over two centers. The study’s objective is to evaluate the safety and performance of the device by measuring reduction in MR as the primary endpoint. Patients were implanted with 3-5 artificial chordae and 100% implantation success, but two patients required reoperation at six months due chord malfunctions leading to recurrent regurgitation (both operations were successful). Reducing MR was initially successful, with all 13 subjects seeing their MR scale drop to at least Moderate from Severe, including 11 whose MR grade was none/trace or mild. However, 12-month results did not hold up as two patients saw their MR grade worsen to moderate, and another two required open surgery (an additional two had not reached 12-months as of November 2016).

Looking forward to CE Mark approval, a 27-patient, five-center study is under way to determine if the Harpoon device will reduce MR in DMR patients. The study was funded by Edwards Lifesciences, granting Edwards an option to acquire Harpoon Medical (contingent on the data collected from the trial). If the deal is exercised, the Harpoon will add to Edwards’ suite of mitral valve devices and will create leverage by serving as the first line treatment to its CardiAQ mitral valve replacement.

**Exhibit 9: Harpoon Medical Mitral Valve Repair System**

Source: Harpoon Medical and Leslie Leonard.

### Beyond Surgical Annuloplasty for FMR: Complex Ideas for a Complex Disease

The Carillon Mitral Contour System from Cardiac Dimensions is a transcatheter system that utilizes a coronary sinus cinching technique for percutaneous mitral annuloplasty to treat FMR. The device comprises a distal and proximal anchor that forms a bow shape within the coronary sinus, a vein adjacent to the mitral valve and it applies pressure to remodel the valve, a technique called indirect annuloplasty. The procedure can be performed in less than 40 minutes and has gained popularity among physicians because it accesses the heart percutaneously through the jugular vein, offering a non-puncture procedure, unlike alternative approaches that deliberately pierce the septal wall or apex for point of entry. The novelty of the approach has raised some questions: since the coronary sinus is not in direct contact with the annulus, the number of eligible candidates could be limited due to the varying anatomies of left ventricle, where thicker heart walls could prevent full efficacy of the device.

Carillon received CE Mark approval September 29, 2011 and is one of the leading repair devices, including three published clinical studies: Amadeus, Titan and Titan II. The Titan II trial (n=30; published July 2012) evaluated the safety of coronary sinus mitral annuloplasty as a means to reverse MR regurgitate volume (p<0.05). To expand on these clinical findings, Cardiac Dimensions initiated the REDUCE FMR trial in early 2016. This is a randomized, double-blinded, 25-center trial evaluating FMR in 180 patients to further test the safety and efficacy of the device measuring regurgitate volume reduction at one year. We expect management will use the data to secure OUS reimbursement for the Carillon device. In the U.S., on December 1, 2016 the company received IDE approval to begin a U.S.
pivotal study (n=400), with the primary endpoints expected to evaluate freedom of major adverse events and reduction of regurgitation levels at one year. Patient enrollment should begin in 1H17E and it is expected reach completion in three years, positioning the company to submit its PMA application to the FDA in 2021E, followed by approval in 2022E. We believe that the Carillon’s coronary sinus approach, with its ability to be repositionable, removable, and easy to implant, should make it part of the primary treatment paradigm compared to replacement.

Exhibit 10: Carillon Mitral Contour System

Source: Cardiac Dimensions.

The Mitralign Percutaneous Annuloplasty System (MPAS) is used to treat FMR through a surgical plication approach. The Mitralign enters the body through a transseptal approach and deploys a set of two polyester, gauze-looking pledges that are anchored to the mitral valve leaflet, pulled together by a suture, and locked in place by a stainless steel lock to minimize the annulus. Since cases of FMR are patient specific depending on the left ventricle and mitral valve anatomy, Mitralign can be customized by the location of the pledges, the distance between pledges, and the number of pledges used (typically, two are deployed—one for each leaflet) to reduce regurgitation. MPAS received CE Mark approval February 22, 2016 after demonstrating safety at 30-day and six-month follow up where the cohort (n=45) met the primary endpoint of significant reduction in diastolic volume (p<0.01) and improved 6 minute walk test (p=0.02). In the U.S., management has shifted resources towards a tricuspid repair product, the Trialign System, which is being evaluated in the SCOUT I IDE early feasibility study. It is estimated that 50% of patients with MR also have moderate to severe tricuspid regurgitation\(^5\). The expanded indication is an advantage to Mitralign as repair for both mitral and tricuspid valves can potentially utilize the same technology platform and surgical approach.

Edwards Lifesciences’s November 28, 2016 acquisition of Valtech for $340 million adds flagship Cardioband device to its expanding minimally invasive mitral valve repair portfolio. Cardioband is an innovative reconstruction implant that uses specially designed anchors to connect to the mitral annulus and prevent MR. The device is delivered through a transseptal approach, becoming one of the few annuloplasty rings implanted through a catheter. The novelty of the Cardioband device is driven by an anchor system that deploys anchors one at a time, allowing the surgeon the flexibility to conform segments of the ring-like device to the patient’s anatomy. The procedure is stepwise and can be reversible to optimize the position of the Cardioband; however, it has been criticized for its steep learning curve, which in turn adds unnecessary time to the operation. Cardioband received CE Mark approval September 14, 2015 after it proved to be a safe and effective option to treat FMR. A multicenter trial (n=61) demonstrated 98.4% implant rate and 85.2% device success rate while the death rate was limited to 3% of the cases. Additionally, 92% of patients recorded an MR score ≤ 2 at 24-months. With the CE Mark data, we expect an FDA IDE clinical trial to begin in 2017E. Additionally,

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Edwards Lifesciences is launching a post-market study in Europe to evaluate the use of Cardioband in patients with moderate-to-severe FMR.

The early data suggest Cardioband could be a first line treatment option for MR as it: 1) does not interfere with existing anatomy, which enables valve replacement as a viable secondary option; 2) can be used in combination with leaflet repair; and 3) reduces the chance of ring sizing errors. Despite the device’s complexity, its precision allows the valve to receive future interventions if needed, including unique patient cases where it has also been coupled with MitraClip—but it is still too soon to acknowledge that this combination therapy is a permanent fix.

Valcare’s flagship product Amend, is a percutaneous annuloplasty ring that mimics the surgical gold standard but does not require sutures to anchor the system and reduce MR. Amend is implanted through a transapical approach where the ring is deployed unassembled and rotates itself into a D-shape from inside the lumen of the left atrium. The ring is docked into the desired position using a support arm without the need for bypass and the surgeon releases a set of 12 hidden anchors that reside inside the ring. The anchors are released in quadrants locking two posterior leaflet zones sequentially, followed by two anterior leaflet anchor sets. The two-step deployment system not only allows for fine tune adjustments of the ring to minimize the annulus and increase coaptation, but it also minimizes procedure time as the anchors are attached in groups instead of one at a time. The device is still in its infancy as Valcare has initial clinical experience with six patients. Three patients experienced a reduction in their MR grade to 2 from 4+ at their seven-month follow-up, while the remaining patients reduced their MR grade to 1 from 4+ at five-month follow up. In addition, procedure time was on average 70 minutes, well below the average 120 minutes annuloplasty procedures through open surgery. Valcare plans to submit an IDE application for its U.S. clinical trial in the 1H17E and to begin enrolling patients in 2H17E.

Exhibit 11: Valtech Cardioband

Source: Valtech.

Valcare plans to submit an IDE application for its U.S. clinical trial in 1H17E and to begin enrolling patients in 2H17E.
Millipede is another start-up looking to deliver a percutaneous mitral valve repair solution by using an innovative annuloplasty ring design to optimize annulus sizing. The Millipede IRIS is a collapsible, nitinol, complete ring that creates a zigzag frame similar to the configuration of a collapsible security gate. The ring is deployed through a transseptal approach and anchored to the annulus where it can be adjusted by tightening corkscrew anchors. The device is in its infancy, first implanted in May 2015 in nine patients using an open procedure in which it demonstrated a reduction in annulus diameter on average of 38%. Since the Millipede IRIS can treat both mitral and tricuspid valves, the device has the potential to correct left and right ventricle remodeling that was caused by regurgitation. Looking forward, we expect the Millipede device to enter U.S. clinical trials in 2017 to test the safety and effectiveness of the device in the treatment of FMR—a primary endpoint of recurrent heart failure hospitalizations at 12 months. Building on the theme that one size does not fit all, we note that Millipede’s zigzag design allows it to: 1) be coupled with the MitraClip device; and 2) serve as a platform to help position a replacement valve for a valve-in-Millipede secondary treatment.

MVRx Arto System is an innovative anchoring and delivery system marrying two promising FMR solutions together. The device utilizes a dual catheter system from a transseptal and transjugular approach. The transjugular catheter enters the coronary sinus and bridges across the annulus to intersect with the second transseptal catheter. These guidewires crisscross, allowing for a two-anchor system to create tension across the annulus and minimize the diameter. This design is particularly useful for aggressive left ventricle remodeling where a stand-alone coronary sinus approach may be ineffective due to the distance between the valve opening and the coronary sinus. In addition to this differentiated treatment process, the Arto system also benefits from the advantages of being a completely reversible and repositionable procedure.
Clinically the device is still a proof of concept, but the MAVERIC trial evaluated the safety and feasibility of the Arto system, with MR associated with congestive heart failure. Phase I of the study observed 11 patients with the primary endpoint to determine major adverse events at 30-day follow-up and MR grade reduction. Phase I was completed with no deaths or strokes in the first 30 days, and with all patients experiencing at least one grade reduction in MR at day 30. While early data is limited, Arto will be moving forward with Phase II (n=8) data collection, and we expect a data update at EuroPCR in May 2017E.

**Exhibit 14: MVRx Arto System**

In January 2016 a 15 patient study began evaluating the VenTouch device in patients with FMR; enrolment is expected to be completed mid-2017E.

VenTouch by Mardil Medical attacks left ventricle remodeling by placing a compliant polyester mesh over the exterior of the heart to reduce wall stress and facilitate reverse left ventricle remodeling. A mini-thoracotomy approach is used to deliver the VenTouch by making a small incision in the chest similar to that necessary for a transapical approach but rather than piercing the apex of the LV, the device is deployed over the beating heart. The thin membrane is then inflated with saline fluid placing light pressure to address both muscular and annular abnormalities, reducing septal-lateral dimensions to improve leaflet coaptation. Additionally, physicians can add or subtract fluid at a later stage without making an incision through a remote port. Clinically, the VenTouch system was successfully implanted in its first two patients in 2014 and continued studies are evaluating the long-term effects. In January 2016 the company initiated a 15-patient study evaluating the safety and efficacy of the device with moderate to severe FMR. Enrollment for this study is expected to be completed in mid-2017E, with a six-month follow-up to evaluate the primary endpoint of MR reduction and a 36-month follow-up to evaluate the secondary endpoint of serious adverse events.

**Exhibit 15: Mardil Medical VenTouch System**
AccuCinch from Ancora Heart (previously Guided Delivery Systems) offers a direct annuloplasty approach to treat FMR through a technique called ventriculoplasty or cinching below the valve. The unique anchoring system of 12-14 anchors is deployed into the ventricle walls, where a cable is tightened to reduce the sub-valvular dimension. Rather than anchoring into the annulus it applies direct pressure below the valve to decrease wall stress, reduce leaflet tenting, and ultimately treat the root cause of FMR. Clinically, in 2014 AccuCinch was used in two trials, RECOVER (n=2) and RESTORE SA (n=8) to reduce FMR. The one-year follow-up results varied, where the annulus diameter was reduced by 40% but anchors pulled out of the tissue yielding a higher or equal regurgitant volume. Since April 2016, the next-generation AccuCinch device has been implanted in six patients in the CINCH 2+ Trial, which is intended to treat FMR by targeting a 20% cinch or diameter reduction. In the U.S., the company plans to begin an IDE early feasibility study in mid-2017E.

![AccuCinch](Source: Ancora Heart)

**Exhibit 16: Ancora Heart AccuCinch**

Other devices early in development and expected to be in clinical trials in the next couple years include:

- Edwards has yet another repair device in the hopper with PASCAL, a mitral valve spacer used to treat FMR and DMR. The device is delivered through a transseptal approach and based on edge-to-edge repair by placing the spacer between the leaflets. Clinically, PASCAL has been implanted in multiple patients and a FIH early feasibility trial and a CE Mark approval study are expected to begin 2017E.

- Cardiac Implants, which uses a proprietary ring delivery system to deploy an annuloplasty ring supported by scaffolding and implanted through 10 barbed anchors.

- Mitral Cerclage Annuloplasty, which is a transcatheter venous procedure that is similar to a coronary sinus annuloplasty, and intended to reduce the annulus diameter. Using multiple guidewires, the device loops around the entire mitral annulus and prevents coronary artery entrapment.

**Call in the Cavalry—Replacement Is Still an Important Treatment**

We are still as enthusiastic about the potential for transcatheter mitral valve repair treatment (TMVR) as we were a year ago, although the commercial timeline has been extended somewhat given more stringent regulatory requirements in Europe. There are still plenty of reasons to be excited for TMVR: 1) it provides a minimally invasive treatment for mitral valve repair; 2) it can be used to treat both DMR and FMR patients; and 3) results may be more durable than repair treatments, which is especially important for patients with FMR. There have been improvements in technical success, patient safety, and efficacy as measured by the patients’ MR grade. Today, the landscape is becoming more competitive as there are now seven TMVR implants in humans, and an additional four beginning first-in-human (FIH) trials in 2017E.
When Edwards announced in July 2015 that it had agreed to acquire CardiAQ Valve Technologies, the company had two shots on goal, including its own Fortis valve and the acquired CardiAQ valve. After a period of several stops and starts for the Fortis program (including a hold for two months between May 19, 2015 and July 13, 2015), it appears to be placed on an indefinite hold. The loudest evidence for this is the fact that Fortis didn’t have a presentation at TCT 2016 in November after having a brief one at TVT 2016 in June. Instead, management has combined the tissue material from the Fortis design to improve on the CardiAQ design, calling the current device the CardiAQ-Edwards Transcatheter Mitral Valve.

A focus on transseptal access to the mitral valve is evident as a new deflectable delivery system was created for this approach, with a controlled articulate to simplify positioning in challenging anatomies, including a deflection indication on the handle to show the articulation status. The device is a self-expanding, bovine pericardium, symmetrical valve that sits intra/supra annularly, trying to limit left ventricular outflow tract (LVOT) obstruction and has a unique anchoring design that engages the annulus and chordae tendineae.

Enrollment has been slow in the year between TCT 2015 and TCT 2016, with an additional four patients enrolled in the Compassionate User Experience. Yet those four new implants were procedural successes, measured as successful valve delivery, valve deployment, and delivery system retrieval, increasing the overall success rate to 92% from 78% y/y. The U.S. Early Feasibility Study is ongoing. For CE Mark approval, the RELIEF Trial is expected to start soon. This trial has been delayed due to more challenging regulatory processes than were anticipated, but is still expected to include approximately 15 centers in Europe and Canada and will include transapical and transseptal delivery systems consistent with the desires of our clinicians. This single arm study will include patients suffering from functional and degenerative mitral regurgitation, and we expect clinical program updates will be shared at scientific meetings in 2017.

**Exhibit 17: Updated CardiAQ Compassionate User Experience**

<table>
<thead>
<tr>
<th></th>
<th>TCT 2015</th>
<th>TCT 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>With Current Design</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td><strong>Baseline Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, %</td>
<td>78%</td>
<td>85%</td>
</tr>
<tr>
<td>DMR</td>
<td>44%</td>
<td>31%</td>
</tr>
<tr>
<td>FMR</td>
<td>56%</td>
<td>69%</td>
</tr>
<tr>
<td>Mean EF</td>
<td>44% [20-72%]</td>
<td>40%</td>
</tr>
<tr>
<td><strong>Procedure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS</td>
<td>11.1%</td>
<td></td>
</tr>
<tr>
<td>TA</td>
<td>88.9%</td>
<td></td>
</tr>
<tr>
<td><strong>Procedural Success</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>78%</td>
<td>92%</td>
</tr>
<tr>
<td><strong>Procedural-related Deaths</strong></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Non-valve Related Deaths</strong></td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>


Neovasc’s Tiara is well on its clinical pathway, having begun an early feasibility trial (n=30), including 15 U.S. and 15 OUS patients. Neovasc’s Tiara device is a self-expanding, tri-leaflet bovine pericardium device designed with an asymmetrical design (D-shaped) to mimic the mitral valve that is delivered through a TA approach.

Edwards’ RELIEF trial is expected to start soon at 15 centers, including: 1) transapical and transseptal delivery systems; and 2) in patients with functional and degenerative mitral regurgitation.
Neovasc is conducting the TIARA-I clinical trial, a multinational, multicenter early feasibility study in the U.S., Canada, and Europe. This is an observational study of high-risk (operable) patients enrolling up to 30 patients (~15 in the U.S., and ~15 in Europe/Canada). The patients that will be included in the trial will be those with severe symptomatic MR, NYHA Class III-IV heart failure, a high surgical risk for open mitral valve surgery. According to clinicaltrials.gov, the primary endpoint is freedom from all-cause mortality and major adverse events at 30 days from the implant procedure or hospital discharge, whichever is later, as well as a number of secondary endpoints (e.g., re-intervention rates, progression of heart failure, device success, NYHA functional class measurements, and days alive and out of hospital). Additional follow-up is expected at three months, six months, and annually thereafter.

At TCT 2016, management updated that 19 subjects have been implanted with the Tiara device, including 5 from the Tiara-1 clinical trial and 14 through a special access program, which is an increase from 7 subjects at TCT 2015. The STS score has dropped to 10.7 on average from 15.1 a year ago, but this is still the highest risk score among those that presented such data. Early results have seen no PVL or LVOT obstruction, with only two cardiac-related deaths.

A year ago, one of the issues we highlighted was the limited valve size options: at that time, management had only one valve size, 35mm. Since then, it has introduced the 40mm device and although management has not provided timing on the 45mm valve, it has highlighted that the 35mm and 40mm sizes are covering a larger percentage of the patient population than originally expected.

### Exhibit 18: Neovasc’s Tiara Compassionate Use Experience

<table>
<thead>
<tr>
<th>Neovasc Tiara</th>
<th>TCT 2015</th>
<th>TCT 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>Baseline Characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>69 [39-82]</td>
<td>73 [39-89]</td>
</tr>
<tr>
<td>Male, %</td>
<td>86%</td>
<td>68%</td>
</tr>
<tr>
<td>NYHA Class III</td>
<td>57%</td>
<td>74%</td>
</tr>
<tr>
<td>NYHA Class IV</td>
<td>43%</td>
<td>26%</td>
</tr>
<tr>
<td>Mean STS Risk Score</td>
<td>15.5 [2.4-47.7]</td>
<td>10.7 [2.1-47.7]</td>
</tr>
<tr>
<td>Baseline Pathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMR</td>
<td>14%</td>
<td>16%</td>
</tr>
<tr>
<td>FMR</td>
<td>43%</td>
<td>63%</td>
</tr>
<tr>
<td>Mixed MR</td>
<td>29%</td>
<td>16%</td>
</tr>
<tr>
<td>Rheumatic MR</td>
<td>14%</td>
<td>5%</td>
</tr>
<tr>
<td>Systolic Pulmonary Artery Pressure</td>
<td>59%</td>
<td>52%</td>
</tr>
<tr>
<td>Procedure Outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>CVA/MI</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Device Malpositioning / Embolization</td>
<td>0%</td>
<td>16%</td>
</tr>
<tr>
<td>Conversion to Open MVR</td>
<td>0%</td>
<td>16%</td>
</tr>
<tr>
<td>LVOT Obstruction</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>Day 30 Outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0%</td>
<td>16%</td>
</tr>
<tr>
<td>Cardiac Related Deaths</td>
<td>0%</td>
<td>11%</td>
</tr>
<tr>
<td>Non-Cardiac Related Deaths</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>CVA/MI</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Reintervention</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>


November and December 2016 were busy months for Neovasc. On November 1, 2016 Neovasc lost a legal battle versus Edwards Lifesciences; 2) it moved forward with its Tiara II trial; and 3) it received an investment from Boston Scientific.
judge denied Edwards CardiAQ’s motion for an injunction that would have shut down the development of its Tiara valve. As a result, the TIARA II trial is proceeding as planned, receiving regulatory approval on November 28, 2016 to begin the study. Tiara II is a 115-patient, non-randomized, prospective clinical study that will evaluate the safety and performance of the Tiara device; first implants are expected in Milan, Italy in 1Q17 and management intends to use the data from this study to file for CE Mark approval for Tiara, with its CE Mark application. We expect the first patient to be enrolled in early 2017E.

On December 6, 2016, management updated that 22 patients have been treated with the Tiara valve, with 1) a technical success rate of 86% (19/22); 2) mild, trace, or absent paravalvular leak rates in 100% of the patients; and 3) all cause 30-day mortality of 15.7% (3/19). The three remaining patients are recovering well. Further, the longest patient with a Tiara implant is nearing three years, with the valve remaining fully functional and reports of zero adverse events related to valve performance.

Rounding out the news trail, Boston Scientific announced on December 13, 2016 that it acquired Neovasc’s advanced biologic tissue components and had made a 15% equity investment in the company for $75 million in cash. In many ways we see this as dating with an option to marry, allowing Boston Scientific a seat at the table as Neovasc continues clinical development of Tiara and works to resolve its legal proceedings.

**Tendyne, which was acquired by Abbott on July 30, 2015 during the great 2015 TMVR race, continues to differentiate itself as fully repositionable and fully removable,** with an apically “tethered” tri-leaflet porcine pericardial valve designed to address functional, degenerative, and mixed etiology mitral regurgitation. The device utilizes a TA approach and has some differentiating features, including 1) multiple valve sizes (single inner valve size, with a number of outer frames: 30-43mm Anterior/Posterior by 34-50 CC); 2) a large effective orifice area; and 3) an anchoring mechanism that tethers to the Apex of the heart to provide stability. Tendyne has commented that it is also pursuing a TF program, but at this point, the implants have been delivered only through a TA approach.

At TCT 2016, data was presented on its 30 subjects from the global feasibility study and its 30-day data was very promising, with no cardiac-related deaths (although there was one non-cardiac death) and 90% of the patients experienced an elimination of mitral regurgitation. The study was closed as of March 2016, with the *Journal of the American College of Cardiology* accepting the study, although there is no timeline on when the extended data will be presented.

- **A CE Mark/Expanded Feasibility Study (n=110) is currently enrolling in 25 centers, including 10 centers in the U.S. (which can test up to 40 U.S. patients). Originally, the device was expected to have a late-2017E European market launch, but the study appears to be slightly delayed from the original 2015 start of enrollment, mostly likely due to the integration into Abbott. With only 15 patients enrolled so far as of TCT 2016, we expect the timeline of the European launch to move out to 2018E.**
Exhibit 19: Tendyne’s Compassionate Use Experience

<table>
<thead>
<tr>
<th>Tendyne Global Feasibility Study</th>
<th>TCT 2015</th>
<th>TCT 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td><strong>Baseline Characteristics</strong></td>
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</tr>
<tr>
<td>Age</td>
<td>75.3 [55-82]</td>
<td>75.6 [55-91]</td>
</tr>
<tr>
<td>Male, %</td>
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<td>Prior Coronary Artery Bypass Graft (CABG)</td>
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<tr>
<td>LVEF &lt; 30%</td>
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<tr>
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<td><strong>Day 30 Outcomes</strong></td>
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<td>Cardiac Related Deaths</td>
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<td>Non-Cardiac Related Deaths</td>
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<tr>
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<tr>
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Medtronic’s Intrepid TMVR device was relatively unknown this time last year when it was owned by Twelve, a private company that got its start through The Foundry, but this has changed since Medtronic’s purchase in August 2015. The Intrepid device is distinguished with an inner and outer stent design, with the inner stent containing a 27mm tricuspid bovine pericardium valve and the outer stent designed to fixate and seal to the annulus and leaflets in an expanding “cork effect.” This creates a device that has the outer stent conform to the dynamic anatomy of the mitral valve while preserving the shape of the inner replacement valve and eliminating the need for rotational alignment or leaflet interaction.

As of TCT 2016, 27 patients have been selected in a multicenter prospective clinical trial; with 24 of 26 patients having successful deployment of the device (deployment was not attempted in one patient). Four patients died related to the procedure, but not related to the device, and an additional two died within 30-days, but these were unrelated to either the procedure or the device. Additional complications included major bleeding in 22% of the procedures. Despite these complications, the 30-day improvement of MR grades were significant: before the procedure all 27 subjects had an MR grade ≥ 3, but the follow-up of 24 of those subjects showed an MR grade ≤ 2.

While pleased with the progress, at TCT2016 management acknowledged that the clinical path is still very early, comparing the progress of transcatheter mitral valve replacement technology to where TAVR
was 10-15 years ago. While additional work is being implemented to complete the product design to ensure recapturability, discussions continue with the FDA regarding the U.S. clinical pathway.

**Additional TMVR Technology Efforts Are Being Made:**

- Highlife is a two-component system that combines a standard bovine pericardium valve with a polymer ring. The valve is self-centering while the ring loops the annulus around the valve to eliminate PVL, although this requires echocardiography to determine the loop positioning. There have been six FIH cases done in the Feasibility Study and Compassionate Use programs, with five successful device deliveries and four patients surviving past 30 days. The four that did survive all experienced a reduction of MR by more than one grade and showed no signs of PVL.

- SinoMed also uses a sealing ring with its unique self-expanding valve body for optimal native valve “clipping” effect, highlighting its low ventricular profile, <14mm. It is currently in preclinical studies and we expect FIH trials to begin in 1H17E.

- Caisson also uses a two-component system, but instead of a ring, it uses a sealing cuff that fastens to the native leaflets to create a seal around the inner valve. Five patients have received the device in the FIH trials (four in the PRELUDE Early Feasibility Study and one in a Special Access Program, with four having successful implantation and three surviving past 30 days. Of the three who survived, two had no PVL at 30-days and the third had mild PVL. An additional 16 patients will be studied in the PRELUDE study in eight centers across the U.S.

- Other devices that expect to have FIH trials in 2017 include: 1) MValve in 2Q17E with the DOCK I Trial; 2) Valtech in 1H17E; and 3) Cephea in 2017E.
Briefly, a Review of Mitral Valve Disease

Heart valves in the human body perform the critical task of maintaining unidirectional blood flow, opening and closing to allow blood to flow depending on the differing pressure on each side of the valve. Unfortunately, heart valve function can become compromised, either through age or disease (e.g., rheumatic fever). It may become stiff and narrow, not fully opening (stenosis) or closing (regurgitation), pumping an insufficient amount of blood through the chambers, leading to heart failure or the development of arrhythmias. Although early-stage heart valve disease may be difficult to detect, in the later stages the patient may experience shortness of breath, water retention (edema), chest pain, rapid heartbeat, and/or fainting. If untreated, heart valve disease is progressive, accelerates over time, and increases rates of morbidity. A study in The Lancet demonstrated that a group of patients with valve disease diagnosed between 1990 and 1995 was expected to have an eight-year survival rate of 61%, but actually declined more rapidly than expected, resulting in a survival rate of 41% in year eight (p<0.0001).

The heart has four valves: the mitral valve, which controls blood flow between the left atrium and left ventricle; the aortic valve, which controls blood flow between the left ventricle and the aorta (to the rest of the body); the tricuspid valve (between the right atrium and right ventricle); and the pulmonary or pulmonic valve (between the right ventricle and the pulmonary artery, which carries blood to the lungs from the heart). In heart valve disease, the mitral and aortic valves are usually affected, less so the tricuspid and pulmonic valves.

Exhibit 20: The Heart Has Four Valves

Compared with an aortic valve for which the focus is primarily on aortic stenosis, the complexities of the anatomical structures and etiologies of the mitral valve have resulted in slow-moving technological advancements. The mitral valve separates the left atrium (LA) from the left ventricle (LV), allowing for the passage (antegrade) of oxygenated blood during diastole to the LV, while preventing the backflow (retrograde) of blood back into the LA during systole. While part of the hurdle toward a percutaneous approach has been the location of the valve, the other part is its complexity. The mitral valve is derived from a number of individual structures that represent a single functional unit (the mitral valve), including 1) the annulus (D-shaped), 2) two leaflets, 3) chordae tendineae, 4) papillary muscles, 5) left ventricle (or ventricle myocardium), and 6) left atrial wall (or atrial myocardium), influencing the function of the annulus and leaflets.

The opening of the valve is surrounded by the mitral annulus, an asymmetrical fibrous ring that looks like a kidney bean, given its elliptical shape (when viewed from above, or axially), and a horse saddle (when viewed in 3-D from the side, similar to a lateral plane). Attached to the annulus are two leaflets, an anterior (denoted “A”) and posterior (denoted “P”) portion, with each having three regions or “scallops” (A1, A2, and A3; and P1, P2, and P3).

These leaflets are supported by the chordae tendineae, which are fibrous strings that extend from the papillary muscles, projecting inward from the ventricle walls. These two papillary muscles are situated at two different locations to stabilize the chordae tendineae, one situated superiorly on the anterior wall of the left ventricle, hence the name, anterolateral papillary muscle, and the second, on the posterior-inferior (back and base) of the left ventricle, known as the posteromedial papillary muscle. For a healthy mitral valve, in functioning as one unit, when systole commences the combination of the chordae tendineae and leaflets create a parachute-like structure preventing the backflow of blood into the left atrium.

**Exhibit 21: Mitral Valve**

![Mitral Valve Diagram](Source: EuroPCR 2015)
Appendix A: Glossary

Annuloplasty: reconstructive surgery of a leaking cardiac valve to narrow the opening and diminish the leak.

Annulus: a ring-shaped structure.

Aorta: the largest artery in the body; it carries blood from the heart to the arteries of all limbs and organs except the lungs.

Aortic stenosis: narrowing of the heart valve between the left ventricle and the aorta, slowing blood flow and increasing stress on the heart.

Aortic valve: the valve connecting the left ventricle of the heart to the aorta.

Arrhythmias: irregular rhythm of the heart.

Barlow’s disease: see mitral valve prolapse.

Calcification: a hardening, usually due to deposits of calcium salt.

Chordae tendineae: inelastic tendons that connect the papillary muscles to the leaflets.

Coaptation: the closing of the two leaflets to form a seamless seal.

Collagen deficiency: the shortage of the major protein in the skin, tendons, cartilage, bone, and connective tissue.

Coronary artery disease: the most common subgroup of cardiovascular disease that is caused by insufficient circulation due to blockage of a blood vessel; includes stable angina, unstable angina, myocardial infarction, and sudden coronary death.

Diastole: the normally occurring state of relaxation and dilation of the heart ventricles, during which they fill with blood.

Degenerative mitral regurgitation: also known as primary mitral regurgitation, caused by mitral valve prolapse.

Dilatation: the process of stretching, enlarging, or expanding an opening.

Edema: an accumulation of excess fluid in cells tissues, or cavities.

Endocarditis: inflammation of the heart valves.

Etiology: the origins and causes for the development of a disease.

Functional mitral regurgitation: also known as secondary mitral insufficiency, due to dilation of the left ventricle while the papillary muscles, chordae, and leaflets are usually in normal conditions.

Ischemic mitral regurgitation: caused when myocardial infarction causes dysfunction of the papillary muscles.

Leaflets: flaps that are pushed open to allow blood flow and which then close together to seal and prevent backflow.

Left atrium: the upper chamber on the left side of the heart into which the oxygenated blood flows from the lungs via the pulmonary veins; the blood is pumped into the left ventricle below, which sends it to the body.
**Left ventricle**: the thick-walled lower chamber of the left side of the heart that receives blood from the left atrium and pumps it out to the body through the aorta.

**Mitral valve**: the valve located on the left side of the heart, between the auricle and the ventricle; has two triangular flaps.

**Mitral valve prolapse**: the displacement of an abnormally thickened leaflet.

**Myocardium**: middle muscular layer of the heart wall.

**Papillary muscles**: conical muscular projections in the ventricles of the heart that attach to the valve leaflets and control their motion.

**Percutaneous**: administered through the skin by injection.

**Primary lesion**: any abnormality directly caused by disease or trauma.

**Pulmonary artery**: the blood vessel that carries deoxygenated blood from the right ventricle to the lungs.

**Pulmonary valve**: a valve in the heart that separates the right ventricle from the pulmonary artery.

**Regurgitation**: backward flowing of blood through a defective (leaking) heart valve.

**Revascularization**: the restoration of perfusion to a body part or organ.

**Rheumatic fever**: an acute childhood disease characterized by fever, painful inflammation of the joints, and damage to the heart valves that appears later in life.

**Right atrium**: the upper chamber of the heart that receives blood from veins and passes it into the right ventricle.

**Right ventricle**: the lower right chamber of the heart, which receives blood from the right atrium and pumps it through the pulmonary artery into the lungs.

**Stenosis**: constriction or narrowing.

**Systole**: the period of contraction of the heart, especially of the ventricles, during which blood is driven out to the aorta and pulmonary artery after each dilation (filling period) or diastole.

**Tricuspid valve**: valve of the heart with three flaps (leaflets) that open to allow blood flow from the right atrium to the right ventricle and close to prevent backflow.

**Valvuloplasty**: surgery related to repair a valve in the heart or a vein.
Companies mentioned (price as of close on January 4, 2017)

Abbott (ABT, $39.36, Outperform)
Boston Scientific (BSX, $22.08, Outperform)
Edwards Lifesciences (EW, $96.54, Outperform)
Medtronic (MDT, $71.27, Outperform)
Neovasc (NVCN, $1.88, Not Rated)
St. Jude Medical (STJ, $80.82, Not Rated)
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Risks: Risks to our price target include new product development, the FDA regulatory environment, adoption of transcatheter heart valves as an alternative to surgery, competitive heart valve launches, and operating leverage on the income statement.

Methodology and Risks to Price Target/Valuation for Medtronic (MDT-NYSE)

Methodology: Our price target is based on 17-18x CY2017 cash EPS estimate.
Risks: Risks to our price target include the overall health of the medical technology market, including pricing and hospital utilization trends, the competitive landscape, new product approvals, emerging market strategy, leverage of the income statement, uses of cash, and Covidien acquisition integration.

Distribution of Ratings (January 03, 2017)

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