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The Treatment of Aortic Valve Stenosis in Patients at Intermediate-High Risk

Paolo Nardi*, Marco Russo, Guglielmo Saitto and Giovanni Ruvolo

Cardiac Surgery Division, Tor Vergata University Policlinic, Rome, Italy

***Corresponding author:** Paolo Nardi, Cardiac Surgery Division, Tor Vergata University Policlinic, Viale Oxford 81, 00133 Rome, Italy, Tel: +39 06 20903536; Fax +39 06 20903538; E-mail: pa.nardi4@libero.it

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Abstract

Aortic valve stenosis (AS) is the most common valvular pathology in the elderly with an estimated prevalence of 4.6% in patients older than 75 years. Most of the patients remain asymptomatic for decades and when they develop symptoms, the prognosis became drastically poor with an estimated mortality of 50% in two years without surgical treatment. Aortic valve replacement (AVR) represents the gold standard for treatment of patients affected by aortic valve stenosis. Introduced in 1960s, AVR is associated with excellent long-term outcomes and low perioperative mortality and morbidity. With the aging of population, number of patients with AS increased progressively and the typical patient's profile has become more and more complex with more associated pathology and higher surgical risk. In this complex scenario the introduction of transcatheter aortic valve implantation (TAVI) has profoundly altered the landscape of cardiovascular medicine.

Keywords: Aortic valve replacement; Valvular pathology; Prognosis; Edwards Sapien device

Introduction

Aortic valve stenosis (AS) is the most common valvular pathology in the elderly with an estimated prevalence of 4.6% in patients older than 75 years. Most of the patients remain asymptomatic for decades and when the symptoms develop, the prognosis became drastically poor with an estimated mortality of 50% within two years without surgical treatment [1].

Aortic valve replacement (AVR) represent the gold standard for treatment of patients affected by aortic valve stenosis. Introduced in 1960s, AVR is associated with excellent long-term outcomes and low perioperative mortality and morbidity [2,3].

With the aging of population, number of patients with AS increased progressively and the typical patient's profile has become more and more complex with more associated pathology and higher surgical risk. In this complex scenario the introduction of trans-catheter aortic valve implantation (TAVI) has profoundly altered the landscape of cardiovascular medicine.

Current European and American Guidelines, as well as the FDA protocols, indicate that TAVI is the treatment of choice in "inoperable" patients and a valid option to surgical AVR in patients judged to be at high risk for surgery by a multidisciplinary team. During years TAVI has become more and more popular and similar to what happened after the emergence of coronary stenting procedure, there has been a trend in clinical practice to treat "lower" risk patients, the so called "grey zone" group of patients.

How indications will be expanding in the coming years regarding the treatment of patients affected by AS at intermediate risk for surgery, remains an unsolved issue. Big data show that patients at intermediate risk undergo TAVI: several reports from International Registry and from European centers demonstrate the shift to intermediate-risk patients has already started in the current clinical practice even in absence of guidelines approval and lack in knowledge of clinical results. First-hand data demonstrate comparable results for TAVI and surgery in the grey-risk zone [4]. Technology progresses could change this scenario profoundly in the upcoming years: TAVI devices are going to be modified to reduce the complications occurred in last decade, but on the other hand surgical procedures, also by means of minimal invasive techniques and the introduction of sutureless aortic valve prostheses, seems to guarantee optimal results, even in high risk patients. Large randomized Trials are ongoing with the potential to confirm these early findings in the intermediate-risk cohorts. The PARTNER IIa Trial has enrolled 2,000 intermediate-risk patients with a STS score between 4 and 8 undergoing TAVI using the Edwards Sapien device [5]. The SURTAVI trial, with an estimated subject enrolment of 2,500, includes patients with an STS score ≥3 and ≤10 undergoing TAVI with the Medtronic Core Valve system [6].

Aortic stenosis (AS) is the most common valvular lesion occurring among elderly patients and has become extremely frequent because of changing demographics in industrialized countries with relevant implications both for medical and surgical treatment. Surgical risk after the age of 70 has increased and the continuous increasing of the age and co-morbidities of patients having surgery justifies an accurate analysis of mortality predictive factors to perform the best

treatment. Not only patients have changed in these last years but also the etiology of the pathologic process of the aortic valve.

Now the estimated risk by the Society of Thoracic Surgeons of AVR, in an asymptomatic 70-year-old patient without other co-morbidities, is less than 1% [6], so the surgical approach to these patients is now extended also to the asymptomatic with a rapidly progressive disease (in case of trans-aortic jet velocities >4.0 m/s or heavy valve calcification), abnormal exercise test results, severe left ventricle hypertrophy or an increase in B-type natriuretic peptide. For these reasons, conventional surgery has been considered, for more than 30 years, the gold standard for the treatment of aortic valve stenosis in patients with low risk profile. In this way, natural history of the aortic stenosis has changed over the past 50 years because its pathogenesis has changed and our management strategies, on the basis of better understanding of its pathophysiology, have altered its outcome.

For inoperable patients the emergence of trans-catheter aortic valve implantation (TAVI) profoundly changed the life expectancy of high-risk patients [7,8]. In the last decade, TAVI has been performed in about 150,000 patients worldwide and indications keep growing at a rate of 40% annually.

The PARTNER B investigated the impact of TAVI (or TAVR) on the out-come of symptomatic patients who were considered to have a prohibitive operative risk when assessed by a team of both surgeons and cardiologists, randomizing 358 patients to TAVR versus standard care [9]. In this very high-risk population, TAVR resulted in a 39% reduction in mortality at 1 year (30.7% *versus* 50.7%) compared with the results of standard therapy. The mortality benefit with TAVI persisted at 2 years (43.3% with TAVI and 68.0% with standard therapy). The PARTNER A investigated the impact of TAVR on the out-come of symptomatic patients who were considered high-risk candidates for surgical AVR with an STS score estimated 30-day mortality of ≥10%. In this arm of the trial, in which 699 patients were randomized to TAVI or surgical AVR, TAVR was found to be non-inferior to surgery in terms of late mortality at 1 year (24.2% *versus* 26.8%) and 2 years (33.9% *versus* 35.0%) [10].

For these results from the last Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery the 2012 Guidelines on the Management of Valvular Heart Disease and the corresponding 2014 USA Guidelines trans-catheter aortic valve implantation or replacement (TAVI, TAVR) is recommended in patients with severe symptomatic AS who are not suitable to undergo conventional AVR as assessed by a heart team, if they are likely to gain improvement in their quality of life (QoL) and if they have a life expectancy >1 year given their co-morbidities [Class of Recommendation (CoR) I, Level of Evidence (LoE) B] and should also be considered also in high-risk patients with severe symptomatic AS who are suitable for surgery but in whom TAVI is favored by a Heart Team as a CoR IIa and LoE B recommendation.

The surgery risk could be estimated by online algorithm. The STS score [6], the logistic EuroSCORE [2] and from 2011 the EuroSCORE II [2] are the most commonly used (based on 24, 12 and 18 covariates respectively). These scores identify accurately the low-risk patient, whereas the accuracy is less in the higher-risk population. The main preoperative patient risk factors are need for emergency surgery, presence of endocarditis, and history of previous cardiac surgery.

In general, patients with STS score of >10% or EuroSCORE of >20% are considered to be high-risk, while the moderate-risk can be identified with STS score between the 5% and 10%. Under the 5% we can consider AVR as a low-risk surgery.

There is a lack in the standardization procedure and algorithm to define a high risk or inoperable patient for operative mortality or morbidity. Such risk factors include end-stage liver disease, prolonged preoperative hospital stay, frailty, immobility or poor mobility due to other medical conditions, degree of obesity, significant abnormalities of other valves, severity of peripheral vascular and aortic disease, previous chest wall radiation, previous infected sternotomy, porcelain aorta and degree of lung disease. For these reasons a significant proportion of patients were considered unsuitable for surgical AVR because of factors unaccounted by the STS score, and the role of the "Heart Team" is crucial, especially in some patients with high value of the logistic EuroSCORE (>20%) or of the STS score (>10).

Frailty and related conditions of debility are well-known risk factors for inability to recover from major heart surgery such as AVR. Frailty likely influences both procedural risk and likelihood of clinical improvement after AVR. Qualitative assessment of frailty has long been incorporated into the clinical evaluation of patients considered for AVR, commonly referred to as the eyeball test.

Current Results

The introduction of trans-catheter aortic valve implantation (TAVI) has revolutionized the treatment of patients with symptomatic AS.

Fourteen years after the first TAVI procedure, current international guidelines indicate that TAVI represents the treatment of choice in "inoperable" patients and a valid alternative to conventional surgical aortic valve replacement in high-risk patients.

The current approach to patients affected by aortic valve stenosis takes origin from two major clinical trials that appeared in literature during the last decade.

The Placement of Aortic Transcatheter Valves (PARTNER) Study is a randomized multicenter clinical trial comparing TAVR with standard-of-care treatments in both inoperable and high surgical risk patients with aortic stenosis, published in 2011. The trial analyzed data of patients treated by the use of Edwards Life sciences Sapien Valve in comparison with conventional AVR procedures or optimal medical therapy including valvuloplasty.

The study was composed of two parallel arms and enrolled 1057 patients in a cohort of 3105 potential screened to be included in the study. In the PARTNER A patients, affected by severe aortic valve stenosis, were required to be high risk for conventional open valve surgery by the determination of a minimal Society of Thoracic Surgeons (STS) score of 10% for death, and the surgeons' assessment of the risk as >15%. For PARTNER B, patients approved for the study were required to have 2 cardiac surgeons agree that they were inoperable based on a combined risk of death and irreversible severe morbidity >50%.

In the PARTNER I-A the all-cause mortality at 30 days was slightly lower with TAVI (3.4% *versus* 6.5%, p=0.07), but was similar at one year (24.2% *vs.* 26.8%), at two years (33.9% *vs.* 35%) and at three years (44.2% *vs.* 44.8%) of follow-up. Although the rates of all neurologic events were higher after TAVI at 30 days and at one year (5.5% *vs*. 2.4% and 8.3% *vs.* 4.3%, p<0.05), rates of major stroke were not significantly different between TAVI and surgical AVR (SAVR) at 30 days (3.8% *vs.* 2.1%, P=0.2) or at one year (5.1% *vs*. 2.4%, p=0.07). Otherwise the rate of major vascular complications at 30 days was higher after trans-catheter approach (11.0% *vs*. 3.2%, p<0.001) whereas the surgical treated population presented more major bleeding (19.5% *vs*. 9.3%, P<0.001) and more frequent new-onset of atrial fibrillation (16.0% *vs*. 8.6%, p=0.006).

For PARTNER B trans-catheter aortic valve replacement showed mortality similar to optimal medical therapy at 30 days (5.0% *vs*. 2.8%, p=0.41). Therefore, at 1 year, mortality rates were respectively 30.7% *versus* 50.7% (P<0.001).

Several issues, that remain still controversial, already appeared at the reading of PARTNER I trial: first of all, TAVI procedures were associated with a consistent risk of neurological events procedure-related; in second instance, an increased risk of PVL was associated with trans-catheter approach, and this data correlate with a marked increased mortality during at two-year follow up period (P<0.001), even in cases of just mild aortic PVL.

Recently, results of PARTNER I A at 5 years have become available. The new follow up results assessed a not significant different risk of death between TAVI and SAVR Groups (67.8% *vs*. 62.4%, hazard ratio 1.04, 95% CI 0.86-1.24; p=0.76) and no differences regarding the incidence of major cardiovascular events included re-hospitalization. Exception was made for more bleeding events in surgical Group and more vascular complications in trans-catheter one. Moderate or severe aortic regurgitation due to PVL occurred in 40 (14%) of 280 patients in the TAVR Group *vs.* 2 patients (1%) of 228 in the SAVR Group (P<0·0001); paravalvular leak 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<0.01) **(Table 1)**.

The Medtronic Core Valve (Medtronic Inc, Minneapolis, MN) is a TAVR prosthesis with a self-expanding nitinol frame containing a trileaflet porcine pericardial valve. This valve has been evaluated by the Medtronic Core Valve US Pivotal Trial, published by Adams and co-authors in 2014 [11].

The risk of 1-year mortality was significantly reduced by TAVR with Core Valve (14.2% *vs.* 19.1%; P=0.04) in high risk surgical population; rates of major stroke were similar in the TAVI and SAVR Groups at 30 days (3.9% *vs*. 3.1%) and at one year (5.8% *vs*. 7.0%) while rates of major adverse cardiovascular and cerebrovascular events at one year were significantly lower with TAVI procedure (20.4% *vs*. 27.3%, P=0.03).

Table 1 5-year results of PARTNER trial.

	S-AVR	TAVI	P
Re-hospitalization, %	34	43	0.17
Myocardial infarction, %	5.9	2.9	0.15
Neurological events, %	14.7	15.9	0.35
Vascular complications, %	4.7	11.9	<0.001
Major bleeding, %	34	26	0.003
Definitive PMK, %	9.1	9.7	0.64

The results previously explained have determined the current approach to patients affected by severe aortic valve stenosis and with high or even prohibitive risk for conventional surgical replacement.

Nevertheless several reports have been published during years and large amount of data regarding results of TAVI are available, it remains unclear if it is justified to expand the indication for TAVI to other patient groups, especially intermediate- or even low-risk patients.

Recently, there has been a trend in clinical practice and trials to treat "lower" risk patients even if, evidence based results have not been yet presented in literature.

Two large randomized clinical trials are actually on-going and the awaited results of the PARTNER II with the Edwards XT valve and of the SURTAVI trial with the Medtronic Core Valve will get answers about the use of trans-catheter approach even in patients judged to be at intermediate risk.

Several reports focused on results of different approaches in lower risk patients.

Observational study of effectiveness of AVR-TAVI procedures for severe aortic stenosis treatment (OBSERVANT) study is an Italian report on 7618 patients (5705 surgically treated, 1652 trans-femoral TAVI and 259 transapical TAVI) treated in 34 interventional cardiology centers and 59 cardiac surgery units. In the 30 days analysis were included 266 matched patients with a mean Logistic EuroSCORE of 9.4% in the surgical group and 8.9% in the TAVI Group. The study population were so considered as at intermediate risk for AVR. 30-days mortality was similar for both groups (3.8%) but in the trans-catheter group 30-day analysis showed more aortic regurgitation (6.1% *vs*. 2.3, P<0.01), higher rate of AV blocks requiring PMK

implantation (12% *vs*. 0.8%, P=0.001) and more vascular complications (5.3% *vs*. zero, P=0.007) [12,13]. One year results were obtained using a propensity score matching analysis on 650 couple of patients (650 S-AVR, mean age 80.3 y, Logistic ES 10.3% *vs*. 650 TF-TAVI, mean age 80.5 y, Log. ES 9.3%). In the propensity score matching analysis surgical procedure and trans-femoral trans-catheter procedure results were similar in term of 1-year all-causes mortality (13.8% *vs.* 13.6%), stroke (4.9% and 6.4%), MACCE (17.6% *vs*. 18.2%), new hospitalization (23.6% *vs*. 21.9%). Permanent pacemaker implantation was the only outcome that was significantly higher in the TAVI group (18.5% *vs*. 7.3%, P<0.001).

Now-day, several studies conclude that in real world in patients at surgical intermediate-risk, TAVI and S-AVR have shown comparable results [13-24].

Piazza and Co-workers [14] published a propensity score analysis on 3,666 patients underwent TAVI or SAVR. After the application of PS, 405 pairs of patients were individuated, of whom. 63% (205) had scores between 3% and 8% and so considered as intermediate-risk. During mid-term follow up, 20 TAVI patients (7.8%) and 18 SAVR patients (7.1%) died (HR: 1.12, 95% CI: 0.58 to 2.15, P=NS). Data after 1 year of follow up confirmed the non-inferiority of TAVI vs. surgical procedure (16.5 *vs.* 16.9%, HR: 0.90, 95% CI0.57 to 1.42, P=NS).

Wenavesser and the group of University of Bern studied 389 consecutive patients underwent TAVI. In this population about 65% of patients had STS between 4 and 8% and about 10% were considered at low risk. Compared with high-risk patients, these two subgroups of patients had lower incidence of major bleeding, major vascular complications, and renal function impairment, with a mortality rate at 1 year less than 5% (p<0.001 *vs*. high-risk group of patients). In this series TAVI is patients with STS-defined intermediate or low risk appeared to have favorable clinical outcomes [15].

Less encouraging data comes from the STACCATO Trial [16]. This study was designed a randomized prospective study to compare results of conventional surgery and trans-apical catheter based aortic valve implantation and enrolled a population of 34 TAVI patients (mean age 80.2, Log. EuroSCORE 9.4%, STS Prom 3.1%) and 36 SAVR (mean age 82.4, Log. EuroSCORE 10.4%, STS Prom 3.4%). The two groups was similar in term of major preoperative features and risk profile. The primary endpoint of 30-day all-causes mortality, stroke or renal failure was met in five (14.7%) patients in the TAVI group; one death on the waiting list, one death following treatment for left coronary artery obstruction, two major thromboembolic strokes, and one case of renal failure. In the SAVR group, one (2.8%) patient fulfilled the primary endpoint criterion (a major perioperative thromboembolic stroke). The difference in primary endpoint rates was statistically not significant (P=0.07). For the excess of adverse events in the TAVI group compared to surgical one, the STACCATO trial was prematurely terminated. These results suggest that a-TAVI in its present form may be associated with complications even similar or higher in comparison with those observed in high-risk patients **(Tables 2 and 3)**.

Table 2 In-hospital results of the OBSERVANT study.

	SAVR (Age 80.3 y)	TAVI-TF (Age 80.5 y)	P-Value
Mortality, %	3.8	3.2	0.5
Stroke, %	2.2	2.3	0.18
Acute renal failure, %	10.9	6.1	0.004
Major vascular complications, %	0.5	7.0	<0.001
Permanent PMK, %	3.6	15.5	<0.001

Table 3 1-year results of the OSERVANT study.

	SAVR (Age 80.3 aa)	TAVI-TF (Age 80.5 y)	P-Value
Mortality, %	136	13.8	0.91
Stroke, %	4.9	6.4	0.243
MACCE, %	17.6	18.2	0.796
Re-hospitalization, %	23.6	21.9	0.473
Need for permanent PMK, %	7.3	18.5	<0.001

Surgical approach to aortic valve disease was recently improved by the introduction of a new tool as the sutureless valve prostheses: the quicker implantation allows to obtain shorter cardiopulmonary bypass and cross-clamp times with a significant reduction of the detrimental effects, especially in frail patients. Moreover, the use of a sutureless prosthesis

permits an easier approach to minimally invasive aortic valve surgery, by means of mini-sternotomy or right superior mini-thoracotomy with better results in term of postoperative length of stay, need for transfusion, pain and quality of life. From this basis, the sutureless aortic valve prosthesis has been considered as a valuable tool in the surgical armamentarium especially in high-risk patients and in direct opposition with TAVI.

To better understand the role of sutureless surgical technology Muneretto and Co-Authors [17] have designed a multicenter non-randomized retrospective study with the aim to define the outcome of a cohort of 991 patients from 7 different Centers across Europe, treated by means of conventional surgical AVR, sutureless-AVR and TAVI. After a 1:1:1 propensity score matching, they obtained 204 patients from each treatment group, obtaining 3 homogeneous populations at intermediate- to high-risk profile (mean logistic EuroSCORE I: SAVR 19.2 ± 7.4; sutureless-AVR 18.9 ± 5.9; TAVR 19.5 ± 6.7, STS PROM: SAVR8.3 ± 4.4; sutureless-AVR 7.9 ± 3.2; TAVI 8.2 ± 4.2, p=NS). Thirty-day mortality was significantly higher in the TAVR group (SAVR 3.4% vs. sutureless-AVR 5.8% *vs*. TAVI 9.8%; P=0.005) and at 24 months of follow-up cardiac death was higher in the TAVI group (SAVR 3 patients (1.5%) *vs*. sutureless-AVR 1 patient (0.5%) *vs*. TAVI 8 patients (4.3%), P=0.028). In this series TAVI was associated with higher incidence of onset AV blocks and paravalvular leakage. Furthermore, the use of a sutureless prosthesis showed a significantly reduced incidence of acute renal failure and continuous veno-venous hemofiltration requirement, thus suggesting the potential benefits of this novel surgical option. Moreover, at 24 months survival free from the composite end-point of major adverse cardiovascular events and paravalvular prosthetic regurgitation were significantly lower in patients undergoing surgical aortic valve replacement and sutureless valve implantation than in TAVI group (SAVR 92.6 ± 2.3% vs. sutureless 96 ± 1.8%, *vs*. TAVR 77.1 ± 4.2%, P<0.001).

As we can see international current literature is full of different evidences and surgical results. The optimal surgical or trans-catheter therapy remains unclear. New and clearer criteria for patient selection, new devices and long-term assessment of valve durability should also contribute to clarify the need of an extension of the indication of TAVI to "lower" risk patients. Results of upcoming trial are now necessary.

Indications and devices for AVR and TAVI (or TAVR)

At the present ESC/EACTS 2012 [2] guidelines and AHA 2014 [3] guidelines represent the most up to date and followed in all over the world. In the settings of a severe aortic stenosis (defined as an aortic valve area <0.8 cm^2, a mean pressure gradient ≥40 mm Hg or a maximum aortic velocity ≥4.0 m per second) the indication for treatment depends on the presence of symptoms (Class IB), even detected by means of exercise test (Class IC), or the presence of left ventricular dysfunction with left ventricle ejection fraction less than 50% (Class IC).

Surgical aortic valve replacement represents the gold standard for the treatment of aortic stenosis, especially for patients at low- intermediate risk (Class I A, AHA). Despite, in recent guidelines TAVI is defined as a good option for patient who are not suitable for AVR (STS >50%) as assessed by a 'heart team' and who are likely to gain improvement in their quality of life and to have a life expectancy of more than 1 year after consideration of their co-morbidities" (Class IB, AHA, ESC/EACTS).

The evaluation of the patient's preoperative risk and the establishment of the life expectancy, guides the decision making process that define which should be the better strategy of treatment: TAVI or surgical AVR. The presence of cardiac surgery on site and the evaluation of the patient by a "multidisciplinary heart team including cardiologists, cardiac surgeons and other specialists" is mandatory during the preoperative assessment.

Logistic Euroscore ≥ 20% and STS PROM score >10% usually define a patient as at high risk for surgery. In this case, international guidelines consider TAVI as a valid option when "favoured by a heart team based on the individual risk profile and anatomic suitability" (Class IIa B).

Regarding the treatment of patients at low-intermediate risk, current guidelines state that TAVI should not be performed and clinical trials are a need.

It is very interesting to underline that several contraindications for TAVI are well reported as in **Table 4**. Contraindication are both clinical and technical aspects. The preoperative assessment should study the vascular access and the accessibility of the cardiac apex in case of transapical approach.

In patients not unsuitable for surgery and not judged to be at high risk for conventional surgery according to Logistic Euroscore or STS PROM several factors could pilot the choice in the direction of trans-catheter approach: porcelain aorta, previous CABG, bioprosthesis dysfunction, poor ejection fraction, history of chest irradiation are example that make surgery technically difficult and more at risk that predicted by calculators; moreover factors as frailty which have been demonstrated to be associated with adverse outcomes are not incorporated in current models: in this cases the heart team evaluation is a crucial step to define the fate of the patient.

Furthermore, the role of the Heart Team cannot be limited to pre-operative assessment and choices regarding valve type and access route; the Heart Team is essential to the management of intraoperative complications as well as postoperative care.

Since the introduction in clinical practice in 2002, TAVI has undergone rapid technological advancements with a focus on procedural simplification and limiting complications associated with the early devices.

First data were collected with the balloon-expandable Edwards SAPIEN and SAPIEN XT (Edwards Life sciences, Irvine, CA, USA) and the self-expanding Core Valve® (Medtronic, Minneapolis, MN, USA). Several factors as high rates of PVL as

well as neurological events or peripheral complications determined the rapid development of new devices with modification of both the valve and the delivery system. At the present different TAVI model can be classified regarding the different type of deployment as balloon-expandable, self-expanding or differential device deployment [18-47].

Table 4 Contraindications to TAVI.

Absolute
Absence of Heart Team and Cardiac Surgery on site
Clinical
Life expectancy <1 year
Improvement of quality of life by TAVI unlikely because of comorbidities
Associated valvulopathy that contributes to symptoms that can be treated only by surgery
Anatomical
Inadequate sizing of the annulus (<18 mm, >29 mm)
Left ventricle thrombosis
Active endocarditis
High risk of acute coronary ostia obstruction
Calcific and mobile plaque/s in aortic arch
Inadequate vascular access
Relative
Bicuspid aortic valve
Need of concomitant procedure
Haemodynamic instability
LVEF <20%

The balloon-expandable device as the SAPIEN, SAPIEN XT and the third generation SAPIEN 3, are trileaflet biological cardiac valve sewn inside an expandable stent frame. These valves need balloon inflation and ventricular pacing for the deployment.

The self-expanding devices, as the Core Valve and its evolution (the Core Valve Evolution R), the Portico™ device (St. Jude Medical, St. Paul, MN, USA), The ACURATE neo™ (Symetis, Ecublens, Switzerland), the Biovalve (Biotronik AG, Bülach, Switzerland) and the CENTERA valve (Edwards Life sciences), are biological valves put inside a self-expanding nitinol-based stent frame, crimped inside a delivery capsule that do not need from an adjunctive procedure for relay. The technological evolution makes this repositionable. New delivery systems are available with more than diameter with less vascular trauma.

The Lotus™ valve (Boston Scientific, Marlborough, MA, USA) and the Direct Flow Medical® valve (Direct Flow Medical, Santa Rosa, CA, USA) are characterized of peculiar type of valve deployment: the first one need a mechanical expansion utilizing the interaction of posts and buckles that are connected to the inner catheter of the delivery system, the second one is composed of two parallel ring that, after the achieving of a good position are fill of a which subsequently solidifies to provide permanent support and position.

The CHOICE trial compared the balloon-expandable with the self-expanding TAVI device (121 Sapien *vs.* 120 Core Valve prostheses): the balloon expandable was related with a higher rate of success (P<0.001) and a lower incidence of permanent pacemaker implantation and paravalvular leak; despite self-expandable shown better results in term of less neurological events, less coronary occlusion and better haemodynamic features. Although these differences, the 30-day mortality was not different. Long-term data on different devices are awaited and at the moment devices are selected on local expertise and patient characteristics.

Conclusion

Currently surgical aortic valve replacement (SAVR), first reported in 1960 by Harken, remains the gold standard for patients at low or intermediate operative risk because this technique is associated with excellent long term outcomes and low perioperative risk. Recently, it has been demonstrated in many publications that patients with symptomatic aortic stenosis who are deemed to be “inoperable” may benefit significantly from TAVI as an alternative to medical management, but in case of intermediate or high risk surgery the appropriate patient selection is a key to improve the patient’s outcomes. Especially in the absence of an established, accurate predictive risk score, optimal patient selection is best accomplished and the figure of the “Heart Team”, consisting in a multidisciplinary team including cardiologists, cardiac surgeons, expert on intraoperative echocardiography and anesthesiologists, is crucial for the preoperative assessment, for the management of intraoperative complications and for the postoperative care. There are no published studies directly comparing TAVI and SAVR in moderate-risk patients. The limited results that are available do not support that TAVI provides better early results in the moderate-risk patients who require isolated AVR but seem to have similar or slightly worse results in terms of MACCE (major adverse cerebrovascular and cardiac events) and mortality compared with conventional surgery. The major advantages of TAVI is absolutely in the less invasiveness: often no cardiopulmonary bypass and mechanical ventilation are not even necessary. Despite the great success and increasing frequency of TAVI use, the volume of SAVR has so far remained constant and it is reasonable that in the next 10 years the evolving technology will extend the clinical application and criteria for patient selection for TAVI as the gold standard to the intermediate risk patients and TAVI will surpass the number of SAVR. Other forthcoming indications for TAVR might include its use for failing surgical bioprosthetic valves (valve-in-valve). Several open issues remain unsolved and extension of the indication to younger and intermediate-risk patients would certainly require further technical improvements and better prevention of severe complications in particularly vascular, bleeding and cerebral complications, as well as AV conduction abnormalities and paravalvular leak. Over all, the first

unsolved problem is the paravalvular leak. Some studies shown how paravalvular leak is associated with a higher mortality. Up to 61% of patients after TAVI procedure has a paravalvular leak of a mild grade, and often it is considered acceptable, although represents a significant risk factor for short-term mortality. Another frequent complication, usually due to arterial sheath insertion during TAVI, is vascular damage (VD). Reported rates of major VD range from 5.5% to 20%. Important issues from the development of TAVI is the long-term durability of TAVI valves and the increasing indications in lower-risk and younger patients makes this question a need. There is not a long term follow-up looking at valve durability but many factors, including the crimping of the valve and the distortion of the stent by a native calcific aortic annulus, could affect valve durability. Even if the results appear excellent the longest reported out-comes are currently at 5 years with smaller experience reported up to 9 years. In the PARTNER trial, no structural valve deterioration requiring SAVR was detected after 5 years and the valve area as well as the mean transvalvular gradient remained stable. The reported mid-term failure rates in surgical bioprostheses are very low, just 1% before 5 years and 10% at 10 years for patients over 65 years old. Another issue concerns the atrio-ventricular conduction disturbance after TAVI and SAVR. The need for implant of a permanent pacemaker is one of the most frequent complications after TAVI and is usually higher than in SAVR. In the PARTNER trial, new PPI was associated with a longer duration of hospitalization and higher rates of repeat hospitalization, mortality, and repeat hospitalization at 1 year. In a recent a meta-analysis that included 11,210 patients undergoing TAVI with a permanent PMK implantation rate of 6% after Edwards Sapien and 28% after Medtronic Core Valve. Second generation of self-expanding devices appear to have a lower rate of pacemaker implantation, but this trend needs to be confirmed. Cerebrovascular events after TAVI usually occur perioperatively or within the first 24 hours. The delayed strokes may be related to post-operative atrial fibrillation or other factors. The incidence of clinically significant stroke is 3%-4% in two recent meta-analyses. As compared to SAVR, the PARTNER trial showed in TAVI group a statistically significant higher rate of stroke and transient ischemic attack at 30 days (2.4 *vs*. 5.5%, P=0.04) and at 1 year, but no statically significant difference at 5 years. In another recent Trial it was not shown an increased risk in stroke rate after TAVI in comparison with SAVR. The development of new embolic protection devices but larger studies must be completed to determine whether using an embolic protection device truly improves neurological outcomes after TAVI. Some other complications rarely occur after TAVI like annulus rupture, myocardial perforation, valve dislodgement, and implantation in a suboptimal position but the incidence of several of them is being reduced over time as shown in a recently published report from the German aortic valve registry (GARY) [44]. Acute kidney injury still remains with an incidence, depending on the definition used, between 3.4 and 57%. Data demonstrate how TAVI procedures are increasing the own indication, reducing the postoperative complications and that patients at intermediate risk are increasingly being treated with TAVI worldwide. The TVT Registry and the German Aortic Valve Registry (GARY) demonstrated a median STS risk score of 7% and 5% respectively in patients treated with TAVI from November 2011 through March 2013. Several reports from European centers demonstrate the shift to intermediate-risk patients in clinical practice and reveal low mortality and stroke rates in these patients comparable with SAVR. The PARTNER IIa Trial has enrolled 2000 intermediate-risk patients with an STS score between 4 and 8 undergoing TAVI with the Edwards Sapien device. The SURTAVI trial, with an estimated subject enrolment of 2500, includes patients with an STS score ≥3 and ≤10 undergoing TAVI with the Medtronic Core Valve system. Both trials have a primary composite end- point of all-cause mortality and disabling stroke at 2 years post-TAVI randomized against SAVR. The role of the Heart Team is of utmost importance to decide in for each patient's optimal treatment based on risk scores, frailty, co-morbidities, patient preference, and potential for improvement in QoL. In conclusion, in the next future TAVR might be extended to younger and/or lower-risk patients, but at the present time surgical AVR remains the gold standard for its excellent results, especially in low- and intermediate-risk patients.

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