UNIVERSITÀ
DEGLI STUDI
DI PADOVA

Sede Amministrativa: Università degli Studi di Padova

Dipartimento di Scienze Cardiologiche, Toraciche e Vascolari

SCUOLA DI DOTTORATO DI RICERCA IN SCIENZE MEDICHE, CLINICHE E SPERIMENTALI
INDIRIZZO "SCIENZE CARDIOVASCOLARI"

CICLO XXVI

CLINICAL AND HEMODYNAMIC OUTCOMES OF TRANS-APICAL AORTIC VALVE IMPLANTATION. INSIGHTS FROM THE I-TA REGISTRY

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ABBREVIATION LIST

AATS	American Association of Thoracic Surgery
ACC/AHA	American College of Cardiology/American Heart Association
AR	Aortic Regurgitation
AVA	Aortic Valve Area
AVR	Aortic Valve Replacement
AVS	Aortic Valve Stenosis
BAV	Balloon Aortic Valvuloplasty
CAD	Coronary Artery Disease
COPD	Chronic Obstructive Pulmonary Disease
CT scan	Computed Tomography scan
ECC	Extracorporeal Cardiac Circulation
ESC/EACTS	European Society of Cardiology/European Association for Cardio-Thoracic Surgery
EuroSCORE	European System for Cardiac Operative Risk Evaluation
I-TA	Trans-Apical Aortic Valve Implantation
LV	Left Ventricle
LVOT	Left Ventricle Outflow Tract
MACCE	Major Adverse Cardiovascular or Cerebrovascular Events
NYHA	New York Heart Association
OHS	Open-Heart Surgery
PET	Polyethylene Terephthalate
PVD	Peripheral Vascular Disease
PVL	Paravalvular Leak
SAVR	Surgical Aortic Valve Replacement
STJ	Sino-Tubular Junction
STS	Society of Thoracic Surgeons
SU-AVR	Aortic Valve Replacement with Sutureless Valves
TAVI	Trans-Catheter Aortic Valve Implantation
TA-TAVI	Trans-Apical-Trans-Catheter Aortic Valve Implantation
Tao-TAVI	Trans-Aortic-Trans-Catheter Aortic Valve Implantation
TEE	Trans-Esophageal Echocardiography
TF-TAVI	Trans-Femoral-Trans-Catheter Aortic Valve Implantation
TS-TAVI	Trans-Subclavian-Trans-Catheter Aortic Valve Implantation
TTE	Trans-Thoracic Ecocardiography
VARC	Valve Academic Research Consortium

SUMMARY

Senile degenerative calcific aortic valve stenosis (AVS) is a progressive disease characterized by a peculiar natural history. When symptoms begin (congestive heart failure and dyspnea, angina, syncope) mortality rate rapidly increase and quality of life dramatically worsen. It has been estimated that the overall survival of patients with severe symptomatic AVS is less than 50% 2 years after the onset of symptoms. The number of patients suffering from AVS worldwide will increase over time as life expectancy progressively extends.

The treatment of choice for severe symptomatic AVS is aortic valve replacement (AVR) that is usually performed under general anesthesia, with median sternotomy and cardiopulmonary bypass. AVR is a well-established procedure, with excellent early and long-term results and valve prostheses have now reached optimal hemodynamic performance and duration. During the last few years, the development of sutureless aortic bioprosthesis has made easier the surgical procedure. In fact, aortic valve replacement with sutureless valves (SU-AVR) needs shorter cardiopulmonary bypass and aortic cross clamp times and can be safely performed through a minimally invasive approach.

However, a recent survey showed that around 30% of patients with severe symptomatic AVS does not undergo AVR for several reasons: they are not referred for surgery by their family physician or by their cardiologist because of age, they are declined surgery for a high preoperative risk profile; they are inoperable for severe ascending aortic calcification (porcelain aorta).

Trans-catheter aortic valve implantation (TAVI) is an alternative therapeutic option in high-risk or inoperable patients. TAVI can be performed through several accesses:

trans-femoral (TF-TAVI), trans-apical (TA-TAVI), trans-aortic (TAo-TAVI) and trans-subclavian (TS-TAVI). This thesis will focus on TAVI and in particular on TA-TAVI in terms of, indications, technique and outcomes.

We will show the results of the Italian Registry of Trans-Apical Aortic Valve Implantation (I-TA) that includes the great majority of patients who underwent TA-TAVI in Italy since this procedure became commercially available in 2008. Furthermore we will present the results of a propensity-matched study that compared all the three available surgical options for patients with severe symptomatic aortic valve stenosis: surgical aortic valve replacement (SAVR), SU-AVR and TA-TAVI. From the results of these two studies it clearly appears that TA-TAVI is an excellent therapeutic options in patients with aortic valve stenosis. The two main issues that still need to be solved are the incidence of paravalvular leak, and valve durability. Paravalvular leak has been demonstrated to have a significant impact on long term survival while the assessment of valve durability needs a longer observation of these patients in order to reach time points when structural valve deterioration is more likely to occur.

RIASSUNTO

La stenosi valvolare aortica (AVS) degenerativa senile è una malattia ad evoluzione progressiva caratterizzata da un significativo aumento della mortalità e da un drammatico peggioramento della qualità della vita dal momento in cui compare la sintomatologia specifica: dispnea (scompenso cardiaco congestizio), angina e sincopi. É stato dimostrato che, dalla comparsa dei sintomi, la sopravvivenza a due anni è inferiore al 50%. La diffusione di questa patologia è in aumento in seguito al progressivo incremento dell'aspettativa di vita, specialmente nei paesi più sviluppati. Il trattamento di prima scelta nei pazienti affetti da AVS severa sintomatica è rappresentato dall'intervento chirurgico di sostituzione valvolare. Questa procedura è generalmente eseguita in anestesia generale attraverso una sternotomia longitudinale mediana e con l'utilizzo della circolazione extracorporea. I risultati dell'intervento di sostituzione valvolare aortica sono ormai ben conosciuti, la sopravvivenza a breve e medio termine è eccellente e le protesi utilizzate hanno dimostrato delle ottime performance sia in termini di durata sia dal punto di vista emodinamico. Negli ultimi anni sono state introdotte sul mercato le bioprotesi aortiche sutureless che non richiedono punti di sutura per ancorarsi sull'anulus aortico. L'intervento di sostituzione valvolare aortica con le protesi sutureless (SU-AVR) richiede, infatti, dei tempi di clampaggio aortico e di circolazione extracorporea inferiori rispetto alle protesi tradizionali ed inoltre può essere più agevolmente eseguito attraverso un accesso mini-invasivo.

Ciononostante, una recente analisi ha evidenziato che circa il 30% dei pazienti affetti da stenosi aortica non sono sottoposti all'intervento cardiochirurgico a causa dell'età molto avanzata o delle severe patologie associate da cui sono affetti.

L'impianto valvolare aortico trans-catetere è un'alternativa terapeutica che può essere considerata nei pazienti ritenuti inoperabili con la tecnica tradizionale oppure per coloro che vengono considerati ad altissimo rischio a causa delle severe patologie coesistenti.

La procedura di TAVI può essere eseguita attraverso diversi approcci: trans-femorale (TF-TAVI), trans-apicale (TA-TAVI), trans-aortico (Tao-TAVI) e trans-succlavio (TS-TAVI). L'argomento di questa Tesi sarà la procedura di TAVI e in particolare rivolgeremo la nostra attenzione alla TAVI trans-apicale in termini d'indicazioni, tecniche e risultati.

In questa tesi saranno presentati i risultati del Registro italiano dell'Impianto Valvolare Aortico per via Trans-Apicale (I-TA registry), in cui sono stati arruolati la grande maggioranza dei pazienti sottoposti a TA-TAVI in Italia dal 2008, anno in cui questa tecnica è stata disponibile. Verranno inoltre presentati i risultati di uno studio propensity-matched in cui sono stati confrontati i risultati di tutte le tre tecniche chirurgiche attualmente disponibili per il trattamento dei pazienti con AVS: SAVR, TA-TAVI e SU-AVR. Dai risultati di questi studi appare chiaramente che la TA-TAVI è una valida alternativa terapeutica nei pazienti con AVS. Ci sono tuttavia ancora due aspetti che richiedono particolare attenzione: l'incidenza di leak paravalvolari e la durata di queste nuove bioprotesi. La presenza di un leak paravalvolare si è dimostrata un fattore prognostico negativo in termini di sopravvivenza a distanza mentre un'effettiva valutazione della durata di queste protesi richiede un'osservazione più prolungata in modo tale da arrivare ad intervalli di tempo in cui il verificarsi di una degenerazione strutturale sia più probabile.

1. THE AORTIC VALVE

1.1 Anatomy of the aortic valve and of the aortic root

The first accurate description of the aortic valve was made by Leonardo Da Vinci between 1508 and 1513. Leonardo, in the "Corpus of Anatomical Studies" (Collection of Her Majesty the Queen at Windsor Castle) describes, through several drawings, anatomy, geometry, dynamics and physiology of the aortic valve and its leaflets. He was the very first scientist to understand the importance of curly vortices in Valsalva sinuses and the mechanisms of leaflets coaptation (Fig.1-2).

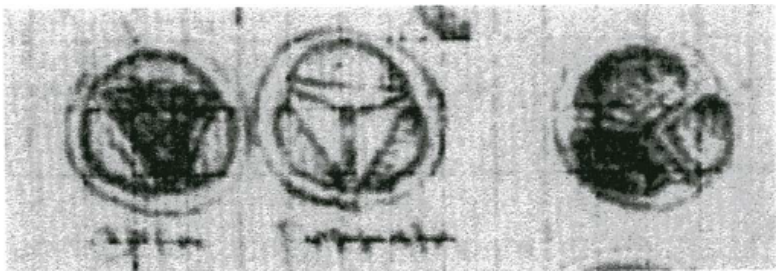


Fig.1: Schematic drawing of the aortic valve made by Leonardo Da Vinci. From the "Corpus of anatomical studies" in the Collection of Her Majesty the Queen at Windsor castle

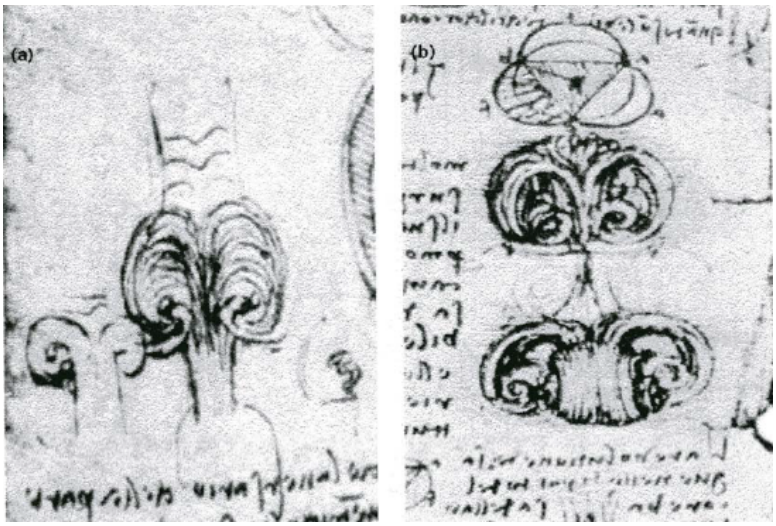


Fig.2: Curly vortices in the aortic root by Leonardo Da Vinci. From the "Corpus of anatomical studies" in the Collection of Her Majesty the Queen at Windsor castle

The aortic root provides the supporting structures for the leaflets of the aortic valve, and forms the bridge between the ascending aorta and the left ventricle. The aortic root, which surrounds and supports the leaflets, extends from the leaflet attachments until the sino-tubular junction. The anatomic ventricular-aortic junction is a circular locus within the root, placed where the supporting ventricular structures give way to the fibro-elastic walls of the aortic sinuses. This ring is markedly discordant with the morphology of the attachment of the leaflets of the aortic valve.

1.1.1 The "aortic annulus"

In order to fully understand the anatomical basis of aortic valve surgery and in particular of trans-catheter aortic valve implantation, it is important to describe the complex structure of the aortic annulus. Under a surgical point of view, the aortic annulus is generally considered as the structure where aortic leaflets are attached to the aortic wall. This structure has a crown-like morphology. For TAVI, the annulus is better described by the concept of the "*virtual basal ring*"(1) constructed by joining together the most proximal parts ("nadir") of each leaflet (Fig. 3).

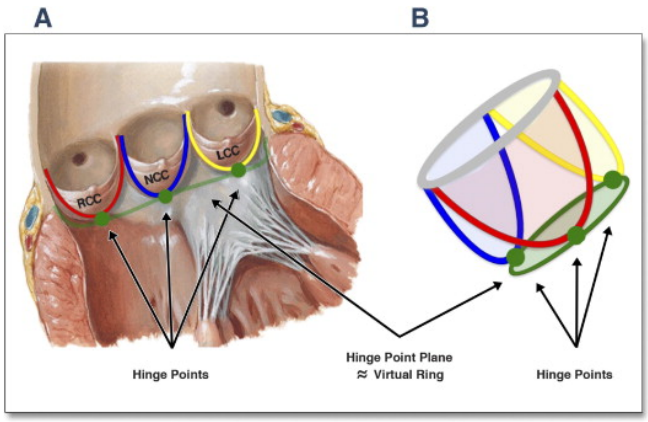


Fig. 3: The "crown-like" shape of the surgical aortic annulus (red, blue and yellow lines) and the "virtual basal ring" (green line)

The latter definition, the so-called "virtual basal ring" is typically analyzed by the echocardiographer and the radiologist when providing measurements and relationships of the annulus diameter and is carefully considered by the implanting physician when planning and performing a TAVI procedure. In fact, valve sizing is a crucial step of procedural planning for TAVI. In order to achieve optimal results, a good evaluation of patient's aortic valve and annulus in terms of morphology (bicuspid, tricuspid), shape (circular, oval), dimensions (diameters, perimeter, area) and distance from the coronary ostia is of outmost importance. It is also important to measure the diameter of the sino-tubular junction and to assess the shape of Valsalva sinuses as well as the aspect of the left ventricular outflow tract. In other words, an in-depth analysis of the entire complex left ventricle outflow tract (LVOT)-aortic root anatomy is mandatory to carry out a successful TAVI procedure.

2. AORTIC VALVE STENOSIS

Aortic valve stenosis (AVS) is an insidious disease that has a slow but inexorably progressive evolution. It is a consequence of reduction of aortic valve area that creates an obstruction to blood flow that ultimately generates a trans-valvular pressure gradient with consequent left ventricular hypertrophy. When symptoms appear, the disease rapidly progresses towards death if it is left untreated (2,3). The incidence of AVS increases with age; after 65 years around 2% of the general population is affected and 29% has echocardiographic signs of leaflet calcifications (4).

2.1 Etiology

The causes of aortic valve stenosis can be categorized as congenital and acquired.

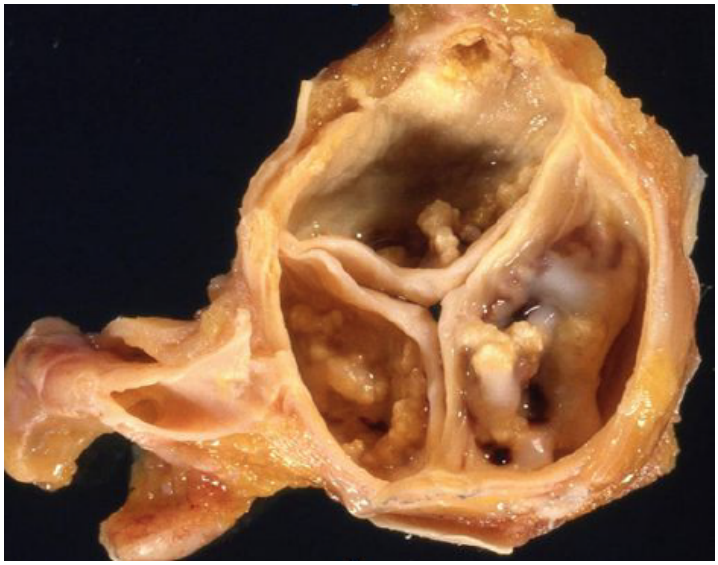


Fig. 4: Senile calcific degenerative aortic valve stenosis

There are three types of congenital aortic valve stenosis: supra-valvular, sub-valvular and valvular. The latter is generally due to unicuspid, bicuspid or malformed tricuspid valves. AVS was found in 85% of

patients with bicuspid aortic valve but only 33% shows severe clinical consequences (5).

Acquired causes of AVS are mainly two: rheumatic disease and senile calcific degeneration. The post-inflammatory rheumatic disease of the aortic valve is characterized by commissural fusion and leaflet retraction and is caused by an immune-mediated reaction that is generated by a Group A Beta hemolytic Streptococci infection of the upper airways. Clinical symptoms of AVS in these cases generally occur in the sixth decade of life.

Senile degeneration is the most frequent cause of AVS and generally occurs in the seventh or eighth decade of life, maybe due to the progressive increase of life expectancy, especially in western countries. It has been recently demonstrated that this degeneration is an active proliferative and at the same time inflammatory process that causes lipid accumulation, up-regulation of Angiotensin Converting Enzyme and also infiltration of macrophages and T-lymphocytes. All together these processes ultimately lead to valve calcification (6). Usually the first lesions appear on the aortic side of the leaflets and with time they proceed deep in the annulus and in the interventricular septum. These lesions are mainly made of localized deposits of calcium together with inflammatory cells and cholesterol infiltration (Fig. 4).

Cholesterol has been identified as an important initiator of the degenerative process that affects valve leaflets creating a progressive atherosclerotic process

through the activation of transcriptional regulators such as Osteopontin and Cbfa1 that are involved in osteoblasts differentiation.

Furthermore, other well known risk factors for the development of atherosclerosis such as high blood levels of LDL, Apolipoprotein A, diabetes mellitus, smoke, arterial hypertension and male sex have been identified as predictors of aortic valve stenosis (7,8)

2.2 Pathophysiology

Normal aortic valve area is 3-4 cm^2. Table 1 shows the classification of aortic valve stenosis according to recent American College of Cardiology/American Heart Association guidelines (9).

Table 1. Classification of aortic valve stenosis severity

	Mild	Moderate	Severe
Jet velocity (m/s)	<3.0	3.0-4.0	>4
Mean Gradient (mmHg)	<25	25-40	>40
Valve area index (cm^2/m^2)			<0.6
Valve area	>1,5	1.0-1.5	<1.0

Reduction of aortic valve area represents an obstacle to cardiac outflow. As a consequence, the left ventricle reacts with a compensatory hypertrophy due to an over expression of genes encoding for collagen type I and II and for

fibronectin (10) in order to maintain an adequate cardiac output and to reduce wall stress. The result of these compensatory mechanisms is that aortic valve stenosis may be completely asymptomatic for many years. As the ventricle becomes hypertrophic, it becomes stiffer as its compliance decreases; a higher left ventricular end-diastolic pressure is needed to maintain the same volume of cardiac output. To achieve a sufficiently high left ventricular end-diastolic pressure (diastolic loading), the heart becomes increasingly dependent on the atrial kick; loss of the atrial kick, as occurs with atrial fibrillation, may result in a significant decline in cardiac output and acute hemodynamic impairment. The combined effects of bigger mass of the left ventricle due to compensatory hypertrophy; less compliance of the left ventricle (LV) that consequently leads to more wall tension and higher systolic ventricular pressure ultimately generate an increase in myocardial oxygen demand. At the same time, coronary artery blood flow is compromised by increased wall tension compressing the vessels and by higher left ventricular diastolic pressure, which lowers the coronary artery perfusion pressure. These factors contribute to inadequate coronary arterial perfusion of the sub-endocardium, leading to chronic ischemia with cell necrosis and fibrosis. Left ventricular hypertrophy may allow the heart to achieve

a normal cardiac output under resting conditions. To do so, however, a pressure gradient across the valve is required, and, as the aortic valve area (AVA) becomes smaller, the gradient across the valve from left ventricle to aorta increases. The relationship of flow across the aortic valve and the trans-valvular pressure gradient is shown in Figure 5.

As the valve area decreases to 1 cm^2, there is little change in the trans-valvular gradient needed to generate the same flow, and patients frequently experience no symptoms. With a valve area of 0.8 cm^2, patients invariably develop symptoms.

2.3 Natural History and Symptoms

The natural history of aortic stenosis was reported by Ross and Braunwald (2). Patient survival is not reduced until symptoms occur and this generally happens when aortic valve area reduces from the normal 3-4 cm^2 to less than 1 cm^2. After symptoms occur, patient survival is drastically reduced. The three principal symptoms of aortic stenosis are angina, syncope, and dyspnea (or congestive heart failure) (Fig. 6).

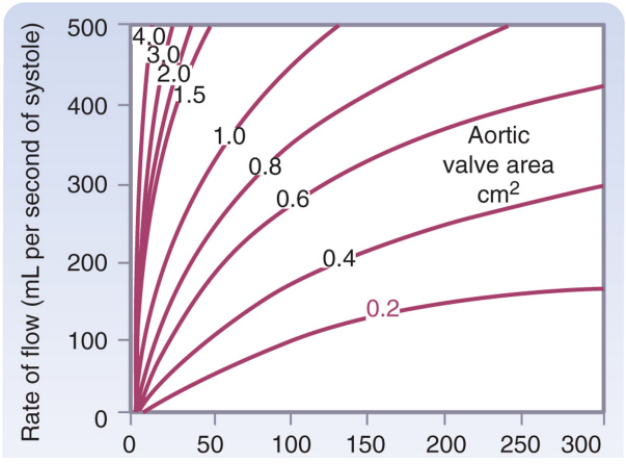


Fig 5: Relationship between flow across the aortic valve and the trans-aortic gradient

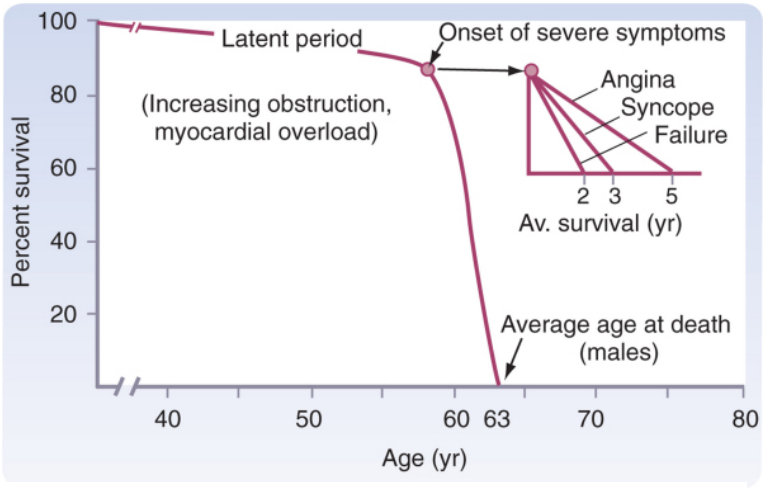


Fig 6 Natural history of aortic valve stenosis

Angina is usually the earliest symptom, and the mean survival of a patient with aortic stenosis and angina is 4.7 years. Angina is present in around 50-70% of patients with severe aortic valve stenosis. Reduced myocardial perfusion is due to ventricular hypertrophy and to an increased end-diastolic pressure and is particularly evident in the sub-endocardium muscular layer. When patient experiences syncope, survival is typically less than 3 years. Syncope is due to the reduced blood flow through the stenotic valve that causes a decreased cerebral perfusion; furthermore, peripheral vasodilatation that occurs during exercise may worsen the situation since cardiac output does not modify. Patients with dyspnea and congestive heart failure, in keeping with their associated left ventricular dysfunction, have a mean survival of 1 to 2 years. Congestive heart failure is the presenting symptom in nearly one third of patients. Dyspnea is the consequence of the reduced capacity of the heart to increase the stroke volume in response to an increased metabolic demand. It can be also a consequence of the diastolic dysfunction (11).

2.4 Treatment

Although conventional aortic valve replacement is the treatment of choice for patients with severe symptomatic aortic valve stenosis and can be generally considered as a routine operation, the progressive increase in life expectancy is leading to a parallel increase in the mean age of patients referring to the surgeon for severe aortic valve stenosis. For this reason, the need for newer and less invasive options, such as sutureless valves and trans-catheter techniques, has emerged during the last decade.

There are four therapeutic options for the treatment of patients suffering from severe symptomatic aortic valve stenosis:

1. Balloon aortic valvuloplasty (BAV)
2. Conventional surgical aortic valve replacement (SAVR)
3. Trans-catheter aortic valve implantation (TAVI)
4. Sutureless aortic valve replacement (SU-AVR)

The choice between these four different techniques is based on age, surgical risk profile, anatomical characteristics and physician's preferences. The following chapters will focus on each treatment option highlighting indications, results and devices.

3. BALLOON AORTIC VALVULOPLASTY

Balloon aortic valvuloplasty plays an important role in the pediatric population but a very limited role, when used in isolation, in adults: this is because its efficacy is low, the complication rate is high (>10%), and restenosis and clinical deterioration occur within 6–12 months in most patients, resulting in a mid- and long-term outcome similar to natural history (12), as shown in figure 7.

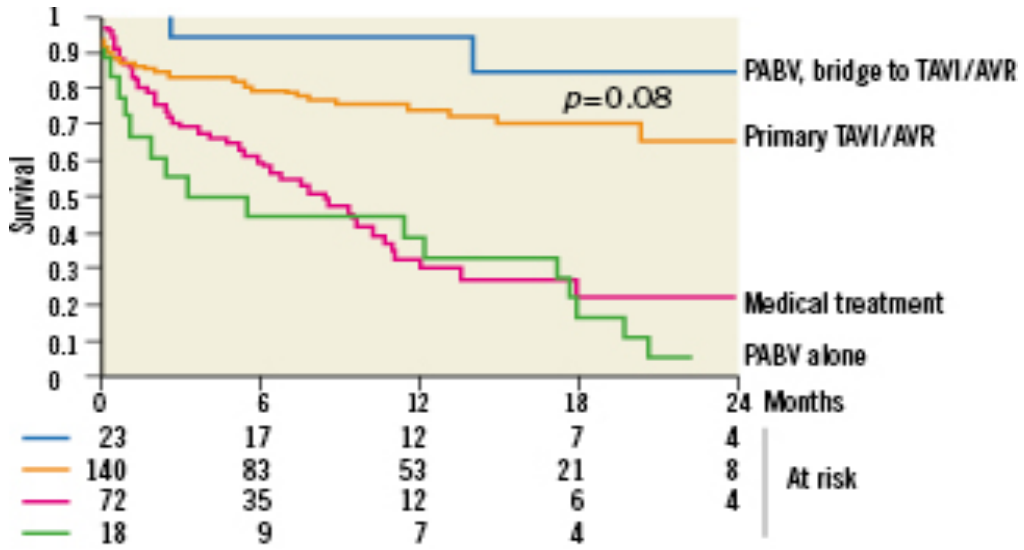


Fig 7 Kaplan-Meier curves showing that there is no difference between balloon aortic valvuloplasty alone (PABV, green line) and medical treatment (red line) in terms of long term prognosis in patients with severe aortic valve stenosis. PABV: Percutaneous aortic balloon valvuloplasty; TAVI: Trans-catheter aortic valve replacement; AVR: Aortic valve replacement.

BAV is generally performed through femoral access and a retrograde approach to the aortic valve. Balloon inflation is usually performed under rapid ventricular pacing (160–220 beats/min). Rapid ventricular pacing helps to temporarily reduce myocardial contractility in order to establish a stable balloon position

during inflation. According to the most recent guidelines issued by the European Society of cardiology in 2012, BAV may be considered as a bridge to surgery or TAVI in selected high-risk patients or in patients with symptomatic severe aortic stenosis who require urgent major non-cardiac surgery (Recommendation class IIb, level of evidence C) (13).

4. CONVENTIONAL AORTIC VALVE REPLACEMENT

Conventional surgical aortic valve replacement (SAVR) is the gold standard as well as the benchmark procedure for severe AS. SAVR is a routine procedure that has been performed in many centers throughout the world for more than 50 years. Results are generally excellent, depending on the individual patient risk profile together with the experience of the surgeon. Operative mortality of isolated AVR for AS ranges from 0.5–3% in patients younger than 70 years and 4–8% in selected older adults. Older age, associated comorbidities, female gender, higher functional class, emergency operation, LV dysfunction, pulmonary hypertension, co-existing coronary artery disease (CAD), and previous bypass or valve surgery were identified as independent predictors for hospital mortality following AVR (14-21). Standard access for AVR is through a full median sternotomy. Alternatively, minimally invasive access, using a partial mini-sternotomy, can be done with good outcomes; this will be discussed in the next paragraph. Conventional AVR requires cardiopulmonary bypass and aortic cross clamping. The diseased aortic valve is excised and the valve prosthesis is implanted under direct surgical vision after careful measurement of the aortic root thus reducing the risk of leak and optimizing hemodynamic outcomes. The 2011 report from the German cardiac surgical national database shows good outcomes in more than 11000 patients receiving AVR every year, with an average mortality of 3% (22). Freedom from valve related mortality in patients

with mechanical prostheses is 90% at 10 years (23) while freedom from structural valve degeneration was is around 90-95% at 15 years with small variations depending on the age at the time of surgery and also on the type of implanted prosthesis (porcine, pericardial, stented, stentless) (24). After successful AVR, symptoms and quality of life are in general greatly improved and in elderly patients long-term survival is similar to that of an age and sex matched population (25). Age, comorbidities, severe symptoms, LV dysfunction, ventricular arrhythmias and untreated co-existing CAD were identified as independent predictors of late death. Valve-related complications and suboptimal prosthetic valve hemodynamic performance may cause poor postoperative outcome. Generally patients 65 years or younger are considered candidates for mechanical valves, whereas patients aged from 65 years upwards are considered candidates for xenografts. However, as we will see in the next chapters, the possibility to perform a "valve-in-prosthesis" implantation using a trans-catheter valve may lead to lower the threshold for using xenografts with the option of subsequent valve-in-prosthesis implantation in case of xenograft degeneration.

4.1 Minimally invasive SAVR.

Minimally invasive access modalities are aimed at reducing the length of incision in order to minimize the effects of surgical trauma. Generally "J-shape" or "inverted T" in the 3rd or 4thintercostal space are performed. Aortic

cannulation is generally directly made in the ascending aorta while venous cannulation can be performed directly in the right atrium or percutaneously through the femoral vein. Overall, results of minimally invasive AVR are comparable to a complete sternotomy approach (20). In a meta-analysis of 4586 patients (2054 mini-sternotomy vs. 2532 full sternotomy) mini-sternotomy was proven to be as safe as conventional sternotomy for AVR, without increased risk of death or any other major complication (26). Major benefits of this technique are related to better and more rapid postoperative recovery and to better aesthetic results.

5. SUTURELESS AORTIC VALVE REPLACEMENT (SU-AVR).

In the last few years many companies have developed new aortic sutureless bioprosthesis. This procedure is similar to conventional SAVR, the only difference being that the surgeon does not need to suture the valve to the annulus but the valve anchors to the annulus thanks to the radial force of its stent. This leads to a more rapid implantation. The advantages of sutureless valves include:

- Complete excision of the diseased valve
- Anatomical tailoring to individual patient anatomy
- A-traumatic introduction with minimal or no crimping of the valve leaflets allowing more predictable long-term outcomes
- Valves are self-anchoring (no need for sutures), self-expanding for easy implantation and good visibility
- Shorter aortic cross clamping and cardiopulmonary bypass times
- Easier minimally invasive cardiac surgery procedures.

There may be a specific subset of patients that could particularly benefit from sutureless devices - for example, those with an increased risk profile who require a fast procedure through a small incision.

Three different prostheses have undergone initial clinical studies and received approval for use in the European Community (CE mark): Medtronic 3F Enable (Medtronic, Minneapolis, Minnesota, USA), Sorin Perceval S (Sorin

Group, Saluggia, Italy) and Edwards Intuity (Edwards Lifesciences, Irvine, California, USA).

5.1 Medtronic 3F Enable Valve

It is based on the ATS 3F Aortic Bioprosthesis with an added self-expanding nitinol frame to hold the valve in its position (Fig. 8).

Fig. 8. Medtronic 3F Enable Sutureless aortic bioprosthesis

It has three equine pericardial leaflets (27, 28). A multicenter clinical study evaluated the safety and efficacy of this bioprosthesis in 140 patients undergoing isolated aortic valve replacement with or without concomitant procedures. Mean systolic gradient was 9.04 ± 3.56 and 8.62 ± 3.16 mm Hg with mean effective orifice area of 1.69 ± 0.52 and 1.67 ± 0.44 at 6 months and 1 year, respectively. Severe paravalvular leaks requiring valve removal were observed in 2.1% of patients. No structural deterioration, valve-related thrombosis or hemolysis was documented in the total accumulated follow-up of 121.8 patient-years (29).

5.2 Sorin Perceval S

Sorin Perceval S (Fig. 9) is made of a nitinol frame and bovine pericardial leaflets. Sinusoidal struts anchor the device in the Valsalva sinus and annular sealing is obtained with brief low-pressure balloon dilation.

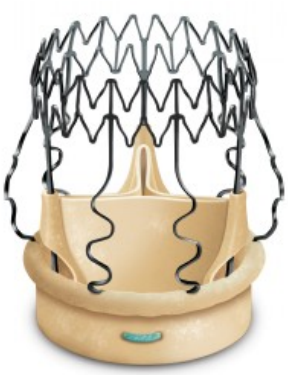


Fig. 9. Sorin Perceval S sutureless aortic bioprosthesis

A European, multicenter, prospective trial evaluated its feasibility in 30 patients. The mean aortic cross-clamp and extracorporeal cardiac circulation (ECC) times were 34±15 min and 59±min, respectively. Hospital mortality was 3.3%. No migration or dislodgement of the valve occurred, but there were two mild paravalvular leakages and two mild intra valvular insufficiencies (30). In a follow up study, mean aortic cross-clamp time for aortic valve replacement was 18±6 minutes. This was associated with excellent early clinical and hemodynamic outcome in high-risk patients (31).

5.3 Edwards Intuity

This prosthesis is based on the Magna Ease aortic valve. It is a stented tri-leaflet bovine pericardial bioprosthesis with a balloon expandable, cloth-covered stent frame at the inflow aspect (Fig. 10).

Fig. 10. Edwards Intuity sutureless aortic bioprosthesis

The valve is positioned supra-annularly using three guiding sutures. The sutures are tied and the frame is expanded with a balloon catheter. Data from the TRITON study (32), a multi-center European prospective study in 152 patients

showed a technical success rate of 96.1%. In isolated AVR, mean aortic cross-clamp times was41.1 ± 10.6 (reduced by 43% if compared to data from the STS National Database). All-cause and valve-related early mortality were 2.1% (3/146) and 1.4% (2/146), respectively. Two early cases of paravalvular leaks (1.4%) (2/146) that remained unchanged over 1 year were reported. Furthermore one late moderate/severe paravalvular leak (0.9%), which required removal of the study device was reported.

6. TRANS-CATHETER AORTIC VALVE IMPLANTATION (TAVI).

6.1 History

A large percentage of suitable candidates for AVR are currently not referred for surgery or are turned down by the cardiac surgeon due to advanced age or severe comorbidities.

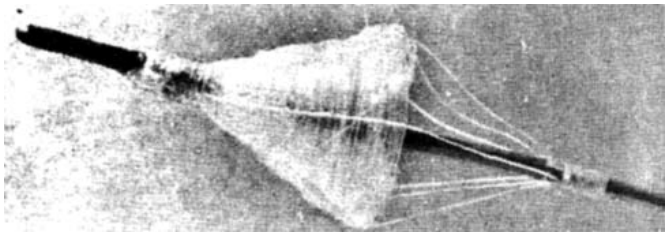


Fig. 11. The first trans-catheter valve developed by Davies in 1965

The first description of a trans-catheter aortic valve implantation was made by Davies who, in 1965, implanted a parachute-like valve in the descending aorta of a dog through a trans-femoral access (Fig. 11) (33, 34).

Six years later, in1971, Moulopoulos et al described three different trans-catheter valve systems, which were temporarily placed in the ascending aorta of dogs with aortic regurgitation (Fig. 12) (35)

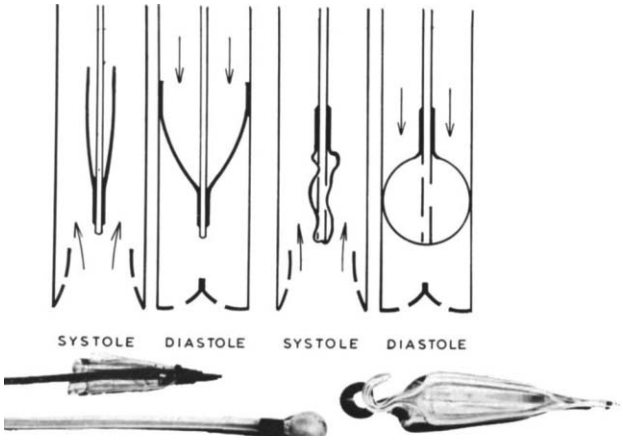


Fig. 12. Umbrella and balloon trans-catheter valves described by Moulopous in 1971. These devices were connected to an external pump that caused inflation during diastole and deflation during systole in order to reduce aortic regurgitation.

Since then on, many different devices were tested in animals. All these valves were designed for palliation of aortic regurgitation and were generally considered as temporary. In the eighties, Alain Cribier developed balloon aortic valvuloplasty in patients suffering from aortic stenosis. (36). This technique showed promising initial results but longer follow-up demonstrated that there was a high incidence of recurrence of aortic stenosis and also that survival was similar to that of untreated patients (37). By 1992, Andersen had reported the permanent sub-coronary implantation of a trans-catheter aortic valve in pigs (38). The valve was constructed of surgical stainless-steel wires folded in repeated loops. A porcine aortic valve was sewn inside the stent, and the valve was crimped on a balloon catheter (Fig. 13).

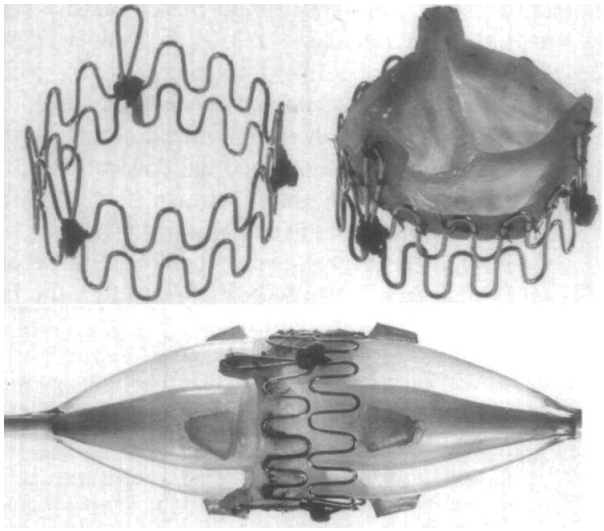
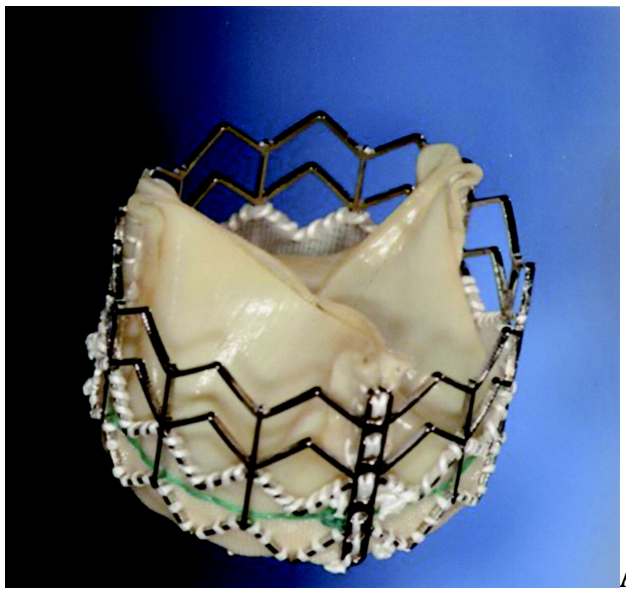


Fig. 13. Trans-catheter aortic valve developed by Andersen in 1992.

Andersen used a retrograde trans-aortic approach to implant this

hand-made device in nine pigs. Hemodynamic results were excellent: low gradients and trivial paravalvular regurgitation. However, coronary flow reduction was observed in one-third of cases.

Although the TAVI procedure of today (with balloon-expandable valves) follows the concept first pioneered by Andersen, it took a further decade to refine and ultimately translated the principle of this technique into clinical practice. In 2002, Cribier performed the first-in-human TAVI procedure using an antegrade, trans-venous approach (Fig. 14-15) (39).


A

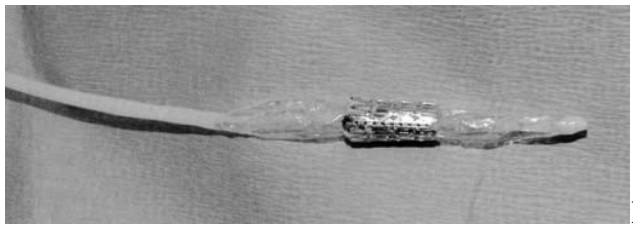

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Fig. 14. The first trans-catheter valve, open (A) and crimped on the balloon catheter (B) developed by Alain Cribier and implanted for the first time in a human being in 2002.

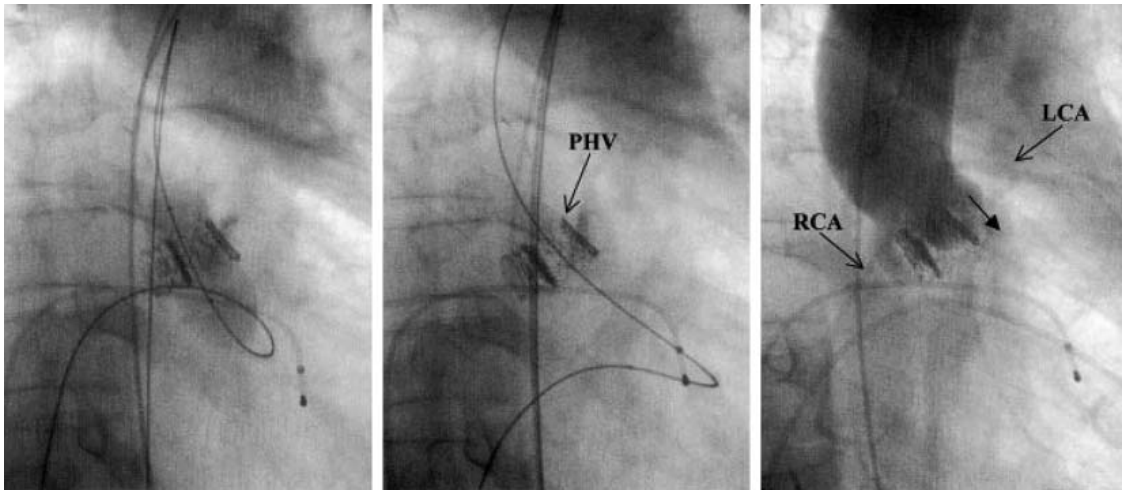


Fig. 15. Fluoroscopic images of the first human implantation of the trans-catheter valve developed by Cribier. In this case a trans-femoral venous approach with a trans-septal puncture was used. PHV: Percutaneous heart valve; RCA: Right coronary artery; LCA: Left coronary artery.

The valve was made of equine pericardium sewn inside a balloon-expandable metal stent. However, the technical complexity and associated risks of the trans-venous approach limited its widespread application and rapidly it was abandoned in favor of the retrograde trans-femoral procedure. This allowed a more technically feasible and reliable procedure. During the same period, the first-in-human TAVI with a self-expandable valve was reported by Grube (40). Shortly after this, the first-in-human trans-apical procedures were performed through a median sternotomy and with the use of cardiopulmonary bypass in Leipzig and through left thoracotomy without extracorporeal circulation in Vancouver, providing an alternative option for patients without suitable vascular access (41-43).

At the beginning, TAVI was an investigational procedure restricted to inoperable patients with symptomatic severe native valve AVS. Subsequently, and despite a steep learning curve, the initial success documented in small

observational registries (44-46) from a limited number of pioneering centers paved the way for large randomized trials to be performed. On the basis of registry data, European CE mark approval for trans-femoral implantation was received for the Medtronic CoreValve in 2007, followed by the Edwards SAPIEN in 2008.

In the United States, the Food and Drug Administration restricts approval to new devices only after large prospective randomized trials. The Placement of AoRTic Trans-catheter Valves (PARTNER) Trials were the first prospective randomized multicenter landmark studies, which compared TAVI with medical management (and optional BAV) in inoperable patients (PARTNER Trial Cohort B) (47, 48) and with surgical AVR in patients considered to be at high operable risk (PARTNER Trial Cohort A) (49). Compared with standard medical management there was an absolute reduction in mortality of 20% with TAVI at 1 year and even greater benefit after 2 years. The FDA approved the Edwards SAPIEN device for trans-femoral delivery in 2011 and for trans-apical access in 2012. Similarly, approval of CoreValve by the FDA is dependent on the results of the ongoing Medtronic CoreValve US Pivotal Trial that will enroll around 1600 patients and has an estimated study completion date of November 2017.

6.2 The "TAVI team"

In order to carry out a successful TAVI program a strong synergy between different specialists is mandatory. The "TAVI TEAM" includes a cardiologist, a cardiac surgeon, an interventional cardiologist, an echocardiographist, an anesthetist and a radiologist. In order to guarantee an optimal safety profile to these extremely delicate patients, all these specialists should be part of a high-level health facility. Components of the TAVI team should participate in all the steps of a potential TAVI candidate: patient selection and screening, preoperative diagnostic pathway, access choice, TAVI procedure and managing of complications. In particular, the construction of a reliable surgical "safety net", with immediate access to extracorporeal circulation and surgical conversion guarantees the best treatment of complication that might occur during TAVI (50).

6.3 The Procedure

The procedure is best performed by the components of the "Heart Team". Depending on the logistics of each center, the procedure may be performed in a standard catheterization laboratory, an operating room, or a hybrid room. The hybrid room is the ideal setting for a TAVI procedure since it combines the advantages of an operating room, providing adequate sterility and a laminar air flow system as well as immediate availability to the cardiopulmonary bypass machine, with the advantages of a catheterization laboratory with high-

resolution images. Moreover, combining the needs of cardiovascular surgeons and interventional cardiologists in one dedicated room allows for an easy surgical conversion if needed (50).

7. TRANS-FEMORAL TAVI

TAVI using retrograde trans-femoral access represents the least invasive approach and is usually considered as the first choice since it can be performed completely percutaneously and with local anesthesia. Due to the large size (up to 24 Fr) of the initially available delivery sheaths, retrograde TAVI procedures were performed through the iliac artery using the so-called "iliac conduit technique". Subsequent technological improvements resulted in smaller sheath profiles and led to the era of purely percutaneous access via the common femoral artery. This is achieved with the use of arterial "pre-closure" devices. A step-by-step approach is mandatory in order to minimize the risk of complications. The first step is to identify the puncture site, which should be above the femoral bifurcation in a segment without or with little calcification, and which can be identified by contrast agent injection from the contralateral access site. Then, the femoral artery is punctured under fluoroscopic guidance and a standard 0.035 inch wire introduced into the femoral artery. Following a 1-2 cm skin incision and blunt dissection of the subcutaneous tissue with surgical clamps, a preclosure suture device is placed. The native aortic valve is retrogradely crossed and a J-shaped (in order to reduce the risk of ventricular perforation) extra-stiff wire (or super-stiff wire) is placed into the left ventricle. A temporary pacemaker is introduced via the femoral vein and positioned in the right ventricle. Balloon aortic valvuloplasty is then performed during rapid

pacing (160-220 bpm). Careful attention should be given to the movement of valve calcifications during balloon inflation, which may obstruct the ostium of the coronary arteries. Contrast agent injection in the aortic root during BAV enables assessment of coronary flow during balloon inflation and mimics valve implantation. After successful balloon dilation, the trans-catheter aortic valve delivery catheter is inserted and the bioprosthesis carefully advanced across the aortic arch. The balloon expandable bioprosthesis is deployed during rapid ventricular pacing, whereas self-expanding valve systems can be released from the delivery system without rapid ventricular pacing. After deployment, the correct positioning of the valve and the absence of aortic insufficiency are checked by means of angiography and echocardiography. The delivery systems and the sheaths are then removed and the femoral artery is closed with the preclosure device. The occlusion of the femoral artery with a balloon coming from the contralateral site before closure is useful since it allows tying sutures in a vessel that has no pressure thus reducing the risk of tears. The integrity of the aorto-iliac axis is then checked with angiography at the end of the procedure. Figure 16 shows the different steps of a TF-TAVI procedure with the balloon-expandable Sapien valve.

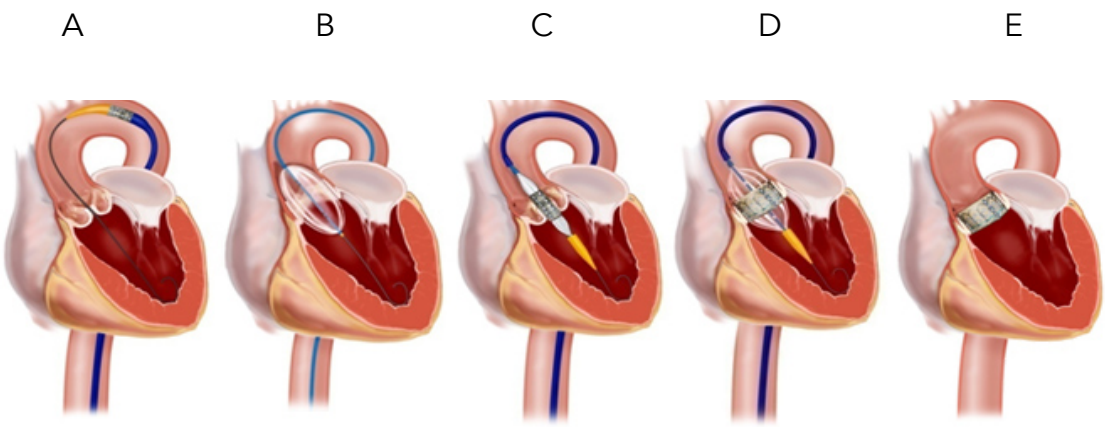


Fig. 16. Procedural steps of TF-TAVI procedure with the Edwards Sapien balloon-expandable device. A. A J-shaped extra-stiff guide is placed in the left ventricle and the balloon catheter is retrogradely advanced through the aortic arch. B. Balloon aortic valvuloplasty is performed during rapid pacing. C. The delivery system with the prosthesis crimped on the balloon is placed in its final position at the level of the aortic annulus. D. The balloon is inflated and the valve is deployed during rapid ventricular pacing. E. The valve prosthesis is correctly positioned and the delivery system together with the guidewire are retrieved.

8. TRANS-APICAL TAVI

To date the most used device for trans-apical TAVI is the Sapien XT valve (Edwards Lifesciences, Irvine, CA, USA), which is a balloon expandable prosthesis whose leaflets are made of bovine pericardium mounted on a chrome-cobalt stent. New trans-apical devices with different technical features have been recently introduced into clinical practice: Jena-Valve (Jena-Valve Technology, Munich, Germany) and Acurate (Symetis, Lausanne, Switzerland). They are made of nitinol and are self-expandable. However, since these new devices are still in their initial clinical phase, this paragraph will describe the implantation technique of the balloon- expandable Sapien XT valve. Trans-apical aortic valve implantation is usually performed under general anesthesia in a hybrid operating room if available, or in the catheterization laboratory. A mini anterior left thoracotomy is performed. The pericardium is opened and the left ventricular apex is exposed. A double purse-string suture is done on the muscular portion of the LV apex with Teflon pledgets reinforcement. Through a needle puncture of the LV apex in the central portion of the purse-string sutures a stiff guide-wire is passed through the native aortic valve and an introducer sheath is inserted in the left ventricle. This sheath will be used to introduce the balloon for the aortic valvuloplasty and the delivery system of the TAVI valve. A balloon aortic valvuloplasty is then performed during rapid pacing (160-220 bpm). In the meanwhile the bioprosthesis is crimped on the balloon of the

delivery system. Once the bioprosthesis is advanced to its correct position (50% above and 50% below the plane of the aortic annulus) rapid pacing is started, the balloon is inflated and the valve is deployed. Since this is a balloon expandable device it is not retrievable after deployment, thus a correct positioning is mandatory. If the prosthesis is malpositioned, embolization in the LV or in the ascending aorta or a severe para-valvular leak can occur. Once the valve has been deployed the sheath is removed and purse-string sutures are tightened in order to achieve a reliable hemostatic closure of the LV apex. Angiographic and echocardiographic controls are always done in order to assess correct positioning and function of the bioprosthesis. Figure 17 shows the procedural steps of TA-TAVI

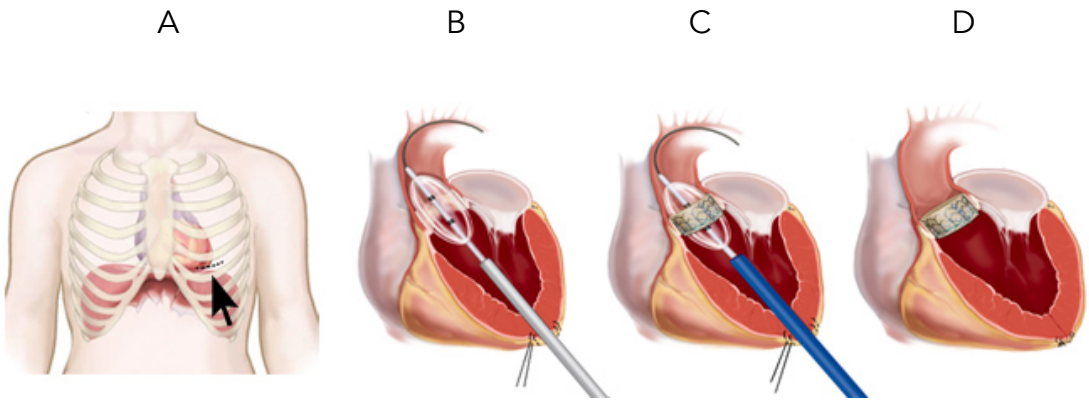


Fig. 17. Procedural steps of TA-TAVI with the Edwards Sapien balloon-expandable device. A. A mini left anterior thoracotomy is performed. The left ventricular apex is exposed and two concentric purse-string sutures are placed on the muscular portion of the apex. B. An extra-stiff wire is placed antegradely in the descending aorta through the aortic valve and balloon aortic valvuloplasty is performed during rapid pacing. C. The delivery system is advanced in the ventricular cavity and the valve is placed in its final position in the aortic annulus. Valve deployment is done during rapid ventricular pacing. D. The valve prosthesis is correctly positioned and the delivery system together with the guidewire are retrieved. The ventricular apex is closed tying the sutures during rapid pacing.

9. TRANS-AORTIC TAVI

Under general anesthesia, a small anterior thoracotomy is performed in the second intercostal space. After opening and suspension of the pericardium the ascending aorta is exposed. Two concentric purse-strings sutures are made as a conventional aortic cannulation. Puncture of the aorta is performed in the middle of the purse-string sutures and, under fluoroscopic guidance, an angiographic guide-wire is inserted retrogradely through the aortic valve in the LV. Since the direction of the guide-wire is not perpendicular to the plane of the aortic valve, particular attention should be given in order to avoid possible lesions to aortic sinuses and to the aortic wall. A 6F sheath is then placed on the guide-wire through the aortic valve in order to exchange the guide-wire with a J-shaped extra-stiff one that will be placed in the left ventricle, following the already described trans-femoral implantation technique (51). The sheath is inserted in the ascending aorta (Fig. 18 A) in order to perform subsequent balloon aortic valvuloplasty and valve deployment. Aortic valvuloplasty is carried out with a 20 mm balloon during induced ventricular tachycardia (160-200 bpm) (Fig 18 B). The prosthesis is then placed in the correct position (50% below and 50% above the aortic annulus) and valve deployment is performed during rapid pacing (Fig. 18 C). Correct valve positioning and the absence of residual aortic valve regurgitation is confirmed by post-procedural aortic angiography (Fig 18 D) and by intraoperative trans-esophageal echo (Fig 18 E).

The sheath is then removed and aortic purse-string sutures are tightened. Trans-aortic TAVI can also be performed through mini sternotomy in 3rd or 4th intercostal space in a "J" or "inverted T" fashion. Figure 18 shows the procedural steps of Tao-TAVI.

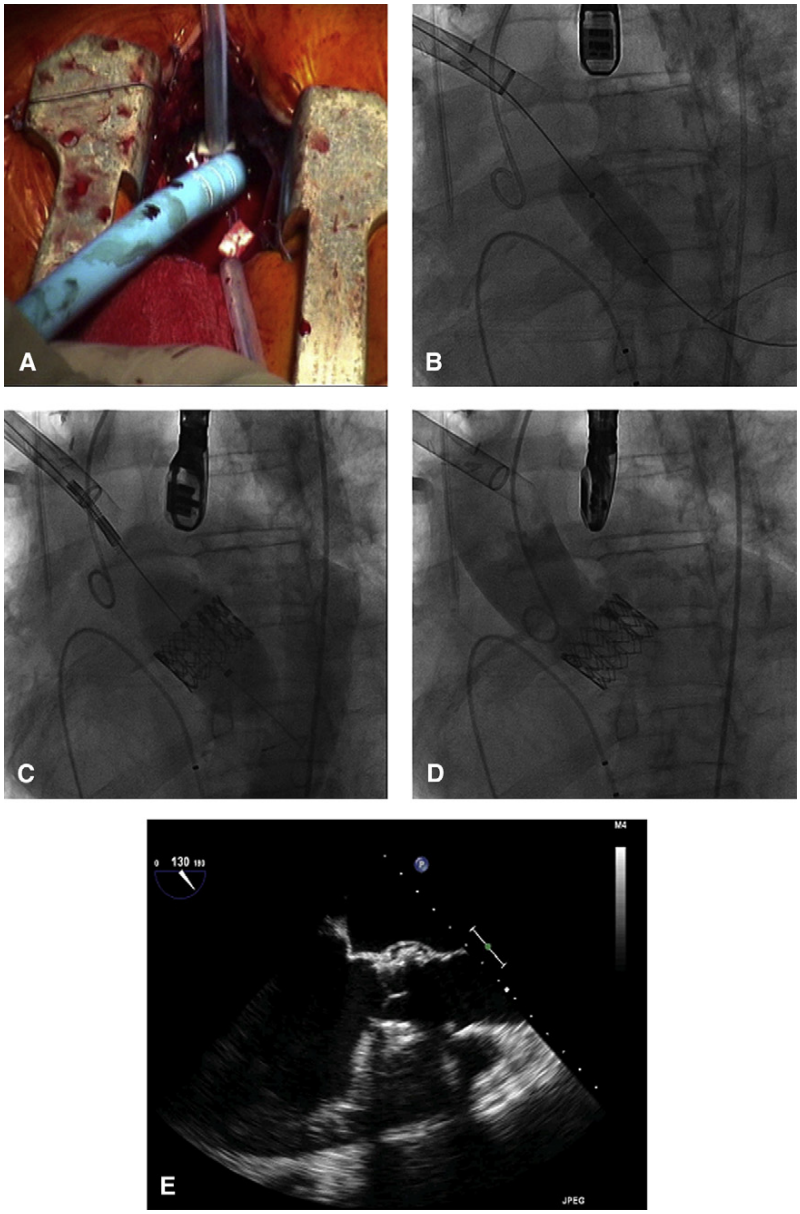


Fig. 18. Procedural steps of TAo-TAVI with the Edwards Sapien balloon-expandable device. A. Double concentric purse string sutures are placed on the ascending aorta and the sheath is introduced after aortic puncture and guidewire insertion. B. Balloon aortic valvuloplasty is performed during rapid pacing. C. The valve is deployed during rapid pacing. D-E. Prosthesis position and function are evaluated by means of aortic angiography and intraoperative trans-esophageal echo.

10. TRANS-SUBCLAVIAN/TRANS-AXILLARY TAVI

This approach is generally carried out if none of the previously described accesses is feasible. It requires a surgical cut-down of the left subclavian artery. Under a technical point of view the procedure is identical to the already described trans-femoral TAVI. The pros of this approach are the relatively easy surgical access, the need for local anesthesia only and that the subclavian artery is usually not diseased. The drawbacks of subclavian TAVI are the risk of major bleeding, the unfavourable sharp 90 degrees angle to access the aortic arch (Fig. 19), and the risk of myocardial ischemia if a mammary artery to left anterior descending coronary artery graft is present.

Fig. 19. Unfavorable sharp angles of TS-TAVI

11. COMPLICATIONS OF TAVI

TAVI should be considered in all respects a "true" surgical procedure and, as every surgical procedure, it should be performed with maximal safety. Safety is a major issue of TAVI, in fact it has been demonstrated that the occurrence of intraoperative complications significantly worsen patient outcomes (52). Rodes-Cabau (53) indentified the need for peri-procedural mechanic hemodynamic support as an independent risk factor for 30-day mortality (OR: 6.84). In view of the strong impact played by intraoperative complications on patient early and late outcomes all efforts should be directed on preventing and effectively managing such occurrence. Prevention can be achieved by careful patient selection, adequate procedural planning (access choice, valve sizing) and execution. The successful management of intraoperative complications needs a strong synergy between physicians and the presence of life saving devices (the already described "safety net") such as, for example, a cardiopulmonary bypass machine with a perfusionist technician in case of acute refractory cardiogenic shock or endovascular occlusion balloons if a damage to the aorta or to a peripheral vessel with severe hemorrhage occurs. TAVI complications are: arterial injury (rupture, dissection), apical access issues, improper positioning, device embolization, coronary obstruction, mitral valve injury, paravalvular regurgitation, cardiac tamponade, heart block, arrhythmias and stroke. In particular, TA-TAVI related complications are: bleeding, left ventricular pseudo-

aneurism, loss of left ventricular function, left lung injury, pleural effusion, pneumothorax, infection of the thoracotomy (54-58).

12. CURRENTLY AVAILABLE TAVI DEVICES

12.1 Edwards Lifesciences Sapien XT THV

The Sapien XT valve is a balloon expandable prosthesis whose leaflets are made of bovine pericardium mounted on a chrome-cobalt stent. The cobalt-chrome based stent frame allows for a more open stent design with fewer and thinner stent struts without loss of radial force. The Edwards Sapien XT trans-catheter heart valve is commercially available in three sizes.

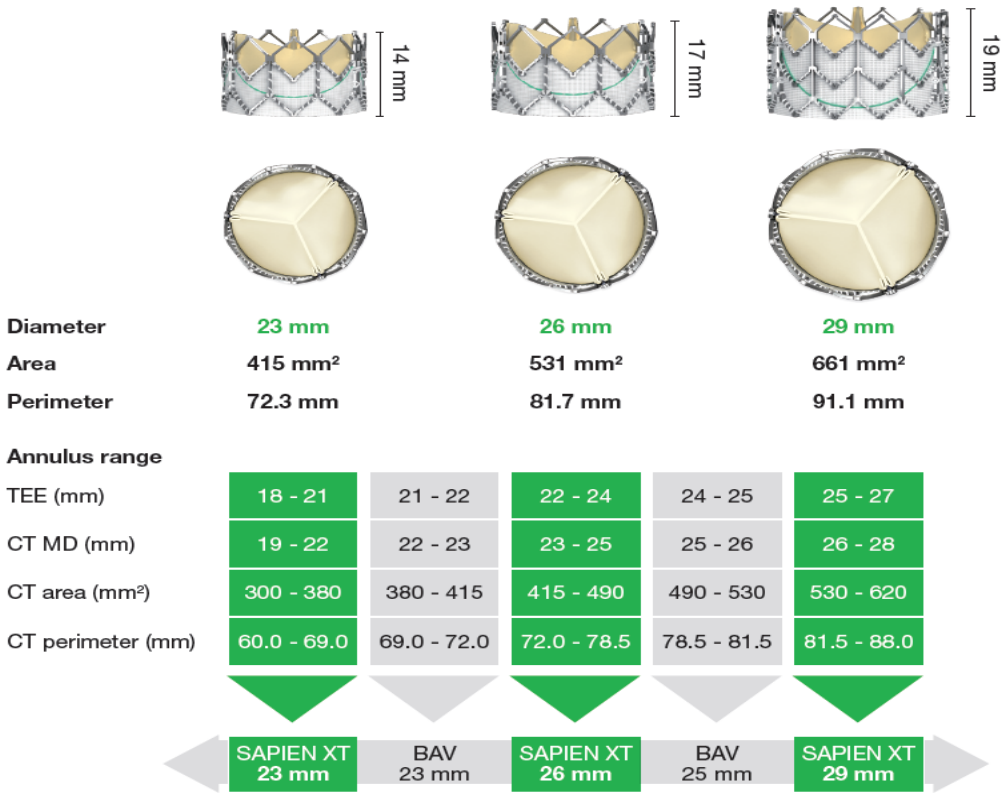


Fig. 20. Edwards Sapien XT sizing chart. TEE: trans-esophageal echo, CT: Computed tomography, MD: Mean diameter, BAV: Balloon aortic valvuloplasty.

Small diameters of the aortic annulus ranging from 18–22 mm are treated with the 23 mm bioprosthesis, whereas annular dimensions ranging from 21–25 mm are treated with a 26 mm bioprosthesis. For large valve dimensions with an annulus measuring in the range of 24–27 mm, a 29 mm Edwards Sapien XT bioprosthesis can be used (59) (Fig. 20)

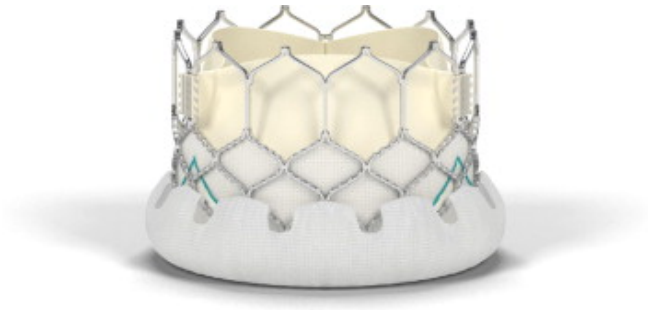


Fig. 21. The new Edwards Sapien 3 trans-catheter aortic valve. This device features a teflon skirt on the external part of the inflow portion that reduces the incidence of paravalvular leaks

The progressive development of smaller sheaths now allows to perform TF-TAVI in a higher number of patients. In fact in the new NovaFlex delivery catheter together with the new E-Sheath the labeled sheath size was reduced to 16 Fr for the 23 mm and 18 Fr for the 26 mm prosthesis. This means that the minimum vessel diameter for a safe TF approach is 6.5 mm for Sapien XT size 23 mm and 26 mm and 7 mm for the 29 mm valve. In addition, Edwards will soon introduce the new Sapien 3 valve that is the evolution of Sapien XT. The Sapien 3 valve has a completely new design that includes a teflon skirt on the external part of the inflow portion of the valve that has the aim of increasing annular sealing thus reducing the incidence of paravalvular leaks. Furthermore the new design allows crimping on smaller catheters both for TF and for TA approach (Fig. 21).

12.2 Medtronic Corevalve

The Medtronic Core-Vale (Medtronic, Minneapolis, Minnesota, USA) uses self-expanding technology and anchors the bioprosthesis in the supra-annular position. The frame is made of Nitinol, which has a shape memory and provides high radial forces. The Nitinol frame, with a single layer of porcine pericardium, can be crimped down to a delivery sheath size of 18 Fr for all valve sizes (23–31 mm). The frame is obtained by laser cutting and generates a high radial force at the distal part of the frame, which serves to anchor the prosthesis within the annulus. The mid-portion of the prosthesis has a concave shape in order to avoid contact with the sinus portion and the origin of the coronary arteries. The proximal part is placed in the ascending aorta and helps to position the prosthesis perpendicular to the native valve. Compared with the balloon-expandable Edwards Sapien trans-catheter valve prosthesis, there is no additional material serving as coverage of the bioprosthesis. The pericardial tissue used to build the three leaflets also serves to form a sealing skirt at the bottom part of the frame. With the latest CoreValve generation (third generation CoreValve, 18 Fr) four different valve sizes are commercially available to cover a broad range of annulus dimensions: small aortic annulus diameters ranging from 18–20 mm are treated with a 23 mm CoreVave Evolut prosthesis, annulus diameters ranging from 20–23 mm require a 26 mm CoreValve prosthesis, annulus diameters ranging from 23–27 mm require a 29

mm prosthesis, while annulus diameters in the range of 26–29 mm are treated with a 31 mm CoreValve bioprosthesis (Fig. 22).

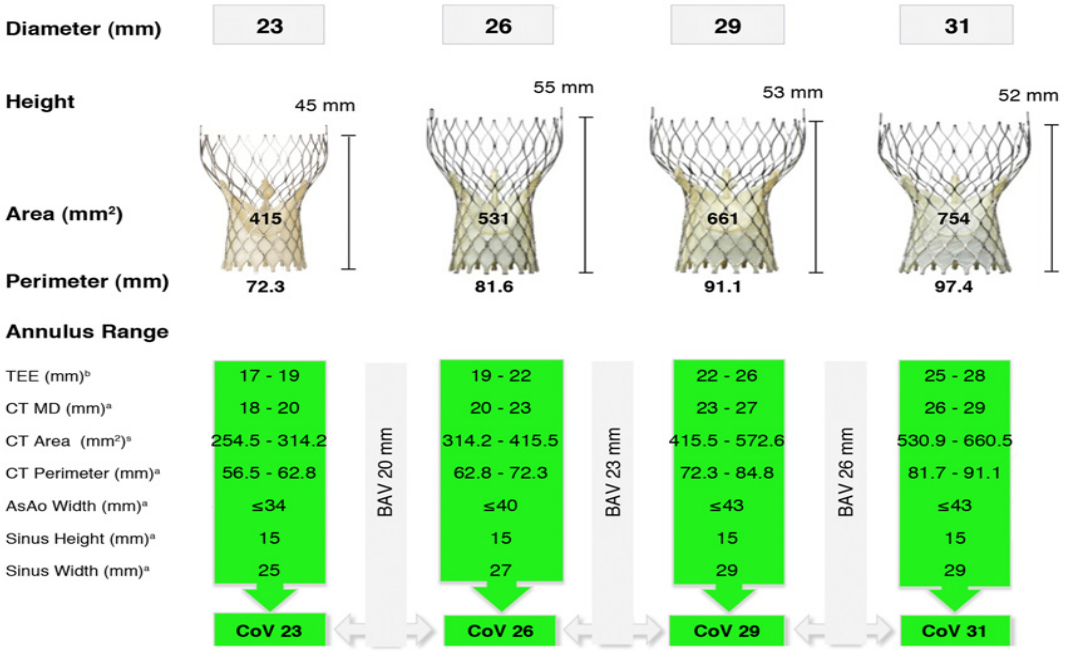


Fig. 22. Medtronic CoreValve sizing chart. TEE: trans-esophageal echo, CT: Computed tomography, MD: Mean diameter, BAV: Balloon aortic valvuloplasty, CoV: CoreValve, AsAo: Ascending aorta.

The Medtronic CoreValve prosthesis is designed for retrograde implantation through femoral access, but has also been successfully implanted through the subclavian artery or using a trans-aortic approach (60).

12.3 Symetis Acurate

Newer generation devices have been designed to improve precise positioning of the prosthesis, enable re-positioning in case of unsatisfactory deployment, and full retrieval whenever needed to improve patient safety and increase

procedural success. Recently, the Symetis Acurate TA trans-catheter heart valve (Symetis, Lausanne, Switzerland) prosthesis was introduced as a new-generation TAVI device (61). The Symetis Acurate prosthesis has self-expanding Nitinol stent frame and a porcine biologic aortic valve. The stent frame has three different segments. The lower segment is tapered and flared in order to provide appropriate fixation within the aortic annulus due to the radial force of the Nitinol. The distal part of this stent segment is covered with PET (polyethylene terephthalate) tissue creating a sealing skirt. The middle segment contains the valve apparatus and three stabilization arms, which form the upper segment of the valve frame. After preparation of the Acurate valve and delivery catheter the device is directly inserted into the left ventricle over a stiff wire in the absence of a delivery sheath. After advancing the trans-catheter valve system through the native aortic valve, all cusps are aligned with the normal anatomical position by manual rotation of the catheter. Stepwise release of the stabilization arms by rotation of the pullback mechanism opens the upper crown and provides fixation of the bioprosthesis in the ascending aorta. By gently pulling on the catheter, the Symetis Acurate TA is placed within the aortic annulus and, during a short period of rapid ventricular pacing, fully released by further unsheathing the

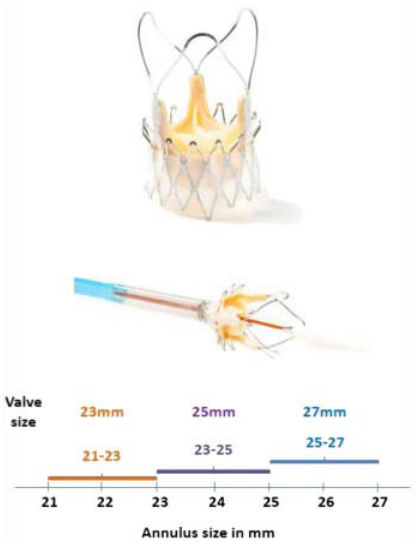


Fig. 23. Symetis Acurate TA trans-catheter aortic valve and its sizing chart.

system. It might be a valuable alternative treatment option for patients with trans-apical access who are not suitable candidates for the balloon-expandable device (e.g. patients with heavily calcified native valves or low distance to the coronary ostia). Devices are available in three different sizes to treat patients with aortic annulus dimensions ranging from 21–27 mm. Using the 23 mm bioprosthesis, small aortic annulus dimensions ranging from 21–23 mm are treated, whereas the 25 mm prosthesis is suitable for annulus dimensions ranging from 23–25 mm, and the 27 mm prosthesis requires annulus dimensions ranging from 25–27 mm (Fig. 23).

12.4 Jena-Valve

The Jena-Valve trans-catheter heart valve device consists of a Nitinol-based stent frame with a regular porcine tissue valve (Elan, Vascutec Inc, Inchinan, UK).

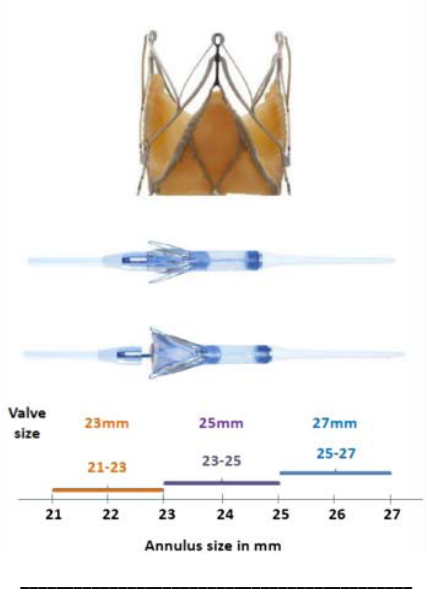


Fig. 24. Jena-Valve trans-catheter aortic valve and its sizing chart.

The stent design includes three dedicated positioning 'feelers', which facilitate appropriate positioning of the prosthesis. The outer part of the device is covered with a sealing skirt of porcine pericardial tissue to reduce the incidence of paravalvular regurgitation. At this point in time the Jena-Valve bioprosthesis is exclusively implanted via the trans-apical access route. After passing the native valve antegradely through a delivery catheter

hosting the crimped bioprosthesis, without the need for a sheath, the three feelers are released in the supra-annular position. By manual manipulation of the catheter an alignment according to the anatomy of the aortic sinus is achieved, thereby embracing the native aortic cusps. During a short period of rapid ventricular pacing the Jena-Valve is then released. The native aortic valve is clipped within the feelers and the base of the stent frame. The radial expansion force of the self-expandable stent frame allows a complete displacement of the degenerated native valve cusps and stable fixation in a sub-coronary position. Currently three different valve dimensions are commercially available to cover a wide range of aortic annulus dimensions (23 mm, 25 mm and 27 mm) (Fig.24).

12.5 St. Jude Portico

The Portico Trans-catheter Aortic Valve Implantation System (St. Jude, Minneapolis, MI, USA) has recently received the CE mark for the treatment of patients with aortic valve stenosis. It has a self-expandable nitinol frame with bovine pericardium valve leaflets and porcine pericardium sealing cuff (Fig. 25). At this point in time the Portico bioprosthesis is exclusively implanted via the trans-femoral access route. The trans-apical delivery is under its final development stages. The outflow portion of the stent frame incorporates 3 retention tabs, which secure the crimped valve to the delivery system. The Portico valve is sized according to the nominal external stent diameter at the

Fig. 25. St. Jude Medical Portico trans-catheter valve

valve level. Currently, only the 23-mm device is available. The catheter consists of a soft tapered nose cone, an 18F capsule that contains the compressed valve, and a 12F shaft. A handle incorporates mechanisms to unsheathe and release the valve using a rotating thumbwheel.

12.6 Direct Flow

The Direct Flow Trans-catheter Aortic Heart Valve System (Santa Rosa, CA, USA) has a metal-free frame and bovine pericardial leaflets. The Direct Flow Medical System incorporates a polymer frame, which is expanded using pressurized saline and contrast for placement, assessment and repositioning. The saline/contrast solution is exchanged for a quick-curing polymer that solidifies and secures the valve in place once optimal positioning is reached. The system is fully repositionable and retrievable until polymer exchange. The metal-free design enables a low-profile (18 French), fully sheathed delivery system for all valve sizes (Fig.26). The device comes in two sizes: 25 mm and 27 mm

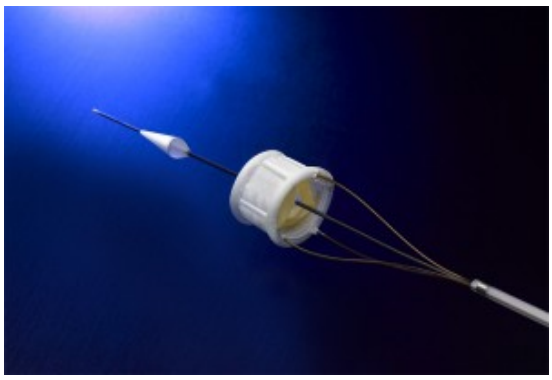


Fig. 26. Direct Flow trans-catheter aortic valve.

that cover annulus diameters from 19 to 24 mm and from 24 to 26,5 mm, respectively. The first results of the DISCOVER trial, a prospective multicenter study that included 100 patients were recently presented at the 2013 Euro-PCR meeting by Joachim Schofer. These results include only procedural and 30-day assessment of patients. Thirty-day mortality was 1% (1 patient), device success (according to the Valve Academic Research Consortium –VARC- definitions) was 91%, and combined safety endpoint (VARC) was 89%. Post-procedure aortic regurgitation ≤mild was found in 99% and mean trans-aortic gradient was 14 mmHg. These results are encouraging but longer follow-up and larger cohorts are required to fully understand the behavior of this device.

12.7 Medtronic Engager

The Engager bioprosthesis (Medtronic 3F Therapeutics, Santa Ana, CA) consists of bovine pericardium leaflets mounted on a nitinol stent. Its current version uses a 29F system (32F crossing profile) for trans-apical delivery. During implantation, the control arms that capture the native leaflets are released and allow for tactile feedback during anatomically correct placement of the valve at a predefined height within the aortic annulus. The lower part of the nitinol stent is covered and formed to have the potential for better sealing of

Fig. 27. Medtronic Engager trans-catheter valve

paravalvular leaks (Fig. 27). The intermediate follow up results from the multicenter Engager European pivotal trial have been recently published (December 2013) in the Annals of Thoracic Surgery. Data show that for all of the attempted implantations (n = 60), the Engager prosthesis was positioned in the correct anatomic position without conversions to surgery, second valve implantation, device malposition, aortic annular rupture, or coronary obstruction. All-cause mortality was 9.9% at 30 days and 16.9% at 6 months. The baseline mean aortic valve gradient was 43.7 ± 16.7 mm Hg and 11.5 ± 5.0 mm Hg at 30 days, and showed similar reduction at 6 months (13.9 ± 6.2 mm Hg). There was no paravalvular regurgitation greater than mild through 6 months (62).

12.8 Boston Scientific Lotus

The Lotus™ Aortic Valve Replacement System (Boston Scientific Corporation, Natick, MA, USA) includes a bioprosthetic aortic valve implant consisting of three bovine pericardial leaflets attached to a braided nitinol frame with a radiopaque marker and a catheter-based system for introduction and retrograde delivery via the femoral artery (Fig. 28). The valve is pre-attached to the delivery system. The Lotus Valve starts working early in deployment,

Fig. 28. Boston Scientific Lotus trans-catheter heart valve.

aiding controlled, precise initial positioning, and repositioning or full retrieval at any point prior to definitive release if required. Rapid pacing is not required during the implant procedure. The valve is designed to expand radially as the valve shortens during deployment. An adaptive seal surrounds the inflow portion of the device and is designed to reduce paravalvular regurgitation. The REPRISE I study (63) evaluated results of Lotus valve implantation in 11 patients. The primary endpoint (clinical procedural success) included successful implantation without major adverse cardiovascular or cerebrovascular events (MACCE). In all patients the first Lotus valve was successfully deployed. Partial resheathing to facilitate accurate placement was attempted and successfully performed in four patients; none required full retrieval. The primary endpoint was achieved in 9 out of 11 patients with no in-hospital major adverse cerebral and cardiovascular events. The cohort's mean aortic gradient decreased from 53.9±20.9 mmHg at baseline to 15.4±4.6 mmHg ($p<0.001$) at one-year; valve area increased from 0.7±0.2 cm2 to 1.5±0.2 cm2 ($p<0.001$). Discharge paravalvular aortic regurgitation was absent, trivial and mild in 8, 1 and 2 patients, respectively. There were no deaths, myocardial infarctions or new strokes through one year.

13. INDICATIONS AND CONTRAINDICATIONS FOR TAVI

According to 2012 European Society of Cardiology/European Association of Cardio-Thoracic Surgery guidelines on the management of valvular heart disease (13) surgical aortic valve replacement is indicated in symptomatic patients with aortic valve area < 1cm^2 and mean trans-aortic gradient >40 mmHg (Fig. 29).

	Class[a]	Level[b]	Ref[c]
AVR is indicated in patients with severe AS and any symptoms related to AS.	I	B	12, 89, 94
AVR is indicated in patients with severe AS undergoing CABG, surgery of the ascending aorta or another valve.	I	C	
AVR is indicated in asymptomatic patients with severe AS and systolic LV dysfunction (LVEF <50%) not due to another cause.	I	C	
AVR is indicated in asymptomatic patients with severe AS and abnormal exercise test showing symptoms on exercise clearly related to AS.	I	C	
AVR should be considered in high risk patients with severe symptomatic AS who are suitable for TAVI, but in whom surgery is favoured by a 'heart team' based on the individual risk profile and anatomic suitability.	IIa	B	97
AVR should be considered in asymptomatic patients with severe AS and abnormal exercise test showing fall in blood pressure below baseline.	IIa	C	
AVR should be considered in patients with moderate AS[d] undergoing CABG, surgery of the ascending aorta or another valve.	IIa	C	
AVR should be considered in symptomatic patients with low flow, low gradient (<40 mmHg) AS with normal EF only after careful confirmation of severe AS.[e]	IIa	C	
AVR should be considered in symptomatic patients with severe AS, low flow, low gradient with reduced EF, and evidence of flow reserve.[f]	IIa	C	
AVR should be considered in asymptomatic patients, with normal EF and none of the above mentioned exercise test abnormalities, if the surgical risk is low, and one or more of the following findings is present: • Very severe AS defined by a peak transvalvular velocity >5.5 m/s or, • Severe valve calcification and a rate of peak transvalvular velocity progression ≥0.3 m/s per year.	IIa	C	
AVR may be considered in symptomatic patients with severe AS low flow, low gradient, and LV dysfunction without flow reserve.[f]	IIb	C	
AVR may be considered in asymptomatic patients with severe AS, normal EF and none of the above mentioned exercise test abnormalities, if surgical risk is low, and one or more of the following findings is present: • Markedly elevated natriuretic peptide levels confirmed by repeated measurements and without other explanations • Increase of mean pressure gradient with exercise by >20 mmHg • Excessive LV hypertrophy in the absence of hypertension.	IIb	C	

AS = aortic stenosis; AVR = aortic valve replacement; BSA = body surface area; CABG = coronary artery bypass graft surgery; EF = ejection fraction; LV = left ventricular; LVEF = left ventricular ejection fraction; TAVI = transcatheter aortic valve implantation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting class I (A + B) and IIa + IIb (A + B) recommendations.
[d]Moderate AS is defined as valve area 1.0–1.5 cm^2 (0.6 cm^2/m^2 to 0.9 cm^2/m^2 BSA) or mean aortic gradient 25–40 mmHg in the presence of normal flow conditions. However, clinical judgement is required.
[e]In patients with a small valve area but low gradient despite preserved LVEF, explanations for this finding (other than the presence of severe AS) are frequent and must be carefully excluded. See text (evaluation of AS).
[f]Also termed contractile reserve.

Fig. 29. Indications for aortic valve replacement in aortic stenosis according to the guidelines issued in 2012 by the European Society of Cardiology

TAVI is recommended in patients with severe symptomatic AS who are, according to the 'heart team', considered unsuitable for conventional surgery because of severe comorbidities (Fig. 30).

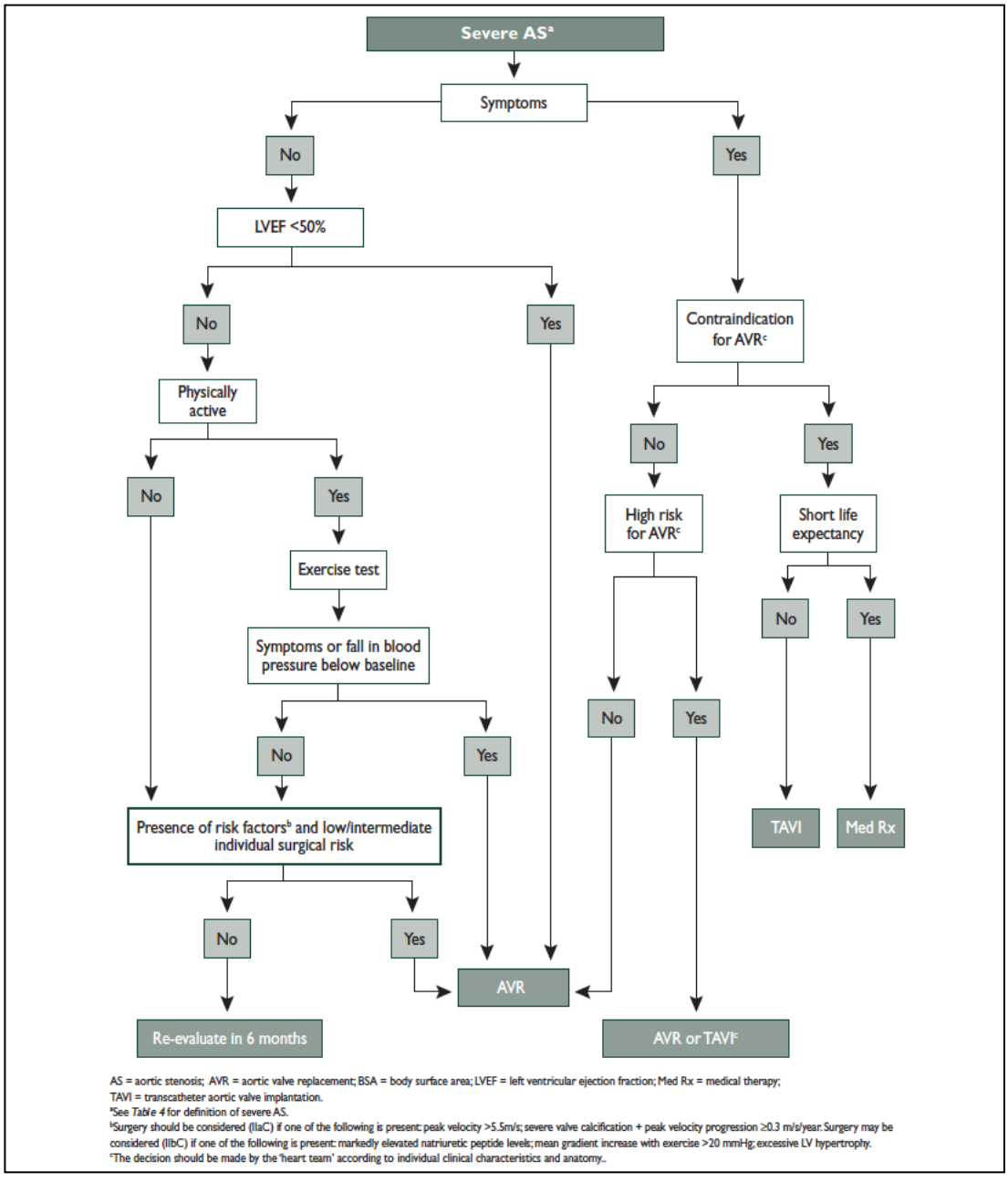


Fig. 30. Management of severe symptomatic aortic valve stenosis according to the guidelines issued in 2012 by the European Society of Cardiology

Among high-risk patients who are still candidates for surgery, the decision should be individualized. TAVI should be considered as an alternative to surgery in those patients for whom the 'heart team' prefers TAVI, taking into consideration the respective advantages/disadvantages of both techniques. A logistic Euro-SCORE ≥20% and/or STS mortality score≥10% have been suggested as cut-off values for TAVI. However, these scores were not developed nor validated in a high-risk elderly population. Thus caution should be used in their use as the only indication for TAVI. Other important conditions such as porcelain aorta, frailty, previous cardiac operations, hostile chest, and chest radiation should lead to schedule a patient for TAVI even if risk scores are not particularly high. The PARTNER II trial (64), that is still ongoing at the present time, is enrolling patients with an intermediate risk profile (STS mortality score >4%) and will probably tell us if TAVI indications can be expanded to patients with lower risk profile. To date, the issues that are still partially unsolved and that have limited TAVI diffusion to intermediate risk patients are mainly related to post-procedural paravalvular leaks and to valve durability. Paravalvular leak occurs in many patients after TAVI (65). Main causes of paravalvular leak are: wrong selection of the size of the device, malposition and bulky eccentric calcification (66-68). There is clear evidence that at least moderate paravalvular leak has a significant impact on survival. On the other hand, there is conflicting evidence about the impact of mild paravalvular leak on survival. Results from the PARTNER trial show that the presence aortic

regurgitation (mild, moderate, or severe vs. none or trace) after TAVI is associated with increased late mortality (hazard ratio, 2.11; 95% CI, 1.43-3.10; P<0.001) (69). Furthermore, the effect of aortic regurgitation on mortality seems to be proportional to the severity of the regurgitation (Fig. 31), but even mild aortic regurgitation is associated with a reduced long-term survival.

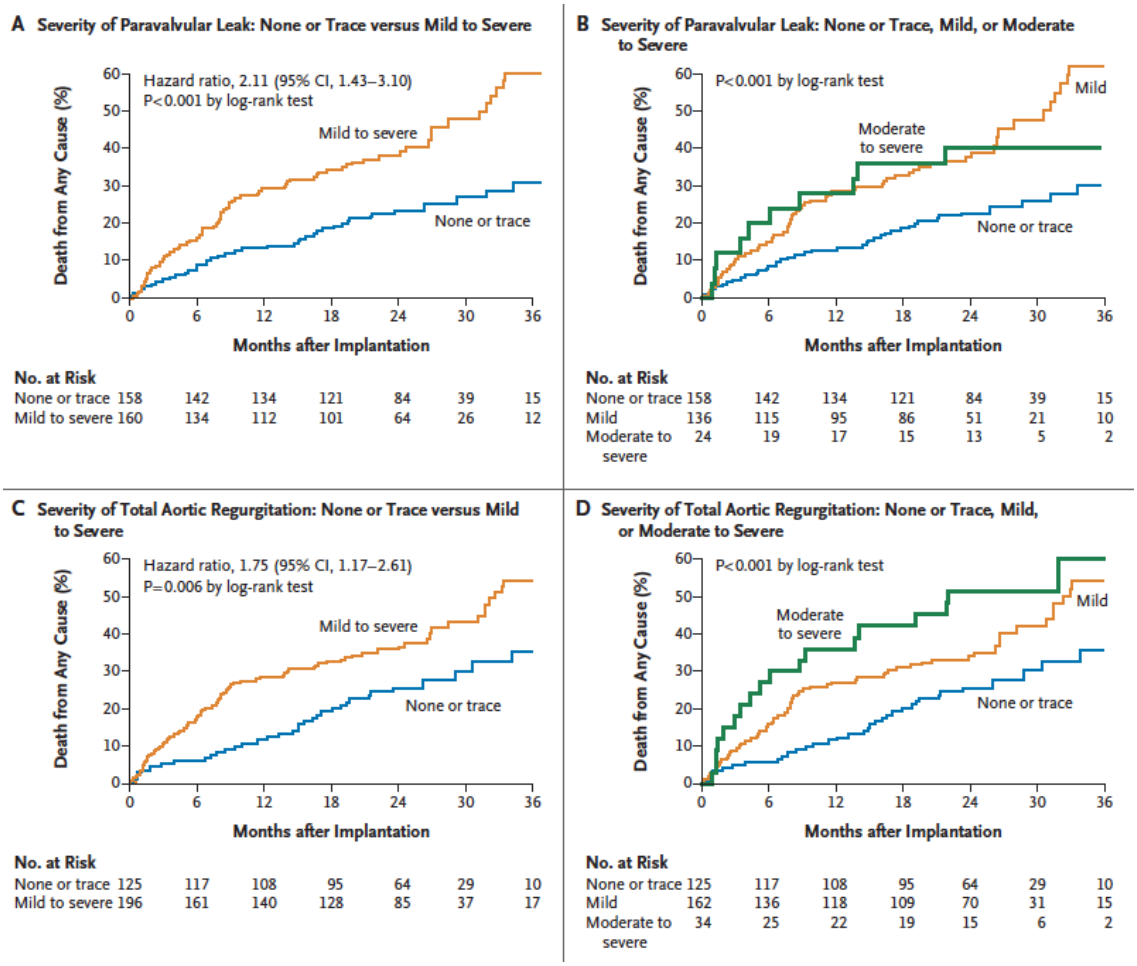


Fig. 31. Relation of aortic regurgitation to all-cause mortality in the TAVI population. Data from the PARTNER trial (69)

Different results are observed when looking at "real world" registries like the German Aortic Valve Registry (GARY) and the FRANCE 2 TAVI Registry. The latter (70) shows that patients with post-procedural paravalvular leak grade 1 (mild) have exactly the same mortality rate than patients with absent regurgitation (i.e. 10% all-cause mortality at 1 year) while patients with at least grade 2 (moderate and severe) Paravalvular leak (PVL) have significantly worse 1 year outcomes (25% all-cause mortality at 1 year, p<0.001), independently from the implanted valve-type(Fig. 32-33).

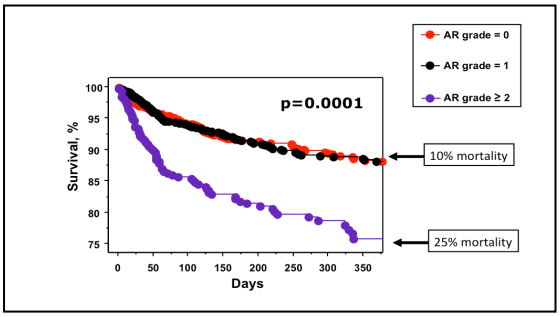


Fig. 32. One year actuarial mortality according to post-procedural aortic regurgitation. Data from the FRANCE 2 registry

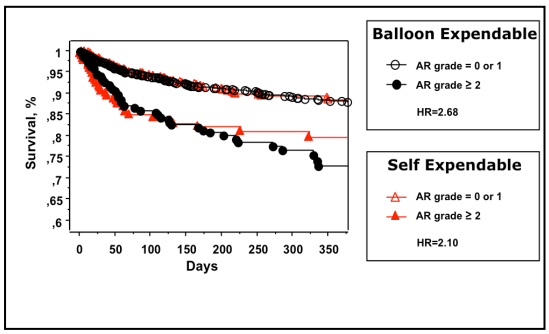


Fig. 33. Impact of paravalvular regurgitation on one-year mortality according to valve type. Data from the FRANCE 2 registry

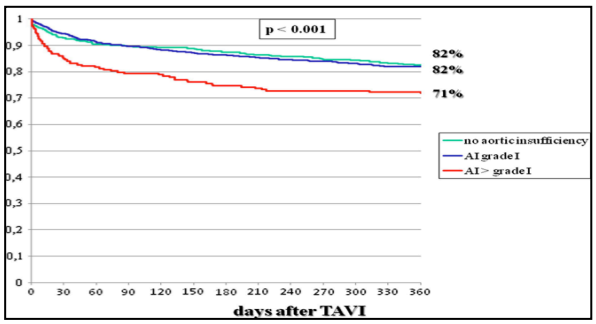


Fig. 34. One-year actuarial mortality according to post-procedural aortic regurgitation. Data from the German Aortic Valve Registry

Same results are visible when looking at data from the German registry (71-73) where patients with none or mild post-TAVI PVL have 82% survival at 1

year versus 71% survival of patients with at least moderate PVL ($p<0.001$) (Fig. 34).

However, it is likely that improvements in valve design as well as in procedural planning and performance will lead to a significant decrease in the rate of PVL. If we look at valve durability, data on long-term behavior of TAVI devices are still lacking since TAVI growth and diffusion is relatively recent. Longer follow up until time points when valve related adverse events are more likely to occur is mandatory. Early structural valve deterioration is a theoretical concern with TAVI since the long-term durability of trans-catheter valves is still unknown. The Edwards Sapien valve is constructed of the same bovine pericardial tissue that has been treated with the same fixation and decalcification processes as the surgical valves, and has the same durability performance by accelerated wear "in vitro" testing. However, we cannot assume that the durability of trans-catheter valves will be the same as surgical valves for several reasons: different design resulting in differing shear forces on the tissue, use of thinner pericardial tissue and above all the crimping process that may cause tissue damage (74, 75). To date there has been no substantive reports of early structural valve deterioration with trans-catheter valves. No cases of operation for structural valve deterioration or changes in aortic valve area and mean trans-valvular gradients were reported in the PARTNER trial at 2 years (69). Obviously experience is too limited to date, with only a small number of patients having intermediate term follow-up, to make statements with any degree of assurance

regarding long-term durability. However, it is reassuring that until now structural valve deterioration has not been an issue. This issue will assume greater importance though as TAVI experience expands into lower risk and younger patients with longer life expectancy. Whereas the mean life expectancy in the current TAVI treated population is 5–7 years, some greater assurance of long-term durability is necessary before significant further expansion occurs. It should also be remembered that with surgically implanted valves, there is decreased valve durability in younger ages and one can assume that trans-catheter valves will follow the same pattern.

Always according to ESC/EACTS guidelines (13), TAVI should only be performed in hospitals with cardiac surgery on-site. Contraindications, both clinical and anatomical, should be identified and are shown in figure 34.

Absolute contraindications
Absence of a 'heart team' and no cardiac surgery on the site
Appropriateness of TAVI, as an alternative to AVR, not confirmed by a 'heart team'
Clinical
Estimated life expectancy <1 year Improvement of quality of life by TAVI unlikely because of comorbidities Severe primary associated disease of other valves with major contribution to the patient's symptoms, that can be treated only by surgery
Anatomical
Inadequate annulus size (<18 mm, >29 mm[a])
Thrombus in the left ventricle
Active endocarditis
Elevated risk of coronary ostium obstruction (asymmetric valve calcification, short distance between annulus and coronary ostium, small aortic sinuses)
Plaques with mobile thrombi in the ascending aorta, or arch
For transfemoral/subclavian approach: inadequate vascular access (vessel size, calcification, tortuosity)
Relative contraindications
Bicuspid or non-calcified valves
Untreated coronary artery disease requiring revascularization
Haemodynamic instability
LVEF <20%
For transapical approach: severe pulmonary disease, LV apex not accessible

AVR = aortic valve replacement; LV = left ventricle; LVEF = left ventricular ejection fraction; TAVI = transcatheter aortic valve implantation.
[a]Contraindication when using the current devices.

Fig. 34. Contraindications for TAVI according to the guidelines issued in 2012 by the European Society of Cardiology

Eligible patients should have a life expectancy of more than 1 year and should also be likely to gain improvement in their quality of life, taking into account their comorbidities. Contraindications for TF-TAVI are mainly related to aorto-iliac vessels diameters, tortuosity and extent of calcifications. Furthermore, extremely tortuous vessels represent a contraindications as well as the presence of circumferential calcifications in arteries with borderline diameters that make vessels completely rigid and non-compliant. The presence of atherosclerotic plaques in the aortic arch, especially if at the origin of supra-aortic vessels may represent another contraindication to TF-TAVI for the risk of plaque disruption and consequent cerebral embolization. Contraindications to TA-TAVI are severe left ventricle dysfunction with an ejection fraction <20% and the presence of LV aneurysm with thrombus stratification. Relative contraindications to TA-TAVI are represented by chest deformities and severe chronic obstructive pulmonary disease (COPD). The presence of diffuse calcifications on the ascending aorta is the main contraindication for Tao-TAVI. Relative contraindications for Tao-TAVI are represented by chest deformity, COPD and previous cardiac operations. If a

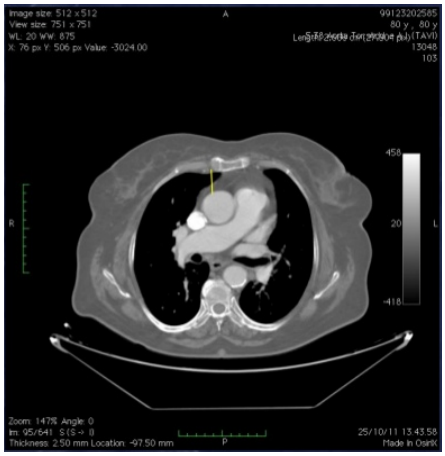


Fig. 35. Preoperative CT scan of a patient scheduled for Tao-TAVI. Less than 50% of the ascending aorta is placed rightward with respect to the right sternal edge (yellow sign). Thus, this patient would be better treated with a mini-sternotomy rather than a mini right thoracotomy.

Tao-TAVI through mini right thoracotomy is scheduled, particular attention should be given to the position of the ascending aorta with respect to the right sternal edge. If the aorta is placed more than 50% rightward, then the access to the aorta will be easy and straightforward. On the other hand, if the aorta is more medial, its approach through right thoracotomy may be more challenging and a mini-sternotomy is therefore suggested (Fig. 35) (76, 77).

14. PREOPERATIVE IMAGING

A careful and complete evaluation of patient's clinical history, general conditions and diagnostic imaging examinations is mandatory for good TAVI outcomes. As every cardiac operation, TAVI requires a complete preoperative screening that includes: cardiac catheterization (with coronary artery angiography, aortic angiography, left ventriculography, right and left pressures measurement), echocardiography, complete arterial Doppler study, pulmonary function evaluation and blood exams. In particular, imaging screening may orient physicians in the choice of the most suitable TAVI device as well as access route for each single patient according to his specific anatomic characteristics. Furthermore, appropriate preoperative imaging allows a precise selection of the size of the chosen device. This chapter will focus on imaging screening examinations that are specific for patients scheduled for TAVI.

14.1 Echocardiography

To assess the size and type of device and reduce the risk of events, a complete imaging dataset is essential (Fig. 36) (78).

The most frequent etiology in TAVI patients is calcific degenerative disease.

	TTE	TEE	MDCT
Aortic valve morphology	++	+++	+++
Annulus			
Diameter	+	++	+++
Distance to RCA	+	++	+++
Distance to LMS	–	+	+++
Aorta			
Sinus diameter	++	+++	+++
Ascending diameter	+	+++	+++
Calcification	+	+	+++
Other			
LV function	+++	+	+
MR severity	+++	+++	–
RV/PA pressure	+++	++	–

Quality of information acquired from echocardiography and MDCT (+++ highest quality). LMS, left main stem; LV, left ventricular; MDCT, multidetector CT; MR, mitral regurgitation; PA, pulmonary artery; RCA, right coronary artery; RV, right ventricle; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography.

Fig. 36. Imaging dataset required for preoperative evaluation before TAVI (78).

However, it is important to evaluate if the patient has a bicuspid valve because this may preclude TAVI or make procedural success less likely due to asymmetric distribution of leaflets and of annular calcifications (79). In calcific degenerative disease, thickening starts at the base of the cusps and progresses towards the leaflets. In tricuspid valves, the assessment of calcium distribution on each leaflet is important because this may predict potential coronary ostia occlusion during deployment. The diameter of the 'echocardiographic annulus' is a key measurement in determining if TAVI can be performed and what should be the size of the device. In fact, undersizing may cause paravalvular leak and also device embolization (80) while oversizing can cause rupture of the annulus that is generally fatal (81). The annulus diameter should be measured at the hinge point between the base of the anterior mitral leaflet and the adjacent aortic cusp in a systolic frame with maximal leaflet separation. Since the annulus

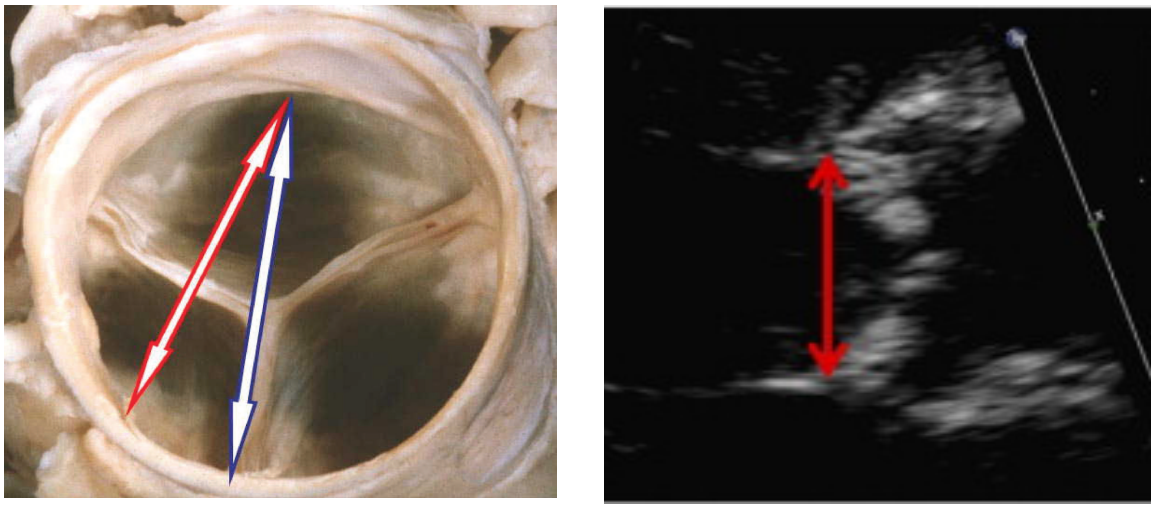


Fig. 37. Anatomic and bidimensional echocardiographic view of human aortic root. Echocardiographic measurement does not transect the full diameter of the annulus (blue arrow) but takes into consideration a shorter cut (red arrow) (1).

shape is also often slightly ellipsoidal rather than circular, it is usually underestimated by transthoracic echocardiography (TTE) and trans-esophageal echocardiography (TEE) (82-83) (Fig. 37).

Thus preoperative or intraoperative 3D TEE is generally recommended. Other than for the measurement of annulus diameter, echocardiography is also important for left ventricle, mitral valve and right ventricle assessment. A careful examination of the left ventricular outflow tract, and in particular the evaluation of septal bulging, may help to prevent severe complications and to guide the choice of the device size. Furthermore, measurement and morphologic evaluation of the aortic root and of the sino-tubular junction (STJ) is another important step in procedural planning. In the presence of a borderline annulus, which may accept either a small or a big device, if aortic sinuses are narrow and STJ is small, the smaller device should be chosen. During a TA-TAVI operation, intraoperative TEE is helpful to find the correct apical site where to place sutures and to insert the sheath.

14.2 Computed Tomography Scan

As opposed to conventional aortic valve replacement, physicians performing TAVI have only a "virtual" visualization of the aortic valve. As a result, imaging is necessary to allow for appropriate valve sizing. CT scan is now becoming the "gold-standard" preoperative diagnostic evaluation for TAVI planning. The

information that CT scan is able to provide is mainly related to: three-dimensional reconstruction of the aortic annulus and measurement of diameters, perimeter and area of the annulus, distance of the annulus from the coronary ostia, length of the aortic valve leaflets, distribution of calcium on the annulus and on the leaflets, evaluation of the best access pathway, assessment of the appropriate fluoroscopic projection angles that permit exactly orthogonal views of the valve (84). Image acquisition remains challenging, however, since a large imaging volume needs to be covered from the aortic arch to the bifurcation of the femoral arteries. The volume of iodinated contrast medium is of concern in many patients because candidates for TAVI frequently have chronic kidney disease. Given the commonly advanced age of patients being considered for TAVI, radiation exposure is of lesser concern. Imaging of the aortic root must be synchronized to the electrocardiogram. Spatial resolution must be high to provide adequate imaging, especially of the aortic root and of the ilio femoral arteries, because in both regions detailed dimensions must be obtained to adequately plan the procedure. Choosing the appropriate prosthesis size requires accurate measurement of the dimensions of the aortic annulus. Measurements of aortic annulus size have historically been performed with TTE and TEE. It has been demonstrated that CT-scan based sizing provides larger aortic annulus dimensions if compared to echography. There are many studies that demonstrate that the use of CT-scan for sizing provides more reliable data and consequently improves TAVI outcomes (85-90). When

assessing the aortic annulus with CT-scan there are three measurements that are suggested by the guidelines: mean diameter, area and circumference.

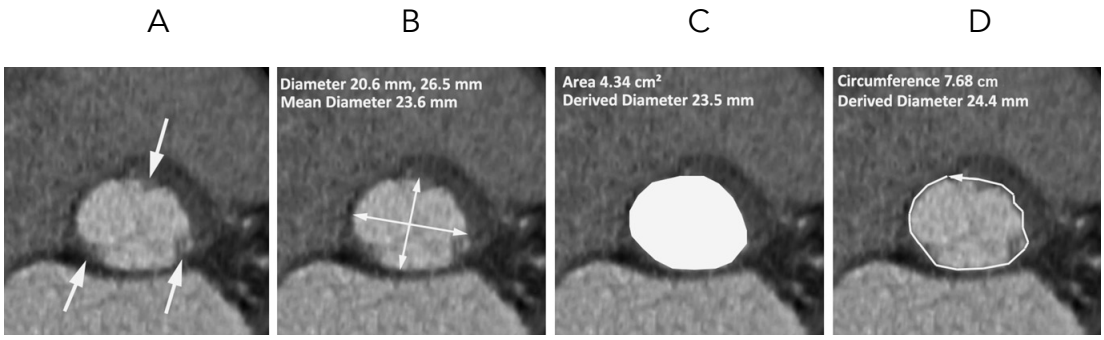


Fig. 38. Measurement of the aortic annulus diameter using CT scan. A. The optimal plane includes the three lowest insertion points of the coronary cusps (arrows). B. The short and long annulus diameters are measured and the mean diameter in calculated. C. The annulus area is measured and the mean diameter is derived assuming circularity of the annulus. D. The perimeter of the annulus is measured and the mean diameter is derived assuming circularity of the annulus.

Besides aortic annulus size, other anatomic measures of the aortic root have relevance for TAVI planning. They include distance of the coronary ostia from the aortic valve plane, aortic cusp length, width of the aortic sinus, width of the sino-tubular junction, and width of the ascending aorta. These measurements are important in order to predict potentially catastrophic complications such as coronary occlusion and root injury. It has also been demonstrated that severity and pattern of distribution of calcium on the aortic annulus and valve leaflets, identified with CT scan, correlate with the presence and with the severity of postoperative paravalvular leak. (91).

15. THE PARTNER TRIAL

The PARTNER (Placement of Aortic Trans-catheter Valves) trial is the first and to date the only prospective randomized trial studying outcomes of TAVI. The PARTNER trial was designed as a multicenter randomized trial comparing open standard aortic valve replacement (AVR) with TAVI in high-risk patients, and also TAVI versus standard medical treatment (47-49, 69). In addition, cost analysis, 2-year data analysis, and stroke analysis have been done, as well as analysis of continued access for TA-TAVI (48, 69, 92, 93). Briefly, PARTNER A patients were required to be high risk for conventional open valve surgery (49, 69). This was determined by a minimal Society of Thoracic Surgeons (STS) score of 10% for death, and the surgeons' assessment of the risk as >15%. For PARTNER B (47, 48) 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%. The device used for this trial was the Edwards Sapien balloon-expandable valve. The design of the PARTNER trial is shown in figure 39.

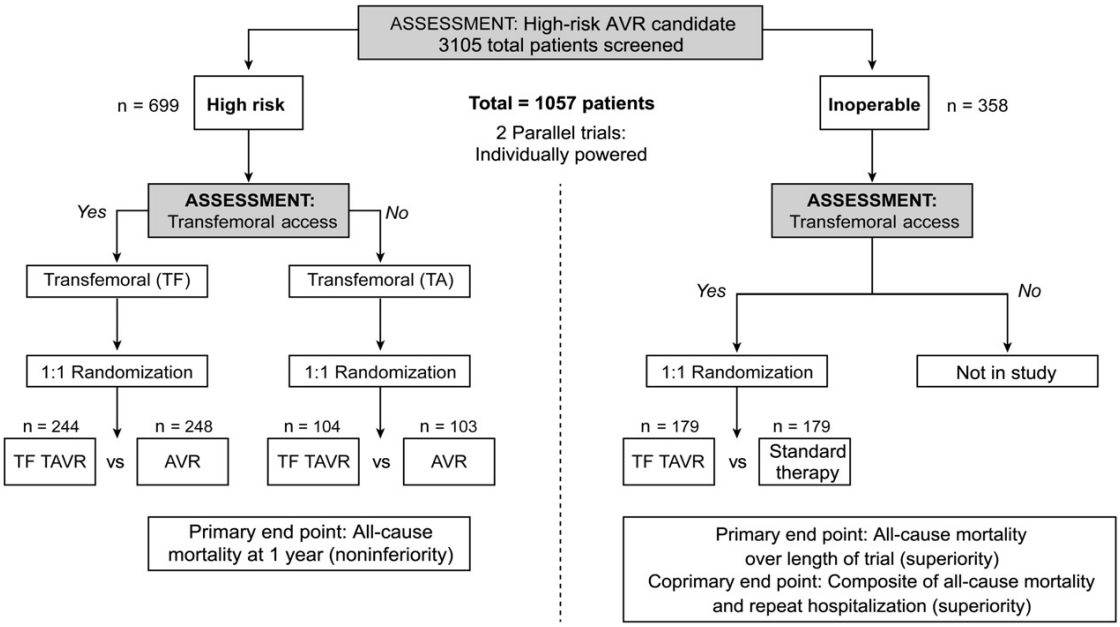


Fig. 39. PARTNER trial design. AVR: Aortic valve replacement, TAVR: Trans-catheter aortic valve replacement, TF: Trans-femoral, TA: Trans-apical

15.1 PARTNER A

For PARTNER A, the trial was designed for non-inferiority of TAVI versus open AVR. In the PARTNER A arm, 351 patients were assigned to AVR and 348 to TAVI, of whom 244 were TF-TAVI and 104 TA-TAVI (69). Thirty-day mortality for intention to treat for was 3.4% for TAVI and 6.5% for AVR (p=0.07); for TF-TAVI, mortality was 3.3% versus 6.2% with AVR (p=0.13). For TA-TAVI, 30-day mortality was 3.8% and control AVR was 7.0% (p=0.32). At 1 year, mortality was 24.2% for TAVI and 26.8% for AVR, with no significant difference; therefore the non-inferiority endpoint was met. Prevalence of neurologic events for TAVI versus AVR at 30 days was 5.5% versus 2.4% (p=0.04); prevalence of major strokes was 3.8% versus 2.1% (p=0.2). For all neurologic events, TF-TAVI versus open AVR was 4.6% versus 1.4% (p=0.05).

15.2 PARTNER B

For PARTNER B the trial was designed to meet superiority of TAVI versus optimal medical management (including balloon aortic valvuloplasty). The primary endpoint was death or rehospitalization at one year. In PARTNER B (47, 48), 358 patients were enrolled, and baseline variables were mostly well balanced. At 30 days after randomization, TAVI mortality was 5.0% and control was 2.8% (p=0.61) while at 1 year the mortality was 30.7% for TAVI and 50.7% for control. For the primary end point, death or rehospitalization, TAVI was also superior to control (p<0.001) and therefore the primary endpoint was met.

Two-year data analysis of PARTNER A and Bconfirmed the two previous reports, but also added further information on late outcomes concerning stroke and paravalvular leaks. In particular, the update of PARTNER A showed an additional 32 TAVI deaths and 25 AVR deaths, with no difference at 2 years (33.9% and 35%, respectively, p=0.78).

The analysis of paravalvular regurgitation of the PARTNER trial is particularly interesting. The incidence of moderate and severe PVL at one year was 7% and 1,9%, respectively (p<0,001). At two years the incidence of moderate and severe PVL was 6.9% and 0.9%, respectively (p<0.001). As described in a previous paragraph, paravalvular or total aortic regurgitation after TAVI was associated with worse survival (p<0.001), and even mild regurgitation increased

mortality.The detailed analysis of stroke after TAVI or AVR in PARTNER A showed that 51% of strokes were procedure related, and 38% occurred within 2 days: 43% of patients ultimately died (94). Analysis by procedure showed that for neurologic events (1.4% at 30 days), open AVR had the lowest risk followed by TF-TAVI (4.6% at 30 days; p=0.05), then group non-TF, with no difference between TA-TAVI and open AVR. Overall, for both TAVI and open AVR, the early multivariable predictors of neurologic events were TAVI versus open AVR, pre-procedure cerebrovascular disease, and smaller indexed native aortic valve area. The late hazard phase predictors were TAVI versus open AVR, higher New York Heart Association class, stroke within 6 to 12 months, non-TF-TAVI group, with less risk with previous percutaneous coronary intervention, and COPD.

16. VARC DEFINITIONS

When reporting data and results on a particular procedure it's important that studies speak the same language in order to be comparable and to make further analysis easier and reliable. To achieve this target, the Valve Academic research Consortium has published in 2011 "Standardized Endpoints Definitions for Trans-catheter Aortic Valve Implantation Clinical Trials" (95). This paper, updated in 2012 (96), aims to propose standardized consensus definitions for important clinical endpoints in TAVI investigations in order to improve the quality of clinical research and to enable meaningful comparisons between clinical trials. Consensus criteria were developed for the following endpoints: mortality, myocardial infarction, stroke, bleeding, acute kidney injury, vascular complications, and prosthetic valve performance. Composite endpoints for TAVI safety and effectiveness were also recommended. Safety is characterized by the avoidance of device related or procedural complications. Effectiveness is a more complex descriptor, as it encompasses both the avoidance of negative disease-related outcomes and objective measures of clinical functional benefit.

17. THE ITALIAN REGISTRY OF TRANS-APICAL AORTIC VALVE IMPLANTATION: THE I-TA REGISTRY

Trans-apical aortic valve implantation is generally considered as a second choice after trans-femoral TAVI because it requires general anesthesia, left thoracotomy and manipulation of the left ventricular apex. Thus, many centers follow a trans-femoral first policy, meaning that trans-apical access is performed only when the trans-femoral one is not feasible due to narrow and/or tortuous aorto-iliac vessels. The ratio between trans-femoral and trans-apical procedures is generally 3:1 and consequently the number of TA-TAVI performed yearly at each center is limited. The rationale behind the development of a TA-TAVI Italian National Registry was to collect data from all patients who underwent TA-TAVI in Italy in order to create a large common database with hundreds of patients coming from several different centers. The advantages of such project are mainly related to the large number of patients that make statistical analysis and results more reliable. The idea was born during spring of 2010 at the Division of Cardiac Surgery of the University of Padova, Italy. The aim was to create a prospective spontaneous, independent and multicenter registry. Spontaneous means that this project was not required by any institution or private company. Independent means that there are no industries that finance our registry thus eliminating the impact of potential conflict of interests. We also aimed at including all cases already performed in Italy since this procedure

became available in 2008. Data from 2008 to 2010 are therefore collected retrospectively while since 2011 data are prospectively collected. Data are collected at each center and then sent to the Division of Cardiac Surgery of Padova for storage and analysis. The first result of this project was an abstract submitted to the 2011 American Association of Thoracic Surgery (AATS) Annual Meeting that was accepted as oral presentation; the full manuscript was then published on the Journal of Thoracic and Cardiovascular Surgery in 2011 (65).To date there are 774 patients enrolled since April 2008 through June 2012 coming from 21 cardiac surgery Italian centers.

In this thesis we are proud to present the two most prestigious studies originated from the I-TA registry.

The first study, entitled "Medium Term Outcomes Of Trans-apical Aortic Valve Implantation: Results From The I-TA Registry " presents the most recently updated results from the registry and analyses medium term outcomes of patients undergoing TA-TAVI. This study was presented at the 2013 Society of Thoracic Surgeons (STS) Annual Meeting and published in the Annals of Thoracic Surgery in 2013 (97).

The second study is a comparison between three different treatment options for patients suffering from severe symptomatic aortic valve stenosis: TA-TAVI, Conventional AVR and Sutureless aortic valve replacement. This study, entitled "Conventional Surgery, Sutureless Valves And Trans-Apical Aortic Valve Replacement: What Is The Best Option In Patients With Aortic Valve Stenosis? A

Multicenter, Propensity-Matched Analysis" was presented at the 2013 AATS Annual Meeting in Minneapolis and subsequently published in the Journal of Thoracic and Cardiovascular Surgery in 2013 (98).

18. MEDIUM TERM OUTCOMES OF TRANS-APICAL AORTIC VALVE IMPLANTATION: RESULTS FROM THE I-TA REGISTRY

Aim of this prospective, multicenter, study was to examine clinical and hemodynamic outcomes of patients undergoing TA-TAVI.

18.1 Patients and Methods

From April 2008 through June 2012, 774 patients underwent TA-TAVI at 21 centers and were enrolled in the I-TA registry. Appendix 1 shows the number of cases enrolled yearly in each center. Data collection was approved by the ethics committee and patient informed consent was always obtained. The dataset of the I-TA registry has been implemented according to the Valve Academic Research Consortium (VARC) updated definitions and endpoints (VARC-2) (95,96). Main indication for TA-TAVI was severe symptomatic aortic valve stenosis (Aortic valve area <0,8 cm2, mean trans-aortic gradient >40 mmHg) associated to one or more of the following: a) porcelain aorta, b) high surgical risk (Logistic Euroscore I >20%, Society of Thoracic Surgeons mortality score >10%), c) other serious comorbidities that advise against the surgical approach as: severe pulmonary disease, previous total chest irradiation, hostile chest, severe liver disease. The majority of centers that participate to the I-TA registry adopt a "trans-femoral first" policy. TA-TAVI procedures were performed usually under general anesthesia and the only implanted devices were the

Sapien and, since mid-2010 the Sapien XT pericardial balloon expandable bioprosthesis (Edwards Lifesciences, Irvine, CA, USA). Preoperative risk factors were defined according to the European System for Cardiac Operative Risk Evaluation (EuroSCORE) (99). The recently updated VARC definitions were used to report safety and efficacy endpoints, valve performance and complications (96). The impact of learning curve on patient outcomes was analyzed by comparing the overall survival of the first 50% versus the second 50% of patients for each center. The impact of case-volume on survival was analyzed by comparing survival of centers with more than 27 cases versus centers with less than 27 cases. We adopted 27 cases as the cut-off value since this was the median number of cases performed in the participating centers.Patients underwent clinical and echocardiographic evaluation at their study site before the procedure, at discharge, between 2 and 6 months after TAVI and 12 months thereafter. Patients who were not able to reach the study site for clinical evaluation received telephone interviews and a copy of the most recent echocardiographic examination was collected. Follow-up was closed on June 30st, 2012.

18.2 Statistical analysis

Continuous data are expressed by mean and standard deviation or median and range as appropriate. Categorical data are summarized by reporting the percentages. Cumulative survival was estimated using the Kaplan-Meier method

and we used the Log–Rank test for comparison between groups. Categorical values were compared by the chi-square or Fisher exact test, and continuous variables were compared by the t-test. A stepwise logistic regression analysis was used to determine the independent predictive factors of VARC mortality. Variables for the multivariate analysis were selected because of recognized clinical importance or because they were significantly different at the univariate analysis. Statistical analyses were performed using SAS release 8.02 by SAS Institute Inc., Cary, NC, USA.

18.3 Results

Pre-operative clinical variables of patients are listed in table 2.

Table 2. Preoperative clinical characteristics of Trans-apical TAVI patients enrolled in the I-TA registry. This table also shows results of the univariate analysis for thirty-day VARC mortality. Variables with the asterisk were included in the multivariate analysis.BMI: body mass index; ES: Euroscore; STS: Society of Thoracic Surgeons; AVAi: aortic valve area index; LVEF: left ventricle ejection fraction; PAPs: systolic pulmonary artery pressure; NYHA: New York Heart Association; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; CABG: coronary artery bypass grafting; AMI: acute myocardial infarction; AF: atrial fibrillation; MR: mitral regurgitation; PCI: percutaneous coronary intervention; BAV: balloon aortic valvuloplasty. (*): variables included in the multivariate analysis.[a]: Chronic kidney failure defined as creatinine >2 md/dL and/or dialysis.

Variable	ALL (N=774) n (%)	ALIVE (N=697) n (%)	30-day VARC mortality (N=77) n (%)	*p* Value
Age (years) *	81.0±6.7	81.0±6.7	82.6±7.9	0.84
BMI (m^2)	25.6±4.9	25.7±5.0	24.5±3.8	**0.01**
Creatinine (mg/dl)	1.3±0.9	1.2±0.6	2.0±2.1	**0.002**
Glomerular filtration rate (ml/min)	47.4±24.9	48.6±25.3	35.2±17.8	**<0.0001**
Hemoglobin (g/dL)	11.9±1.7	12.0±1.7	11.4±1.6	**0.007**
Logistic ES I (%)	25.6±16.3	24.7±15.7	33.3±19.4	**0.0003**
ES II (%)	9.4±11.0	8.7±9.8	16.5±20.8	**0.003**
STS predicted mortality score (%)	10.3±8.4	8.7±10.3	15.2±13.0	0.07
Peak aortic gradient (mmHg)	80.1±22.9	80.4±22.6	77.8±25.3	0.36
Mean aortic greadient (mmHg)	49.8±15.4	50.1±15.3	49.2±15.9	0.62
AVAi (cm^2/mq)	0.48±0.13	0.55±0.19	0.49±0.18	**0.013**
LVEF (%) *	52.9±12.8	53.3±12.4	50.3±13.4	**0.048**
PAPs (mmHg)	42.8±13.0	42.6±13.0	44.1±13.2	0.43
Female *	446 (57.6)	405 (58.1)	41 (53.2)	0.41
Obesity (BMI≥30) *	103 (13.3)	96 (13.8)	7 (9.1)	0.29
Arterial hypertension *	671 (86.7)	601 (86.2)	70 (90.9)	0.25
Diabetis Mellitus *	205 (26.5)	188 (27.0)	17 (22.1)	0.36
NYHA ≥ III	621 (80.2)	574 (82.4)	75 (97.4)	**0.0007**
PVD *	384 (49.6)	334 (47.9)	50 (65.0)	**0.005**
COPD (ES)	247 (31.9)	224 (32.1)	23(30.0)	0.68
Neurologic dysfunction *	66 (8.5)	54 (7.8)	12 (15.6)	**0.02**
Critical preoperative state *	31 (4.0)	17 (2.4)	14 (18.2)	**<0.0001**
Previous cardiac surgery * Previous CABG	167 (21.6) 87 (11.2)	153 (22.0) 82 (11.7)	15 (19.5) 6 (7.8)	0.62 0.30
AMI *	23 (3.0)	17 (2.4)	6 (7.8)	**0.02**
Logistic ES I< 10%	116 (15.0)	109 (15.6)	7 (9.1)	0.12
Logistic ES I≥ 20%	417 (53.9)	363 (52.1)	54 (70.1)	**0.003**
Chronic kidney failure[a] *	80 (10.3)	64 (9.2)	16 (20.8)	**0.002**
Dyalisis	28 (3.6)	21 (3.0)	7(9.1)	**0.008**
AF	169 (21.8)	151 (21.7)	18 (23.4)	0.73
Severe MR *	39 (5.0)	30 (4.3)	9 (11.7)	**0.02**
Previous PCI	139 (18)	126 (18.0)	13 (16.9)	0.80
Pocelain aorta	122 (15.8)	108 (15.5)	14 (18.2)	0.54
Previous aortic BAV	70 (9.0)	64 (9.2)	6 (7.8)	0.68
Volume center (<28 cases) *	197 (25.5)	173 (24.8)	24 (31.2)	0.22
Learning curve (first 50% of each center) *	368 (47.5)	323 (46.3)	45 (58.4)	**0.043**

Mean age was 81.0±6.7 years, mean logistic EUROscore I, EUROscore II and STS score was 25.6±16,3%, 9,4±11,0% and 10.6±8.5%, respectively. New York Heart Association (NYHA) functional class III or IV was assigned to 621 (80.2 %) patients. Almost 50% of patients were suffering from severe peripheral vascular disease. Patients who already underwent a cardiac surgery operation were 167 (21.6%), while 139 (18,0%) patients underwent percutaneous coronary angioplasty before TAVI. Sapien/Sapien XT valve size 23, 26 and 29 mm was used in 279 (36.1%), 426 (55.0%) and 69 (8.9%) patients, respectively. Device success was 95,9% (742 patients). Device success criteria were not met in 32 (4,1%) patients for the following reasons: suboptimal performance of the prosthetic heart valve in 19 (2.5%) patients; 6 (0.8%) rescue "Valve-in-Valve"; 5 (0.6%) prosthesis embolization; successful access failure in 2 (0.2%) patients. Incidence of permanent pacemaker implantation for complete atrio-ventricular block was 5.4% (42 patients). Incidence of disabling stroke was 0.6% (5 patients), while five other patients experienced minor stroke or transient ischemic attack. Incidence of acute myocardial infarction was 1,9% (15 patients), six (0.7%) patients required bailout percutaneous angioplasty for coronary ostia occlusion. Median stay in the intensive care unit was 2 days (Interquartile range: 1-3) and median hospital stay was 8 days.

All-cause mortality at 30 days or during index procedure hospitalization (also in rehabilitation facilities) was 9.9% (77 patients). Cardiovascular mortality was 5.0% (39 patients): intra-procedural mortality occurred in 6 (0.7%) patients, 21

(2.7%) patients died for heart failure, 7 (0.9%) for major ventricular arrhythmias; there were 3 (0.4%) deaths for ischemic stroke and 2 (0.3%) sudden deaths. Mortality was classified as non cardiac in 4.9% (38 patients): multi-organ failure in 13 (1.7%) patients; sepsis in 12 (1.6%) patients, respiratory failure in 7 (0.9%) patients, severe hemorrhage in 3 (0.4%) patients, mesenteric ischemia in 2 patients (0.3%) and one suicide (0.1%).

The combined early safety endpoint at 30 days, according to VARC-2 definitions was met in 168 (21,7%) patients while 606 (78,3%) patients had an uneventful 30-day outcome.

We observed 10 apex-related complications (1,2%); of these 2 required the institution of cardio-pulmonary bypass (one with conversion to median sternotomy) while the remaining 8 were successfully treated off-pump through the mini-thoracotomy.

18.3.1 Follow-up

Median follow-up was 12 months, ranging from 1 to 44 months. One-year overall Kaplan-Meier survival was 81,7±1,5%, two-year and three-year survival was 76,1±1,9% and 67,6±3,2%, respectively (Fig. 40).

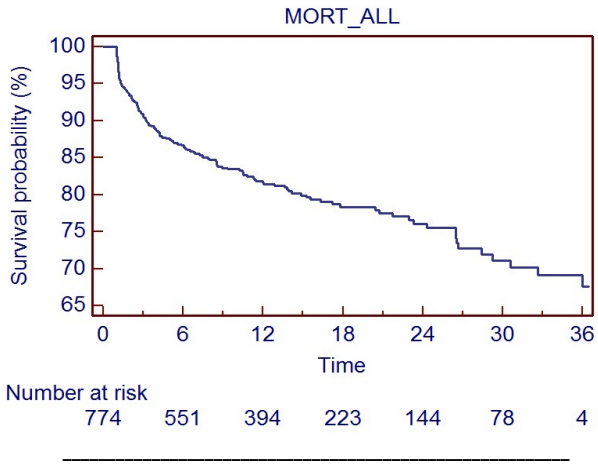


Fig. 40. Kaplan-Meier analysis of overall survival of patients enrolled in the I-TA registry

One-year, two-year and three-year freedom from cardiovascular mortality was 91,2±1,1%, 87,4±1,6% and 83,1±2,4%, respectively (Fig. 41).

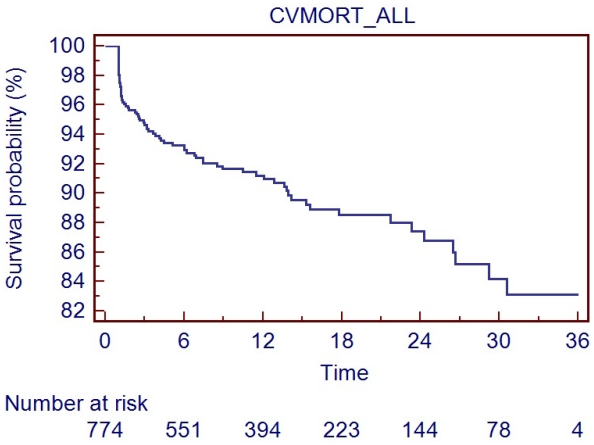


Fig. 41. Kaplan Meier freedom from cardiovascular mortality of patients enrolled in the I-TA registry

There were neither cases of structural valve deterioration nor endocarditis of the aortic bioprosthesis during follow-up. The combined clinical efficacy endpoint at one year, according to VARC-2 definitions, was met in 207 patients (26,7%). Furthermore we observed a significant improvement of NYHA functional class during follow up: preoperatively 82,4% (574 patients) of patients was in class III-IV versus 18,6% (130 patients) postoperatively (p<0,001).

18.3.2 Learning curve and procedural volume

We did not observe significant differences of survival at follow up related to the learning curve. In fact, Kaplan-Meier analysis of survival found similar overall three-year survival of the first 50% patients (66,9±3,8%) versus the second 50% patients of each center (69,3±5%) (p=0,64) (Fig. 42).

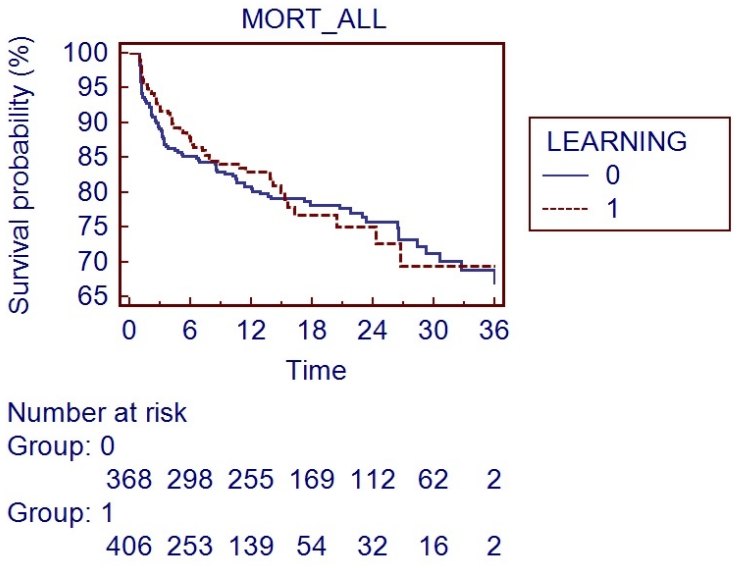


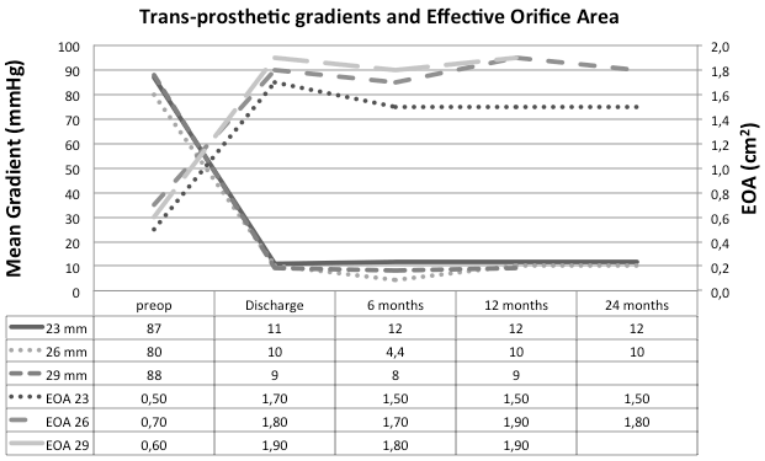
Fig. 42. Kaplan-Meier analysis of overall mortality of the first 50% and the second 50% patients of each center

However, thirty-day VARC mortality was significantly higher in the first 50% patients (45 out of 368 patients, 12,2%) than the second 50% (32 out of 406 patients, 7,9%) (p=0,04). Thirty-day VARC mortality of low-volume centers was 12,2% (24 out of 197 patients) while in high-volume centers it was 9,1% (53 out of 577 patients) and this difference was not significant (p=0,22).

18.3.3 Echocardiographic data

At discharge, no aortic regurgitation was found in 375 patients (53,8%), mild (1+/3+), moderate (2+/3+) and severe (3+/3+) aortic insufficiency were found in 261 (37,4%), 57 (8,2%) and 4 (0,6%), respectively. Peak and mean trans-aortic gradients at discharge were 21,0±10.3 mmHg and 10,2±4,1 mmHg, respectively; these values remained stable during follow-up. Figure 43 shows

mean gradient and effective orifice area of Sapien/Sapien XT bioprosthesis at discharge and during follow up by size.



	preop	Discharge	6 months	12 months	24 months
23 mm	87	11	12	12	12
26 mm	80	10	4,4	10	10
29 mm	88	9	8	9	
EOA 23	0,50	1,70	1,50	1,50	1,50
EOA 26	0,70	1,80	1,70	1,90	1,80
EOA 29	0,60	1,90	1,80	1,90	

Fig. 43. Transprosthetic gradients and effective orifice area measured preoperatively, at discharge ad at different follow-up intervals. EOA: Effective orifice area

18.3.4 Multivariate analysis

Variables that were used in the multivariate analysis are shown in table 2 with an asterisk.

The multivariate analysis identified as independent predictors of 30-day VARC mortality: chronic kidney failure (serum creatinine ≥2 mg/dL or dialysis) (OR: 2,2, 95% Confidence Interval: 1,1-4,2; p: 0,02), neurologic dysfunction (OR: 2,1; 95% CI: 1,0-4,3; p: 0,049), peripheral vascular disease (OR: 2,0; 95% CI: 1,2-3,4; p:0,008), critical preoperative state (OR: 8,8; 95% CI: 4,0-19,6; p<0,0001), learning curve (second 50%) (OR: 0,57; 95 CI: 0,34-0,94; p: 0,02).

18.4 Discussion

This study shows the results of trans-apical TAVI in a "real world" population. Our main findings are that trans-apical TAVI can be performed with an acceptable mortality rate, safety at 30-day, efficacy at one year as well as three-year survival and freedom from cardiovascular mortality, in particular if we consider the high surgical risk of these patients. All cause mortality was 9,9%, this value is similar to that reported by other registries (60, 70, 100). The 30-day combined safety endpoint is a composite of patient-oriented endpoints (death, stroke, bleeding, kidney injury, myocardial infarction, vascular complications) together with a repeat procedure in the first 30 days to treat valve dysfunction (balloon valvuloplasty, valve-in-valve). Safety reflects the impact of TAVI on early hospital outcomes. In our study, 19,1% of patients met the safety endpoint, of these 9,5% were deaths and the remaining 9,6% were complications. This value is consistent to that reported by other investigators (101). On the other hand, efficacy at one year incorporates major clinical (death and failure of current therapy) and valve performance factors (prosthetic valve dysfunction like stenosis or regurgitation), thus reflecting the impact of TAVI on delayed outcomes (one year or longer period). In our study, the efficacy endpoint was met in 20% of patients. These values should be considered with caution since these are relatively new criteria, specifically developed for TAVI, and there are no studies that use these definitions to evaluate the performance of conventional aortic valve replacement (102). A study focused on this issue

would be important in order to compare the two procedures and validate these composite endpoints. Another important aspect is that out of the 19% of patients that met the safety endpoint, in 9,6% a severe complication occurred. The complications that are included in the composite safety endpoint are usually life threatening and the fact that patients were able to survive such events highlights the importance of a multidisciplinary team approach to TAVI. In fact, a multidisciplinary team is able to carefully select patients, predict potential adverse events, identify and treat complications in a timely and effective manner (50). TAVI is a complex procedure that requires a specific training and consequently the learning curve may affect outcomes. We observed that patients who received trans-apical TAVI during the first half experience of each center had a significantly higher 30-day VARC mortality when compared to patients operated on during the following period. Nevertheless, survival at follow up was similar, reflecting once again the importance of comorbidities. The learning curve is therefore crucial for patient selection and procedure performance (valve sizing, access, positioning, post-dilatation) and at the multivariate analysis it was identified as an independent predictor of 30-day mortality. On the other hand, procedural volume does not seem to have a significant impact on outcomes since 30-day mortality was similar between "low-volume" and "high-volume centers". Medium term survival, up to three years, was 67,6% but freedom from cardiovascular mortality was 83,1%. This data confirm that the impact of patient comorbidities play a

major role in determining survival at follow up (103) and show that probably, the extension of indications towards a less compromised population, could improve overall survival. Another aspect that is in favor of the indications to TAVI for younger patients is that we did not report any case of structural valve deterioration in the entire experience. Furthermore, we observed that the hemodynamic performance of Sapien bioprosthesis is good, with low gradients and significant valve area improvement, and that it remains stable during follow up. However, there is still an issue that causes caution and perplexity with regard to extension of indications to TAVI to younger or less compromised patients: postoperative aortic regurgitation. In this registry, 45% of patients had a mild or moderate aortic regurgitation at hospital discharge. This should be taken into careful consideration since it has been demonstrated that even mild aortic insufficiency significantly reduces survival over time (69).

This study has several limitations: this is a trans-apical only population that does not consider comparable trans-femoral TAVI, trans-aortic TAVI nor conventional surgery. There is a not homogeneous distribution of patients among the different centers. However this is a common problem related with multicenter registries and results reflect the "real world" nature of the study. We did not have a central core-lab for echocardiographic examinations and VARC adverse events were assigned by the referring center and not by an ad-hoc committee.

In conclusion, trans-apical TAVI provides good early and medium term (up to three years) clinical and hemodynamic results. Thus, it can be considered as a good therapeutic option in high-risk or inoperable patients suffering from severe symptomatic aortic valve stenosis. In particular, the hemodynamic performance of the Sapien valve is good and it's stable over time. Postoperative aortic insufficiency represents still a major issue and it should be solved with new generation devices in order to extend indications to TAVI. Chronic kidney failure, neurological dysfunction, peripheral vascular disease, critical preoperative state and learning curve were identified as independent predictors of VARC thirty-day mortality

Appendix 1: Number of patients enrolled yearly in the I-TA registry by study site

	Institution	*2008 (April-December)*	*2009*	*2010*	*2011*	*2012 (Jan-Jun)*	***Total***
1	Centro Cardiologico Monzino, Milan	14	49	19	12	1	**95**
2	Clinica Montevergine, Mercogliano	32	40	12	5	-	**89**
3	University of Padova	-	23	26	29	3	**81**
4	San Camillo Hospital, Rome	-	15	32	25	5	**77**
5	San Bortolo Hospital, Vicenza	3	33	7	9	3	**55**
6	University of Bologna	2	12	12	11	1	**38**
7	Humanitas Gavazzeni Hospital, Bergamo	6	10	13	7	2	**38**
8	University of Pavia	-	8	12	14	3	**37**
9	University of Turin	-	19	5	11	1	**36**
10	Clinica S. Anna, Catanzaro	-	-	16	14	1	**31**
11	G. Pasquinucci Heart Hospital, Massa	2	6	17	2	-	**27**
12	Ospedale Mauriziano Umberto I, Turin	-	5	13	8	-	**26**
13	S. Raffaele Hospital, Milan	6	9	6	4	-	**25**
14	Hesperia Hospital, Modena	-	-	7	15	2	**24**
15	Humanitas Gavazzeni Hospital, Rozzano	-	2	2	14	2	**20**
16	Ospedale dell'Angelo, Venice-Mestre	-	12	5	-	-	**17**
17	University of Parma	-	6	2	7	-	**15**
18	S. Maria della Misericordia Hospital, Udine	-	8	6	-	-	**14**
19	S. Croce e Carle Hospital, Cuneo	-	-	-	14	-	**14**
20	Ospedali Riuniti, Trieste	-	4	4	-	-	**8**
21	University of Verona	-	-	5	2	-	**7**

19. CONVENTIONAL SURGERY, SUTURELESS VALVES AND TRANS-APICAL AORTIC VALVE REPLACEMENT: WHAT IS THE BEST OPTION IN PATIENTS WITH AORTIC VALVE STENOSIS? A MULTICENTER, PROPENSITY-MATCHED ANALYSIS.

Aim of this multicenter, propensity-matched study, was to compare hospital clinical and hemodynamic outcomes of SAVR, TA-TAVI and SU-AVR.

19.1 Patients and Methods

This study was approved by ethic committees and patient informed consent for data collection and treatment was always collected.

19.1.1 Trans-apical Aortic Valve Replacement

We reviewed data from 566 patients enrolled in the Italian Registry of Trans-Apical Aortic Valve Implantation (I-TA) from April 2008 through May 2011. Main indication for TA-TAVI was severe symptomatic aortic valve stenosis (Aortic valve area <0,8 cm2, mean trans-aortic gradient >40 mmHg) associated to one or more of the following: a) porcelain aorta, b) high surgical risk (Logistic Euroscore I >20%, Society of Thoracic Surgeons mortality score >10%), c) other serious comorbidities as: severe pulmonary disease, previous total chest irradiation, hostile chest, severe liver disease. TA-TAVI procedures were performed usually under general anesthesia and the only implanted devices

were the Sapien and, since mid-2010 the Sapien XT pericardial balloon expandable bioprosthesis (Edwards Lifesciences, Irvine, CA, USA). Absolute contraindications for TA-TAVI were: a) left ventricular aneurysm with or without thrombotic stratification and b) extremely poor left ventricular ejection fraction (<15%).

19.1.2 Sutureless Aortic Valve Replacement

We prospectively collected and analyzed data of 38 patients who underwent isolated SU-AVR with the Perceval S bioprosthesis (Sorin Biomedica Cardio, Saluggia, Italy) at 3 Italian centers from March to September 2011. Sutureless valve data were collected using the same data set of the I-TA to obtain homogeneous, comparable, and, most important, reliable data. All SU-AVR procedures were performed under moderately hypothermic (32° C) cardiopulmonary bypass with aortic cross-clamping and cardioplegic arrest of the heart. A transverse aortotomy was performed around 3 to 3.5 cm above the aortic annulus, the native valve was removed, and annular decalcification was performed. Annular decalcification is not as extensive as for conventional surgery, but it is aimed at removing bulky calcifications to obtain a homogeneous, round-shaped annulus for sutureless valve implantation. After decalcification, the aortic annulus was sized and the correct prosthesis was selected. Prosthesis size "small" was selected, with an annulus diameter between 19 mm and 21 mm. Size "medium" was selected, with an annulus

diameter between 21 mm and 23 mm. During the study period, size "large" was still not available. Three 4-0 prolene guiding sutures are passed through the aortic annulus at the nadir of each sinus. The delivery system was guided in its correct position using these sutures and the valve was deployed. After deployment, the delivery system and sutures were removed, and a balloon was inserted in the valve and expanded for 30 seconds at a pressure of 3 atm. Indications for SU-AVR were as follows: severe symptomatic aortic valve stenosis (Aortic valve area <0,8 cm2, mean trans-aortic gradient >40 mmHg)and a high surgical risk profile for advanced age (>75 years), comorbidities, and patient frailty. Exclusion criteria for the use of a Perceval S valve were: a) previous implantation of a valve prosthesis or annuloplasty ring not being replaced by the sutureless bioprosthesis, b) double or multiple valve surgery, c) aneurysmal dilatation (≥45 mm) or dissection of the ascending aorta, d) active endocarditis, e) bicuspid aortic valve and f) recent (<90 days) myocardial infarction. SU-AVR was performed with full sternotomy, mini sternotomy or mini thoracotomy, according to the type of intervention, the associated procedures, and, ultimately, the surgeon's preferences. In particular, SU-AVR procedures were performed through full sternotomy, mini sternotomy and mini right thoracotomy in 23 (60,5%), 4 (10,5%) and 11 (29%) patients, respectively. Mean aortic cross-clamp and cardiopulmonary bypass time were 44±17 and 69±44 minutes, respectively.

Since there are no guidelines, position statements nor recommendations about SU-AVR, the choice between TAVI and SU-AVR, especially in high-risk elderly patients, was made by each single surgeon based on patient's preoperative characteristics and clinical observation.

19.1.3 Surgical Aortic Valve Replacement

We retrospectively collected data from 349 consecutive patients who underwent isolated SAVR from January 2009 through December 2011 at the University of Padova. We collected data of SAVR patients specifically for this study using exactly the same dataset and definitions of SU-AVR and TA-TAVI patients. Data were obtained directly from an "ad-hoc" review of official hospital medical charts and not from already existing databases. All SAVR procedures were performed through full sternotomy, with moderately hypothermic cardiopulmonary bypass. Cold-blood cardioplegia was usually administered both in antegrade and retrograde fashion. Prostheses were implanted with 2-0 braided pledgeted horizontal mattress sutures (pledgets on the ventricular side). Bioprostheses and mechanical prostheses were used in 332 (95,1%) and in 17 (4,9%) patients, respectively. Mean aortic cross-clamp and cardiopulmonary bypass time were 93±27 and 124±33 minutes, respectively.

Patients of all groups underwent clinical and echocardiographic assessment at the study site before the procedure and at hospital discharge. Echocardiographic measurements were done according to current recommendations (9). Prosthetic aortic regurgitation was classified as none or trace, mild (1+/3+), moderate (2+/3+), or severe (3+/3+) according to recent recommendations (10).

19.1.4 Risk factors and endpoints

Preoperative risk factors were defined according to the EuroSCORE I classification (99), and postoperative outcomes and endpoints were defined according to the Valve Academic Research Consortium definitions (95). The recently updated VARC 2 definitions (96) were still not available at the time of data analysis. For analysis, patients were classified as receiving TA-TAVI or "open-heart surgery" (OHS; SU-AVR or SAVR). The database records 10 explanatory variables: age, sex, body surface area, Logistic Euroscore I, New York Heart Association (NYHA) functional class, left ventricular ejection fraction, concomitant mitral valve disease, chronic obstructive pulmonary disease, peripheral vascular disease and aortic valve area. The dependent variable is a categorical variable comparing results of TAVI technique with OHS technique. Within OHS we further analyzed results of TA-TAVI vs. SU-AVR and TA-TAVI vs. SAVR. Our primary study end-points, defined before analysis, were: all cause 30-day mortality, disabling stroke, permanent pace-maker implantation, renal

replacement therapy, peri-procedural acute myocardial infarction (within 72 hours after the index procedure), aortic regurgitation at discharge (≥1+/3+) and trans-aortic gradient at discharge.

19.2 Statistical analysis

Analyses were performed using Stata vers.12.1 (StataCorp, Lakeway Drive College Station, TX, USA). Preoperative demographic, risk related variables and post-operative (30-day) mortality and morbidity outcomes were investigated. Categorical variables were expressed as frequencies and compared using the Fisher exact and chi-squared test. Continuous variables were expressed as mean ± standard deviation and compared using the unpaired t-test.

Standardized differences were used to assess the degree of baseline variable balance by a well-validated technique (104). We estimated the propensity score of the treatment category on our 10 explanatory variables using a logit model and a default p-value of 0.01. The balancing property was satisfied stratifying 953 of the original patients in 17 blocks (105). Subsequently a 1:1 match on the propensity score, without replacement, was performed using the psmatch2 procedure (106) with a conservative caliper width of 20% of the standard deviation of the log of propensity score (107). Two hundred and eighty six patients were successfully matched (143 TA-TAVI and 143 OHS). The psmatch2 common support option also retained 347 unmatched TAVI. In these patients the matching weight was missing, therefore we calculated a weight proportional

to the inverse of their inclusion probability within their original stratification block. Statistical significance of results was robust to several different weight specifications. Comparisons between groups were performed considering the matched nature of the propensity score-matched sample. In particular, paired t-test or Wilcoxon signed rank test were used for continuous variables and McNemar test was used for binary (dichotomous) variables. A multivariable logistic analysis of the odds ratio of mortality and morbidity was finally performed on the 633 patients in common support region adjusting for SU-AVR and SAVR technique, preoperative covariates and propensity score. To this purpose a weighted logistic model, saturated with event related variables and with propensity score inclusion, was used.

19.3 Results

Two hundred and eighty six patients were successfully matched: 143 underwent TA-TAVI and 143 underwent OHS. Six hundred and thirty three patients were included in the common support region of the propensity analysis. Preoperative clinical characteristics of patients of the OHS and TA-TAVI cohorts are listed in tables 3, 4 and 5. These tables show the unmatched cohorts, the cohorts after matching in the common support region and the cohorts after caliper matching. In the unmatched cohort (table 3) TA-TAVI patients were older (80,6±6,8 vs. 72,7±10,1 years; p<0,001) and with a significantly higher logistic Euroscore (25,5±15% vs. 14,2±11,2%; p<0,001). Furthermore, TA-TAVI patients had a worse New York Heart Association (NYHA) functional class and were more likely to suffer from peripheral vascular disease (PVD) (51,2% vs. 36,7%; p<0,001) and from chronic obstructive pulmonary disease (COPD) (35,7% vs. 20,9%; p<0,001). After matching the two cohorts were similar in terms of body surface area, logistic Euroscore, left ventricular ejection fraction, PVD and COPD. After matching age was still significantly different among groups, however age is an important component of logistic Euroscore, therefore we are confident that multivariate logistic regression may adjust for this residual imbalance in the observed baseline covariates. Table 6 shows study end-points in the 633 patients matched in the common support region. Thirty-day overall mortality was significantly lower in SAVR than in TA-TAVI (8,6% vs. 0,9%, p=0,002) while

there were no differences between SU-AVR and TA-TAVI regarding mortality. Causes of death in TA-TAVI patients were: multi-organ failure in 15 patients (35,7%), sepsis in 10 patients (23,8%), arrhythmias in 6 patients (14,3%), renal insufficiency in 2 patients (4,8%), severe hemorrhage in 6 patients (14,3%) and mesenteric ischemia in 3 patients (7,1%). One patient died in the SAVR matched group for multi-organ failure. No deaths were observed in the SU-AVR matched cohort. TA-TAVI had significantly lower trans-aortic gradients when compared to SAVR (10,3±4,4 mmHg vs. 16,5±5,8 mmHg, p<0,001) but it was found to have a higher incidence of at least mild (≥1+/3+) aortic regurgitation (34,1% vs. 1,8%; p<0,001). Furthermore, SAVR showed a lower incidence of postoperative pacemaker implantation (0,9% vs. 6,1%; p=0.018) and need for renal replacement therapy (0% vs. 7,6%; p=0,001). The other endpoints did not appear to be different neither between TA-TAVI and SAVR nor between TA-TAVI and SU-AVR. The analysis of end-points in the 286 caliper 1:1 matched patients is shown in table 7. There was still a difference of mortality between TA-TAVI and SAVR although the statistical significance was less pronounced than the analysis of the common support region (7% vs 1,8%; p=0,026). Also in the 1:1 matched cohort, TA-TAVI demonstrated significantly lower gradients than SAVR (10,7±4,4 mmHg vs. 16,5±5,8 mmHg, p<0,001) and higher incidence of aortic regurgitation (28,7% vs. 1,8%; p<0,001). The multivariate analysis showed that SU-AVR had a protective effect, although not statistically significant, against aortic regurgitation, pacemaker implantation and renal

replacement therapy with respect to TA-TAVI. On the other hand, when compared to TA-TAVI, SAVR demonstrated significant protection against aortic regurgitation (OR=0,04, p<0,001) and a trend towards protection against death, pacemaker implantation and myocardial infarction. The effect of SAVR and SU-AVR on the pre-defined endpoints, with respect to TA-TAVI, is shown in table 8.

Table 3. Characteristics of patients' cohorts before matching. OHS: Open-heart surgery (Sutureless and surgical aortic valve replacement); TA-TAVI: Trans-apical aortic valve replacement; BSA: Body surface area; LVEF: Left ventricular ejection fraction; AVAi: Aortic valve area index; NYHA: New York Hear Association; PVD: Peripheral vascular disease; COPD: Chronic obstructive pulmonary disease: MR: Mitral regurgitation.

Variable	OHS (n=387)	TA-TAVI (n=566)	p-value
Age (years)	72,7±10,1	80,6±6,8	<0,001
BSA (m^2)	1,8±0,2	1,7±0,2	<0,001
Logistic Euroscore (%)	14,2±11,2	25,5±15	<0,001
LVEF (%)	59,1±10,6	52,7±13,6	<0,001
AVAi (cm^2/m^2)	0,51±0,1	0,55±0,2	0,001
Male Sex (%)	48,3	40,8	0,02
NYHA ≥3 (%)	33,1	83,4	<0,001
PVD (%)	36,7	51,2	<0,001
COPD (%)	20,9	35,7	<0,001
MR (%)	9,6	9,2	0,07

Table 4. Characteristics of patients' cohorts after matching in the common support region. OHS: Open-heart surgery (Sutureless and surgical aortic valve replacement); TA-TAVI: Trans-apical aortic valve replacement; BSA: Body surface area; LVEF: Left ventricular ejection fraction; AVAi: Aortic valve area index; NYHA: New York Hear Association; PVD: Peripheral vascular disease; COPD: Chronic obstructive pulmonary disease: MR: Mitral regurgitation.

Variable	OHS (n=143)	TA-TAVI (n=490)	p-value
Age (years)	73,5±12,6	80,4±7	<0,001
BSA (m^2)	1,8±0,3	1,7±0,2	0,001
Logistic Euroscore (%)	18,3±14,6	24,5±14,1	<0,001
LVEF (%)	58,1±10,9	53,4±13,6	<0,001
AVAi (cm^2/m^2)	0,55±0,2	0,54±0,2	0,93
Male Sex (%)	49,7	40,8	0,07
NYHA (%)	54,5	81,2	<0,001
PVD (%)	37,1	48,8	0,17
COPD (%)	25,9	33,9	0,08
MR (%)	24,5	68,2	<0,001

Table 5. Characteristics of patients' cohorts after caliper 1:1 matching. OHS: Open-heart surgery (Sutureless and surgical aortic valve replacement); TA-TAVI: Trans-apical aortic valve replacement; BSA: Body surface area; LVEF: Left ventricular ejection fraction; AVAi: Aortic valve area index; NYHA: New York Hear Association; PVD: Peripheral vascular disease; COPD: Chronic obstructive pulmonary disease: MR: Mitral regurgitation.

Variable	OHS (n=143)	TA-TAVI (n=143)	p-value
Age (years)	73,5±12,6	77,6±9	0,003
BSA (m^2)	1,8±0,3	1,7±0,2	0,12
Logistic Euroscore (%)	18,3±15,6	20,2±12,5	0,22
LVEF (%)	58,1±10,9	56,1±13	0,15
AVAi (cm^2/m^2)	0,55±0,2	0,55±0,2	0,93
Male Sex (%)	49,7	37,1	0,03
NYHA (%)	54,5	65	0,08
PVD (%)	37,1	42,7	0,43
COPD (%)	25,9	32,2	0,25
MR (%)	24,5	32,9	0,06

Table 6. Postoperative outcomes after TA-TAVI, SU-AVR and SAVR. Analysis made on the 633 patients of the common support region. TA-TAVI: Trans-catheter aortic valve replacement; SU-AVR: Sutureless aortic valve replacement; SAVR: Surgical aortic valve replacement; PPM: Permanent pacemaker Replacement; RRT: Renal replacement therapy, AMI: Acute myocardial infarction, AR: Aortic regurgitation. Two tail Fisher test & ** unpaired t. test

Outcome	TA-TAVI (n=490)	SU-AVR (n=31)	SAVR (n=112)	p-value TA-TAVI vs. SU-AVR	p-value TA-TAVI vs. SAVR
Death, n (%)	42 (8,6)	0	1 (0,9)	0.16	0.002
Stroke, n (%)	12 (2,5)	0	0	1	0,14
PPM, n (%)	30 (6,1)	1 (3,2)	1 (0,9)	1	0.018
RRT, n (%)	37 (7,6)	1 (3,2)	0	0.72	0.001
AMI, n (%)	9 (1,9)	0	1 (0,9)	1	0.70
Postoperative AR (≥1+/3+)	167 (34,1)	6 (19,4)	2 (1,8)	0.12	<0.001
Mean Gradient (mmHg)	10,3±4,4	11,1±3,4	16,5±5,8	0.36 **	<0.001 **

Table 7. Postoperative outcomes after TA-TAVI, SU-AVR and SAVR. Analysis made on the 286 patients with caliper matching 1:1. TA-TAVI: Trans-catheter aortic valve replacement; SU-AVR: Sutureless aortic valve replacement; SAVR: Surgical aortic valve replacement; PPM: Permanent pacemaker Replacement; RRT: Renal replacement therapy, AMI: Acute myocardial infarction, AR: Aortic regurgitation. Two tail Fisher test & ** unpaired t. test

Outcome	TA-TAVI (n=143)	SU-AVR (n=31)	SAVR (n=112)	p-value TA-TAVI vs. SU-AVR	p.value TA-TAVI vs. SAVR
Death, n (%)	10 (7)	0	1 (1,8)	0,21	0,026
Stroke, n (%)	4 (2,8)	0	0	1	0,13
PPM, n (%)	7 (4,9)	1 (3,2)	1 (0,9)	1	0,082
RRT, n (%)	7 (4,9)	1 (3,2)	0	1	0,019
AMI, n (%)	5 (3,5)	0	1 (0,9)	0,59	0,23
Postoperative AR (≥1+/3+)	41 (28,7)	6 (19,4)	2 (1,8)	0, 37	<0,001
Mean Gradient (mmHg)	10,7±4,4	11,1±3,3	16,5±5,8	0,69 **	<0,001 **

Table 8. Postoperative clinical outcomes after matching and multivariate analysis.SU-AVR: Sutureless aortic valve replacement; TA-TAVI: Trans-apical aortic valve replacement; SAVR: Surgical aortic valve replacement; OR: Odds ratio; AR: Aortic Regurgitation; PM: Pace-maker; RRT: Renal replacement therapy; AMI: Acute myocardial infarction. *multivariable adusted, logistic Z test

Outcome	SU-AVR vs. TA-TAVI	p-value *	SAVR vs. TA-TAVI	p-value *
Death (OR)	1,00	-	0,23	0,17
Postoperative AR (≥1+/3+) (OR)	0,55	0,23	0,04	<0,001
Stroke (OR)	1,00	-	1,00	-
PM implantation (OR)	0,51	0,53	0,97	0,14
RRT (OR)	0,61	0,68	1,00	-
AMI (OR)	1,00	-	0,38	0,47
Mean gradient at discharge (OR)	1,02	0,56	1,19	<0,001

19.4 Discussion

The complete portfolio of aortic valve substitutes includes SAVR, SU-AVR and TAVI. This is the first study that evaluates and compares, with a propensity matched analysis, the results of all these techniques in patients suffering from severe symptomatic aortic valve stenosis. Although this should be considered a preliminary study, it gives some important insights into this contemporary and controversial issue. The main findings of this study were that SU-AVR and SAVR might potentially have some advantages over TAVI, in selected patients. This may be due to the patient selection process that occurred in our analysis. The attempt to match these three cohorts has selected the "worse" open-heart patients and the "best" TAVI patients. This was clearly shown in tables 3, 4 and 5, where the matched TA-TAVI cohort had less comorbidities and lower logistic Euroscore values than the unmatched cohort and where matched SAVR patients had more comorbidities and higher logistic Euroscore values than the unmatched cohort. Thus, as stated in our previous article, these patients belong to a "grey-zone" where there is an overlap of indications for the different procedures (108). However, even if the three groups after matching were similar (especially after 1:1 caliper matching), other factors that might have a significant impact on patient outcomes, such as frailty, were not taken into account. It is likely that these patients, who belong to they "grey-zone" of surgical risk, were assigned to one treatment or to the other one due to one of these unaccounted

conditions. The empiric proportions in table 4 and 5 show that SAVR has a significantly lower rate of death than TA-TAVI in matched patients. This seems to be in contrast with the results from the PARTNER trial (49) but it could be explained by several reasons. The PARTNER trial was a prospective randomized trial with strict inclusion and exclusion criteria, which was conducted in selected centers that considered both trans-apical and trans-femoral TAVI, while our study was based on the analysis of data from patients that were operated on in the "real world". We only took into consideration TA-TAVI and not trans-femoral TAVI. Furthermore, patient characteristics were different from the PARTNER trial; in particular the Logistic Euroscore of PARTNER SAVR patients was 29% while in our study it was 18% (taking into account also SU-AVR patients) and this could explain the different rate of 30-day mortality between these two studies (PARTNER: 6,5%, our study: 0,9%). However the power of the test in 1:1 match is 46 % and in the multivariate analysis, TA-TAVI was not found to be an independent predictor of mortality, thus this result should be interpreted with caution. Even if the rate of aortic regurgitation (AR) in SU-AVR patients could seem high (19%) one should consider that all leaks were mild (1+/3+), that this incidence is similar to other series (31) and that this was a very early experience with learning curve-related issues. In the multivariate analysis SU-AVR seems to reduce the risk of post-operative AR, permanent pacemaker implantation and renal replacement therapy over TA-TAVI. However, the only statistically significant difference was found to be the reduction of AR in SAVR

patients vs. TA-TAVI patients. Postoperative AR is a highly debated issue, especially after the results of the PARTNER trial at 2-years that showed that even a mild degree of AR significantly worsen patient survival (69). The reason for an AR reduction in SU-AVR are mainly due to the "open-heart" implantation of sutureless valves; this enables the surgeon to remove valve leaflets as well as annular calcifications and to directly measure the aortic annulus in order to choose the most appropriate prosthesis size. Furthermore, the prosthesis is implanted under direct vision and, if the final result is not satisfactory, the valve can be removed and repositioned either during the same aortic clamping or with a second aortic clamping if the leak is discovered only with intraoperative trans-esophageal echo (30). The presence and distribution of calcium within the aortic annulus has been demonstrated to predict AR after TAVI (91), thus its removal may have an impact on reducing postoperative AR. All the above-mentioned mechanisms explain also the advantage of SAVR over TAVI in the reduction of the risk of AR. In fact, postoperative AR is still a major issue that should be solved before TAVI indications could be expanded towards younger patients and in general towards a lower risk population. Another important issue related to TAVI is the rate of postoperative permanent pacemaker implantation. Although self-expandable devices were associated with a significantly higher incidence of pacemaker implantation than balloon-expandable valves (109), there was still a significant advantage of "open-heart" devices over TAVI. In fact, the "blind" lateral displacement of aortic annulus calcifications that occurs

during TAVI (both during balloon aortic valvuloplasty and during valve deployment) rather than their "surgical" removal that is usually performed in SU-AVR and SAVR, might explain the higher incidence of conduction tissue injuries. We also found that TA-TAVI patients have significantly lower gradients than "open-heart" devices. The hemodynamic behavior of trans-catheter valves was therefore better than that of conventional aortic prostheses. However, further larger studies with longer follow-up will be able to tell if these differences also have a significant clinical impact. With this study we want to highlight that surgical aortic valve replacement is still the best choice in patients with aortic valve stenosis. However, new therapeutic options such as TAVI and sutureless aortic valve prostheses provide good results in selected patients. A center that is able to offer to its patients all these therapeutic alternatives may select the most appropriate technique tailoring the choice on each single patient taking into consideration all crucial characteristics like age, comorbidities, frailty and anatomy. A particularly careful evaluation is needed in the "grey-zone" patients who can benefit from either one or another technique. An experienced "aortic team" will be able to make the most appropriate choice. The limitations of this study were mainly related to the retrospective nature of the study, to the different procedures made in different centers, to the inclusion of TA-TAVI only patients and to the small number of patients in the SU-AVR cohort. In conclusion, our data show that there are no main differences in outcomes among SAVR, TA-TAVI and SU-AVR. SAVR was associated with a

significant reduction of postoperative aortic regurgitation when compared to TA-TAVI that, however, showed lower trans-aortic gradients. SU-AVR, when compared to TA-TAVI, did not show significant differences even if a trend towards less aortic regurgitation was evident. Further larger and possibly prospective studies are needed to confirm our preliminary results.

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DR. AUGUSTO D'ONOFRIO: PERSONAL CONTRIBUTION DURING THE PH.D. PERIOD (2010-2013)

ARTICLES ON INDEXED PEER-REVIEWED JOURNALS

1 2013

Russo N, Compostella L, Tarantini G, Setzu T, Napodano M, Bottio T, D'Onofrio A, Isabella G, Gerosa G, Iliceto S, Bellotto F. Cardiac rehabilitation after transcatheter versus surgical prosthetic valve implantation for aortic stenosis in the elderly. Eur J Prev Cardiol. 2013. ISSN: 2047-4873, doi: 10.1177/2047487313494029

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RINGRAZIAMENTI

Quando raggiungiamo un traguardo e ci volgiamo indietro, guardando al percorso che abbiamo seguito, non possiamo non renderci conto di quanto il nostro impegno personale, sebbene ci sia parso intenso, non sarebbe bastato, da solo, ad ottenere quel risultato. Con un po' di umiltà e di spirito critico, ci accorgiamo invece di come, senza l'aiuto di molte persone, quel traguardo sarebbe stato irragiungibile.

Questi tre anni di Dottorato di Ricerca, dal 2011 al 2013, sono stati testimoni di eventi molto importanti per la mia vita personale e professionale. Il primo e più importante ringraziamento, non me ne vogliano gli altri, va alla mia famiglia. Arianna, Matilde e Caterina, sono state, sono e saranno per sempre la mia forza, il mio sostegno, il mio entusiasmo, la mia gioia. Hanno sopportato con pazienza la mia assenza durante i congressi, le notti al lavoro, le ore rubate nei giorni festivi. Senza il loro amore incondizionato tutto questo non sarebbe stato possibile.

Un grazie a mia madre che appoggia e accetta la mia scelta di lontananza, nonostante questo significhi per lei vivere senza tutti i suoi affetti più cari.

Un grazie a mio padre che sento sempre vicino, mi manchi.

Una persona importante che mi ha cresciuto, sostenuto ed indirizzato, sia professionalmente sia umanamente in questi ultimi quindici anni è il Dott. Alessandro Fabbri. Grazie per avermi fatto amare questa professione e per essere sempre stato disponibile in qualunque momento, a qualunque ora, in qualunque parte del Mondo.

A Gennaio 2010 è iniziata la mia avventura nella Cardiochirurgia di Padova. Un grazie sincero al Prof. Gino Gerosa che ha creduto in me e che mi ha accolto nella sua equipe. Grazie per avermi messo nelle condizioni ottimali per sviluppare il progetto del registro I-TA, oggetto primario di questo Dottorato. Grazie per i preziosi consigli e per permettermi di mantenere una costante crescita tecnica, culturale e scientifica.

Grazie al Prof. Gaetano Thiene che, nonostante la sua esperienza e la sua posizione accademica, mantiene sempre vivo l'interesse e la curiosità per tutti gli aspetti della Patologia Cardiovascolare, dal basic science alla ricerca clinica. Grazie alla Prof.ssa Cristina Basso che mi ha consigliato e guidato in questi anni di Dottorato.

Un grazie a tutti i membri del "TAVI Team" che hanno reso il programma TAVI dell'Università di Padova tra i più apprezzati sia a livello nazionale sia a livello internazionale.

Un grazie agli specializzandi, infermieri, tecnici, segretarie e a tutti coloro che hanno collaborato per raccogliere i dati, eseguire le analisi, inviare gli abstract, preparare i manoscritti e le diapositive per tutti gli studi che sono stati prodotti nel corso di questo Dottorato.

Infine, un grazie a tutti i colleghi della Cardiochirurgia di Padova che mi hanno permesso di vivere l'esperienza negli USA, un indimenticabile periodo sia dal punto di vista professionale sia, soprattutto, da quello umano.