CASE REPORT

Transcatheter Aortic Valve Implantation Two Decades of Evolution - TAVI From Current Perspective

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doi: 10.5455/aim.2023.31.312-321

ACTA INFORM MED. 2023, 31(4): 312-321

Received: SEP 10, 2023

Accepted: OCT 25, 2023

ABSTRACT

Background: In the treatment of valvular heart diseases, transcatheter therapies have changed the rules of the game, especially in the case of aortic stenosis and mitral regurgitation. Since the first in man transcatheter aortic valve intervention (TAVI) performed by Dr. Alain Cribier in 2002 in a non-operable aortic stenosis (AS) patient, TAVI has changed the lives of so many patients for whom medical treatment was, up to then, the only option. **Objective:** This article outlines patient selection and pre-procedure evaluation, current perspectives, recent advances, current and future devices, current guidelines informing the use of TAVI, expanding indications for TAVI, ongoing challenges and the future of TAVI. **Methods:** The use of these percutaneous techniques has also increased significantly in the past few years with its first application in 2002, transcatheter aortic valve implantation (TAVI) has revolutionized the management of aortic stenosis and has become the standard of care for patients with AS at prohibitively high surgical risks, as well as a preferred treatment for elderly patients with intermediate and high-risk AS. **Results:** Since the first pioneering procedure was performed 22 years ago, transcatheter aortic valve implantation (TAVI) has evolved into a routine procedure increasingly performed under conscious sedation via transfemoral access. On a global market worth $2 billion per year, over 300 000 patients have received a transcatheter aortic valve, demonstrating its clinical and market impact. TAVI may be used in lower risk, younger, asymptomatic populations with ongoing studies using an expanding portfolio of devices. Also, for patients deemed unsuitable for cardiac surgery, mitral transcatheter therapies represent the treatment of choice. Percutaneous repair techniques have had the most clinical experience to date. **Conclusion:** During this 20-year period, the increased knowledge on pre-procedural planning, the important technological improvements in transcatheter valves, the increased experience and the numerous studies that have been carried out have permitted an expansion of the indications for TAVI, from inoperable patients to high- and intermediate-risk patients. This article outlines patient selection and pre-procedure evaluation, current perspectives, recent advances, current and future devices, current guidelines informing the use of TAVI, expanding indications for TAVI, ongoing challenges and the future of TAVI.

Keywords: Aortic stenosis, Aortic valve replacement, Transcatheter aortic valve implantation TAVI, Transcatheter heart valve THV.

1. BACKGROUND

Since the first in man transcatheter aortic valve intervention (TAVI) performed by Dr. Alain Cribier in 2002 in a non-operable aortic stenosis (AS) patient, TAVI has changed the lives of so many patients for whom medical treatment was, up to then, the only option. In the treatment of valvular heart diseases, transcatheter therapies have changed the rules of the game, especially in the case of aortic stenosis and mitral regurgitation. The use of these percutaneous techniques has also increased significantly in the past few years for the aortic, mitral and tricuspid valves for several reasons, including:

a) Surgical risk, age, perceived life expectancy, and valve durability influence the choice between surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI).

b) Mitral and tricuspid regurgitation is one of the most prevalent conditions associated with poor clinical outcomes despite medical treatment, often resulting in right ventricular heart failure as a result.

c) Patients with aortic, mitral and tricuspid valve disease have traditionally been treated with surgical valve repair or replacement, but surgical valve intervention has been found to be associated with high mortality rates, and

d) most patients with aortic, mitral and tricuspid pathology are denied cardiac surgery due to their comorbidity burden.

Thus, in this context the development of less invasive catheter-based therapies would be of high clinical relevance. Such therapies should be less invasive and easier to apply than conventional methods. They should also provide better safety and efficacy profiles. This article outlines patient selection and pre-procedure evaluation, current perspectives, recent advances, current and future devices, current guidelines informing the use of TAVI, expanding indications for TAVI, ongoing challenges and the future of TAVI (2,3,15).

Transcatheter aortic valve implantation (TAVI) has revolutionized the management of aortic stenosis (AS). Since its introduction in 2002 and has become the standard of care for patients with AS who are at prohibitive surgical risk, as well as the preferred treatment for many elderly patients with intermediate and high-risk AS. With over 300 000 patients receiving transcatheter aortic valves each year, this industry is worth $2 billion. In terms of clinical impact and market impact, it cannot be overstated. As transcatheter valve designs have advanced, improvements have been made in patient selection, procedural planning, and technique, resulting in stepwise improvement in effectiveness and a reduction in complication rates (15, 16).

Modern transcatheter valve designs and optimizations of patient selection, surgical planning, and technique have led to stepwise improvements in efficacy and complication reduction. There has been a dramatic reduction in complication rates due to a simplified procedure, accumulating clinical experience, and improving valve design and delivery systems. As a result of these advances, PARTNER 2A and SURTAVI trials have established a clear evidence base for use in intermediate-risk populations.

Cardiologists, surgeons, clinical investigators, and the device industry have worked in collaboration to make TAVI such a success. Despite being a durable and established treatment for AS that was first performed in 1960, surgical aortic valve replacement (SAVR) is deemed unsuitable for up to a third of patients because of the excess procedural risk involved. Cribier-Edwards transcatheter valve was developed, developed, and clinically applied because there were no alternative therapeutic options. In the decade since the first procedure was performed, it has been successfully translated into routine clinical practice through a series of landmark clinical trials involving more than 15,000 patients (including eight randomized controlled trials (RCTs)).

There are new frontiers for TAVI on the horizon, as well as potential hurdles. The use of percutaneous valve replacements is challenging SAVR in lower risk patient cohorts, and trials in patients with asymptomatic AS and moderate AS with heart failure may undermine the traditional indications for valve replacements. Questions still remain about long-term valve durability, stroke risk, and complications including hemorrhage, conduction abnormalities, and paravalvular leaks (PVLs). This paper reviews the state-of-the-art in TAVI, describing recent and ongoing trials, the contemporary device portfolio, clinical guidelines, and strategies to further reduce complication rates (2,3,4,15,16).

2. OBJECTIVE

This article outlines patient selection and pre-procedure evaluation, current perspectives, recent advances, current and future devices, current guidelines informing the use of TAVI, expanding indications for TAVI, ongoing challenges and the future of TAVI.

3. MATERIAL AND METHODS

Patient selection and pre-procedure evaluation.

Patient selection determines the success of the intervention. For confirming the severity of AS and evaluating the necessity of intervention, a detailed, stepwise, multiparametric and usually multimodal evaluation is necessary. The diagnosis of severe AS relies heavily on echocardiography (transthoracic, stress and transesophageal echocardiography, in particular with 3D), which provides valuable insight into left ventricular function, the presence of other valve diseases, pulmonary hypertension, and right ventricular dysfunction. Heart team discussions should consider these prognostic data, which go beyond AS severity. The use of other imaging modalities such as cardio-pulmonary exercise testing, cardiac computer tomography (CCT), cardiac magnetic resonance imaging, and biomarkers should be considered for patients with discordant gradings or when the severity is not consistent with the patient's symptoms. After the pre-procedural evaluation, the heart team discusses the patient's condition and decides between SAVR and TAVI based on the risk of the surgical intervention, the patient's age and estimated life expectancy, and certain anatomical and procedural characteristics that could favor TAVI (feasible transfemoral TAVI, porcelain aorta, previous chest radiation, severe chest deformation, the presence of a coronary graft passing behind the sternum, or a high likelihood of severe patient–prosthetic mismatch) or SAVR (aortic annulus dimensions unsuitable for TAVI, high risk of coronary artery obstruction due to coronary ostia implantation <10mm from the annulus or heavy leaflet/left ventricular outflow calcifications, or the presence of bicuspid aortic valve (17,18,44).

Cardiovascular catheterization or hybrid operating rooms can be used to perform the procedure. For many years, TAVI was performed under general anesthesia with angiography and transesophageal echocardiography guidance, but today most centers perform the procedure under conscious sedation and local anesthesia with only angiographic guidance. In the ipsilateral leg, a venous sheath is inserted through which a temporary pacemaker is placed in the right ventricle through femoral arterial access for aortic angiography. It is necessary to cannulate the contralateral artery. A guidewire remains in place in the left ventricle once the aortic valve has been crossed with anticoagulant. A delivery sheath is then inserted in the descending aorta. The balloon aortic valvuloplasty is performed while the heart is being paced rapidly. In rapid ventricular pacing, the prosthesis is advanced retrogradely to the

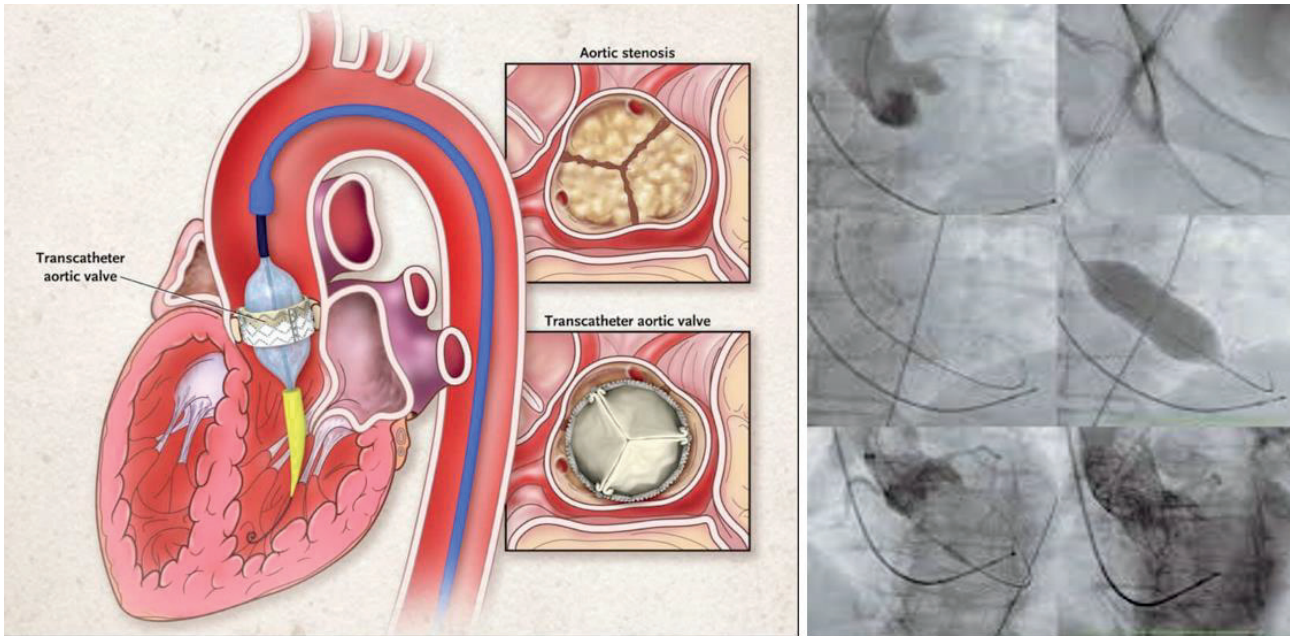

Figure 1. Transcatheter aortic valve replacement is a less invasive approach for replacing a diseased aortic valve.

ascending aorta, where the valve is deployed after confirmation of the appropriate location with angiography. During the transvalvular gradient measurement, we evaluate the presence of paravalvular regurgitation or Leak (PVR or PVL). If significant PVL is present, post-dilatation is performed. As soon as the sheath is removed, blood pressure is monitored carefully and contrast is administered at the iliac arteries for determining the possibility of a vascular complication, which should be treated as soon as possible.

The incidence of PVL after TAVI has decreased significantly in the last two decades, due to the detailed pre-procedural evaluation with improvements in patient and prosthesis selection (avoiding under-sizing, recognizing the importance of severe valvular calcifications in predicting the risk of PVL), the technological advancements seen in the design of prosthetic valves and the increased experience. To assess the function of the prosthesis, specifically the severity of aortic regurgitation, and to detect any new wall motion abnormalities that could indicate coronary artery obstruction or pericardial effusion, a transthoracic echocardiography is performed at the end of the procedure. Before the patient leaves the hospital, a transthoracic echocardiography is performed as a follow-up test (18,19).

TAVI Complications

Overall, the incidence of complications after TAVI has decreased significantly due to the increase in experience, the use of CCT as the main imaging modality for evaluating the feasibility of TAVI, the significant technological advancements in the design of the prostheses, and the decrease in the size of the sheaths. Complications after TAVI has decreased significantly but the incidence of stroke, new pacemaker implantation and paravalvular leak remains higher compared to SAVR according to the complications which has been reported in published trials. Complications of TAVI can be classified into periprocedural and long-term complications. Periprocedural complications of TAVI can be from vascular access injury, malpositioning of valve, paravalvular leak affecting valve function, stroke, myocardial ischemia/injury, acute kidney injury, and heart block. AR, stroke, myocardial infarction, prosthetic valve thrombosis, acute coronary syndrome, bleeding, permanent pacemaker implantation, and prosthetic valve endocarditis are some associated long-term complications of TAVI. The most common peri-procedural complications from PARTNER I trials were major arrhythmias (17%), major vascular complications (13%), major bleeding (12%), and minor vascular complications (8%, Arnold et al., 2014). Device landing zone rupture, device embolization, coronary occlusion, and stroke are some rarer complications of the TAVI procedure (28,29,30).

4. RESULTS

Current clinical 2021 ESC/EACTS Guidelines for the management of valvular heart disease

Valvular heart disease management guidelines were updated in 2021 by the European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) not only provide straightforward recommendations for TAVI or SAVR, but also give the treating Heart Team considerable discretion. The guidelines emphasize the importance of the Heart team in assessing patients based on key clinical (e.g., extracardiac comorbidities, risk of surgery), anatomical (pathological or congenital variation, TAVI feasibility), and procedural (e.g., imaging feasibility, local procedural experience, and outcomes) factors before selecting between SAVR and TAVI in the management of aortic stenosis. Several parameters can be used to categorize the severity of AS, including but not limited to; the mean pressure gradient across the valve, the peak transvalvular velocity, the valve area, and the stroke volume (the volume of blood ejected from the left ventricle during systole contraction).

There are several factors that affect left ventricular ejection fraction: left ventricular hypertrophy, left ventricular hypertrophy, and blood pressure control. In patients with severe, high-gradient AS (mean gradient > 40 mmHg, peak velocity > 4.0 m/s, and valve area > 10 mm2), intervention is indicated. New guidelines outline that intervention should also be considered in symptomatic patients with severe, low flow, low gradient aortic stenosis with normal ejection frac-

tion, and in patients with reduced ejection fractures without demonstrated flow (contractile) reserve. It should be noted, however, that patients with low-flow, low-gradient AS should not be considered for intervention before additional testing has excluded pseudo severe AS. Left ventricular dysfunction (ejection fraction 50%) is indicated in asymptomatic patients with severe stenosis. No intervention is recommended for patients with severe comorbidities because it is unlikely to improve quality of life and outcome. In patients who are deemed unsuitable for surgery (patients over 75 years, previous cardiac surgery history, porcelain aorta, reduced mobility, difficult rehabilitation, frailty, significant chest wall deformities, radiation-induced sequelae, sternotomy risks affecting previous coronary bypass grafts, favorable transfemoral access, and expected patient-prosthetic mismatches will be at higher surgical risk, while EuroSCORE II scores greater than 8 indicate increased surgical risk (Vahanian et al., 2022).).

The EuroSCORE cardiac risk calculator uses 18 items of information about the patient, the heart state, and the proposed surgery to predict mortality after cardiac surgery. EuroSCORE II, published in 2012, is an updated version of EuroSCORE I first published in 1999 (Nashef et al., 2012). Based on STS risk models, the STS Short-Term Risk Calculator calculates a patient's mortality and morbidity risk following the most commonly performed cardiac surgeries (O'Brien et al., 2018; Shahian et al., 2018) (2,3,4,12,13,14).

The Future

As the population ages, the number of TAVI procedures is expected to grow by four to ten times over the next decade. In many countries, cost and infrastructure development are already limiting the implementation of TAVI, rather than clinical evidence. Transfemoral delivery and simplified procedures are increasing availability, but maintaining high quality decision-making, excellent outcomes and specialist training in a Heart Valve Centre are essential. Structure interventionists trained in cardiology, surgery, or hybrid training routes will be necessary to meet the logistic challenges of delivering TAVI care. In a competitive market of valves with broad clinical equivalence, the relative cost of devices will be scrutinized more closely, improving affordability and cost-effectiveness (2,3,25,31).

Currently, TAVI is a low-risk, refined procedure with intermediate durability for replacing aortic valves. TAVI is likely to show non-inferiority to SAVR within a few years, and may be more effective than active surveillance in asymptomatic patients. As TAVI is used by younger patients, it must demonstrate durability equivalent to surgical bioprostheses, and options need to be available for handling SVD when it occurs. The development of new valves is necessary to achieve comparable outcomes, particularly for challenging anatomical structures (especially BAV). Different antiplatelet and OAC combinations may benefit specific patient subsets, and these remain to be identified. A further important requirement before TAVI can be widely used in younger patients is the reduction of the amount of PPM needed and the minimization of PVL incidence. Despite these challenges, they are not insurmountable. After successfully navigating infancy and adolescence, TAVI looks to have a very bright future (26,31).

As a result of the new data, the ESC guidelines for managing severe AS for 2021 recommend transfemoral TAVI as the first-line treatment for patients over 75 years of age, those at high risk (STS PROM/EuroSCORE II >8%) or those who are unsuitable for surgery. It is also recommended for remaining patients depending on their clinical, anatomical, and procedural characteristics (2). In 2020, ACC/AHA guidelines recommend transfemoral TAVI over SAVR for patients with severe symptoms of AS over the age of 80, as well as for younger patients with a life expectancy of at least ten years and no anatomical contraindications. As a Class I procedure, TAVI is now recommended for patients aged 65-80 years with severe symptomatic AS, ranging from prohibitive to low-surgical risk (3). As TAVI is increasingly being used on younger and lower-risk patients, a shared decision-making process should be implemented. Prior to deciding whether TAVI or SAVR is best for the patient, it is important to evaluate his or her life expectancy and the durability of his or her valve (Figure 2). To determine which approach is most appropriate for a given patient, anatomical and procedural factors must be considered, as well as the risks and benefits associated with each option (15,16).

5. DISCUSSION

Current perspectives on transcatheter aortic valve implantation

There are two types of transcatheter valves, balloon-expandable and self-expandable. The third generation of balloon-expandable SAPIENTM valves (Edwards Lifesciences Corporation, Irvine, CA, USA) includes the SAPIEN 3 and the SAPIEN 3 Ultra valves. They are composed of a cobalt–chromium cylindrical stent into which three symmetric leaflets made of bovine pericardium are mounted. They have a sealing skirt meant to decrease the risk of PVL. The short frame height and the open cell geometry of the SAPIEN 3 Ultra valve are meant to facilitate coronary access after TAVI. The most widely used self-expanding valve is the CoreValveTM (Medtronic, Inc., Minneapolis, MN, USA), which consists of an asymmetrical, self-expanding nitinol frame, into which are mounted three leaflets of porcine pericardium. TAVI's breakthrough success is attributed to a combination of

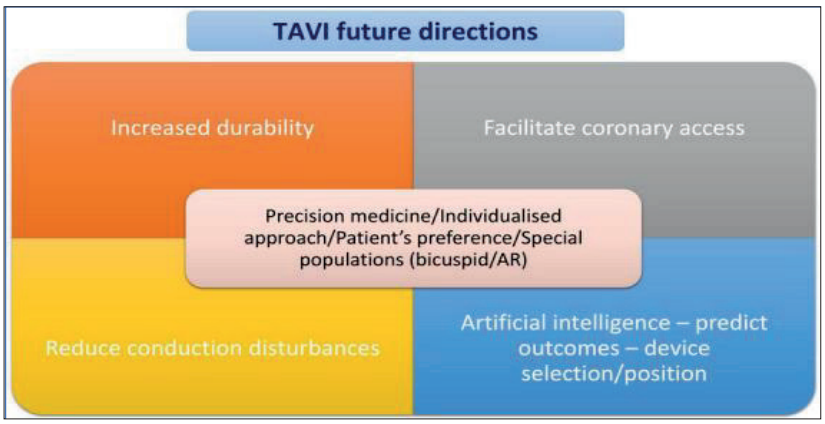

Figure 2. The future and TAVI future directions. (16)

patients' need and collaboration between cardiologists, surgeons, clinical investigators, and device manufacturers. Although surgical aortic valve replacement (SAVR), first performed in 1960, is a durable and established treatment for AS, up to a third of patients may not be eligible for it because of excessive procedural risks. The Cribier-Edwards balloon-expandable transcatheter valve was developed, developed, and clinically applied due to a lack of alternative therapeutic options. Since 2007, a series of landmark clinical trials have enrolled over 15000 patients [including eight randomized controlled trials (RCTs)] to validate the first procedure.

Clinical experience with TAVI has resulted in substantial simplification of the procedure. Transformative improvements have been made in valve technology and delivery catheter technology. Compared to earlier models, newer devices have improved sizing, deliverability, and positioning, and using expandable sheaths and/or atraumatic, small-bore delivery catheters, approximately 90% of patients can now be positioned using transfemoral access. Computed tomography (CT) imaging has emerged as the most accurate tool for pre-procedure planning and valve selection, as it provides information on vascular access, annular dimensions, and valve morphology.

In most cases of TAVI, the procedure is performed under conscious sedation, local anesthesia, and transthoracic echocardiography, which is considered a 'minimalist' approach. In most European countries, conscious sedation is routinely used for transfemoral TAVI, as it reduces procedural time, speeds up recovery, and reduces costs, but also leads to a reduction in peri-procedural transesophageal echocardiography (TOE). Fluoroscopy, aortography, hemodynamic measurements, and standby transthoracic imaging can be used to guide valve deployment and assessment of residual aortic regurgitation, but the use of contrast and risk of postoperative aortic regurgitation are increased without TOE guidance. CS is associated with a shorter hospital stay and reduced short-term mortality in almost 11 000 US propensity-matched patients undergoing transfemoral TAVI, according to emerging US propensity-matched data. The approach chosen should be tailored to the needs of the patient: for patients with chronic kidney disease where contrast use is restricted, a limited post-procedural TOE may be helpful. High-risk patients requiring continuous echocardiographic guidance may also benefit from intracardiac echocardiography.

As a result of this evolution, procedural mortality and major complication rates have decreased. In the UK TAVI registry, mortality rates prior to hospital discharge decreased significantly (9.09% in 2008, 1.84% in 2016), and in French, German, Japanese, and US registry studies, mortality and complications rates were also reduced. There was a reduction in stroke incidence of 3.4% to 2.2%, hemofiltration requirements from 6.4% to 0.9%, and tamponade requirements from 5.3% to 1.4% between 2008 and 2016. Improvements in patient outcomes have been associated with a reduction in length of stay; from 130 hours in 2013 to 64 hours in 2016, the median time from procedure to discharge has fallen. Structured early discharge programmes are likely to reduce this number further. Using a minimal procedure, avoiding routine intensive care, and using criteria-led discharge, preliminary results from the Vancouver 3M Clinical Pathway demonstrate safe one-day discharge in up to 80% of patients after transfemoral TAVI. In a US cohort of 360 patients with uncomplicated transfemoral TAVI using a Sapien valve, male sex, no atrial fibrillation, lower creatinine levels, and young age were associated with a safe discharge the next day (2,3,4).

Expanding indications for transcatheter aortic valve implantation

The excellent efficacy and safety results of transfemoral TAVR in all surgical-risk categories has led to an increasing interest in expanding the indications of invasive management of AS toward severe asymptomatic AS and moderate AS In light of the declining incidence of complications associated with TAVI, the classical indications for aortic valve replacement are being questioned. Using a minimally invasive technique that is highly acceptable to patients, transcatheter aortic valve implantation may allow safe intervention earlier in the natural history of AS. It must, however, be supported by high quality clinical evidence since long-term valve durability is not yet established, and redo valve procedures and coronary interventions after TAVI may be more challenging. There are two distinct groups of patients being tested: those with moderate AS and impaired ventricular function, as well as patients with severe AS who are asymptomatic (2,3,11).

Moderate aortic stenosis with impaired ventricular function

Over 85 percent of patients with heart failure suffer from impaired left ventricular function, which often coexists with AS. Reducing afterload can improve cardiac output and organ perfusion in patients with heart failure. Patients with severe aortic valve disease and left ventricular dysfunction benefit from aortic valve replacement by reducing afterload and improving their symptoms, contractility, and survival. An extensive series of patients with moderate AS and left ventricular dysfunction found that 48% of patients were hospitalized or died after four years of follow-up due to heart failure. In patients with impaired ventricular function and moderate AS, however, it is unclear whether valve replacement can improve outcome.

The ongoing TAVR UNLOAD trial (NCT02661451) is a strategy trial for patients with moderate aortic stenosis, left ventricular dysfunction (EF 20- 50%) and heart failure symptoms comparing transfemoral TAVR with standard heart failure regimens. (31) TAVR UNLOAD trial will address precisely this question in patients with symptomatic heart failure, impaired left ventricular function (ejection fraction <50%, but >20%), and moderate AS. In a randomized trial, patients will be randomized to a transfemoral TAVI procedure using the Sapien 3 valve or to optimal heart failure therapy. In this study, the primary outcome is the hierarchical occurrence of all-cause death, disabling stroke, hospitalization for heart failure, symptomatic aortic valve disease, and non-disabling stroke at one year. The other studies-PROGRESS (Prospective, Randomized, Controlled Trial to Assess the Management of Moderate Aortic Stenosis by Clinical Surveillance or Transcatheter Aortic Valve Replacement) and the Evolut EXPAND TAVR II Pivotal Trial -include patients with moderate AS and evidence of "cardiac damage/dysfunction," There is less observational data to support early treatment of moderate AS in that setting, although time will tell with the results of these trials will also provide prospective data on the moderate

AS population (33,39,42).

Asymptomatic severe aortic stenosis

There have traditionally been concerns that the upfront risks of SAVR outweigh the benefits of intervention in asymptomatic AS. Until symptoms or left ventricular impairment emerge, an active surveillance strategy is used. Several problems arise with this approach. When symptoms are present, or AS is definitively to blame, it is not always straightforward to determine whether AS is to blame. Each year, 1% of asymptomatic patients die suddenly from AS despite surveillance. A few patients develop fibrosis and irreversible declines in cardiac function prior to SAVR, which increases their procedural risk as well as their left ventricular dysfunction. In patients with a negative stress test ('truly asymptomatic'), even with exercise treadmill testing or stress echocardiography, sudden death is still a risk (33, 34, 35,36).

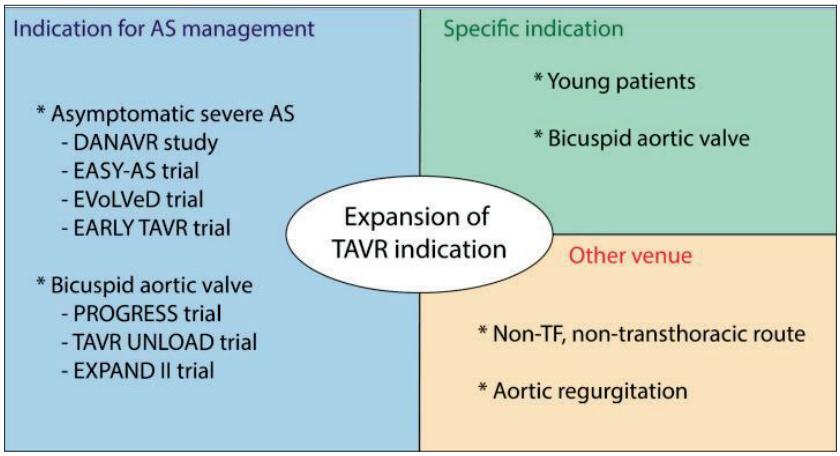

Figure 3. Future direction in TAVR indication; AS, aortic stenosis; TF, transfemoral. (39)

The treatment of asymptomatic severe AS is the focus of a number of randomized controlled trials. AVATAR (Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis) and RECOVERY (Randomized Comparison of Early Surgery Versus Conventional Treatment in Very Severe Aortic Stenosis (NCT01161732) were designed to understand whether early surgical intervention might be beneficial rather than ongoing monitoring. In this regard, both trials have shown early surgical aortic valve replacement (SAVR) to be beneficial in terms of all-cause mortality and new-onset heart failure compared with conservative management (34).

The recent VALVENOR (Suivi d'une Cohorte de Patients Présentant une Sténose Valvulaire Aortique en Région Nord-Pas-de-Calais) study showed that, compared with the general population, patients with symptomatic moderate AS experienced higher cardiovascular mortality compared with mild AS (although still less than that of patients with severe AS). (32) In this regard, the PROGRESS (A Prospective, Randomized, Controlled Trial to Assess the Management of Moderate Aortic Stenosis by Clinical Surveillance or Transcatheter Aortic Valve Replacement [NCT04889872]) trial, TAVR-UNLOAD (Transcatheter Aortic Valve Replacement to Unload the Left Ventricle in Patients With Advanced Heart Failure: A Randomized Trial [NCT:02661451]), and the EXPAND TAVR II Pivotal Trial (NCT05149755) will assess TAVR versus clinical monitoring for patients with symptomatic moderate AS.

The EARLY TAVR Trial: Evaluation of TAVR Compared to Surveillance for Patients With Asymptomatic Severe Aortic Stenosis (NCT03042104) will examine the safety and effectiveness of the Edwards SAPIEN 3/ SAPIEN 3 Ultra transcatheter heart valve (THV) versus careful observation (or clinical surveillance) in patients with severe aortic stenosis without symptoms. The purpose of the trial is to compare results of patients that have their valves replaced early in the disease process versus patients that have the disease monitored. The study is an ongoing multi-centric trial, where 901 participants were recruited using parallel randomized assignments to be assigned to either of the groups. In this study using the balloon-expandable SAPIEN-3 prosthetic (Edwards Lifesciences, Irvine, CA), which has completed enrollment, may provide more insight into whether earlier percutaneous intervention would be beneficial compared with conservative management in asymptomatic severe AS. The Early TAVR. The primary outcome of the study is to document all-cause death and two years' risk of hospitalization for stroke and cardiovascular reasons. Additional outcomes that are being considered as secondary outcomes are the Kansas City Cardiomyopathy Questionnaire (KCCQ) score improvement, improvement in echocardiographic findings, documented improvement in LV health including improvement in LVEF, the incidence of new-onset atrial fibrillation, and disabling stroke or death. Though the initial results shared in press media are said to be positive favoring TAVR over conservative management, the official results and recommendations are still awaited (33, 34, 35,36).

There are two recently published studies, AVATAR and RECOVERY trials, the both trials included patients with asymptomatic severe aortic stenosis of different etiologies. The majority of the patients (85%) in the AVATAR trial had degenerative aortic valve stenosis. In contrast, only 33% of the patients had degenerative aortic stenosis in the RECOVERY trial and 61% had bicuspid aortic valve disease. Meta-analysis of two published randomised trials, AVATAR and RECOVERY, included 302 patients and showed that early intervention resulted in 55% reduction in all-cause mortality (HR=0.45, 95% CI 0.24 to 0.86; I2 0%) and 79% reduction in risk of hospitalization for heart failure (HR=0.21, 95% CI 0.05 to 0.96; I2 15%). There was no difference in risk of cardiovascular death between the two groups (HR=0.36, 95% CI 0.03 to 3.78; I2 78%). Additionally, meta-analysis of eight observational studies showed improved mortality in patients treated with early intervention (HR=0.38, 95% CI 0.26 to 0.56; I2 77%). This meta-analysis provides evidence that, in patients with severe asymptomatic aortic stenosis, early intervention reduces all-cause mortality and improves outcomes compared with conservative management. While this is very encouraging, further randomised controlled studies are needed to draw firm conclusions and identify the optimal timing of intervention (33, 34, 35,36).

The Evolut Low Risk trial randomized patients with severe aortic stenosis at low surgical risk who had an indication for

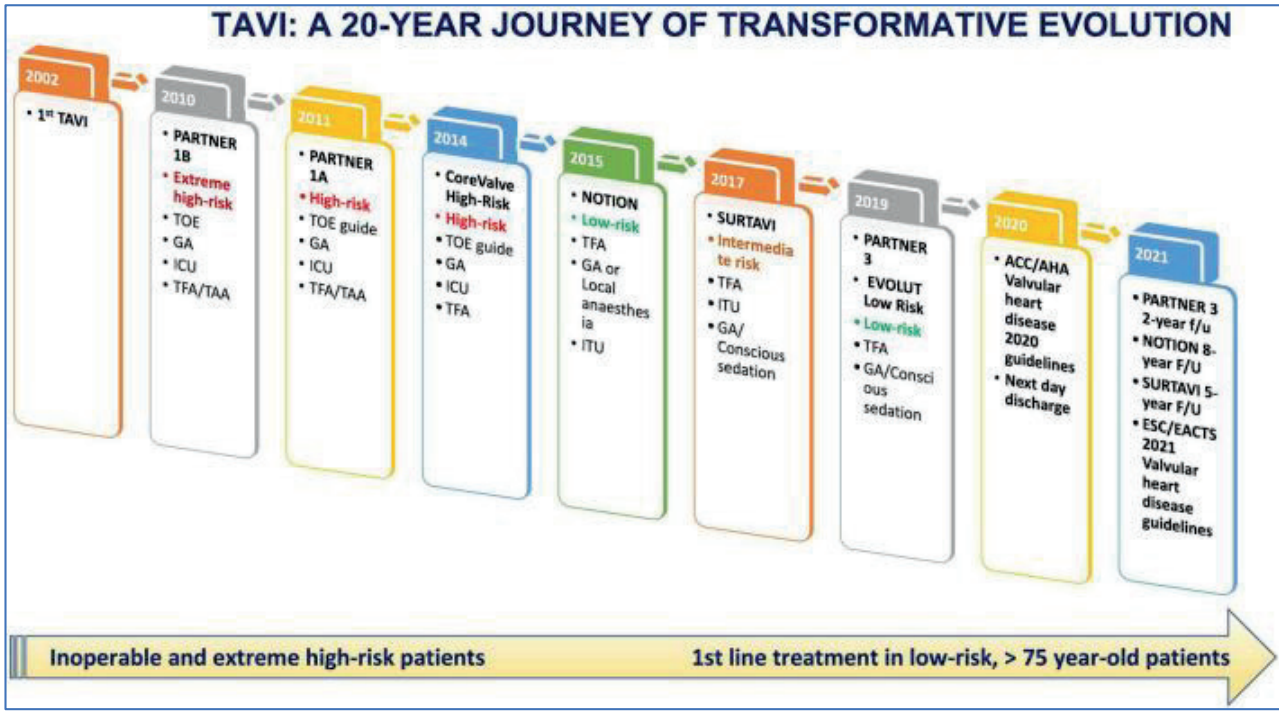

Figure 4. TAVI: A 20-year journey of transformative evolution from high-risk inoperable patients to the most recent European and US guidelines and low-risk younger patients along with landmark trials. (16)

aortic valve replacement to either TAVR or surgery. All patients in the Evolut Low Risk trial have now completed 3-year follow-up. Analysis of 3-year clinical outcomes, TAVR at 3 years showed durable benefits compared with surgery with respect to all-cause mortality or disabling stroke. (Medtronic Evolut Transcatheter Aortic Valve Replacement in Low Risk Patients; NCT02701283) (33,42).

Transcatheter aortic valve implantation in bicuspid aortic valve

In younger patients, bicuspid aortic valve (BAV) accounts for approximately 50% of cases requiring SAVR, with an estimated incidence of 2% (45). In addition to exhibiting a very heterogeneous morphology, BAVs exhibit significant differences in leaflet geometry, leaflet orientation, and raphe presence or absence, as well as severe calcification of the aortic valve and its adjacent structures. There have been several schemes proposed so far to classify BAV-all of which address all of these morphological characteristics (56-59). Since there are a variety of morphological conditions, there are only limited data on which BAV anatomy favors TAVI, which device and implantation strategy will deliver optimal results, which sizing strategy should be used, and the durability of the transcatheter heart valve (THV) over the long run in these heterogeneous environments. However, it is unanimously accepted that severe and asymmetric leaflet and LVOT calcification, the presence of more elliptical aortic annulus that exceeds available sized THVs, a dilated ascending aorta > 45 mm, and the presence of raphe calcification can result in suboptimal THV frame expansion and potentially worsen outcomes (2,3,45).

Current and future devices

After two decades of clinical experience, the TAVI procedure has undergone a transformative evolution (Figure 4). The new generation transcatheter heart valve (THV) with improved sizing, deliverability, and positioning compared to their predecessors, the advent of new hydrophilic, small bore, expandable and atraumatic sheaths, as well as the introduction of intravascular lithotripsy have now made transfemoral TAVI feasible in > 95% of patients. (16). The Edwards Sapien and Medtronic CoreValve are the most commonly used TAVI valves, but a number of newer systems are competing on design, repositionability, retrievability, and price. The size and design of the valves as well as the smaller delivery catheters have significantly reduced PVL and post-procedural complications, and this trend is likely to continue in the future (15).

There are now many valves which incorporate sealing systems to reduce paravalvular aortic regurgitation, such as the Sapien 3's outer skirt and the Evolut PRO's pericardial wrap. Acurate valves (Boston Scientific, formerly Symetis) are self-expanding supra-annular valves that have a low rate of permanent pacemaker implantation. With a leaflet geometry that is designed to function in both elliptical and round configurations, the Portico valve (Abbott) expands, is fully resheatheable and retrievable and is fully resheatheable. Due to problems with its release mechanism, the Lotus Valve, which is repositionable and retrievable, has been recalled worldwide. JenaValves (JenaValve Technology, Germany) and J-valves (JieCheng Medical, China) have active fixation mechanisms that anchor the prosthesis to the valve leaflets, enabling stability in the case of aortic regurgitation. As of now, JenaValve is the only transcatheter valve with a Conformité Européenne (CE) mark for use in patients with aortic regurgitation. There are two more Chinese valves at an advanced stage of development: the Venus-A® valve (Venus Medtech) and VitaFlow® valve (Microport). Both have high rates of procedural success in patients with bicuspid aortic valve disease (BAV) (20,21,22,23,24).

Current and Ongoing Challenges

In the growing age of TAVI, there are a number of potential obstacles to overcome. Percutaneous valve replacement

	Acurate (Boston Scientific)	Allegra (NVT)	Centera (Edwards)	Evolut PRO (Medtronic)	Evolut R (Medtronic)	JenaValve (JenaValve)	Portico (St Jude)	Sapien 3 (Edwards)	VenusA (Venus Medtech)
									
Design (leaflets, frame and delivery)	Porcine pericardium Nitinol Self-expanding	Bovine pericardium Nitinol Self-expanding	Bovine pericardium Nitinol Self-expanding	Porcine pericardium Nitinol Self-expanding	Porcine pericardium Nitinol Self-expanding	Porcine pericardium Nitinol Self-expanding	Bovine pericardium Nitinol Self-expanding	Bovine pericardium Cobalt-chromium Balloon-expandble	Porcine pericardium Nitinol Self-expanding
Delivery routes and sheath size	TF, TA, TS 18 Fr/19 Fr	TF 18 Fr	TF, TS 14 Fr	TF, TAo, TS 16 Fr	TF, TAo, TS 14 Fr	TF, TA 18 Fr	TF, TA 18 Fr/19 Fr	TF, TA, TAo 14 Fr/16 Fr	TF, TA, TS 18 Fr/20 Fr
CE mark (years)	2011	2017	Awaited	2017	2013	2011 (AS) 2013 (AR)	2012	2014	NA
Specific advantages	Low PPM requirement	Resheathable up to 70% of deployment	Resheathable up to 85% deployment. PTFE skirt to reduce PVL. Motorized delivery system	Resheathable up to 80% deployment Double layer porcine pericardial skirt	Resheathable up to 80% deployment. Upcoming RCT data in low risk population	Active fixation for use in AR	Resheathable up to 85% deployment	External skirt to reduce PVL. Upcoming RCT data in low risk population	Experience in bicuspid valve population in China; reduced cost

Figure 5. Comparative overview of selected transcatheter aortic valve systems. AS: aortic stenosis, AR: aortic regurgitation, PVL: paravalvular leak, PPM: permanent pacemaker, TA: transapical, TAo: transaortic, TS: trans-subclavian, TF: transfemoral.

may overturn traditional indications for valve replacement in patients with asymptomatic AS and moderate AS with heart failure, where ongoing trials are challenging SAVR in lower risk patient cohorts. Infection, hemorrhage, conduction abnormalities, and paravalvular leaks (PVLs) remain issues regarding valve durability and stroke risk.

It is undeniable that TAVI has been a success, but there are still numerous challenges to overcome. Most studies to date have focused on short-medium-term safety and early technical success. In addition to a recent statement from the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery (ESC/EACTS), an internationally agreed-upon VARC-2 endpoint, as well as a VIVIV consensus document, trials focusing on long-term durability and late complications will be standardized. A new gold standard should not only be established for patients undergoing valve intervention, but also to match SAVR (2,3,31).

Valve durability and function

Degeneration and/or dysfunction of a valve caused by structural valve deterioration (SVD) (calcification, pannus, and leaflet failure) can result in valvular stenosis or intra-prosthetic regurgitation. The valve design and the age of the patient at the time of implantation strongly influence the risk of SVD. Long-term outcomes for surgical bioprosthetic valves have been well documented, but the rate of freedom from SVD at 15 years ranges from 67% in patients aged 60 to 92% in patients over 70. SVD can be predicted by valve design, examples of which include the Ionescu-Shiley pericardial tissue valve as well as the St. Jude Toronto SPV valve.

There have not been any reports of early SVD associated with transcatheter valves, with 5-year outcomes from PARTNER I showing that interventions are rare (~0.2%). Moderate or severe transvalvular regurgitation developed in 3.7% after TAVI, increasing over time. A multicenter registry study of 1521 TAVI patients found 4.5% developed an increase in mean transvalvular gradient of 10 mmHg over a period of 20 x 13 months, with a mean increase of 0.30 x 4.99 mmHg per /year. These factors were independent predictors, as were a valve-in-valve procedure and higher body mass index. (8,42)

In spite of this medium-term follow-up, studies of surgical bioprostheses indicate that SVD is rare before 10 years, and continued close follow-up is necessary to establish transcatheter valves' long-term durability. Among patients who received first-generation valves in the early 2020s, only a relatively small number of data will be available. As TAVI moves into lower age groups, establishing durability in large cohorts and determining the relative freedom from SVD of different valve designs will take longer, but it is crucial. Research and engineering priorities also include the development of transcatheter strategies for treating degenerated TAVI valves (redo-TAVI) (2,7,8,36).

SVD appears rare, but subclinical leaflet thrombosis may be a cause for concern. Subclinical leaflet thrombosis of bioprosthetic aortic valves after transcatheter valve replacement (TAVR) and surgical aortic valve replacement (SAVR) has been found with CT imaging. Demonstrated on CT imaging in 10-15% of TAVI patients, this phenomenon manifests as thickened leaflets with reduced movement. The causes of subclinical leaflet thrombosis are not clear, but regional stent frame under expansion leads to increased leaflet thickening, while post-dilatation of self-expanding valves and a supra-annular valve position seem to reduce its incidence. A recent study of 931 patients in the combined RESOLVE-SAVORY registry indicates that oral anticoagulant (OAC) therapy (but not dual antiplatelet therapy, DAPT) appears to prevent and resolve the phenomenon. According to a recent analysis of 931 patients from the combined RESOLVE-SAVORY registry, valve dysfunction is uncommon, but occurs more frequently in patients with valve thrombosis (14% vs. 1%, $P < 0.0001$). Due to the temporal separation between the CT and the clinical event, leaflet thrombosis was associated with an increased risk of transient ischemic attack (4.18 vs. 0.6 per 100 person years, $P = 0.0005$). However, these findings must be interpreted with caution. The results of ongoing studies examining different regimens of OAC or anti-platelet therapy following TAVI are eagerly awaited, and long-term OAC may prove necessary in some cases (2,3,5,8,15,42).

6. CONCLUSION

The first transcatheter aortic valve intervention (TAVI) has been performed in man for more than 20 years, and during that time the technique has evolved impressively. It has been extended from non-operable patients to high-risk, intermediate-risk, and even low-risk patients who have aortic stenosis, and complications have decreased. The rate of complications after TAVI has decreased overall, but the incidence of stroke, new pacemaker implantation and paravalvular leak remains higher compared to SAVR. Transcatheter aortic valve implantation (TAVI) has revolutionized the management of aortic stenosis (AS). As transcatheter valve designs have advanced, improvements have been made in patient selection, procedural planning, and technique, resulting in stepwise improvement in effectiveness and a reduction in complication rates.

TAVI has pushed the boundaries of invasive management of AS, with several randomized trials exploring early intervention in asymptomatic severe AS with preserved LVEF and in moderate symptomatic AS. In the growing age of TAVI, there are a number of potential obstacles to overcome. Percutaneous valve replacement may overturn traditional indications for valve replacement in patients with asymptomatic AS and moderate AS with heart failure. We need more data on the long-term durability of transcatheter prosthesis and, at the current moment, we have little or no evidence for using TAVI in low-risk and young patients; SAVR remains indicated in these patients but the future of TAVI remains bright. As per ESC/EACTS guidelines, centralized care with on-site surgery is recommended for TAVI at heart valve centers.

- **Author's contribution:** The author was involved in all steps of preparation of this article, including final proofreading.
- **Conflict of interest:** The author doesn't have any conflicts of interest to disclose.
- **Financial support and sponsorship:** None.

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