SECTORAL
ASSET MANAGEMENT

NEWSLETTER

JANUARY 2014

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HEALTHCARE MARKET REVIEW AND OUTLOOK

Healthcare stocks rounded off the year with another quarter of strong performance, as the MSCI World Healthcare Index rose 8.9%, vs an increase of 8.0% for the MSCI World Index. The caution we expressed toward healthcare stocks in general and biotech stocks in particular at the end of last year proved to be wrong, or at least premature. The MSCI World Healthcare Index jumped 36.3%, clearly outpacing the MSCI World Index (+26.7%). This strong performance was driven by pharma, the largest index component, which was up by 32.1%, and by biotechs, services, and life-sciences tools. The biotech performance was particularly impressive – the MSCI World Biotech Index increased 67.7% – especially as it followed an already solid 44% rise in 2011. This growth brought the two-year performance to a staggering 141.6%. Globally, the only real disappointment came from emerging markets, where healthcare stocks suffered from fears of the impact of Fed tapering, as well as from local regulatory concerns (particularly in India). On the bright side, we note that the MSCI Emerging Markets Healthcare Index nonetheless outpaced the MSCI Emerging Markets Index, showing a 9.1% increase vs a 2.6% decline.

BIOTECH: UP, UP AND …?

In our last newsletter, we concluded that the rise of biotechs, despite some frothiness, was to a large extent supported by improving fundamentals: the solid commercial performance of recently launched products, an improved regulatory environment in the US, several significant new product approvals, clinical success across the board (with only few exceptions), and a sustained high level of M&A activity. In all respects, the last quarter of the year provided further ground for optimism. Stellar financial performance from most of the biotech majors refueled biotech

INDEX	CLOSE 12/31/2013	RETURN					ANNUALIZED VOLATILITY	
		1 MONTH	3 MONTH	6 MONTH	9 MONTH	12 MONTH	3 MONTH	6 MONTH
MSCI World Index (all country)	181.0	1.7%	7.3%	15.8%	15.3%	22.8%	8%	8%
MSC World Index	4331.0	2.1%	8.0%	16.8%	17.6%	26.7%	9%	8%
MSCI World Healthcare Index	214.6	1.0%	8.9%	16.1%	19.3%	36.3%	10%	9%
MSCI World Pharma	176.6	0.9%	8.4%	14.0%	15.6%	32.1%	9%	9%
MSCI World Biotech	969.2	0.4%	9.3%	30.2%	35.3%	67.7%	19%	18%
MSCI World Equip and Suppl	262.4	0.9%	8.0%	10.8%	11.6%	24.3%	11%	11%
MSCI World Healthcare Providers	321.5	1.0%	11.2%	16.7%	27.7%	38.9%	11%	10%
MSCI Emerging Market Healthcare	465.0	0.4%	4.6%	7.0%	6.5%	9.1%	13%	12%

investors' enthusiasm, following a bout of profit-taking at the beginning of the quarter. The expected new-product approvals – including Gilead's Sovaldi in Hep C and Theravance's Anoro in COPD – materialized, as did some more or less unexpected positive regulatory developments. United Therapeutics reported the approval of oral Remodulin (Orenitram) for pulmonary arterial hypertension after last year's rejection, and Ariad managed to bring Iclusig back to the market despite a clinical hold on its Phase III program and an initial FDA-mandated market withdrawal. In the same vein, Biogen-Idec secured European designation as a "new active substance" for Tecfidera, giving the MS drug 10 additional years of market exclusivity in the region and opening up a significant new commercial potential. On the clinical front, several positive, or at least encouraging, data sets were released. The American Society of Hematology meeting was the stage for positive findings for Celgene (MM-020), as well as for Geron (Imetelstat in myelofibrosis), Karyopharm (Selinexor in multiple indications), and Acceleron (Sotatercept in beta-thalassemia). In other therapeutic areas, we note the strong showing by Gilead's Sovaldi (sofosbuvir) and its NS5A inhibitor ledispasvir in fixed-dose combination (ION trials); these results set the stage for a single-tablet regimen without interferon and ribavirin in Genotype 1 Hep C patients. In addition, Vertex' ivacaftor reported Phase III results in in cystic-fibrosis patients with the R117H mutation. Although the trial missed its primary endpoint, a subset analysis of patients aged 18 and above strongly suggests the drug has benefits, thereby leaving the door open for a label (and market) expansion. The main negative development on the regulatory/clinical front came from the new LDL guidelines issued by the FDA, which adversely impacted investor confidence in the PCSK9 programs of Regeneron and Amgen. Finally, M&A and corporate-partnering news made the biotech feast complete: Bayer acquired its partner Algeta and Shire bought Viropharm, while Celgene and Oncomed signed a significant development-and-commercialization partnership around several of Oncomed's anti-cancer stem-cell therapeutics.

Since the lows of September 2011, biotech valuations have more than doubled. The industry now trades at an EV/Sales multiple of 8x, clearly the upper end of the normalized historical range. We reiterate our cautious optimism for biotechs. While fundamentals have improved and sales growth should remain comfortably in the 15-20% p.a. range, or even slightly above, we note that, in several cases, the success of early-stage compounds is baked into the valuations. Drug development remains a risky business, and the odds of clinical success have not changed. Another potential challenge is biosimilars. In the last twelve months, the outlook for biosimilar producers has markedly improved because of regulatory clarification and (relative) leniency, as well as payer support. Biologics have long been, and still are, largely viewed as being immune to generic competition. This immunity may change, challenging some well-established franchises while benefiting some of the leading biologics producers, such as Amgen or Biogen-Idec, which have a stake in the game. Therefore, we advocate increasing selectivity in biotech investments. Opportunities still exist, particularly among small and micro-caps, but they will be harder to come by.

GROWTH P.A. 2012-2015E					
	SALES	EPS	PE14E	EV/SALES14E	COGS
Pharmaceuticals	2-4%	4-6%	15x	3.5x	15-20%
Generics	10-15%	10-15%	16x	2.3x	25-55%
Biotechs	15-20%	20-25%	23x	8.0x	10-20%
Medtechs	10-15%	15-20%	17x	2.9x	20-40%

Based on Sectoral estimates / median numbers

NAVIGATING CHINESE WATERS: RISKY BUT POTENTIALLY REWARDING

Emerging markets have been under pressure in the recent past, and China is no exception. Aside from the potential negative impact of QE tapering on emerging countries' financial markets, investors have also worried about growth deceleration and the implementation risks linked to the new central government's economic-transition plans. Chinese equities were modestly up in 2013. Both the MSCI China Index (HK) and the MSCI China A Share Index edged up about 4% in USD.

As in other emerging markets, healthcare stocks outperformed. China is in the midst of a major reform aimed at modernizing the healthcare infrastructure and expanding healthcare benefits to the whole population. At the same time, the middle class is growing rapidly, increasing disproportionately its spending on healthcare. As a result, healthcare markets are expanding, in the 20-30% range, and companies are benefiting. The MSCI China Healthcare Index (HK) was up 24.1%, while the MSCI China Healthcare A Share Index jumped 33.3%. Although the outperformance vs the local market is significant, it merely reflects earnings growth in the sector.

The current macroeconomic uncertainties are creating a jittery investment environment in emerging markets, particularly in China. However, the unpredictability also offers a good opportunity for the discerning investor to build up or expand positions in emerging-markets healthcare stocks. The underlying trends are clearly in place. Driven by increasing disposable income and an aging population, spending on healthcare goods and services will continue to grow faster than GDP. MNCs and, increasingly, local players stand to benefit. Here, too, China is no exception, although there are multiple challenges in a country where the government keeps a controlling hand over the economy and is trying to manage the transition from a state-run economy to a free market.

Taking advantage of the market's vagaries may prove rewarding, provided investors clearly understand the risks they face in the upcoming year. We believe three key risks need to be evaluated carefully: anti-corruption activities, provincial tenders, and new GMP standards.

The anti-corruption activities were triggered by Chinese television reports, which caught a company representative red handed. Corruption in China is endemic, as doctors and nurses in public hospitals (and thus the government) rely on kickback from industry to be paid adequately. Based on our recent research, we believe the impact from the recent government anti-corruption focus will be limited in scope and time, with Q3 and Q4 2013 being the most negatively affected quarters. Going forward, the government probably will maintain its long-term goal of transitioning the system to global practices while avoiding a witch hunt. Hence, companies negatively affected by the recent focus on anti-corruption may represent attractive long-term investments.

A series of provincial tenders (at least 10, according to industry sources), will potentially lead to significant price cuts for certain players. The Chinese provincial government, faced with an increasing healthcare-cost burden, will be eager to rein these in. One should expect older products and products with multiple competitors to be most affected. Therefore, any price weakness in stocks of companies with relatively young and unique product portfolios relating to provincial tenders may be interesting investment candidates.

Finally, pharmaceutical producers face the challenge of new GMP standards. In 2011, SFDA required drug manufacturers of plasma products, vaccines, or injectables to be in compliance with the new GMP standard by the end of 2013. SFDA also required the remaining manufacturers to bring their facilities up to the new GMP standards by the end of 2015. By the end of 2013, 40% of the plasma, vaccine, or injectable manufacturers had yet to pass the new GMP standards. Only 20% of the solid-dosage-form producers, were in compliance in Q4 2013. The risk and opportunities are clear for compliant and non-compliant companies.

Although these risks will mainly have very stock specific implications, we see two clear investment themes emerging. First, Chinese drug distributors should remain relatively immune from the production standard changes, benefit from the moderation of the anti-corruption activities and continue to grow at the market rate. By focusing on the leading distributors, the consolidators in a still very fragmented market, growth rates steadily ahead of the market are realizable. Second, focus on domestic quality providers. Both national preference and the drive to increase local standards and practices will favor the local blue-chip companies.

Michael Sjöström, CFA
Chief Investment Officer

MITRAL VALVE THERAPY GOING MINIMALLY INVASIVE, THE NEXT PARADIGM SHIFT IN MEDTECH?

The introduction of disruptive technologies in cardiology has dramatically changed the therapeutic landscape over the last decade. The development of minimally invasive solutions as alternatives to surgery has led this phenomenon, most notably in coronary artery diseases, where stents have largely replaced arterial bypasses. More recently, transcatheter aortic valve replacement (TAVR) has rapidly become a solution of choice for the treatment of aortic stenosis. In fact, the global market for TAVR already exceeds USD 1.0B, despite the fact that second-generation systems have yet to reach commercialization.

In truth, numerous diseases still await new approaches to achieve better clinical outcomes and more cost-effective solutions. The next paradigm shift could occur in mitral valve diseases. Disorders such as mitral regurgitation are broad and complex, while current therapies are for the most part limited to invasive surgery. At the same time, even though professional associations such as the American Heart Association recommend that patients with severe degenerative mitral valve regurgitation undergo surgery, the invasiveness of the procedure excludes a large group of older, frailer patients at high risk, leaving them without treatment options.

As a consequence, the long awaited transcatheter mitral valve repair (TVMR) and replacement technologies are expected to take the center stage in the near future. After numerous failed attempts, a renewed pipeline of devices is on the cusp of entering human testing. In this report, we sketch a picture of the market, highlighting the challenges and opportunities ahead for mitral valve therapy.

MITRAL VALVE DISEASE: A MAJOR ISSUE

The function of the mitral valve is to allow oxygenated blood to flow from the left atrium to the left ventricle of the heart, while preventing back flow during left ventricular systole. (Heart blood flow is illustrated on Figure 1.) Importantly, valve function is dependent on six key components: two leaflets,

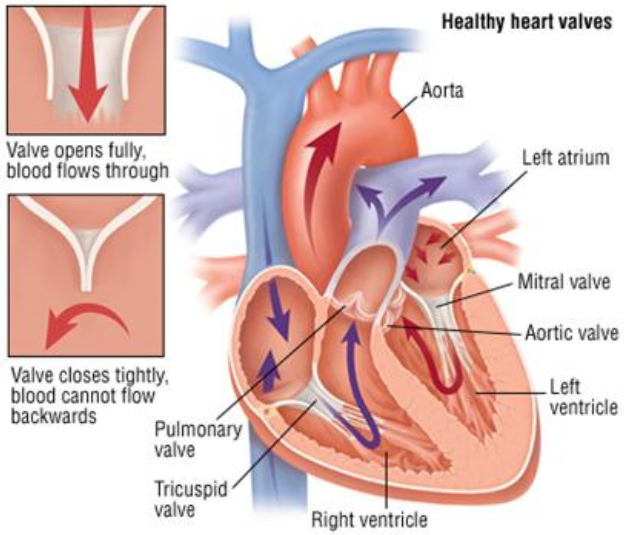

Figure 1: Heart blood flow.
Source: www.drugs.com, December 2013

chordae tendineaes, papillary muscles, the annulus, the left atrium and left ventricle.

Mitral diseases are the most common type of valvular lesion and are frequently seen with other cardiac morbidities. These diseases, which are identified as mitral stenosis, mitral regurgitation or mitral valve prolapse, are varied and generally complex to treat.

Mitral stenosis (MS) is defined as a narrowing of the mitral valve, which leads to improper valve opening, causing the blood to pool in the left atrium. The main causes of MS are rheumatic fever (which has been declining steeply in developed worlds) and aging.

Thickened and enlarged valve leaflets, which causes impaired valve closing, characterize **mitral valve prolapse** (MVP). The cause is unknown, but genetics is hypothesized.

Mitral regurgitation (MR) refers to the leakage of blood backwards into the atrium. This form of valvular disease has the greatest risk of mortality; indeed, patients with severe degenerative MR are estimated to have a two-fold higher annual mortality

risk than do those in the general population.[1] When the leaflets do not close completely (improper coaptation) blood flows back into the left atrium, leading to a decrease in circulation to the rest of the body. This condition leads to left-ventricle overload, as the chamber must compensate by pushing the necessary amount of oxygenated blood throughout the body. Over time, the over-activity of the left ventricle enlarges the chamber, causes contractile dysfunction and, ultimately, induces congestive heart failure (CHF). MR is progressive and induces extreme fatigue and shortness of breath, eventually making simple tasks almost impossible to achieve and increasing a patient's overall cardiac risk.

MR diseases can be divided in two types, degenerative and functional. Degenerative MR (DMR) stems from such structural abnormalities of the valve as damaged leaflets or chordae tendineaes. In contrast, in functional MR (FMR), the valve components are normal, but the surrounding apparatus causes improper mitral valve closure. For example, dilation of the mitral valve annulus can be caused by left ventricle enlargement stemming from ischemic heart disease or dilated cardiomyopathy.

Unfortunately, few treatment modalities are available for mitral degenerative regurgitation. Medication is limited to symptom management and has no effect on progression of the disease. On the other hand, surgical intervention aims to treat the disease and ensure normal cardiac function by preventing the development of irreversible changes in the left atrium and ventricle. However, the risk-benefit profile of surgical intervention must be considered before a treatment decision is made. Among the key decision-making factors are disease severity, patient age, and the presence of symptoms. Ideally, surgery should be performed before damage to the left ventricle becomes irreversible. Based on the currently available surgical options, the favored approach is valvular repair rather than replacement, thanks to its lower risk of morbidity and stroke, as well as its acceptable durability.

For FMR, the standard of care is less well-established. Medical management of symptoms, using such

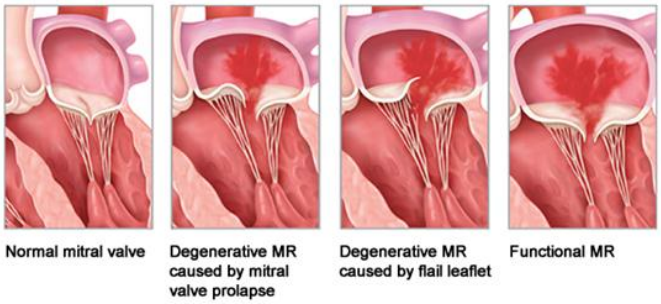

Figure 2: Mitral valve disorders.
Source: www.abbottvascular.com, December 2013

pharmacotherapies as antihypertensive drugs, angiotensin-converting enzyme inhibitors, beta-blockers, and diuretics, is usually the preferred first-step treatment. Cardiac resynchronization therapy is a subsequent option, while surgical repair is used only for a minority of patients, despite the recent publication of clinical research suggesting that treating FMR during revascularization surgery may be beneficial. Unfortunately, the morbidity associated with surgery, coupled with a paucity of clinical data, has prevented mitral valve repair/replacement from gaining widespread acceptance in FMR. As a consequence, the scarcity of treatment options available for patients with FMR underscores the need for novel, safe and effective therapies.

THE OPPORTUNITY COULD BE HUGE

As described above, there is a spectrum of valve disorders. However, not all of the aforementioned conditions are appropriate targets for the new, minimally invasive devices. At present, the most attractive initial opportunity is in severe FMR. Patients who would be candidates for surgery but are too frail or sick to undergo treatment would benefit the most from minimally invasive therapies that could improve their quality of life without exposing them to unreasonable procedural risk. Indeed, transcatheter approaches would eliminate the need for a sternotomy, allowing the procedure to be performed while the heart is beating. Not only would such techniques reduce potential complications induced by cardiopulmonary bypass, they also would shorten recovery time.

It is estimated that MR affects approximately 4 million Americans and nearly 10% of the population over the age of 75.[2] About 60-70% of today's surgical interventions are for DMR, but FMR comprises a large portion of the non-surgically treated cases. According to Wells Fargo, more than 500,000 patients are diagnosed each year with severe MR, but only 20% are treated with surgery, despite a 5-year incidence rate of cardiac death and major cardiac events in asymptomatic severe degenerative MR of 14% and 33%, respectively. As a reference, this pool of patients with severe MR is three times greater than the population with untreated severe aortic stenosis (400,000 vs. 120,000). This phenomenon reflects the risks associated with surgery and preference for "watchful waiting" in the absence of symptoms. Nevertheless, by not intervening, MR patients face the possibility that their disease will rapidly progress.

We estimate that there are respectively 200,000 and 300,000 new cases of FMR and DMR each year in the US. Assuming a similar price point to TAVR (i.e. ~USD 25,000 per device) and that a fifth of this population would benefit from transcatheter mitral valve, the sole US opportunity could exceed USD 2.5 billion. Furthermore, assuming that the incidence rate in Europe and the rest of world is comparable to that in the US, we estimate the total inflow of new patients annually could represent a global market of USD 7.0 billion. In addition, while probably more difficult to reach, the market could significantly be boosted by the large group of prospective untreated patients already waiting on the sidelines.

As discussed above, the market prospect for surgery is limited. At the early stage of the disease, the symptoms do not outweigh the risks of surgery, supporting a watchful-waiting strategy. However, if the disease evolves faster than anticipated and remains untreated, surgery may become too risky. In fact, there appears to be an association between early intervention and higher life expectancy. The advantage of early surgical intervention was recently highlighted in a paper published in JAMA (Journal of the American Medical Association). For patients with MR, clinical outcomes for those receiving early surgical intervention or watchful waiting were compared. The registry patients who had mitral surgery saw greater long-term survival and a lower risk of heart failure[3]. In addition, treating MR was shown to prevent heart remodeling and partially reverse disease progression. Thus, the development of less invasive therapies would allow clinicians to intervene earlier in the disease process and achieve better clinical outcomes for the patients.

MINIMALLY INVASIVE THERAPY ENTAILS MAJOR DEVELOPMENT HURDLES

The development of transcatheter solutions for mitral and aortic valve diseases began at the same time more than a decade ago. However, transcatheter

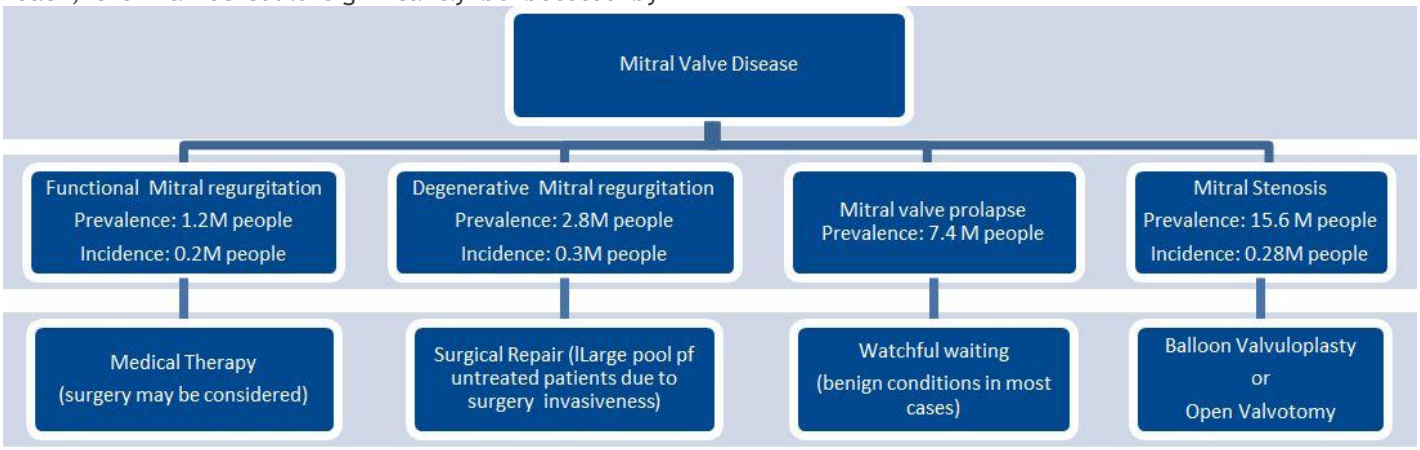

Figure 3: Mitral valve US opportunity. Source: Sectoral, Cleveland Clinic, AHA - Heart Disease and Stroke Statistics—2013 Update, Nature Reviews Cardiology - Epidemiology of valvular heart disease in the adult

aortic valve replacement has been commercialized for several years, while transcatheter mitral valve therapy has yet to become a viable option. Despite the experience with transcatheter aortic valve implants, mitral valve development has been far more challenging; several attempts to create a viable approach have failed. Among the more notable efforts, Edwards Lifesciences, the global leader for artificial heart valves, terminated at least two programs a few years ago due to inconclusive clinical outcomes.

One reason for the disparate results is the morphology of the two valves differs. The aortic valve is often described as uniform and static, while the mitral valve is characterized as heterogeneous and dynamic. Therefore, the technological challenges involved in implanting a mitral valve are wide-ranging and stem from the anatomical complexity of the valve. As noted above, valve function is influenced by six key components: leaflets, papillary muscles, chordae tendineaes, annulus, and the left ventricle and the left atrium. Therefore, valve dysfunction can be specific to one component or a product of their interplay. Several pathophysiological scenarios are possible, complicating both the diagnosis and intervention.

During open heart surgery, the surgeon has the flexibility to correct all sources of malfunction at once. On the other hand, for percutaneous repair, maneuverability in the heart is restrained, complicating the intervention.

Moreover, the morphology of the valve annulus is a challenge in itself. In fact, the mitral valve annulus is substantially larger than the annulus of the aortic valve; it also has a wider dimensional range, varies with the motion of the heart during cardiac cycles, and has a lower rigidity. Consequently, anchoring is critical to maintain the mitral valve implant in place, prevent dislodgement, minimize paravalvular leak, and avoid interference with other parts of the paravalvular apparatus. For these reasons, mitral implantation can be a more difficult procedure, compared with aortic valve stenosis, which provides calcified leaflets as a radial force to anchor the artificial valve.

Another difference between the two surgeries is the pressure gradient sustained by the valves. Although the gradient is influenced by the severity of the disease, the variation in pressure between the aorta and the left ventricle is usually significantly smaller, compared with the pressure between the left atrium and left ventricle. Because the force dynamic sustained by the mitral valve is affected by a wide variety of factors, acute implantation and long-term function are difficult to achieve. This means that ensuring the durability of the implant and stable positioning without dislodgement are critical for a successful procedure. Finally, percutaneous delivery compounds the challenge because of constraints related to valve size and tortuous access. Establishing sufficient clinical evidence to support adoption and reimbursement will be important, especially in the case of FMR, where the valve itself is not the source of the dysfunction and treatment is often questioned.

AN IMPRESSIVE LIST OF CONTENDERS WITH A VARIETY OF APPROACHES, BUT NO WINNER YET

There have been several attempts to develop sustainable solutions to mitral valve diseases, but so far failure has been the norm. We believe the current research environment is more promising. As described below, there are a wide variety of innovative replacement or repair solutions under development that are on the cusp of moving into the clinic.

This time around, the aforementioned technological challenges have been approached from various angles. For instance, many companies have explored transapical heart access to avoid having to take the more tortuous, but less invasive, transfemoral route. (In transapical access, a small incision between the ribs is made before the valve is inserted through the apex of the heart.) As delivery system sizes become narrower and the procedures more refined, the transfemoral approach is expected to become the standard access.

Venture-backed companies are pursuing most of the development programs, but some of the larger strategic names have internal programs as well. (A non-comprehensive list of firms is presented in the tables below.) So far, few transcatheter technologies have obtained approval, and commercial uptake has been mixed. However, there is one exception: Abbott's MitraClip.

As the different programs advance, long-term clinical data will be critical to monitor. Acute results are important, but the data should be analyzed with caution. Long term findings will be essential, as recurrence of regurgitation is frequently observed several months post-surgery in FMR patients.

Company Name	Description
LEAFLET APPROACH	
Abbott (Mitraclip)	Leaflet repair based on a surgical technique called "edge-to-edge." Device is US approved and has obtained CE Mark.
Cardiosolutions (Mitra-Spacer)	Reversible anchoring mechanism with spacer positioned between the leaflets providing a sealing surface. The procedure allows for future repair or replacement.
CHORDAL IMPLANTS	
NeoChord (DS 1000)	Chordal implants delivered transapically. Device is CE Mark.
TransCardiac Therapeutics (MitraFlex)	Chordal implants delivered transapically.
Valtech (V-Chordal)	Chordal implants. V-Chordal implantable artificial chordae system enables off-pump procedure; echocardiographic-guided and chord-length modification allows optimal coaptation.
ANNULOPLASTY	
Cardiac Dimensions (Carillon)	Indirect annuloplasty implant placed in a vein on the outside of the heart adjacent to the mitral valve. The device is threaded into the heart via the jugular vein. CE Mark and enrolling a registry study.
Guided Delivery Systems (Accucinch)	Annuloplasty implant delivered through the femoral artery. The implant consists of an adjustable ring of anchors over a cable inserted into the muscle below the mitral valve. Clinical study is ongoing.
Mardil Medical (VenTouch)	Extracardiac annuloplasty system that does not require access to any blood vessels and will leave nothing inside the heart. First human testing is expected in 2014.
MiCardia Corp. (enCor)	Annuloplasty system that allows dynamic adjustment of the valve annulus shape to further enhance coaptation of the leaflets. CE mark and sold in Europe.
Mitralign	Percutaneous direct annuloplasty procedure allowing customization of the treatment if regurgitation reoccurs.
Valcare Medical	Annuloplasty delivered in a linear configuration and adjusting the geometry of the annulus after deployment.
Valtech (Cardioband)	Sutureless direct annuloplasty band delivered through the transfemoral venous access. Multi-center study is ongoing in Europe.

Figure 4: Mitral valve repair programs.
Source: Sectoral, Companies' website, December 2013

MITRAL VALVE REPAIR

Minimally invasive approaches have initially targeted repair rather than replacement influenced by current surgical techniques, which have demonstrated efficacy. Percutaneous repair could potentially minimize or eliminate surgical drawbacks such as invasiveness, time of intervention, the on-pump procedural need and the lengthy recovery period for the patient. Nevertheless, with repair, one solution will not fit all needs. As a consequence, repair techniques may need to be combined.

In mitral regurgitation, the therapeutic objective is to reset the leaflets' coaptation. A common repair technique for leaflets consists of partial resection of redundant tissue. This procedure is generally used with patients suffering from degenerative MR due to a prolapse of the middle scallop of the leaflet.

A second technique targeting specifically the leaflets is called "edge-to-edge" and it aims to correct mitral valve function rather than anatomy. The approach entails suturing the two valve leaflets together at the point where the regurgitation is located. Additional techniques target the valvular apparatus, such as the annulus. One such procedure, annuloplasty, aims to restore normal annular size and geometry by applying

a prosthetic ring directly over the annulus or by placing a distal device (in the coronary sinus, for instance). This device applies external pressure over the valve, thereby improving the leaflets' coaptation. A fourth type of repair involves the implantation of artificial chordal tendineae. The implants are designed to replace damaged chordae by fastening the papillary muscle to the prolapsing portion of the leaflet.

It is important to point out that many other techniques are being explored. Minimally invasive repair is complex and requires highly skilled clinicians. Therefore, procedure streamlining will be necessary before these approaches are widely adopted. Figure 4 shows a non-comprehensive list of repair technologies in development.

MITRAL VALVE REPLACEMENT

Following successful outcomes with transcatheter aortic valve replacement and mixed results with catheter-based mitral valve repair, mitral valve replacement has moved into the investigational spotlight. As described previously, minimally invasive repair is complex, requiring highly skilled clinicians.

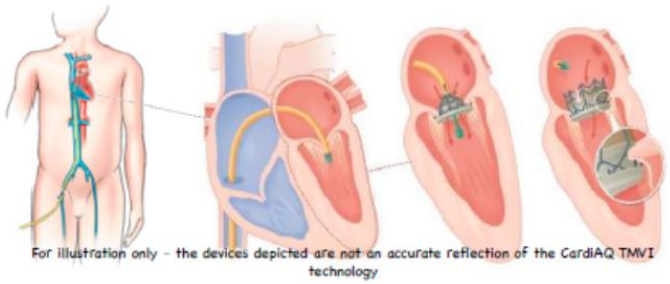

Figure 5: Transfemoral delivery of mitral implants.
Source: CardiAQ Valve Technologies

Consequently, the rationale for total valve replacement is to simplify and standardize the procedure across a wider range of lesions.

Figure 5 shows how an artificial mitral valve is delivered using a transfemoral approach. Once inside the heart, the implant is positioned on top of the natural valve. However, delivering a frame that is adaptable to the shape of the annulus with a reliable anchoring system are still important challenges in valve replacement.

Figure 6 presents a non-comprehensive list of replacement technologies in development.

Company Name	Description
Medtronic	Self-expanding and D-shape valve using transatrial access. First human study is expected in 2014.
Edwards	Clinical outcome data expected in 2014.
CardiAQ	Second generation valve delivered through transvenous access. System has a proprietary anchoring system for annular attachment without radial force. Human study for the 2nd generation valve is expected in 2014.
HighLife SAS	Minority investment by Sorin with an option-to-buy. In development.
Micro interventional Devices (Endovalve)	Transapical access. In development.
Mitrassist	"Valve-in-valve" concept preserves the natural valve functionality. Implant is delivered transapically. Human studies expected in 2016.
Neovasc (Tiara)	Repositionable self-expanding frame implanted transapically. Human study anticipated in the first half of 2014.
Valtech (CardioValve)	Transapical system with expected development of a transfemoral access. Currently under preclinical evaluation and expected to enter clinical testing during 2014.

Figure 6: Mitral valve replacement programs.
Source: Sectoral, companies' websites, December 2013

THE CASE OF MITRACLIP

In 2009, Abbott made a bold move in mitral valve diseases, acquiring Evalve for USD 320M. Since then, Evalve's MitraClip has been approved both in the US and Europe.

MitraClip targets the treatment of severe MR using a minimally invasive technique to repair mitral leaflets called "edge-to-edge." The two leaflets are sutured in the middle, leaving openings on both sides for the blood to flow. As with other transcatheter devices, MitraClip is delivered inside the heart through the femoral

vein in the leg.

Figure 7: The MitraClip System.
Source: http://www.hivehealthmedia.com/mitraclip-approach-managing-valvular-heart-diseases/, December 2013

In the US, a multicenter, randomized trial compared outcomes for patients undergoing MitraClip repair with conventional surgery. The results showed the device to be safe and durable, but less effective than surgery: at the 1-year endpoint, 20% of MitralClip patients required surgery for mitral valve dysfunction, versus 2% for surgical patients. Even though highly skilled physicians performed the MitraClip repair, the overall procedural success rate was only 85%, demonstrating the technical challenges associated with the device. At Abbott's FDA advisory committee hearing, the panel confirmed the safety of the MitraClip system, but raised concerns about its efficacy, due to what the members felt were shortcomings in the analysis of the combined cohorts and ambiguity in the wording of the proposed indication. In the end, the committee endorsed the mixed data set and recommended approval, affirming that the benefits outweighed the risks in patients with significant symptomatic MR who are poor candidates for surgery. The FDA subsequently approved MitraClip in October 2013.

Abbott is conducting additional clinical trials to evaluate the effect of MitraClip treatment on the progression of heart failure and collect substantiating efficacy data to improve the rate of reimbursement. To this end, a pair of prospective, randomized trials are underway: COAPT in the United States and RESHAPE-HF in Europe. Outside the US, the repair system is used principally in high-risk patients who suffer from FMR. Despite the modest efficacy data, MitralClip has achieved an annual run rate of USD150MM, demonstrating the need for less invasive solutions to mitral valve disorders.

CONCLUSION

The future of minimally invasive techniques to restore mitral valve function is bright. The market is sizable, under penetrated, and there is a strong demand for better alternative therapies. The variety of clinical approaches under investigation will be interesting to follow over the next 12 to 24 months, with numerous first-in-man trials set to begin. Over time, as acute and chronic data are published, we will be in a better position to assess the competitive profile of each therapy.

No doubt the mitral market remains a difficult investment opportunity at present, with only a few large publically traded companies and a long list of privately owned firms active in the mix. Acknowledging the limited amount of information on the technologies being developed, we like the competitive positions of CardiAQ and Valtech. CardiAQ replacement implant has already been tested on humans, and enhancements are being incorporated on a second-generation platform. Valtech's toolbox approach, which offers a range of repair and replacement solutions, is also worth watching. Meanwhile, among the publically traded companies, Edward Lifesciences could be an interesting way to play mitral valve. The company is an artificial heart valves pure play and is the market leader in TAVR. Admittedly, TAVR is under competitive pressure, but the next leg of growth could lie in Edwards' mitral valve program, which is about to enter human trials. As the feasibility of these approaches becomes better established and clinical outcomes improve, we expect that the investment hurdle will abate, as privately owned firms take the IPO route or get acquired by larger companies looking to become engaged in the market.

Notably, while the progress made with minimally invasive repair has been encouraging, replacement technologies have the potential to further disrupt the market by simplifying and standardizing the procedure across a wider range of lesions. It is important to remember that the different approaches are in early stages of development, and many hurdles are still to be cleared. The most prominent outstanding barriers are valve durability and anchoring sustainability. Therefore, expectations should be held in check.

Finally, minimally invasive approaches might not only change how therapies are performed, but also when they are performed. Being potentially less risky than their surgical counterpart, minimally invasive procedures could potentially be undertaken earlier in the course of disease, before the onset of heart failure symptoms and left ventricle dysfunction. As a result, patient survival and quality of life could be enhanced.

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