EVOLUTION CAPITAL

ASX: AVR

Anteris Technologies Limited

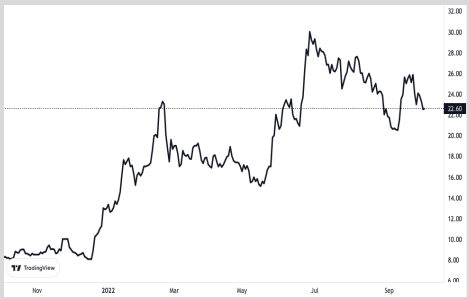
Equity Research

4 October 2022

BUY

Share Price	$22.60
Price Target	$66.32

52-Week Range	$8.00 - $30.89
AVR Shares Outstanding	13.9m
Unlisted Options	3.85m
Market Capitalisation	$314.14m
Cash (30 June 2022)	$33.1m
Enterprise Value	$284.2m
Substantial Shareholders	
Perceptive Advisors, LLC	13.2%
L1 Capital Pty Ltd	8.09%
Sio Capital Management, LLC	3.73%
Top 20 Holders	43.2%
Board & Management:	
John Seaberg	Chairman
Wayne Paterson	Managing Director/CEO
Stephen Denaro	Non-Executive Director
Dr Wenyi Gu	Non-Executive Director
David St Denis	Chief Operating officer
Mathew McDonnell	Chief Financial Officer



Source: Tradingview

ANTERIS A Structural Heart Company

AVR's heart is in the right place

Overview: Anteris Technologies (ASX: AVR) focuses on the development and commercialisation of structural heart solutions for the multi-billion dollar aortic valve replacement market. The company's main product is DurAVR™ a novel 3D single-piece aortic valve replacement solution, that employs its next generation ADAPT® tissue science technology. Compared to existing aortic replacement valves, the DurAVR™ has demonstrated a potential to deliver hemodynamic performance and superior durability, which can be administered through both the traditional surgical route and the transcatheter method which is less invasive in nature.

Investment Proposition

The transcatheter aortic valve replacement (TAVR) procedure: The procedure is less invasive than the traditional surgical procedure (open heart) and was designed primarily as a non-invasive solution for the treatment of patients with severe aortic stenosis who are deemed to be at high risk for surgical procedures. While the TAVR method was initially approved for the "high risk" category patients (usually those aged above 80 years), the FDA in 2019 approved the use of TAVR in younger patients. This has caused the average age of TAVR patients to decrease in a span of less than two years from 85 to 73, with a further fall expected over the coming years. This will effectively double the addressable market to US$8bn p.a. and highlights the need for more durable leaflet tissue technology to be used, such as the company's patented ADAPT® treated tissue.

DurAVR™ world's first 3D single piece aortic valve: Selected as "Best Innovation" at PCR London Valves, the world's leading interventional cardiovascular conference focused on transcatheter therapies for valvular heart disease. DurAVR™ is manufactured using 90% less sutures than the incumbent products from Edwards Lifesciences and Medtronic. The DurAVR™ valve has also shown to deliver increased orifice area for blood flow and a lower pressure gradient (less restriction) than the commonly used CoreValve and Sapien 3 TAVR device from its respective competitors.

Global market growing at a rapid pace: The global aortic valve replacement market has shown to grow at a CAGR of 16-20% over the past five years to US$4bn. This is forecast to grow at an annual rate of 14% over the next eight years. Most of the growth is expected to come from the growing TAVR market, particularly as the average age of eligible TAVR patients continues to decrease overtime.

Clinical results demonstrating superiority to current products: DurAVR™ has shown clinical superiority to current products in clinical studies to date. As demonstrated for the first time in humans, pre-disease flow dynamics (i.e., restoring the patients valve function to that of the normal pre-disease valve).

Potential acquisition target: Anteris is attempting to enter a market dominated by two large medical device companies, Edwards (market cap $US52bn) and Medtronic (US$102bn). If the company continues to validate DurAV™ as a superior aortic replacement valve to existing solutions, it will create competitive tension potentially leading to an acquisition of the company.

Near-term catalyst: Anteris is expected to present at the PCR London Valves conference at the end of November, it is expected that the all-important 12-month follow-on data will be released on the first five patients implanted with the DurAVR™ valve.

Recommendation

We have placed a **BUY** recommendation on Anteris, deriving a price target of $66.32 (undiluted), and an implied return of 193% from current levels. This gives the company an overall valuation of $922m, which we believe is suitable given that it continues to clinically demonstrate the continued superiority of DurAVR™ in comparison to the approved TAVR and SAVR that are currently on the market.

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Aortic stenosis

Aortic stenosis (AS) is a common type of valvular heart disease (VHD) predominantly affecting global Western populations. According to the Euro Heart Survey in which a sample of five thousand patients from 25 European countries were analysed, AS was found to be the most frequent, single, native-left-sided valve disease. As such, AS is considered a major societal and economic burden. Therefore, an urgent understanding of pathophysiological processes leading to AS is required at the most fundamental level to aid preventive and therapeutic strategies.

Aortic valve disease is a progressive chronic disease which begins with mild fibrocalcific leaflet changes, termed as aortic sclerosis. This then progresses to severe calcification with the end stage causing a major obstruction to ejection of the left ventricle. Furthermore, AS develops over a period of time, typically decades and once the symptoms start to appear it leads to a poor prognosis. There are currently no medical therapies to prevent and/or promote the regression of the disease and the only proven therapy for severe AS is an aortic valve replacement.

1.1 Etiology

The etiology of AS is further marked by congenital and acquired disease state. A congenitally abnormal valve with superimposed calcification can cause AS and bicuspid aortic valve (BAV) is the most common cause of AS in patients who are under the age of 70 in developed nations.

The acquired disease state in developing nations is the rheumatic valve disease. The commissures of the leaflets fuse to leave a small central orifice. Other causes also include:

1. calcification of the tri-leaflet valve;
2. systemic lupus;
3. irradiation; and
4. metabolic diseases such as Fabry disease.

Mineral metabolism disturbances, such as end-stage renal disease have also shown to contribute to the calcification of the valve. Further, obstruction to the left ventricular (LV) outflow can occur above or below the valve, causing both supravalvular stenosis and subvalvular stenosis respectively.

1.2 Epidemiology

According to Agasthi et al, the prevalence of calcific aortic sclerosis is about 1% to 2% in patients aged 65 or less and 29% in patients aged 65 or more. About 2 to 9% of patients aged greater than 75 have severe AS. The relative prevalence of AS in patients with tri-leaflet versus congenitally abnormal valves differs with age. The causes of AS vary geographically as calcific stenosis is more common in North America and Europe, while rheumatic valve disease occurs more commonly in developing nations.

1.3 Pathophysiology

The normal aortic valve consists of several layers of fibroblast-rich tissue, which contains both collagen and elastin fibres, covered by a monolayer of endothelial cells. Histopathologic studies have demonstrated that the development and progression of calcific AS is based on an active process that shares similarities to atherosclerosis. Scientific studies have suggested that aortic valve lesions begin with a disruption of valve endothelium predominantly on the aortic side due to high shear stress. Aortic valve lesions typically present with areas of sub-endothelial thickening representing the early stages of AS. An increased thickening of aortic valve leaflets is characterised by the accumulation of inflammatory infiltrates of macrophages and T-lymphocytes, lipids, oxidised lipids and inflammatory markers.

The calcification of aortic valve leaflets tends to occur more predominantly in the later stages of AS and is located deeper in the lesion. Active calcification is a major factor in reducing valvular mobility in severe AS. Furthermore, AS is classified as a heterogenous disease, however, there are two clinically evidenced common causes of the disease which includes AS developing in a previously normal trileaflet valve, and the congenitally bicuspid aortic valves. Given that AS mainly develops in otherwise normal valves in aged individuals, this has been defined as degenerative AS, implying a relationship to the normal process of "wear and tear" within the valve.

The pathogenesis of AS is said to be impacted by the Left Ventricular (LV) obstruction caused by stenosis of the valve which increases LV systolic pressure. It also results in increased LV ejection time (LVET), decreased aortic pressure, and increased LV-end diastolic pressure.

The increased afterload together with an increase in the LV volume overload leads to an overall increase in the LV mass, ultimately leading to LV dysfunction and heart failure. Furthermore, the myocardial oxygen consumption increases with increased LV systolic pressure, LV mass, and LVET, while the myocardial perfusion time decreases with increased LVET. Hence, the LV function deteriorates further with increased myocardial oxygen consumption and decreased myocardial oxygen supply.

1.4 Physical decline and symptoms relating to AS

The acquired AS exists with exertional dyspnea, syncope, angina and ultimately, heart failure. The symptoms typically begin at the age of 50 to 70 years in patients with bicuspid aortic valve and in greater than 70 years of age in patients with tri-leaflet valve calcific stenosis. Patients progressively experience a slow decrease in exercise tolerance, dyspnea on exertion, and fatigue.

Severe exertional dyspnea, paroxysmal nocturnal dyspnea, orthopnea, and pulmonary edema demonstrate various degrees of pulmonary venous hypertension. Angina results from a combined need for increased oxygen in the hypertrophied myocardium and reduction of oxygen delivery secondary to the excessive compression of coronary vessels. Syncope is caused by a decrease in the cerebral perfusion occurring during exertion as the arterial pressure declines as a result of systemic vasodilation and an inadequate increase in cardiac output related to stenosis. It also occurs due to a malfunction of the baroreceptor mechanism in severe cases of AS.

The non-cardiac symptoms include gastrointestinal (GI) bleeding and cerebral emboli. GI bleeding is observed in patients with severe AS and is often associated with angiodysplasia or other vascular malformations. It occurs due to the shear stress-induced platelet aggregation and reduction in the von Willebrand factor. On the other hand, cerebral emboli occur due to microthrombi formation on the thickened bicuspid valves. Upon examination, the carotid upstroke can be observed on palpation, a slow-rising, late-peaking, and a low amplitude carotid impulse as demonstrated through clinical findings in severe AS.

2 Evaluation of AS

Echocardiography is the standard approach method used in evaluating and following-up patients with AS and ultimately stratifying the patient population for surgery. The method allows imaging of the valve anatomy and demarcating the severity of valve calcification as well as providing direct imaging of the orifice area. A more sensitive measure of LV function predicting adverse events, including mortality, is the longitudinal systolic strain imaging. Exercise testing also helps to unmask symptoms in asymptomatic patients but should be avoided in symptomatic patients.

The use of cardiac computed tomography (CT) is also increasing in patients with calcific aortic valve disease. It is predominantly utilised when all the non-invasive tests are inconclusive. Cardiac magnetic resonance imaging (MRI) can also examine the LV mass, function, and volume when the information isn't readily obtained in echocardiography.

3 Treatment overview and Management options for AS

Several studies have demonstrated that medical therapy does not significantly affect disease progression and hence aortic valve replacement (AVR) is a superior alternative to medical therapy in severe symptomatic AS patients, as proven in observational studies and randomised control trials.

As hypertension accompanies AS most of the time, it is understandable that there may be some hesitancy in treating hypertension in this subset of patients as AS is known to be a condition with a fixed afterload. Further, vasodilation is not offset by an increase in stroke volume. However, some studies have demonstrated that patients with severe AS have vasodilation, otherwise accompanied by an increase in stroke volume.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are preferentially considered as treatment methods. AVR is indicated in patients with heart failure and volume overload, but diuretics can help decrease congestion and provide symptomatic relief before surgery. Balloon aortic valvuloplasty has modest improvement in the hemodynamic status of patients although it provides a short-term improvement in the survival and quality of life (QOL), the benefits remain unsustainable over a longer period of duration.

AVR is recommended in adults with symptomatic AS, even if symptoms appear to be mild. The following is also recommended in asymptomatic patients with severe AS:

a. the LVEF rate is greater than 50%;

b. patients who are undergoing coronary artery bypass grafting (CABG) or any other form of heart surgery;

c. an abnormal exercise treadmill test;

d. a peak velocity of greater than 5 m/sec and mean pressure gradient greater than 60.

e. an annual progression of peak velocity of greater than 0.3 m/s/year.

There are two major types of replacement techniques: surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR). Symptoms such as exertional dyspnea and angina are relieved in most patients, and a majority will experience an increase in exercise tolerance.

The LVEF often improves after surgery, but the longitudinal strain might still be impaired. The operative mortality in SAVR is about 3.2% in patients undergoing isolated AVR and it is less than 1% in patients aged less than 70 who have minimal comorbidities. A higher age group should not be considered a contraindication to the surgery, and the 30-day mortality is about 4.2%.

On the other hand, TAVR has transformed the treatment of patients in calcific aortic stenosis over the last decade. It was initially shown to be superior to medical therapy in patients who are not candidates for surgery. However, it later turned out to be superior to SAVR in both high-risk and intermediate-risk patients as well.

4 Difficulty in diagnosing AS

The majority of symptoms accompanying AS such as syncope and angina also tend to overlap with other disease processes, and so the diagnosis can be missed in an acute setting. However, the standard pulmonary function tests and the cardiopulmonary exercise testing can help differentiate between the overlapping conditions.

5 Prognosis

In asymptomatic patients, repeat imaging is typically carried out every three to five years for mild, one to two years for moderate and six to 12 months for severe AS and if and when they become symptomatic.

It is extremely challenging to predict the rate of progression of AS as it is highly variable. However, old age, severe leaflet calcification, hypertension, obesity, smoking, hyperlipidemia, renal insufficiency, metabolic syndrome, elevated circulating levels of lipoprotein A and an increased activity of lipoprotein-A are associated with rapid hemodynamic regression. The doppler aortic jet velocity is the strongest predictor of symptom progression in asymptomatic patients and prognosis remains excellent once moderate to severe AS occurs.

A lack of contractile reserve in patients with low-flow, low gradient, low EF aortic stenosis, high levels of B-Type Natriuretic Peptide (BNP) and a low mean gradient (less than 20 mm Hg) are some of the fundamental factors in determining risk stratification in predicting symptom onset and event-free survival in symptomatic patients. Other factors include oxygen-dependent lung disease, advanced renal dysfunction, and very high Society of Thoracic Surgeons (STS) scores. In moderate AS cases, an elevated level of BNP can be helpful, however, its role in disease progression is yet to be fully defined. The survival outcome in symptomatic patients is poor, even while the symptoms are mild, the average survival without AVR treatment is only about one to three years after the symptom onset.

Complications arising from AS

a. Several complications can arise from AS. Severe symptomatic AS patients are at a high risk of sudden death. Hence, this patient population requires a prompt referral for an AVR. Although sudden death is common in symptomatic patients, it can occasionally occur in asymptomatic patients as well.

b. Heart failure is also one of the most common complications of AS. Most patients will have left ventricular hypertrophy with normal systolic function. Diastolic function develops secondary to hypertrophy with fibrosis and often persists even after AVR treatment. In some cases, patients can also present with systolic dysfunction secondary to the afterload mismatch, resulting in low ejection fraction.

c. Pulmonary hypertension is also one of the most prevalent complications to occur as a result of chronic elevation in the LV diastolic filling pressure along with another noted complication, conduction abnormalities. This occurs as a result of hypertrophy and calcium extension from the valve to the intraventricular septum.

d. Patients with AS are at an increased risk for infective endocarditis, most commonly found in patients with the bicuspid aortic valve.

e. Patients with AS are also at an increased risk of bleeding, most commonly GI bleeding due to acquired von Willebrand syndrome. Further complications such as systemic emboli can also occur due to calcific emboli from the valve.

6 Treatment Modalities for AS

Treatment of AS depends on the severity of the patient's condition. Mild and or non-existent symptoms are simply kept under observation with moderation in life-style changes and prescribed medications. Further deterioration by asymptomatic and symptomatic AS requires surgical intervention to replace the impaired aortic valve.

- **Aortic valve replacement -** The use of AVR to treat AS can be accomplished via surgical and transcatheter approaches. The ideal valve prosthesis would entail, a convenient implant with minimal complications, have low gradients, require no anticoagulation, and have infinite durability. However, no such prosthesis is currently available and therefore the choice of procedure and implant device requires careful consideration by both the patient and cardiac team in respect to patient-specific factors, procedural risks and the projected longevity of the patient.

- The procedural risks of morbidity and mortality are defined by the use of risk assessment tools that are regularly updated and based on large registries of data i.e, the Society of Thoracic Surgeons Predicted Risk of Mortality and the European System for Cardiac Operative Risk Evaluation II.

- The procedural risk/s of AVR is classified into:

a. Low;

b. Intermediate;

c. High, and

d. Extreme (inoperable) risk-groups

Furthermore, the risk assessment tools are constantly re-evaluated to deliver clinical accuracy, however, there are some risk factors that have not been included in the risk assessment tool such as frailty, nutritional status, pulmonary hypertension, aortic disease, malignancy and radiation exposure and should be considered as part of the risk assessment framework.

SAVR can be achieved with mechanical, stented, or stentless biologic prostheses, homograft tissue, or pulmonic root autograft with simultaneous pulmonic root homograft replacement (Ross procedure). SAVR is often performed through smaller, more cosmetically appealing incisions that offers advantages and disadvantages, including procedural methods such as partial sternotomy or minimal right anterior thoracotomy which may reduce blood transfusion requirements.

Further benefits include a lower length of stay in intensive care, reduced risk of renal failure, perioperative atrial fibrillation and reduced hospital costs. However, the reduction in surgical exposure provided by these smaller incisions can increase the technical demand and may hinder the ability to address additional pathology such as coronary artery disease (CAD) and/or intraoperative surgical complications. The introduction of novel sutureless valves provides an easier implantation using these smaller incision methods with early reports of midterm durability, however, long-term efficacy is yet to be determined.

SAVR conducted via a mechanical or biological prosthesis is a relatively straightforward operation, complying with the institution of cardiopulmonary bypass and cardioplegic arrest of the heart, the aorta is opened a few centimetres above the AV, followed by removal of the cusps and debridement of any calcium in the annulus. The valve is then secured either in an intra-annular or supra-annular position with any of the suturing techniques, such as inverted mattress, continuous sutures and non-inverted mattress.

Given the simplicity of the SAVR procedure, the perioperative (30-day mortality) is low in modern times. A real-world review of the STS database of isolated mechanical and bioprosthetic, demonstrated a perioperative mortality of 2%, 6%, and 13% in the low, medium, and high-risk patients for the SAVR procedure. This is also consistent with randomised controlled trials that compared TAVR and SAVR, whereby the perioperative mortality for both procedures was equivalent to, in the following patient population: low-(<1%), intermediate-(2%-4%), and high-risk patients (3%-7%) respectively.

Regardless of the valve type chosen, AVR is still associated with risk of perioperative complications that include heart block, atrial fibrillation, a permanent pacemaker (PPM), paravalvular regurgitation, respiratory failure, renal failure, infection, stroke and death. These complications arise at different rates following SAVR and TAVR as compared by several randomised clinical trials, the most severe differences have been noted in PPM and paravalvular regurgitation rates in favour of SAVR, while renal and respiratory complications remain in favour of TAVR.

Prosthesis	Advantages	Disadvantages
Surgical		
Mechanical	Easy implantation Long durability	Requires anticoagulation Thromboembolic complications
Stented Bioprosthetic	Easy implantation No anticoagulation	Occurrence of structural valve deterioration (SVD)
Stentless Bioprosthetic	No anticoagulation Outstanding hemodynamics Very good durability	Moderate surgical complication Occurrence of SVD
Homograft	No anticoagulation Often used in endocarditis	Moderate surgical complication Poor durability
Ross procedure	No anticoagulation Excellent durability Excellent hemodynamics	High surgical complication High perioperative morbidity in low volume centres
Transcatheter		
Bioprosthetic	Less invasive Excellent hemodynamics Lower stroke rates	Unknown long-term durability Higher rates of conduction system injury Higher rates of paravalvular regurgitation

Source: Evolution Capital Pty Ltd

TAVR has revolutionised the treatment of AS over the past decade. It initially started as an experimental treatment in inoperable patients and has now become the most common treatment for AS in the United States and other parts of the world. The transcatheter valves currently on the market have a similar design consisting of a trileaflet pericardial bioprosthesis anchored on a metal stent that is deployed within the native AV annulus.

The Food and Drug Administration (FDA) has approved three prostheses as follows: -

a. The balloon-expandable SAPIEN valve series (Edwards Lifesciences).

b. The self-expandable CoreValve series (Medtronic); and

c. The mechanically expandable LOTUS Edge Valve (Boston Scientific).

The SAPIEN and CoreValve TAVR platforms have been widely adopted, while the LOTUS Edge was recalled in 2021 and has since been withdrawn from the market by Boston Scientific.

A further four additional self-expandable systems have received the Conformité Européenne (CE) Mark including the:

a. Portico (Abbott Laboratories);

b. ACURATE neo (Boston Scientific);

c. Hydra (Sahajanad Medical Technology Pvt Ltd); and

d. Allegra (Biosensors International Group).

A prospective randomised trial comparing the Portico to other commercially available TAVR valves demonstrated that it had a higher primary composite endpoint for safety at the 30-day mark, however, similar death and stroke rates were observed at the two-year mark. In a similar randomised, non-inferiority trial in Europe, the ACURATE neo failed to meet non-inferiority of safety and clinical efficacy at 30 days compared to the SAPIEN 3 (latest offering of the SAPIEN platform). The SAPIEN 3 is the latest valve offering from Edwards Lifesciences, it is made from bovine pericardium mounted on a cobalt-chromium stent encapsulated in an outer sealing skirt.

Prior to delivery, the valve is tightly compressed using a crimping mechanism onto a balloon catheter that is both inflated and deflated to be used at the AV annulus. Once deployed, the SAPIEN valve cannot be repositioned, on the other hand the Evolut PRO+, the latest valve offering from Medtronic is made from porcine pericardium mounted on a Nitinol stent wrapped with an external pericardial wrap. The self-expanding Evolut Pro+ allows for partial repositioning (two-thirds), evaluation of repositioning and recapturing of the valve.

Unlike SAVR, which requires cardiopulmonary bypass and cardioplegic arrest, TAVR can be performed percutaneously, given under local anesthesia with or without conscious sedation. TAVR requires large-bore arterial access for valve deployment, a second smaller arterial access for aortography and an establishment of the coplanar view, and if required, a venous access for rapid pacing during deployment. The common femoral artery is the preferred site of access for TAVR, it is used in more than 95% of cases. However, femoral access may not be feasible if the vessels are too small or have greater calcification. In such situations, consideration is given to other access sites such as axillary or subclavian arterial access for nontransfemoral TAVRs.

The perioperative mortality between TAVR and SAVR have been similar in the AS patient population (<1% in low-risk, 2%-4% in intermediate risk, and 3%-7% in high-risk patients). However, the morbidity profile largely differs owing to the different nature of the procedure. The most significant TAVR complications include conduction abnormalities requiring pacemaker insertion, paravalvular leak, stroke and vascular complications. The lesser common complications include coronary obstruction and annular rupture.

Common complications in the use of TAVR include:

a. **Conduction abnormalities:** following TAVR, abnormalities occur from mechanical trauma applied by the valve frame onto the conduction system. Advanced heart blockage requires placement of PPM, which is associated with increased mortality and repeated hospitalisation. The balloon-expandable valves have a higher PPM rate than surgery, however, the self-expandable valves and the mechanically expanded valves have generated higher pacemaker rates due to a lower implant depth in the left ventricular outflow tract or due to greater radial force generation. Patients with pre-existing conduction delays and those receiving large prostheses relative to the size of the left ventricular outflow tract are more likely to require a PPM following TAVR.

b. **Paravalvular leak**: occurs as a result of incomplete apposition of a prosthesis to the aortic annulus, leading to regurgitation around the prosthesis. Although mild PVL does not appear to affect the long-term outcome of TAVR, patients with moderate to severe PVL have higher mortality.

c. Clinical studies have demonstrated significantly higher rates of moderate to severe PVL with TAVR compared with SAVR, with rates ranging from 11% to 12% in high-risk patients, compared with 1%-2% with surgery.

d. The most recent low-risk PARTNER 3 trial, (Prospective Randomised, Controlled, Multi-Centre study to Establish the Safety and Effectiveness of the Edwards SAPIEN 3 Transcatheter Heart Valve in Low risk Patients Who have Severe, Calcific, Aortic Stenosis Requiring Aortic Valve Replacement) using balloon-expandable valves did not demonstrate a difference in PVL between TAVR and SAVR at the 1-year follow up, although PVL was still significantly worse in low-risk patients who received a self-expandable valve. **Stroke:** occurs in 2%-5% of patients undergoing TAVR. In most of the randomised controlled trials, stroke rates have been comparable between TAVR and SAVR. The PARTNER 2 S3i trial (investigating intermediate-risk patients) and PARTNER 3 trial (investigating low-risk patients), used the latest generation balloon-expandable valves, both the trials demonstrated a lower stroke rate in comparison to surgery, however, these trials did not include a neurologist adjudication for stroke across all patients. Primarily, 90% to 100% of TAVR patients have procedural silent ischemic embolic events as detected by MRI, similarly, 50% to 60% of SAVR patients experience procedural silent ischemic embolic events.

e. **Vascular complications:** occur as a result of large-bore access required for TAVR in a patient population that has significant peripheral vascular disease. The most common vascular complications include dissection, access site hematoma and perforation. Major vascular complications have ranged from 8% to 16% with first-generation devices that required larger sheaths placed in surgically inoperable patients in earlier times for TAVR. However, only 2% to 4% in the latest trials with devices require a smaller sheath placed in lower-risk patients. Vascular complications are mainly associated with bleeding, transfusions, renal failure and mortality.

7 Balloon Valvuloplasty

The role of balloon valvuloplasty has been redefined and reduced in favour of TAVR therapies, although it was once considered a conventional therapy for AS. The newer modified, hourglass shaped and perfusion-preserving balloon-tipped catheters have improved performance, however, it still only creates a modest increase in the aortic valve (AV) area.

It further reduces transvalvular pressure gradient which improves symptoms transiently. The gradient reduction and symptomatic improvement are short-lived in the order of months to weeks and offers no survival advantage in adults. The role of valvuloplasty still features amongst children as it provides more growth before a definitive surgical valve replacement. As for the adult population, the role of valvuloplasty has transitioned to being a bridge to TAVR, most commonly in the context of refractory pulmonary edema or cardiogenic shock. Additionally, balloon valvuloplasty may sometimes be utilised to palliate symptoms and transiently improve QOL in patients who are prohibitively at risk for either surgical or transcatheter AVR.

8 Limitations of Current Treatments Options

Aortic valve replacement solutions have improved over the course of time with accelerated research, development and innovation. However, despite the progression achieved, challenges still remain, pertaining to the durability and hemodynamics of current solutions.

In 2019, the FDA approved the use of TAVR in younger patients, with the average age of the treatable patient decreasing from 85 to 73. This age bracket is expected to reduce into the 60s over the coming years.

The shift towards younger patient population emphases challenges currently faced by existing aortic replacement valve solutions. Modern valves are now required to last over 15 years to reduce the risk of re-operation, which involves greater health risks than the initial valve replacement procedure along with significant economic burden on the healthcare system.

9 Addressable issue

The initial development for TAVR therapy was focused on safe delivery and reliability, now that these issues have been largely addressed, attention should now be focused on the main issue of longer-term valve performance and durability.

These key issues are becoming more important as TAVR therapy moves to a younger and healthier patient population with longer life expectancy. Further, as the average age of eligible TAVR patients continue to reduce to target a more active patient subset, the need for a valve replacement to mirror a pre-disease hemodynamics of the anatomical size and area of a patient's native aortic valve becomes even more crucial. An insufficient effective orifice area (EOA) limits a patient's ability to achieve the required aortic blood flow to maintain higher levels of physical activity and performance.

10 The Fundamentals of Design

Heart valve durability is largely influenced by design. Materials including bovine pericardium, porcine valve tissue, and bovine venous valve tissue have been studied extensively, with each displaying characteristics contributing to *in vivo* durability in the aortic, mitral and pulmonic positions. Beyond material application, the design of the supporting structure for the valve leaflets may also have crucial implications on the durability, e.g., bovine pericardium and porcine aortic leaflet tissue have excellent durability when the tissue is held within the supporting architecture (ring and struts) of the valve.

The Magna (Edwards Lifesciences) and the Mosaic (Medtronic) valves are examples of this type of design which supports the structure. On the other hand, when the design places the pericardial leaflets outside of the frame of the valve, such as the Mitroflow device (Sorin Group) and Ionescu-Shiley valve (Shiley Inc., Pfizer subsidiary), durability tends to suffer. These concepts underscore the need for careful study of the design characteristics for current transcatheter valves, as well patient data in order to devise an accurate understanding of TAVR durability and hemodynamic performance.

11 Durability

Long-term durability data is typically defined as ten years or more, however, this is currently unavailable in the TAVR treatment population. Unlike SAVR, where biologic valves have been used in all age groups for decades (although recommended for those 60 years or older and, more recently, 50 years or older). As previously noted, TAVR was only initially applicable in the elderly inoperable patients with many comorbidities.

The five-year all-cause mortality for TAVR has been reported up to 71%, and therefore, most of these patients are not available for long-term review. As treatment moves towards the lower-risk patients with increasing life expectancy, careful monitoring of ongoing valve function will provide insight into the durability of TAVR. Although a ten-year data is lacking for TAVR, an important six-year follow-up data from the NOTION trial was published in 2019.

The NOTION trial was the first study to randomise lower-risk patients between SAVR and TAVR using early generation self-expanding valves and ensued 11, six-year follow-up of hemodynamic performance. The results demonstrated sustained low (single-digit) gradients, unchanged from year-one through to year-six.

More importantly, the valve gradient was substantially lower and the EOA was significantly greater than with surgical valves at every interval. This supports the concept that supra-annular design may allow improved hemodynamics versus the intra-annular design in older-generational surgical valves.

Further, as the average age of eligible TAVR patients continue to reduce to target a more active patient subset, the need for a valve replacement to mirror a pre-disease hemodynamics of the anatomical size and area of a patient's native aortic valve becomes even more crucial.

There are several issues that affect the durability and hemodynamics of currently available treatment valves; these are:

- **Calcification:** a condition in which calcium deposits build up on the aortic valve, causing the opening of the valve to narrow, and may become severe enough to reduce the blood flow back to pre-operative levels.

- **Glutaraldehyde:** most commercially available valves use glutaraldehyde to provide bio-mechanical stability, however, some studies have found that the use of glutaraldehyde can increase the calcification process in aortic valve replacements.

- **Complex three-piece valve construction:** existing aortic valve replacements are built using multiple pieces (usually three), which poses as anatomically incorrect, and results in the reduced effectiveness and increased wear of the aortic valve replacement.

- **Too many sutures:** most other solutions use up to 600 sutures in the construction of aortic replacement valves. As a result, each valve has hundreds of suture holes that comprise the coherence of each valve, accelerating its mechanical wear.

12 Anteris the solution to some of heart's problems

12.1 ADAPT® tissue technology

AVR's success to date has been anchored by its patented ADAPT® tissue technology, which has been used in more than 20,000 non-heart surgical repair patients globally. ADAPT® is a next generation regenerative bioscaffold platform technology being used to address multiple cardiovascular procedures and repairs including, a product (DurAVR™) in development for TAVR procedures.

The platform technology entails three processes involving:

- Process 1- **Accellurisation:** targets collagen and elastin driving the removal off cell structures, membranous phospholipids and alpha gal epitope. This leads to the outcome of a pure collagen bioscaffold with zero DNA, zero cell debris and no antigen response that helps to curb unwanted immune responses.

- Process 2- **Crosslink:** this unique monomeric aldehyde provides ultra-low concentration and precise pH and temperature, leading to a strong durable bioscaffold which in turn preserves the mechanical properties of the extracellular matrix (ECM).

- Process 3- **Detoxification:** a proprietary process in which glutaraldehyde (GA) toxicity is eliminated by chemical detoxification.

- The process works by removing, binding and detoxifying the calcium binding sites, while also removing binds and detoxifying residual aldehydes, ultimately giving rise to a reparative healing environment.

In summary, the platform technology detoxifies and removes cell structures and calcium binding sites to produce a pure collagen bioscaffold with zero DNA and zero calcium binding sites. Therefore, DurAVR™ represents a transformational product with tissue made from the company's patented ADAPT® technology demonstrating clinical durability with no calcification found in ten-year longitudinal follow-ups.

12.2 Durability with DurAVR™

DurAVR™ is the world's first 3D single-piece aortic valve for the treatment of aortic stenosis with its unique design and ADAPT® technology, it addresses the key issues impacting valve durability, including:

Zero calcification: when heart valves become calcified, the leaflets become hard which eventually leads to the narrowing of the valve.
This causes an increase in the blood flow pressure which in turn results in cardiac arrest and/or sudden death. Therefore, there remains a large unmet need for aortic replacement valves to have anti-calcification properties. As noted above, the present aortic replacement valves on the market exhibit calcification over-time losing their effectiveness.

Zero glutaraldehyde: Valves are typically fixed in glutaraldehyde before the implantation procedure. This method aids to stabilise the tissue against proteolytic and/or enzymatic degradation which occurs after implantation. It also helps to reduce both thrombogenicity and immunogenicity by cross-linking and hiding the antigens, thus reducing the possibility for a hyper acute rejection by the recipient. Glutaraldehyde also makes the valves 'immunologically inert' and helps to extend its storage life. The valves are thoroughly washed in saline immediately before the implant procedure and despite this protocol, aldehyde residues still remain. Making the material less biocompatible and more susceptible to calcification. Anteris, through its ADAPT® tissue technology produces zero residual glutaraldehyde.

Superior unibody design: Anteris has developed a specialised machinery and a novel processing technique to reduce the thickness of native pericardia and yield tissue with the desired thickness to make its 3D single-piece aortic valve. A major manufacturing breakthrough was made when the company was able to replicate between the processed and native tissue, simply mirroring the human physiological tissue functionality. As such, DurAVR™ has shown to increase leaflet coaptation (defined as a rough area on the top side of the valve's surface) by 85% followed by a reduction of 35% in leaflet stress. Furthermore, any deformities in the coaptation zone can prevent the valve from functioning properly and increases the stress of surrounding leaflets, resulting in poor hemodynamics.

Less sutures: DurAVR™ requires about 20-30 sutures and has demonstrated zero suture tears in almost 600 million cycles of testing, it should be noted that the FDA requires a minimum of 200 million cycles of testing to ascertain mechanical wear and tear, this translates to a lower manufacturing cost and a more reliable product.

12.3 ComASUR™ Delivery System

Anteris have also developed the ComASUR™ catheter, which is a commissural alignment device. ComASUR™ simply allows surgeons to accurately place the replacement valve by following through the aortic arch and aligning with the native valve, this provides better blood flow and reduces the risk of human error. The system is highly lauded by physicians as it addresses the limitations of current delivery systems presently available on the market. In Q3 2021, the company was awarded a 20-year patent for the sterilised packaging system associated with its ComASUR™ device.

The awarding of this patent further bolsters the company's intellectual property barrier and validates the commercial value proposition of Anteris' technologies. A series of acute animal studies demonstrated the feasibility of the DurAVR™ THV and the ComASUR™ delivery system. The studies were specifically designed to demonstrate the ComASUR™ delivery system's ability to access the arterial vasculature using minimally invasive techniques, moreover, the studies demonstrated the deflection features of ComASUR™ delivery system as it traversed the anatomical features as well as its ability to align the DurAVR™ THV with the native commissures of the aortic valve prior to implantation. The post-implant ECG and CT scan confirmed the functionality of the DurAVR™ THV with stable positioning and good hemodynamic function.

Head-to-Head Value Comparisons with Valves

The direct comparisons with commercially available products so far have been impressive with increased hopes of a functional cure (return to pre-disease hemodynamics) with the DurAVR valve when measured by changes in two key dimensions:

- Mean gradient (ΔP (mmHg)), and
- EOA (cm^2)

	(ΔP (mmHg)	EOA (cm^2)
Normal (Healthy)	4.0-5.0	3.50-4.00
DurAVR™	3.86-5.34	3.04-3.28
Corevalve	7.76-10.27	1.44-1.66
Sapien	11.66	1.35

Source: Anteris

Superior hemodynamic performance (ΔP mean <6mmHg EOA > 2.9cm^2)

Design Option	Inner Diameter of Annulus or Surgical Valve	ΔP mean (mmHg)	EOA (cm^2)
DurAVR (25mm)	23	4.89	3.07
	21	5.17	3.04
DurAVR (25mm)	22	5.34	3.26
	21	3.86	3.28
Corevalve (26mm)	21	7.76±0.14	1.66±0.05
Corevalve (23mm)	21	10.27±0.18	1.44±0.05
Sapien (23mm)	21	11.66±0.22	1.35±0.02

Source: Anteris

Pre-clinical studies

Anteris have conducted multiple pre-clinical studies of their DurAVR™ aortic valve replacement and ADAPT® tissue technology. The findings from the pre-clinical studies are centred on the specific test/studies as follows:

a. **Accelerated wear testing:** Anteris assessed the durability of its DurAVR™ valve replacement using an accelerated wear testing stimulator. The assessment showed complete absence of wear on the valve for over 850 cycles, this many number of cycles conducted is equivalent to more than 14-15 years in the human body. In comparison, similar testing of a competitor valve found evidence of wear at an equivalent of a six-year time frame.

b. **Ovine (sheep) model study:** the ovine study was performed on six juvenile sheep and is the preferred animal model for bioprosthetic valve function. The key findings from the study included normal valve function in a post-operative setting, stable valve function after six months, and no noted material failure or fatigue of the valve material. Further, the echocardiography also showed low gradients and no significant regurgitation across implanted valves.

Source: Anteris

d. **Anticalcification comparison study:** the results from this study demonstrated that the ADAPT® treated tissue, used in the DurAVR™ had around 38% less calcium concentration compared with the Medtronic AOA™ porcine arm (the tissue used in commercially available TAVR valves), while it contained 26% less calcium in the bovine arm. A well-established rat model was used to determine if different anti-calcification methods are likely to have clinical relevancy. Four tissue samples (ADAPT®, AOA™ Porcine, AOA™ Bovine and control= GA treated bovine pericardium) were implanted subcutaneously in a total of 48 rats. Furthermore, these results correlated with existing clinical data and those of the prior head-to-head study with a similar protocol which produced significant differentials between the ADAPT® tissue and Edwards Life Sciences' Thermafix™ tissue at the eight to 12-month mark.

e. **Early TAVR animal (pig) study:** In Q2 2020, Anteris implanted the DurAVR™Transcatheter Heart Valve into the first three animals as part of the TAVR study. The aim of this study was to confirm DurAVR™valve deployment and fixation (anchoring) as well as understanding the insight into the valve's hemodynamic function. The three pigs were implanted with a 25-millimetre valve via a trans-apical approach. The EOAs were 2.45cm2 on the initial readings, remaining consistent with the positive results observed in patients with the surgical implant in the first-in-human SAVR clinical study.

13 Clinical studies

13.1 SAVR Trials

Anteris commenced its first-in-human SAVR trial of the DurAVR™ valve in May 2020 at the Leuven University Hospital in Belgium. The 15-patient trial followed the favourable ovine trial with the primary objective of evaluating safety and performance of the ADAPT valve in adult patients requiring replacement of the aortic valve. The SAVR trial had successfully treated four patients with encouraging early findings presented at the European Association for Cardio-Thoracic Surgery (EACTS) Annual Conference in late 2020. Preliminary results presented, supported the clinical hypothesis that the DurAVR™ valve, given its anatomically correct design and superior anti-calcification treatment properties of ADAPT has 'the potential to offer patients a functional cure'.

	Patients with other surgical valves* (N>1400)	DurAVR Patient 1
Peak Gradient mm Hg	87 mmHg	11 mmHg
Mean Gradient mm Hg	55 mmHg	5 mmHg
EOA cm^2	1.9	2.9

Source: Anteris

The SAVR trial conducted assessed the hemodynamic performance of the DurAVR valve with early results of the feasibility study outlining that the ADAPT treated 3D single piece aortic valve is easy to handle and achieves commissural fixation. The post operative results also included the following:

- Impressive hemodynamics
- Low gradients
- Impressive EOA

13.2 TAVR Trials

In November 2021, Anteris announced the first successful implantation of DurAVR™ into five TAVR patients as part of the company's first-in-human (FIH) study to assess the DurAVR™ THV system for treating severe aortic stenosis. The study was carried out at the Tbilisi Heart and Vascular clinic in Tbilisi, Georgia. The interim results for the FIH are noted below. The formal study protocol is 30 days and one year. A total of 13 patients were enrolled for the study, with an initial five patient cohort enrolled followed by the enrolment of a further eight patient cohort.

At the 30-day follow up point, the first five patients showed (formal follow up):

a. no adverse events i.e., no death, stroke, myocardial infarction and reintervention.
b. an average of 86% improvement in the mean gradient (standard measure of stenosis severity) from pre-treatment levels. The mean gradients were up to 50% lower than other TAVR devices when matched to annular size. All patients were in the normal or near-normal range when compared to the general population with normal valve function;
c. the average EOA was up to 45% larger than those reported with the approved TAVR devices in the matched annual sizes;
d. no conduction (heart rhythm) disturbances due to the procedure;
e. no clinically significant paravalvular regurgitation despite very complex and heavily calcified anatomy of the patients;
f. the Echocardiographic and CT imaging data displayed consistent lamina flow throughout the valve and long coaptation length in all five patients. These features are indicative of lower leaflet strain therefore leading to long term durability of the aortic valve replacement;
g. a 20% increase from baseline in the 6-minute walk test (a measure of a patient's exercise tolerance ability). This was a 170% greater improvement compared to observational studies of the approved TAVR valves.

h. Exercise performance is a critical marker of cardiac health, and this result indicates a marked improvement in patients' functional status and exercise tolerance.

At the six-month follow up point, the first five patients showed (informal follow up):

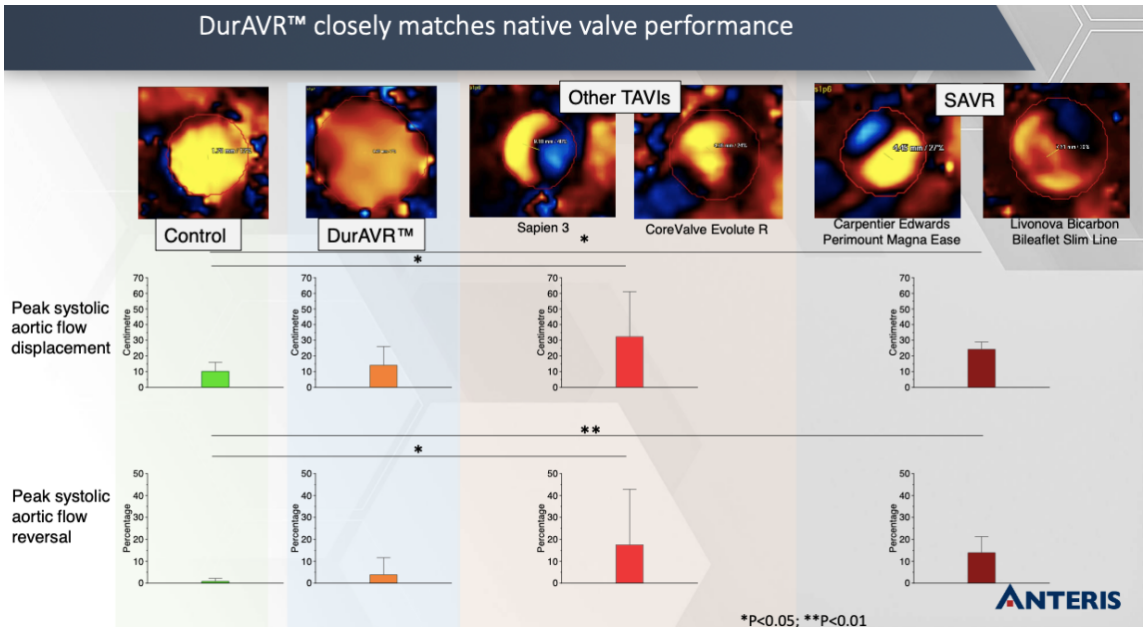
a. exceptional hemodynamics (peak mean gradient had reduced 86% since baseline and 6% since the three-month follow up);
b. the six-minute walk improved 46% since baseline and showed a further 21% improvement between three and six months, demonstrating how much more active and fit these patients are able to become;
c. the lamina flow in MRI continued to show significant improvements when compared to existing valves. This aspect of DurAVR™'s performance is expected to bring significant clinical/patient benefits in the future.

In Q2 2022, Anteris reported on the 30-day follow-up results on the second cohort of eight patients:

a. the findings showed an average of 81% decline in Mean Pressure Gradient with an average 400% increase in the EOA, denoting a marked improved in the valve's surface area, and hence, an improved blood flow;
b. 13 patients showed marked improvements in their clinical status compared with pre-treatment levels. **The study will now be reported at the 12-month mark; DurAVR™ continues to demonstrate outstanding hemodynamics despite the complex anatomy.**

13.3 Overview of the Preliminary Results

Anteris presented at the Transcatheter Cardiovascular Therapeutics (TCT) conference, the world's most prominent meeting of interventional cardiologists in September 2022. The preliminary results demonstrated for the first-time restoration of normal pre-disease blood flow for its DurAVR™ THV technology. In a study of 22 patients comparing valve flow amongst the current aortic valve replacement technologies, Anteris showed no significant difference to the normal healthy aortic valve's flow with DurAVR™ THV. When current generation, TAVR and SAVR valves were compared to the healthy aortic valve, both groups demonstrated a statistically significant worse flow. This data continues to demonstrate the superiority of the DurAVR™ THV design with leaflets mimicking the native aortic valve due to its shape. Furthermore, the continued superiority of the hemodynamic performance was further complemented by the restoration of normal lamina flow. The demonstration of normal lamina flow has been shown for the very first time, although this data is preliminary, it continues to offer support and encouragement because it depicts a valve prosthesis. In other words, demonstrating flow dynamics which is equal to that of a typical healthy native valve. The image below emphasises the importance of hemodynamics and the goal of bio-prosthetic valves matching as closely as possible, the anatomical area of patients' native aortic valves.

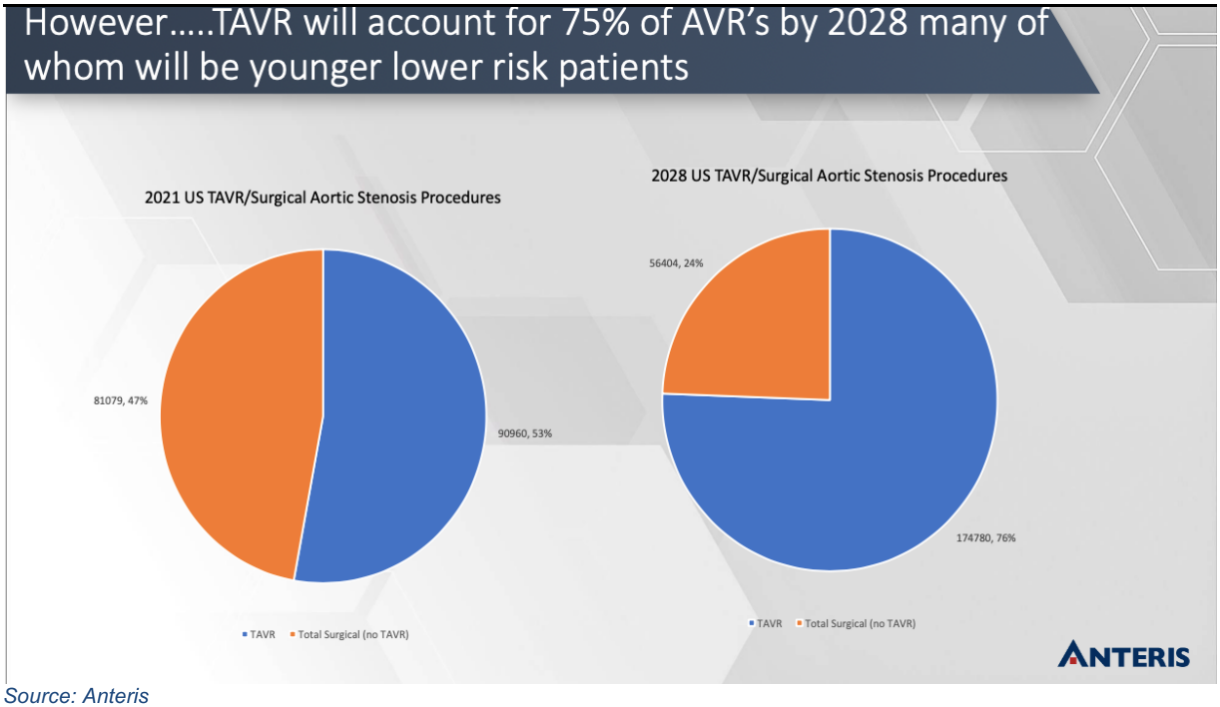


Source: Anteris

14 Market Overview

The global aortic valve replacement market has exhibited strong growth from 2015-2020. This number is set to expand further as demonstrated by a research study undertaken by Straits Research forecasting 14% annual growth through to 2030. The growth drivers include increasing number of valvular diseases, as well as technological advances in the heart valve market. The world's population continues to age with a total number of older people expected to grow from 962 million in 2017 to 2.1 billion in 2050. The market growth will be further accelerated by the rise of minimally invasive surgeries like TAVR along with the development of valves that do not require stitches, which is expected to have a positive effect on the overall market.

In 2019, there were 72,991 TAVR procedures in the US, which for the first time exceeded the number of aortic valves implanted by open chest surgery, with the number totaling only 57,626. According to data released by Medicare and Medicaid, the number of people getting diagnosed over the age of 65 for AS is growing quickly, thus highlighting the need for and importance of new technologies and treatment options. Along with this, good insurance and reimbursement policies are expected to be one of the most fundamental drivers of the AVR market in coming years. The Centers for Medicare and Medicaid Services (CMS), USA have stated that the Medicare National Coverage Determination policy would cover TAVR treatment procedures. In determining coverage for different procedures, different insurance providers have varying rates.



Source: Anteris

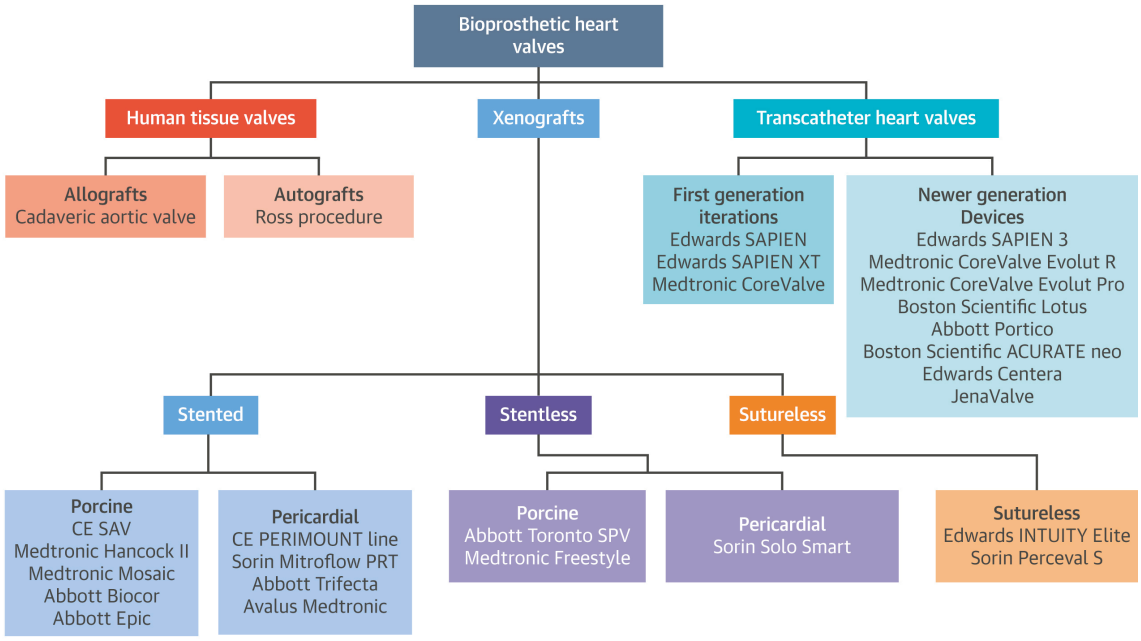
14.1 Competitive landscape

The global TAVR and SAVR markets is currently dominated by a few major medical device companies such as Edwards Lifesciences, Medtronic, Abbott Laboratories, and Boston Scientific. Edwards Lifesciences and Medtronic predominately command the greatest market share of aortic valve replacements. As of September 2022, Edwards Lifesciences and Medtronic each have market capitalisations of $52 billion and $108 billion respectively. In the SAVR market, Edwards holds a 58.4% market share, while Medtronic and Abbott Laboratories each hold 19.7% and 16.3% market share respectively. Edwards Lifesciences has three separate SAVR products (Inspris Resilia, Edwards Intuity and the Magna Ease Valve).

On the other hand, Medtronic has seven types of SAVR products including both tissue (Avalus™ Bioprosthesis, Hancock™ II Bioprosthesis, Mosaic™ Bioprosthesis and Freestyle™ Aortic Root Bioprosthesis) and mechanical (Open Pivot ™ Aortic Valved Graft and Open Pivot™ Mechanical Heart Valves) while Abbott Industries has the Trifecta™ GT Valve.

The TAVR market is a duopoly dominated by Edwards, occupying a 63.3% market share and Medtronic taking 32.4% market share respectively. In this area, Edwards' has three products (Sapien 3 Ultra, Sapien 3, and Sapient XT), while Medtronic has two products (Evolut Pro and Evolut R). In August 2019, the FDA expanded indications for TAVR to include low-risk patients. The Sapien 3 and CoreValve Evolut R system both received approval for this indication on the same day. The approval was widely anticipated following the success of clinical trials with both products performing on par and/or better than traditional surgical methods. These two approvals greatly expand the number of patients that can be treated using a minimally invasive approach. It is also estimated that up to 50% of all TAVR patients could be catergorised as low risk by 2026. Many surgeons have also observed an increase in patients requesting TAVR over SAVR due to the minimally invasive nature of the procedure. However, the main limiting factor in this expansion is the lack of long-term durability clinical data as noted previously.

A



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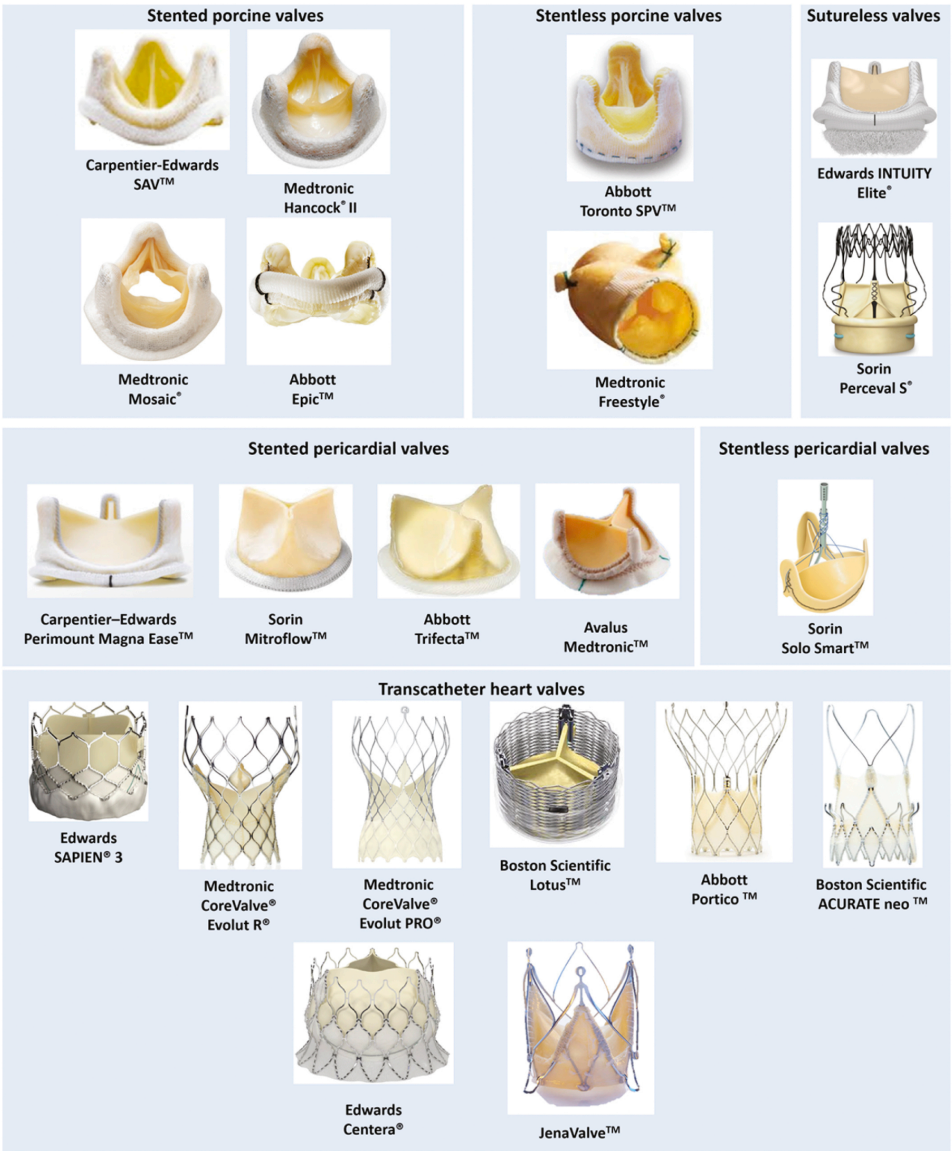


Source: Journal of the American College of Cardiology

14.2 M&A Activity in the Cardiac Device Market

The cardiovascular medical device market is broad in nature and includes both invasive and non-invasive heart monitoring devices. Aortic valve replacements are considered to be in the highest risk category for medical devices, pertaining to the FDA category 3 device. As such, the most stringent clinical and regulatory measures are taken for a pathway towards commercialisation. The table below depicts a list of transactions which includes the acquisition of companies comparable to Anteris. The list outlines both aortic and mitral valve replacement devices, albeit at varying stages of commercialisation. As evident from the list below, there is a defined pattern involving transactions of privately held medical device companies who demonstrate positive results in preclinical and/or clinical trials and are notably acquired by one of the four major listed industry players in this space (Edwards, Medtronic, Abbott and Boston Scientific).

As highlighted below, transactions occurring from 2015 onwards, entails a relatively tight band for transactional values based on differential stages of target companies. To demonstrate this point further, the least advanced of the target companies, Tendyne was acquired for the lowest price of (US$225m) and was also acquired prior to commencing its enrolment for a European clinical trial. On the contrary, the other three target companies were in advanced stages of clinical trials and in the case of Symetic it had already received CE mark approval in Europe. As such, we believe the previous transactions in the cardiac device space provides a good indication of a potential valuation and upside for Anteris, albeit noting, that the last material TAVR transaction had taken place in 2017 and hence, the addressable market for TAVR has increased materially due to the FDA approval in the younger and lower-risk patients.

Target	Exchange	Acquirer	Year	US$m	AU$m*	Summary
Symetis	Private	**Boston Scientific**	2017	435	570	Symetis had developed TAVR solutions to treat severe AS, also known as Accurate TA and Accurate neo/TF systems. The company had already received the CE mark at the time of acquisition
Tendyne	Private	**Abbott**	2015	225	298	At the time of acquisition, Tendyne was developing a TMR solution to treat patients with mitral valve regurgitation. The company planned to begin enrolments for a European study in 2016.
CardiAQ	Private	**Edwards Life Sciences**	2015	350	475	CardAQ Valve technologies Inc. was developing a TMVR solution to treat patients with mitral valve regurgitation. At the time of acquisition, the company had received an Investigational Device Exemption (IDE) from the FDA to conduct an early feasibility study for up to 20 patients. The company was also planning to initiate a CE mark study in Europe.
Twelve Inc.	Private	**Medtronic**	2015	458	639	Twelve Inc was developing a TMVR solution to treat patients with mitral valve regurgitation. At the time of acquisition, the company was undergoing a ten-patient cohort trial. It also hadn't received any regulatory approvals at the time of acquisition.
Ventor	Private	**Medtronic**	2009	325	509	Ventor Technologies was developing a transapically-implantable TAVR solution for the treatment of severe AS. The technology was called Ventor Embracer, which at the time was under clinical investigation in Europe and had not yet received clinical investigation approval in the US.
CoreValve	Private	**Medtronic**	2009	900	1,410	CoreValve had developed a transfemoral TAVR solution for the treatment of severe AS called the Revalving System, which at the time was approved in Europe (2007) and had the FDA approval pending for commencement of a pivotal trial in the US.

**Based on exchange rate at the time of acquisition.*

15 Valuation

Conducting early-stage valuation on medical device companies can be a complicated process, and this is particularly the case with early-stage valve replacement companies as the vast majority of these companies are private. Taking a device of this nature through to market requires the most stringent path to FDA and EMA approval, which typically can take anywhere between three to seven years (sometimes even longer depending on the risks associated) and significant amounts of capital. Furthermore, the cardiac valve replacement device market is predominantly dominated by a few large medical technology companies, and as such, the vast majority of smaller device companies who show promise, are usually acquired before they go to market.

The FIH study continues to prove DurAVR™ properties in comparison to marketable valves. The company's current focus remains on starting its US multi-centre, Phase II EFS as part of its FDA approval process. Simultaneously, the company is also embarking on its European clinical trials in an equivalent patient population towards a potential CE Mark filing in 2023. To gain European approval, a trial involving around 100 patients will be required, with European approval most likely to be received before the US approval. In the US, Anteris will first conduct a feasibility study in around 15 patients, with the expected recruitment time of a few weeks. The company will then conduct a pivotal IDE study in the US and Australia, this is expected to take around one year to recruit. Anteris will be eligible for reimbursement for these procedures (US$25,000 per device). Patients will be followed for one year. This study is expected to start in Q1 2024 and may include around 400 patients. We also estimate the device could be approved by the FDA in late 2024, with first commercial sales commencing in 2025.

The global aortic valve replacement market is forecast to grow at a CAGR of 15% to around $8B by 2025. By this time, it is estimated that around 88% of all revenue will be derived from TAVR, which has a significantly higher average device price (circa US$20,900 globally and over US$30,000 in the US) compared to SAVR (US$4,400).

We have valued Anteris using a risk-adjusted net present value (rNPV) method to discount future cashflows through to FY2030. Our valuation approach assumes a discount rate of 12% and conservative assumptions, including a probability of success of 40%, commencement of sales in 2025 and an initial market penetration of 15% before increasing to a peak market penetration rate of 50% and achieving peak sales of $3.8B by 2030. We have estimated a gross margin of 70% and SG&A of 25% of sales revenue. Based on the above, we have placed a **BUY** recommendation on Anteris, deriving a price target of $66.32 (undiluted), reflecting an implied return of 193% from current levels. This gives the company an overall valuation of $922m, which we believe is suitable given the consistency to clinically demonstrate the continued superiority of DurAVR™ in comparison to the approved TAVR and SAVR valves.

We also note, that in deriving this valuation, we have not considered the impact of dilution, which would increase depending on whether the company raises more capital as it progresses to more advanced clinical trials, whilst also noting that the impact of dilution would be offset by an increasing probability of success as the company passes each milestone and follow-on reviews.

		Probability of Success					
		15%	20%	25%	30%	35%	40%
Discount	8%	$29.30	$39.10	$49.00	$58.70	$68.40	$78.30
Rate	10%	$27.00	$36.00	$45.00	$54.00	$63.00	$72.00
	12%	$24.88	$33.16	$41.45	$49.74	$58.03	$66.32
	14%	$22.95	$30.60	$38.25	$45.90	$53.55	$61.20
	16%	$21.20	$28.27	$35.34	$42.42	$49.50	$56.56

Source: Evolution Capital Pty Ltd

16 Investment thesis

Innovation of heart's complexities

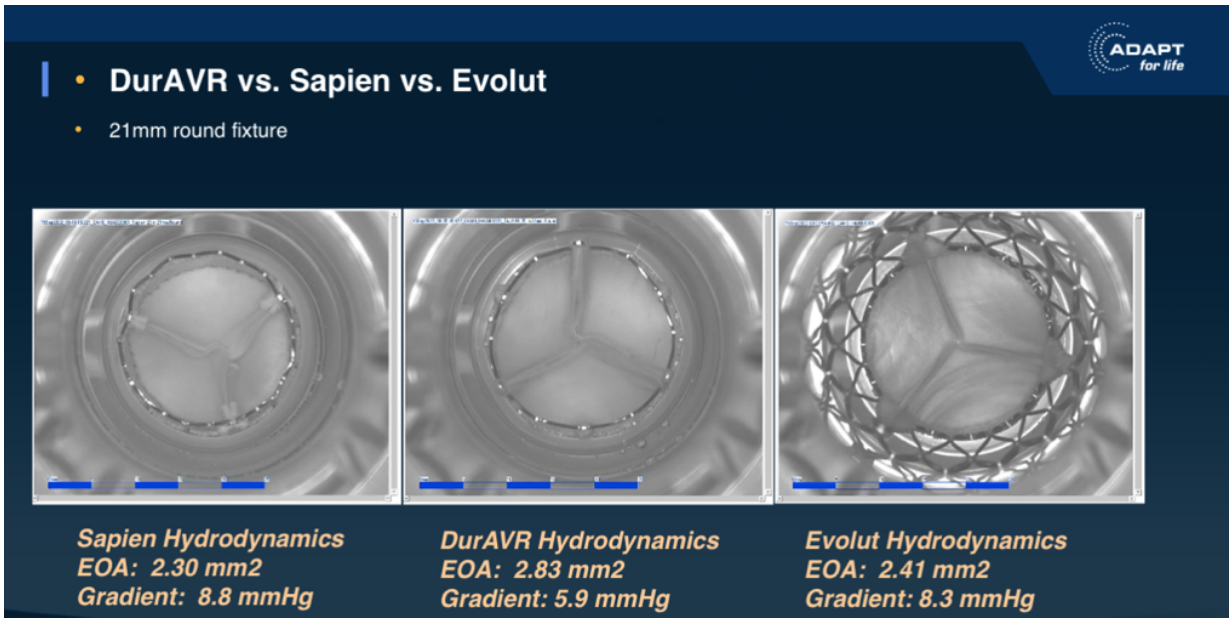
Further growth and expansion of the TAVR market will continue in testing the shortcomings of current generation bioprosthetic valves, and as such drive-up demand for innovative features that will help to achieve a healthy outcome for patients suffering from AS. As noted previously, the first-generation TAVR valves largely focused on delivery systems, precisely, (frames and stents) and less on the technology itself. As such, we believe this represents significant opportunity for new medical device companies to gain market share with differentiated technology that can improve current valve offerings through the following expansional features:

- Durability
- EOA:
- Shear stress
- Mean peak gradients

The key investment points are noted below-

DurAVR™: a superior solution to a key problem:

- EOA: DurAVRs™ EOA is significantly larger than both the competitor valves, and it also reduces the pressure more than Sapien 3 (Edwards) and CoreValve (Medtronic).
- Design: consists of a single 3D piece, while the competitor valves are sown together using three pieces. DurAVR™ 3D also delivers perfect lamina flow through the aorta.
- Mean pressure gradient: The competitor valves still leave patients with a mild form of stenosis after implant, whereas the Anteris valve returns the patient to a healthy state with a mean pressure gradient across the valve of 5-10mmHg.
- Competing valves also begin to wear out around 300-400 million cycles, whereas the Anteris valve has shown to last for between 750-800 million cycles. The valve has demonstrated to operate for 15 years under simulated wear testing.



Source: Anteris

Global market growing at a rapid pace: The global aortic valve replacement market has shown to grow at a CAGR of 16-20% over the past five years. This is expected to grow at an annual rate of 14% over the next eight years. Most of the growth is expected to come from the growing TAVR market, particularly as the average age of eligible TAVR patients continues to decrease overtime.

Promising pre-clinical and clinical trial results: Anteris has conducted numerous pre-clinical and FIH trials of their ADAPT® tissue technology and DurAVR™ replacement valve. Results to date have been promising.

Potential acquisition target: Anteris is attempting to enter a market dominated by two large medical device companies. If the company continues to validate DurAV™ as a superior aortic replacement valve to existing solutions, it will create competitive tension, possibly leading to an acquisition.

17 Board & Management

Name & Position	Description
John Seaberg Chairman	Between 2007 and 2014, John was Founder, Chairman and CEO of NeoChord Inc, a venture capital-backed company commercializing technology developed at the Mayo Clinic for the repair of the mitral valve via minimally invasive techniques. Previously, John spent 10 years at Guidant Corp where he held various executive level positions in sales and marketing, including Director of Bradycardia Marketing for Cardiac Rhythm Management (CRM) and Vice President of Sales for Cardiac Surgery, where he managed a sales team of more than 600 people and over $1 billion in revenue. In 1991, John co-founded ACIST Medical and served as its first President and CEO. He was also founder and CEO of Seaberg Medical, a regional distributor of implantable cardiovascular devices.
Wayne Paterson Managing Director/CEO	Over the last 25 years, Wayne has held numerous senior positions at multi-national companies around the world. He has been responsible for building and managing multi-billion-dollar businesses, including mergers, integrations, acquisitions and major restructures as president and CEO. From 2005 to 2013, he held senior positions at Merck KGaA, most recently as President of Europe, Canada and Australia. Prior to this, he was President of Emerging Markets, President of Japan and Global Head of Cardiovascular medicine. Between 1999 and 2005, Wayne served at Roche Pharmaceuticals where he was Head of Pharmaceuticals in Roche's South Korean operation, following his role as Head of Commercial Operations for Roche China based in Shanghai.
Stephen Denaro Non-Executive Director & Company Secretary	Stephen has extensive experience in mergers and acquisitions, business valuations, accountancy services, and income tax compliance gained from positions as Company Secretary and Chief Financial Officer of various public companies and major accountancy firms in Australia and the UK. He provides company secretarial services for a number of technology start-ups, ASX listed (Anatara Lifesciences Limited "ASX: ANR" and Oventus Medical Limited "ASX: OVN") and unlisted public companies; and also serves as a Non-Executive Director and Chair of the Audit & Risk Committee of a not-for-profit company, National Affordable Housing Consortium Limited.
David St Denis Chief Operating Officer	David is an accomplished senior healthcare leader with a systematic and metrics-driven approach spanning 20 years of proven business results at the regional and global levels within the life sciences and pharmaceutical sectors. Most recently at Merck in Germany, he headed commercial operations for Europe and Canada.

Mathew McDonnell Chief Financial Officer	Matthew worked for KPMG for over 24 years' including 10 years as a partner. He has a broad range of industry experience and corporate governance acumen, having delivered audit, accounting, and advisory services to a broad range of sectors, including financial services, transport, industrial markets, health, childcare and energy. He has experience in restructures, acquisitions, divestments, privatisations and other significant financial transactions, including the Queensland Government restructures and privatisations; Linc Energy's re-listing on the Singapore Exchange, acquisitions such as Virgin Australia's purchase of SkyWest. He was also Director of the State Library of Queensland and was the Chair of the Audit and Risk Management Committee for eight years.

18 Risks

- **Failure in clinical trials:** The most significant risk for Anteris is the failure of clinical trials. Anteris has a proven technology with extensive accumulated in-human data. However, the near-term prospects rely heavily on the outcome of both its SAVR and TAVR trials.
- **Technology risk:** Notwithstanding the major structural heart market players, the wider tissue engineering industry is extremely competitive, with companies developing products for multiple therapeutic indications. Therefore, risks remain from newer and emerging technologies that may match or surpass the uniqueness of ADAPT® engineered tissue.
- **Funding risk:** The company is currently funding all of its clinical programs and as such will require the need to raise capital over the course of time. Any shortfall in the amount raised may contribute to funding risk.
- **Regulatory risk:** Anteris is seeking approval for new applications of the ADAPT® technology. Although Anteris has validated the technology and accumulated extensive in-human data, there are no guarantees that future products using the ADAPT® technology will be approved by the FDA or international regulatory bodies for marketing in the US.

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