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Horizon Scanning report N°1

TransApical Transcatheter Aortic Valve Implantation (TA-TAVI)

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Methods:

Agenas is a public body. Its mission is to promote innovations and developments within the Italian national healthcare service and develop a Horizon Scanning (HS) function within healthcare technologies.

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Limitations:

This report is based on information available when the searches were made and does not contain data on subsequent developments or improvements of the evaluated technology. The observations made on effectiveness, safety or cost-effectiveness of the technology evaluated in the report are to be considered temporary.

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Name of technology/procedure: **TransApical Transcatheter Aortic Valve Implantation (TA-TAVI)**

Target population

The procedure of Transapical Transcatheter Aortic Valve Implantation (TA-TAVI) is indicated in patients suffering from severe aortic stenosis with a high risk of death during a conventional surgical procedure. These patients are generally elderly and without treatment have a high risk of death. Their existing co-morbidities influence the risk/benefit ratio of a surgical intervention to replace the aortic valve (cardiopulmonary by-pass, CPB).

Description of the procedure and technology

The surgical procedure consists of the insertion of a prosthetic valve which functionally replaces the damaged aortic valve, using fluoroscopic or ecographically-guided percutaneous procedures. The prosthetic valve (which is made from bovine pericardium) comprises of a metallic frame that is mounted within a delivery system that allows the release and positioning of the valve without sutures and without requiring open heart surgery. Today this procedure can be performed using two different approaches: transfemoral (TF) or transapical (TA). The TF-TAVI is performed through the femoral artery. The TA-TAVI (the object of this report) is performed by carrying out a mini-thoracotomy, delivering the valve through the cardiac apex [Walther, 2009].

Clinical importance and burden of disease

Calcific aortic stenosis is a common condition in western countries, especially among the elderly. Approximately 50,000 valve replacement procedures are performed annually in Europe and the USA. The prevalence of clinically relevant stenosis is approximately 20% in the age range 65-75, 35% in the age range 75-85 and 48% in patients over 85 [Carabello, 2009].

Without treatment, severe aortic stenosis evolves progressively towards a marked symptomatology and complete disability with a mean survival rate of 50% and 20% at 2 and 5 years respectively. [Carabello, 1997, 2002; Lester, 1998].

To prevent irreversible damage to the cardiac muscle, the calcific aortic stenosis requires surgical intervention, replacing the damaged valve with a prosthetic mechanical or biological valve. Depending on the health of the patient (e.g. age and co-morbidities), in some cases a surgical intervention could entail high risk. The condition of the patient can be classified according to the NYHA (New York Heart Association) classes. NYHA is a functional classification system linking the patient's symptoms and his quality of life to normal life activities [www.americanheart.org/].

Operative risk is generally assessed by using two main risk models:

- EuroSCORE: the European System for Cardiac Operative Risk Evaluation calculates the predictive operative mortality of patients that undergo cardiac surgery. For high-risk patients, the more accurate logistic EuroSCORE is used. This model can consider also particular combinations of the risk factors [www.euroscore.org/].

- STS score: it is a risk model developed by the Society of Thoracic Surgeons based on clinical and demographic data in an adult population and used to predict operative mortality and morbidity after cardiac surgery. The model is based on clinical and epidemiological data of a given population who have received cardiac surgery [www.sts.org/].

Although these indicators have been validated for several surgical procedures, they may not be suitable for innovative procedures and emerging technologies such as the TAVI [Osswald 2009; Brown 2008].

Manufacturers, distributors and approval

We identified a single manufacturer of technology for TA-TAVI: Edwards Lifesciences LLC (April 2009). The manufacturer also directly distributes the kit (Edwards Sapien valve with Ascendra delivery system) to the Italian market. The valve, Edwards Sapien 9000TFX gained the CE mark in December 2007 and is available in two sizes with a diameter of 23mm or 26mm. Technical details are available from the Repertorio nazionale Dispositivi Medici (RDM, Italian medical devices inventory). At the time of writing (April 2009) the device has not yet gained FDA (US Food and Drug Administration) approval.

According to the Manufacturer's indications, Edwards Lifesciences LLC the technology *"is indicated for use in patients with symptomatic aortic stenosis (aortic valve area <0.8 cm^2) requiring aortic valve replacement who have high risk for operative mortality, or are "non-operable", as determined by either or both of the following risk assessments: 1) Logistic EuroSCORE >20, or 2) STS Score >10"*.

Currently, other manufacturers are developing technologies for percutaneous valvular replacement: Endoluminal Technology Research; ATS Medical; Hansen Medical; Direct Flow Medical; Sadra Medical; Sorin Group; JenaValve Technology; Heart Leaflet Technologies; ValveXchange; Advanced Bioprosthetic Surfaces [Chiam, 2009].

Manufacturers	Distributors	CE Mark	RDM	FDA
Edwards Lifesciences	Edwards Lifesciences	☑	☑	□

Key: RDM = Repertorio nazionale Dispositivi Medici (Italian medical devices inventory); FDA = US Food and Drug Administration

Setting

The procedure is generally performed in a hospital, in a cardiac operating theatre or a hybrid operating room (sterilised and equipped with specific instrumentations needed for the procedure).

☐ Home	☑ Hospital	☐ Out patients
☐ Accident and Emergency	☐ Other:	

Roll out in Italy

The Edwards Sapien 9000TFX valve with Ascendra delivery system has been on the Italian market since January 2008. Italy is the fourth most important market after Germany, France and the UK. At the 31st of March 2009 104 TA-TAVI procedures have been performed in Italy. The centres that use this technology are distributed in 8 Regions: Campania, Emilia-Romagna, Friuli Venezia Giulia, Lombardia, Piemonte, Puglia, Toscana, Veneto.

☐ Pre-marketing	☐ On the market for 1-6 months	☐ On the market for 7-12 months
☑ On the market for more than 12 months	☐ Not identified	

Comparators

In principle, the main comparators are:

- Pharmacological treatment;
- Percutaneous aortic balloon valvuloplasty;
- Surgical aortic valve replacement;
- Transfemoral transcatheter aortic valve implantation (TF-TAVI).

However, a proper comparator cannot be identified since comparative studies are not yet available. At present, the technology is available to high-risk patients but no published studies have demonstrated that TA-TAVI has better outcomes than conventional surgery. To address this issue, in April 2007 a multi-center randomised trial was started: the Placement of AoRtic TraNscathetER Valve Trial (PARTNER trial, NCT00530894). The study aims to enroll 1040 patients across USA, Canada and Germany. Patients will be allocated to two arms: Arm A with conventional surgery versus percutaneous and transapical treatment; Arm B with percutaneous versus pharmacological treatment [www.clinicaltrial.gov].

Effectiveness and safety

Initial searches were run on the CRD (DARE & HTA) and EuroScan databases to identify English language Horizon Scanning reports and rapid Health Technology Assessment reports on TA-TAVI.

Three reports on *Horizon Scanning* and *rapid Health Technology Assessment* were identified. The reports were produced in Australia [ANZHSN, 2007, update 2008], Belgium [KCE, 2008] and UK [NICE, 2008] during 2007-2008. Another report (written in French) was identified by the manufacturer [HAS, 2007].

The EMBASE, Medline, and Cochrane Library databases were searched, starting from the 1st January 2008. We did not search again for the original studies already assessed in the retrieved HTA reports and simply reported their extraction of data in our table of evidence (table 1). Table 1 reports an example of some of the variables of interest. Type of studies consisted of 2 case-series, the first was a multi-center study carried out across different countries [Walther, 2007, 2008], and one a feasibility study [Svensson, 2008]. This is the only study assessing the use of the equine pericardium valve, the others report the use of bovine pericardium. Five studies were retrieved from other reports (and included in the Table 1): four studies were case-series [Zierer, 2008; Spargias, 2008; Ye, 2008; Walther, 2009], and one study was referred to a prospective register [Rodés-Cabau, 2008]. The number of patients in the studies ranged from 4 to 59 ([Spargias, 2008] and [Walther, 2007] respectively). Three out of eight studies reported outcomes at 12 months of follow-up [Walther, 2008; Ye, 2008; Walther, 2009].

As TA -TAVI is an emerging technology, we analysed “grey literature” (such as registers and abstracts of presentations at meetings) documents, notwithstanding that this kind of literature may be considered less authoritative than peer reviewed published literature. A European register (SOURCE) (started in November 2007) is operating in 12 countries (including Italy) and is managed by the Manufacturer. By October 2008 SOURCE had registered 309 TA-TAVI procedures; 30-days survival was 88.4%. In addition, improvements in NYHA class at 6 months (27 out of the 65 patients treated) were reported in the multicentric study PARTNER EU.

Potential benefits to patients

The technology could potentially allow treatment for high-risk patients that currently do not receive any definitive treatment (e.g., pharmacological therapy) thereby increasing life expectancy.

☑ Mortality reduction or increased survival	☐ Reduction of the morbidity	☐ Improved quality of life (patient/user)
☐ Improved patient monitoring	☐ Other:	☐ Not identified

Cost of the technology/procedure

The cost of the Edwards Sapien valve with Ascendra delivery system kit, is € 28.000 (+VAT at 4%) according to the RDM. The management and costs of personnel training (cardiosurgeon, interventional cardiologist, anaesthetist, operating room assistant, ecographers) is currently borne by the manufacturer.

☐ Increased costs compared to alternative treatments	☐ Increased costs due to increased demand	☑ Increased costs due to required investment
☐ New costs	☐ Other:	

Potential structural and organisational impact

Structural impact

The procedure must be performed in the appropriate settings that allow a multidisciplinary approach and patient safety (such as a surgical or hybrid operating suite). A cardiology room with a haemodinamics laboratory and cardiosurgery suite are required [Vahanian, 2008].

☑ Increase in requirement of instruments	☐ Always be used	☑ Can be used only under specific circumstances
☐ Decrease in requirement of instruments	☐ Other:	☐ Not identified

Organisational impact

The procedure must be performed by a multidisciplinary staff (cardiac surgeon, interventional cardiologist, anaesthetist, operating room assistant, ecographist), previously trained in the centres designated by the Manufacturer (these are in Germany and France). In particular, the first operator must be experienced in balloon valvuloplasty, catheterising procedures, biologic valve implantation procedures and must be 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. These conditions are recommended by the BCIS and SCTS [http://www.improvement.nhs.uk/heart/] and are related to the learning curve observed in the use of the system [Walther, 2008].

☑ Increase in the number of procedures*	☑ Re-organisation required	☑ Training required for users
☐ Reduction in the number of procedures	☐ Other:	☐ Not identified

* defined as the increase of treatment of cases that currently only receive symptomatic treatment.

Conclusions

Transapical transcatheter aortic valve implantation (TA-TAVI) can be considered an emerging technology in Italy and worldwide. TA-TAVI seems to have a positive impact , when used in the appropriate population. However, benefits to the patients must to be confirmed and quantified by further studies with a broader population range and longer follow-up.

The available evidence is mainly referred to case-series in small groups of patients with follow-up periods shorter than 12 months.

Some registers exist or are in a start-up phases: the SOURCE register is operative in Europe; an Italian register is under construction, as well as a regional register in Piemonte (DGR 16-11109/2009). In order to assess the effectiveness of the procedure, The ongoing PARTNER TRIAL should provide further valuable information. The procedure must be performed by a previously trained multidisciplinary staff in high-standard facilities.

Future prospects

- Population: the number of procedures could increase due to extension of indications for use (patients with lower risk profiles) and identification of patients that currently are untreated (for clinical or diagnostic limits).

- Intervention: miniaturization of the current devices (small diameters catheters) and development of new access routes.

- Comparators: launch of other concurrent TA-TAVI technologies and improvement in the current technology.

- Outcomes: improvements in the methods for evaluation of patient status and health outcomes.

Table 1: Description of included studies – Effectiveness and Safety reported in literature.

Ref. [study design]	Inclusion criteria for patients selection	n° (%F, %M)	Age	1) EuroSCORE 2) STS score 3) NYHA class	4) AVA 5) TVG 6) EF	Success of the procedure	Mortality at 30 days	Follow-up (patient survival)		
								30 days	6 months	1 year
Walther et al. 2007 (multicentric) [Cases-series]	Symmetric calcific aortic valve; Age ≥ 75 EuroSCORE > 11% Aortic annulus ≤ 24 mm	59 (74.6%, 25.4%)	81.4 ± 5.8	1) 26.8% ± 13.5% 3) 3.4 ± 0.5	4) 0.5 ± 0.15 cm^2 6) 47% ± 16%	93% (55/59)	13.6% (8/59)	86.4% (51/59)	NR	NR
Walther et al. 2008 (Germany) [Cases-series]	Severe aortic stenosis; Age ≥ 75 EuroSCORE > 11% Aortic annulus ≤ 24 mm	50 (78%, 22%)	82.4 ± 5	1) 27.6% ± 12.2% 2) 15.8% ± 9.1% 3) 3.3 ± 0.5	6) 53% ± 14%	92% (46/50)	8% (4/50)	92% (46/50)	73.9%	71.40%
Svensson et al. 2008 (USA) [Feasibility study]	Severe aortic stenosis; Age ≥ 70 AVA ≤ 0.6 cm^2 STS score > 15%	40 (48%, 52%)	83.0 (69–93)	1) 35.5% ± 15.3% 2) 13.4% (4–47) 3) 3.33 ± 0.47	4) 0.62 ± 0.12 cm^2 5) 40.2 ± 9.8 mm Hg 6) 51.5% ± 15.1%	87.5% (35/40)	17.5% (7/40)	82.5% (33/40) NYHA = 2.25 ± 0.79 AVA = 1.61 ± 0.37 cm^2 TVG = 7.7 ± 2.5 mm Hg EF = 55% ± 19.2%	58.7% NYHA = 2.08 ± 0.51 AVA = 1.49 ± 0.24 cm^2 TVG = 7.4 ± 2.4 mm Hg EF = 58% ± 16.7%	NR
Zierer et al. 2008 (Germany) [Cases-series]	Severe aortic stenosis; Age ≥ 75 EuroSCORE > 20% AVA ≤ 0.8 cm^2 Aortic annulus ≤ 24 mm	26 (77%, 23%)	84.3 ± 6.5	1) 36.5 ± 5.8 3) 3.5 ± 0.4	4) 0.6 ± 0.1 cm^2	96% (25/26)	15% (4/26)	85% (22/26) 5) 6 ± 2 mm Hg	NR	NR
Rodés-Cabau et al. 2008 (Canada) [Prospective reg.]	Severe aortic stenosis	12 (67%, 33%)	81.8 (62–89)	1) 25.4% 3) 3.08	4) 0.62 cm^2 6) 52.3%	NR	0%	NR	NR	NR
Spargias et al. 2008 (Greece) [Cases-series]	Calcific aortic valve; EuroSCORE > 20% STS score > 10% AVA ≤ 0.8 cm^2	4 (50%, 50%)	82.75 (76–86)	1) 45.25% 3) 3.5	4) 0.65 cm^2	100%	0%	100%	NR	NR
Ye et al. 2008 (Canada) [Cases-series]	Symptomatic aortic stenosis; Femoral accesses not suitable for percutaneous procedure;	26 (50%, 50%)	80.1 ± 9.1	1) 37% ± 20% 2) 11% ± 6% 3) II (19%) III (65%) IV (12%)	4) 0.5 ± 0.1 cm^2 5) 44.5 ± 13.7 mm Hg 6) 56% ± 13%	100% (26/26)	23% (6/26)	77% (26/6)	NR	65% (17/26) AVA=1.7 ± 0.5 cm^2 TGV=8.9 ± 5.0 mm Hg EF=63% ± 9% (non sign.)
Walther et al. 2009 (Germany) [Cases-series]	Symptomatic aortic stenosis; Patients that had received other cardiac surgery; EuroSCORE ≥ 9 pts Aortic annulus < 25 mm	25 (60%, 40%)	78 (64–89)	1) 39% (14–72) 2) 18% (6–43) 3) III (III–IV)	NR	100% (25/25)	12% (3/25)	88%	NR	72%

Key: Ref. = reference; n° = number; F = females; M = males; AVA = aortic valvular area; TVG = transvalvular aortic gradient; EF = ejection fraction; reg. = register; NR = not reported.

Evidence searches

Serches were run with the following keywords:
(percutaneous OR transapical) AND (('heart'/exp OR 'heart') AND ('valve'/exp OR 'valve') AND ('prosthesis'/exp OR 'prosthesis')) AND [english]/lim AND [humans]/lim AND [2008-2009]/py

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Glossary

AVA: aortic valvular area, expressed in cm^2.

BCIS: British Cardiovascular Intervention Society.

CPB: cardiopulmonary by-pass.

EF: ejection fraction, expressed as percent.

EuroSCORE: operative mortality risk, expressed as a percent, according to the European System for Cardiac Operative Risk Evaluation.

Grey literature: a body of material produced by organisms (government, academic or industrial) for which publishing is not the main aim. Examples of gray literature include technical reports, working papers, white papers, or preprints.

Mini-thoracotomy: small incision in the intercostal space.

Operative mortality: traditionally, operative mortality has been defined as any death occurring (i) within 30 days after surgery in or out of the hospital, and (ii) after 30 days during the same hospitalization subsequent to the surgery.

NYHA class: functional class of the New York Heart Association.

SCTS: Society of Cardiothoracic Surgeons.

Severe symptomatic aortic stenosis: aortic stenosis is a narrowing of the aortic orifice with subsequent obstruction to blood flow from the left ventricles to the aorta that creates a pressure gradient ≥ 10 mm Hg. Aortic stenosis is defined as “symptomatic severe” when the speed of blood across the stenosis (measured by ecodoppler) is > 4 m/s, the mean transvalvular pressure gradient is > 40 mm Hg, and the aortic orifice area is < 1 cm^2.

STS Score: percent of operative mortality and morbidity after cardiac surgery calculated according to the risk model of the Society of Thoracic Surgeons.

Success of procedure: percent of procedures in which the valve was positioned correctly.

TA-TAVI: TransApical Transcatheter Aortic Valve Implantation.

TVG: transvalvular aortic gradient, expressed as mm Hg.