BRYAN, GARNIER & CO

MedTech

TAVI is VITAL

December 2016

Healthcare

Healthcare White Paper

Transcatheter Aortic Valve Implantation/Replacement is a minimally-invasive surgical technique which is the best alternative to Surgical Aortic Valve Replacement in inoperable or high-risk patients. The procedure is gaining increasing interest among surgeons and its approx. USD2bn market size could double towards 2020, showing a healthy 18% CAGR. While large players are dominating the US market for now, the dynamics of the European market have favoured the emergence of smaller players which are gaining ground.

- **TAVI is a young technology pioneered in Europe to treat severe symptomatic aortic stenosis (3.4% of >75yo people)** and provides an alternative to patients deemed at high-risk for Surgical Aortic Valve Replacement/open-heart surgery and otherwise inoperable. It consists of replacing the aortic valve either through the femoral artery or transapically (small incision in the chest).

- **The approx. USD2bn TAVI market could double towards 2020, harbouring a healthy 18% CAGR**. TAVI's penetration is still relatively low in the >400k high-risk patients eligible for the procedure in the US, Europe and Japan. A growing body of clinical evidence and cost-effectiveness of the procedure should drive penetration further. Although penetration in low-risk patients should be slower, it represents a significant growth reservoir (80% AS patients are of intermediate to low-risk).

- **Currently in a duopoly situation, the US market should be shaken-up with the entrance of large players within the next two years. The structure of the European market has favoured the emergence of smaller players** which are putting the emphasis on differentiated clinical data, strong customer service and involvement of surgeons in the development process to gain market shares on the back of large players operating from the US.

- **We see transcatheter systems to also be used for mitral replacement** and believe that this would potentially enable smaller players to catch-up with large ones in a population group three-times larger than aortic stenosis. First systems are currently being developed in this indication.

Contents

1. Do not open your heart to anything

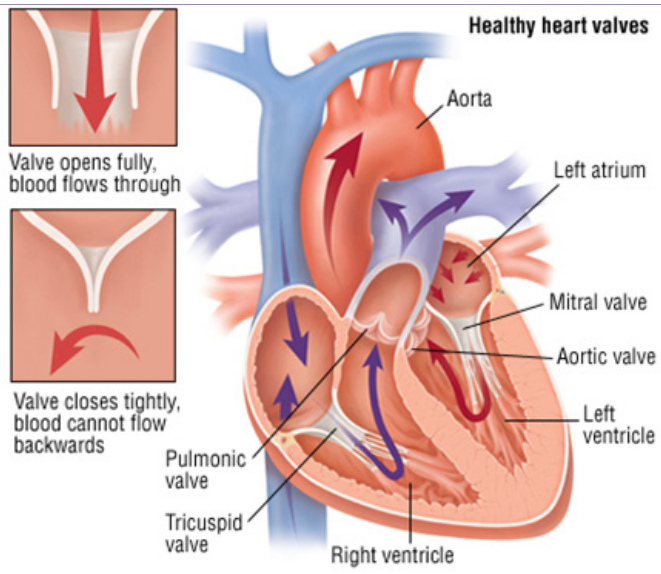
1.1. Heart valve functions

The heart-valve system is composed of four valves which have a key role in operating the heart and managing the blood flow through the circulatory system. **Heart valves open when the heart pumps so that the blood can flow forward, and closes in between every heartbeat so the blood cannot flow backward (regurgitation).**

Aortic valve holds the oxygen rich blood in the left ventricle, the strongest and largest chamber in the heart.

First, the tricuspid valve opens to allow blood coming in from the body to flow into the heart (right atrium to right ventricle). Then, the pulmonary valve will allow blood to be pumped from the heart to the lungs through the pulmonary artery where it will receive oxygen. The oxygen-rich blood will be collected via the mitral valve which separates the left atrium from the left ventricle. Finally, the aortic valve will hold the oxygen-rich blood in the left ventricle, the strongest and largest chamber in the heart, before it is pumped out into the body.

Fig. 1: Human heart (structural overview)



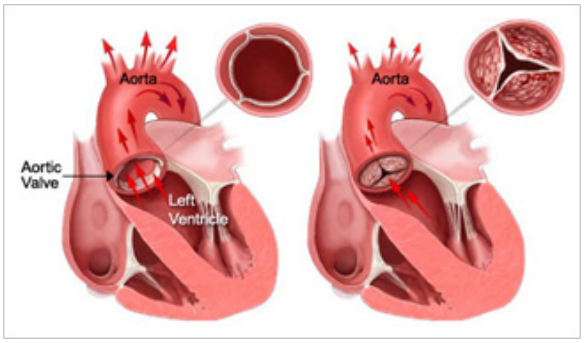
Source: Health.harvard.edu.

1.2. Aortic Stenosis is a common disease

AS is a condition that limits the blood flow into the body

Heart-valve diseases can affect any of the four valves. Aortic Stenosis (AS), either from congenital or degenerative aetiology, is one of main aortic valve diseases. In people with AS, the aortic valve narrows (down from ~4cm^2 to <1cm^2 in severe AS) and does not completely open during contraction (systole), **limiting the blood flow (stenosis) into the aorta and hence into the body**. This condition can occur together with a leakage of the valve, leading the blood to **flow backward (regurgitation)** as it closes after each heartbeat, when the left ventricle expands again (diastole).

Fig. 2: Aortic Stenosis (AS)



Source: http://healthcare.utah.edu/cardiovascular/.

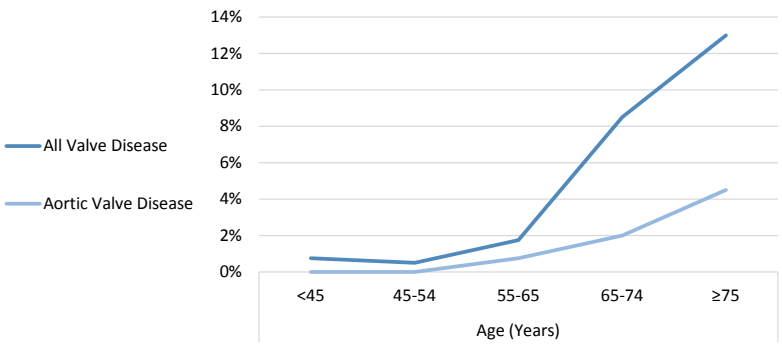
Patients suffering from degenerative AS represent >50% of cases.

Patients suffering from congenital AS (bicuspid valve with a fusion of two out of the three leaflets of the valve) represent 40-50% of patients with AS and the condition often occurs in the younger age group. Patients suffering from degenerative AS represent over 50% of cases. **Ageing and scarring of the aortic valve leads to progressive calcification of the leaflets in this population group which tends to be older**. Note that a third aetiology representing a marginal portion of people is due to rheumatic fever.

Prevalence of up to 9.8% in patients aged 80 to 89 years old. Prevalence of 3.4% in the elderly (>75 years old).

Degenerative AS is an age-related condition. While prevalence is <1% in patients aged 50 to 59 years old, it increases to **up to 9.8% in patients aged 80 to 89 years old (*British Medical Journal*)**. AS is often preceded by aortic sclerosis, which is defined as aortic-valve thickening seen on echo but without flow limitation. The latter condition affects approx. 25% of >65 years old people, and 17% of people with aortic sclerosis will progress to AS. A recent meta-analysis based on data from seven trials (n=9,723) found that the pooled prevalence rate of AS in the elderly, i.e. >75 years old, was 12.4% and the **prevalence of severe AS patients was 3.4%** (*Osnabrugge RJ* et al.*; Aortic Stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic-valve replacement: a meta-analysis and modelling study; JACC*). **Out of this patient pool, 75.6% were symptomatic AS patients.**

Fig. 3: Prevalence of moderate or severe valvular heart disease by age



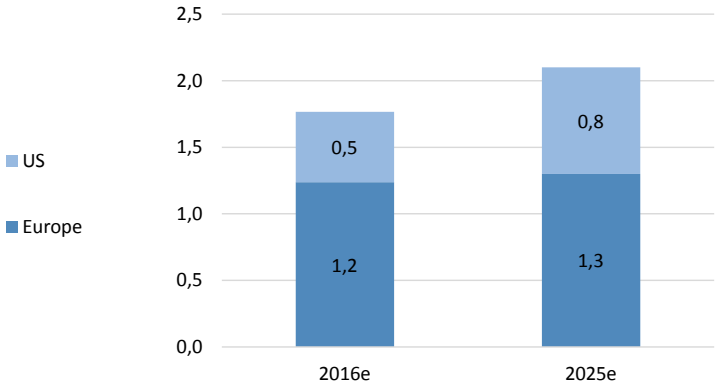
Source: Nkomo VT et al.*, Burden of valvular heart diseases: a population-based study, 2006; Lancet.*

Symptomatic severe AS population to increase 2.5% p.a. towards 2025.

Demographic trends show that the number of patients suffering from symptomatic severe AS should increase ~2% p.a. towards 2025. While approx. 1.2m elderly people across Europe and 0.5m people in the US are estimated to have severe symptomatic AS, ageing of the population should be the main driver, with an estimated 1.3m and 0.8m patients suffering from the disease in 2025 in Europe and the US, respectively.

Please see the section headed "Important information" on the back page of this report.

Fig. 4: Demographics increase severe symptomatic AS population (in millions)



Source: adapted from Osnabrugge RJ et al. *(Full reference on page 4 of this report).*

50% mortality at 2 years, no treatment to prevent the progression of AS

Patients with symptomatic severe AS have a poor prognosis with mortality from the onset of symptoms of approx. 25% at one year, 50% at two years and 80% at five years (*Ross J Jr., Braunwald E. Aortic stenosis. Circulation 1968; 38:61*). On top of the high mortality rate, AS is a very debilitating disease in its severe stage (chest pain, syncope, heart failure). There is currently no approved treatment except for surgery to prevent the progression of AS.

1.3. Current SoC leaving plenty untreated

SVAR is the current SoC

Surgical Aortic Valve Replacement (SAVR) is still the most commonly-used procedure for patients suffering from severe AS. Such a procedure would require a cardiothoracic surgeon to perform a sternotomy (opening up the patient's chest) and the use of a heart-lung machine to maintain the blood flow into the patient's body as the procedure is performed. The surgeon, via the aorta, will replace the aortic valve by either a mechanical valve or a biological one (also called bioprosthesis). In recent years, the market has shifted towards an increased use of biological valves. Indeed, haemodynamic demands on the valve are less in older patients (>75 years old) who represent the bulk of patients undergoing SAVR. Mechanical valves, however, remain the favoured alternative for younger patients due to their increased durability and despite lifelong administration of an anticoagulant. Surgical progress now enables mini-invasive valve surgery (MIVS) which does not require a sternotomy and implies less scarring.

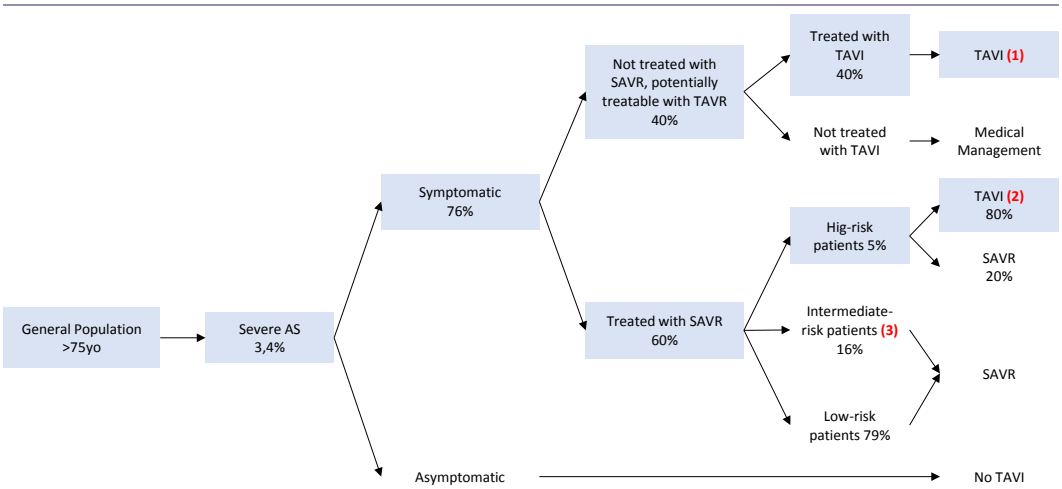
Fig. 5: Mechanical and tissue (biologic) aortic valve for SAVR

Source: Livanova - Fitline Bicarbon (mechanical valve) and Mitroflow (biological valve).

40% of patients turned down, mainly due to age

Although the number of patients suffering from symptomatic severe AS is significant, less than 60% of them undergo SAVR/MIVS each year as eligibility for a major surgical procedure is dependent on each patient's health score and the assessment of an interdisciplinary "heart team". The decision of the "heart team" to do a surgical intervention would be based on the consideration of a risk assessment score, amongst other discretionary criteria. The STS-PROM score is mostly used in the US while the EuroSCORE is the reference score in Europe. Note that a patient would be deemed at high risk with a STS (Society of Thoracic Surgeons) score of >10 (STS risk calculator allows for the calculation of a patient's risk for cardiac surgery and other morbidities) while the log. EuroSCORE would consider that a patient is at high-risk for cardiac surgery if his mortality risk is >20%.

Fig. 6: Prevalence of severe AS and treatment paradigm



Category	Area	Eligible patients (2016; in k)
(1) no SAVR → TAVI	Europe	198k
	USA	84k
	Japan	69k
(2) SAVR high-risk → TAVI	Europe	30k
	USA	13k
	Japan	4k
Total	Europe	228k
	USA	97k
	Japan	79k
	Europe + USA + Japan	**404k**
(3) SAVR Intermediate-risk → TAVI	Europe	12k if 10% penetration
	USA	5k if 10% penetration
	Japan	4k if 10% penetration

Source: Osnabrugge RJ et al. *(Full reference on page 4; STS-PROM score considered); World DataBank.org*

It is estimated that approx. 40% of patients (>75 years old) are left untreated. Indeed, the invasiveness of open heart surgery carries significant risks for the elderly, not only for those with concomitant severe systolic heart failure or coronary artery diseases but also patients with comorbidities (chronic kidney disease, chronic respiratory dysfunction …). Postoperative morbidity is also important in the elderly with close to 10% of patients over 80 years old undergoing SAVR dying within 30 days after surgery. For these patients which are more than 400,000 in the US, Europe and Japan, TAVI is the best alternative to SAVR.

2. TAVI is the best alternative to SAVR

TAVI was pioneered in France in 2002.

Transcatheter Aortic Valve Implantation (TAVI or TAV Replacement) is a relatively new surgical procedure which is gaining increasing recognition from surgeons in both the US and Europe as it is benefiting from a growing body of positive evidence. It was pioneered in 2002 with the first in-human performed in Rouen (France) by interventional cardiologist Alain Cribier, who also co-founded Percutaneous Valve Technology, a US start-up bought by Edwards LifeSciences in 2003 for USD125m (plus USD30m in milestones). The first valve received its CE mark in 2007. As of today, more than 10 valves have been approved for implantation using TAVI in severe symptomatic AS patients either in Europe or the US. Over the past decade, not only has **TAVI allowed patients deemed at high risk and ineligible for surgery to be operated but it has also become a reliable therapeutic alternative to SAVR in lower-risk patients**.

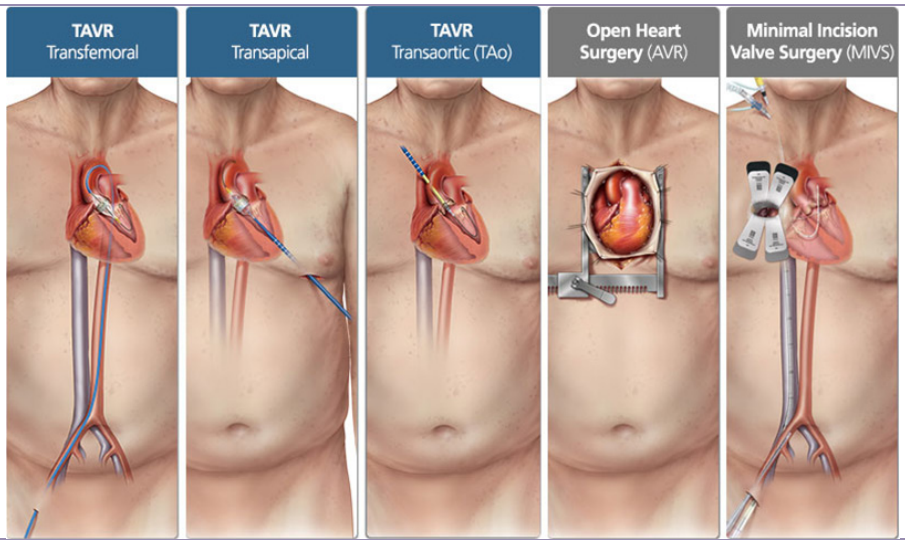
The technology is gaining momentum as a growing body of clinical evidence shows it is a reliable alternative to SAVR.

2.1. Less cumbersome surgical procedure

TAVI is a mini-invasive alternative to open heart surgery

In contrast to SAVR, TAVI consists of the replacement of the aortic valve without removing the old one through very small chest openings that leave all the chest bones in place. The procedure which can be done either through the femoral artery (transfemoral, TF) or transapically (TA;between the ribs through the heart's wall) wedges a new valve into the aortic's valve place. When the new valve expands, the old leaflets are pushed out of the way and the replacement valve's leaflets start to regulate the blood flow. Note that other approaches such as direct aortic (TAo), subclavian or transcarotid could also be used when patients are ineligible for transfemoral or transapical. Patient's risk for cardiac surgery as well as comorbidities and concomitant diseases are the main decision-making drivers for the "heart team", closely followed by ease of access which will influence the route chosen by surgeons. We would note that while interventional cardiologists, known for being early adopters, have rapidly adopted the transfemoral route, conversion of the cardiac surgeons from transfemoral to the transapical took longer.

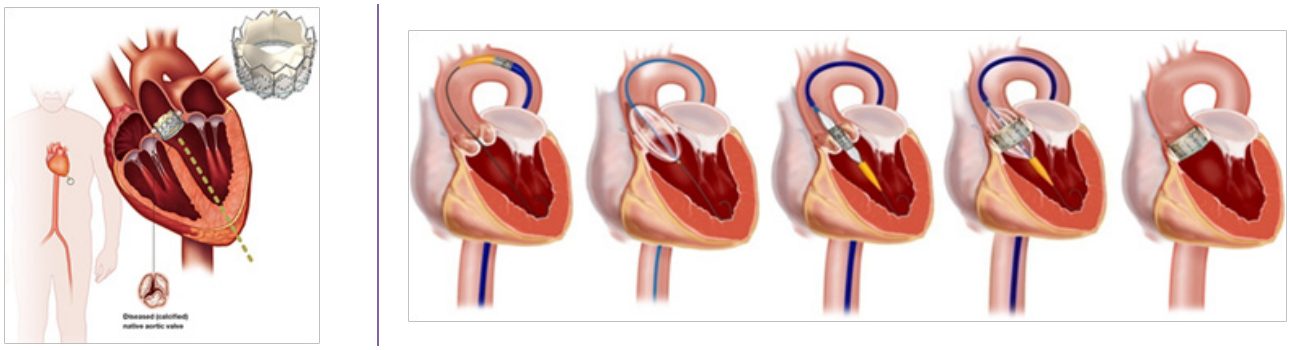
Fig. 7: TAVI vs. open heart surgery



Source: MIOT institute of Cardiac Care.

A TAVI valve's leaflets are either made of porcine or bovine heart tissue which are held in place by a compressible metallic frame (stent). A skirt (in PET or fabric) is integrated on the outside of the metallic structure which comes in contact with the aortic valve annulus to minimise paravalvular leaks.

Fig. 8: Transcatheter valve

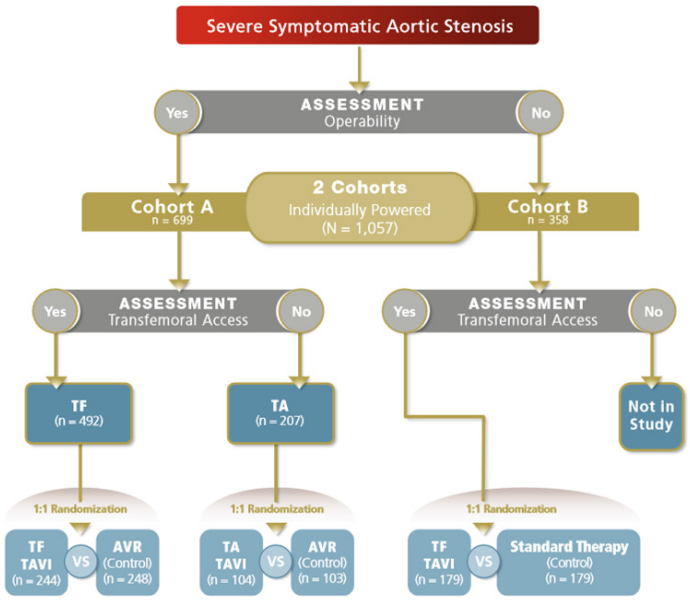


Source: http://www.heartvalvexpert.com.

2.2. A growing body of clinical evidence

The PARTNER trial, sponsored by Edwards, was the first prospective, randomised, and controlled trial to assess the safety and efficacy of TAVI in high-risk patients with severe symptomatic AS either surgically eligible (cohort A, n=699) or deemed inoperable (cohort B, n=358). Results from this trial which demonstrated the non-inferiority of TAVI compared to SAVR were the base for the filing for FDA approval of the first TAVI device in 2011. The long-term results of the trial were also encouraging for TAVI. At two-years, overall survival in both TAVI groups either deemed inoperable or surgically eligible was 56.7% and 66.1% vs. 32% and 65% for the control groups being pharmacological treatment and SAVR respectively.

Fig. 9: PARTNER trial protocol and results



	30 Days[4]			1 Year[4]		
Outcome	Edwards SAPIEN THV (n = 348)	AVR (n = 351)	*P* Value	Edwards SAPIEN THV (n = 348)	AVR (n = 358)	*P* Value
All-Cause Mortality	3.4%	6.5%	.07	24.2%	26.8%	.44
All Stroke or TIA	5.5%	2.4%	.04	8.3%	4.3%	.04
Major Stroke	3.8%	2.1%	.20	5.1%	2.4%	.07
Major Vascular Complications	11.0%	3.2%	< .01	11.3%	3.5%	< .01
Major Bleeding	9.3%	19.5%	< .01	14.7%	25.7%	< .01
New Atrial Fibrillation	8.6%	16.0%	< .01	12.1%	17.1%	< .07
New Pacemaker	3.8%	3.6%	.89	5.7%	5.0%	.68

Source: Edwards Lifesciences.

The findings of the above-mentioned trial have been confirmed in several studies conducted over the past five years either with the use of a self-expanding or a manually-expanding valve (*cf Chapter 3.2*). It is important to note that most of completed or ongoing trials allow the use of any surgical device to be compared to TAVI, which is a reflection of the real-life setting in our view. Indeed, most of the devices can be used in approx. 80% of patients.

2.3. TAVI not only benefiting the patients

Less perioperative risks

The TAVI procedure carries less perioperative risks which has to be considered in a high-risk profile patients' population. Its non-invasiveness, coupled with the shortened time of the procedure compared to surgical aortic-valve replacement and the non-requirement for a heart-lung-machine, makes it a preferred alternative.

Cost-effectiveness

- Despite higher procedural costs for TAVI versus SAVR, several studies have shown the cost-effectiveness of the procedure due to reduced post-surgical costs (post-operative hospital stay amongst others). A cost utility study carried out in a UK high-risk AS population with the National Institute of Clinical Excellence (NICE) references, known for being tough, demonstrated that on a GBP20,000 willingness to pay threshold per Quality of Life (QALY) gained, TAVI had a 65% likelihood of being cost-effective vs. 35% for SAVR (*Fairbairn T* et al.*; The cost-effectiveness of TAVI versus SAVR in patients with severe aortic stenosis at high operative risk; Heart 2013 Jul.).* The procedure is recommended by NICE.

Easy scheduling of procedures

- Moreover, not only does TAVI allow surgeons to schedule surgery easily but it also means hospitals and clinics do not have to use operating theatres as the procedure can be carried out in a catheter lab or a hybrid room, making it easily more profitable compared to SAVR.

Fig. 10: Advantages of TAVI over SAVR

TAVI procedure superior to SAVR on all key parameters

	SAVR	TAVI
Procedure length	3 to 4 hours	1 to 2 hours
Anaesthesia	General	General or Local + Sedation
Heart-Lung -Machine	YES (heart is stopped, bypass necessary)	NO (heart functioning during surgery)
Post-operative Hospital Stay	~2 weeks	~1 week

Source: Bryan, Garnier & Co estimates.

No mid- to long-term alternative to TAVI

While TAVI is a promising surgical alternative to SAVR and the use of mechanical or tissue heart valves, we see no medium- to long-term alternative to TAVI which could either: 1/ prevent the development of AS (i.e. pharmacological treatment), or 2/ replace TAVI procedures.

3. Fastest growing segment in Medtech

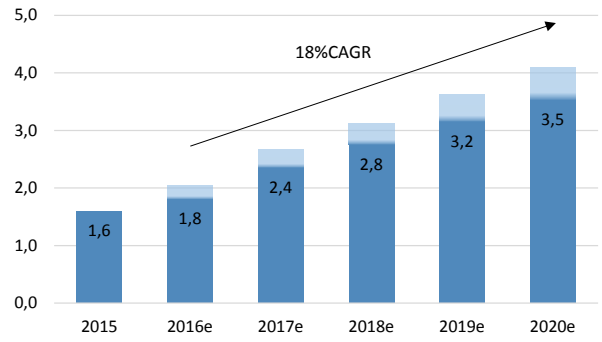
3.1. TAVI market to double by 2020

A USD2bn market growing >18%CAGR

USD2bn market to be worth USD3.5-4.1bn towards 2020, growing >18% p.a.

TAVI is a buoyant market which is estimated to be slightly above the USD2bn mark in 2016. Penetration should accelerate in the coming years supported by demographics, innovation and the growing body of evidence. There are different views on TAVI's global market size towards 2020. While the most bearish scenario estimates it at around USD3.5bn, the bulls view it above USD4bn. All in all, average market growth should be 18%p.a., making it one of the fastest growing segment in Medtech.

Fig. 11: Worldwide TAVI market (2015-2020e)

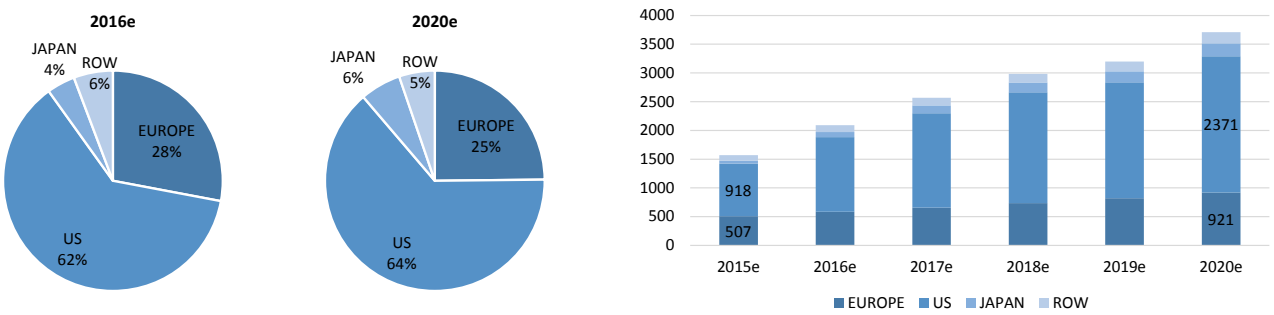


Source: Edwards Lifesciences; St Jude; Research and Markets, Millennium Research.

European population eligible for TAVI more than twice as large as in the US. However US representing 2/3rd of the market

While the European population eligible for TAVI is more than twice as large as it is in the US, Europe accounts for less than half of procedures (i.e. 45%). Lower pricing (>40% discount) and country by country reimbursement decisions do not make all European countries attractive for TAVI players. Hence, the market in value is largely geared towards the US which in 2020 should represent around 65% of the global TAVI market. It is important to note that 1/ share of the US will be dependent on the adoption pace of TAVI in lower-risk populations (see *Chapter 3.3.*) and 2/ Europe should still represents 25% of the TAVI markets towards 2020 as lower prices may render it less likely to price competition.

Fig. 12: Evolution of TAVI's market geographical split (USDm)

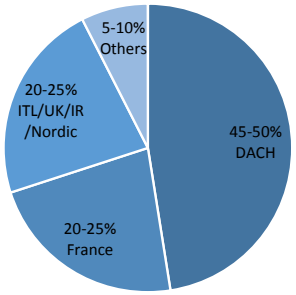


Source: Edwards; St Jude Medical (acquired by Abbott); Research and Markets, Millennium Research.

Segmented European market with high penetration in DACH

The European market is estimated to be worth around EUR600m in 2016, representing almost one-third of the global TAVI market. Penetration rates in the region vary widely and country by country reimbursement decisions have led to a fast adoption of TAVI in countries with a Diagnosis-Related Group (DRG) in place such as Germany. DRG codes have given hospitals the opportunity to make TAVI procedures highly profitable. However, countries in which implantable medical devices are not included in the hospital budget list have seen lower adoption rates (e.g. Spain, Portugal). Hence, looking at volumes, the penetration of TAVI is amongst the highest in the world in DACH (Germany, Austria and Switzerland) which represents almost 45% of the European market with ~200 implants per million inhabitants (p.m.i.), followed by France which is accounts for ~25% of the European market (~115 implants p.m.i.). The rest of Europe benefitting from lower reimbursement has a lower penetration rate: ~49 p.m.i. in Italy, ~56 p.m.i. in the Nordics countries, ~34 p.m.i. in the UK/Ireland. Rest of Europe (excluding DACH & France) represent around 40% of the European market.

Fig. 13: European TAVI market (in units sold) - reimb. attractiveness by country



Reimbursement Attractiveness of TAVI	
DACH	+++
Italy	++
UK/Ireland	++
Nordic Countries	++
France	++
Spain and Portugal	+
BeNeLux	+

Source: BIBA; Bryan, Garnier & Co.

US market worth >USD1bn

The US market is estimated to be worth in excess of USD1bn. Higher barriers to entry in the country (i.e. IDE studies) have prompted large TAVI players to increase their footprint in the region where the average selling price (ASP) of TAVI devices are >40% higher than in Europe.

3.2. Innovation driving penetration further

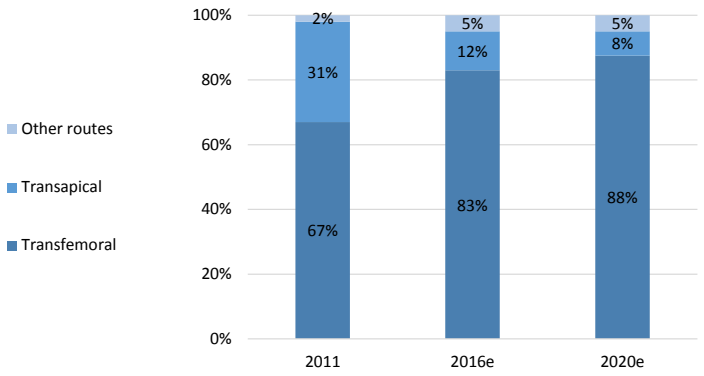
■ Over the past decade, TAVI has been a highly innovative segment

Transfemoral versus Transapical or mini- to ultra-mini-invasive surgery

Transfemoral procedures represent 85% of TAVI procedures

While initial TAVI procedures where performed through the transapical (TA) route at the beginning of the decade, transfemoral (TF) now holds the lion's share. It is estimated that TF TAVI procedures now represent roughly 85% of all TAVI procedures. TA which involves: 1/ general anaesthesia and 2/ a mini-thoracotomy (small incision in the patient's chest) represents around 10% of all TAVI surgeries. The latter approach is used when the patient's artery is too narrow for the catheter to pass through (atherosclerosis). Alternative routes (direct aortic, subclavian…) represent around 5% of procedures. In order to reduce vascular complication rates, TAVI players are miniaturising vascular access sheaths and delivery systems with sizes down from 24French (0.8cm or 0.31in) in the early 2000s to 14/16F (0.47/0.53cm or 0.18/0.21in) for the latest valves.

Fig. 14: TAVI mix by access site (frequency of use as a % of all TAVI procedures)



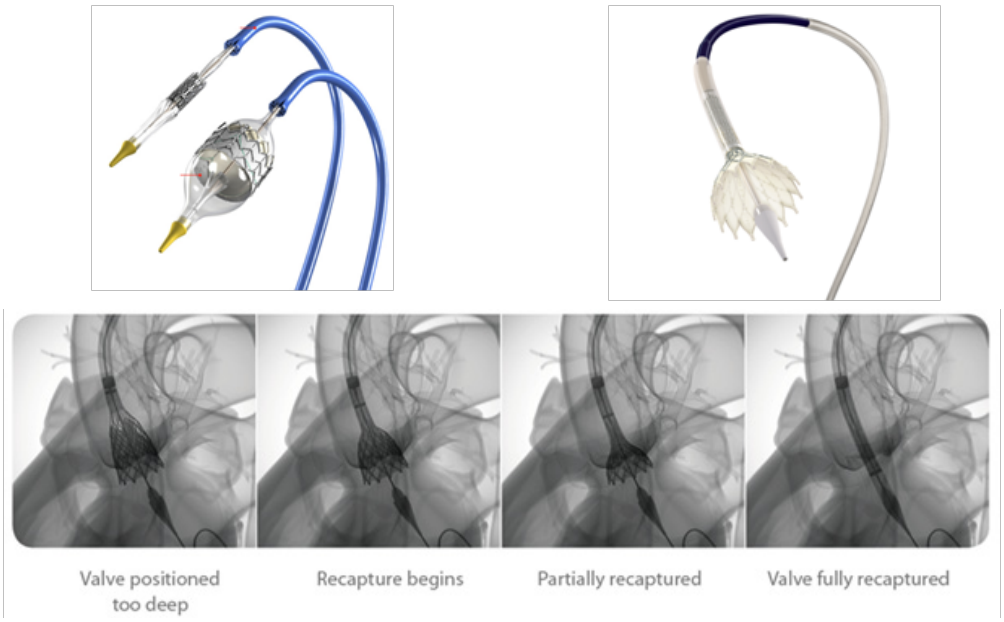
Source: BIBA, St Jude Medical (acquired by Abbott).

Two main systems:
- manually-expanding,
- self-expanding valves

Manually-Expanding or Self-Expanding, re-sheathable or not

Once put in place by the surgeon, and depending on its type, the valve can either: 1/ be expanded manually with the help of a balloon (Balloon-Expanded, BE or Manually-Expanding valves ME), or 2/ self-expand (Self-Expanding valve SE) when released from the delivery catheter.

Fig. 15: TAVI delivery systems (balloon-expanded, left / self-expanding, right) and recapture of self-expanding valve (bottom)



Source: Edwards SAPIEN 3 transcatheter aortic heart valve (BE/ME) and Medtronic CoreValve (SE)

Manually-expandable valve for precise positioning but could cause annular rupture

The technique behind manually-expandable valves relies on a fast and controlled expansion of the balloon and, hence, the valve. While this allows for a precise positioning as surgeons are deploying the valve for less time, it could cause an annular rupture. This situation, which has been exclusively observed after the use of a balloon-expandable valve, is often fatal. Conversely, self-expandable valves expand slowly due to heat generated by the continuous movement of the heart. By the time these valves fully deploy, they could move to the wrong position. Hence, the need for "recapturability" as a solution to avoid leakage-impaired haemodynamics and other complications. Note that "recapturability" can only be done with self-expanding valves.

"Recapturability" of self-expanding valve is a significant milestone

Need for "recapturability" initially driven by high pacemaker rate from bottom-up deployment of self-expanding valves

The need for recapturability has been driven by the bottom-up deployment technique of most self-expanding aortic valves. Indeed, when the valve is opened in a bottom-up fashion, i.e. against the blood flow, it is less stable during its positioning in the aorta and could be "ejected". To address this issue, interventional cardiologists initially started to deploy the valve low in the left ventricle triggering high pacemaker rates.

3.3. All eyes on lower-risk patients

While it is widely recognised that TAVI is either the only option or the best alternative to SAVR in high-risk patients suffering from symptomatic severe AS and deemed inoperable or ineligible to surgery respectively, an increasing focus is being put on its use in lower-risk patients.

■ Encouraging results in intermediate-risk patients

TAVI non-inferior to SAVR in intermediate-risk patients

The PARTNER II trial evaluated the non-inferiority of TAVI (transfemoral and transapical) vs SAVR in 2,032 patients with severe Aortic Stenosis and an intermediate-risk clinical profile. The primary endpoint at two years was met and showed no significant difference between the two treatment groups. Death from all-causes or a disabling stroke in TAVR patients was 19.3% vs. 21.1% for patients who underwent SAVR (HR 0.89; 95% CI, 0.73-1.09; p=0.25; ITT analysis). Note that a pre-specified non-inferiority margin of 1.2 was set for the upper band of the hazard ratio. Despite being powered to show non-inferiority, detailed analysis of the trial makes us believe that TAVR could well become a preferred option in intermediate-risk patients. While vascular complications were more frequent in the TAVR group as early as 30 days, life-threatening conditions such as major bleeding (likely driven by transfusion), acute kidney injury (1.3% vs. 3.1%, p=0.006; not reported in the table below) and new onset of atrial fibrillation (abnormal heart rhythm) were significantly higher in patients who underwent open heart surgery. These findings were confirmed at two years.

Lower life threatening events with TAVI as early as 30 days

Fig. 16: PARTNER II results

	at 30 DAYS			At 1 YEAR			at 2 YEARS		
Outcome	**TAVR (n=1011)**	**SAVR (n=1021)**	***p-value***	**TAVR**	**SAVR**	***p-value***	**TAVR**	**SAVR**	***p-value***
All-cause Mortality	6.1%	8.0%	*0.11*	14.5%	16.4%	*0.24*	19.3%	21.1%	*0.33*
All Stroke or TIA (Transient Ischaemic Attack)	6.4%	6.5%	*0.94*	10.1%	9.7%	*0.76*	12.7%	11.0%	*0.25*
Disabling Stroke	3.2%	4.3%	*0.20*	5.0%	5.8%	*0.46*	6.2%	6.4%	*0.83*
Major Vascular Complications	7.9%	5.0%	*0.008*	8.4%	5.3%	*0.007*	8.6%	5.5%	*0.006*
Major Bleeding	10.4%	43.4%	*<0.001*	15.2%	45.5%	*<0.001*	17.3%	47.0%	*<0.001*
New Atrial Fibrillation	9.1%	26.4%	*<0.001*	10.1%	27.2%	*<0.001*	11.3%	27.3%	*<0.001*
New Pacemaker	8.5%	6.9%	*0.17*	9.9%	8.9%	*0.43*	11.8%	10.3%	*0.29*

Source: MB. Leon et al.*, TAVR or SAVR in Intermediate-Risk Patients; N Engl J Med 2016; 374:1609-1620*

Potential significant advantage of transfemoral TAVI over SAVR

Moreover, we would note that transfemoral-access TAVR (1,550 patients vs 482 enrolled in the transapical cohort) resulted in a statistically-significant, and not only non-inferior, lower rate of death from any cause or disabling stroke vs. SAVR, i.e. 16.8% vs 20.4% respectively (HR 0.79; 95% CI, 0.62-1.00; p=0.05; ITT analysis). With transfemoral patients representing 76% of the cohort and the p-value being on the border of significance, it might be too early to assert superiority. Nevertheless, it suggests a potential significant advantage in this population subgroup. Based on these findings, EDW gained FDA expanded approval in intermediate-risk patients (summer 2016).

Although the results should be extrapolated carefully, they bode well for use of TAVI in the low-risk group. Indeed, low-risk patients might even be better candidates as they would have better access sites favouring transfemoral procedures. Note that this population is currently being evaluated in EDW's PARTNER III study which should have a readout in H2 2018 (end of enrolment in mid-2017).

■ Still at the beginning of the adoption curve but penetration could be slower…

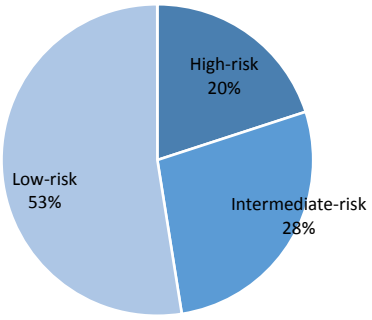
Penetration of TAVI in low-risk patients could be slower than in high-risk patients

We do not rule out that the results from this trial might accelerate the trend towards the adoption of TAVI in intermediate-risk patients. However, while some believe that moving-up earlier in the treatment course could significantly broaden the TAVI market, potentially making it worth USD5bn towards 2021, we believe that the adoption curve in the intermediate-risk population is likely to be slightly slower than initially expected. This cautiousness does not call into question our long-term view that TAVI would supplant SAVR. EDW's Analysts' Day on December 8th should provide more granularity on the development in lower-risk populations.

Inexperienced centres could slow TAVI's adoption rate in intermediate-risk patients

- Moving up in lower-risk patients, which represents a much larger population (see chart below), implies two main impacts. Firstly, it implies that existing centres in which TAVR in high-risk patients is high add capacity. While TAVR allows for a higher number of cases a day, the inflexion is likely to be seen when new centres open. Secondly, the opening of new centres which are inexperienced in the procedure might take time to become so and some may simply be reluctant to either add capacity or adopt new surgical procedures such as TAVI. Also, one needs to consider that new centres might not have all the specialists needed in a heart team.

Fig. 17: Severe symptomatic AS population split depending on risk profile



Source: Nkomo 2006; Iivanainen 1996; Aronow 1991; Bach 2007.

Lack of long-term durability studies for TAVI

- Implantation of TAVI devices in lower-risk patients who are below 75 years old for most of them also raise the issue of the durability of the catheter valve. Results from a long-term follow-up study of 378 patients presented at the 2016 EuroPCR reported that approx. 50% of patients undergoing TAVI had a structural valve degeneration at 8 years. Degeneration in this trial was defined by echocardiography using central lab adjudicated criteria of moderate/severe intravalvular regurgitation and/or Aortic Stenosis rather than the need for re-intervention which defines the degeneration of surgical valve. Considering the pace of innovation in TAVI, we remain confident that the next-generation of TAVI valves or the adaptability of TAVI to alternative procedures such as valve-in-valve (for degenerated bioprosthesis) and the subsequent body of clinical evidence would be supportive of the long-term durability of valves.

4. Competitive Environment

4.1. US market, a lovely duopoly…for now

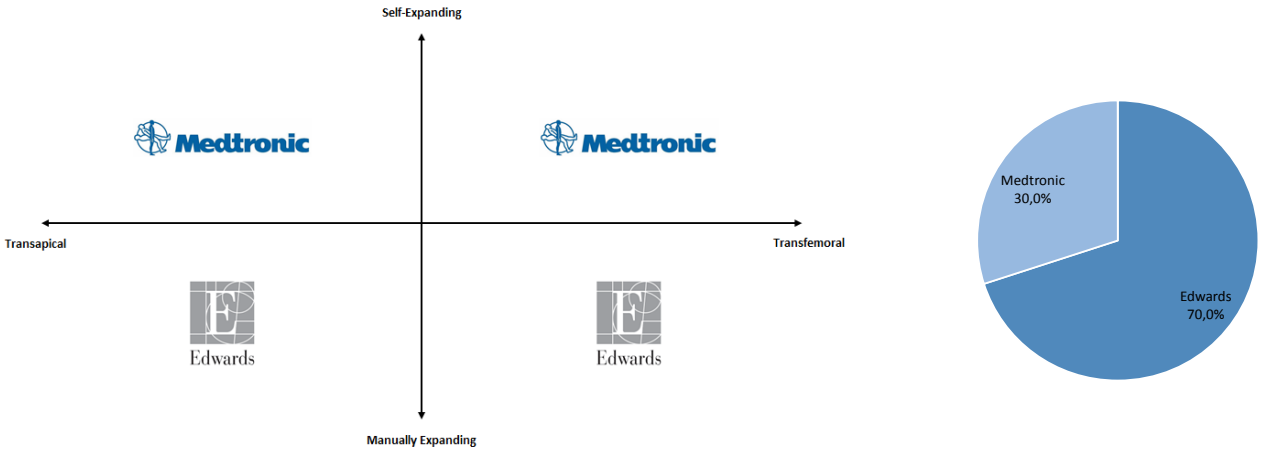
EDW and MDT operating the US market

Need for IDE studies represents high barriers to entry

EDW to reinforce its US leadership by expanding in low-risk patients in H2 2018

The US market, which has high barriers to entry with large and expensive IDE trials that are necessary to file for approval of *de novo* medical devices, has only two players, namely, Edwards and Medtronic. While Edwards entered the US market with its SAPIEN manually-expandable valve in 2011, Medtronic entered the self-expanding segment with the CoreValve in 2014. Since then, Edwards Lifesciences has taken the number one position in the US and has recently reinforced its leadership with the label extension to intermediate-risk patients for its third generation of valve, the SAPIEN 3. Note that Medtronic is lagging approx. one year behind its only competitor as it is expecting the results from its trial in intermediate-risk patients (SURTAVI) to readout in the coming months. Edwards is pursuing a very aggressive, and effective, strategy to keep competition on the sidelines for now. The company locks in small centres with exclusive contracts and has been the first to bet on the expansion of TAVI in lower-risk patients. Indeed, the company is expecting the readout from its clinical study in low-risk patients in H2 2018.

Fig. 18: Competitive mapping of the US TAVI market and estimated market shares



Source: Bryan, Garnier & Co ests

BSX and ABT to enter the US market in 2017 and 2018

JenaValve's positioning in aortic regurgitation for its TA valve

Boston Scientific and St Jude Medical (acquired by Abbott in April 2016) should be the third and fourth entrants in the US market, respectively. Boston Scientific's IDE trial of its Lotus Valve system, REPRISE III, should have its readout in H1 2017 (NCT02202434) with potential approval by mid-2017, while the results from St Jude's study for the Portico valve system are expected in H2 2018 (NCT02000115). Privately-held JenaValve is likely to be the fifth company to enter the US market with its valve system over the course of 2019. The company aims at positioning its valve not only as a treatment for severe Aortic Stenosis but also for aortic regurgitation.

Increased competition in the US would trigger the need for leveraging centres with a broadened transcatheter system offering (TMVR?)

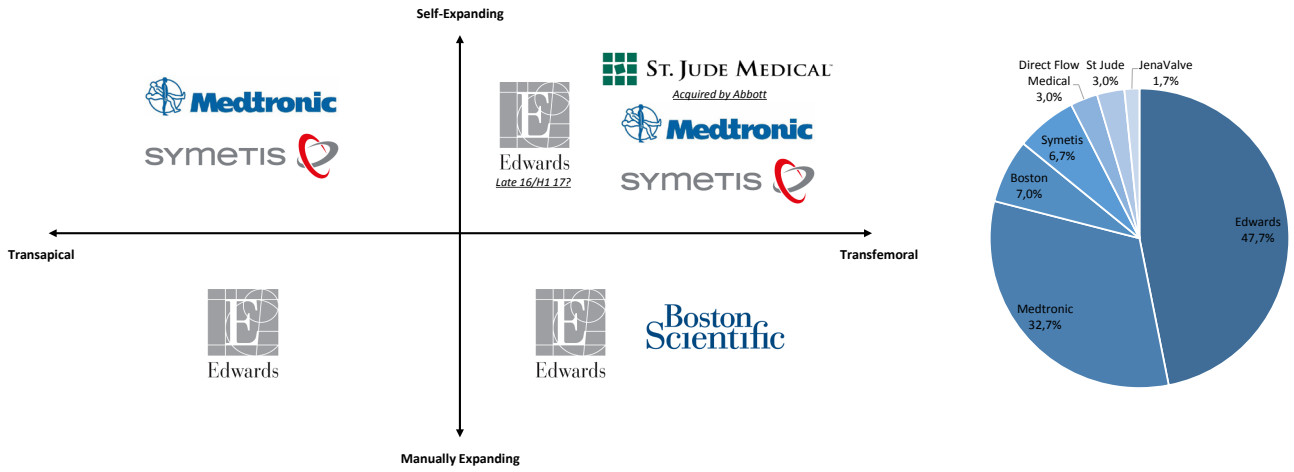
While US average selling prices (ASP) have been constant over the past five years (i.e. approx. USD30k per system), we believe that there will be a disruption with the potential entry of three other companies within the next three to four years. As such, we do not rule out that the ASP decline by 2% to 5% p.a., reinforcing the need for differentiation. Differentiation could come from the ability of companies to leverage centres by moving into the burgeoning transcatheter mitral valve replacement field.

4.2. European market…small is beautiful

Smaller European players include:
- Boston Scientific,
- St Jude Medical (ABT),
- Symetis.

TAVI has a European heritage as well as less restrictive barriers to entry (i.e. IDE trials) which favoured the emergence of smaller players. By mid-2016, EDW's market share in the region has shrunk by over 500bp (vs. Q2 2015) to ~48% on the back of increased competition from Medtronic and above all smaller players, of which Boston Scientific, Symetis and St Jude (now Abbott) by market share position. As shown on Fig. 12, the European market in which TAVI penetration is above 20% is largely geared towards DACH as a consequence of more favourable reimbursement and greater access to reimbursement. Note that Direct Flow Medical does not appear on our European competitive mapping as the company is close to bankruptcy and JenaValve's strategy to develop in TA only does not appear sustainable as TF should become the standard in our view.

Fig. 19: Competitive mapping of the European TAVI market and estimated market shares



Source: BIBA; Bryan, Garnier & Co ests.

■ Many players… what are interventional cardiologists looking for?

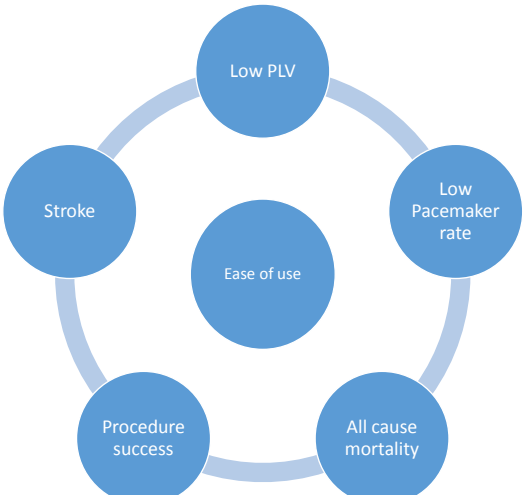
Three systems on the shelf is an opportunity for smaller players to penetrate the market

One size does not fit all. While: 1/ transfemoral access is gaining ground over transapical and 2/ catheter labs are increasingly being used for TAVI procedures vs operating theatres, this could ultimately result in an increased number of interventional cardiologists doing TAVI vs. cardiac surgeons. We believe that this could benefit smaller players as interventional cardiologists usually work with three products (or more) on the shelf vs. only two for cardiac surgeons.

Valves' clinical results
- Paravalvular Leak,
- Pacemaker rate,
- Stroke
- Procedure Success
- All-cause mortality

When it comes to choosing a valve, what are interventional cardiologists looking for? In a much more competitive European market where surgeons have the choice, the valve's performance, i.e. clinical results, is facing increased scrutiny. Feedback from surgeons as well as the review of clinical trial designs suggest that **five main criteria have to be considered to assess the performance of a valve: Paravalvular leak (PVL), Pacemaker rate (PPM), Stroke, Procedure Success and All-Cause Mortality (ACM).**

Fig. 20: Surgeons' decision-making criteria for a valve

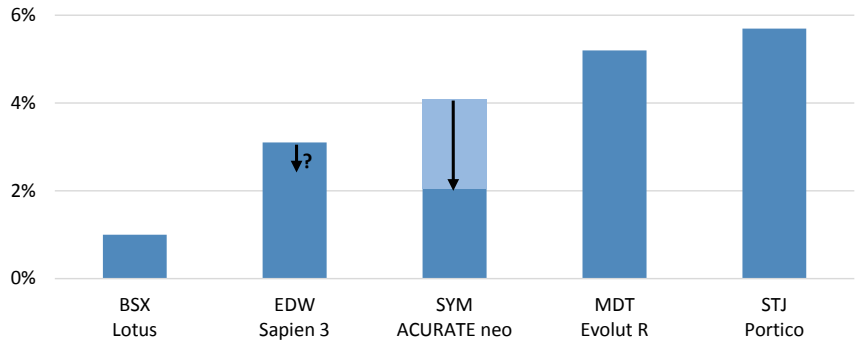


Source: Bryan, Garnier & Co.

PVL is the main criteria to be considered by surgeons

- **Paravalvular leak (PVL)** is a frequent complication of TAVI, seen at a much higher rate after TAVI than SAVR. Privately-held company JenaValve does not appear in the chart below as it is only available through a transapical approach, which should limit its use as transfemoral continues to gain ground. Boston Scientific is also below the 1% mark. Looking at other TAVI players, we would underline that Symetis is developing an improved version of its ACURATE neo, the ACURATE AS (Advanced Seal) which showed a 50% reduction in PVL≥2 (*source: cvpipeline.com*). This might enable the company to be the second best valve in terms of PVL on the European TAVI market, ahead of EDW for which a fourth generation of valve, the CENTERA, has not reported a PVL rate yet. We do not rule out that should most of the patients currently in the PVL≥2 group had a PVL=2, lowering the volume of leakage could enable Symetis to have a PVL≥2 rate close to 0%. Note that both new generation valves (ACURATE neo AS and CENTERA) are not available for commercialisation in Europe (CE mark) yet.

Fig. 21: Available aortic valves (CE marked and TF route) and related PVL ≥ 2 rate



Source: JenaValve; EDW; BSX; STJ; MDT; www.cvpipeline.com.

PPM becomes more important as TAVI is moving in lower-risk patients

- **Pacemaker implantation rate is becoming more important.** At a time when the scientific community is adopting the use of TAVI in lower-risk patients, it is important to make sure that the likelihood of a second surgery for younger patients is minimal. Hence, surgeons are looking

for valves that decrease the post-operative risk of having to implant a pacemaker in patients. PPM is becoming a discriminating factor. Clinical data available to us at the time of analysis put Symetis as a leader in terms of PPM.

Hard to read Stroke and ACM

- **Stroke and All-Cause Mortality (ACM) should be read carefully.** We view these two criteria as composite considering that they could both be linked to the surgical procedure, the patient's health status, the anaesthesia, co-morbidities or concomitant diseases among other. It is not easy to read Stroke and ACM rates and, consequently, consider them valve-related or not. Moreover, we would note that the magnitude of these results are not as high as for PVL and PPM.

Fig. 22: CE marked valves, clinical results

Company	Valve	PVL ≥2	PPM	Stroke	ACM	Pro Suc*
Boston Scientific	Lotus	1.0%	29.0%	5.9%	4.1%	100.0%
Edwards Lifesciences	Sapien 3	3.1%	12.0%	1.2%	2.0%	99.2%
Medtronic	Evolut R	5.2%	16.0%	3.2%	2.5%	99.1%
St Jude (acquired by Abbott)	Portico	5.7%	14.0%	3.1%	3.6%	97.7%
Symetis	ACURATE neo	4.1%	8.0%	1.9%	1.3%	99.1%
Average		3.8%	15.8%	3.1%	2.7%	99.0%
Median		4.1%	14.0%	3.1%	2.5%	99.1%
Min - Max		1.0% - 5.7%	8.0% - 29.0%	1.2% - 5.9%	1.3% - 4.1%	97.7% - 100.0%

**Procedure Success rate*

Source: Meredith2014 (n=120); Wendler2016 (n=1695); Williams2016 (n=241); Manoharan2016 (n=222); Möllmann216 (n=1000).

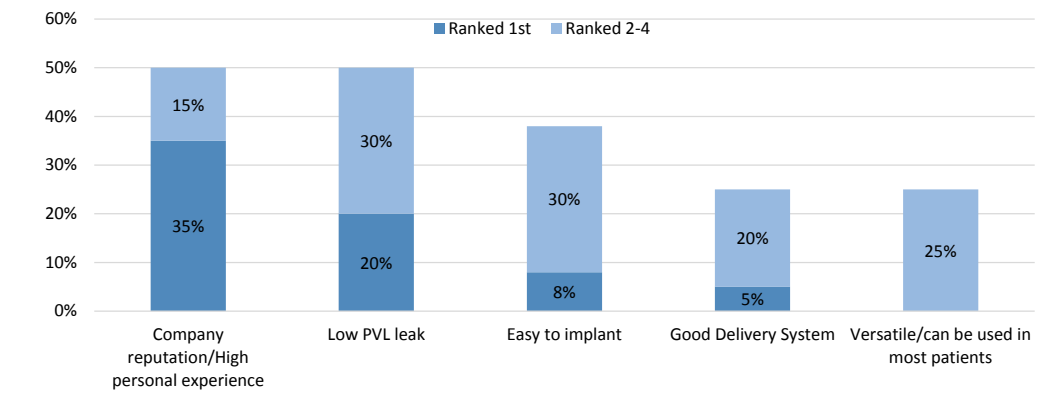
Ease of use important in mini-invasive surgery

- **Ease of use should not be overlooked** in mini-invasive surgery. Moreover, as TAVI is gaining increased ground over SAVR, it is likely that surgeons would prefer to have two to three products that feature an increased use of use. This observation would apply even more as small centres switch from SAVR to TAVI.

EDW's European leadership due to its long-term presence more than valve performance?

Interestingly, while EDW has a strong footprint in Europe, the survey carried out among European surgeons shows that, at the moment, the company does not stand out for the clinical results of its valve but for its long-term presence (first mover advantage). This reinforces our confidence on the positive outlook for smaller players.

Fig. 23: Top 4 reasons why the SAPIEN 3 valve is in the top 4 most used?



Source: MEDEX research (survey carried out in Europe among 26 Cardiac Surgeons and 14 Interventional Cardiologists; 20min in-depth phone interview).

Beyond clinical results, what else is necessary to gain a foothold on the market?

Other market dynamics in the European market need to be considered. We believe they could favour local smaller players.

Gaining recognition by implicating surgeons in the development process

- **Implication of surgeons in the development process**. As final users, surgeons are increasingly looking to be involved in the development processes of products that would most, if not all, of the time be approved first on the European market. Hence, European players (such as Symetis) might be better positioned to create a virtuous circle in which they could anticipate the needs of physicians in their development processes.

Customer service is key

- **Distribution** network is critical in the European market where TAVI has a higher penetration rate than in the US. Smaller players are differentiating against large competitors by putting more resources in product specialists and proximity services, i.e. marketing support, as TAVI is not only a demanding procedure for surgeons but also for "heart teams" more broadly. Networking carried out by smaller players in their local markets (vs. the large US players) to gain brand recognition should not be overlooked as reputation is one of the main reasons why a "heart team" would choose one supplier over another.

Pricing pressure not a competitive driver at this stage

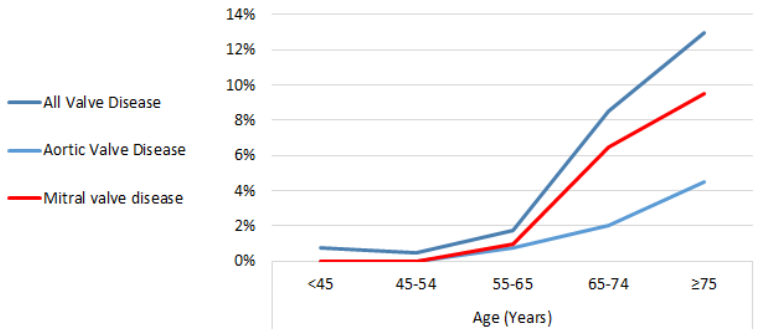
- **Although not being the main competitive driver at this stage, pricing** should also play an important role in the mid-term as TAVI is becoming a more common procedure in hospitals. Democratisation alongside pressure from payers imply price competition (price attrition is a fact of life in Medtech) and we do not rule out that EDW's 20% premium on some of its TAVI systems might be one of the reasons at the source of the recent market share loss. This would reinforce the need for differentiation and supportive clinical data packages.

4.3. TMVR is the next logical step

TMVR market at least twice as big as TAVI

As mentioned previously (*Chapter 3.3. All eyes on lower-risk patients*), broadening the patient base would be the next step of transcatheter valve replacement, firstly in lower-risk patients suffering from Aortic Stenosis, secondly in other areas… and the development of transcatheter mitral valve replacement (TMVR) is underway. TMVR has recently been under the spotlight with the acquisition of several companies such as CardiAQ (Edwards), Tendyne (Abbott) or Twelve (Medtronic) by large TAVI players over the past 12-24 months. However, first results are not clear cut as they are in TAVI. Indeed, mitral valve degeneration might be due to a combination of diseases which makes us believe that the market should evolve towards a combination of repair and replacement. The addressable market for TMVR is two- to three-times larger than that for TAVI.

Fig. 24: Prevalence of moderate or severe valvular heart disease by age



Source: Nkomo VT, et al.*, Burden of valvular heart diseases: a population-based study, 2006; Lancet.*

Currently no approved TMVR system either in Europe or in the US

It is important to note that there is currently no approved TMVR system either in Europe or the US. Indeed, TAVI systems are in some rare cases used in patients as a compassionate treatment when it is the only mini-invasive available option for a patient that does not involve the replacement but the reparation of the mitral valve in patients experiencing regurgitation (when the blood flow backs-up to the left atrium). Replacement is normally done through open heart surgery (SMVR). For both existing alternatives (valve repair or SMVR), we would highlight that the haemodynamic is not preserved and could trigger complications, hence the high unmet medical need. Entering the TMVR market would enable TAVI players to leverage the trust built up with surgeons and, ultimately, their sales forces and revenues. While near-term focus of physicians remains mitral repair, we do not rule out that feasibility studies currently conducted in mitral repair should trigger an increased interest and accelerate consolidation in this niche segment. Note that around 30 private companies are operating in the field. Considering multi-years development timelines, small players would potentially be able to catch-up with larger ones in this field.

5. Appendices

Multiples table

Company	Ticker	Mkt Cap (USDbn)	EV/Sales			EV/EBITDA			P/E			3-y CAGR (15-18e)		
			2016e	2017e	2018e	2016e	2017e	2018e	2016e	2017e	2018e	Sales	EBITDA	EPS
Boston Scientific	BSX US	99,5	4,9x	4,1x	3,7x	15,6x	13,5x	11,8x	16,5x	15,8x	14,3x	17%	16%	6%
Edwards Lifesciences	EW US	17,8	6,3x	5,6x	5,1x	23,1x	19,5x	16,9x	29,0x	24,5x	21,6x	16%	18%	19%
Medtronic	MDT US	27,7	4,0x	3,7x	3,4x	15,5x	13,5x	12,5x	18,5x	16,2x	14,2x	10%	12%	15%
Abbott	ABT US	55,8	2,8x	2,7x	2,5x	12,1x	11,4x	10,6x	17,2x	15,6x	14,3x	6%	6%	7%
LivaNova	LIVN LN	2,2	1,8x	1,7x	1,6x	10,6x	8,4x	6,8x	16,4x	13,0x	11,0x	11%	23%	-
Average			**3,9x**	**3,5x**	**3,2x**	**15,4x**	**13,3x**	**11,7x**	**19,5x**	**17,0x**	**15,1x**	**12%**	**15%**	**12%**
Median			**4,0x**	**3,7x**	**3,4x**	**15,5x**	**13,5x**	**11,8x**	**17,2x**	**15,8x**	**14,3x**	**11%**	**16%**	**11%**

Source: IBES Estimates (as of Dec. 2nd, 2016)

Selected transactions in the cardiovascular space

Year	Target	Acquirer	Total Deal Value	Upfront	Milestones	Segment	Comments
2003	Percutaneous Valve Tech.	Edwards	155	125	30	TAVI	founded in 1999
2009	Evalve Inc.	Abbott	410	320	90	Mitral	founded in 1999; mitral valve
2009	CoreValve	Medtronic	850	700	150	TAVI	founded in 2001
2009	Ventor	Medtronic	325	325		TAVI	founded in 2004
2010	AGA Medical	St Jude	1 300	1 300		IV-occluder dev, Vascular plugs	~6xEV/Sales
2011	Sadra Medical	Boston S	386	193	193	TAVI	for remaining 86% share
2015	CardiAQ	Edwards	400	350	50	Mitral	
2015	Cephea Valve Tech.	Abbott	nd			Mitral	
2015	Thoratec	St Jude	3 400			Ventricular Assist Devices	~7x sales
2015	Tendyne	Abbott	225	225		Mitral	for remaining stake
2015	Twelve	Medtronic	458	408	50	Mitral	
2016	HeartWare	Medtronic	1 100			Ventricular Assist Devices	~4x sales
2016	Abbott	St Jude	25 000			Cardiovascular	~5x sales
2016	Valtech Cardio	Edwards	690	340	350	Mitral	mitral repair only

Source: Companies above mentioned.

Glossary

Aorta	Main artery in the human body, originating from the left ventricle
AS	Aortic Stenosis. Narrowing of the exit of the left ventricle of the heart (where the aorta begins)
Atherosclerosis	condition in which plaque builds up inside the arteries
Bioprosthesis valve	Replacement valve with functional properties similar to those of native valves
Diastole	Part of the cardiac cycle when the heart refills with blood following systole (contraction)
DRG	Diagnosis-related group. System used to classify hospital cases
French	Used to measure the size of a catheter; D (mm) = Fr / 3
Haemodynamic	Dynamics of blood flow
Heart-lung-machine	Cardiopulmonary bypass (CPB) temporarily takes over the function of the heart and lungs during surgery
Regurgitation	A leaking (or regurgitant) aortic valve allows blood to flow in two directions
SAVR	Surgical Aortic Valve Replacement
Stenosis	Abnormal narrowing in a blood vessel or other tubular organ or structure
Systole	Part of the cardiac cycle when the ventricles contract
TAVI/TAVR/TMVR	Transcatheter Aortic Valve Implantation/Replacement, Transcatheter Mitral Valve Replacement,
Transapical	Passing through a direct puncture into the apex of the heart's left ventricle, accessed through a small incision
Transfemoral	Passing through or performed by way of the femoral artery

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- **Hervé Ronin** joined Bryan, Garnier & Co.'s Paris office in September 2010 as a Partner in Healthcare Investment Banking. Hervé has over 18 years of corporate finance experience, successfully advising M&A and ECM transactions across all healthcare segments. Prior to Bryan Garnier, Hervé worked for BNP Paribas Corporate Finance in the healthcare team.

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- **Brigitte de Lima** joined Bryan, Garnier & Co.'s London office in May 2016 as a Managing Director in Healthcare Investment Banking. Brigitte brings over 12 years of healthcare / life sciences experience and is responsible for the firm's healthcare and life sciences practice in the UK and across Continental Europe. Prior to working as a corporate finance adviser to healthcare companies, Brigitte was a highly rated biotechnology equity research analyst at Bank of America Merrill Lynch, London.

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- **Thomas Ranson** joined Bryan, Garnier & Co.'s Paris office in March 2016 as a Director in Healthcare Investment Banking. Thomas has over 10 years of financial and healthcare experience, with a strong scientific background. Prior to Bryan Garnier, Thomas led corporate development as well as portfolio valuation projects at Pharnext, a French biotechnology company, and conducted numerous asset licensing deals across Europe within the M&A activity of Bionest Partners, a global healthcare-focused advisory firm.

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Please see the section headed "Important information" on the back page of this report.

About Bryan, Garnier & Co

Bryan, Garnier & Co is one of the leading independent investment banks specialized in European healthcare growth companies. We have a dedicated franchise of 20 senior professionals including investment bankers, equity research analysts and institutional sales professionals. Our team covers the key market sub-categories such as: biotechnology, large cap and specialty pharmaceuticals, life science tools, medical technology, diagnostics, healthcare information technology and services.

In 2015, Bryan, Garnier & Co completed over 10 transactions for European healthcare growth companies, raising a total of approximately $1 billion. We top the European healthcare fundraising league tables (number one Investment bank for Healthcare fund raising on Euronext) with landmark transactions such the IPOs of Bone Therapeutics and Amoeba on Euronext.

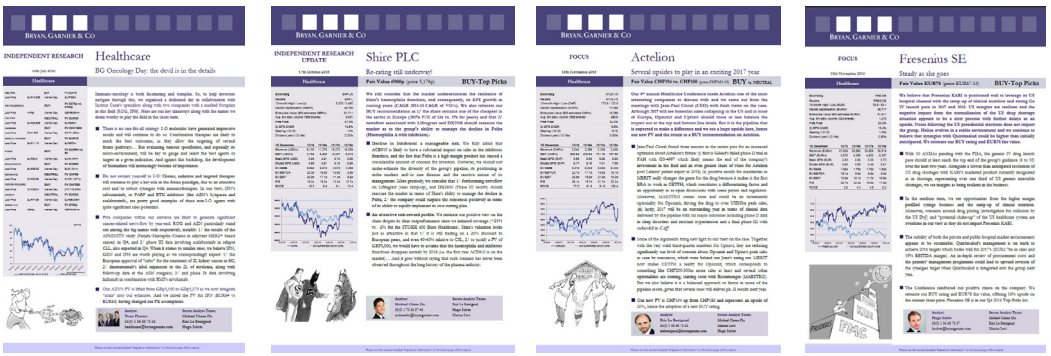
In the past 24 months, Bryan, Garnier & Co was the most active investment bank involved in the IPO of European healthcare growth companies on the US Nasdaq. We are the number one European investment bank on NASDAQ and in 2015 we achieved the largest ever IPO of European Biotech company on NASDAQ (Galapagos – $317 million).

Corporate Transactions

Bryan Garnier & Co leverage in-depth sector expertise to create fruitful and long lasting relationships between investors and European growth companies.

Research

With seasoned research methodology and fundamental bottom-up approach, Bryan Garnier's analysts provide opinionated investment insights with leading perspective across all aspects of the healthcare sector. Bryan Garnier & Co developed the most dedicated healthcare research platform in Europe, with more than 40 stocks covered across the full market cap and sub-sector spectrum / therapeutic areas.



Bryan Garnier & Co, with more than 150 professionals based in London, Paris, New York and Munich, combines a range of services and expertise of top-tier investment banks with the level of attention to clients of a boutique.

Please see the section headed "Important information" on the back page of this report.

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