

APPLICATION OF HTA
METHODOLOGY TO ASSESS
THE TRANSCATHETER AORTIC
VALVE IMPLANTATION (TAVI)
FOR THE MANAGEMENT OF
PATIENTS AFFECTED BY SEVERE
SYMPTOMATIC AORTIC
VALVE STENOSIS

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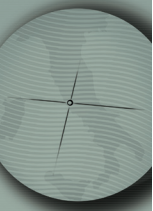
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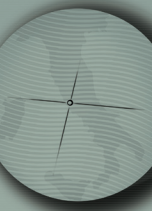
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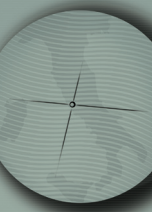


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Preface

The working team of the Graduate School of Health Economics and Management (Altens) of the Università Cattolica del Sacro Cuore, has produced an application of HTA methodology to assess transcatheter aortic valve implantation (TAVI) for the management of patients affected by severe symptomatic aortic valve stenosis, in order to provide an overview of the current and

potential impact of the use of this technology within the International context.

In order to do so, a systematic review of existing literature has been performed. Evidence has been selected in accordance with pre-defined inclusion criteria and summarized based on the HTA domains under the framework of the EuNetHTA Core Model® 3.0.



Executive summary

Background

The published literature on TAVI is wide and consolidated, especially regarding the efficacy, safety and economic outcomes in the mid-long term in the elderly population. Few evidences were found on the organizational impact of these technologies. Nevertheless, TAVI results a widely used technology in the clinical practice in patients affected by aortic stenosis.

Objective

The aim of this report is to provide an overview of the clinical, economic, organizational and ethical impact of use of transcatheter aortic valve implantation (TAVI) in the treatment of patients affected by severe symptomatic aortic valve stenosis; assess the heterogeneity of the different HTA reports, the level of knowledge achieved about the TAVI procedure; evaluate the added value provided by the replication of these reports. This study poses a particular focus on the International setting.

Methods

In order to achieve the aim of this research both a literature review and a field research were performed. Two reviewers blindly screened the records retrieved against pre-defined inclusion/exclusion criteria. The selected studies were summarized narratively, following a simplified version of the EuNetHTA Core Model® 3.0. A specific methodology has been designed in order to synthesize the completeness and soundness of the evidence generated by multiple HTA Reports, metanalysis, systematic reviews, registries and TRIALS.

Health problem and current use of the technology

Aortic stenosis (AS) is a congenital or acquired aortic valve disease, that occurs when heart's aortic valve narrows. It represents the most common valvular disease, implying the

progressive and rapid development of a heart failure. Aortic valve stenosis can occur due to many causes, including congenital heart defect, calcification, rheumatic fever. It is the most common native heart valve disease among adults in Europe [1,2]. The prevalence of this disease is strongly linked to the population ageing, and as such is expected to represent an increasingly important public health problem [3]. Symptoms of AS can include angina pectoris, dyspnoea, heart failure, syncope and in some cases sudden death. After the onset of symptoms, the prognosis could be potentially lethal for patients without treatment. The average survival rate, since the symptoms' onset, is equal to 50% at 2 years and 20% at 5 years [3]. The key diagnostic tool for AS and its severity is echocardiographic examination and doppler [1,2]. A valve opening area below 0.6 cm²/m² of body surface area is a marker of severe AS. The choice of the intervention mode should take into account the cardiac and extracardiac characteristics of the patient, the individual risk of surgery, which is assessed by the judgement of the Heart Team in addition to scores, the feasibility of TAVI and the local experience and outcome data [4].

Technical features of the technology

TAVI is a less invasive alternative to open cardiac surgery for treating aortic stenosis, avoiding the need for sternotomy and cardiopulmonary bypass. Transcatheter access to the aortic valve is achieved mainly by the retrograde transfemoral (TF), transapical (TA) or transaxillary/subclavian routes. Other routes of access are: direct aortic access and transcarotid access [5].

Safety and Efficacy

Evidence showed that TAVI has significant clinical benefits compared to standard therapy or conventional surgical aortic valve repair. Lifetime success and complication rates in the long term of the procedure require more supporting evidence.

Costs and economic evaluation

There are numerous evidences about cost-effectiveness rate of TAVI procedure. Orlando et al. [6] proposed a model to evaluate the cost-effectiveness of TAVI compared with standard therapy in patients who require aortic valve replacement but are high risk or not fit for conventional surgery (SAVR). The base-case results showed TAVI as costlier but more effective than the medical management, with an ICER of £12,900 per QALY. A US study also evaluated the cost-utility of TAVI compared with standard care in patients with severe AS that are ineligible for conventional SAVR. The results of the study found that TAVI generated an additional 1.3 QALYs at an increased cost of \$79,837/patient. As such, the incremental cost effectiveness of TAVI was estimated to be \$61,889 per QALY. Different studies and institutions provide information about resource consumption related to TAVI procedures. In detail, resource utilization, in terms of economic impact, is estimated at around 24,000€/intervention. Results of CE analysis performed, in the Italian context, show that considering the SSN Perspective TAVI would be considered cost-effective at frequently cited willingness to pay thresholds in Europe. Similar conclusions emerged over a range of analyses performed considering different time horizons and also modelling real-life scenarios to better depict the context, current technologies and improved learning curves with respect to the literature. Further studies may help shading light about CE of TAVI in real-life scenarios and even considering real costs [7].

Organizational aspects

General re-organisation and a specific training are necessary to adopt a new technique. Different studies state that it is premature to discuss the organizational prerequisites for a nationwide TAVI interventions program. It requires a learning curve in the procedural success and international experts stress the importance of a collaboration among a "Heart Team". These procedures are technically challenging and can only be considered by experienced clinicians and cardiology teams.

Expertise in interventional and surgical management of vascular diseases and complications must be available. Comprehensive

recording of performance and patient outcome data at the level of the given heart valve centre is essential, as well as participation in national or ESC/EACTS registries.

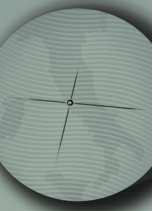
Social and ethical aspects

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex and sexual orientation: not adverse impact across any of these groups was expected.

In order to compare the different evidences included in this report, the evidence has been summarized and evaluated according to various aspects: robustness, generalisability and internal coherence. The general assessment shows that, except for organizational, ethical and social aspects, the domains identified according to the EuNetHTA Core Model® 3.0 have been discussed and argued in each item. Therefore, despite the heterogeneity of the different reports, the achievement of a good level of knowledge has been demonstrated about TAVI procedure in the international setting, to the point that the scientific literature about it seems to have been sufficiently argued and discussed in every respect.

Conclusions

Aortic stenosis is a congenital or acquired aortic valve disease, which occurs when the heart's aortic valve narrows. Currently, there is no effective pharmacological treatment to solve this disease definitely; to date the aortic valve replacement surgery is the reference procedure worldwide suggested in several guidelines. Minimally invasive techniques have been recently introduced for this category of patients, such as the transcatheter aortic valve implantation (TAVI). Evidence showed that transcatheter aortic valve implantation has significant clinical benefits compared to standard therapy or conventional surgical aortic valve repair. Long-term success and complication rates of the procedure has been widely documented but registred studies has been necessary to motoring the technology for time life. In conclusion, considering this context, as shown in the report, it is important establishing guidelines on the use



of TAVI in the clinical practice. The evidence supporting this technology are wide; as above described in this document, many HTA reports have been developed, with varying degrees of robustness of the selected evidence. It would be important, in the general context of HTA, consistent with the approach proposed by this methodology try to consider exclusively reports with a high and consistent degree of evidence.

The latter are the only which should be taken into consideration, having a "less is more" approach. ALTEMS having reviewed most of the above evidence, recommends the use of TAVI in the patients' subgroups considered in this report as an effective and safe alternative. Further evidence would be necessary in order to investigate on the long-term period safety and efficacy in other target patients' subgroup.

Abbreviations

AS: Aortic Stenosis

AVR: Aortic Valve Replacement

CMT: Conventional Medical Treatment

ESC: European Society of Cardiology

EACTS: European Association for Cardio-Thoracic Surgery

HTA: Health Technology Assessment

ICER: Incremental Cost-Effectiveness Ratio

IC: Incremental Cost

IE: Incremental Effect

INAHTA: International Network of Agencies for Health Technology Assessment

LY: Life Years

NHS: National Health Service

PICO: Population, Intervention, Comparator, Outcomes

QALY: Quality-Adjusted Life Year

QoL: Quality of Life

RCT: Randomised Controlled Trials

SAVR: Surgical Aortic Valve Replacement

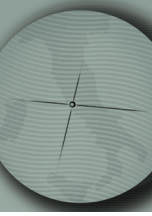
STS: Society of Thoracic Surgeons

TAVI: Transcatheter Aortic Valve Implantation

TAVI-TF: Transcatheter Aortic Valve Implantation via transfemoral

TAVI-TA: Transcatheter Aortic Valve Implantation via transapical



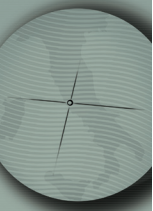


Objective

The aim of this report is to provide an overview of the clinical, economic, organizational and ethical impact of the use of transcatheter aortic valve implantation (TAVI) in the treatment of patients affected by severe symptomatic aortic valve stenosis;

assess the heterogeneity of the different reports, the level of knowledge achieved about TAVI procedure; evaluate the added value provided by the replication of these reports. This study poses a particular focus on the International setting.





Methods

In order to achieve the aim of this research both a literature review and a field research were performed.

THE LITERATURE REVIEW

Research question definition

The research question was made explicit by using the PICO model including the population under analysis (P), the intervention being assessed (I), the comparator (C), and the outcomes of interest (O). Table 1 describes the PICO model underlying this research.

Search strategy

In a recent overview by Hawlik et al. [8] looking at the duplication of HTAs on single technologies, it was demonstrated that 22 HTA reports were produced in Europe to evaluate transcatheter aortic valve implantation (TAVI). Furthermore, to explore the international environment, the search was extended to involve other HTA reports produced on TAVI, through the application of the INAHTA Checklist and further tools [8,9].

No temporal and language limits were imposed to our search strategy. Further evidence was identified though manual search.

In additional, in this report have been included HTA reports, RCTs, Metanalysis, Systematic reviews and registry studies published after 2014. A total of 31 has been included in this report.

Inclusion/exclusion criteria

Records retrieved though the search strategy were considered eligible unless they met one or more of the following exclusion criteria:

- Not relevant to the technology under study;
- Not relevant to the condition under study;
- Type of study not relevant.

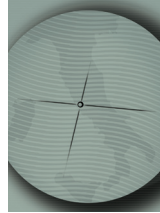
Reporting of results

Results from the present review have been discussed. Evidence has been organized based on selected items of the EuNetHTA Core Model® 3.0. Appendix I reports the list of items considered in the current analysis.

TABLE 1

| PICO TABLE | |
|--------------|--|
| Population | Patients affected by severe symptomatic aortic valve stenosis |
| Intervention | Transcatheter aortic valve implantation (TAVI) |
| Comparator | Conventional surgery or medical management |
| Outcomes | <ul style="list-style-type: none"> • Effectiveness • Safety • Economic Impact • Organizational impact • Ethical and social implications |





1. Results

After the inclusion, studies were summarized and evidence reports was used to discuss assessment elements reported in Appendix I.

Studies included after 2014 have been summarized in figure below (figure 1).

1.1 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY

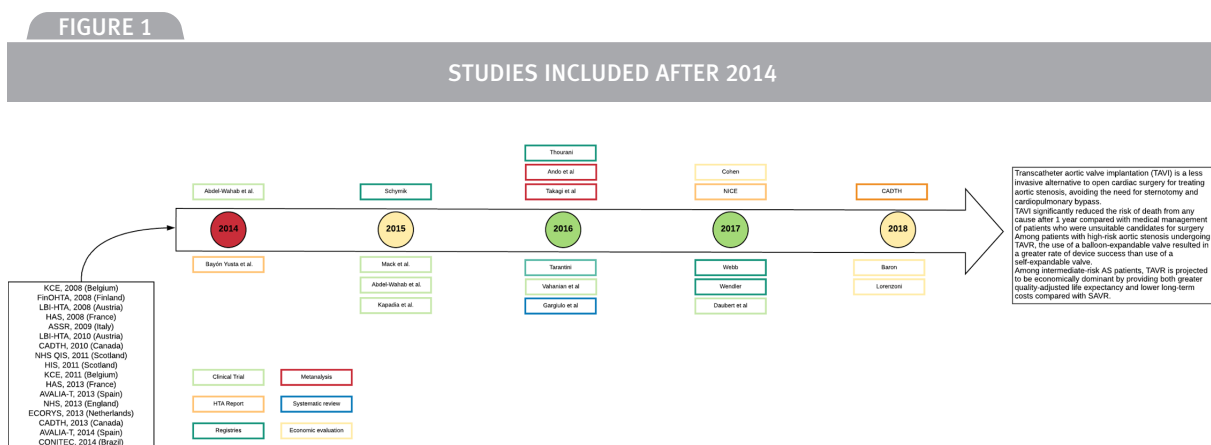
1.1.1 Target Condition

Aortic stenosis (AS) is a congenital or acquired aortic valve disease, that occurs when heart's aortic valve narrows. It represents the most common valvular disease, implying the progressive and rapid development of a heart failure. The narrowing prevents the valve from fully opening, reducing or blocking the blood flowing from heart into the aorta and, thus, to the rest of the organism. It is the most common valvular heart disease in adults and generally has a degenerative nature, resulting from a progressive age-dependent accumulation of calcium in the aortic valve. Aortic valve stenosis can occur due to many causes, including congenital heart defect, calcification, rheumatic fever. It is the most common native heart valve disease among adults in Europe [1,2]. The prevalence of this disease is strongly linked to the population ageing, and as such is expected to represent

an increasingly important public health problem [3]. Age-related aortic stenosis usually begins after age 60, but often does not show symptoms until 70 or 80 [3]

Generally, signs and symptoms of AS develop when the narrowing of the valve is severe. Indeed, some people affected by AS may not experience symptoms for many years. AS symptoms usually develop gradually after an asymptomatic latent period of 10-20 years. Furthermore, it can be difficult to ascertain if a specific symptom such as dyspnoea, fatigue or angina can be ascribed to AS or whether be attributable to another cardiac or non-cardiac condition. It has multiple levels of severity, assessed based on the difference in pressure between the left ventricle and aorta. Symptoms of AS can include angina pectoris, dyspnoea, heart failure, syncope and in some cases sudden death. After the onset of symptoms, the prognosis could be potentially lethal for patients without treatment. The average survival rate, since the symptoms' onset, is equal to 50% at 2 years and 20% at 5 years [3]. The key diagnostic tool for AS and its severity is echocardiographic examination and doppler [1,2]. A valve opening area below 0.6 cm²/m² of body surface area is a marker of severe AS.

Similarly, to the majority of cardiac valvular disease, the prevalence of AS is positively correlated with age.



Epidemiological studies established that the probability to develop moderate or severe AS is higher than 1/8 among people over 75 [10]. A systematic review estimated, among people over 75, an AS prevalence equal to 12.4%, while, for severe AS, it equals 3.4% [11]. After the symptoms' onset, the median life expectancy is only 2-3 years [12]. Although survival in asymptomatic patients is comparable to that in age- and sex-matched control patients, it decreases rapidly after symptoms appear.

Poor mobility, as assessed by the 6-minute walk test, and oxygen dependency are the main factors associated with increased mortality after TAVI and other VHD treatments. Frailty is associated with increased morbidity and mortality after surgery and TAVI [4].

Risk stratification applies to any sort of intervention and is required for weighing the risk of intervention against the expected natural history of VHD as a basis for decision making. Most experience relates to surgery and TAVI. The EuroSCORE¹ overestimates operative mortality and its calibration of risk is poor. Consequently, it should no longer be used to guide decision making. The EuroSCORE II and the Society of Thoracic Surgeons (STS) score (<http://riskcalc.sts.org/stswebriskcalc/#/>) more accurately discriminate high- and low-risk surgical patients and show better calibration to predict postoperative outcome after valvular surgery. Scores have major limitations for practical use by insufficiently considering disease severity and not including major risk factors such as frailty, porcelain aorta, chest radiation etc. While EuroSCORE I markedly overestimates 30-day mortality and should therefore be replaced by the better performing EuroSCORE II in this regard, it is nevertheless provided in this document for comparison, as it has been used in many TAVI studies/registries and may still be useful to identify the subgroups of patients for decision between intervention modalities and to predict 1-year mortality. Both scores have shown variable results in predicting the outcomes of intervention in TAVI but are

useful for identifying low-risk patients for surgery. New scores have been developed to estimate the risk of 30-day mortality in patients undergoing TAVI, with better accuracy and discrimination, albeit with numerous limitations [4].

1.1.2 Target Population

SAVR is the reference procedure worldwide suggested in several guidelines, for both symptomatic patients with severe AS and asymptomatic AS with reduced ejection fraction (<50%). However, some conditions, such as comorbidities and advanced age, make this surgical procedure too dangerous or impossible to perform (this scenario occurs to a third of the eligible elderly population). In this regard, minimally invasive techniques have been recently introduced for this category of patients, such as the transcatheter aortic valve implantation (TAVI) [12].

In 2012, ESC/EACTS (European Society of Cardiology/European Association for Cardio-Thoracic Surgery) Guidelines [12] defined severe AS is defined by the following echocardiographic characteristics: Aortic valve area: <1 cm²; velocity ratio: <0.25; indexed valve area <0.6 cm²/m² body surface area; jet velocity: >4.0 m/s; mean transvalvular pressure: >40 mmHg. TAVI is indicated in patients with severe symptomatic AS who are not suitable for aortic valve replacement (AVR), according to cardiological evaluation and for patients considered in high risk who may still be suitable for surgery, but in whom TAVI is favored by a cardiological examination of the individual risk profile. Guidelines stress that age is not a contraindication to surgery [12,13].

1.1.3 Current Management

The choice of the intervention mode should take into account the cardiac and extracardiac characteristics of the patient, the individual risk of surgery, which is assessed by the judgement of the Heart Team in addition to scores, the feasibility of TAVI and the local experience

¹ it stands for European System for Cardiac Operative Risk Evaluation. You can read about it in here in the literature, and use it here in our multi-lingual online calculator. Operative mortality is a good measure of quality of cardiac surgical care, as long as patient risk factors are taken into consideration. EuroSCORE is a method of calculating predicted operative mortality for patients undergoing cardiac surgery.

and outcome data. Data on TAVI are still very limited for patients <75 years of age and for surgical low-risk patients, in whom SAVR remains the reference method. It has to be emphasized that younger patients differ with regard to anatomy (more bicuspid valves), which affects the results of TAVI (bicuspid valves were also in general excluded in clinical trials), and that lifetime durability data for TAVI prosthetic valves are still lacking. Available data from randomized controlled trials and large registries in elderly patients at increased surgical risk show that TAVI is superior in terms of mortality to medical therapy in extreme-risk patients, non-inferior or superior to surgery in high-risk patients and noninferior to surgery and even superior when transfemoral access is possible in intermediate-risk patients. In the two large studies on intermediate risk, the mean ages of patients were 82 and 80 years, mean STS scores were 5.8% and 4.5%, and a high percentage were considered frail. Overall, rates of vascular complications, pacemaker implantation and paravalvular regurgitation were significantly higher for TAVI, while the

degree of excess depended on the device used. On the other hand, severe bleeding, acute kidney injury and new-onset atrial fibrillation were significantly more frequent with surgery, whereas no difference was observed in the rate of cerebrovascular events. The favourable results of TAVI have been reproduced in multiple large-scale, nationwide registries supporting the generalizability of outcomes observed in randomized controlled trials. This favour the use of TAVI over surgery in elderly patients at increased surgical risk. However, the final decision between SAVR and TAVI (including the choice of access route) should be made by the Heart Team after careful individual evaluation [4].

In Table 1 have been described indication about the TAVI reported in ESC/EACTS guidelines.

The spectrum of interventional procedures in addition to TAVI should include mitral valvuloplasty, mitral valve repair (edge-to-edge), closure of atrial septal defects, closure of paravalvular leaks and left atrial (LA) appendage closure as well as percutaneous coronary intervention (PCI). Expertise in

TABLE 1

ESC/EACTS GUIDELINES PUBLISHED IN 2017 [4]

| Recommendations | Class | Level |
|--|-------|-------|
| Indications for myocardial revascularization | | |
| PCI should be considered in patients with a primary indication to undergo TAVI and coronary artery diameter stenosis $\geq 70\%$ in proximal segments. | IIA | C |
| Bioprostheses | | |
| Dual antiplatelet therapy should be considered for the first 3–6 months after TAVI, followed by lifelong single antiplatelet therapy in patients who do not need oral anticoagulation for other reasons. | IIA | C |
| Single antiplatelet therapy may be considered after TAVI in the case of high bleeding risk. | IIB | C |
| Choice of intervention in symptomatic aortic stenosis | | |
| TAVI is recommended in patients who are not suitable for SAVR as assessed by the Heart Team | I | B |
| In patients who are at increased surgical risk (STS or EuroSCORE II $\geq 4\%$ or logistic EuroSCORE I $\geq 10\%$ or other risk factors not included in these scores such as frailty, porcelain aorta, sequelae of chest radiation), the decision between SAVR and TAVI should be made by the Heart Team according to the individual patient characteristics, with TAVI being favoured in elderly patients suitable for transfemoral access | I | B |
| Balloon aortic valvotomy may be considered as a bridge to SAVR or TAVI in haemodynamically unstable patients or in patients with symptomatic severe aortic stenosis who require urgent major non-cardiac surgery. | IIIB | C |
| Balloon aortic valvotomy may be considered as a diagnostic means in patients with severe aortic stenosis or other potential causes for symptoms (i.e. lung disease) and in patients with severe myocardial dysfunction, pre-renal insufficiency or other organ dysfunction that may be reversible with balloon aortic valvotomy when performed in centres that can escalate to TAVI. | IIIB | C |

interventional and surgical management of vascular diseases and complications must be available. Comprehensive recording of performance and patient outcome data at the level of the given heart valve centre is essential, as well as participation in national or ESC/EACTS registries [4].

1.2 TECHNICAL FEATURES OF THE TECHNOLOGY

1.2.1 Technical features

TAVI is a minimally invasive procedure used for the implantation of replacement aortic valves without the invasiveness of open surgery. Transcatheter access to the aortic valve is achieved mainly by the retrograde transfemoral (TF), transapical (TA) or transaxillary/subclavian routes. The TA and transaxillary/ subclavian routes have developed as alternative approaches for patients with peripheral vascular disease that precludes femoral access. TAVI involves catheter-guided transport of a new aortic valve that displaces the old diseased valve and is expanded in place. The TA procedure involves a mini-thoracotomy to gain access to the aortic valve through the apex of the left ventricle and hence is not strictly percutaneous [6,14].

The surgical procedure consists in implanting a prosthetic valve which functionally replaces the damaged aortic valve, using fluoroscopic or ecographically-guided percutaneous procedures. The prosthetic valve comprises a metallic frame that is applied within a delivery system that allows the release and positioning of the valve without sutures and without requiring open heart surgery. The new prosthetic valve is manipulated into position and inserted inside the existing aortic valve [15, 16]. TAVI can be done with the patient under general anaesthesia or using local anaesthesia with or without sedation [16]. Actually, the use of TAVI is restricted to elderly patients that are considered inoperable or at high or intermediate risk for conventional surgery, due to a variety of comorbidities, such as chronic obstructive pulmonary disease, severe left ventricular dysfunction or general frailty. The suitability for patients to be treated with a TAVI is restricted by aortic annulus dimensions and depends on the accessibility of a patient's arterial tree as well. There are different factors influencing the treatment decision, including the assessed patient risk score, pre-existing comorbidities, procedures-related, age, patient preference and the referral process [3,6,17].

In table below has been summarized TAVIs technologies commercialized in Europe and clinical indications [5].

TABLE 2

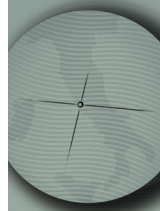
TAVIs TECHNOLOGIES COMMERCIALIZED IN EUROPE AND CLINICAL INDICATIONS [5].

| Device | Manufacturer | CE mark for inoperable patients and patient with high surgical risk | CE mark for patient intermediate high surgical risk |
|--------------------------|---------------------|---|---|
| SAPIEN 3 SAPIEN XT | Edwards Lifescience | 2014 2010 | 2014 NO |
| EVOLUT R | MEDTRONIC | 2014 | 2016 |
| EVOLUT PRO | MEDTRONIC | 2017 | 2017 |
| CENTERA | Edwards Lifescience | 2018 | NO |
| CORE VALVE | MEDTRONIC | 2007 | NO |
| ACURATE TA ACURATE TF | Boston Scientific | 2011 2014 | NO NO |
| ENGAGER | MEDTRONIC | 2013 | NO |
| LOTUS EDGE | Boston Scientific | 2011 (LOTUS VALVE) 2014 (EDGE VALVE) | NO NO |
| DIRECT FLOW | DIRECT FLOW MEDICAL | 2013 | NO |
| JENA VALVE | JENA TECHNOLOGIES | 2011 | NO |
| PORTICO | SANT JUDE | 2012 2015 (UPDATE) | NO |

1.3 REPORT HTA PUBLISHED BEFORE 2014

| Report included | Year | Country | Health problem and current use of the technology | Technical features of the technology | Safety and Effectiveness | Costs and economic aspects | Organizational aspects | Social and ethical aspects |
|-----------------|------|---------|---|---|---|---|--|----------------------------|
| KCE [3] | 2008 | Belgium | Aortic stenosis (AS) is the most common valvular heart disease in adults and generally is degenerative in origin, resulting from a progressive age-dependent build-up of calcium in the aortic valve. Its prevalence is strongly related to population ageing, and as such is expected to represent an increasingly important public health problem. | The Edwards-Sapien PAV is a bioprosthesis that is made of bovine pericardium and is integrated into a stainless steel, balloon expandable, and stent frame. Although it was initially intended for use via the antegrade venous approach, the retrograde transarterial and the transapical approach have become more common. The Core Valve PAV consists of a bioprosthetic porcine pericardial tissue valve that is mounted and sutured in a self-expanding nitinol stent. It is designed for a retrograde arterial approach. Devices for transapical delivery have been introduced recently. The suitability for PAV is dependent on aortic annulus dimensions. | Unpublished data report success rates up to 100%. Safety issues, demonstrated by a 30-days mortality rate of 6.4 to 22.5%, represent a major drawback for implementation of this technology. In surgical series from the Mayo Clinic, an estimated 30-day mortality of 23.6% sharply contrasted with an observed mortality of only 5.8%. Patients with a similar predicted operative risk (25.4%) enrolled in PAV series, had a 30-days mortality that was 6.4-13.2% in transfemoral, and 8.0-22.5% in transapical series. This suggests that patients with AS that are considered at high risk for conventional AVR, may actually present lower mortality rates if treated surgically than if treated by means of PAV insertion. Vascular complications of PAV insertion especially occur with the transfemoral approach in 10-15% of patients. Stroke has also been observed more frequently in the transfemoral approach (3-10% of cases). | On the one hand, the cost of the initial intervention is higher due to the high cost of the device. Furthermore, it is not clear how the prices were set. More transparency on this other hand, a shorter hospital length of stay may positively impact on both costs and QoL. It is necessary collect data on safety, efficacy, QoL to be able to perform a reliable full economic evaluation. | It is premature to discuss the organisational prerequisites for a nationwide percutaneous heart valves interventions program, as long as no hard effectiveness data have become available. However, international experts point to a learning curve in the procedural success and note the importance of a close collaboration between interventional cardiologists / paediatricians, surgeons and anaesthesiologists, in order to avoid the uncontrolled diffusion of this technique. | N.A. |
| FinOHTA [18] | 2008 | Finland | Aortic valve stenosis is the most common valvular disease requiring open heart surgery. The incidence of valvular heart disease is expected to increase over the next several decades. It has been established that surgical aortic valve replacement in symptomatic patients with severe aortic stenosis both relieves symptoms and prolongs life. Conversely, conservatively managed patients have a dismal prognosis. Almost one third of symptomatic patients with aortic valve disease are never referred for surgery because of advanced age or co-morbidities. | The bioprostheses are implanted in the annulus of the aorta via the femoral artery (transfemorally) or via the apex of the heart (transapically). | Haemodynamic results after successful stent-valve implantation were uniformly excellent with low post-procedural aortic valve gradients and satisfactory aortic valve areas. 30-day mortality was lower (8-25%) than expected with different risk calculators (logistic EuroScore). | N.A. | N.A. | N.A. |

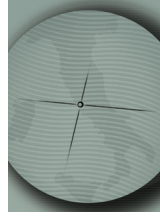
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| LBI-HTA [19] | 2008 | Austria | It is estimated that the aortic valve stenosis in 2-4% of the adult population over 65 occurs. The standard therapy for severe aortic valve stenosis is the surgical aortic valve replacement. However, as AS often occurs in elderly patients with comorbidities, and thus the operative risk is increased, about one-third of elderly patients affected by severe aortic valve stenosis are considered inoperable. | Two catheters are pushed from the groin into the vascular system. One is for "anatomical orientation"; the second expands the restricted area with the help of a balloon. Following this procedure, the balloon catheter is removed and an implantation catheter is inserted with a collapsed and highly cooled aortic stent (about 4 ° C) and a biological aortic valve. The placement and release of the stent take place under fluoroscopy. | The strength of the evidence is low due to the lack of comparison groups. However, a short-term relief seems proved. All patients (NYHA III and IV) improved their performance with an average of NYHA (III or II). The mortality rate after 1 month varies between 11% and 50% and it is strongly dependent on the operated patients (only NYHA III and IV or even NYHA II) and the experience. The effective 1-month mortality was significantly lower than expected for open heart surgery. However, serious adverse events occurred, in particular, strokes, myocardial infarction, severe peritoneal bleeding, atrial fibrillation, paravalvular leakage, mitral or aortic perforation catheter. | Cost estimates are estimated at around 24,000€/intervention. It works through a treatment with a considerable amount of personnel and material expenses. The duration of the inpatient stay for patients is usually 14 days (minimum 10 to a maximum of 25 days). | N.A. | N.A. |
| HAS [20] | 2008 | France | Stenosis is the consequence of the alteration of the aortic valve, which is narrowed. It creates an obstacle to the ejection of blood from the left ventricle to the aorta. The stenosis may lead to the development of heart failure and/or coronary insufficiency. The prevalence of AS is 2 to 7% in subjects over 65, 3% with tight aortic stenosis (half of whom asymptomatic). | Bioprostheses, made from a valvular or pericardial tissue of bovine, porcine or equine origin, make it possible to recover hemodynamics close to normal, and do not require long-term anticoagulant treatment. However, their durability is more limited with a rapid deterioration in the case of hypercalcemia, compared with AVR. These valves are implanted preferentially in subjects over 65 years of age or for whom anticoagulation treatment is contraindicated. | Results show a survival rate of 71 to 84% at 6 months for the retrograde transfemoral approach and 68% for the transapical approach (the expert group had set the acceptable survival rate at 55% at 6 months). | N.A. | The optimal realization of the technology would require a so-called "hybrid" angiosurgical room. In order to allow an optimal and safe diffusion of the technology, and taking into account the learning curve, the experts defined the necessary preliminary training. | N.A. |



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| ASSR [21] | 2009 | Italy | <p>The Regional Cardiac and Cardiac Surgery Commission believes that the implantation of percutaneous or transapical aortic valve prostheses is now applicable to patients with the following concomitant clinical features: severe aortic valvular stenosis; symptoms related to aortic narrowing (NYHA functional class greater than 2 or 1 with ventricular ejection fraction $\leq 40\%$); contraindications to valve replacement intervention such as severe comorbidities associated with and/or high operative risk (logistic Euroscore greater than 15/20 and / or STS above 10).</p> <p>A serious deterioration of cognitive abilities and/or a life expectancy of less than one year, regardless of the basic aortic pathology, represent exclusion criteria to the implantation procedure.</p> | <p>The valve prosthesis implant can be performed using different types of biological prostheses: percutaneously (femoral arterial access) or by the surgical route through the apex of the left ventricle, without the need for a circulation stop and extra-body circulation, in case of a peripheral vascular disease that prevents the progress of the prostheses from the femoral artery to the valvular or porcelain aorta orifice. If the anatomical situation is not suitable for the ascent of the percutaneous prosthesis from the femoral artery, it is performed an intervention of implanting only of the Edwards-Sapien valve through surgery through the apex of the left ventricle.</p> | <p>Transfemoral route: The six-month follow-up in the published studies shows a survival rate ranging between 71 and 84% and an improvement of the NYHA functional class.</p> <p>Transapical route: The only study with six months of follow-up shows a survival rate of 68% and an improvement of the NYHA functional class.</p> | N.A. | <p>The procedures for implanting prostheses by percutaneous and transapical route should preferably be performed in the "Hybrid" Cardiosurgical Operating Room or it can also be performed in the haemodynamic laboratories that guarantee the best conditions of asepsis, similarly to what is required for surgical procedures. The hybrid operating theatre must reflect all the sterility requirements required for a conventional operating room, have the technology to deal with emergencies and must be equipped. The procedures must be carried out at facilities that have accredited operating units of Cardiology with the Laboratory of Hemodynamics and Cardiac Surgery.</p> <p>The professionals who perform the aortic valve prosthesis implants by percutaneous or transapical route must have followed a training course that requires the use of instruments on simulators and participation in prosthetic implants in high-volume reference centers of these procedures. The first 10 percutaneous implants and the first 4 transapical implants must be performed in the presence of a highly experienced Tutor.</p> | N.A. |
| LBI-HTA [22] | 2010 | Austria | N.A. | N.A. | <p>The effectiveness and safety results of last year's reviews are confirmed: the pathway seems to have a palliative effect, with a high mortality rate above 10% (within 30 days and about a quarter within 6 months). High mortality and vascular complications as well as neurological consequences and prosthetic migration.</p> | N.A. | N.A. | N.A. |

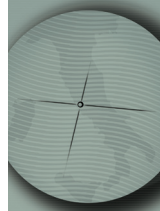
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| CADTH [23] | 2010 | Canada | Aortic stenosis is primarily an age-related degenerative disease that results in narrowing of the aortic valve and resistance to the flow of blood from the left ventricle to the aorta. In patients with aortic regurgitation, the aortic valve leaks allowing blood from the aorta to flow back into the ventricle. This backflow results in dilation of the left ventricle and may cause heart failure. | There are numerous percutaneous aortic heart valve devices under development. Two devices have been reported most frequently in the literature: Edwards-Sapien (Lifesciences, USA) and CoreValve (Medtronic, USA). These devices consist of a stent frame with animal pericardial valve leaflets and are available in different sizes. There are two different insertion techniques actually in use. The transarterial retrograde approach involves insertion of a sheath through the femoral, iliac, or subclavian artery to the aorta and aortic valve. It may not be suitable for patients with vascular disease. The transapical technique requires a small incision in the ribcage and through the apex of the ventricle to access the aortic valve. The antegrade trans-septal technique has fallen out of use. | Percutaneous aortic valve replacement is feasible and can provide hemodynamic and clinical improvement for up to 2 years in patients with severe aortic stenosis who are high-risk or unable to undergo surgical valve replacement. Long term safety and valve durability are unknown. | N.A. | N.A. | N.A. |
| CADTH [24] | 2010 | Canada | N.A. | N.A. | The 30-day mortality was 12% to 25% using trans-arterial retrograde insertion and 8% to 18% using the trans-apical approach. In the observational studies included in the CADTH rapid response, the 30-day mortality ranged from 9.5% to 25%. The comparative safety and efficacy of percutaneous valve replacement were unknown. | The MUHC report included a systematic review of the literature, a case series report of the first 12 patients who underwent TAVI at MUHC, and estimates annual budget impact adopting the procedure: \$720, 719 annually. | N.A. | N.A. |



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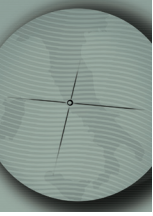
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|-----------------|------|----------|---|---|--|--|--|--|
| NHS QIS [14] | 2011 | Scotland | AS is the most common native heart valve disease in adults in Europe. Without intervention, patients with severe symptomatic AS have a poor prognosis with an average survival of 2–3 years. It has been estimated that more than one third of elderly patients with severe symptomatic AS in Europe are not referred for SAVR. Patients who are not referred for surgery are more likely to be older than those who are, and more likely to have left ventricular dysfunction and comorbidities. TAVI has been advocated for the treatment of patients who are unsuitable for conventional AVR as the risks of surgery are unacceptably high because of advanced age, frailty and/or the presence of cardiac or non-cardiac comorbidities. | Transcatheter aortic valve implantation (TAVI) is a minimally invasive procedure in which the replacement valve is delivered percutaneously through the vascular system inside a catheter. Transcatheter access to the aortic valve is achieved mainly by the retrograde TF, TA or transaxillary/subclavian routes. The TA and transaxillary/subclavian routes have developed as alternative approaches for patients with peripheral vascular disease that precludes femoral access. The TA procedure involves a mini-thoracotomy to gain access to the aortic valve through the apex of the left ventricle and hence is not strictly percutaneous. The Edwards SAPIEN™ valves can be implanted using the retrograde TF or the TA approach, and CoreValve® devices by the retrograde TF or transaxillary/subclavian arterial route. | In the only RCT, TAVI significantly reduced the risk of death from any cause after one year compared with conservative management, not suitable candidates for surgery. TAVI was associated with a significantly higher incidence of major strokes. There are few data on long-term outcomes following TAVI. | There is insufficient information to reliably estimate the cost-effectiveness of TAVI (no published evidence comparing TAVI with SAVR or medical management). Several unpublished developmental economic models that were identified have important limitations. | Patient selection for TAVI should be undertaken by a multidisciplinary team, including a cardiologist, cardiac surgeon and cardiac anaesthetist. | No adverse impact across any of 6 equality groups is expected. |
| HIS [25] | 2011 | Scotland | AS is the most common native heart valve disease in adults in Europe. Without intervention, patients with severe symptomatic AS have a poor prognosis with an average survival of 2–3 years. It has been estimated that more than one third of elderly patients with severe symptomatic AS in Europe are not referred for SAVR. Patients who are not referred for surgery are more likely to be older than those who are, and more likely to have left ventricular dysfunction and comorbidities. TAVI has been advocated for the treatment of patients who are unsuitable for conventional AVR as the risks of surgery are unacceptably high because of advanced age, frailty and/or the presence of cardiac or non-cardiac comorbidities. | Transcatheter aortic valve implantation (TAVI) is a minimally invasive procedure in which the replacement valve is delivered percutaneously through the vascular system inside a catheter. Transcatheter access to the aortic valve is achieved mainly by the retrograde TF, TA or transaxillary/subclavian routes. The TA and transaxillary/subclavian routes have developed as alternative approaches for patients with peripheral vascular disease that precludes femoral access. The Edwards SAPIEN™ valves can be implanted using the retrograde TF or the TA approach, and CoreValve® devices by the retrograde TF or transaxillary/subclavian arterial route. | In the only randomised controlled trial (RCT) (PARTNER cohort B), TAVI significantly reduced the risk of death from any cause after 1 year compared with medical management in patients who were unsuitable candidates for surgery. In the only RCT (PARTNER cohort A), TAVI was not inferior to surgical aortic valve replacement with respect to death from any cause after 1 year in candidates for surgery who were at high risk of increased operative complications and death. TAVI was associated with a significantly higher incidence of major vascular complications and neurological adverse events, in both cohorts A and B. There are limited published data on TAVI outcomes beyond 1 year of follow up. | There are currently no published evaluations of the cost effectiveness of TAVI compared with surgical AVR or medical management. Several unpublished developmental economic models that were identified have important limitations. | Patient selection for TAVI should be undertaken by a multidisciplinary team, including a cardiologist, cardiac surgeon and cardiac anaesthetist. | No adverse impact across any of 6 equality groups is expected. |

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| KCE [26] | 2011 | Belgium | N.A. | <p>TAVI is a highly invasive and challenging procedure addressing elderly people in poor general condition. The procedure takes on average over 4 hours (skin-to-skin time 2 to 3 hours). It involves prolonged general anaesthesia, the administration of contrast media, and trans-oesophageal echocardiography. There are two variants of this procedure: "transfemoral TAVI" and "transapical TAVI".</p> | <p>The procedure is complicated with hemorrhagic vascular adverse events in more than 50% of patients. In the PARTNER Cohort A trial, in patients with aortic stenosis who are at very high surgical risk, TAVI and surgery are associated with a similar mortality rate at 30 days and 1 year and produce similar improvements in cardiac symptoms. The approximate doubling in the rate of stroke 1 year after TAVI (8.3%) compared to surgery (4.3%) remains a concern. In patients with severe aortic stenosis who are no candidates for surgery, TAVI significantly reduces the rate of death from any cause (ARR 2.0% at 1 year) as compared with standard therapy. In the Continued Access population, TAVI had an absolute 12.7% higher mortality at 1 year as compared with standard therapy. Stroke rate at 1 year was twice as high in TAVI patients compared to standard therapy (10.6% vs. 4.5%). Subgroup analysis of those patients showed a more favourable effect of TAVI at 30 days (4.4% absolute survival difference) and after 1 year (8.8% absolute difference) compared to patients with medical prohibitive conditions.</p> | <p>In the PARTNER Cohort A trial, a substantial incremental cost for TAVI versus AVR in combination with minimal incremental effects results in relatively very high ICERs. The average ICER is about €750,000 per LYQ or per QALY TAVI device cost from €18,000 to €10,000, the average ICER remains above €450,000 per LYQ or per QALY gained. In the PARTNER Cohort B trial Based on the results of the pivotal PARTNER trial, and assuming a lifetime treatment effect, the average ICER is about €37,400 per QALY. Lowering the price from €18,000 to €10,000 per device results in an ICER of about €30,000 per QALY gained.</p> | <p>It is proposed that heart centres that want to practice TAVI should have at least a yearly volume of 100 patients undergoing aortic valve surgery. A second proposition formulated is the requirement for each patient of an a priori approval for TAVI by a cardiologist and a cardiac surgeon appointed by the RIZIV/INAMI.</p> | N.A. |

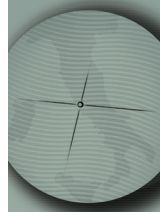


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| CADTH [27] | 2011 | Canada | N.A. | N.A. | <p>Short term procedural success was observed in the majority of TAVI patients (94%). Greater haemodynamic improvement was reported. 75% of the TAVI group were asymptomatic or had mild symptoms, compared to 42% in the standard therapy group. There were fewer deaths observed in the TAVI group at 1 year compared with the standard therapy group (31% versus 51%) (beyond 30 days). Similar rates of mortality (cardiovascular cause) (5%) within 30 days were found in the TAVI group and the SAVR group. A higher rate of stroke or transient ischemic attack was reported at one year in the TAVI group (8%) compared to the SAVR group (4%). There was a higher proportion of patients with major vascular complications within one year in patients with TAVI compared to those with SAVR (18% versus 5%).</p> | N.A. | <p>Patient selection should be carried out by a multidisciplinary team including interventional cardiologists, a cardiac surgeon and a cardiac anaesthetist</p> | N.A. |



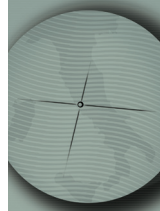
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| HAS [28] | 2012 | France | <p>The etiological profile of aortic valve stenosis has changed in recent years. Actually, degenerative disorders are the most frequent whereas rheumatic origin is in decline. The diagnosis of this pathology often occurs during the sixth decade. Epidemiological studies estimate the prevalence of AS in subjects over 75 years of age at 5% and 3% for tight aortic stenosis. Half of these patients are asymptomatic.</p> | <p>The JENAVALVE bioprosthesis is a porcine aortic valve with its root sewn on a radiopaque lattice self-expandable Nitinol. On its upper part, the prosthesis has three eyelets which will be housed in the corresponding cavities at the level of the crown of the catheter.</p> <p>The delivery system consists of two parts: the size 32 F catheter and the handle. The catheter is intended to be introduced into the left ventricle via the apex of the heart. The deployment of the valve is controlled and performed in three stages with the possibility of repositioning the bioprosthesis.</p> | <p>Implantation of a TAVI is performed without extracorporeal circulation and can be performed under local anesthesia for the retrograde transfemoral approach. It is shown that the management of patients contraindicated to surgery is improved with the implantation of a transarterial aortic valve compared to standard medical treatment with a survival gain at 1 year. This same study, however, shows a significant rate of stroke and a significant rate of vascular complications after implantation of this type of valve. For patients at high risk of surgery, another RCT did not show a 1-year survival gain following transcatheter or retrograde retrograde aortic valve implantation compared with conventional surgery. Furthermore, each alternative presents its risks and complications with bleeding for surgical aortic valve replacement and stroke followed by transcatheter aortic valve replacement. No study to date directly compares the different types of currently available valves implanted transarterially or transapically.</p> | N.A. | N.A. | N.A. |



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| AVALLIA-T [29] | 2013 | Spain | AS is associated with a high mortality after the onset of symptoms. The average survival from this moment is 2-3 years with a high probability of sudden death. The recommendations of the main guidelines indicate that the candidates for valve replacement would be patients with severe symptomatic AS. However, in patients with high surgical risk or contraindication for surgery, the TAVI seems to be a better option. | TAVI consists of placing the prosthesis in the position of the native valve with a catheter. The approach can be performed percutaneously (usually transfemoral) or through a mini-thoracotomy (transapical route). Actually, there are different devices for the transcatheter implantation of aortic valves, the most commonly used being the CoreValve prosthesis and the Edwards SAPIEN. | There was a higher frequency of paravalvular regurgitation with TAVI than with conventional surgery, and the transfemoral approach seemed to be associated with a higher rate of vascular complications. It appeared that patients treated with the CoreValve prosthesis had a greater need of pacemaker implantation than those who had the Edwards SAPIEN transcatheter heart valve implanted. Despite these complications, TAVI registered a mortality rate similar to that of surgery. | The average cost of valve replacement transfemorally was 33 391.22€ and 35 289.45€ for the transapical approach. It includes the valvular prosthesis (Edwards SAPIEN) of €22,068.53, hemodynamic tests, stay in ICU and follow-up consultation (7 days). | It requires specialists in interventional cardiology, cardiac imaging as well as in Cardiovascular Surgery, trained anesthetists, nurses, etc. The technique requires a training and the first cases must be done under the supervision of an expert. | N.A. |
| NHS [30] | 2013 | England | AS is the most common valvular heart disease in Western countries, affecting approximately 2% of people over the age of 65 years. In patients with severe symptomatic AS, the risk of death is approximately 2% per month, and typical survival is 2 to 3 years. | TAVI involves catheter-guided transport of a new aortic valve that displaces the old diseased valve and is expanded in place. Valve implantation is achieved by keyhole catheter technique (without bypass and open-heart surgery) in which the new valve, loaded within a catheter, is delivered with radiographic guidance into the native valve. It may be undertaken in a number of ways. | In centres experienced in conducting TAVIs, procedural success may be around 90% or more and closely linked to experience, with greater learning resulting in better patient selection and outcomes. Some studies have shown high rates of success and more recent studies showed procedural mortality rates of 0-10%. Thirty-day mortality may range from 5% to 18%. Studies of long-term mortality show 2-year survival rates of 70-80%. Moderate to severe paravalvular regurgitation is higher in TAVI than in SAVR patients at 30 days, 1 year and 2 years. | Comparing TAVI with medical management, the base-case results show that TAVI is more costly but more effective than the comparator, with an ICER of £12,900 per QALY. In the deterministic sensitivity analysis, the only case in which the ICER exceeded £20,000 per QALY was when the QoL scores were taken to an extremely low value. The ICER was below £20,000 per QALY for over 99% of model runs in the probabilistic sensitivity analysis. | Patients have to be assessed by multidisciplinary teams comprising cardiac surgeons, cardiologists and anaesthesiologists. In-hospital and 30-day mortality was not affected by the learning curve. | N.A. |
| ECORYS [31] | 2013 | Netherlands | AS is a condition in which the aortic valve is narrowed. The heart then has to work harder to pump the blood around, causing the heart muscle to weaken over time. With moderate to severe AS symptoms, symptoms such as chest pain may occur during exercise and fainting. Without an adequate treatment, AS patients may die. | TAVI is a minimally invasive procedure in which the replacement valve is delivered percutaneously through the vascular system inside a catheter. Transcatheter access to the aortic valve is achieved mainly by the retrograde TF, TA or transaxillary/subclavian routes. It represents a valid option for patients who are not operable due to advanced age and comorbidity or at high surgical risk. | N.A. | N.A. | N.A. | N.A. |

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| CADTH [32] | 2013 | Canada | Aortic stenosis, the most common valvular heart disease, occurs when there is a narrowing of the aortic valve opening. It is typically caused by age-related progressive build-up of calcium and scarring of the aortic valve, which creates obstructed blood flow out of the left ventricle to the rest of the body. Left untreated, aortic stenosis can lead to heart failure. Prognosis in the absence of treatment is poor; most patients will die within five years. | N.A. | Among the evaluations that examined patients who were not candidates for surgery, there was a consensus that TAVR was an adequate or effective alternative to SAVR. Among the assessments that examined patients who were not surgical candidates, there was consensus that TAVR was either an adequate or effective alternative to SAVR. Of the assessments that reported on patients for whom surgery is considered high risk, there was support for the use of TAVR in this population. The HQO assessment noted that in patients for whom surgery is considered high risk, TAVR has a mortality rate similar to SAVR, and was associated with significant adverse effects. | The HQO assessment conducted an economic analysis to evaluate the cost-effectiveness of TAVR compared with standard of care in inoperable patients, and TAVR compared with SAVR in operable patients. The assessment reported the cost of a valve to be \$37,606. The cost per life-year of TAVR compared with standard therapy in inoperable patients was \$33,141. The cost per life-year of TAVR compared with SAVR in operable patients was \$870,143. The assessment concluded that TAVR may be cost-effective for inoperable patients, but it is not cost-effective for patients who are operable. | N.A. | N.A. |
| CADTH [33] | 2013 | Canada | According to a 2011 report, approximately 300,000 people worldwide have been diagnosed with severe aortic stenosis and approximately one-third of them are considered to be at too high a risk for open heart surgery. ⁷ Currently, the two most common approaches for TAVR are transfemoral and transapical procedures. There are two commercially available systems for TAVR: SAPIEN (Edwards LifeSciences Corporation, Irvine, CA, US) and CoreValve (Medtronic Inc., Minneapolis, MN, US). | Transcatheter aortic valve replacement (TAVR), sometimes called transcatheter aortic valve implantation (TAVI), was developed as an alternative for patients with severe aortic stenosis who require aortic valve replacement but who are not eligible for conventional surgical aortic valve replacement (SAVR). | The benefits of TAVR with up to one-year follow-up was demonstrated in two randomized controlled trials (RCTs) — PARTNER cohorts A and B — which showed that TAVR has statistically significant clinical benefits compared with standard therapy, or SAVR, as summarized in a previous Rapid Response review. With the aim to review long-term success and complication rates of the procedure, this report provides a review of the use of TAVR at more than 12 months follow-up in patients with severe aortic stenosis compared with SAVR or standard treatment (medical therapy plus balloon aortic valvuloplasty, if needed). | N.A. | N.A. | N.A. |



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| AVALIA-T [34] | 2014 | Spain | <p>AS is the most common valve disease in developed countries. Its prevalence increases with age (2.8% for over 75). The most common aetiology is degenerative calcification of the aortic valve, associated with advanced age. It can also have a congenital origin (frequently in young adults). Other causes, such as rheumatic fever, are becoming increasingly rare. Mortality is linked to the progression of the disease and the onset of symptoms. After the onset of symptoms, the average survival is 2-3 years, with a high risk of sudden death. The severity of AS is classified into three levels: mild, moderate and severe.</p> | <p>TAVI consists of the placement of the valve prosthesis in the position of the native valve with a catheter. The approach can be performed by percutaneous arterial (usually transfemoral) or through a mini-thoracotomy (transapical route). Actually, there are different devices, although the most used are the Edwards SAPIEN balloon expandable bioprosthesis and the CoreValve self-expanding bioprosthesis (CE marked since 2007).</p> | N.A. | N.A. | <p>The adequate selection of patients is a key factor for the use of TAVI. It is proposed that decision-making for the selection of patients be made within the framework of a multidisciplinary hospital committee with experience in valvular diseases, in which cardiologists participate (clinical and interventional) and cardiac surgeons, and that can count on the participation of other professionals (anaesthetists, geriatricians, specialists in cardiac imaging).</p> | N.A. |

1.4 SAFETY AND EFFICACY

1.4.1 HTA report published after 2014

NHS Scotland in 2014 has published an “Evidence Note” about Transcatheter aortic valve implantation (TAVI) for severe symptomatic aortic stenosis in adults at high surgical risk. The authors concluded that the rapid progress is being made in TAVI device modification and patient selection such that the published evidences may not fully involve the latest generation of TAVI devices. In the PARTNER trial (cohort A), TAVI was not inferior to surgical aortic valve replacement (SAVR) comparing with the death for other cause after 1 year in candidates for surgery who were at high risk of operative complications and death. No difference in all-cause mortality was shown after 2 years of follow-up. In the PARTNER trial (cohort A), TAVI was associated with a higher incidence of major vascular complications and neurological adverse events, including stroke. Major bleeding was less common with TAVI, but moderate or severe paravalvular regurgitation was more common compared with surgical valve replacement [35].

Onorati et al. in 2014 [36] have assessed, in a propensity-matched population of the OBSERVANT study, and Italian multicenter Registry, the superior outcomes of transcatheter aortic valve implantation (TAVI) comparing TAVI and surgical aortic valve replacement (AVR). 162 patients (81 TAVI vs 81 AVR) with severe left ventricular systolic dysfunction (ejection fraction $\leq 35\%$) were included in the study. The 30-day mortality was comparable ($P = 0.37$) between the 2 groups. The incidence of periprocedural acute myocardial infarction ($P = 0.55$), low output state ($P = 0.27$), stroke ($P = 0.36$), and renal dysfunction ($P = 0.57$) was also similar between the 2 groups. It was showed a higher rate of postprocedural permanent pacemaker implantation ($P = 0.01$) using the TAVI, while, with the AVR, a higher percentage of periprocedural transfusions ($P < 0.01$), despite a similar transfusion rate per patient (2.8 ± 3.7 for TAVI vs 4.4 ± 3.8 for AVR; $P = 0.08$). The postprocedural intensive care unit stay (median, 2 days after TAVI vs 3 days after AVR; $P = 0.34$), intermediate

care unit stay (median, 0 days after both TAVI and AVR; $P = 0.94$), and hospitalization (median, 11 days after TAVI vs 14 days after AVR; $P = 0.51$) were comparable. The authors concluded that both TAVI and AVR are valid treatment options, with comparable hospital mortality and periprocedural morbidity [36].

The NHS Scotland in 2014 has published an “Evidence Note” about Transcatheter aortic valve implantation (TAVI) for severe symptomatic aortic stenosis in adults who are not eligible for surgery. The authors concluded that in the randomized controlled PARTNER trial (cohort B), “TAVI significantly reduced the risk of death from any cause after 1 year compared with medical management of patients who were unsuitable candidates for surgery” [35]. The reduction was sustained up to 2 years of follow up. In the PARTNER trial (cohort B), TAVI significantly improved quality of life up to 1 year of follow up compared with medical management in patients who were unsuitable candidates for surgery. In the PARTNER trial (cohort B), TAVI was associated with a significantly higher incidence of major vascular complications and neurological adverse events including stroke.

Bayón Yusta et al. [17] assessed the safety and effectiveness of the transcatheter implant percutaneously or transapically of biological prostheses of aortic valves in the treatment of symptomatic severe aortic stenosis. A systematic review of the literature was performed in the main databases. According to the selection criteria, 12 evaluation reports and 25 primary studies were included in the systematic review. According to available evidence, TAVI showed a greater frequency of paravalvular regurgitation (valvular leaks) compared to conventional surgery and the transfemoral approach seemed to be associated with a higher rate of vascular complications. Despite these complications, TAVI showed a mortality rate similar to surgery. The authors concluded that transcatheter implantation and conventional surgery had a similar effect in the treatment of symptomatic aortic stenosis in patients at high surgical risk. Therefore, TAVI are recommended for selected patients, with a surgical risk considered unacceptable or with strong contraindications for the surgery [17].

NICE in 2017 in an Interventional procedure's guidance have evaluated the efficacy and safety outcomes associated with TAVI. The authors concluded that the current evidence on the safety and efficacy of transcatheter aortic valve implantation (TAVI) for aortic stenosis is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent, and audit.

Details of all patients should be entered into the TAVI registry. Adverse events should be reported to the Medicines and Healthcare products Regulatory Agency. During the consent process, patients should be told about all treatment options and their advantages and disadvantages. TAVI is a technically challenging procedure that should only be done in specialized centers and only by clinicians and teams with special training and experience in complex endovascular interventions [16].

In 2018 CADTH in a Rapid Response report have evaluated the comparative clinical effectiveness and safety of TAVI compared to SAVR for severe aortic stenosis in inoperable, high, intermediate, and low surgical risk patients [37]. A limited literature search was conducted on key resources between January 1, 2008, and January 12, 2018. Six publications (three systematic reviews, 13 RCTs) have been included in the report. The main results have been summarized in Table 2.

1.4.2 Systematic Reviews, Metanalyses and clinical trials published after 2014

Abdel-Wahab et al. [38,39] investigated on aortic regurgitation (AR) after transcatheter aortic valve implantation (TAVI) with the self-expandable Medtronic CoreValve (MCV) (Medtronic Inc., Minneapolis, Minnesota) versus balloon-expandable Edwards Sapien XT valve (ESV) (Edwards Lifesciences, Irvine, California). Background AR after TAVI has been associated with poor survival, but limited data exist comparing MCV with ESV. Authors pooled the prospective TAVI databases of 2 German centers. The primary endpoint was more-than-mild post-TAVI AR assessed by echocardiography. Authors also assessed device success and survival within 1 year. Endpoints were adjudicated according to the Valve Academic Research Consortium criteria and analyzed by unadjusted and propensity-score-adjusted models. A total of 394 patients were included, 276 treated with MCV and 118 with ESV. Morethan- mild AR was significantly higher with MCV than with ESV (12.7% vs. 2.6%, $p = 0.002$). This difference remained significant after propensity adjustment (adjusted odds ratio [OR]: 4.59, 95% confidence interval [CI]: 1.03 to 20.44). The occurrence of any degree of AR was also higher with MCV (71.6% vs. 56.9%, $p = 0.004$). Device success was mainly influenced by the occurrence of AR and was consequently higher with ESV (95.8% vs. 86.6%, $p = 0.007$), but this was not significant after propensity adjustment (adjusted

TABLE 2

MAIN RESULTS OF CADTH, 2018 [37]

| | |
|---------------------------------------|--|
| Inoperable (TAVI-TF) | Reduced risk of all-cause death and rehospitalization while maintaining the similar risk of all strokes up to 5 years and similar risk of major bleeding and new pacemaker implantation at 2 years. Increased risk of major vascular complications up to 1 year. |
| High risk (TAVI-TF, not-TF) | Maintained similar risk of all-cause death, all strokes, rehospitalization while reducing the risk of major bleeding up to 5 years. Increased risk of moderate or severe regurgitation for up to 5 years. Risks of all-cause mortality and rehospitalization at 5 years were less with TAVI-TF than TAVI-TA. |
| Intermediate risk (TAVI-TF, non-TAVI) | Maintained similar risk of all-cause death, all strokes and rehospitalization while the increased risk of moderate or severe regurgitation, and new pacemaker implantation up to 2 years. |
| Low risk (TAVI-TF, non-TF TAVI) | Maintained similar risk of all-cause death and all strokes while reducing the risk of major bleeding at 1 month. Increased risk of major vascular complication, moderate or severe regurgitation new pacemaker implantation. |

OR: 0.34, 95% CI: 0.11 to 1.03, $p = 0.06$). At 1 year, survival was comparable between both valve types (83.8% MCV vs. 88.2% ESV, $p = 0.42$), but was significantly worse in patients with more-than-mild AR (69.8% vs. 87.4%, $p = 0.004$) and in those with device failure (65.6% vs. 87.4%, $p < 0.001$). More-than-mild AR after TAVI was more frequent with MCV than with ESV. This finding deserves consideration, as more-than-mild AR was associated with higher mortality at 1 year [38]. Thus, the use of a balloon-expandable transcatheter heart valve resulted in a greater rate of device success compared with a self-expandable transcatheter heart valve. Abdel-Wahab evaluated clinical and echocardiographic outcome data at longer term follow-up. The results discussed below have a follow up of 1 year and the data derived from the CHOICE randomized clinical trial. The investigator-initiated trial randomized 241 high-risk patients with symptomatic severe aortic stenosis and anatomy suitable for treatment with both balloon- and self-expandable transcatheter heart valves to transfemoral transcatheter aortic valve replacement with either device. Patients were followed-up for 1 year, with assessment of clinical outcomes and echocardiographic evaluation of valve function. At 1 year, the rates of death of any cause (17.4% vs. 12.8%; relative risk [RR]: 1.35; 95% confidence interval [CI]: 0.73 to 2.50; $p = 0.37$) and of cardiovascular causes (12.4% vs. 9.4%; RR: 1.32; 95% CI: 0.63 to 2.75; $p = 0.54$) were not statistically significantly different in the balloon- and self-expandable groups, respectively. The frequencies of all strokes (9.1% vs. 3.4%; RR: 2.66; 95% CI: 0.87 to 8.12; $p = 0.11$) and repeat hospitalization for heart failure (7.4% vs. 12.8%; RR: 0.58; 95% CI: 0.26 to 1.27; $p = 0.19$) did not statistically significantly differ between the 2 groups. Elevated transvalvular gradients during follow-up were observed in 4 patients in the balloon-expandable group (3.4% vs. 0%; $p = 0.12$); all were resolved with anticoagulant therapy, suggesting a thrombotic etiology. More than mild paravalvular regurgitation was more frequent in the self-expandable group (1.1% vs. 12.1%; $p = 0.005$). Despite the higher device success rate with the balloon-expandable valve, 1-year follow-up of patients in CHOICE (Randomized Comparison of Transcatheter Heart Valves in High Risk Patients With Severe Aortic Stenosis: Medtronic CoreValve Versus Edwards SAPIEN XT Trial), with limited statistical power, revealed clinical outcomes after transfemoral transcatheter

aortic valve replacement with both balloon- and self-expandable prostheses that were not statistically significantly different [38,39].

The same author, in 2015, investigated on whether the balloon-expandable device is associated with a better success rate than the self-expandable device. As mentioned before in the report, the CHOICE study was an investigator-initiated trial in high-risk patients with severe aortic stenosis and an anatomy suitable for the transfemoral TAVR procedure. The primary endpoint was device success, which is a composite endpoint including successful vascular access and deployment of the device and retrieval of the delivery system, correct position of the device, intended performance of the heart valve without moderate or severe regurgitation, and only 1 valve implanted in the proper anatomical location. Secondary endpoints included cardiovascular mortality, bleeding and vascular complications, postprocedural pacemaker placement, and a combined safety endpoint at 30 days, including all-cause mortality, major stroke, and other serious complications. Device success occurred in 116 of 121 patients (95.9%) in the balloon-expandable valve group and 93 of 120 patients (77.5%) in the self-expandable valve group (relative risk [RR], 1.24, 95%CI, 1.12-1.37, $P < .001$). This was attributed to a significantly lower frequency of residual more-than-mild aortic regurgitation (4.1% vs 18.3%; RR, 0.23; 95%CI, 0.09-0.58; $P < .001$) and the less frequent need for implanting more than 1 valve (0.8% vs 5.8%, $P = 0.03$) in the balloon-expandable valve group. Cardiovascular mortality at 30 days was 4.1% in the balloon-expandable valve group and 4.3% in the self-expandable valve group (RR, 0.97; 95% CI, 0.29-3.25; $P = 0.99$). Bleeding and vascular complications were not significantly different, and the combined safety end point occurred in 18.2% of those in the balloon-expandable valve group and 23.1% of the self-expandable valve group (RR, 0.79; 95%CI, 0.48-1.30; $P = .42$). Placement of a new permanent pacemaker was less frequent in the balloon-expandable valve group (17.3% vs 37.6%, $P = .001$). In conclusion, among patients with high-risk aortic stenosis undergoing TAVR, the use of a balloon-expandable valve resulted in a greater rate of device success than use of a self-expandable valve [40].

Daubert et al., in 2017 [41], tried to investigate on the long-term performance of transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR)

through longitudinal echocardiographic analysis. The long-term performance of the SAPIEN TAVR is not well-described. Therefore, authors examined the hemodynamic and valvular profile of the SAPIEN TAVR over 5 years. All patients receiving TAVR or SAVR with first post-implant (FPI) and 5-year echoes were analyzed for aortic valve (AV) peak velocity, AV mean gradient, AV area, peak left ventricular (LV) outflow tract and in-stent velocities, Doppler velocity index, aortic regurgitation (AR), LV mass index, stroke volume index, and cardiac index. The FPI and 5-year data were compared using a paired t test or McNemar's analyses. There were 86 TAVR and 48 SAVR patients with paired FPI and 5-year echocardiograms. Baseline characteristics were similar between groups. The AV area did not change significantly 5 years after TAVR ($p = 0.35$). The AV mean gradient also remained stable: 11.5 ± 5.4 mm Hg at FPI to 11.0 ± 6.3 mm Hg at 5 years ($p = 0.41$). In contrast, the peak AV and LV outflow tract velocities decreased ($p = 0.03$ and $p = 0.008$, respectively), as did in-stent velocity ($p = 0.015$). Correspondingly, the TAVR Doppler velocity index was unchanged ($p = 0.07$). Among TAVR patients, there was no change in total AR ($p = 0.40$), transvalvular AR ($p = 0.37$), or paravalvular AR ($p = 0.26$). Stroke volume index and cardiac index remained stable ($p = 0.16$ and $p = 0.25$, respectively). However, there was a significant regression of LV mass index ($p < 0.0001$). The longitudinal evaluation among SAVR patients revealed similar trends. There was a low rate of adverse events among TAVR and SAVR patients alive at 5 years. Longitudinal assessment of the PARTNER (THE PARTNER TRIAL: Placement of AoRTic TraNscatheter Valve Trial) I trial demonstrates that valve performance and cardiac hemodynamic are stable after implantation in both SAPIEN TAVR and SAVR in patients alive at 5 years. (THE PARTNER TRIAL: Placement of AoRTic TraNscatheter Valve Trial [PARTNER]; NCT00530894) [42].

Kapadia et al. [43], claimed that based on the early results of the Placement of Aortic Transcatheter Valves (PARTNER) trial, transcatheter aortic valve replacement (TAVR) is an accepted treatment for patients with severe aortic stenosis who are not suitable for surgery. However, little information is available about the late clinical outcomes in such patients. Authors did this randomised controlled trial at 21 experienced valve centres in Canada, Germany, and the USA. Authors enrolled

patients with severe symptomatic inoperable aortic stenosis and randomly assigned (1:1) them to transfemoral TAVR or to standard treatment, which often included balloon aortic valvuloplasty. Patients and their treating physicians were not masked to treatment allocation. The randomisation was done centrally, and sites learned of the assignment only after a patient had been screened, consented, and entered into the database. The primary outcome of the trial was all-cause mortality at 1 year in the intention-to-treat population, here we present the prespecified findings after 5 years. This study is registered with ClinicalTrials.gov, number NCT00530894. Authors screened 3015 patients, of whom 358 were enrolled (mean age 83 years, Society of Thoracic Surgeons Predicted Risk of Mortality 11.7%, 54% female). 179 were assigned to TAVR treatment and 179 were assigned to standard treatment. 20 patients crossed over from the standard treatment group and ten withdrew from study, leaving only six patients at 5 years, of whom five had aortic valve replacement treatment outside of the study. The risk of all-cause mortality at 5 years was 71.8% in the TAVR group versus 93.6% in the standard treatment group (hazard ratio 0.50, 95% CI 0.39–0.65; $p < 0.0001$). At 5 years, 42 (86%) of 49 survivors in the TAVR group had New York Heart Association class 1 or 2 symptoms compared with three (60%) of five in the standard treatment group. Echocardiography after TAVR showed durable haemodynamic benefit (aortic valve area 1.52 cm² at 5 years, mean gradient 10.6 mm Hg at 5 years), with no evidence of structural valve deterioration. TAVR is more beneficial than standard treatment for treatment of inoperable aortic stenosis. TAVR should be strongly considered for patients who are not surgical candidates for aortic valve replacement to improve their survival and functional status. Appropriate selection of patients will help to maximise the benefit of TAVR and reduce mortality from severe comorbidities [45].

Regarding the PARTNER trial we found also the study by Mack et al. [44]. The Placement of Aortic Transcatheter Valves (PARTNER) trial showed that mortality at 1 year, 2 years, and 3 years is much the same with transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) for high-risk patients with aortic stenosis. Authors reported in this study the 5-year outcomes. Authors did this randomised controlled trial at 25 hospitals,

in Canada (two), Germany (one), and the USA (23). Authors used a computer-generated randomisation sequence to randomly assign high-risk patients with severe aortic stenosis to either SAVR or TAVR with a balloon-expandable bovine pericardial tissue valve by either a transfemoral or transapical approach. Patients and their treating physicians were not masked to treatment allocation. The primary outcome of the trial was all-cause mortality in the intention-to-treat population at 1 year, we present here predefined outcomes at 5 years. The study is registered with ClinicalTrials.gov, number NCT00530894. Authors screened 3105 patients, of whom 699 were enrolled (348 assigned to TAVR, 351 assigned to SAVR). Overall mean Society of Thoracic Surgeons Predicted Risk of Mortality score was 11.7%. At 5 years, risk of death was 67.8% in the TAVR group compared with 62.4% in the SAVR group (hazard ratio 1.04, 95% CI 0.86–1.24; $p=0.76$). They recorded no structural valve deterioration requiring surgical valve replacement in either group. Moderate or severe aortic regurgitation occurred in 40 (14%) of 280 patients in the TAVR group and two (1%) of 228 in the SAVR group ($p<0.0001$), and was associated with increased 5-year risk of mortality in the TAVR group (72.4% for moderate or severe aortic regurgitation vs 56.6% for those with mild aortic regurgitation or less; $p=0.003$). In conclusion, their findings show that TAVR as an alternative to surgery for patients with high surgical risk results in similar clinical outcome [44]. Another study we would like to mention in this conclusive paragraph is the study by Vahanian et al. [45]. This study sought to investigate outcomes of transcatheter aortic valve implantation (TAVI) with the SAPIEN 3 transcatheter heart valve (THV) in patients at intermediate risk for surgery. The 30-day results of the transfemoral cohort are reported. The SAPIEN 3 European approval trial intermediate-risk cohort included a total of 101 patients with severe, symptomatic aortic stenosis, at intermediate risk for surgery suitable for TAVI via the transfemoral route (TF). Outcomes were adjudicated by a clinical events committee. Echocardiography, computed tomography and electrocardiography exams were analysed in core laboratories. The mean STS-PROM score and logistic EuroSCORE of the study population were 5.2 ± 1.7 and 13.2 ± 3.8 , respectively. A completely percutaneous procedure was performed in 90.1% of patients and conscious sedation and/or local anaesthesia was utilised in

54.5%. Technical success was achieved in 98.0% of patients. At 30 days, mortality was 1.0%, with stroke in 3.0% and a new permanent pacemaker in 4.0% (4.3% of patients without pre-procedural permanent pacemaker). No patients had severe aortic regurgitation after the procedure, only one patient had moderate aortic regurgitation, and 70.8% of patients had no or trace aortic regurgitation. TF-TAVI using the SAPIEN 3 THV in patients at intermediate risk for surgery is associated with a very low risk of death and complications, including new pacemakers and paravalvular leaks. Although compelling, these initial results are being confirmed in larger global studies before expanding the indications for TAVI in severe aortic stenosis [45].

Ando et al. in 2016 [46] published the study “Sapien 3 versus Sapien XT prosthetic valves in transcatheter aortic valve implantation: A meta-analysis”. The S3 prosthetic valve was introduced to overcome several issues with its predecessor, the SXT, in transcatheter aortic valve implantation (TAVI), however, the clinical outcomes of this new model are not clearly defined. Authors performed a meta-analysis to compare the outcomes in Sapien 3 (S3) and Sapien XT (SXT) recipients. A literature search through PUBMED and EMBASE was conducted. Articles that included at least one of the clinical outcomes of interest were included in the meta-analysis: moderate to severe paravalvular regurgitation (PVR), permanent pacemaker implantation (PPI), major vascular complications (MVC), cerebrovascular events (stroke and transient ischemic attack) (CVE), failure rate of device implantation, life-threatening, disabling or major bleeding, need for post-dilation and early all-cause-mortality. A total of 9 observational cohort studies were included. S3 was implanted in 945 and SXT in 1553 patients. S3 was associated with a lower incidence of moderate to severe PVR (1.6% vs 6.9%, $p < 0.0001$), lower MVC (5.1% vs 8.9%, $p=0.01$) and less serious bleeding (8.1% vs 15.2%, $p=0.003$) compared to the SXT. Device deployment failure rate was lower in the S3 (1.2% vs 5.9%, $p=0.004$) and the S3 required less post-dilation (16.9% vs 26.9%, $p=0.05$). Rates of CVE, perioperative mortality and PPI were similar between the two valves. Implantation of the S3 prosthetic valve results in lower rates of moderate to severe PVR, MVC, post dilation and serious bleeding however it does not improve on the SXT in

terms of CVE, PPI and early mortality [46].

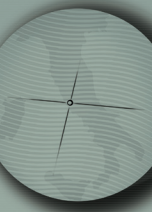
Gargiulo et al., in 2016 [47], published the study “Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement. Authors claimed that the comparative benefits and harms of transcatheter aortic valve implantation (TAVI) and surgical aortic valve replacement (SAVR) for patients with aortic stenosis are unclear. The objective of the study was to compare clinical outcomes, including early (≤ 30 -day) and midterm (≤ 1 -year) mortality, in adults with severe aortic stenosis undergoing either TAVI or SAVR. In the analysis, five randomized trials and 31 observational matched studies comparing mortality outcomes after TAVI or SAVR were observed and assessed. 16,638 patients were analyzed. Overall, there was no statistically significant difference between TAVI and SAVR in early (odds ratio [OR], 1.01 [95% CI, 0.81 to 1.26]) or midterm (OR, 0.96 [CI, 0.81 to 1.14]) all-cause mortality. Analyses restricted to trials (early: OR, 0.80 [CI, 0.51 to 1.25]; midterm: OR, 0.90 [CI, 0.64 to 1.26]) were inconclusive, with wide CIs, whereas analyses of matched studies were similar to the overall results. Transfemoral TAVI provided mortality benefits over SAVR in trials. Analyses restricted to studies of patients at low to intermediate risk showed statistically nonsignificant reductions in early (OR, 0.67 [CI, 0.42 to 1.07]) and midterm (OR, 0.91 [CI, 0.67 to 1.23]) mortality with TAVI. Incidence of periprocedural myocardial infarction, major bleeding, acute kidney injury, and new onset atrial fibrillation was lower with TAVI, but risk for pacemaker implantation, vascular complications, and paravalvular leak increased. Overall, there was a statistically nonsignificant increased risk in long-term (2- to 5-year) all-cause mortality with TAVI (OR, 1.28 [CI, 0.97 to 1.69]), whereas long-term mortality outcomes in patients at low to intermediate risk were inconclusive, with wide CIs (OR, 1.06 [CI, 0.59 to 1.91]). This study has also limitations. In fact, the number of trials was limited, and study designs and patient characteristics were heterogeneous. However, compared with SAVR, TAVI may have similar or better early and midterm outcomes for adults with aortic stenosis, including those at low to intermediate risk [47].

Another meta-analysis was published by Takagi et al. [48]. Authors identified 19 reports of 18 eligible studies enrolling a total of 6606 patients with AS. A pooled analysis

of 9 studies demonstrated a statistically significant 61% increase in perioperative (30-day) all-cause mortality with TA- relative to TF-TAVI in the fixed-effects model (OR, 1.61; 95% confidence interval [CI], 1.21–2.13; $P = 0.0009$). A pooled analysis of 12 studies demonstrated a statistically significant 25% increase in midterm (6 - 42 months) all-cause mortality with TA- relative to TF-TAVI in the fixed effects model (HR, 1.25; 95% CI, 1.09–1.44; $P = 0.002$). There was minimal trial heterogeneity and accordingly little difference in the pooled results from random-effects modelling. Exclusion of any single study from the analysis did not substantively alter the overall results of our analysis. To assess publication bias they generated a funnel plot of the logarithm of effect size vs the precision (reciprocal of standard error) for each study. There was no evidence of significant publication bias ($P = 0.90/0.09$ for perioperative/midterm mortality, respectively). The meta-regression coefficient was not statistically significant for mean age ($P = 0.27$), logistic EuroSCORE ($P = 0.22$) and follow-up duration ($P = 0.11$); and proportion of patients with PVD ($P = 0.24$). That for proportion of men, however, was significantly positive (0.04111; 95% CI, 0.00175–0.08047; $P = 0.04$). The results of our analysis suggest that TA-TAVI may be associated with worse perioperative and midterm all-cause mortality than TF-TAVI, which was robust in sensitivity analyses without publication bias. One of meta-regression analyses would indicate that as proportion of men increases, TF-TAVI is more beneficial in reducing midterm mortality. Results of the following adjusted observational studies and meta-analysis could explain the survival benefit for TF- over TA-TAVI demonstrated in the present meta-analysis. TA-TAVI was the only independent predictor of a higher rise in creatine kinase-MB and one of the independent predictors of a higher rise in cardiac troponin T (cTnT) following the procedure, and the degree of increase in cTnT was identified as the independent predictor of cardiac mortality at 9 ± 10 months of follow-up [48].

1.4.3 Registries published after 2014

Webb et al. have examined 30-day and 1-year outcomes in a large cohort of high-risk patients undergoing VIV TAVR [49].



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|---------------------------------|---|
| Main author, year | John G. Webb; 2017 [49] |
| Nation | USA (21 centers), CANADA (3 centers), Germania (1 center) (centers of the trial PARTNER) |
| N° of patients monitored | 365 |
| Outcome monitored | -Primary endpoint: all cause of mortality at 1 year -Secondary endpoints: major vascular complications, stroke, acute kidney injury, new permanent pacemaker insertion, myocardial infarction, and clinical improvements in symptoms, quality of life (QOL), Kansas City Cardiomyopathy Questionnaire (KCCQ) responses. |
| Results | Death -Any cause 10 (2.7%) - 43 (12.4%) -Cardiovascular 9 (2.5%) -31 (9.0%) Repeat hospitalization 21 (5.9%) -53 (15.9%) Stroke (all) 10 (2.7%) - 16 (4.5%) MI: -All 5 (1.4%) -5 (1.4%) -Periprocedural 5 (1.4%) -5 (1.4%) Vascular complications: -All 27 (7.4%) -28 (7.7%) -Major 15 (4.1%) -16 (4.4%) Acute kidney injury 27 (7.5%) -31 (8.7%) Life-threatening or major bleeding 76 (20.8%) -84 (23.2%) New pacemaker 7 (1.9%) -9 (2.6%) KCCQ score 70.6 - 76.2 NOTE: Data are presented before at 30 days and then at 1-year follow-up |
| Recommendations | In high-risk patients, TAVR for bioprosthetic aortic valve failure is associated with relatively low mortality and complication rates, improved hemodynamics, and excellent functional and quality-of-life outcomes at 1 year |

The SOURCE XT Registry< (Edwards SAPIEN XT Aortic Bioprosthesis Multi-Region Outcome Registry) assessed the use

and clinical outcomes with the SAPIEN XT (Edwards Lifesciences, Irvine, California) valve in the realworld setting.

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|---------------------------------|--|
| First author, year | Gerhard Schymik; 2015 [50] |
| Nation | Austria (2 centers); Belgium (4); Canada (10); Czech Republic (1) Denmark (1); Finland (2); France (16); Germany (29); Greece (1); Israel (4); Italy (9); Netherlands (1); Norway (1); Poland (1); South Africa (5); Spain (10); Switzerland (2); United Kingdom (5). |
| N° of patients monitored | 2,688 patients |
| Outcome monitored | -Primary endpoints: all cause of mortality, cardiac death, stroke. -Secondary endpoints: major vascular complications, major and life-threatening bleeding, acute kidney injury, permanent pacemaker insertion, procedure- and device-related complications, functional status, and echocardiographic assessment of the valve and heart function. |
| Results | All-cause death: 6.3% - 19.4% Cardiac death: 3.0% - 9.5% Stroke: 3.6% - 6.3% All vascular complications 15.8% - 17.1% Major 6.5 7.9 3.5 <0.0001 7.2 8.3 4.6 0.0003 All bleeding 19.7% - 22.9% Life-threatening 5.5% - 6.7% Major 10.2% - 12.0% Major/life-threatening 14.9% - 17.2% Myocardial infarction 0.6% - 1.8% Acute kidney injury 17.8% - 20.6% |

| | |
|------------------------|---|
| Results | Rehospitalizations 6.4% - 29.5% Endocarditis 0.2% - 1.1% New permanent pacemaker 9.5% - 11.0% New-onset atrial fibrillation 5.3% - 7.9% NOTE: Data are presented before at 30 days and then at 1-year follow-up |
| Recommendations | The SOURCE XT Registry demonstrated appropriate use of the SAPIEN XT THV in the first-year post-commercialization in Europe. The safety profile is sustained, and clinical benefits have been established in the real-world setting. |

The aims of the study conducted by Tarantini et al in 2016 [51] was to assess the epidemiology of atrial fibrillation (AF) in patients treated with transcatheter aortic valve replacement (TAVR) and included in the large prospective SOURCE

XT (SAPIEN XT Aortic Bioprosthesis Multi-Region Outcome Registry) study and to evaluate their outcomes according to the presence of pre-existing or new-onset AF (NOAF) (defined as AF occurring within 30 days after TAVR).

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|---------------------------------|--|
| Main author, year | Giuseppe Tarantini; 2016 [51] |
| Nation | Austria (2 centers); Belgium (4); Canada (10); Czech Republic (1) Denmark (1); Finland (2); France (16); Germany (29); Greece (1); Israel (4); Italy (9); Netherlands (1); Norway (1); Poland (1); South Africa (5); Spain (10); Switzerland (2); United Kingdom (5). |
| N° of patients monitored | 2,688 |
| Outcome monitored | -The main outcome measures were all-cause death, cardiac death, and stroke. -Secondary measures included major vascular complications, major and life-threatening bleeding. |
| Results | All-cause death: 178 (26.1%) - 44 (32.1%) Cardiac death: 88 (13.8%) - 21 (16.4%) Stroke: 42 (6.9%) - 11 (8.6%) All vascular complications 120 (18.0%) - 23 (17.0%) Major vascular complications: 52 (7.7%) - 8 (5.8%) Minor vascular complications: 62 (9.2%) - 14 (10.4%) Non-access-related vascular complication: 8 (1.4%) - 1 (0.7%) All bleeding 163 (25.0%) - 46 (34.2%) Major/life-threatening bleeding events: 120 (18.2%) - 28 (20.5%) Life-threatening bleeding events: 46 (7.0%) - 9, 10 (6.8%) Major bleeding events: 86 (13.1%) - 22 (16.1%) Minor bleeding events 59 (9.5%) - 20 (15.7%) Myocardial infarction: 14 (2.5%) - 2 (1.5%) Renal failure: 157 (24.1%) - 44 (32.5%) Rehospitalization: 225 (37.4%) - 53 (44.0%) Endocarditis: 5 (0.9%) - 2 (1.7%) New permanent pacemaker: 85 (13.0%) - 13 (9.7%) |
| Recommendations | In the large dataset of the SOURCE XT registry, the presence of either pre-existing or NOAF (new-onset atrial fibrillation) increased all-cause and cardiac mortality and bleeding events. NOAF was associated with increased stroke rates at long-term follow-up. |

Wendler O. et al [52] have presented the 30-day outcomes of patients who underwent TAVI with a SAPIEN 3 in Europe after postmarked

approval and were enrolled in the SOURCE 3 Registry [33]. The summarized results are reported in the table below:

| | |
|--------------------------|---|
| Main author, year | Olaf Wendler, 2017 [52] |
| Nation | 10 European countries: Germany, France, United Kingdom, Italy, Switzerland, Finland, Denmark, Netherlands, Slovakia, Spain |

| | |
|---------------------------------|---|
| N° of patients monitored | 1950 patients. Of those, 1947 patients underwent transcatheter aortic valve implantation (TAVI) with the SAPIEN 3 (mean age, 81.6±6.6 years; 48.1% female) |
| Monitored years | July 2014 - October 2015 (1 year) |
| Outcome monitored | Outcomes measured in the SOURCE 3 Registry were: all-cause death, cardiac death, stroke, disabling stroke, major vascular complications, life-threatening bleeding, myocardial infarction, acute kidney injury (II-III), new-onset atrial fibrillation, permanent pacemaker insertion, procedural complications, functional status, and echocardiographic assessment of valve function. |
| Results | Implantation success (1 valve in the intended location) was 98,3% . Conversion to conventional surgery (0,6%) and use of cardiopulmonary bypass (0,7%) were rare. Adverse events were low, with site-reported 30-day all-cause mortality of 2.2% , cardiovascular mortality of 1.1% , stroke of 1.4% , disabling stroke of 0.5%, major vascular complications of 4.1% , life-threatening bleeding of 5% , myocardial infarction of 0.3%, acute kidney injury of 1.1%, new-onset of atrial fibrillation of 6.2% and post-TAVI pacemaker implantation of 12% . Moderate or greater paravalvular regurgitation was observed in 3.1% of reporting patients. |
| Recommendations | The 30-day results of the SOURCE 3 Registry demonstrate that TAVI with the SAPIEN 3 results in high procedural success with low procedural complications and excellent postimplantation hemodynamics. This, in combination with the growing experience of patient. These results demonstrate favorable outcomes with this third-generation transcatheter heart valve in clinical practice. |

Between July 2014 and October 2015, Wendler O. et al [53] activated a European post-approval multicentre and observational registry (SOURCE 3), aimed to evaluate the

safety and performance of the SAPIEN 3 (3rd generation) transcatheter heart valve (THV) in 'real-life' practice [35]. The summarized results are reported in the table below:

| | |
|---------------------------------|--|
| Main author, year | Olaf Wendler, 2017 [53]. |
| Nation | 10 European countries: Germany, France, United Kingdom, Italy, Switzerland, Finland, Denmark, Netherlands, Slovakia, Spain |
| N° of patients monitored | 1946 patients (mean age 81.6 ± 6.7 years, 52% male) with severe, symptomatic aortic stenosis, consecutively treated using the SAPIEN 3 |
| Monitored years | July 2014 - October 2015 (1 year) |
| Outcome monitored | <u>One-year clinical outcomes:</u> All-cause mortality; Cardiovascular mortality; Stroke; Disabling stroke; Transient ischaemic attack; Myocardial infarction; New onset of atrial fibrillation; New permanent pacemaker; Endocarditis; Valve thrombosis; Re-hospitalisation. |
| Results | One-year outcomes of SOURCE 3, the largest registry on TAVI using the SAPIEN 3, demonstrate that the low 30-day mortality and high procedural success rate, translates to a low all-cause mortality at 1 year. All-cause mortality was estimated around 12.6% , of which main causes of deaths were of cardiovascular origin (62%). Non-cardiovascular fatal complications were observed in 38% of the total cohort of the elderly high-risk patients. <u>Detailed results:</u> Cardiovascular mortality (8.0%); Stroke (3.1%); Disabling stroke (1.4%); Transient ischaemic attack (1.2%), Myocardial infarction (0,9%); New onset of atrial fibrillation (7,9%); New permanent pacemaker (13,2); Endocarditis (1,3%); Valve thrombosis (0,4%); Rehospitalisation (8,1%) |

| | |
|------------------------|---|
| Recommendations | SOURCE 3 is a large, 'real-world' registry, which confirms the good performance and safety of the SAPIEN 3 at 1-year post-TAVI. The results will inform medical teams in their discussions to identify the optimal treatment option for their patients with aortic stenosis. It provides further evidence on the indication of TAVI and is important for the evaluation of this technique towards lower risk patients. However, longer follow-up is vital to get a better understanding about the durability of this new THV. |
|------------------------|---|

The study by Thourani V.H et al. (2016) [54] has been aimed to report 1-year outcomes with SAPIEN 3 TAVR (Transcatheter Aortic Valve Replacement) in intermediate-risk patients and then to use a prespecified propensity score

analysis to compare these outcomes with those for similar patients given surgical aortic valve replacement in the PARTNER 2A randomised trial [53]. The summarized results are reported in the table below:

| | |
|---------------------------------|--|
| Main author, year | Vinod H. Thourani, 2016 [54] |
| Nation | USA and Canada |
| N° of patients monitored | 1077 intermediate-risk patients, who received TAVR (Transcatheter Aortic Valve Replacement) with the SAPIEN 3 valve (952 [88%] via transfemoral access) |
| Monitored years | Feb 17, 2014 - Sept 3, 2014 |
| Outcome monitored | Assessed outcomes (at 30 days and at 1 year): all-cause mortality, cardiac death, incidence of strokes, disabling stroke, rehospitalisation, myocardial infarction, life-threatening or disabling bleeding, major vascular complication, acute kidney injury (stage 3), new atrial fibrillation, new permanent pacemaker endocarditis and aortic valve re-intervention at 1 year after implantation |
| Results | At 1 year follow-up of the SAPIEN 3 observational study, 79 of 1077 patients who initiated the TAVR procedure had died (all-cause mortality 7.4% ; 6.5% in the transfemoral access subgroup), and disabling strokes had occurred in 24 (2.3%), aortic valve re-intervention in six (1%), and moderate or severe paravalvular regurgitation in 13 (2%). Other results: cardiac death (4.5%), any stroke (4.6%), rehospitalisation (11.4%), myocardial infarction (0.3%), new atrial fibrillation (5.9%), new permanent pacemaker (12.4%), endocarditis (0.8%). |
| Recommendations | TAVR with SAPIEN 3 resulted in excellent clinical outcomes after 1 year follow-up, including low rates of death, stroke, and cardiac symptoms. Paravalvular regurgitation was also low at 1 year and the presence of a higher proportion of patients with mild regurgitation after TAVR did not affect mortality. |

1.5 COSTS AND ECONOMIC ASPECTS

1.5.1 Cost-effectiveness evidences

Actually, there are numerous evidences about the cost-effectiveness rate of TAVI procedure. Literature results are reported in this section.

Two studies demonstrated that TAVI may be cost-effective, while the other four studies found that TAVI may be either dominated by AVR or associated with a high cost per QALY. Because the outcomes associated with TAVI

and AVR appeared to be similar, the focus within the economic evaluations tended to turn to the relative costs of the interventions. The additional procedural cost associated with TAVI did not appear to be offset by reductions in other healthcare costs, which led to the conclusions that TAVI did not appear to be cost-effective for this patient group [1,2]. Canadian studies demonstrated that TAVI, compared with medical management, was associated to an incremental QALY gain of 0.49 and an incremental cost of \$15,687, resulting in a cost per QALY gain of \$32,170. According to Bayón Yusta et al (2014) [17], an economic analysis was developed

applying a Markov model that compared the TAVI procedure in comparison with the AVR (aortic valvular replacement) in symptomatic patients with severe valvular aortic stenosis. The result of the economic evaluation for the base-case indicated that the TAVI alternative was more costly than AVR and more effective in terms of QALYs. The mean cost for the TAVI procedure was €39,861 compared to €30,789 for AVR and quality-adjusted life years were 1.66 versus 1.58. The mean incremental cost was €9,072 and the mean incremental QALY was 0.08. Regarding life years gained, the AVR procedure was superior to the TAVI, with 2.65 versus 2.31 LY gained. The incremental cost-effectiveness ratio of TAVI versus AVR was €119,575/QALY. The cost-effectiveness acceptability curve indicated that for an acceptability threshold of €30,000/QALY, the standard usually accepted in Spain, the probability of obtaining an incremental net benefit greater than zero for the TAVI alternative compared to AVR was 39% [55]. Queiroga et al 2013 [56], in the HTA report performed by CONITEC [57], developed a predictive model to assess the cost-effectiveness of the TAVI in the long-term. In a standard scenario, where the TAVI cost was estimated of R\$ 65 million, the ICER value (cost/LY) in 5 years was R\$ 72,520.65. When the time horizon was adjusted for 10 years, this amount decreased to R\$ 41,653.01. By employing TAVI in the treatment of inoperable patients with severe AS, the estimated total cost of treatment, over five years, was R\$ 123,019.76. This value included: procedure cost, valve prosthesis, consultations with specialists, hospitalization expenses and costs of adverse events. The cost of the standard treatment (pharmacological) was estimated at R\$ 35,815.12, with the addition of costs of specialists and hospitalizations. Patients treated with TAVI had longer life expectancy compared to patients who underwent only conservative therapy. In five years of analysis, the mean survival in the group treated with TAVI was 2.5 years. In the group that received only standard treatment, the mean survival was 1.53 years. For the standard scenario, in which the cost of TAVI was set at R\$ 65,000, the value of the ICER (cost/LY) at five years was R\$ 90,161.29. However, changing the time horizon, the ICER value decreased to R\$ 55,130.84. Additionally, the value of the valve prosthesis was altered, between R\$ 30,000 and R\$ 65,000 (base-case value), with this variance in the cost of the valve prosthesis, ranged between R\$ 49,770.00 and R\$ 85,957.00. It was

observed that most of the simulations had their results in quadrant 1 (99.9%) [58].

Regarding the cost-effectiveness we found further evidence related to the PARTNER 2A and Sapien 3 intermediate risk trials [59-61]. Previous studies have demonstrated that TAVR is cost-effective compared with medical therapy for patients with severe AS and extreme surgical risk and compared with SAVR for patients at high surgical risk. Whether TAVR is cost-effective compared with SAVR for intermediate risk patients is currently unknown. The analytic perspective was from the US healthcare system. Two population were analysed: P2A as treated population (XT-994, SAVR-944) and S3i as valve implant population (S3- 1068, SAVR-936). The general approach of the study was to consider a time horizon in trial (24 month) based on observed data, followed by pt-level lifetime projections of survival, quality-adjusted life expectancy and costs. Future costs and benefits were discounted at 3%/year. Probabilistic matching used to link trial patients with medicare claims data. Index hospitalizations costs were calculated using a combination of resource-based accounting (for TAVR/SAVR procedures) and hospital billing data (from Medicare claims). Regarding the methods they observed mortality between 6 and 24 months compared with age/gender specific mortality from US life-tables (SAVR group). Then, they recalibrated life tables used to project patient-level survival beyond 24 months. Regarding the TAVR group, they used hazard ratio (TAVR vs. SAVR) derived from 6-24 months landmark analysis of trial data. Since observed HR (1.07, 95% CI 0.78 to 1.45) did not differ from unity, base case analysis assumed HR = 1.0. Finally, QALYs were measured at baseline, 1,6,12, and 24 months using EQ-5D and used to calculate within-trial and lifetime QALYs. Although procedural costs for TAVR remain substantially higher than for surgical AVR, for intermediate risk patients with severe AS, TAVR using the SAPIEN-XT valve led to substantial reductions in hospital LOS, resulting in initial treatment costs that were only slightly higher than for SAVR. Over the ensuing 6-12 months, follow up costs were substantially lower with XT-TAVR such that total medical care costs were lower with TAVR than SAVR at 1 and 2-year follow up. Over a lifetime horizon, XT-TAVR was projected to be an economically dominant strategy – providing both greater quality-adjusted life expectancy and lower long-term costs than SAVR with a high degree of

confidence. Results using the SAPIEN-3 valve and more contemporary care patterns demonstrated outcomes that were even more favourable with TAVR (lifetime cost savings 10,000 \$ / patients and significant gain in QALYs).

In patients with severe aortic stenosis (AS) at intermediate surgical risk, treatment with transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) results in similar rates of death or stroke at 2 years. Whether TAVR is cost-effective compared with SAVR for intermediate-risk patients remains uncertain. Between 2011 and 2014, 3110 intermediate-risk AS patients were treated with TAVR or SAVR in the PARTNER-2 Trial. 2032 patients were randomized to receive TAVR using the SAPIEN-XT valve (XT-TAVR) or SAVR in the PARTNER-2A Trial, while the PARTNER-S3i Registry included an additional 1078 patients treated with TAVR using the SAPIEN-3 valve (S3-TAVR), which offers a lower delivery profile and sealing skirt designed to reduce paravalvular regurgitation compared with XT-TAVR. Procedural costs were estimated using measured resource utilization. Other in-trial costs were assessed by linkage of trial data with Medicare claims (n=2333) or by linear regression models for unlinked patients (n=682). Health utilities were estimated using the EQ-5D at baseline, 1, 12, and 24 months. Using a Markov model informed by in-trial costs, utilities, and survival data, lifetime cost-effectiveness from the perspective of the U.S. healthcare system was estimated in terms of cost per quality-adjusted lifeyear gained. Although procedural costs were ~\$20,000 higher with TAVR than SAVR, total cost differences for the index hospitalization were only \$2888 higher with XT-TAVR (p=0.014) and \$4155 lower with S3-TAVR (p<0.001) owing to reductions in length of stay with TAVR. Follow-up costs were significantly lower with XT-TAVR ($\Delta=-\$9304$; p<0.001) and S3-TAVR ($\Delta=-\$11,377$; p<0.001) compared with SAVR. Over a lifetime horizon, TAVR was projected to lower total costs by \$8000-\$10,000 and to increase quality-adjusted survival by 0.15-0.27 years. XT-TAVR and S3-TAVR were found to be economically dominant compared with SAVR in 84% and 97% of bootstrap replicates, respectively. Among intermediate-risk AS patients, TAVR is projected to be economically dominant by providing both greater quality-adjusted life expectancy and lower long-term costs compared with SAVR. If long-term data demonstrate comparable late mortality with TAVR and SAVR, these findings suggest that TAVR may be the preferred treatment strategy

for intermediate-risk AS patients based on both clinical and economic considerations. This study should be interpreted in the context of several important limitations. Firstly, the S3-TAVR vs. SAVR comparison was derived from a non-randomized study. While the PARTNER 2A trial and S3i registry did use identical inclusion and exclusion criteria and a pre-specified propensity score was used to adjust for differences between the groups, it is still possible that observed differences in health status and costs were affected by confounding factors. Secondly, these results were based on a single clinical trial program that studied two balloon-expandable TAVR devices, and costs were derived from Medicare claims. As such, these results cannot necessarily be generalized to patients of different surgical risk, to other TAVR devices, to other health care systems outside the U.S., or to other payment models other than Medicare within the U.S. Thirdly, extrapolation of both clinical outcomes and costs beyond the trial period was based on assumptions and hence, may not be accurate. Nonetheless, the methods used to project cost, health status, and survival are similar to ones used in previous economic analyses, are supported by data from other TAVR vs. SAVR trials, and wherever possible, our assumptions were intentionally conservative. Finally, the long-term durability of the both the SAPIEN-XT and SAPIEN-3 valves is unknown. As such, lifetime costs associated with TAVR may be higher than we have assumed owing to the need for more frequent repeat valve procedures. Nonetheless, sensitivity analyses demonstrated that TAVR would remain economically dominant unless follow-up costs increased substantially from our base case assumptions. In conclusion, for patients with severe AS at intermediate surgical risk, TAVR with either the SAPIEN-XT valve or SAPIEN-3 valve is projected to be an economically dominant strategy from the perspective of the U.S. healthcare system by providing both greater quality-adjusted life expectancy and lower long-term costs when compared with SAVR. If long term data demonstrate comparable late mortality with TAVR and SAVR, these findings suggest that TAVR may be the preferred treatment strategy for intermediate-risk AS patients based on both clinical and economic considerations [58].

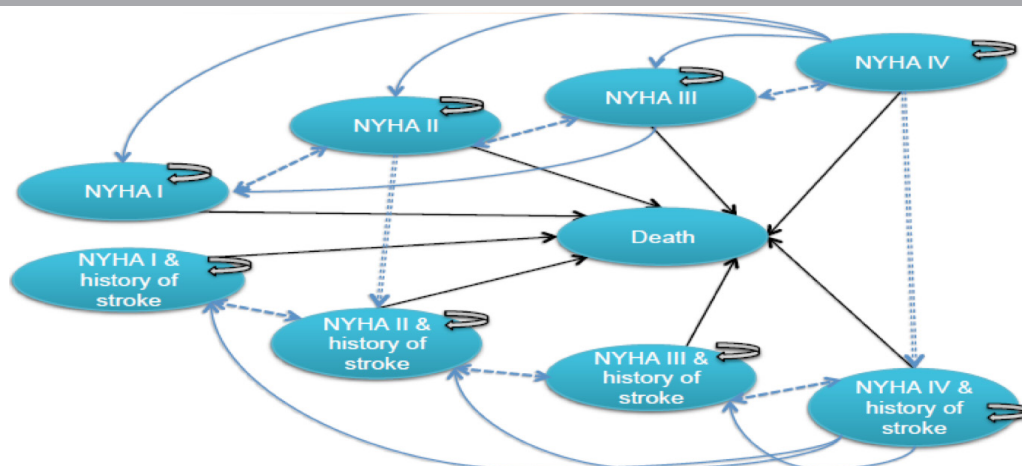
In the Italian context, Lorenzoni et al. [7] assessed the cost-effectiveness of TAVI considering the perspective of the Italian national Health System (INHS), a mid and long-term time horizon and patients' groups with different surgical risk. In figure 2, we are reporting the structure of

the model. A Markov model with 1-month cycle length and comprising eight different health-states, defined by New York Heart Association functional classes (NYHA I-IV) with and without stroke, plus death was used to estimate the CE of TAVI versus surgical aortic valve replacement for intermediate- and high-risk patients, and versus medical treatment for inoperable considering the INHS perspective, over a mid- (5 years) and long-term (15 years) horizon. Patients transitioned between health-states and experienced procedural complications and follow-up events. In the base-case analysis: clinical data were derived from the PARTNERS trials (and extrapolation from them); total direct costs (in EUR) were estimated from national tariff and quality-adjusted-life-years (QALY) were derived in each risk-group to calculate incremental cost-effectiveness ratio (ICER) in each risk group. A real-life scenario was modelled over a 5-years' time horizon combining data from the PARTNER trails with expert opinions of clinicians from four Italian clinical centres and including post-intervention rehabilitations. All outcomes and costs were discounted at 3% per annum. One-way (OWSA) and probabilistic (PSA) sensitivity analyses were performed to assess robustness of results. In the base case analysis and considering a 5-years' time horizon costs and QALY were always higher for TAVI with higher costs for index hospitalization being partly offset by costs of patients' managements and follow-up events. Additional costs for TAVI increased according to patients' risk ranging from about € 4,000/patient to about € 11,000/patient, for intermediate-risk and inoperable groups respectively, similarly for QALY. ICERs were higher in intermediate-risk

patients while decreased in high risk inoperable. Results appeared consistent at PSA and mortality was among the main drivers in OWSA. When considering a 15-years' time horizon differences in costs and QALY increased accordingly to patients' risk. Results of the CE analysis over a long-term horizon showed ICERs quite homogenous all over risk-groups. In fact, over that time frame the increasing trend of ICERs was not observed because differences in the incidence of clinical events between TAVI and comparator were diluted in the long-term horizon. When considering the real-life scenario and including rehabilitation, that strongly impact on direct costs especially SAVR, additional costs for TAVI were less than 1,000 €/patient in both intermediate- and high-risk patients and were about 11,000€/patient among inoperable. ICERs for the intermediate- and high-risk groups were well below the conventional thresholds. PSA showed high probability of TAVI being-cost effective or even dominant among intermediate- and high-risk patients. At OWSA mortality remained one of the most important drivers of results. Results of the CE analysis performed show that considering the Italian National Health Perspective TAVI would be considered cost-effective at frequently cited willingness to pay thresholds in Europe. Similar conclusions emerged over a range of analyses performed considering different time horizons and also modelling real-life scenarios to better depict the context, current technologies and improved learning curves with respect to the literature. Further studies may help shading light about CE of TAVI in real-life scenarios and even considering real costs.

FIGURE 2

STRUCTURE OF THE MODEL OF LORENZONI ET AL [7].



1.5.2 Resource utilization

According to the estimates obtained by four Canadian centers, the average intra-hospital cost associated with a TAVI intervention in Quebec was \$38,911. These estimated results illustrated that the cost of acquiring the implant represented, on average, the largest cost component. However, given that this cost component was relatively not variable across the sample, its importance may fluctuate depending on the patient examined. In conclusion, the results of this evaluation made it possible to determine that the portion related to the acquisition of the implant represents 60% of this amount. The costs related to the fees of treating physicians and the total cost to one year following the TAVI intervention must be added [62].

1.6 ORGANIZATIONAL ASPECTS

1.6.1 Education and training of the staff

General re-organisation and a specific training are necessary to adopt a new technique. Different studies state that it is premature to discuss the organizational prerequisites for a nationwide TAVI interventions program. It requires a learning curve in the procedural success and international experts stress the importance of a collaboration among interventional cardiologists/paediatricians, surgeons and anaesthesiologists. These procedures clearly are technical challenges that can only be considered by clinicians and cardiology teams with special expertise. Few centres worldwide have substantial experience with these interventions. Furthermore, a reduction in procedure related mortality has been reported to be related to professional experience, although it is not clear whether this is due to improved skills or to different patient selection. The adoption of new technology has to represent a new opportunity of care for patients and a new opportunity to improve for healthcare professionals, but it is important that, mainly, the decision do not translate in a waste of resources and do not cause damages to patients. Indeed, a surgeon's skill and ability to perform a procedure is irrelevant if the procedure should not be done in the first place [2].

In particular, the first operator must be experienced in balloon valvuloplasty,

catheterising procedures, biologic valve implantation procedures and trained to use the valve-delivery system. The training course and a minimum of 24 cases to treat per year are indispensable for issuing of the kits by the manufacturer. The procedure must be performed by a multidisciplinary staff (cardiac surgeon, interventional cardiologist, anaesthetist, operating room assistant, ecographist), previously trained in the specific centres [15].

1.6.2 Process-related Costs

Hybrid operating rooms are also rapidly gaining popularity as a (costly) environment technology for TAVI. Hybrid ORs with their interdisciplinary capabilities are advertised as both catheter lab and operating room. The acquisition costs are stated as 1 million euros, with a patient volume of 1,200, amortizable in 3-5 years. So, to work economically, a high patient turnover is necessary.

Estimates of consequences and costs, advantages and disadvantages are listed below [63]:

- Opportunity of conversion from a percutaneous to an open procedure, rapidly;
- High cost (including the interdisciplinary team). For this reason, a "business plan" for the use of the hybrid operating room is also proposed;
- There is a large amount of space ($\geq 80 \text{ m}^2$);
- The ideal positioning of the C-arm of the CT is still unclear;
- Risk of radiation exposure to personnel, in particular those working close to the C-arm (including anaesthesiologists), must be observed and reduced;
- Higher risk of infection;
- Cross-training of the interdisciplinary team and team rotation, as well as rotation of different tasks;
- Multiple information on angiography, echocardiography and hemodynamic monitoring on both sides of the operating table.

Patient selection for TAVI should be undertaken by a multidisciplinary team, including a cardiologist, cardiac surgeon and cardiac anaesthetist [1,2,25,27,34,57,64].

In Quebec, about 20% of medical records

did not record any documentation related to a surgical consultation [62].

According to HTA report performed by CONITEC [57], it was developed an analysis of budgetary impact (BIA), in order to simulate the financial impact of the introduction of TAVI in the private healthcare system. This analysis was performed by comparing the cost of the first years of treatment of inoperable patients with severe AS. Thus, the budgetary impact of this new technology compared the cost of acquisition of the valve bioprosthesis (for this group of patients) with the other current treatment option. The BIA demonstrated that, in the current scenario, the estimate of total expenditures over the time horizon of five years would be approximately R\$ 56.9 million. Both hypothetical (baseline and alternative) scenarios showed increases in budgetary impact. In the baseline scenario, in which the distribution of TAVI values was obtained from the expert panel, the budgetary impact was R\$ 127 million over five years. In both hypothetical scenarios, the budgetary impact is due primarily to the cost of the valve prosthesis for transcatheter implantation, accounting for approximately 43% of total costs in the baseline scenario, when compared to other costs analyzed in the model (hospitalization and medication expenses, among others). In the alternative scenario, the valve prosthesis was responsible for approximately 55% of the costs, since its market distribution would be higher in that scenario.

1.7 SOCIAL AND ETHICAL ASPECTS

Healthcare Improvement Scotland is committed to equality and diversity in

respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex and sexual orientation. The assessment conducted [1,2] showed that not adverse impact across any of these groups was expected.

Furthermore, in the environmental scan reported by Morrison, it was observed that, in order to define a technology really impactful, there must be a reasonable probability that quality of life (related to functional capacity, autonomy, and activities of daily living/ domestic activities) would significantly improve following the procedure and be maintained for at least 1 year [65].













1.8 SYNTHESIS OF EVIDENCE OF HTA REPORTS

Synthesis and validation of evidence published after 2014 have been reported in table below.

Generalizability, Robustness and Internal coherence have been evaluated of HTA report published before 2014 for each domain of Core Model. In particular:

- Robustness: represents the evaluation of how much of the results can be influenced by changes in the methods and models used;
- Generalizability: represents the external validity of the conclusions drawn from a study and therefore if the results of the study can be adapted to other contexts;
- Internal coherence: represents the quality of the study in terms of application of the HTA methodology.

TABLE 1

| SYNTHESIS AND VALIDATION OF EVIDENCES | | | | |
|---|--|--|---|---|
| Domains | Results - Key Points | Robustness | Generalizability | Internal coherence |
| Health problem and current use of the technology | <ul style="list-style-type: none"> Aortic stenosis (AS) is a congenital or acquired aortic valve disease, that occurs when the heart's aortic valve narrows. Aortic valve stenosis can occur due to many causes, including congenital heart defect, calcification, rheumatic fever. Generally, signs and symptoms of AS develop when the narrowing of the valve is severe. After the onset of symptoms, the prognosis could be potentially lethal for patients without treatment. The average survival rate, since the symptoms' onset, is equal to 50% at 2 years and 20% at 5 years [2]. Epidemiological studies established that the probability to develop moderate or severe aortic stenosis is higher than 1/8 among people over 75 [9]. Currently, there is no effective pharmacological treatment to definitely solve this disease; to date the aortic valve replacement surgery is the reference procedure worldwide suggested in several guidelines. Minimally invasive surgery techniques have been recently introduced for this category of patients, such as the transcatheter aortic valve implantation (TAVI). |  |  |  |
| Technical features of the technology | <ul style="list-style-type: none"> Transcatheter aortic valve implantation (TAVI) is a less invasive alternative to open cardiac surgery for treating aortic stenosis, avoiding the need for sternotomy and cardiopulmonary bypass. Transcatheter access to the aortic valve is achieved mainly by the retrograde transfemoral (TF), transapical (TA) or transaxillary/subclavian routes. The TA and transaxillary/subclavian routes have developed as alternative approaches for patients with peripheral vascular disease that precludes femoral access. The TA procedure involves a mini-thoracotomy to gain access to the aortic valve through the apex of the left ventricle and hence is not strictly percutaneous. |  |  |  |
| Safety and Efficacy | <ul style="list-style-type: none"> Evidence showed that trans-catheter aortic valve implantation has statistically significant clinical benefits compared to standard therapy or conventional surgical aortic valve repair. Long term success and complication rates of the procedure are uncertain. Strict patient and procedural access selection are critical for a successful trans-catheter aortic valve implantation procedure. Evidence from systematic reviews and RCTs showed that reduced or maintained the risk of all-cause death, all strokes and rehospitalization rate in patients with severe aortic stenosis is at all levels of risk for open surgery. |  |  |  |
| Costs and economic aspects | <ul style="list-style-type: none"> Actually, there are numerous evidences about cost-effectiveness rate of TAVI procedure. Orlando et al. purposed a model to evaluate the cost-effectiveness of TAVI compared with standard therapy in patients who require aortic valve replacement but are high risk or not fit for conventional surgery (SAVR). The base-case results showed TAVI as expensive but more effective than the medical management, with an ICER of £12,900 per QALY [14]. Also, an US study evaluated the cost-utility of TAVI compared with standard care in patients with severe AS that are ineligible for conventional surgical aortic valve replacement. The results of the study found that TAVI generated an additional 1.3 QALYs, and at an increased cost of \$79,837. As such, the incremental cost effectiveness of TAVI was estimated to be \$61,889 per QALY. Different studies and institutions provide information about resource consumption related TAVI procedure. In particular, the cost of the Edwards Sapien valve with Ascendra delivery system kit is equal to € 28,000 (+VAT at 4%). The management and costs of personnel training is currently borne by the manufacturer. Clearly, it generates increased costs due to required investment [15]. In detail, resource utilization, in terms of economic impact, is estimated at around 24,000€/intervention. |  |  |  |

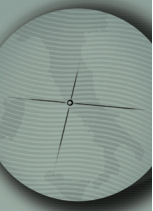


TABLE 1

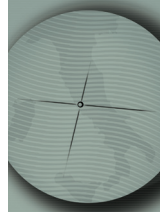
| SYNTHESIS AND VALIDATION OF EVIDENCES | | | | |
|---------------------------------------|--|------------|------------------|--------------------|
| Domains | Results - Key Points | Robustness | Generalizability | Internal coherence |
| Organizational aspects | <ul style="list-style-type: none"> • General re-organisation and a specific training are necessary to adopt a new technique. Different studies state that it is premature to discuss the organizational prerequisites for a nationwide TAVI interventions program. It requires a learning curve in the procedural success and international experts stress the importance of a collaboration among interventional cardiologists/paediatricians, surgeons and anaesthesiologists. These procedures clearly are technically challenges that can only be considered by clinicians and cardiology teams with special expertise. • Few centres worldwide have substantial experience with these interventions. • TAVI adoption produces an increase in requirement of instruments and a limited use only to specific circumstances. The procedure is generally performed in a hospital. In fact, the procedure must be performed in the appropriate settings that allow a multidisciplinary approach and patient safety, such as a surgical or hybrid operating room (sterilised and equipped). A cardiology room with a haemodynamics laboratory and cardiosurgery are required [15]. | | | |
| Social and ethical aspects | <ul style="list-style-type: none"> • Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex and sexual orientation: not adverse impact across any of these groups was expected. • Morrison [65] observed that, in order to define a technology really impactful, there must be a reasonable probability that quality of life (related to functional capacity, autonomy, and activities of daily living/domestic activities) would significantly improve following the procedure and be maintained for at least 1 year [65]. | | | |

1.9 SYNTHESIS OF EVIDENCE PUBLISHED AFTER 2014

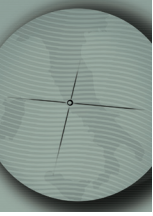
Synthesis and validation of evidence of metanalysis, systematic review, registries studies and RCT have been reported in table below.

Generalizability, Robustness and Internal coherence have been evaluated the evidence published after 2014.

Appendix II shows the summary of the evidence of HTA reports published after 2014.



| Domains | Type of evidence published after 2014 | Results - Key Points | Robustness | Generalizability | Internal coherence |
|------------------------------|---|---|------------|------------------|--------------------|
| | HTA report | <p>TAVI was not inferior to surgical aortic valve replacement (SAVR) comparing with the death for other cause after 1 year in candidates for surgery who were at high risk of operative complications and death in patients with aortic stenosis at high surgical risk.</p> <p>TAVI significantly reduced the risk of death from any cause after 1 year compared with medical management of patients who were unsuitable candidates for surgery” [35].</p> <p>The current evidence on the safety and efficacy of transcatheter aortic valve implantation (TAVI) for aortic stenosis is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent, and audit.</p> <p>In 2018, CADTH in a rapid response report have evaluated inoperable and high-risk patients. The main results were summarized as follow: Reduced risk of all-cause death and rehospitalization while maintaining the similar risk of all strokes up to 5 years and similar risk of major bleeding and new pacemaker implantation at 2 years. Increased risk of major vascular complications up to 1 year for inoperable patients. Regarding high risk patients, TAVI Maintained similar risk of all-cause death, all strokes, rehospitalization while reducing the risk of major bleeding up to 5 years. Increased risk of moderate or severe regurgitation for up to 5 years. Risks of all-cause mortality and rehospitalization at 5 years were less with TAVI-TF than TAVI-TA [37].</p> | | | |
| Safety & Efficacy | Systematic Reviews and Metanalyses | <p>Despite the higher device success rate with the balloon-expandable valve, 1-year follow-up of patients in CHOICE (Randomized Comparison of Transcatheter Heart Valves in High Risk Patients with Severe Aortic Stenosis: Medtronic CoreValve Versus Edwards SAPIEN XT Trial), with limited statistical power, revealed clinical outcomes after transfemoral transcatheter aortic valve replacement with both balloon- and self-expandable prostheses that were not statistically significantly different [38].</p> <p>Among patients with high-risk aortic stenosis undergoing TAVR, the use of a balloon-expandable valve resulted in a greater rate of device success than use of a self-expandable valve [39].</p> <p>Valve performance and cardiac hemodynamic are stable after implantation in both SAPIEN TAVR and SAVR in patients alive at 5 years. (THE PARTNER TRIAL: Placement of Aortic Transcatheter Valve Trial [PARTNER]; NCT00530894) [41,42].</p> <p>TAVR is more beneficial than standard treatment for treatment of inoperable aortic stenosis. TAVR should be strongly considered for patients who are not surgical candidates for aortic valve replacement to improve their survival and functional status. Appropriate selection of patients will help to maximise the benefit of TAVR and reduce mortality from severe comorbidities [43].</p> <p>TAVR as an alternative to surgery for patients with high surgical risk results in similar clinical outcome [44].</p> <p>TF-TAVI using the SAPIEN 3 THV in patients at intermediate risk for surgery is associated with a very low risk of death and complications, including new pacemakers and paravalvular leaks. Although compelling, these initial results are being confirmed in larger global studies before expanding the indications for TAVI in severe aortic stenosis [45].</p> <p>Rates of CVE, perioperative mortality and PPI were similar between the two valves. Implantation of the S3 prosthetic valve results in lower rates of moderate to severe PVR, MVC, post dilation and serious bleeding however it does not improve on the SXT in terms of CVE, PPI and early mortality [46].</p> <p>Compared with SAVR, TAVI may have similar or better early and midterm outcomes for adults with aortic stenosis, including those at low to intermediate risk [47].</p> <p>TA-TAVI may be associated with worse perioperative and midterm all-cause mortality than TF-TAVI, which was robust in sensitivity analyses without publication bias. One of meta-regression analyses would indicate that as proportion of men increases, TF-TAVI is more beneficial in reducing midterm mortality. Results of the following adjusted observational studies and meta-analysis could explain the survival benefit for TF- over TA-TAVI demonstrated in the present metanalysis [48].</p> | | | |



| Domains | Type of evidence published after 2014 | Results - Key Points | Robustness | Generalizability | Internal coherence |
|---|---------------------------------------|--|------------|------------------|--------------------|
| Safety & Efficacy | Registries | <p>Primary endpoint: all cause of mortality at 1 year.</p> <p>Secondary endpoints: major vascular complications, stroke, acute kidney injury, new permanent pacemaker insertion, myocardial infarction, and clinical improvements in symptoms, quality of life (QOL), Kansas City Cardiomyopathy Questionnaire (KCCQ) responses [49].</p> <p>Primary endpoints: all cause of mortality, cardiac death, stroke.</p> <p>-Secondary endpoints: major vascular complications, major and life-threatening bleeding, acute kidney injury, permanent pacemaker insertion, procedure- and device-related complications, functional status, and echocardiographic assessment of the valve and heart function [50].</p> <p>The main outcome measures were all-cause death, cardiac death, and stroke.</p> <p>-Secondary measures included major vascular complications, major and life-threatening bleeding [51].</p> <p>Outcomes measured in the SOURCE 3 Registry were: all-cause death, cardiac death, stroke, disabling stroke, major vascular complications, life-threatening bleeding, myocardial infarction, acute kidney injury (I-II), new-onset atrial fibrillation, permanent pacemaker insertion, procedural complications, functional status, and echocardiographic assessment of valve function [52].</p> <p>One-year clinical outcomes: All-cause mortality; Cardiovascular mortality; Stroke; Disabling stroke; Transient ischaemic attack; Myocardial infarction; New onset of atrial fibrillation; New permanent pacemaker; Endocarditis; Valve thrombosis; Re-hospitalisation [53].</p> <p>Assessed outcomes (at 30 days and at 1 year): all-cause mortality, cardiac death, incidence of strokes, disabling stroke, rehospitalisation, myocardial infarction, life-threatening or disabling bleeding, major vascular complication, acute kidney injury (stage 3), new atrial fibrillation, new permanent pacemaker, endocarditis and aortic valve re-intervention at 1 year after implantation [54].</p> | | | |
| Cost and economic evaluations published after 2014 | | <p>The incremental cost-effectiveness ratio of TAVI versus AVR was €119,575/QALY. The cost-effectiveness acceptability curve indicated that for an acceptability threshold of €30,000/QALY, the standard usually accepted in Spain, the probability of obtaining an incremental net benefit greater than zero for the TAVI alternative compared to AVR was 39% [55].</p> <p>Results of the CE analysis performed by Lorenzoni et al show that considering the Italian National Health Perspective TAVI would be considered cost-effective at frequently cited willingness to pay thresholds in Europe. Similar conclusions emerged over a range of analyses performed considering different time horizons and also modelling real-life scenarios to better depict the context, current technologies and improved learning curves with respect to the literature. Further studies may help shading light about CE of TAVI in real-life scenarios and even considering real costs [7,58].</p> <p>Among intermediate-risk AS patients, TAVR is projected to be economically dominant by providing both greater quality-adjusted life expectancy and lower long-term costs compared with SAVR. If long-term data demonstrate comparable late mortality with TAVR and SAVR, these findings suggest that TAVR may be the preferred treatment strategy for intermediate-risk AS patients based on both clinical and economic considerations [58].</p> | | | |

1.10 CONCLUSIONS

Aortic stenosis is a congenital or acquired aortic valve disease, which occurs when the heart's aortic valve narrows. It represents the most common valvular disease, implying the progressive and rapid development of a heart failure. Currently, there is no effective pharmacological treatment to solve this disease definitely; to date the aortic valve replacement surgery is the reference procedure worldwide suggested in several guidelines. Minimally invasive techniques have been recently introduced for this category of patients, such as the transcatheter aortic valve implantation (TAVI). Evidence showed that trans-catheter aortic valve implantation has significant clinical benefits compared to standard therapy or conventional surgical aortic valve repair. Long-term success and complication rates of the procedure are uncertain. Different studies and institutions provide information about resource consumption related TAVI procedure. Regarding to cost-effectiveness evaluation, Orlando et al. purposed a model to compare TAVI with standard therapy in patients who require aortic valve replacement but at high risk or not fit for conventional surgery (SAVR). The base-case results showed TAVI as expensive but more effective than the medical management, with an ICER of £12,900 per QALY. Comparing with the surgery, in high-risk candidates, TAVI induced an increase in QALY (0.03) and in cost (€20,397). Thus, the ICER reached € 750,000/QALY. Furthermore, general re-organisation and a specific training are necessary to adopt a new technique. Indeed, the procedure must be performed in the appropriate settings that allow a multidisciplinary approach and patient safety, such as a surgical or hybrid operating room (sterilised and equipped). In order to compare the different evidences included in this report, Table 3 summarizes and evaluates

various aspects: robustness, generalisability and internal coherence. In detail, the *robustness* of the evidence is evaluated considering the systematicity of the methods used (search engines and agencies consulted, selection process defined, and inclusion/exclusion criteria adopted); the outputs of an HTA process can be considered *generalizable* if their results are valid even in different contexts compared to original, without needing any adjustment; finally, the *internal coherence* of the reports is evaluated between the methodology and rationale specified and results and conclusions reported. The general assessment shows that, except for organizational, ethical and social aspects, the domains identified according to the EuNetHTA Core Model® 3.0 have been discussed and argued in each item. Therefore, despite the heterogeneity of the different reports, the achievement of a good level of knowledge has been demonstrated about TAVI procedure in the international setting, to the point that the scientific literature about it seems to have been sufficiently argued and discussed in every respect. In this context, as shown in the report, it is important establishing guidelines on the use of TAVI in the clinical practice. The evidence supporting this technology are wide; as above described in this document, many HTA reports have been developed, with varying degrees of robustness of the selected evidence. It would be important, in the general context of HTA, consistent with the approach proposed by this methodology try to consider exclusively reports with a high and consistent degree of evidence. The latter are the only which should be taken into consideration, having a "less is more" approach. ALTEMS having reviewed most of the above evidence, recommends the use of TAVI in the patients' subgroups considered in this report as an effective and safe alternative. Further evidence would be necessary in order to investigate on the long-term period safety and efficacy in other target patients' subgroup.



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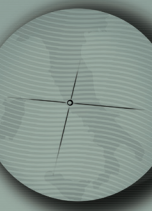
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WEBSITES

http://www.inahta.org/wp-content/uploads/2014/04/INAHTA_HTA_Checklist_English.pdf





Appendix I: assessment elements

| Domain | Topic | Issue |
|--|-------------------------------------|---|
| Health Problem and Current Use of the Technology (CUR) | Target Population | What is the target population in this assessment? |
| | | How many people belong to the target population? |
| | Target Condition | What is the disease or health condition in the scope of this assessment? |
| | | What are the known risk factors for the disease or health condition? |
| | | What is the natural course of the disease or health condition? |
| | | What are the symptoms and the burden of disease or health condition for the patient? |
| | Current Management of the Condition | How the disease or health condition is currently managed according to published guidelines and in practice? |
| | Utilisation | For which health conditions and populations, and for what purposes is the technology used? |
| | | How much are the technologies utilised? |
| | | What kind of variations in use are there across countries/regions/settings? |
| Description and technical characteristics of technology (TEC) | Features of the technology | What is this technology and the comparator(s)? |
| | | What is the claimed benefit of the technology in relation to the comparators? |
| | Regulatory Status | For which indications has the technology received marketing authorisation or CE marking? |
| | | What is the reimbursement status of the technology? |
| Safety (SAF) | Patient's safety | How safe is the technology in relation to the comparator(s)? |
| | | How does the frequency or severity of harms change over time or in different settings? |
| | Safety risk management | Can different organizational settings increase or decrease harms? |
| | | How can one reduce safety risks for patients (including technology-, user-, and patient-dependent aspects)? |
| Efficacy (EFF) | Mortality | What is the expected beneficial effect of the technology on mortality? |
| | Morbidity | How does the technology affect progression (or recurrence) of the disease or health condition? |
| | Function | What is the effect of the technology on return to previous living conditions? |
| Organisational aspects (ORG) | Health delivery process | How does the technology affect the current work processes? |
| | | What is the process ensuring proper education and training of the staff? |
| | Process-related costs | What are the processes related to purchasing and setting up the new technology? |
| | | What are the likely budget impacts of implementing the technologies being compared? |

| Domain | Topic | Issue |
|--|--|---|
| Costs and economic evaluation (ECO) | Resource utilization | What types of resources are used when delivering the assessed technology and its comparators (resource-use identification)? |
| | | What amounts of resources are used when delivering the assessed technology and its comparators (resource-use measurement)? |
| | Measurement and estimation of outcomes | What is (are) the measured and/or estimated health-related outcome(s) of the assessed technology and its comparator(s)? |
| | Examination of costs and outcomes | What are the estimated differences in costs and outcomes between the technology and its comparator(s)? |
| Social and Ethical aspects | Beneficence/ nonmaleficence | What are the known and estimated benefits and harms for patients when implementing or not implementing the technology? |
| | Justice and Equity | How does implementation or withdrawal of the technology affect the distribution of health care resources? |
| | | Are there factors that could prevent a group or person from gaining access to the technology? |

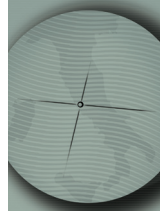


Appendix II: table of contents

| Report included | Year | Country | Health problem and current use of the technology | Technical features of the technology | Safety and Effectiveness | Costs and economic aspects | Organizational aspects | Social and ethical aspects |
|-----------------|------|---------|---|---|--|----------------------------|------------------------|----------------------------|
| CADTH [37] | 2018 | Canada | <p>Aortic stenosis is a pathological condition in which progress sive failure of the aortic valve to open fully leads to syncope, angina, heart failure, and sudden death; if left untreated, most patients will die within five years.¹ Aortic stenosis is the most common type of valve disease affecting close to 3% of patients older than 75.^{1,2} Treatment options for severe aortic stenosis include standard medical therapy or surgical treatment such as surgical aortic valve replacement (SAVR). Transcatheter aortic valve replacement (TAVR), or transcatheter aortic valve implantation (TAVI), was originally developed as an alternative to SAVR for patients with extremely high surgical risk (Society of Thoracic Surgeons predicted risk of mortality [STS PROM]³→15%), or high surgical risk (STS PROM 8% to 15%). A recent prevalence and distribution study on the general population age 60 years or older estimated 3.2 million people around the world have severe aortic stenosis, with 1.9 million eligible for SAVR. Of the patients eligible for TAVR, over 485,000 are high surgical risk or inoperable patients age 75 or older, over 152,000 are intermediate surgical risk age 75 or older, and over 378,000 have low surgical risk and are age 65 or older. In Canada, an estimated 95,691 people have severe aortic stenosis, with 56,225 of these eligible for surgical aortic valve replacement.</p> | <p>There are three commercially available systems for TAVI: Edwards SAPIEN (LifeSciences, Irvine, CA, US), CoreValve (Medtronic, Minneapolis, MN, US), and Acurate Neo (Boston Scientific, Marlborough, MA, US). Currently, the two most common approaches for TAVI are transfemoral (TF) and transapical (TA) procedures, but other non-transfemoral (non-TF) approaches such as direct aortic (DA) and transsubclavian (TS) routes are also used.</p> | <p>A previous CADTH report in 2013 has found that, in general, for patients with severe aortic stenosis with high surgical risk, TAVI was similar to SAVR with respect to mortality rate, symptom reduction, pacemaker implantation rate, and valve hemodynamic improvement at two years follow up, but major vascular complications and aortic valvular regurgitation were more common after TAVI.¹⁴ Observational studies have shown that in intermediate risk patients TAVI is associated with low mortality, stroke, and regurgitation at one year. Canadian, American and European documents recommend the use of TAVI in patients with severe aortic stenosis who are at higher risk from open surgery.¹⁶⁻¹⁸ With TAVI use extended to patients with intermediate risk (STS PROM 4 to 8%), and low risk (STS PROM <4%) with open surgery, a review of the evidence on the clinical effectiveness of TAVI compared to standard therapy or SAVR in patients with different risk levels is timely to guide patient selection. This Rapid Response report aims to review the comparative clinical effectiveness and safety of TAVI compared to SAVR for severe aortic stenosis in inoperable (extreme high risk), high, intermediate, and low surgical risk patients.</p> | N.A. | N.A. | N.A. |

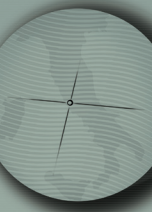
| Report included | Year | Country | Health problem and current use of the technology | Technical features of the technology | Safety and Effectiveness | Costs and economic aspects | Organizational aspects | Social and ethical aspects |
|-----------------|------|----------|---|--|--|--|--|--|
| NICE [16] | 2017 | England | Aortic stenosis causes impaired outflow of blood from the heart and is usually progressive. The increased cardiac workload leads to left ventricular hypertrophy and heart failure. Symptoms of aortic stenosis typically include shortness of breath and chest pain on exertion. | Different devices are available for this procedure containing material derived from animal sources. | Current evidence on the safety and efficacy of transcatheter aortic valve implantation (TAVI) for aortic stenosis is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit. Mortality rates were high in symptomatic patients. | N.A. | Patient selection should be carried out by an experienced multidisciplinary team, which must include interventional cardiologists experienced in the procedure, cardiac surgeons, an expert in cardiac imaging and, when appropriate, a cardiac anaesthetist and a specialist in elderly medicine. The multidisciplinary team should determine the risk level for each patient and the TAVI device most suitable for them. | N.A. |
| INESSS [62] | 2016 | Canada | Aortic valve stenosis is the third most common cardiovascular disease in adults and the most common heart valve disease in the elderly. After the onset of symptoms such as dyspnea, angina or syncope, the disease progresses rapidly and is accompanied by a limitation of physical activity, heart failure and a high risk of mortality. | N.A. | The 30-day mortality decreased from 6.1% to 4.1%. The rate of intra-hospital stroke at the TAVI intervention centre increased from 2.4% to 4.4%. The incidence of all bleeding and major bleeding decreased from 21.4% to 14.7% and from 12.9% to 8.5%, respectively. The need for a blood transfusion during hospitalization before or after a TAVI intervention decreased from 29.9% to 24.7%, which is still a quarter of patients. These comparisons were not statistically significant. | According to the estimates obtained, the average intra-hospital cost associated with a TAVI intervention in Quebec is \$ 38,911. According to the estimates obtained, the average intra-hospital cost associated with a TAVI intervention in Quebec is \$ 38,911. | | |
| HIS [35] | 2014 | Scotland | AS is the most common native heart valve disease in adults in Europe. Without intervention, patients with severe symptomatic AS have a poor prognosis with an average survival of 2–3 years. It has been estimated that more than one third of elderly patients with severe symptomatic AS in Europe are not referred for SAVR. Patients who are not referred for surgery are more likely to be older than those who are, and more likely to have left ventricular dysfunction and comorbidities. TAVI has been advocated for the treatment of patients who are unsuitable for conventional AVR as the risks of surgery are unacceptably high because of advanced age, frailty and/or the presence of cardiac or non-cardiac comorbidities. | TAVI devices have developed rapidly since the first in-man procedure was reported in 2002. The choice of implantation route depends on patient characteristics as well as the device. The most common approach is the TF route. The subclavian/transaxillary, TA and as alternative approaches for patients with peripheral vascular disease that not allow the access through the femoral artery. | In the PARTNER A trial, TAVI was not inferior to SAVR with respect to death from any cause after 1 year in candidates for surgery who were at high risk of operative complications and death. No difference in all-cause mortality was shown after 2 years of follow up. However, TAVI was associated with a significantly higher incidence of major vascular complications and neurological adverse events including stroke. Major bleeding was less common with TAVI, but moderate to severe paravalvular regurgitation was more common compared with SAVR | Two of the six studies demonstrated that TAVI may be cost effective, while the other four studies found that TAVI may be either dominated by AVR or associated with a high cost per QALY. However, considering the intervention costs, the additional procedural cost associated with TAVI does not appear to be offset by reductions in other healthcare costs. Thus, TAVI does not appear to be cost effective for AS patients at high surgical risk (other four studies found TAVI may be dominated by AVR or associated with a high cost per quality-adjusted life year (QALY)). | N.A. | No adverse impact across any of 9 equality groups is expected. |

| Report included | Year | Country | Health problem and current use of the technology | Technical features of the technology | Safety and Effectiveness | Costs and economic aspects | Organizational aspects | Social and ethical aspects |
|-----------------|------|----------|---|--|--|---|---|--|
| HIS [35] | 2014 | Scotland | AS is the most common native heart valve disease in adults in Europe. Without intervention, patients with severe symptomatic AS have a poor prognosis with an average survival of 2–3 years. It has been estimated that more than one third of elderly patients with severe symptomatic AS in Europe are not referred for SAVR. Patients who are not referred for surgery are more likely to be older than those who are, and more likely to have left ventricular dysfunction and comorbidities. TAVI has been advocated for the treatment of patients who are unsuitable for conventional AVR as the risks of surgery are unacceptably high because of advanced age, frailty and/or the presence of cardiac or non-cardiac comorbidities. | TAVI devices have developed rapidly since the first in-man procedure was reported in 2002. The choice of implantation route depends on patient characteristics as well as the device. The most common approach is the TF route. The subclavian/transaxillary, TA and transaortic routes have developed as alternative approaches for patients with peripheral vascular disease that not allow the access through the femoral artery. | In the PARTNER B RCT, TAVI significantly reduced the risk of death from any cause after 1 year compared with medical management in patients who were unsuitable candidates for surgery. However, TAVI was associated with a significantly higher incidence of major vascular complications and neurological adverse events including stroke. | Two out of three UK economic evaluations concluded that TAVI may be cost effective. Conversely, three out of five non-UK analyses suggested that TAVI may not be cost effective. In particular, where TAVI was assumed to be associated with an absolute annual mortality reduction of 220% compared with medical management, TAVI resulted cost-effective. | Patient selection for TAVI should be undertaken by the multidisciplinary team including interventional cardiologists, cardiac surgeons, a cardiac anaesthetist, and an expert in cardiac imaging. | No adverse impact across any of 9 equality groups is expected. |
| OSTEBA [17] | 2014 | Spain | Aortic stenosis caused mainly by degeneration of the aortic valve (calcific aortic stenosis in elderly patients) has become the most common type of heart valve disease in Europe and the United States. Individuals are initially asymptomatic but once symptoms occur, if not treated properly, the prognosis is poor. | N.A. | N.A. | It can be concluded that for the baseline case and an acceptability threshold of 30,000/QALY, TAVI versus AVR in symptomatic patients with severe aortic stenosis considered high risk for AVR, is not cost-effective (119,575/QALY). | N.A. | N.A. |



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| Report included | Year | Country | Health problem and current use of the technology | Technical features of the technology | Safety and Effectiveness | Costs and economic aspects | Organizational aspects | Social and ethical aspects |
|-----------------|------|---------|--|---|---|--|--|----------------------------|
| AVALIA-T [34] | 2014 | Spain | AS is the most common valve disease in developed countries. Its prevalence increases with age (2.8% for over 75). The most common aetiology is degenerative calcification of the aortic valve, associated with advanced age. It can also have a congenital origin (frequently in young adults). Other causes, such as rheumatic fever, are becoming increasingly rare. Mortality is linked to the progression of the disease and the onset of symptoms. After the onset of symptoms, the average survival is 2-3 years, with a high risk of sudden death. The severity of AS is classified into three levels: mild, moderate and severe. | TAVI consists of the placement of the valve prosthesis in the position of the native valve with a catheter. The approach can be performed by percutaneous arterial (usually transfemoral) or through a mini-thoracotomy (transapical route). Actually, there are different devices, although the most used are the Edwards SAPIEN balloon expandable bioprosthesis and the CoreValve self-expanding bioprosthesis (CE marked since 2007). | N.A. | N.A. | The adequate selection of patients is a key factor for the use of TAVI. It is proposed that decision-making for the selection of patients be made within the framework of a multidisciplinary hospital committee with experience in valvular diseases, in which cardiologists participate (clinical and interventional) and cardiac surgeons, and that can count on the participation of other professionals (anaesthetists, geriatricians, specialists in cardiac imaging). | N.A. |
| CONITEC [57] | 2014 | Brazil | Aortic stenosis is a serious disease of accelerated course from symptom onset that may progress to death or serious complications, such as stroke. It is estimated that 3 to 5% of elderly patients over 75 years old may be affected. The gold standard treatment is surgery with prosthetic valve implantation. The disease usually affects elderly patients, who sometimes are not able to undergo surgery due to the presence of advanced comorbidities or anatomical issues (porcelain aorta). In this group of patients, the standard treatment is clinical treatment, with the rare use of balloon aortic valvuloplasty. Survival in this group is small and difficult to estimate. | N.A. | There is only one randomized clinical trial (Partner B) showing an absolute reduction of 24.7% of death in 2 years (68% control x 43.3% TAVI). The intervention increases the risk in the first 30 days after the procedure, especially for death (5% TAVI x 2.8% standard) and stroke (6.7% TAVI x 1.7% standard). | The Markov model presented was considered to be inadequate, making analysis difficult. The applicant estimates the incremental cost-effectiveness ratio (ICER) at BRL 72,520.65/life year gained (LYG). Regarding te budget impact, the applicant estimated an incremental impact in 5 years of 65 million. This value was reviewed, reaching an estimation of BRL 952.963.174.08. | It requires great team expertise and complex structural conditions, such as the hybrid room. Population with restricted survival, likely higher benefit in the subgroup of anatomical indications (porcelain aorta) with no major comorbidities; however, there are no literature data supporting this assessment. The initial recommendation made by CONITEC was against the incorporation of the technology. | N.A. |



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