*FACULTAD DE MEDICINA Y ODONTOLOGÍA* *DEPARTAMENTO DE CIRUGÍA*


*TESIS DOCTORAL*

# 'REPLACEMENT OR TRANS-CATHETER IMPLANT ODDS'

# A NEW DISCRIMINATION SCORE FOR PREOPERATIVE ASSESSMENT IN HIGH-RISK AORTIC VALVE REPLACEMENT SURGERY

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*To Blanca,*

*Hero and Victim during her disease.*

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# Prologue

*If you can keep your head when all about you*
*Are losing theirs and blaming it on you;*
*If you can trust yourself when all men doubt you,*
*But make allowance for their doubting too:*

*If you can wait and not be tired by waiting,*
*Or being lied about, don't deal in lies,*
*Or being hated don't give way to hating,*
*And yet don't look too good, nor talk too wise;*

*If you can dream—and not make dreams your master;*
*If you can think—and not make thoughts your aim,*
*If you can meet with Triumph and Disaster*
*And treat those two impostors just the same*

*If you can bear to hear the truth you've spoken*
*Twisted by knaves to make a trap for fools,*
*Or watch the things you gave your life to, broken,*
*And stoop and build 'em up with worn-out tools;*

*If you can make one heap of all your winnings*
*And risk it on one turn of pitch-and-toss,*
*And lose, and start again at your beginnings*
*And never breathe a word about your loss:*

*If you can force your heart and nerve and sinew*
*To serve your turn long after they are gone,*
*And so hold on when there is nothing in you*
*Except the Will which says to them: 'Hold on!'*

*If you can talk with crowds and keep your virtue,*
*Or walk with Kings—nor lose the common touch,*
*If neither foes nor loving friends can hurt you,*
*If all men count with you, but none too much:*

*If you can fill the unforgiving minute*
*With sixty seconds' worth of distance run,*
*Yours is the Earth and everything that's in it,*
*And—which is more—you'll be a Man, my son!*

R. Kipling. *Rewards and Fairies.* 1910.

# Abstract / Resumen


## *OBJETIVOS*

Hasta el momento actual no se ha descrito ninguna herramienta clínica para la toma de decisiones preoperatoria en la cirugía valvular aórtica de alto riesgo, con vistas a poder dirigir al paciente hacia el recambio valvular transcatéter o hacia la cirugía convencional. Esto origina una disparidad en los criterios de selección de pacientes entre los diferentes estudios publicados en la literatura médica, que se basan fundamentalmente en consensos de expertos o recomendaciones comerciales.

El presente estudio esta basado en la hipótesis de que existen factores de riesgo preoperatorios con que influyen de manera diferente en la mortalidad perioperatoria en la cirugía valvular aórtica de alto riesgo en función del tipo de procedimiento (recambio valvular aórtico convencional o transcatéter) que se realice. Pretende identificar estos factores así como cuantificar su impacto potencial en la mortalidad, con la finalidad de poder evaluar y discriminar mejor a futuros pacientes hacia la técnica quirúrgica más apropiada.

## *METODOS*

Se recogen de manera retrospectiva los datos de una serie consecutiva de pacientes que recibieron un recambio o implante valvular aórtico (asociado o no a revascularización coronaria) en un solo centro (Consorcio Hospital General Universitario, Valencia, España) entre 2007 y 2012. Las cohortes recogidas incluyeron 53 casos de implante transcatéter y 415 de recambio valvular aórtico convencional.

Se realizó un emparejamiento estadístico por técnicas de regresión logística y nivelación del grado de propensión (propensity score matching) considerando las principales variables de riesgo preoperatorio y comorbilidad para identificar 67 controles adecuados dentro del grupo de recambio valvular convencional frente a los 53 casos del grupo transcatéter. Se realizó un análisis estadístico entre los casos y los controles emparejados para variables descriptivas, mortalidad y morbilidad mayor perioperatoria, duración de la estancia hospitalaria así como un análisis univariante y multivariante para mortalidad perioperatoria y el evento compuesto de mortalidad perioperatoria o complicaciones mayores neuro o cardiovasculares (MACCE) y un estudio de supervivencia a largo plazo.

Los análisis principales se basaron en el diseño de un índice estadístico de clasificación y discriminación hacia la técnica transcatéter o la convencional en pacientes de alto riesgo, basándose en la mortalidad perioperatoria observada en casos y controles emparejados, y en las variables identificadas como predictores independientes de mortalidad en el análisis multivariante de regresión logística. Del mismo modo se realizó un análisis comparativo de resultados quirúrgicos (mortalidad y morbilidad mayor) entre ambos grupos. Como análisis secundarios se consideraron los análisis de subgrupos entre los abordajes transapical y transfemoral dentro del grupo de implante transcatéter; y entre los grupos de bajo riesgo quirúrgico frente a los de alto riesgo quirúrgico en la serie global. También se realizó un estudio de la duración de la estancia hospitalaria y de supervivencia a largo plazo

## *RESULTADOS*

Arteropatía extracardiaca, hipertensión pulmonar severa y disfunción del ventrículo izquierdo fueron factores identificados como predictores independientes de mortalidad en el análisis multivariante de regresión logística (con coeficientes de regresión B de 2.080, 1.662 y 1.083 respectivamente). Cada paciente se clasificó como “Perfil Bajo” o “Perfil Alto” en función de la presencia o ausencia de estos factores para posteriormente construir un Árbol de Regresión y Regresión (CRT) y así

discriminar entre los procedimientos transcatéter o convencional para la mortalidad perioperatoria en función del perfil asignado. La curva operador-receptor (COR) obtuvo un área bajo la curva de 0.835 (0.38-1.000).

No se hallaron diferencias relevantes en relación a variables preoperatorias de riego o comorbilidades, así como en la mortalidad perioperatoria ni en la supervivencia a largo plazo entre los casos de implante transcatéter y los controles emparejados de recambio convencional. El evento compuesto MACCE fue significativamente mayor en el grupo transcatéter (17,0% vs. 4,5%, $p<0.05$) que en el control, así como la tasa de ritmo de marcapasos al alta (20,8% respecto a 0%, $p<0,001$). También se apreciaron resultados significativos en cuanto a la duración de la estancia en la unidad de cuidados intensivos en el grupo transcatéter (2,03 +/- 2,58 días) respecto al grupo control (3.33 +/- 1.80 días ), aunque estas diferencias desaparecieron en el análisis de subgrupos al utilizar un valor de EuroSCORE logístico > 15 como puto de corte.

## *DISCUSIÓN*

La aparición de las técnicas de implante valvular aórtico transcatéter han supuesto un hito en el tratamiento de la estenosis aórtica calcificada degenerativa, y probablemente el mayor avance tecnológico en el campo de la cirugía cardiaca de la última década. Ha transformado la visión general y la aproximación quirúrgica a la enfermedad cardiaca valvular, obligando a cirujanos, cardiólogos clínicos e intervencionistas a colaborar estrechamente en pro del beneficio del paciente.

La perspectiva actual en el estudio de las técnicas transcatéter pretende aportar guías clínicas a cirujanos y cardiólogos involucrados en esta terapia hacia identificar aquellos subgrupos de pacientes en los que este procedimiento puede aportar mayores o menores beneficios, o incluso suponer un riesgo adicional. En nuestro estudio se identificaron factores preoperatorios que actúan como predictores independientes de mortalidad en la serie estudiada, mediante técnicas

estadísticas de regresión logística multivariante: arteropatía extracardiaca, hipertensión pulmonar severa  disfunción del ventrículo izquierdo. Se demostró que estos factores no solo juegan un papel importante en la mortalidad perioperatoria, sino que también que su impacto relativo para cada técnica (trancatéter o convencional) es diferente. De este modo, el nuevo índice de clasificación actúa como una herramienta de fácil uso en la valoración preoperatoria de los pacientes candidatos a cirugía valvular aórtica de alto riesgo, con capacidad de discriminación entre ambos procedimientos. Mediante la clasificación de los pacientes como un índice de “Perfil Bajo” o “ Perfil Alto” resulta sencillo elegir entre la técnica más adecuada. Sin embargo, la validación externa de estos resultados es una cuestión todavía pendiente de valoración en futuros análisis.

# I. INTRODUCTION

# 1. Natural history of aortic stenosis in adults

The most common cause of valvular aortic stenosis (AS) in adults is calcification of a normal trileaflet or congenital bicuspid valve (1). Calcific AS is characterized by lipid accumulation, inflammation, fibrosis, and calcification (2) and is the most frequent heart valve disease in Europe and the United States. It typically presents in older individuals (i.e. >75 years) in contrast to bicuspid AS, which presents a decade or more earlier. Rheumatic AS, uncommon in the Western world, occurs due to fusion of the commissures with scarring and calcification of the cusps, and retraction of the leaflets resulting in the valve being both regurgitant and stenotic.

In individuals with normal aortic valves, the effective area of valve opening equals the cross-sectional area of the left ventricular outflow tract, which is about 3.0 to 4.0 cm2 in adults. As aortic stenosis develops, a minimal valve gradient is present until the orifice area becomes less than one-half normal. The natural history of aortic stenosis therefore begins with a prolonged asymptomatic period associated with minimal mortality.

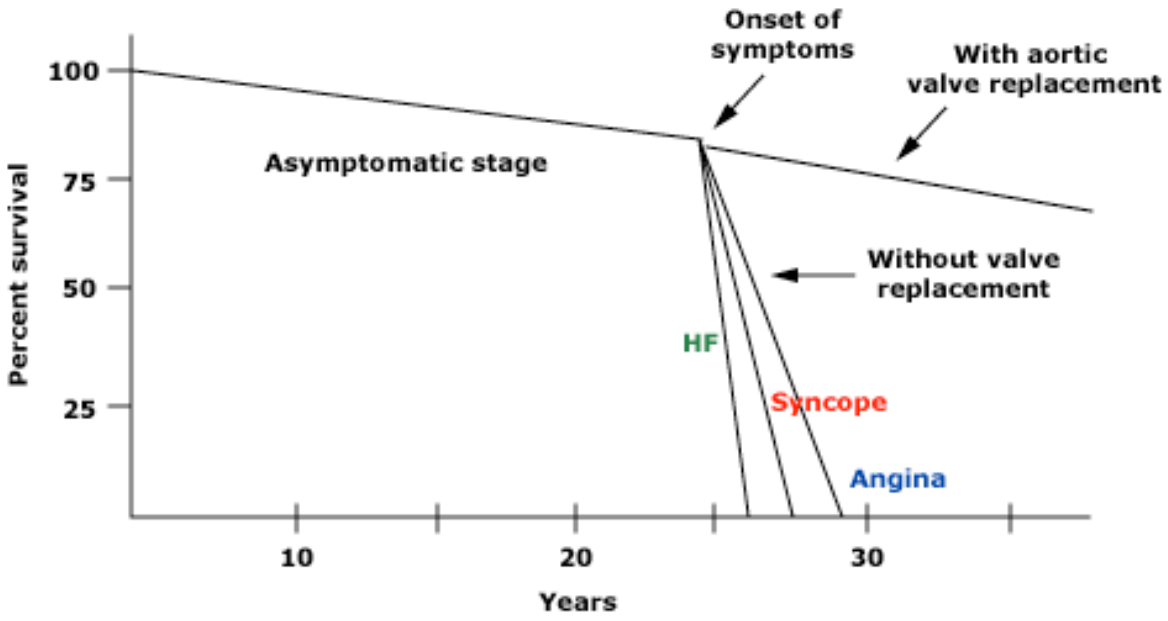
In adults with valvular AS, the obstruction develops gradually, typically over many years during which the left ventricle (LV) adapts to the systolic pressure overload with progressive concentric hypertrophy that results in diastolic dysfunction (3), reduced coronary reserve (4), myocardial ischemia, and eventually, depressed contractility resulting in LV systolic dysfunction (5). Ultimately, in some patients, heart failure or sudden death occurs.

Typically, patients with AS are free from cardiovascular symptoms (i.e., angina, syncope, and heart failure) until late in the course of the disease. However, once symptoms manifest, the prognosis is poor, with the interval from the onset of symptoms to the time of death being approximately 2 years in patients with heart failure, 3 years in those with syncope, and 5 years in those with angina. Gardin et al. reported that among symptomatic patients with moderate-to-severe AS treated

medically, mortality rates after the onset of symptoms were approximately 25% at 1 year and 50% at 2 years (6), with approximately 50% of deaths being sudden. In the elderly high-risk patients in the PARTNER (Placement of Aortic Transcatheter Valve) trial who were treated medically (Cohort B), the survival at 1 year was only 50% (7).

Serial hemodynamic examinations over periods ranging from two to nine years reveal significant and initially silent progression in most but not all patients. This progression is manifested by a reduction in the aortic valve area and an increase in the transvalvular systolic pressure gradient. The development of symptoms is an indication for valve replacement since the prognosis in untreated symptomatic patients is poor (figure 1) (7–12).

*Figure 1.*



*Schematic representation of the natural history of aortic stenosis and of the major impact of aortic valve replacement. Survival is excellent during the prolonged asymptomatic phase. After the development of symptoms, however, mortality exceeds 90 % within a few years. Aortic valve replacement prevents this rapid downhill course.*

Estimation of aortic valve area, aortic jet velocity, and transvalvular gradient by echocardiography or, less often, cardiac catheterization has been used to define patients as having mild, moderate, or severe aortic stenosis (table 1). Severe AS is said to be present when the calculated effective valve area is less than 1.0 cm2. Critical aortic stenosis is said to be present when the calculated effective valve area is less than 0.75 cm2 or the Doppler aortic jet velocity is over 5 m/sec (13) (discussed later in this section).

*Table 1. Severity of aortic stenosis in adults*

| | Aortic jet velocity, m/sec | Mean gradient, mmHg | Valve area, cm2 |
|---|---|---|---|
| **Normal** | ≤2.0 | <5 | 3.0-4.0 |
| **Mild** | <3.0 | <25 | >1.5 |
| **Moderate** | 3.0-4.0 | 25-40 | 1.0-1.5 |
| **Severe** | >4.0 | >40 | <1.0* |

*Critical aortic stenosis has been defined hemodynamically as a valve area <0.75 cm2 (<0.6 cm2/m2) and/or an aortic jet velocity >5.0 m/sec. However, the decision about valve replacement is not based solely on hemodynamics as some patients who meet these criteria are asymptomatic, while others with less severe measurements are symptomatic. In patients with severe aortic stenosis who also have a low cardiac output state the aortic jet velocity and mean gradient may be lower than indicated above (low-gradient aortic stenosis).*

Some consideration of body size should be included in any estimation of valve area (14). However, simply normalizing for body surface area can lead to misleading conclusions, especially in obese patients.

The term “symptomatic AS” refers to AS that is causing cardiac symptoms such as heart failure, anginal chest discomfort, or syncope. Nevertheless, the most common symptoms in patients who are followed prospectively are nonspecific (eg, decreased exercise tolerance and dyspnea on exertion)(11). Care should be taken to avoid attributing noncardiac symptoms to aortic stenosis: dyspnea may be due to deconditioning or lung disease, ankle edema has many causes other than heart failure, and nonanginal chest or shoulder pain is not a symptom of AS.

Symptoms in patients with aortic stenosis and normal left ventricular systolic function rarely occur until the valve area is <1.0 cm2, the aortic jet velocity is over 4.0 m/sec, and/or the mean transvalvular gradient exceeds 40 mmHg. However, many patients do not develop symptoms until even more severe valve obstruction is present, while some patients have symptoms when the stenosis is less severe, particularly if there is coexisting aortic regurgitation or systemic atrial hypertension.

Studies of patients undergoing serial cardiac catheterization have identified subgroups of patients with aortic stenosis with distinctly different progression rates (15,16). Serial echocardiography studies have provided data similar to that obtained in cardiac catheterization studies, although the time intervals between follow up have been shorter and these studies are less prone to selection bias (17–24). The average rate of progression has been similar in numerous studies, but the rate of progression varies widely among individual patients (17).

- The average rate of increase in the mean systolic gradient is 4 to 7 mmHg per year, but some patients show an increase of as much as 15 to 19 mmHg per year.
- Valve area declines at an average rate of 0.1 cm2 per year but some patients have little or no progression and others progress more rapidly.

- Aortic jet velocity increases by an average of 0.3 m/sec per year.

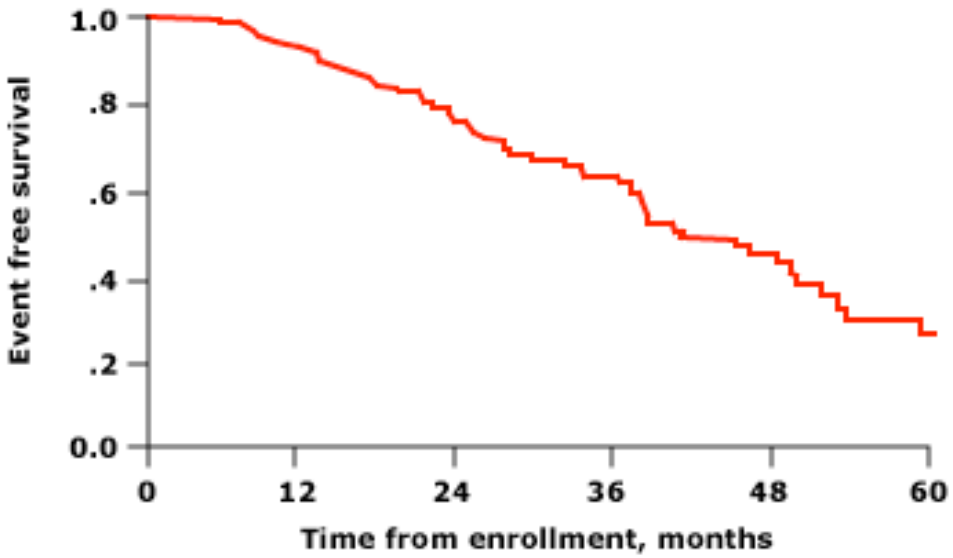
Patients with mild disease (ie, aortic jet velocity less than 3.0 m/sec) are unlikely to develop symptoms due to aortic stenosis over the ensuing five years. A substantial number of patients with severe aortic stenosis are not yet symptomatic but these patients have low event free survival rates (56 to 63 % at two years and 25 to 33 % at four to five years) (17-24).

Data from observational studies of patients with asymptomatic aortic stenosis suggest that peak aortic velocity and/or rate of progression of peak aortic velocity is associated with risk of death or aortic valve replacement. Studies at three different sites illustrate the range of predictive factors and rates of progression:

1. University of Washington — The importance of hemodynamic factors was demonstrated in a prospective study of 123 patients with aortic stenosis in whom yearly echocardiography and exercise testing were performed for a mean of 2.5 years (18). Entry criteria included an aortic jet velocity ≥2.5 m/sec and the absence of symptoms due to aortic stenosis. The end point was defined as death or aortic valve surgery.

- Event-free survival at one, three, and five years was 93, 62, and 26 %, respectively (figure 2).

*Figure 2.*




*Kaplan-Meier analysis shows survival without valve replacement for 123 patients with valvular aortic stenosis who were initially asymptomatic.*

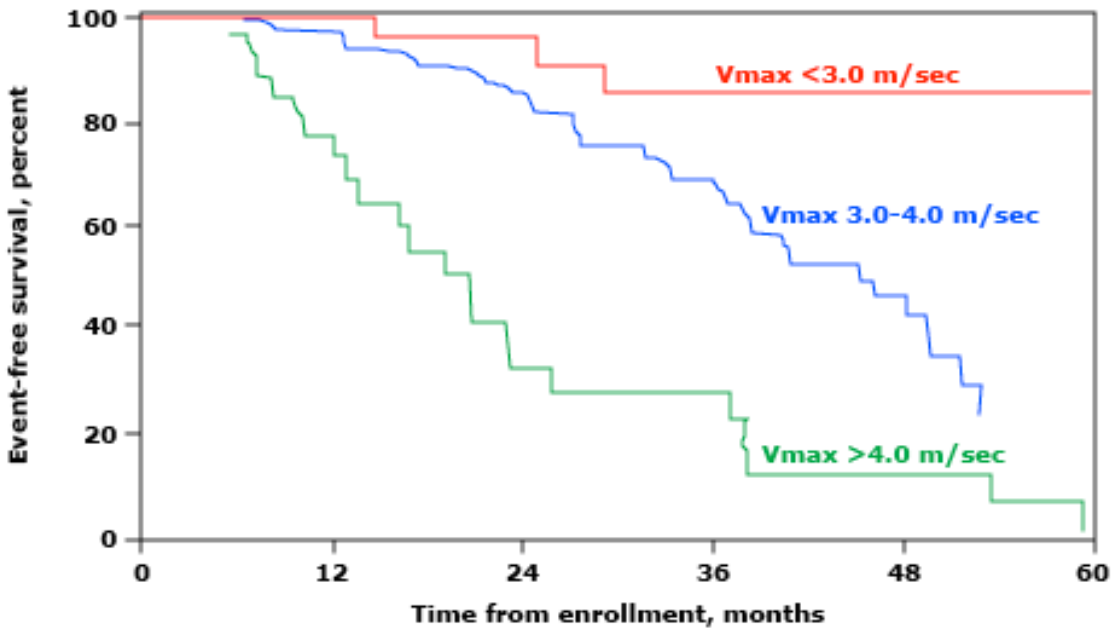
- The aortic jet velocity increased by 0.32±0.34 m/sec per year, the mean gradient by 7±7 mmHg per year, and the aortic valve area decreased by 0.12±0.19 cm2 per year. Multivariate predictors of outcome were jet velocity at baseline, the rate of change of aortic jet velocity, and functional status score. Factors such as age, sex, or cause of aortic stenosis were not predictive of outcome.

- The likelihood of remaining alive and free of valve surgery at two years varied inversely with disease severity as estimated from the baseline aortic jet velocity: the respective values were 84, 66, and 21 % when the baseline aortic jet velocity was <3.0, 3.0 to 4.0, and >4.0 m/sec, respectively (figure 3). These values defined patients with mild, moderate, and severe aortic stenosis.

2. Medical University of Vienna — A prospective study evaluated 126 asymptomatic patients with severe aortic stenosis, defined as an aortic jet velocity ≥4 m/sec, who were followed for a mean of 22 months (19).

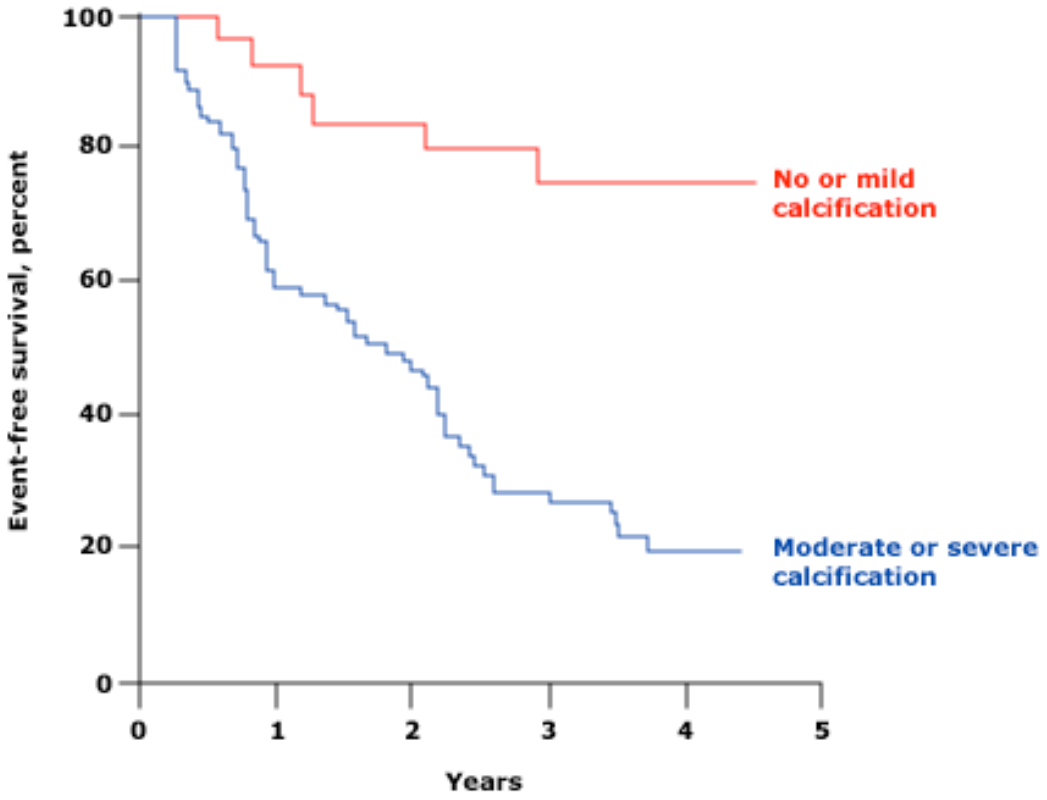
- Event-free survival (with end point defined as death or aortic valve replacement for symptoms) was 67 % at one year, 56 % at two years, and 33 % at four years.
- Only the extent of aortic valve calcification was an independent predictor of outcome. Patients with no or mild valvular calcification, compared to those with moderate or severe calcification, had significantly higher rates of event-free survival at one and four years (92 versus 60 % and 75 versus 20 %, respectively) (figure 4).

*Figure 3.*



*Event free survival in patients with aortic stenosis who are initially asymptomatic is related to the aortic jet velocity (Vmax) at entry. Aortic jet velocity varies inversely with valve area.*

*Figure 4.*




*In a study of 126 patients with asymptomatic severe aortic stenosis followed for a mean of 22 months, Kaplan-Meier analysis shows that event-free survival (death or aortic valve replacement) is related to the degree of aortic valve calcification observed on echocardiography.*

- Patients who had events had a higher rate of progression of stenosis. Among patients with moderate to severe calcification with increase in aortic jet velocity of ≥0.3 m/sec within one year, the cardiac event rate was 79 % (20).
- Event-free survival (with the end points of death or indication for aortic valve replacement including symptoms, left ventricular systolic dysfunction, or rapid hemodynamic progression) was 64, 36, 25, 12 and 3 % at one, two, three, four, and six years.
- Peak aortic valve velocity, but not aortic valve area, was an independent predictor of event-free survival. Patients with a peak aortic valve velocity ≥5.5 m/s had event-free survivals of 44, 25, 11, and 4 % at one, two, three, and four years compared with 76, 43, 33, and 17 % for patients with peak aortic velocities between 5.0 and 5.5 m/s.
- All but seven patients had moderate to severe aortic valve calcification. Valve calcification was not associated with event-free survival.

3. Mayo Clinic — A large retrospective study included 622 patients with severe, asymptomatic aortic stenosis (peak aortic jet velocity ≥4 m/sec and mean aortic valve area 0.9 cm2) (25).

- The probability of remaining free of cardiac death and aortic valve replacement was 80, 63, and 25 % at one, two, and five years; the rate of remaining free of cardiac symptoms and unoperated was 82, 67, and 33 % at the same time points.
- Patients with peak aortic jet velocity ≥4.5 m/sec had increased event rates (relative risk 1.34 for symptoms and 1.48 for valve replacement or death).
- The rate of sudden death while still asymptomatic and without surgery was less than 1 % per year.

The rate of progression of the stenotic lesion and the time to onset of symptoms varies significantly among patients. Whether patients at high risk for rapid progression can be successfully identified remains controversial. Several prospective series have attempted to identify risk factors for progression in asymptomatic patients (with symptomatic patients being treated surgically) (21,25–27). Among the factors that may be important are:

- Aortic jet velocity and valve area
- Degree of valve calcification
- Response to exercise testing
- Cause of aortic stenosis
- Hypercholesterolemia
- Renal insufficiency
- Hypercalcemia

Serial hemodynamic measurements alone have not been proven clinically useful in asymptomatic patients since the absolute valve area or transvalvular pressure gradient does not determine the onset of symptoms and the optimal time for valve replacement. As many as one-third patients with symptomatic AS do not have critical AS (valve area less than 0.75 cm2). However, serial echocardiography, which also provides information about left ventricular function and associated lesions, is an important part of an integrated approach that includes a detailed history, a careful physical examination, and evaluation of exercise tolerance

Concerning ethiologies, there are three primary causes of valvular AS: a congenitally bicuspid valve with superimposed calcification (unicuspid or bicuspid); degenerative calcific disease of a trileaflet valve; and, much less common in developed countries, rheumatic valve disease.

Among patients with congenital or degenerative disease, progression to valve replacement occurs earliest with a unicuspid valve, later with a bicuspid valve, and

latest with a tricuspid valve. These relationships were illustrated in a study of 932 adults who underwent surgery for isolated AS (1). Patients with mitral valve replacement or mitral stenosis were excluded to ensure that patients with rheumatic valve disease were not included. Also excluded were patients with a previous aortic valvotomy, indicating severe valve obstruction due to congenital disease.

An anatomically abnormal valve was present in 54 %: 49 % had a bicuspid valve and 4 % had a unicuspid valve, but the frequency varied importantly with age:

- Among the 7 % of patients who underwent surgery at ≤50 years of age, approximately two-thirds had a bicuspid valve and one-third had a unicuspid valve
- Among the 40 % of patients who underwent surgery between the ages of 50 and 70, approximately two-thirds had a bicuspid valve and one-third a tricuspid valve; only rare patients had a unicuspid valve.
- Among the remaining patients over age 70, approximately 60 % had a tricuspid valve and 40 % had a bicuspid valve.

……..

A different aspect regards aortic valve thickening (sclerosis) without stenosis, which is common in elderly adults. It is typically detected either as a systolic murmur on physical examination or by echocardiography, and is associated with increased cardiovascular mortality

Aortic sclerosis may progress to significant aortic stenosis. In a review of 2131 patients with aortic valve thickening detected on echocardiography, aortic stenosis developed in 338 (16 %) after seven years (28). The stenosis was mild to moderate in 84 % of these patients and severe in 16 %. Only mitral annular calcification was significantly associated with progression in multivariable analysis.

Patients with symptomatic severe AS who do not undergo valve replacement have a poor prognosis (figure 1). Mortality in patients with AS dramatically increases after the development of the cardiac symptoms. As a result, prompt valve replacement is recommended in such patients. The high mortality rates observed in symptomatic patients who do not undergo valve replacement may be in part due to comorbidities that preclude surgery. The following examples demonstrate the high mortality rate associated with severe symptomatic AS:

- A review of studies performed during 1913 to 1970 found that mean survival after onset of heart failure ranged from 0.5 to 2.8 years, after onset of syncope ranged from 0.8 to 3.8 years, and after onset of angina ranged from 2 to 4.7 years (29). Studies performed during 1967 to 1982 reported two-year actuarial mortality rates of 24 to 69 % in patients with New York Heart Association functional class III to IV symptoms.
- In the PARTNER trial, 179 patients with AS with heart failure symptoms were assigned to the standard therapy arm (7). The majority of these patients received balloon aortic valvuloplasty (64 % during the first 30 days and 20 % later). The mortality rate at one year was 51 % in this group.
- In an observational study of symptomatic AS patients not eligible for a transcatheter aortic valve implantation trial, 274 patients received medical treatment (including balloon aortic valvuloplasty in 65 %) (12). Mortality was 32 % during median follow-up of one year.

To end with, pulmonary hypertension (pulmonary artery pressure >30 mmHg) commonly occurs in symptomatic patients with aortic stenosis and is associated with a more severe clinical picture and a poor prognosis after aortic valve replacement.

These relationships were illustrated in a study of 388 symptomatic patients with isolated aortic stenosis who underwent cardiac catheterization; pulmonary hypertension was absent in 35 %, mild to moderate pulmonary hypertension

(defined as pulmonary artery systolic pressure 31 to 50 mmHg) was present in 50 % and severe pulmonary hypertension in 15 % (30). The only factors associated with severe pulmonary hypertension were overt heart failure and elevated left ventricular end-diastolic pressure; neither the aortic valve area nor the left ventricular ejection fraction was related to the pulmonary artery pressure.

# 2. Diagnosis of aortic stenosis

## *2.1. ECHOCARDIOGRAPHY VERSUS CATHETERIZATION.*

Although invasive cardiac catheterization has historically been the standard for quantification of AS, this function has been largely replaced by echocardiography (31,32).

Echocardiographic diagnosis is made by the observation of a calcified valve with restricted leaflet opening by two-dimensional (2D) echocardiography with quantification of the peak and mean AV gradient made by applying the simplified Bernoulli equation ($\Delta p=4v^2$) to the maximal velocity recorded through the aortic valve by continuous-wave Doppler. Multiple imaging windows (apical 4-chamber and long-axis, right parasternal, suprasternal notch, and subcostal views) should be obtained to assure acquisition of the maximal velocity and to avoid angle-related errors. Although aortic valve area (AVA) can be measured by planimetry, it is more accu- rately assessed by application of the continuity equation, using pulsed-wave Doppler in the left ventricular outflow tract (LVOT) and continuous-wave Doppler across the valve.

Severe stenosis is defined in the guidelines (13,14) as a peak velocity >4.0 m/s, a mean gradient >40 mm Hg, OR valve area <1.0 cm2 when LV systolic function is normal. To account for patient size, the valve area is often indexed to body surface area, with 0.6 cm2/m2 considered to be the threshold for severe AS. An important exception is when the gradient suggests less severe stenosis than the valve area, most commonly due to low stroke volume, either in dilated ventricles with low ejection fraction (EF) or small ventricles with normal EF. In this setting, a dobutamine stress study, may be helpful. If the maximum jet velocity rises over 4 m/s with the dobutamine-induced increase in stroke volume whereas the AVA remains less than 1.0 cm2, then the valve is truly severely stenotic. On the other hand, if stroke volume increases with little rise in gradient (causing valve area to increase substantially),

then the AS is only mild to moderate in severity, and the LV dysfunction is due to causes other than AS (33–35).

Occasionally, the AVA appears larger than the elevated gradient would suggest, usually due to elevated stroke volume from aortic regurgitation (AR), anemia, fever, or hyperthyroidism. Sometimes, though, it reflects a technical error in applying the continuity equation, when the blood accelerates within the LVOT due to an upper septal bulge, which may result in an overestimation of valve area. To avoid this, one can try to measure the LVOT area at the point of maximal velocity, though the geometry is often quite distorted in this region, making estimation of the LVOT area difficult.

Alternatively, one can use the LV stroke volume (from 2D or three-dimensional [3D] measurements of the LV, ideally with contrast infusion) or right ventricular (RV) stroke volume (from RV outflow tract) as the input into the continuity equation. Dividing this stroke volume by the time velocity integral of the AV continuous-wave Doppler will also yield the AVA, independent of any distortion in the LVOT.

Despite the convenience and widespread applicability of transthoracic echocardiography (TTE), there are occasions when invasive measurements are needed, such as in patients with a discrepancy between clinical and echocardiographic assessments. In such cases, catheterization should generally be performed with dual catheters, 1 placed in the LV, the other in the proximal aorta to obtain simultaneous pressure measurements and obtain the most accurate assessment of the gradient. Infusion of dobutamine may allow assessment of low-output, low-gradient AS in the catheterization laboratory (36). Other adjunctive testing used in quantifying AS includes transesophageal echocardiography (TEE) (37), computed tomography scanning (dynamic or gated during systole) (38), and cardiac magnetic resonance imaging (39).

## *2.2. STRESS TESTING.*

The presence or absence of symptoms should guide the management of AS patients, yet in many cases, this important clinical benchmark is difficult to establish, owing to the subjective nature of the symptoms and comorbid conditions such as chronic lung disease in this patient population. In general, stress testing is contraindicated when symptoms are present because of the potential for complications in these patients. However, in patients with equivocal symptoms, stress testing, and in particular stress echocardiography, can be very helpful (40). Simple determination of functional capacity may help show limitations of which a patient may be unaware. Isolated echocardiographic changes during the stress test without symptoms or change in blood pressure should not be interpreted as a positive indicator of severe AS. Other potential markers for AS severity include signs of LV dysfunction on exercise echo or a rise in left atrial or right ventricular pressure (13,14).

## *2.3 SPECIAL CONSIDERATIONS*

### 2.3.1. SYMPTOM STATUS.

With severe, symptomatic, calcific AS, AVR is the only effective treatment that improves symptoms and prolongs survival (41,42). These results are partly dependent on LV function. In the setting of LV dysfunction caused by afterload mismatch, survival is still improved, although improvement in LV function and resolution of symptoms might be incomplete after AVR. Age itself is a risk factor for adverse outcome, but it is not a contraindication to AVR even in the very elderly (43,44).

### 2.3.2. ASSOCIATED CORONARY ARTERY DISEASE.

In patients with moderate AS, who are undergoing coronary artery bypass graft surgery (CABG), AVR should be performed at the time of revascularization irrespective of symptoms related to moderate AS (45,46). There are no data to support performing AVR for mild AS at the time of CABG. Patients undergoing surgical AVR with significant stenoses (>50% to 70% stenosis) in major coronary arteries should be treated with concomitant CABG. Options in patients with combined AS and CAD continue to grow with the use of hybrid procedures where PCI is followed by valve surgery. It is possible that such a strategy could be performed in the setting of TAVR (45,46).

### 2.3.3. ASSOCIATED LESIONS — AORTIC REGURGITATION, MITRAL REGURGITATION, PULMONARY HYPERTENSION, TRICUSPID REGURGITATION.

Patients with severe AS often have additional associated significant valvular heart disease. Treatment of these lesions in patients undergoing AVR should be under- taken using standard criteria. However, treatment of associated valvular lesions may increase the risk of AVR (47). A special circumstance is that of pulmonary hypertension (PH) either primary or secondary (reactive or related to increased LV end-diastolic pressure). Both conditions may increase the risk of AVR and must be taken into consideration in the risk/benefit ratio.

PH can be present in patients with severe AS, either from the transmission of increased LV diastolic and/or left atrial pressures, associated mitral regurgitation (MR), or from a secondary increase in pulmonary vascular tone. The prevalence of PH in patients with AS is undefined, varying widely on the definition used and the population studied (48,49). Clinically, PH associated with critical AS portends a poor prognosis and is associated with an increased risk of sudden cardiac death (50). The presence of PH makes patients more susceptible to any hemodynamic and electrical

instability related to the procedure and may increase the risk of postprocedural complications. In addition, PH may result in right heart failure and severe tricuspid regurgitation (TR), both of which complicate management and increase risks.

In the setting of severe AS and PH several treatment strategies have been used (51). Persistently elevated left-sided cardiac filling pressures increase the risk of pulmonary edema when challenged with a pulmonary vasodilator. Pulmonary vasodilators, such as nitric oxide, prostacylin, and sildenafil, have been administered during and following cardiac surgery with improved hemodynamic effects (52). However, their overall clinical utility in improving late survival in the surgical population remains unclear.

### 2.3.4. LOW GRADIENT–LOW EJECTION FRACTION.

As mentioned, the combination of overt congestive heart failure and low aortic valve gradient is relatively common. This may be a consequence of excessive afterload (despite left ventricular hypertrophy [LVH]) or reduced contractile function likely due to increased myocardial fibrosis (53). When there is overt heart failure due to low forward flow and a low transvalvular gradient (mean gradient <30 mm Hg), both mechanisms may be present. Because of reduced contractility in the low-flow/low-gradient AS patient, prognosis with surgical AVR is adversely affected with operative mortality as high as 20%. However the 5-year survival is still reported to be better in patients treated surgically (54,55). When the primary reason for poor LV performance is excessive afterload, the prognosis following surgical AVR is usually good (5). In general, patients with low gradient, low EF who have the best prognosis are those with inotropic reserve (shown by an increase in stroke volume with dobutamine infusion), who have limited coronary disease and a mean gradient that al- though low, still exceeds 20 mm Hg (54).

### 2.3.5. BASAL SEPTAL HYPERTROPHY—OUTFLOW TRACT GRADIENTS.

Although infrequent, proximal septal bulging with LVOT obstruction may present unique issues in the presence of AS. While this can be readily addressed during AVR via myomectomy, such an approach would not be possible with transcatheter procedures. Thus, careful preprocedural echocardiographic screening is recommended to specifically avoid this scenario in patients being considered for transcatheter aortic valve replacement.

## 3. Indications for valve replacement in aortic stenosis

In individuals with normal aortic valves, the valve area is 3.0 to 4.0 cm2. As aortic stenosis (AS) develops, a minimal valve gradient is present until the orifice area falls by more than 50 %. In general, symptoms in patients with AS and normal left ventricular systolic function rarely occur until aortic stenosis is severe (generally defined as a valve area <1.0 cm2, usually accompanied by an aortic jet velocity >4.0 m/sec and/or mean transvalvular gradient >40 mmHg). However, many patients do not develop symptoms until obstruction is even more severe, while some become symptomatic with lesser obstruction, particularly if there is coexisting aortic regurgitation.

Surgical replacement of the aortic valve is the only effective treatment for severe AS. Although there is some lack of agreement about the optimal timing of surgery, it is still possible to develop rational guidelines for the evaluation and management of most patients (13,14). Particular consideration must be given to the natural history of symptomatic and asymptomatic patients and to the operative risk and the outcome after surgery.

The recommendations are generally in accord with the 2006 American College of Cardiology/American Heart Association (ACC/AHA) valvular heart disease guidelines with 2008 focused update (table 2) (14). Recommendations in the 2007 European Society of Cardiology (ESC) guidelines are similar but differ somewhat in their recommendations for asymptomatic patients (13) (table 3).

*Table 2. 2008 ACC/AHA Guideline Summary: Indications for aortic valve replacement (AVR) in aortic stenosis (AS)*

| |
|---|
| ***Class I - There is evidence and/or general agreement that AVR is indicated in patients with AS in the following settings*** |
| • Symptomatic severe AS. |
| • Severe AS in patients undergoing coronary artery bypass graft surgery or surgery on the aorta or other heart valves. |
| • Severe AS with a left ventricular ejection fraction less than 50 %. |
| ***Class IIa - The weight of evidence or opinion is in favor of the usefulness of AVR in patients with AS in the following setting*** |
| ***• Moderate AS in patients undergoing coronary artery bypass graft surgery or surgery on the aorta or other heart valves.*** |
| ***Class IIb - The weight of evidence or opinion is less well established for the usefulness of AVR in patients with AS in the following settings*** |
| ***• Severe AS in asymptomatic patients who have an abnormal response to exercise such as the development of symptoms or hypotension.*** |
| ***• Severe AS in asymptomatic patients with a high likelihood of rapid progression (as determined by age, valve calcification, and coronary heart disease).*** |
| ***• Severe AS in asymptomatic patients in whom surgery might be delayed at the time of symptom onset.*** |
| ***• Mild AS in patients undergoing coronary artery bypass graft surgery in whom there is evidence, such as moderate to severe valve calcification, that progression may be rapid.*** |
| ***• Extremely severe AS (aortic valve area less than 0.6 cm2, mean gradient greater than 60 mmHg, and aortic jet velocity greater than 5.0 m/sec) in asymptomatic patients in whom the expected operative mortality is 1 % or less.*** |
| ***Class III - There is evidence and/or general agreement that AVR for AS is not useful in in the following settings*** |
| ***• For the prevention of sudden cardiac death in asymptomatic patients who have none of the class IIa or IIb findings.*** |

*Table 3. 2007 ESC Indications for aortic valve replacement in aortic stenosis*

| | **Class** |
|---|---|
| ***Patients with severe AS and any symptoms*** | *IB* |
| ***Patients with severe AS undergoing coronary artery bypass surgery, surgery of the ascending aorta, or on another valve*** | *IC* |
| ***Asymptomatic patients with severe AS and systolic LV dysfunction (LVEF <50 %) unless due to other cause*** | *IC* |
| ***Asymptomatic patients with severe AS and abnormal exercise test showing symptoms on exercise*** | *IC* |
| ***Asymptomatic patients with severe AS and abnormal exercise test showing fall in blood pressure below baseline*** | *IIaC* |
| ***Patients with moderate AS* undergoing coronary artery bypass surgery, surgery of the ascending aorta or another valve*** | *IIaC* |
| ***Asymptomatic patients with severe AS and moderate-to-severe valve calcification, and a rate of peak velocity progression ≥0.3 m/s per year*** | *IIaC* |
| ***AS with low gradient (<40 mmHg) and LV dysfunction with contractile reserve*** | *IIaC* |
| ***Asymptomatic patients with severe AS and abnormal exercise test showing complex ventricular arrhythmias*** | *IIbC* |
| ***Asymptomatic patients with severe AS and excessive LV hypertrophy (≥15 mm) unless this is due to hypertension*** | *IIbC* |
| ***AS with low gradient (<40 mmHg) and LV dysfunction without contractile reserve*** | *IIbC* |

## *SYMPTOMATIC PATIENTS*

Angina, dizziness or syncope, and heart failure (eg, dyspnea) are the primary manifestations of severe AS, usually occurring with exertion. Average survival after the onset of these symptoms is only two to three years, with a high risk of sudden death. As a result, symptomatic AS is an indication for valve replacement.

Observational studies have found that corrective surgery in this setting is almost always followed by symptomatic improvement and a substantial increase in survival (56). The potential magnitude of these benefits can be illustrated by the following observations:

- In a retrospective review of 99 elderly patients with AS and, in almost all, New York Heart Association class III or IV, follow-up at 55 months revealed that 91 % of survivors were in NYHA class I or II (table 4) (57).

*Table 4. Comparison of three methods of assessing cardiovascular disability*

| ***Class*** | ***New York Heart Association functional classification*** | ***Canadian Cardiovascular Society functional classification*** | ***Specific activity scale*** |
|---|---|---|---|
| ***I*** | *Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.* | *Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina with strenuous or rapid prolonged exertion at work or recreation.* | *Patients can perform to completion any activity requiring ≥7 metabolic equivalents, eg, can carry 24 lb up eight steps; do outdoor work (shovel snow, spade soil); do recreational activities (skiing, basketball,* |

| | | | |
|---|---|---|---|
| | | | *squash, handball, jog/walk 5 mph).* |
| ***II*** | *Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.* | *Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, in wind, or when under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.* | *Patients can perform to completion any activity requiring ≤ 5 metabolic equivalents, eg, have sexual intercourse without stopping, garden, rake, weed, roller skate, dance fox trot, walk at 4 mph on level ground, but cannot and do not perform to completion activities requiring ≥ 7 metabolic equivalents.* |
| ***III*** | *Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.* | *Marked limitation of ordinary physical activity. Walking one to two blocks on the level and climbing one flight in normal conditions.* | *Patients can perform to completion any activity requiring ≤ 2 metabolic equivalents, eg, shower without stopping, strip and make bed, clean windows, walk 2.5 mph, bowl, play golf, dress without stopping, but cannot and do not perform to completion any activities requiring > 5 metabolic* |

| | | | |
|---|---|---|---|
| | | | *equivalents.* |
| ***IV*** | *Patient with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.* | *Inability to carry on any physical activity without discomfort - anginal syndrome may be present at rest.* | *Patients cannot or do not perform to completion activities requiring > 2 metabolic equivalents. Cannot carry out activities listed above (Specific activity scale III).* |

- In a retrospective study of 144 symptomatic patients, survival at three years was 87 % in 125 who underwent valve replacement compared to 21 % in 19 nonoperated patients (10).

A problem with such retrospective observational studies is that the better outcomes with surgery in symptomatic AS could represent selection bias (ie, healthier patients are chosen for surgery). Nevertheless, it is generally recommended that virtually all symptomatic patients with severe AS should undergo aortic valve replacement. A possible exception is the rare patient with end-stage left ventricular dysfunction that is usually due to coexisting coronary disease.

Operative mortality (in-hospital regardless of timing and 30-day regardless of location) for aortic valve replacement (for any indication) with or without coronary artery bypass graft surgery (CABG) was reported for 2002 to 2006 data from the Society of Thoracic Surgeons (STS) National Cardiac Surgery Database (58):

- For isolated aortic valve replacement, the operative mortality rate was 3.2 %. Adverse event rates ranged from 1.5 % for stroke to 10.9 % for prolonged ventilations.
- Combined aortic valve replacement and coronary artery bypass graft surgery (CABG) is associated with higher operative mortality and adverse event rates than isolated aortic valve replacement. Mortality was 5.6 % and adverse event rates ranged from 2.7 % for stroke to 17.6 % for prolonged ventilation.

A variety of factors affect survival after aortic valve replacement for AS. These include patient age, left ventricular function and New York Heart Association (NYHA) functional class, the presence of low gradient disease, and the volume of procedures performed at the hospital. In addition, the in-hospital outcome is worse in patients with emergency/salvage procedures, recent infarction, reoperations, or renal failure (58–60).

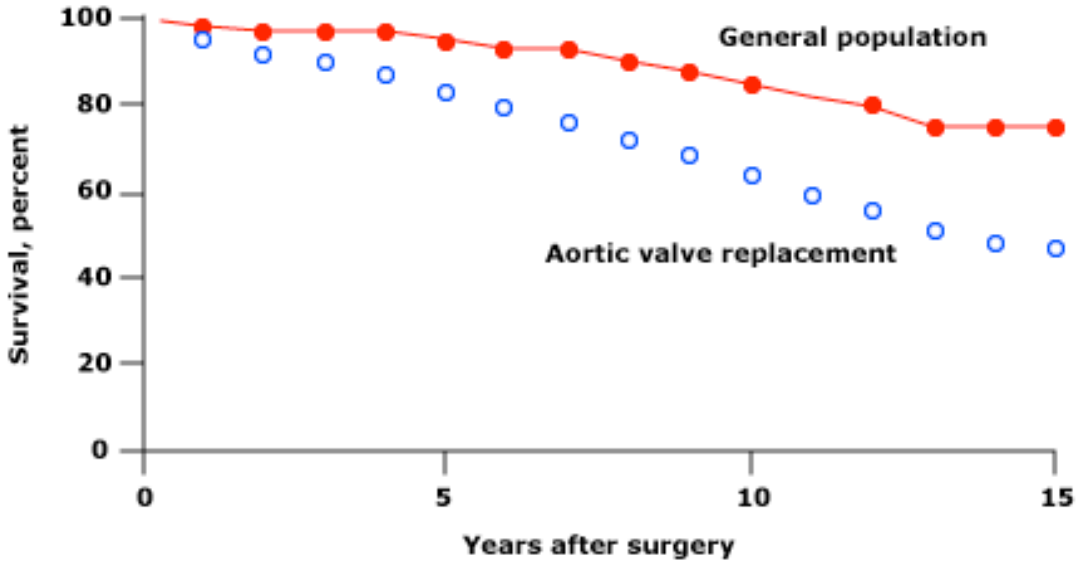
- AGE

Aortic valve replacement is performed in patients with a wide age range, but the proportion of elderly patients undergoing this procedure is increasing. Age is not a critical factor for outcome, as older patients generally tolerate valve replacement surgery well. As an example, a retrospective review of 1100 patients ≥80 years of age reported a 30-day and all-cause mortality of 4.0 and 6.6 % (61). After the first 30 postoperative days, 70 % of deaths were due to noncardiac causes. Actuarial survival at one and five years was 89 and 69 %, respectively.

The impact of age and other risk factors on survival after aortic valve replacement was analyzed in another study of 2359 patients who underwent a first valve replacement, 39 % of whom had concomitant coronary artery bypass graft (CABG) surgery (42). Mortality within 30 days of surgery was 5.6 %. The observed survival at 5, 10, and 15 years was 83, 63, and 46 %, respectively. During each of the

first 12 years of follow-up, the mortality was higher than expected in a reference age- and gender-matched cohort in the general population (figure 5).

*Figure 5.*




*Among 2227 patients undergoing aortic valve replacement who survived the first postoperative month, the observed long-term mortality (open blue circles) is higher during the entire follow-up period when compared to that expected in the general population (closed red circles).*

Factors associated with mortality included advanced NYHA functional class (III or IV) and preoperative atrial fibrillation. Patients in the oldest age group had a decreased observed survival, but an excellent relative survival, suggesting that age was not a risk factor.

- LEFT VENTRICULAR FUNCTION

The outcome of surgery is in part dependent upon the state of left ventricular (LV) function, as both systolic and diastolic dysfunction are independent risk factors for early and late mortality (62). The results of valve replacement are similar in patients with normal ventricular function and those with modest depression of contractility (ie, left ventricular ejection fraction [LVEF] between 40 and 50 %). The depressed ejection fraction in many, if not most, patients is caused by excessive afterload that is immediately corrected by valve replacement. Diastolic asynchrony is normalized later when hypertrophy and fibrosis regress (63).

In comparison, patients with severely depressed ventricular function (ie, LVEF of 20 to 35 %) may not experience complete resolution of symptoms after valve replacement. However, survival is still improved in this setting. This was illustrated in a report of 154 patients with an LVEF ≤35 % who underwent aortic valve replacement; simultaneous CABG was performed in 51 %. The following results were noted (41):

- Thirty day mortality was 9 %; multivariate analysis identified significant coronary disease (≥two vessel or left main) as the only predictor of mortality.
- Five year survival was 58 %; multivariate analysis indicated that the only predictors of mortality were significant coronary disease and a lower preoperative cardiac output.
- NYHA functional classification improved by at least one class in 88 % of patients and by two or more classes in 66 %; an improvement in LVEF occurred in 76 %.

- LOW GRADIENT AORTIC STENOSIS

Patients with AS and left ventricular dysfunction may have a low transvalvular pressure gradient despite significant valve narrowing. Such patients are said to have low gradient AS, which is defined as a transaortic pressure gradient of less than 30 mmHg and a calculated aortic valve area <1.0 cm2 in association with low flow.

Some patients with low gradient AS have true severe AS, whereas others have "pseudostenosis," with a low transvalvular pressure gradient because of the combination of moderate AS and low cardiac output. The distinction between true stenosis and pseudostenosis is made by evaluation of characteristic changes in hemodynamic and structural measurements in response to pharmacologic interventions that augment cardiac output.

Patients with low gradient true AS have a high perioperative and postoperative mortality. Nonetheless, surgery is still recommended in most patients because valve replacement is associated with better outcomes than continued medical therapy (45). Stress echocardiography is helpful in risk stratifying patients with severe true AS and in determining the appropriate therapy. Patients with contractile reserve in response to dobutamine have a much better outcome after surgery.

## *ASYMPTOMATIC SEVERE AORTIC STENOSIS*

With infrequent exceptions, such as patients undergoing coronary artery bypass graft surgery or surgery on the aorta or other heart valves, the 2006 ACC/AHA guidelines on the management of valvular heart disease concluded that valve replacement should not be routinely performed for isolated severe AS in asymptomatic patients (13).

On the other hand, careful monitoring is required since asymptomatic patients with severe AS have a low rate of survival free from valve replacement (56 to 63 % at two years and 25 to 33 % at four to five years in two studies) (19,25). This is associated with a progressive reduction in aortic valve area that averages 0.1 cm2/year and a progressive increase in aortic jet velocity that averages 0.3 m/sec per year. Risk factors for progression include small valve area, left ventricular hypertrophy, and moderate to severe valve calcification.

Outcomes worsen as AS progresses and a markedly elevated peak aortic jet velocity (>5.0 or 5.5 m/s) is an independent predictor of cardiac mortality (20,64).

- SURGICAL VERSUS MEDICAL THERAPY

Consideration of surgery in an asymptomatic patient with severe AS requires an appreciation of the relative risks of surgical and medical therapy. The surgical mortality of aortic valve replacement varies widely. If it is not well under 2 to 3 %, then the operative risk clearly exceeds the risk of sudden death in an asymptomatic patient who does not undergo surgery. Furthermore, valve replacement does not abolish the risk of sudden death. In one report that retrospectively analyzed the postoperative course of 599 patients, the late annual mortality was 3.6 %; sudden death accounted for 24 % of these deaths (65).

Insertion of a prosthetic heart valve is also associated with appreciable morbidity. Among the complications of prosthetic heart valves are prosthesis dysfunction, paravalvular leak, thrombus formation, arterial embolism, endocarditis, and the problems associated with anticoagulation. The incidence of serious complications depends upon the type of valve and a number of clinical variables, but significant complications occur at a frequency of at least 3 % per year, and death due directly to the valve occurs at the rate of approximately 1 % per year (57,65).

- VERY SEVERE AORTIC STENOSIS

Improved outcomes with aortic valve replacement in patients with asymptomatic very severe AS were suggested by an observational study (64). Very severe AS was defined as an aortic valve area of ≤0.75 cm2 (critical AS) accompanied by a peak aortic jet velocity ≥4.5 m/sec or a mean transaortic pressure gradient ≥50 mmHg. Early surgery was performed on 102 patients and a conventional treatment strategy (surgery for symptomatic AS) was followed in 95 patients.

- During a median four year follow-up, the operated group had no operative mortalities, no cardiac deaths, and three noncardiac deaths while the conventional treatment group had 18 cardiac and 10 noncardiac deaths.
- For 57 propensity score-matched pairs, the risk of all-cause mortality was significantly lower in the operated group than in the conventional treatment group (HR, 0.135, 95% CI, 0.030 to 0.597).

The results suggest that early surgery can be beneficial in patients with very severe AS with low operative risk.

## *AORTIC VALVE REPLACEMENT AND CORONARY ARTERY BYPASS GRAFT*

There are two settings in which aortic valve replacement and coronary artery bypass graft surgery (CABG) intersect:

- Patients who are candidates for aortic valve replacement in whom coronary angiography demonstrates significant coronary artery disease that could be corrected at the time of valve replacement. The role of coronary angiography prior to surgery and the indications for concurrent CABG at the time of aortic valve replacement issue will be reviewed here.
- Patients who are candidates for CABG who also have AS that might be corrected at the same surgery. This issue is discussed separately.

Despite the limited indications for cardiac catheterization to assess the valve disease, most patients require coronary angiography before aortic valve replacement because significant coronary disease is common in these patients, and about 40 % of those undergoing valve replacement require concurrent coronary bypass grafting (42).

Most of these patients have angina, but this symptom can also be induced by AS alone. Thus, symptoms do not predict the presence or absence of concurrent coronary disease and the ECG and noninvasive stress testing may be nondiagnostic. To sum up, the likelihood of coronary disease increases with age.

The 2006 ACC/AHA and the 2007 ESC guidelines on the management of valvular heart disease recommended coronary angiography before aortic valve surgery in three settings if they are not severely hemodynamically unstable (table 5) (13):

- Patients with chest pain, other objective evidence of ischemia or a history of coronary disease.
- In patients at risk for coronary disease, which was defined as men ≥35 years of age, premenopausal women ≥35 years of age who have coronary risk factors, and postmenopausal women.
- When a pulmonary autograft (Ross procedure) is considered in patients in whom the origin of the coronary arteries was not identified by noninvasive testing.

*Table 5. ACC/AHA guideline summary: Coronary angiography to diagnose coronary artery disease in patients with valvular disease*

| *Class I - There is evidence and/or general agreement that coronary angiography should be performed in patients with valvular disease in the following settings* |
| --- |
| *• Before valve surgery (including for infective endocarditis) in patients with chest pain (although angina is a poor marker for coronary disease in patients with aortic stenosis), other objective evidence of ischemia, or a history of coronary disease.* |

- *Before valve surgery in patients at risk for coronary disease defined as men ≥35 years of age, premenopausal women ≥35 years of age who have coronary risk factors, and postmenopausal women. Patients undergoing mitral balloon valvotomy do not require coronary angiography solely on the basis of coronary risk factors.*
- *In patients with apparently mild to moderate valve disease who have progressive angina, objective evidence of ischemia, or either asymptomatic or symptomatic left ventricular dysfunction.*
- *When a pulmonary autograft (Ross procedure) is considered in patients with aortic stenosis or in adolescents or young adults with aortic regurgitation in whom the origin of the coronary arteries was not identified by noninvasive testing.*

*Class IIa - The weight of evidence or opinion is in favor of the usefulness of surgery without coronary angiography in patients with valve disease in the following setting*

- *Before emergency valve surgery for acute valve regurgitation, aortic root disease, or infective endocarditis.*

*Class IIb - The weight of evidence or opinion is less well established for the usefulness of coronary angiography in patients with valve disease in the following setting*

- *Patients in whom cardiac catheterization is performed to confirm the severity of valve lesions before valve surgery who do not have a history of coronary disease, multiple coronary risk factors, or advanced age.*

*Class III - There is evidence and/or general agreement that coronary angiography in patients with valve disease is NOT useful in in the following settings*

- *Young patients undergoing nonemergent valve surgery who have no need for further hemodynamic assessment by cardiac catheterization who do not have a history of coronary disease, multiple coronary risk factors, or advanced age.*
- *Before valve surgery in patients who are severely hemodynamically unstable.*

On the other hand, the 2006 ACC/AHA guidelines reached the following conclusions about CABG at the time of aortic valve replacement (13):

- CABG was recommended in patients with ≥70 % stenosis of major coronary arteries.
- Among patients undergoing CABG, the weight of evidence favored use of a left internal mammary artery graft for ≥50 to 70 % stenosis left anterior descending coronary artery.
- CABG was considered reasonable in patients with 50 to 70 % stenosis of major coronary arteries.

# 4. Current non-medical treatment options for aortic stenosis

## *SURGICAL AORTIC VALVE REPLACEMENT*

Aortic valve replacement (AVR) is the only effective treatment considered a Class I recommendation by ACCF/AHA and ESC guidelines in adults with severe symptomatic AS (13,14). Not only does it offer symptomatic relief, the operation improves long-term survival. Since 1960, when AVR was first introduced, advancement in prosthetic technology including improved hemodynamics, durability and thromboresistance, and techniques in cardiac surgery such as cardioplegia, management of the small aortic root, resection of associated subvalvular disease, and replacement of associated aortic aneurysm have resulted in improvements in both operative and long-term results.

Current AVR options include mechanical, bioprosthetic, and in specific situations homograft and autograft techniques. Each has their advantages and drawbacks, but the trend in some centers in the recent era has been toward tissue valve replacement in a majority of patients because of improved durability and the lack of requirement for anticoagulation therapy.

- MECHANICAL VALVES

Mechanical valves are now extremely durable, have excellent hemodynamics, and are minimally thrombogenic with adequate anticoagulation. Current anticoagulation is mostly based on Vitamin K antagonists. Newer agents such as oral direct thrombin inhibitors and factor Xa inhibitors have been studied in other patient populations, mainly atrial fibrillation, and have been found to be associated with decreased bleeding risk and minimum drug or food interaction (43). With acenocumarol there is a risk of serious thromboembolism of approximately

0.5% a year and a similar risk of major hemorrhage annually (66). Mechanical valves are typically preferred in younger patients given their reliable long-term durability.

- BIOPROSTHETIC VALVES

Compared with mechanical valves, bioprosthetic valves do not require anticoagulation with acenocumarol, and thus have a lower risk of bleeding. However, long-term durability varies substantially with age for these valves. Structural valve degeneration leading to symptoms or reoperation, commonly associated with calcification of the biologic leaflets, occurs at an average of 10 to 12 years in younger patients and 15 to 18 years in older patients. Actuarial freedom from reoperation following implant of a modern bioprosthetic valves is approximately 95% at 5 years, 90% at 10 years, but drops to 70% at 15 years (67). Thus, bioprosthetic valves are generally preferred in older patients who are unlikely to tolerate bleeding risk associated with anticoagulation treatment and in whom a 15-year durability is reason- able. In patients with bioprosthetic valves, if prosthetic dysfunction occurs, TAVR may play an important role in solving the clinical issues in the future.

…….

Both mechanical and bioprosthetic valves have been used for aortic valve replacement (AVR). Issues to consider when choosing the appropriate valve include (68):

- Mechanical valves are more durable.
- Mechanical valves require lifelong anticoagulation.
- Some biological aortic valve options are technically more challenging than others (Ross procedure > aortic homografts > stentless AVR > stented AVR)
- Stented tissue valves are associated with smaller effective orifice areas (EOA) than stentless tissue valves, due to the space occupied by the supporting

stents. This can be particularly important in patients with a small aortic annulus who are a risk for patient-prosthesis mismatch.

- Tissue valves have a low risk for thromboembolism, and do not require lifelong anticoagulation.
- Although observations have varied, infection generally occurs with equal frequency on mechanical and bioprosthetic devices during the first postoperative year
- Reoperations after certain biological valves (eg, homografts) are technically more challenging than after implantation of standard bioprosthetic valves.

The 2006 American College of Cardiology/American Heart Association (ACC/AHA) and the 2007 European Society of Cardiology (ESC) guidelines for the management of valvular heart disease guidelines made the following general recommendations for the choice of aortic valve, recognizing that patient preference may also play a role (13,14):

- A mechanical valve is recommended in patients who already have a mechanical valve in the mitral or tricuspid position (and therefore already need anticoagulation).
- A mechanical valve is reasonable (a weaker recommendation) in patients under 65 years of age who do not have a contraindication to anticoagulation.
- A bioprosthesis is recommended in patients of any age who will not take or have major contraindications to anticoagulation therapy.
- A bioprosthesis is reasonable in patients ≥65 years of age who do not have risk factors for thromboembolism and in patients under age 65 who choose this approach for lifestyle reasons after a detailed review of the risks of anticoagulation compared to the greater likelihood of a second valve surgery in the future.
- Valve re-replacement with a homograft is reasonable in patients with active prosthetic valve endocarditis.
- The evidence was considered less well established for a bioprosthesis in women of childbearing age.

- A mechanical valve may be recommended for patients with small aortic roots in whom annular enlargement is high risk or contraindicated.

- PATIENTS < 65 YEARS OF AGE

Given the similar survival with both valve types, these findings emphasize that valve choice in adults <65 years of age should take patient preferences into account, specifically regarding the likelihood of repeat valve surgery versus need for long term anticoagulation. A detailed and balanced discussion of the issues is vital for informed consent.

- ELDERLY PATIENTS

There is a particular preference for a bioprosthetic valve in elderly patients, which is based in part upon the observation that the longevity of these valves is inversely related to age (68,69). The actuarial estimate of the rate of structural deterioration of bioprosthetic aortic valves at 15 years varied from 63 % between the ages of 40 and 49 (and perhaps higher under age 40) to 10 % over age 70 (68). The lower rate of valve failure in elderly adults is due at least in part to decreased activity in older patients. The net effect is that the life expectancy of an octogenarian is shorter than the expected functional life of a bioprosthesis.

- PRE-EXISTING CORONARY ARTERY BYPASS GRAFTS

The morbidity and mortality associated with valve reoperation may be higher in some patient populations, such as those with coronary artery bypass grafts. Retrospective data indicate that operative mortality rates are high for aortic valve replacement with pre-existing coronary artery bypass grafts (and higher than for combined aortic valve and bypass graft surgery) (70). In the presence of a patent

internal mammary artery (IMA) graft, aortic valve surgery poses a potential risk of IMA graft injury and myocardial infarction (46). The increased risk associated with valve reoperation should be considered in choosing a valve for a patient with coronary artery bypass grafts.

- HOMOGRAFTS

Homograft aortic valves are most often used for treatment of endocarditis because the homograft is supplied as a composite valve, aortic root, and part of the anterior mitral leaflet. This additional tissue may be used to reconstruct the areas adjacent to the valve, which can be of particular value if the infection has extended into the annulus, basal septum, or base of the mitral valve. Otherwise, homografts do not have any specific advantages, compared to other tissue valves, in terms of durability or resistance to infection.

A disadvantage of homograft valves is that fibrosis (involving the adjacent pulmonary artery) and calcification (frequently involving the coronary button reattachment) of the composite root and valve makes it more difficult to perform repeat surgical intervention, which often is needed on long term follow-up.

- PULMONARY AUTOGRAFT (ROSS PROCEDURE)

The Ross procedure is an alternative to valve replacement with a mechanical valve or bioprosthesis. It involve replacing the aortic valve with a pulmonary valve autograft and right-sided reconstruction with an aortic or pulmonary homograft (71). Use of the Ross procedure has been limited because of its technical complexity, complications with both the aortic autograft and the pulmonic homograft, and the availability of simpler and effective alternatives, ie, mechanical valves and bioprostheses including stentless bioprosthetic valves.

There are a number of potential advantages of the Ross procedure (71,72):

- Autologous tissue with documented long-term viability
- Optimal hemodynamic data
- Regeneration capacity
- Possible resistance to infection (eg, 0.2 to 0.3 %/patient year as compared to >0.4 %/patient year for recipients of prosthetic valves).
- Lack of valve noise
- Freedom from anticoagulation due to rates of thromboembolic complications ranging from 0 to up to 1.2 % per year

Strong relative contraindications to the Ross procedure include the following (72):

- Advanced three vessel coronary disease
- Other extensive valve pathology requiring replacement
- Severely depressed left ventricular function
- Multisystem organ failure
- Pulmonary valve pathology
- Marfan syndrome or other connective tissue disorders
- Size mismatch between the pulmonic and aortic annulus

The Ross procedure has been used most successfully in children and adolescents, but has also been performed in adults less than 50 years of age with single valve pathology, mechanical or bioprosthetic valve failure, endocarditis limited to the aortic root, and athletes or young patients in whom anticoagulation is contraindicated and for whom optimal hemodynamics are desired (eg, a female of reproductive age).

The pulmonary autograft in the aortic position provides excellent hemodynamics at rest and with maximum exercise; however, there may be a moderately high gradient across the homograft in the pulmonary valve position (73).

A number of studies have noted good short-term results with the Ross procedure. In a meta-analysis of 39 reports published from 2000 to 2008, the pooled early mortality rates for consecutive adult and pediatric series, adult series and pediatric series were 3.0, 3.2 and 4.2 %, respectively (74). However early mortality rates varied from 0.3 to 6.8 % even among these selected centers.

Longer term results suggest a high risk of reoperation (75–77):

- At 20 years after operation in the pioneering series of 131 patients (age 11 to 52), survival was 61 %, freedom from autograft reoperation was 75 %, and freedom from pulmonary homograft reoperation was 80 %.
- At 16 years after operation in a series of 487 patients (age 2 days to 62 years), actuarial survival was 82 %, freedom from autograft failure (reoperation and valve-related death) was 74 %, and freedom from pulmonary allograft reoperation was 80 %. Actuarial freedom from valve-related morbidity (includes autograft and pulmonary allograft failure, endocarditis, and valve-related death) was 63 % at 16 years.

Use of the Ross procedure in adults is controversial and the procedure is only performed at a few experienced centers. There may be more perioperative complications since the surgery is longer and more complicated than simple aortic valve replacement. Dilation of the pulmonic autograft with autograft failure is a significant late complication associated with surgical technique in some series but not others. Since patients with preoperative aortic regurgitation and dilated aortic annulus are at risk for future dilation and failure of the pulmonary autograft, some recommend avoidance of the Ross procedure in such patients. On the other hand , the pulmonary homograft is also prone to stenosis, sometimes early after surgery (74,76).

## *AORTIC VALVOTOMY*

Aortic valve replacement is the mainstay of treatment of symptomatic aortic stenosis (AS). Aortic valve replacement offers substantial improvements in symptoms and life expectancy. However, aortic valve surgery entails substantial risks for some patients with severe comorbidities, and for some considered at “extreme” risk, surgery is not appropriate. In others, technical limitations, eg, porcelain aorta, may mean that surgery is not feasible. Percutaneous aortic valvotomy was developed as a less invasive means to treat AS but has important limitations. Subsequently developed catheter-based techniques for aortic valve implantation may provide an alternative method for treating AS in patients with unacceptably high estimated surgical risks.

Percutaneous aortic balloon valvotomy is a procedure in which a balloon is placed across the stenotic aortic valve and inflated (78). The aim is to relieve the stenosis by fracturing calcific deposits within the valve leaflets. Stretching of the annulus and separation of the calcified commissures also may contribute.

There are a number of important limitations to the use of percutaneous valvotomy (78–81):

- Despite a moderate reduction in the transvalvular pressure gradient, which is often accompanied by an improvement in symptoms, the postprocedure valve area rarely exceeds 1.0 cm2, leaving the patient with persistent severe AS.
- In historical series (79), serious complications (stroke, aortic regurgitation, myocardial infarction, major access-related complications) occurred in approximately 10 to 20 % of patients. In-hospital mortality rates were also about 10 to 20 %. However, anecdotal experience suggests that morbidity and mortality in contemporary practice is better than this due to improvements in balloons and technique.

- Restenosis and clinical deterioration occur in most cases within 6 to 12 months, and the long-term outcome resembles the natural history of untreated AS. Repeat balloon valvotomy can be performed, but most patients fail within six months.

Given the limitations observed with aortic valvotomy, the 2006 ACC/AHA valve disease guidelines (with 2008 update) concluded that balloon valvotomy is not a substitute for valve replacement in adults, although selected young adults without valve calcification may represent an exception (table 6) (13). In addition, balloon valvotomy is frequently used in children with valvular AS.

*Table 6. 2008 ACC/AHA guideline summary: Balloon aortic valvotomy (BAV) for aortic stenosis (AS) in adolescents and young adults*

| |
|---|
| BAV is indicated in the following settings is this population: |
| • With symptoms of angina, syncope, or dyspnea on exertion and catheterization peak left ventricular (LV)-to-peak aortic gradient greater than or equal to 50 mmHg* in the absence of a heavily calcified valve. |
| • For asymptomatic individuals with catheterization peak LV-to-peak aortic gradient >60 mmHg. |
| • For asymptomatic individuals with ST or T wave changes over the left precordium on the electrocardiogram (ECG) at rest or with exercise and a peak LV-to-peak aortic gradient >50 mmHg*. |
| BAV is reasonable in the following settings in this population: |
| • Asymptomatic individuals who want to play competitive sports or become pregnant who have a catheterization peak LV-to-peak aortic gradient >50 mmHg*. |
| • BAV is probably recommended over valve surgery if BAV is possible. Such patients should be referred to a center with expertise with BAV. |
| BAV should NOT be performed in the following setting in this population: |
| • Asymptomatic individuals who, have a catheterization peak LV-to-peak aortic gradient <40 mmHg without symptoms or ECG changes. |

Although the evidence is not well established, the guidelines noted two specific settings in adults in which balloon valvotomy might be reasonable :

- As a bridge to surgery in hemodynamically unstable patients who are at high risk for aortic valve replacement. However, mortality remains high in these patients after valvotomy (82).
- Use for palliation in patients with serious comorbid conditions that prevent performance of aortic valve replacement.

In addition, there are two other settings in which balloon valvotomy has been considered:

- As a bridge to delivery in symptomatic pregnant women. Although there are case reports suggesting success, balloon valvotomy can induce aortic regurgitation even in experienced hands, the postdilation bicuspid aortic valve remains susceptible to infective endocarditis irrespective of its functional state, the ascending aorta still harbors an abnormal media, and recurrent stenosis is common within 6 to 12 months.
- In patients who require urgent noncardiac surgery. However, the ACC/AHA guidelines and others have concluded that most asymptomatic patients with severe AS can undergo urgent noncardiac surgery at relatively low risk with careful intraoperative and postoperative management, including monitoring of anesthesia and careful attention to fluid balance. Balloon valvotomy was not recommended; aortic valve replacement should be considered if preoperative correction of AS is warranted .

## *TRANSCATHETER AORTIC VALVE IMPLANTATION (TAVI)*

Transcatheter aortic valve implantation has been developed for the treatment of patients with severe symptomatic AS who have an unacceptably high estimated surgical risk, or in whom TAVI is preferred due to technical issues with surgery, eg, a porcelain aorta or prior significant mediastinal radiation, prior pericardiectomy with dense adhesions or prior sternal infection with complex reconstruction, or a patent left internal mammary graft lying beneath the sternum (as identified by computed tomography angiography). Thus, accurate estimation of the risk of surgical aortic valve replacement performed by an experienced cardiothoracic surgeon and multidisciplinary valve team is vital to appropriate evaluation of potential candidates for this emerging experimental procedure. Risk calculators are available to estimate the risk of valvular surgery. However, risk estimates are subject to inaccuracies (eg, the logistic EuroSCORE appears to overestimate mortality risk in patients undergoing high-risk aortic valve replacement) and the models do not account for some clinical characteristics (eg, porcelain aorta, systemic pulmonary hypertension, or RV dysfunction) that may impact surgical mortality (see further in the present section). In patients undergoing aortic valve replacement, the Society of Thoracic Surgeons (STS) model may provide more accurate risk stratification than the logistic EuroSCORE). Of note, these scoring systems are only applicable to patients undergoing surgery and are not validated nor considered accurate in a TAVI eligible cohort of patients. However, no other scoring systems are currently available although they are being developed.

- DEVICE DESCRIPTION

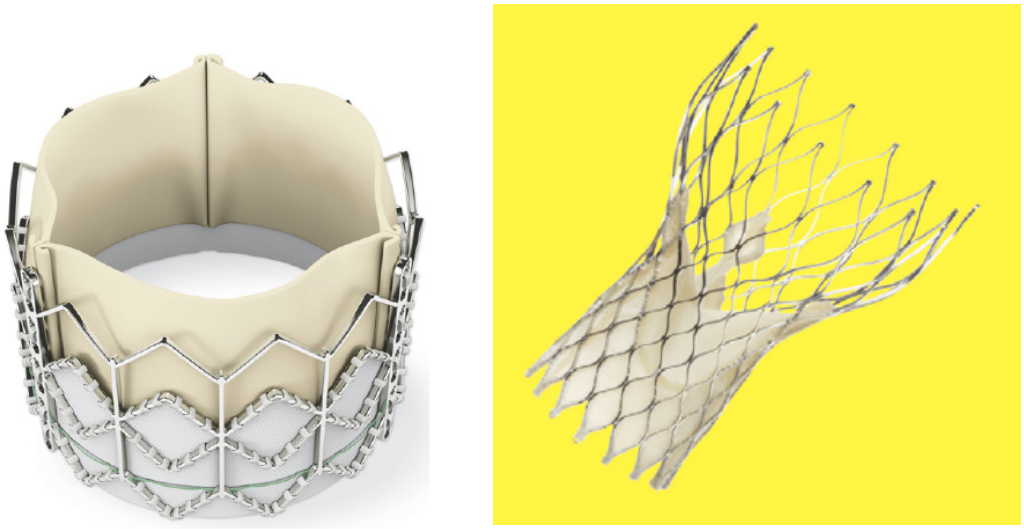
At the present time, the most data available for TAVR are based upon 2 specific devices—the Sapien valve (Edwards Life Sciences, Inc., Irvine, CA, USA) and the CoreValve (Medtronic, Inc., Minneapolis, MN, USA) (Figure 6).

The first device is composed of a trileaflet bovine pericardial valve mounted with a tubular slotted balloon-expandable stent composed of a cobalt chromium alloy. The Sapien valve is available in 23-mm and 26-mm sizes in the United States and 23-mm, 26-mm, and 29-mm sizes in Europe. The initial devices required a 22- or 24-French sheath for delivery of the prosthesis. Recent iterations (NovaFlex) have decreased this to 18-French. The first and second generations of this device have been tested in randomized controlled trials for both transfemoral and transapical implantation.

The second device (CoreValve) is comprised of 3 porcine pericardial tissue leaflets mounted in a self- expanding nitinol frame. It is available in 3 sizes—26 mm, 29 mm, and 31 mm. This valve has also continued to evolve, with the initial devices being 25-French, but now 18-French delivery sheaths are used. This valve has only been used by a retrograde approach—either via transfemoral, subclavian, or direct aortic access.

Specific anatomic issues must be considered in device design. These include the rigid structure of the pattern of valvular calcification and aortic annulus, and the need for as full apposition as possible to the annulus in an attempt to minimize periprosthetic leak which, given sometimes eccentric, bulky calcification, may be difficult. The close proximity to the coronary ostia, the width and height of the sinuses, the membranous ventricular septum with the His bundle and the anterior leaflet of the mitral valve are also important anatomical considerations. In addition, the size and degree of severity of peripheral arterial disease are all factors that could limit catheter size. Other issues include avoidance of central prosthetic leak, leaflet durability, hemodynamic performance, ability to treat both tricuspid and bicuspid valve anatomy, surfaces designed to minimize thrombogenicity, and the need to optimally position the devices and retrieve and reposi- tion when necessary (83).

*Figure 6. Sapien (left) and CoreValve (right) valves*



*Source: Edwards Lifesciences. Medtronic, Inc.*

Fundamental issues for all current and future devices are hemodynamic results, valve durability, and residual or new aortic regurgitation (AR). The initial hemodynamic performance of TAVI valves must be similar or superior to that obtained with surgical AVR. This is crucial because high residual transprosthetic gradients result in less symptomatic improvement and poorer regression of left ventricular mass [95]. These transprosthetic gradients are a function of prosthetic size as well as the specific type of prosthesis and can result in patient– prosthesis mismatch. Typical immediate postprocedural gradients after surgical AVR range from 8 mm Hg to 12 mm Hg, whereas the AV area or effective orifice area (EOA) ranges from 1.4 to 1.9 cm2.

There are only limited clinical data on the durability of TAVR valves—up to 2 years—in the PARTNER trial and up to 5 years in other registry experiences (84–86). Although the absolute number of patients is small, there have been no reports of structural valve deterioration. The fundamental clinical need for durability may depend in part on the specific patient population. In the PARTNER trial, the mean age at implant was 83 years, and serious comorbidities were frequent. In this setting, the need for durability of 20 years is less important than if the patient selection

criteria are broadened to include patients in their early to mid 60s who have isolated AS without comorbid conditions. In this latter group, the TAVI valve must have at least equivalent clinical durability to currently available surgically implanted valves.

- DELIVERY TECHNIQUES

Two major catheter-based techniques for replacing the aortic valve have been investigated: retrograde percutaneous implantation and direct apical puncture. In addition, there is rapidly growing use of direct aortic access via either ministernotomy or right anterior thoracotomy

*a) Retrograde transfemoral approach*

A retrograde femoral arterial approach (transfemoral or TF) via the aortic arch and through the stenotic valve is an alternative to the antegrade approach, and devices were designed to overcome some of the limitations seen with the initial transseptal antegrade delivery. Two stent-valve devices with slightly different designs have been successfully implanted in humans using the retrograde femoral approach: a balloon-expandable valve (Edwards SAPIEN, which has replaced the Cribier-Edwards valve) and a self-expanding valve (Medtronic CoreValve) (87). The Medtronic CoreValve had also been delivered in a retrograde fashion from the subclavian/axillary artery (88) and via direct aortic access via either ministernotomy or right anterior thoracotomy.

*b) Transapical approach*

An alternate catheter-based approach consists of direct left ventricular apical puncture and antegrade aortic valve implantation via a small anterolateral thoracotomy without cardiopulmonary bypass or sternotomy (transapical approach or TA). This approach is particularly suited to patients with severe peripheral artery

disease and heavily calcified ascending aorta and arch (porcelain aorta) who have an increased risk of stroke and other embolic events using other approaches.

- OUTCOMES OVERVIEW

- *Comparison to medical therapy*

Evidence of a benefit of TAVI compared to standard medical care was provided by the PARTNER multicenter trial (cohort B) (7). The investigators randomly assigned 358 patients with aortic stenosis who were not considered surgical candidates to either standard therapy (including balloon aortic valvotomy) or TAVI with an Edwards SAPIEN valve via transfemoral approach. The two treatment groups were similar although the logistic EuroSCORE was slightly lower in the TAVI group (mean 26.4 versus 30.4). The following findings were noted:

- At one year, the rate of death was reduced with TAVI compared to standard therapy (HR 0.44, 95% CI 0.40 to 0.74). The rate of the composite end point of death or repeat hospitalization was also reduced with TAVI (42.5 versus 72.6 %).
- Among survivors at one year, 75 % who had undergone TAVI as compared to 42 % who had received standard therapy had no or mild symptoms (NYHA functional class I or II).
- At 30 days, the TAVI group had more major vascular complications (16 versus 1 %) and more major strokes (5 versus 1 %, p = 0.06).
- Among patients who underwent TAVI, at 30 days the mean aortic valve area increased from 0.6±0.2 cm2 to 1.5±0.5 cm2, and the mean aortic valve gradient decreased from 44.5±15.7 to 11.1±6.9 mm Hg. These improvements were maintained at one year.
- In the TAVI group, moderate or severe paravalvular aortic regurgitation was identified in 11.8 % at 30 days and in 10.5 % at one year. Moderate or severe transvalvular aortic regurgitation was observed in 1.3 % at 30 days and 4.2 %

at one year. In the standard therapy group, moderate or severe transvalvular aortic regurgitation was observed in 16.9 % at 30 days and 15.2 % at one year.

- *Comparison to surgical therapy*

The 699 patients in cohort A of the PARTNER trial were randomly assigned to undergo either TAVI (by transfemoral or transapical approach) or surgical aortic valve replacement (89). The following findings were noted:

- Mortality rates in the TAVI and surgical group were similar at 30 days (3.4 and 6.5 %, p = 0.07) and at one year (24.2 and 26.8 %).
- Strokes and transient ischemic attacks were more frequent after TAVI than after surgical AVR at both 30 days (5.5 versus 2.4 %) and at one year (8.3 versus 4.3 %). Rates of major stroke in the TAVI and surgical group were similar at 30 days (3.8 and 2.1 %) but continued to trend higher for TAVI at one year (5.1 and 2.4 %, p = 0.07).
- More patients undergoing TAVI reported symptom improvement at 30 days, but at one year symptom improvement was similar in the two groups.
- Differences in certain 30-day adverse event rates were observed:
- TAVI was associated with more frequent major vascular complications (11.0 versus 3.2 %).
- Surgical aortic valve replacement was associated with more frequent major bleeding (19.5 versus 9.3%) and new-onset atrial fibrillation (16.0 versus 8.6 %).

- EARLY OUTCOMES

*a) Transfemoral*

Early outcomes were reported following retrograde implantation of the Edwards SAPIEN valve between November 2007 and January 2009 in 463 patients (mean age 82 years) with high estimated surgical risk (mean logistic EuroSCORE 26) (90).

The following findings were noted:

- Procedural success was 95 %.
- Procedural outcomes included conversion to open aortic valve replacement surgery in 1.7 %, valve-in-valve implantation (a SAPIEN valve placed within a SAPIEN valve) due to malposition or moderate/severe aortic regurgitation after placement of the first SAPIEN valve in 0.6 %, greater than moderate (2+) aortic regurgitation in 1.6 %, coronary obstruction in 0.7 %, and transfusion was required in 9.9 %.

Major complications at 30 days included death (6.3 %), stroke (2.4 %), renal failure requiring dialysis (1.3 %), and heart block resulting in permanent pacemaker implantation (6.7 %). Vascular complications included access-related complications (17.9 %), aortic dissection (1.9 %), and non-access-related complications (1.1 %).
In an echocardiographic study of 88 patients undergoing retrograde Cribier-Edwards or Edwards SAPIEN valve implantation, the mean transaortic valve gradient fell from a preprocedure baseline of 39±14 mmHg to 9±3 mmHg one day after the procedure and was 11±4 two years later (91).

Similar results were found in a multicenter study of retrograde implantation of a self-expanding stent valve (CoreValve) in 646 patients (mean age 81) with a mean logistic EuroSCORE of 23 (92):

- Procedure success was 97 % and the mean transaortic valve gradient decreased from 49 to 3 mmHg.

- Procedural outcomes included death in 1.5 %, conversion to open aortic valve replacement surgery in 0.5 %, and implantation of a second valve (including valve-in-valve) in 2.6 %. Paravalvular regurgitation was common but usually mild and not more than moderate.

At 30 days, mortality was 8 %, heart block was treated with permanent pacemaker implantation in 9.3 %, myocardial infarction occurred in 0.6 % and stroke occurred in 1.9 %.

*b) Transapical*

The following early outcomes were reported following transapical implantation of the Edwards SAPIEN valve in 575 patients (mean age 81 years) with logistic EuroSCORE of 29% (90,93–95).

- The valve prosthesis was implanted successfully in 93 % with a 3.5 % rate of conversion to open surgery. The early incidence of greater than moderate (2+) aortic regurgitation was 2.3 %.
- At 30 days, major complications included death (10.3 %), stroke (2.6 %), major vascular complication (2.4 %), myocardial infarction (0.7 %), need for dialysis (7.1 %), pacemaker implantation (7.3 %), and bleeding requiring reoperation (2.1 %).

Outcomes for 100 patients undergoing transapical aortic valve implantation (mean age 83, mean logistic EuroSCORE 29% were comparable to those for 100 propensity-matched controls undergoing conventional aortic valve replacement (mean age 82, mean EuroSCORE 30) (96). Transapical aortic valve implantation was successful in 97 patients, and three patients required conversion to open surgery. There were no strokes in the transapical group and two strokes in the conventional group. The mortality rates for the transapical and conventional surgery groups were similar: 10 and 15 % at 30 days and 27 and 31 % at one year.

- ONE AND TWO YEAR OUTCOMES

One year outcomes were reported for 1038 patients from 32 centers in the European Edwards SAPIEN registry (95). Patients treated with the transapical approach (n = 575) have greater frequency of comorbidities and higher logistic EuroSCORE (29 versus 25.8 %) compared to those treated with the transfemoral approach.

- One year mortality rates were 27.9 and 18.9 % for transapical and transfemoral patients, respectively.
- Multivariable analysis identified logistic EuroSCORE, renal disease, liver disease, and smoking as the variables with the highest hazard ratios for one year mortality.

Early and two-year outcomes were reported for a multicenter cohort of 126 patients with symptomatic severe aortic stenosis who received the CoreValve between 2006 and 2008 (97). The mean EuroSCORE was 23 %. The cohort was retrospectively classified into moderate surgical risk (54 patients), high-risk operable (51 patients), and high-risk inoperable (21 patients) groups.

- The technical success rate was 83.1 %. Thirty-day mortality was 15.2 % without significant differences in the subgroups. Of note, this study started enrollment before other studies (90,92) and the lower observed technical success rate as well as higher early mortality rate are likely largely due to learning curve issues.
- At two years, mortality was 38.1 % with a significantly higher mortality in the combined high-risk groups as compared to the moderate-risk group (45.8 versus 27.8 %).
- Functional class improved in 80 % of patients and remained stable at two-year follow-up. The mean aortic valve gradient was unchanged at two-year follow-up (8.5 at 30 days and 9.0 at 2 years).

Recent findings from 2-year analysis of the randomized PARTNER trial were as follows: mortality after TAVI remained similar to that after surgical replacement, stroke frequency was similar in the surgery and TAVI groups after 30 days, periprocedural complications (strokes, major bleeding, and major vascular events) affected mortality after TAVR or surgical replacement; aortic regurgitation (even mild) after TAVI was associated with increased long-term mortality, and valve performance in the TAVI group was main- tained during follow-up and was similar to that in the surgery group (85).

Early (30-day) mortality after TAVI has decreased to approximately 5% in several recent studies, probably because of a combination of improvements in patient selection, procedural tech- niques, and device technologies. However, 1 and 2-year mortality rates have remained above 20% and 30%, respectively, rais- ing a concern that TAVI may be associated with important late complications. The results from the PARTNER trial reveal similarly high mortality at 2 years with TAVI and with surgical replacement, indicating that coexisting conditions play a role in late mortality. The multivariable analysis from the combined TAVI and surgery groups affirms the importance of coexisting conditions, because the STS risk score was a significant predictor of mortality at 2 years.

- VALVE-IN-VALVE

A valve-in-valve procedure involves catheter-based valve implantation inside an already implanted bioprosthetic valve. This approach may provide an alternative to replacement of a degenerated surgically-implanted valve, or a means of salvaging suboptimal implantation of a catheter-based valve during the initial implantation procedure.

Preliminary reports have demonstrated the feasibility of transcatheter placement of a prosthetic valve within a degenerated bioprosthetic valve. As an

example, valve-in-valve implantation was performed on 24 high-risk patients with aortic (n = 10), mitral (n = 7), pulmonary (n = 6), or tricuspid (n = 1) failed (stenotic and/or regurgitant) bioprostheses (98). Implantation was unsuccessful for one (mitral) case. There were no deaths during the procedure. There was one stroke and one death in 30 days; the death was related to attempted transseptal mitral positioning. The NYHA functional class improved from 88 % in class III or IV at baseline to 88 % in class I or II at last follow-up.

Valve-in-valve implantation has been used to salvage suboptimal initial transcatheter aortic valve implantation and significant paravalvular aortic regurgitation. In a series using Edwards SAPIEN valves, valve-in-valve implantation was performed in 0.6 % of 463 retrograde procedures and 3.3 % of 575 transapical antegrade procedures. In a series of 646 retrograde CoreValve procedures, moderate to severe aortic regurgitation during the implantation procedure was treated with balloon re-dilatation (in 21.2 % of procedures) and/or valve-in-valve placement (in 2.6 %) (92). None of the 628 patients with successful CoreValve implantation had greater than moderate aortic regurgitation.

- TECHNOLOGY EVOLUTION

Next-generation devices promise the potential for im- provements, offering expanded clinical utility with ad- vances that include: lower profile delivery catheters, more accurate positioning, reduced paravalvular leak, and ability to either reposition or even retrieve (Figure 7) (99). Many of the new device technologies utilize a self-expandable, high radial strength repositionable prosthesis consisting of pericardial tissue on a nitinol frame. Two additional valves have recently received approval for commercial sale in Europe. The JenaValve (JenaValve Technology, Munich, Germany) and Acurate Valve (Symetis, Inc., Lausanne, Switzerland) are both delivered currently via a transapical approach.

Other valve designs currently in early clinical studies include Portico Valve (St. Jude Medical, St. Paul, MN, USA), Direct Flow Medical (Direct Flow Medical, Santa Rosa, CA, USA), and Sadra Lotus Valve (Sadra Medical, Los Gatos, CA, USA). Other new designs include flexible sealing membranes aimed at more optimal conformation to the calcified native annulus to reduce paravalvular leaks. New valve designs and materials can also pro- vide the possibility of new prosthesis technology. The Lutter valve was created in an effort to create a more physiological heart valve by utilizing tissue engineering (100). The PercValve (Advanced Bioprosthetic Surfaces, San Antonio, TX, USA) uses nanotechnology in its elastic nitinol frame and leaflets. These leaflets are designed to allow for the growth of endothelial cells, essentially converting it to a tissue valve. Initial animal studies have shown complete endothelialization of the e-nitinol leaflets within 10 days and may eliminate the need for anticoagulation (101). A final novel approach involves anchoring the prosthesis by using an injectable polymer that cures in position to maintain the implant permanently in place. The outcome with these new technologies will be the focus of multiple registries and then randomized trials.

*Figure 7. New transcatheter valve designs*

| Device | Company | Expansion Mechanism | Valve Material | Stent Material | Repositionable | Retrievable | Clinical Trials | FIM | CE Mark | French Size |
|---|---|---|---|---|---|---|---|---|---|---|
| Colibri Heart Valve | Endoluminal Technology Research | Balloon- and self-expandable | Pericardium | Stainless steel/ Nitinol | No | No | No | 2003 | No | Balloon: 16 Self: 12 |
| Direct Flow | Direct Flow Medical | Polymer-injected | Pericardium | Polymer | Yes | No | No | 2006 | No | 22 |
| Lotus | Sadra Medical | Self-expandable | Pericardium | Nitinol | Yes | No | No | 2007 | No | 21 |
| JenaValve | JenaValve Technology | Self-expandable | Pericardium | Nitinol | Yes | No | No | 2007 | Yes | 28 |
| Heart Leaflet | Heart Leaflet Technologies | Self-expandable | Pericardium | Nitinol | Yes | Yes | No | N/A | No | 16 |
| Lutter | N/A | Self-expandable | Tissue engineered | Nitinol | No | No | No | N/A | No | N/A |
| PercValve | Advanced Bioprosthetic Surfaces | Self-expandable | e-Nitinol | e-Nitinol | No | No | No | N/A | No | 10 |
| Portico | St. Jude | Self- expandable | Pericardium | Nitinol | Yes | Yes | Yes | 2011 | No | 22 |
| Acurate | Symetis | Self-expandable | Pericardium | Nitinol | Yes | Yes | Yes | 2009 | Yes | 28 |

CE = Conformité Européenne, a mandatory conformity for products placed on the market in the European Economic Area; FIM = first in man; N/A = not applicable; TAVR = transcatheter aortic valve replacement.

# 5. Estimation of operative risk in aortic valve surgery

## *REGISTRIES AND RISK SCORES*

Current data from The Society of Thoracic Surgeons (STS) registry documents a mortality that is under 3% for all patients undergoing AVR. As with any procedure, operative mortality is strongly correlated with the severity of the disease and comorbidity of patients. The operative risks can be estimated with online risk calculators from the STS and the European System for Cardiac Operative Risk Evaluation (EuroSCORE).

In selected patients with minimal comorbidity, mortality and major morbidity are under 1% each in many centers. In general, perioperative stroke rates are 1.5% and other major complications are relatively rare. Renal failure, pulmonary failure, and gastrointestinal complications are not common. As older, more frail patients with extensive comorbidities undergo AVR, the risk of death and morbid- ity as well as length of hospitalization increases significantly. In addition to comorbidity, preoperative functional performance is also a maker of postoperative morbidity/mortality (58).

Patient selection for AVR for AS is well outlined by ACC/AHA and ESC guidelines as previously described (13,14). Problems arise when the clinicians and patients note significant symptoms and significant structural disease that are complicated by the presence of significant comorbidity. While current STS risk score and EuroSCORE give information concerning short-term operative risks and benefits, they are not able to predict symptom resolution, quality-of-life improvement, or return to independent living.

Although a number of risk algorithms for cardiac surgery have been developed, the STS and logistic EuroSCORE are the most commonly used. While both are accurate in low-risk patients, accuracy is less in higher risk subsets. These 2 scores include different covariates. The logistic EuroSCORE is based on 12 covariates

derived from 14,799 patients undergoing all types of cardiac operations (mostly coronary bypass) in 8 European countries in 1995. On the other hand, the STS risk predictor is based on 24 covariates derived from 67,292 patients undergoing isolated AVR only in the United States over a relatively more contemporary period between 2002 and 2006.

The present models do not include some risk factors that may be particularly important in the prediction of outcomes for very high-risk populations including frailty, porcelain aorta, and the presence of hepatic dysfunction, although all have been added to a recent upgraded EuroSCORE version (EuroSCORE 2) which is currently under development (102,103).

The prognostic value of the risk models depends upon the population to which the models are applied. Several studies have found that the EuroSCORE overestimates mortality for various cardiac surgery populations (104–106), including patients undergoing mitral valve surgery, and patients undergoing high-risk aortic valve replacement (107–109).

In patients undergoing aortic valve replacement, the STS model may provide more accurate perioperative risk estimation than the EuroSCORE (109). In various studies, the EuroSCORE often overestimated perioperative risk, while the STS model has been observed to under or overestimate early postoperative mortality (12,110). The EuroSCORE and STS score also correlate with long-term postoperative mortality risk, though the relative strengths of these associations varies among series, and other clinical factors (such as presence of renal failure) may have greater predictive value in some groups.

## *SPECIFIC SURGICAL RISKS: STROKE*

Although ischemic stroke can result from many causes after AVR, a major concern is the role of thromboembolism. The risks of thromboembolism are usually

greater in the first few days and months after bioprosthetic AVR implantation before the sewing ring of the prosthesis is endothelialized; risks after mechan- ical AVR continue. The risk of stroke within 30 days among 67,292 cases of AVR in the STS Registry was 1.5%; this data set was used to develop a model for predicting 30-day stroke risk (58). Overall, embolic stroke risks are greater with mechanical valves, which require long-term oral anticoagulation, than with bioprosthetic valves, which have a 0.7% per year risk of thromboembolism in patients with normal sinus rhythm without warfarin anticoagulation (58).

## *OTHER COMPLICATIONS*

Aside from other surgical complications of renal, hepatic, neurological, and pulmonary disease compromise, a major risk of conventional AVR is sternal wound infection. In most centers, this risk is under 1% for deep infection, but the risk of any type of infection is still present and particularly increased in patients with diabetes, obesity, smoking, immunosuppressive therapy, and prior radiation therapy. With the advent of negative pressure wound therapy and continued advances in surgical technique, these risks are now rarely fatal, but remain morbid.

## *INOPERABILITY OR PROHIBITIVE RISK*

Despite substantial contemporary experience with successful AVR in elderly patients, multiple series have documented that 30% to 40% of patients with severe AS do not undergo surgery owing to advanced age, LV dysfunction, multiple coexisting conditions, and patient preference or physician recommendation (111–113).

The definitions used to describe patient populations considered for TAVI vary; for example, prohibitive risk would describe a patient in whom the procedure could be performed from a technical standpoint but would be associated with

prohibitively high morbidity and mortality. Inoperability might identify a patient group in whom technical success would not be possible; for example, no vascular access. Different trials have used these terms for patient enrollment; for example, the CoreValve Trial identifies extreme risk, whereas the PARTNER (Placement of AoRtic TraNscathetER Valve) Trial used the term inoperable (7).

Assessment of inoperability is also driven by surgeon and institutional experience and thus varies. Whereas practice guidelines have been developed to assist physicians and surgeons in determining appropriate use of treatment options, there are, however, no specific recom- mendations for defining inoperability. Current ACCF/ AHA guidelines acknowledge that special considerations are required for the management of advanced elderly patients with AS, since age-related and comorbid conditions commonly exist in patients in their 80s and 90s even though AVR is technically feasible even in this group (13,14).

In the absence of literature evidence and guidelines recommendations, the determination of inoperability in any given patient depends on the judgment of the medical team. It is generally agreed that patients with limited life expectancy due to concurrent conditions such as malignancy, dementia, primary liver disease, chronic obstructive pulmonary disease (COPD), among others, are not appropriate for AVR. Frailty and related conditions of debility and deconditioning are known to result in inability to recover from major heart surgery such as AVR, despite operative survival and hospital discharge. These conditions can potentially con- tribute to increased surgical mortality and morbidity in the elderly (114).

Inoperability from the surgeon's judgment may result from technical considerations that preclude safe performance of AVR, such as prior mediastinal irradiation, porcelain aorta or severe periannular calcification, severe aortic atheromatous disease, prior cardiac operations, among others including the internal mammary artery crossing the midline. Although infrequent, aortic valve bypass with a LV apex-to-descending aortic conduit has been used in some patients with severe

AS judged to be inoperable via a mediastinal approach and cardiopulmonary bypass (115).

# II. METHODS

# 1. Work hypothesis

The present study is based upon the following hypothesis:

- Preoperative risk factors or comorbidities play a different role on perioperative mortality in high-risk aortic valve replacement surgery depending on the procedure (TAVI or conventional AVR) that is performed.

This work seeks to identify these factors and quantify their potential impact on mortality in order to evaluate and discriminate future patients towards the most appropriate surgical technique.

# 2. Objectives

This retrospective study presents de data of a consecutive series of patients who underwent aortic valve replacement surgery (+/-coronary artery revascularization) in a single institution (Consorcio Hospital General Universitario, Valencia, Spain) between 2007 and 2012.

## *PRIMARY ENDPOINTS*

1. To design a statistical model for preoperative scoring and patient discrimination towards transcatheter or conventional aortic valve surgery in high-risk patients, based in the observed mortality between both groups and the variables identified as independent predictors for that mortality after statistical analysis)

2. To assess a comparative study of operative outcomes (perioperative mortality and major morbidity) between the novel TAVI technique versus a statistically matched control group formed among patients who received conventional aortic valve surgery during the same period.

3. To assess a comparative study of operative outcomes with the composite endpoint of perioperative mortality, major cardiovascular or neurologic events (MACCE) between the novel TAVI technique versus a statistically matched control group formed among patients who received conventional aortic valve surgery during the same period.

## *SECONDARY ENDPOINTS*

1. To describe the observed intensive care and hospital length of stay between the TAVI and the matched AVR control groups.

2. To describe and compare postoperative pacemaker rhythm rates between the TAVI and the matched AVR control groups.

3. To describe and compare long term survival between the TAVI and the matched AVR control groups, and assess the possibility of time or learning curve effect in the techniques.

4. To describe postoperative outcomes of TAVI subgroups: transfemoral (TF) and transapical (TA) approaches.

# 3. Patient selection

## *TRANSCATHETER (TAVI) GROUP*

- INDICATIONS

Selection of candidates for TAVI, especially risk assessment, involved a multi-disciplinary consultation between one cardiologist, and two cardiac surgeons, with the additional collaboration of imaging specialists and anesthesiologists whenever was necessary.

Patient selection criteria for TAVI was based on four steps: a) confirmation the severity of AS; b) evaluation of symptoms; c) analysis of the risk of surgery and evaluation of life expectancy and quality of life; d) assessment of the feasibility and exclusion of contraindications for TAVI.

*a) Confirmation of the severity of aortic stenosis*

TAVI was performed only in severe aortic stenosis (AS). Echocardiography was the preferred tool to assess the severity of AS according to a combination of measurements of valve area and flow-dependent indices. Low-dose dobutamine echocardiography was useful to differentiate between severe and 'pseudo severe' AS in patients with low LV ejection fraction and low gradient.

*b) Evaluation of symptoms*

TAVI was only proposed in patients with severe symptoms that can definitely be attributed to valve disease and a functional NYHA class > II.

*c) Analysis of the risks of surgery, and evaluation of life expectancy and quality of life*

TAVI was restricted to patients at high-risk (predicted logistic EuroSCORE mortality over 15%) or with contraindications for conventional surgery. The team took into account risk factors that are not covered in scores but often seen in practice such as chest radiation, previous aorto-coronary bypass with patent grafts, porcelain aorta, liver cirrhosis, etc.

At this stage, TAVI was not recommended for patients who simply refused surgery on the basis of personal preference.

Life expectancy was considered to be most significantly influenced by comorbidities (which were carefully looked for), rather than age alone. TAVI was not performed in patients whose life expectancy was considered to be below 1 year.

*d) Assessment of feasibility and exclusion of contraindications of transcatheter aortic valve implantation*

The following steps were taken to assess the feasibility of TAVI:

- <u>Assessment of the coronary anatomy</u>

Coronary angiography was systematically performed. If associated coronary artery disease requiring percutaneous revascularization was found, whether to proceed previously to the valve implant or in a hybrid manner (concomitant to the TAVI procedure) , was subject of individualized discussion based on the patient's clinical condition and anatomy. TAVI was recommended in patients with severe proximal coronary stenoses not amenable to percutaneous coronary interventions.

On the other hand, the position of the coronary arteries relative to the aortic cusps was assessed using aortography and multislice computed vascular tomography.

- Measurement of the aortic annulus

Correct sizing of the valve was critical to minimize the potential for paravalvular leakage and to avoid prosthesis migration after placement; however, a gold standard method of measurement was not established. TEE was found to show larger values than transthoracic echocardiography, thus, it was performed if borderline values lead to doubt the feasibility of the procedure. (Fig.1)

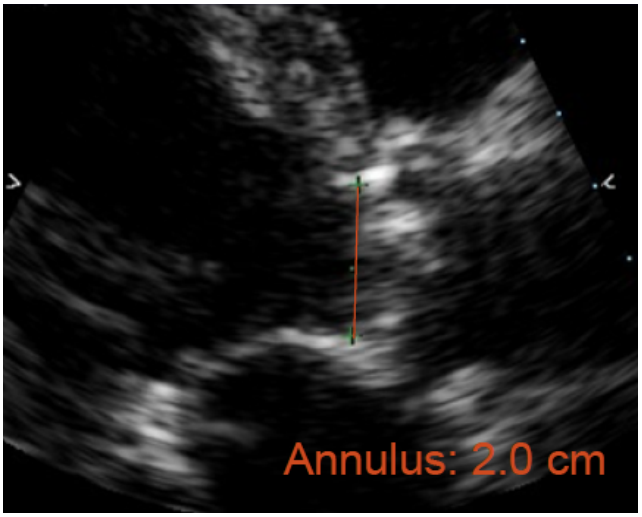
Multislice computed tomography or magnetic resonance imaging were used for this purpose. Finally, aortography measurements performed during balloon valvuloplasty were also useful.

Echocardiography was the preferred tool for the assessment of the morphology of the LV outflow tract and, before implanting self-expandable devices, the dimensions of the aortic root.

- *Evaluation of size, tortuosity, and calcification of peripheral arteries*

Vascular angiography was the reference; however, multislice computed tomography was also used (or magnetic resonance imaging in patients with renal insufficiency).

*Fig. 1. Measurement of the aortic annulus by ultrasound imaging.*




*Source: Edwards Lifesciences*

In conclusion, the main inclusion criteria for TAVI procedure are presented on Table 1.

*Table 1.*

| INCLUSION CRITERIA FOR TAVI PROCEDURE (116) |
|---|
| 1. Patients must have co-morbidities such that the surgeon and cardiologist concur that the predicted risk of operative mortality is ≥15% as measured by logistic EuroSCORE scale. |
| 2. Patient has senile degenerative aortic valve stenosis with echocardiographically derived criteria: mean gradient >40 mmHg or jet velocity greater than 4.0 m/s or an initial aortic valve area of < 0.8 cm2 |
| 3. Patient is symptomatic from his/her aortic valve stenosis, as demonstrated by NYHA Functional Class II or greater |
| 4. The subject or the subject's legal representative has been informed of the nature of the study, agrees to its provisions and has provided written informed consent. |
| 5. The subject, after formal consults by a cardiologist and two cardiovascular surgeons agree that medical factors and co-morbidities preclude conventional operation, based on a conclusion that the probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement. |

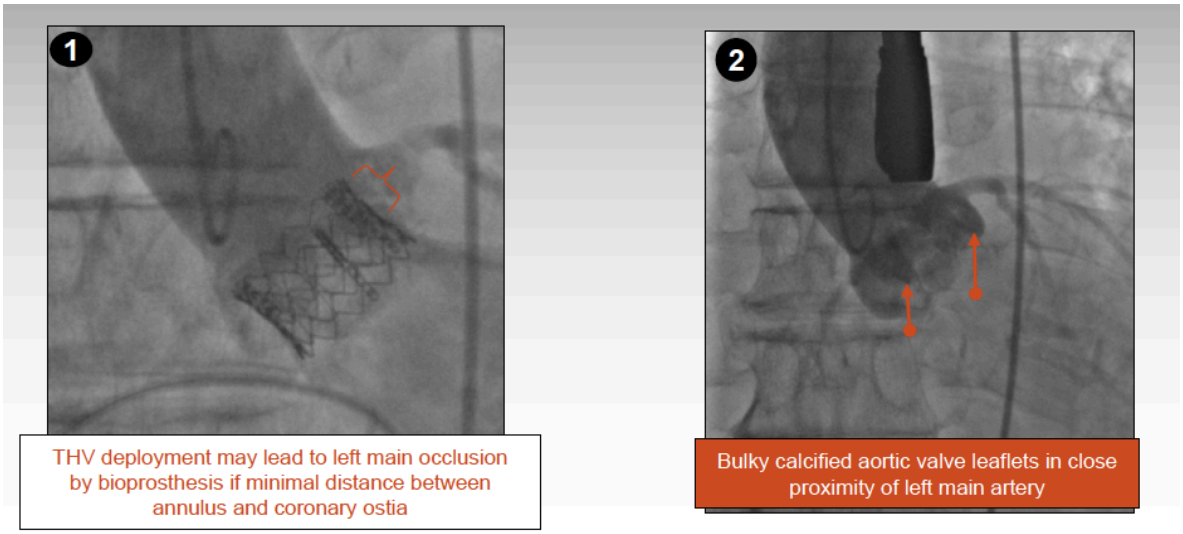
- CONTRAINDICATIONS

Contraindications for TAVI were considered as general, approach- or device-specific.

- *General contraindications for TAVI:*
    - Aortic annulus <18 or >25 mm for balloon-expandable and <20 or >27 for self-expandable devices
    - Bicuspid valves (because of the risk of incomplete deployment of the prosthesis)

- Presence of asymmetric heavy valvular calcification, which may compress the coronary arteries during TAVI (Fig 2.)
- Aortic root dimension >45 mm at the aorto-tubular junction for self-expandable prostheses.
- Presence of apical LV thrombus.
- Sinus of Valsalva width <27mm and height <15mm for self-expandable devices

*Fig. 2*




*Source: Edwards Lifesciences*

The complete list for exclusion criteria are presented on Table 2.

*Table 2.*

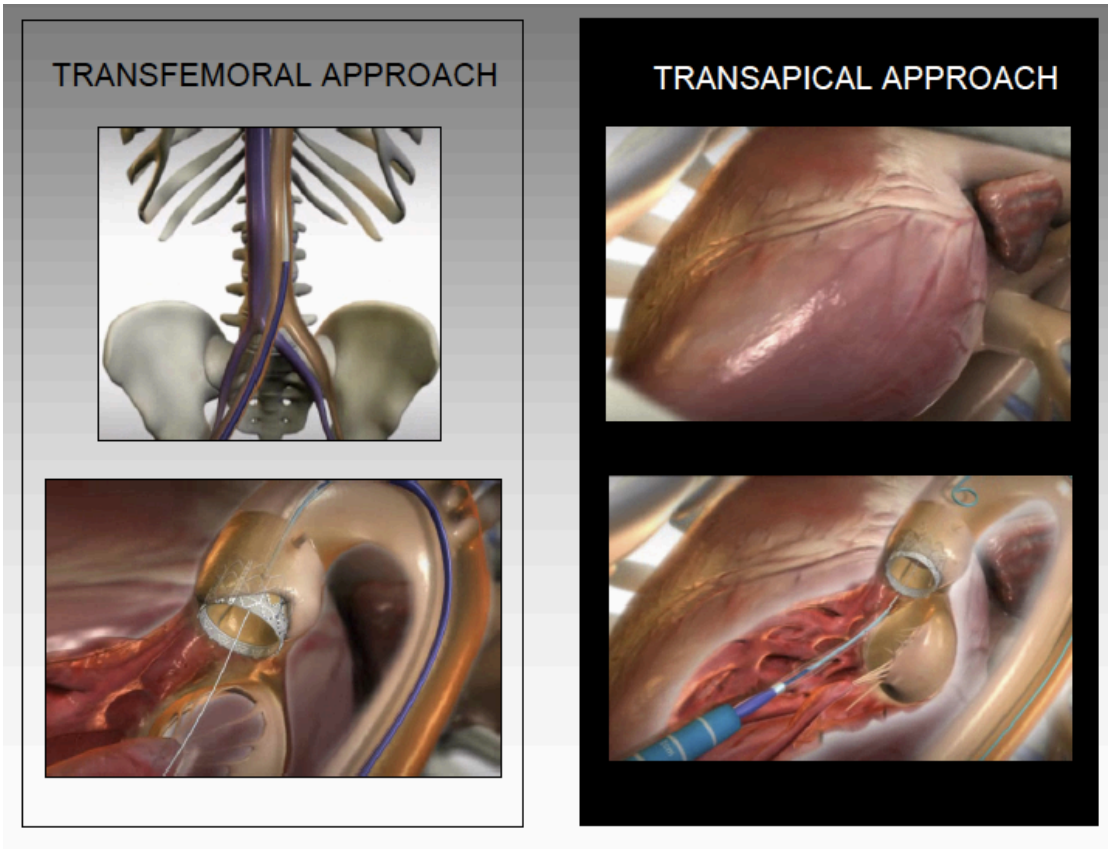
| EXCLUSION CRITERIA FOR TAVI PROCEDURE (116) |
|---|
| 1. Evidence of an acute myocardial infarction ≤ 1month before the intended treatment |
| 2. Aortic valve is a congenital unicuspid or bicuspid valve; or is non-calcified |
| 3. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with |

| |
|---|
| predominant aortic regurgitation >3+) |
| 4. Any therapeutic invasive cardiac procedure performed within 30 days of the index procedure. |
| 5. Pre-existing prosthetic heart valve in any position, prosthetic ring, or severe (greater than 3+) mitral insufficiency |
| 6. Blood dyscrasias as defined: Leukopenia, acute anemia, thrombocytopenia, history of bleeding diathesis or coagulopathy |
| 7. Hemodynamic instability requiring inotropic support or mechanical heart assistance. |
| 8. Need for emergency surgery for any reason |
| 9. Hypertrophic cardiomyopathy with or without obstruction |
| 10. Echocardiographic evidence of intracardiac mass, thrombus or vegetation |
| 11. Active peptic ulcer or upper GI bleeding within the prior 3 months |
| 12. A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine, or clopidogrel, or sensitivity to contrast media, which cannot be adequately pre-medicated |
| 13. Native aortic annulus size < 16mm or > 27mm per the baseline echo as estimated by the LVOT |
| 14. Patient has been offered surgery but has refused surgery. |
| 15. Recent (within 6 months) CVA or a TIA |
| 16. Life expectancy < 12 months due to non-cardiac co-morbid conditions. |
| 17. Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5cm or greater; marked tortuosity (hyperacute bend), aortic arch atheroma or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe "unfolding" and tortuosity of the thoracic aorta (applicable for transfemoral patients only). |
| 18. Iliofemoral vessel characteristics that would preclude safe placement of at least an 18F introducer sheath such as severe obstructive calcification, severe tortuosity or vessels size less than 6 mm in diameter (applicable for transfemoral patients only). |

- TRANSFEMORAL OR TRANSAPICAL INDICATIONS

The specific indications for transfemoral and transapical approaches were discussed according to patient condition and local expertise of the Heart Team.

*Fig. 3. Transfemoral and transapical approaches*

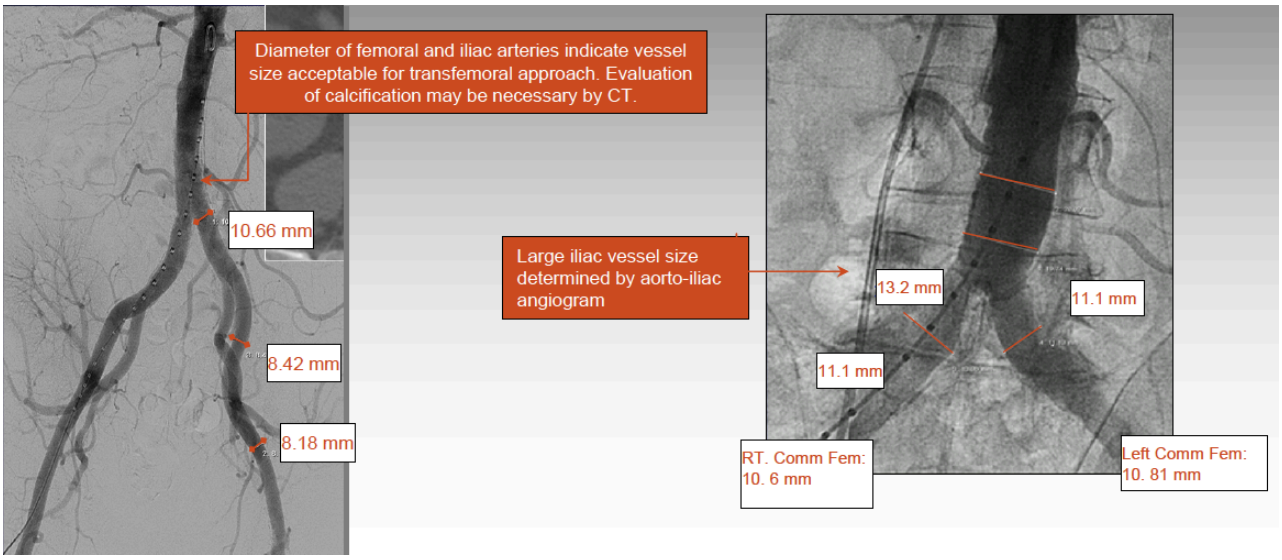



*Source: Edwards Lifesciences*

- <u>Contraindications of the transfemoral approach:</u>
    - Iliac arteries: severe calcification, tortuosity, small diameter (<6mm for CoreValve devices, <7mm for Edwards SAPIEN devices), previous aorto-femoral bypass (Fig 4, 5,6).
    - Aorta: severe angulation, severe atheroma of the arch, coarctation, aneurysm of the abdominal aorta with protruding mural thrombus.
    - Presence of bulky atherosclerosis of the ascending aorta and arch detected by TEE or CT (Fig 7.)

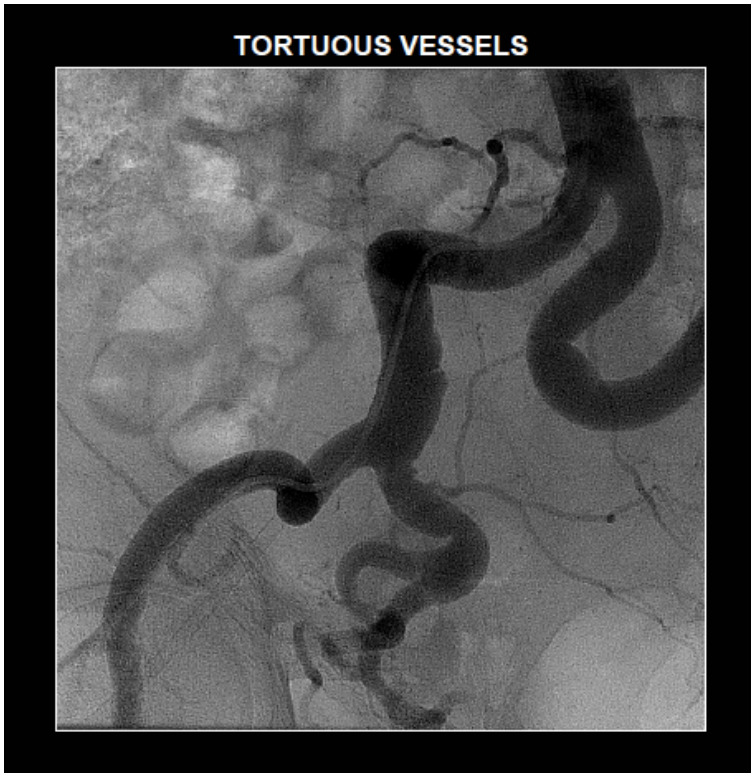
- Transverse ascending aorta (balloon-expandable device) (Fig. 8).

*Fig 4.*



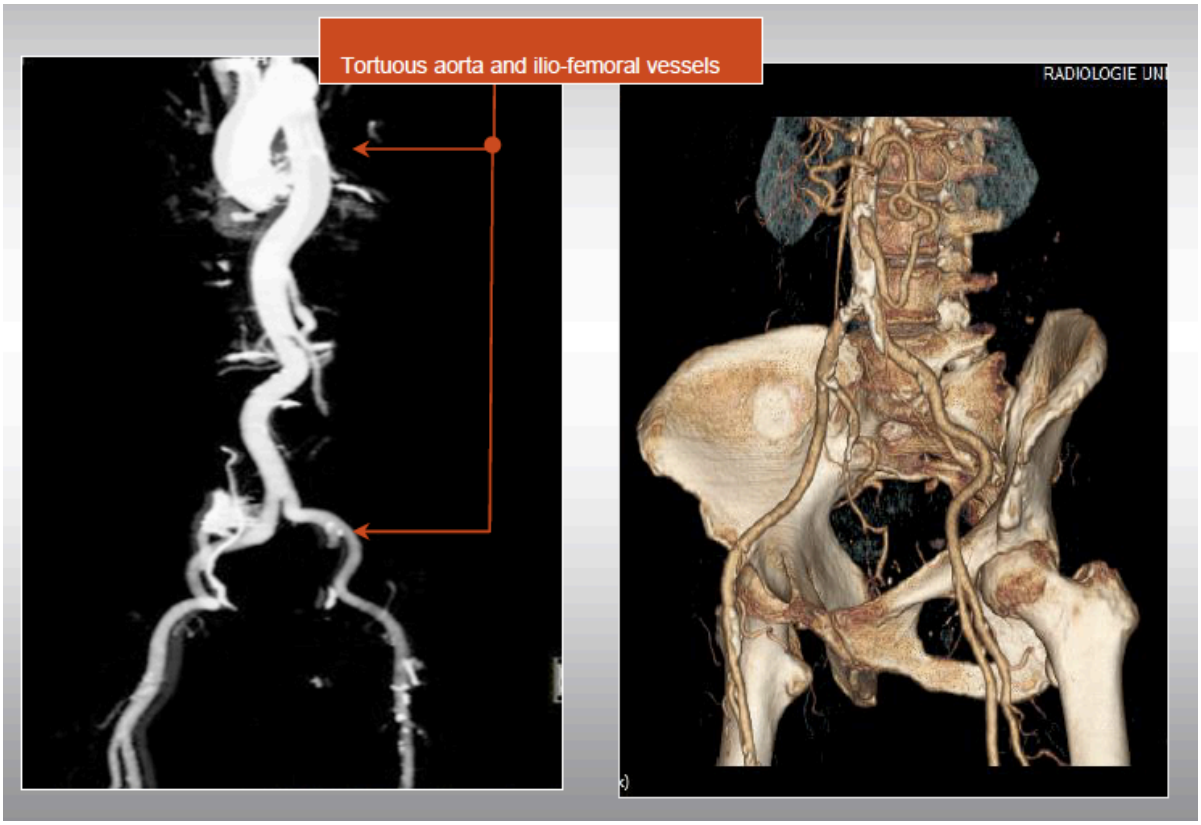

*Source: Edwards Lifesciences*

Fig. 5



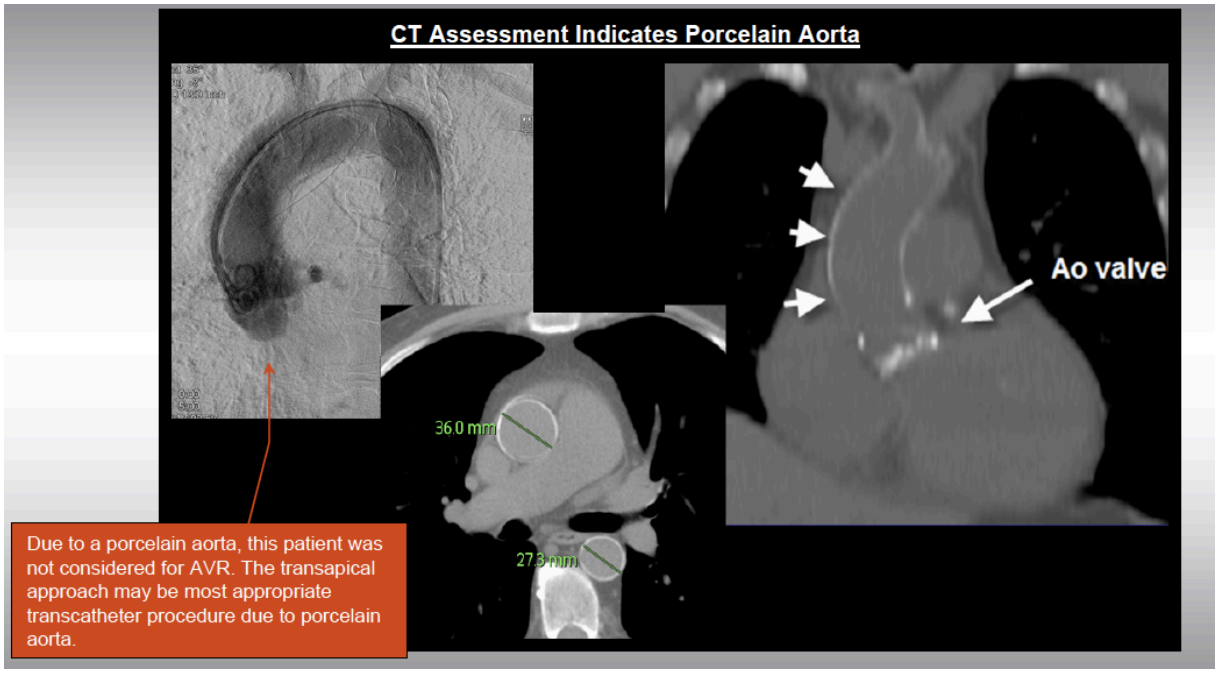

*Source: Edwards Lifesciences*

Fig. 6.



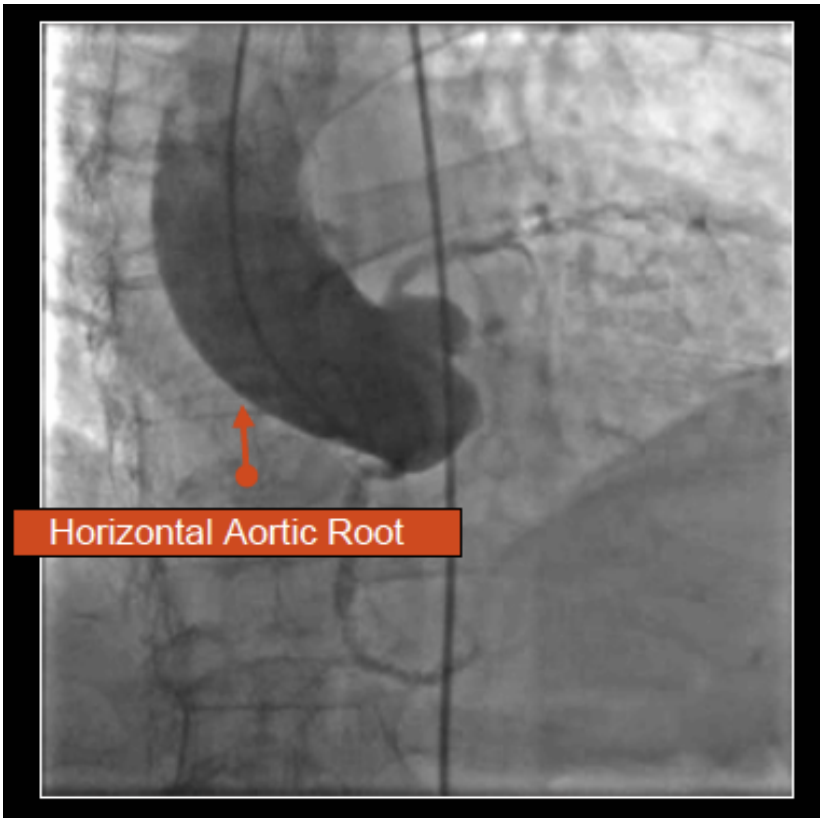

*Source: Edwards Lifesciences*

Fig 7.



*Source: Edwards Lifesciences*

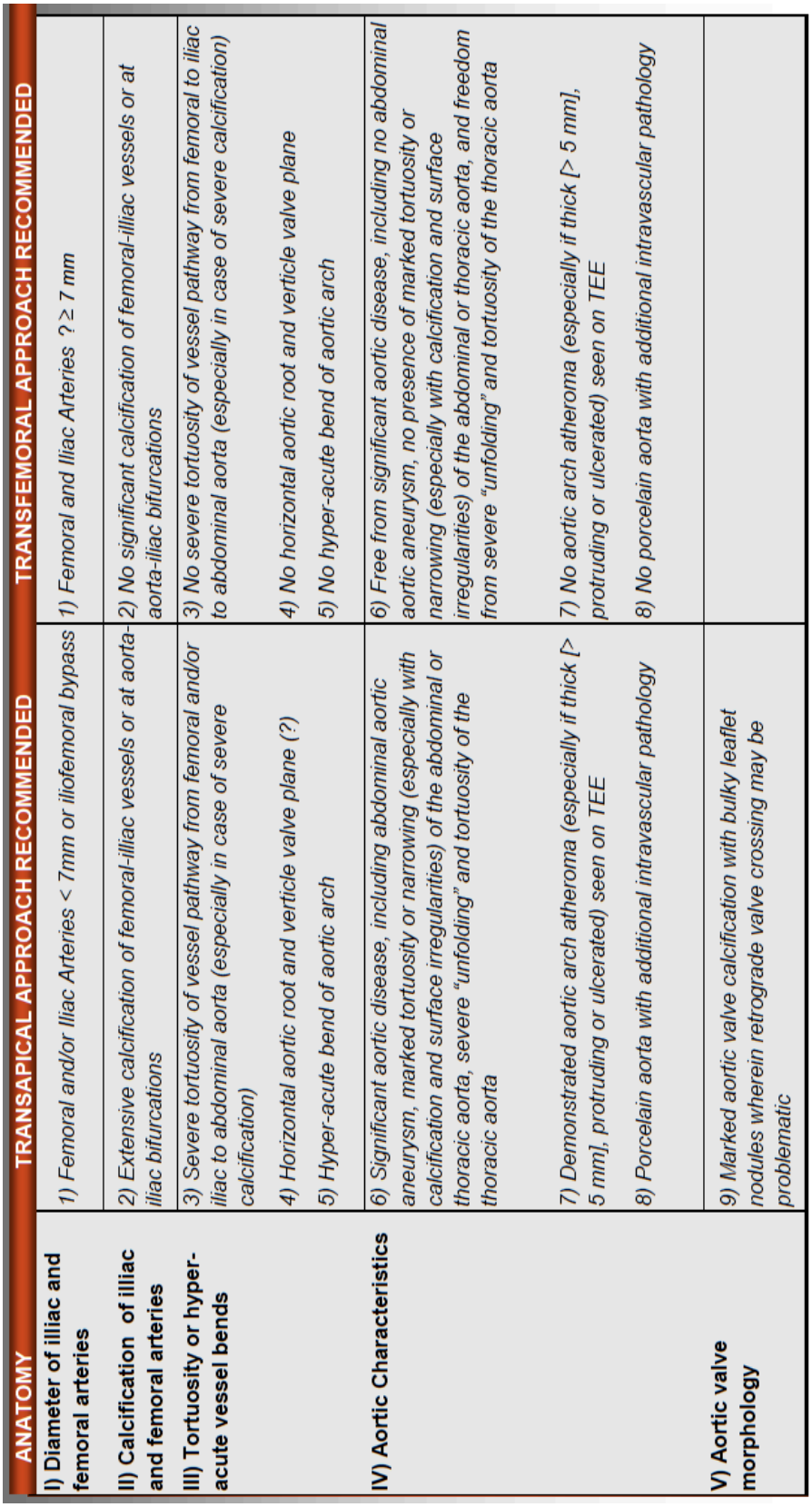
*Fig. 8.*




*Source: Edwards Lifesciences*

- <u>Contraindications for the transapical approach (Fig 9,10):</u>
    - previous surgery of the LV using a patch, such as the Dor procedure;
    - calcified pericardium;
    - severe respiratory insufficiency;
    - non-reachable LV apex.

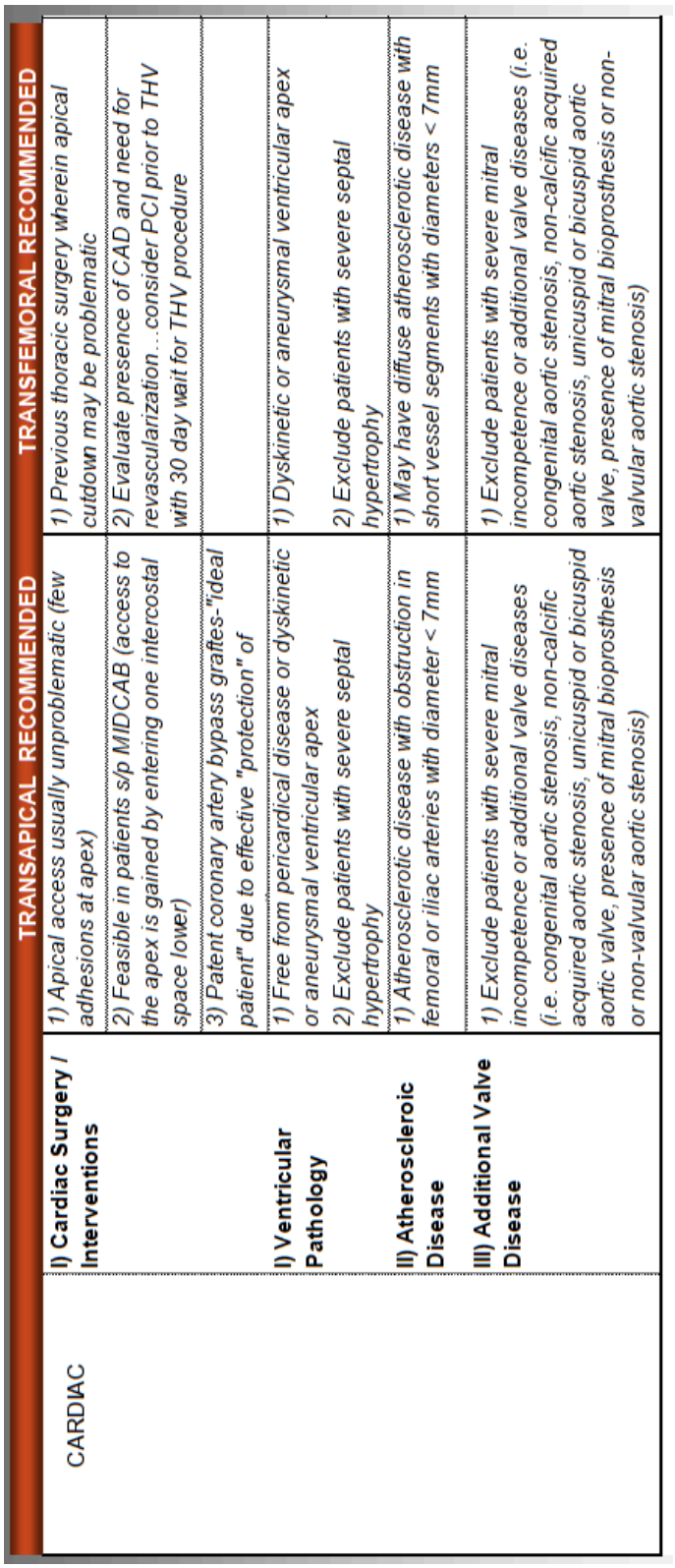
*Fig. 9. Preferences for transapical or transfemoral approaches I*



| ANATOMY | TRANSAPICAL APPROACH RECOMMENDED | TRANSFEMORAL APPROACH RECOMMENDED |
|---|---|---|
| **I) Diameter of iliac and femoral arteries** | *1) Femoral and/or Iliac Arteries < 7mm or iliofemoral bypass* | *1) Femoral and Iliac Arteries ? ≥ 7 mm* |
| **II) Calcification of illiac and femoral arteries** | *2) Extensive calcification of femoral-illiac vessels or at aorta-iliac bifurcations* | *2) No significant calcification of femoral-illiac vessels or at aorta-iliac bifurcations* |
| **III) Tortuosity or hyper-acute vessel bends** | *3) Severe tortuosity of vessel pathway from femoral and/or iliac to abdominal aorta (especially in case of severe calcification)*<br>*4) Horizontal aortic root and verticle valve plane (?)*<br>*5) Hyper-acute bend of aortic arch* | *3) No severe tortuosity of vessel pathway from femoral to iliac to abdominal aorta (especially in case of severe calcification)*<br>*4) No horizontal aortic root and verticle valve plane*<br>*5) No hyper-acute bend of aortic arch* |
| **IV) Aortic Characteristics** | *6) Significant aortic disease, including abdominal aortic aneurysm, marked tortuosity or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe "unfolding" and tortuosity of the thoracic aorta*<br>*7) Demonstrated aortic arch atheroma (especially if thick [> 5 mm], protruding or ulcerated) seen on TEE*<br>*8) Porcelain aorta with additional intravascular pathology* | *6) Free from significant aortic disease, including no abdominal aortic aneurysm, no presence of marked tortuosity or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, and freedom from severe "unfolding" and tortuosity of the thoracic aorta*<br>*7) No aortic arch atheroma (especially if thick [> 5 mm], protruding or ulcerated) seen on TEE*<br>*8) No porcelain aorta with additional intravascular pathology* |
| **V) Aortic valve morphology** | *9) Marked aortic valve calcification with bulky leaflet nodules wherein retrograde valve crossing may be problematic* | |

*Source: Edwards Lifesciences*

*Fig.10. Preferences for transapical or transfemoral approaches II.*



| | | TRANSAPICAL RECOMMENDED | TRANSFEMORAL RECOMMENDED |
|---|---|---|---|
| CARDIAC | **I) Cardiac Surgery / Interventions** | *1) Apical access usually unproblematic (few adhesions at apex)* | *1) Previous thoracic surgery wherein apical cutdown may be problematic* |
| | | *2) Feasible in patients s/p MIDCAB (access to the apex is gained by entering one intercostal space lower)* | *2) Evaluate presence of CAD and need for revascularization…consider PCI prior to THV with 30 day wait for THV procedure* |
| | | *3) Patent coronary artery bypass grafts-"ideal patient" due to effective "protection" of* | |
| | **I) Ventricular Pathology** | *1) Free from pericardical disease or dyskinetic or aneurysmal ventricular apex* | *1) Dyskinetic or aneurysmal ventricular apex* |
| | | *2) Exclude patients with severe septal hypertrophy* | *2) Exclude patients with severe septal hypertrophy* |
| | **II) Atherosclerotic Disease** | *1) Atherosclerotic disease with obstruction in femoral or iliac arteries with diameter < 7mm* | *1) May have diffuse atherosclerotic disease with short vessel segments with diameters < 7mm* |
| | **III) Additional Valve Disease** | *1) Exclude patients with severe mitral incompetence or additional valve diseases (i.e. congenital aortic stenosis, non-calcific acquired aortic stenosis, unicuspid or bicuspid aortic valve, presence of mitral bioprosthesis or non-valvular aortic stenosis)* | *1) Exclude patients with severe mitral incompetence or additional valve diseases (i.e. congenital aortic stenosis, non-calcific acquired aortic stenosis, unicuspid or bicuspid aortic valve, presence of mitral bioprosthesis or non-valvular aortic stenosis)* |

*Source: Edwards Lifesciences*

### *CONTROL (AVR) GROUP*

Control group was formed in a retrospective review of the Consorcio Hospital General Universitario database of patients who received conventional aortic valve replacement (AVR) surgery (isolated AVR or combined with coronary artery bypass) between 2007 and 2011. Only patients with degenerative calcific aortic stenosis (either pure aortic stenosis or associated with significant regurgitation) were included. Selection criteria excluded different ethiologies rather than calcific AS (rheumatic, endocarditis, etc), emergent status, pure aortic regurgitation and combined surgery of the aortic root.

Statistically selected controls inside this group were identified by propensity core matching and logistic regression criteria to match cases in the experimental group. (will be described forward in the present section)

# 4. Procedures

## *ANESTHETIC CONSIDERATIONS*

In patients with aortic stenosis attempts should be made to avoid tachycardia with the choice of premedication and induction of anesthesia. Preload and afterload are closely monitored and maintained in the early stages of the operation. During induction and maintenance of anesthesia, an alpha-adrenergic agent, such as phenylephrine may be necessary to sustain adequate systemic pressures. A narcotic-based anesthetic agent avoids myocardial depression, hypotension and arrhythmias. Atrial flutter or fibrillation is treated with synchronized cardioversion to avoid reduction in cardiac output. If the patient's cardiac status deteriorates on induction, emergency institution of cardiopulmonary bypass may be required.

- Monitoring: ECG, 1 invasive arterial pressure line, O2 saturation, capnography, anesthetic gases concentration and temperature. Mechanical ventilation monitoring and neuromoritoring (BIS® and INVOS®)
- Central venous access: Preferably right internal jugular vein. Trilumen catheter with venous pressure monitoring and Swan-Ganz® catheter access.
- Fluid output: standard Foley® urinary catheter
- Temperature monitoring: nasopharyngeal and/or tympanic probes
- External pacemaker: St. Jude Medical® 8083 external pulse generator
- Anticoagulation: Activated clotting times >250 seconds for TAVI procedures and >300 for conventional AVR.

## *TRANSESOPHAGEAL ULTRASOUND MONITORING.*

For the presurgical evaluation, the standard views according to the guidelines of the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists are used. (Shanewise JS, Anesth Analg 1999)

The transgastric short-axis view (TG mid-SAX) is chosen initially to estimate the left ventricular function and screen for regional wall motion abnormalities in the left ventricle. Reliable and valid assessments of the degree of aortic stenosis are made by using Doppler measurements in the transgastric longaxis view (TG LAX) or in the deep transgastric long-axis view (deep TG LAX).

Pressure gradients should be measured under constant and optimal loading conditions. In addition, left ventricular outflow tract blood flow profiles are registered using pulsed-wave Doppler in order to exclude any subvalvular stenosis. The evaluation is completed by the measurement of left ventricular outflow tract and aortic root diameters.

For further evaluation of the aortic valve, the midesophageal long-axis (ME AV LAX) and midesophageal short-axis (ME AV SAX) views are used. The ME AV SAX allows the leaflets to be examined for morphology. The annulus of the diseased valve also should be inspected for the presence of calcification.

ME AV LAX is used for the standard measurement of aortic root diameter as well as the diameters of the sinus of Valsalva, the sinotubular junction, and the ascending aorta.

The postsurgical evaluation focuses on valve position, valve function (regurgitation and stenosis), presence of new regional wall motion abnormalities (clue to coronary ostial obstruction), and the assessment of the biventricular function. The sutureless implantation technique of stent-fixed aortic valve prosthesis means that the risk of paravalvular aortic regurgitation is significantly higher than conventional AVR. The detection, localization, and quantification of aortic regurgitation are crucial to guide intraoperative decision making. Paravalvular and intravalvular regurgitation should be evaluated in multiple views including the ME AV LAX, the ME AV SAX, deep TG LAX, and the TG LAX views. The severity of aortic regurgitation can be quantified by the pressure half-time method and regurgitation jet width in relation to the left ventricular outflow tract.

The echocardiographer and the anesthesiologist must be aware of multiple rare cardiac complications throughout the procedure such as coronary obstruction, mitral valve injury, annular and root rupture, aorto-atrial shunt, and cardiac perforation with the development of sudden cardiac tamponade. Thus, perioperative TEE is a baseline, essential assessment for instantaneous valve evaluation as well as for further comparisons during transthoracic echocardiographic follow-up measurements.

## *TRANSCATHETER AORTIC VALVE IMPLANT*

- GENERAL OVERVIEW

TAVI is currently carried out using two different approaches (retrograde transfemoral and anterograde transapical), which share the same main principles. All procedures are carried out under general anesthesia, although regional anesthesia may suffice for transfemoral patients.

Peri-procedural transoesophageal echocardiography (TEE) monitoring is mandatory to correctly position the valve as well as to detect complications.

After crossing the aortic valve, BAV is performed to pre-dilate the native valve and serve as a rehearsal for TAVI. Simultaneous rapid pacing decreases cardiac output, stabilizing the balloon during inflation. Normal blood pressure must be completely recovered between sequences of rapid pacing.

The following imaging methods can be used to position the prosthesis at the aortic valve:

- Fluoroscopy to assess the level of valve calcification.

- Aortography, using different views, performed at the beginning of the procedure and eventually repeated with the undeployed prosthesis in place, to determine the position of the valve and the plane of alignment of the aortic cusps.
- Echocardiography: TEE is helpful, in particular, in cases with moderate calcification. Three dimensional real-time TEE provides an additional value.

When positioning is considered correct, the prosthesis is released. Rapid pacing is used at this stage in balloon expandable but not in self-expanding devices.

Immediately after TAVI, aortography and, whenever available, TEE or, in the absence of TEE, eventually Transthoracic echocardiogram (TTE) are performed to assess the location and degree of aortic regurgitation and the patency of the coronary arteries and to rule out complications such as haemopericardium, and aortic dissection. The haemodynamic results are assessed using pressure recordings and/or echocardiography.

After the procedure, the patients should stay in intensive care for at least 24 h and be closely monitored for several days especially as regards haemodynamics, vascular access, rhythm disturbances (especially late atrioventricular block), and renal function.

The following are the specific issues related to the different approaches.

- In the transfemoral approach, close attention should be paid to the vascular access.
- The common femoral artery can be either prepared surgically or approached percutaneously. Echo-guided femoral access could be useful. Manipulation of the introductory sheaths should be careful and fluoroscopically guided. Depending on the size of the device, closure of the vascular access can be effected surgically or using a percutaneous closure device.

- For the transapical approach, femoral access and cardiopulmonary bypass should be on standby in patients in whom surgical conversion is an option in case of complications. The technique requires an antero-lateral mini-thoracotomy, pericardiotomy, identification of the apex, and then puncture of the left ventricle using a needle through purse-string sutures. Subsequently, an introductory sheath is positioned in the LV, and the prosthesis is implanted using the anterograde route.

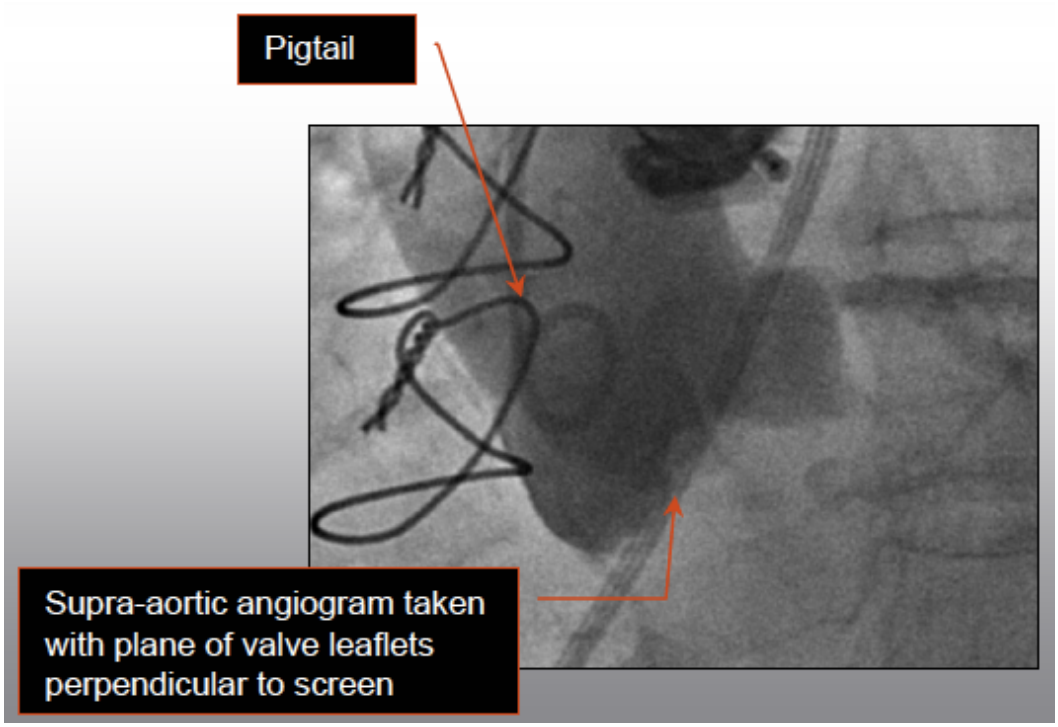
Administer a bolus of heparin at the start of the procedure. During the procedure, heparin should be administered so that the ACT is maintained at ≥ 250 sec.

- TRANSAPICAL APPROACH

***a) Baseline parameters***

1. Place radial arterial line for continuous arterial blood pressure monitoring.
2. Place an internal jugular vein line for monitoring central venous pressures and volumes via standard techniques.
3. Prepare and place a 6F (2.0 mm) sheath into a femoral artery, per standard techniques. Through the femoral artery sheath, advance a 5F (1.67 mm) or 6F (2.0 mm) pigtail catheter into the descending aorta and perform a supra-aortic angiogram with the projection of the native aortic valve perpendicular to the screen (Fig.11).

*Fig. 11. Placement of pigtail catheter*



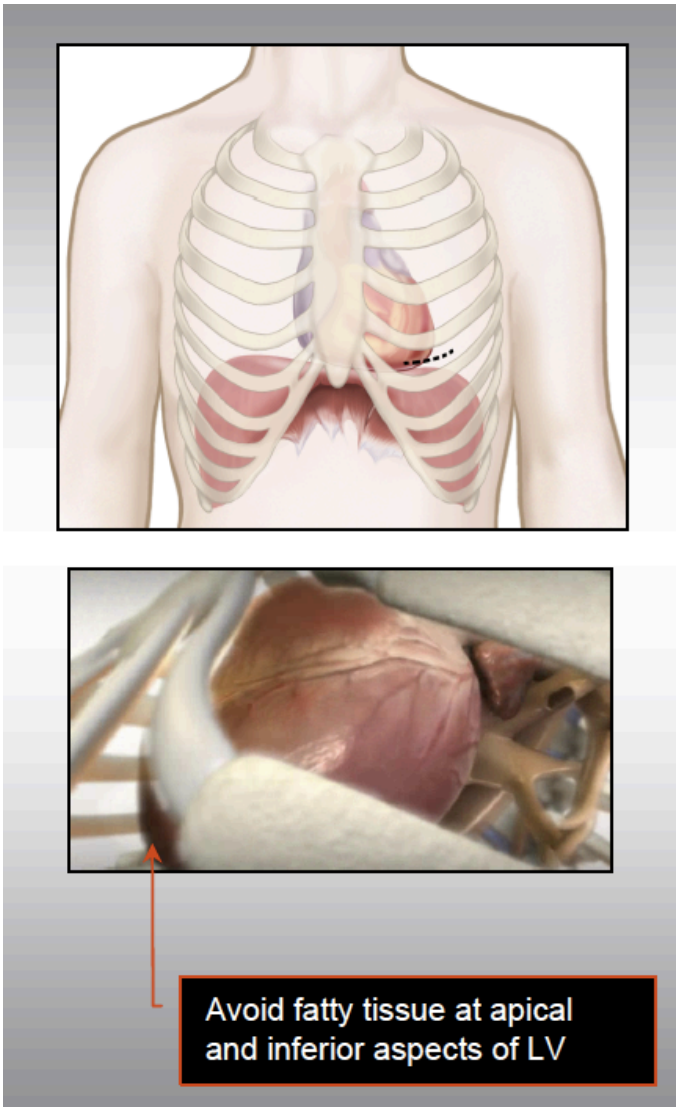

*Source: Edwards Lifesciences*

4. Evaluate the height between the inferior aspect of the annulus and the inferior aspects of the lowest coronary ostium for subsequent prosthetic aortic valve implantation.
5. Set the stimulation parameters, test pacing at 200 to 220 b/min (See Edwards Rapid Pacing Protocol) and then start pacing on demand at 80 beats/min or as clinically indicated.

***b) Apical access and native valve predilatation***

1. Access the apex of the pericardium through a mini-anterior thoracotomy at the 5th or 6th intercostal space. Incise the pericardium to expose the apex of the left ventricle (LV).

*Fig.12. Transapical access*

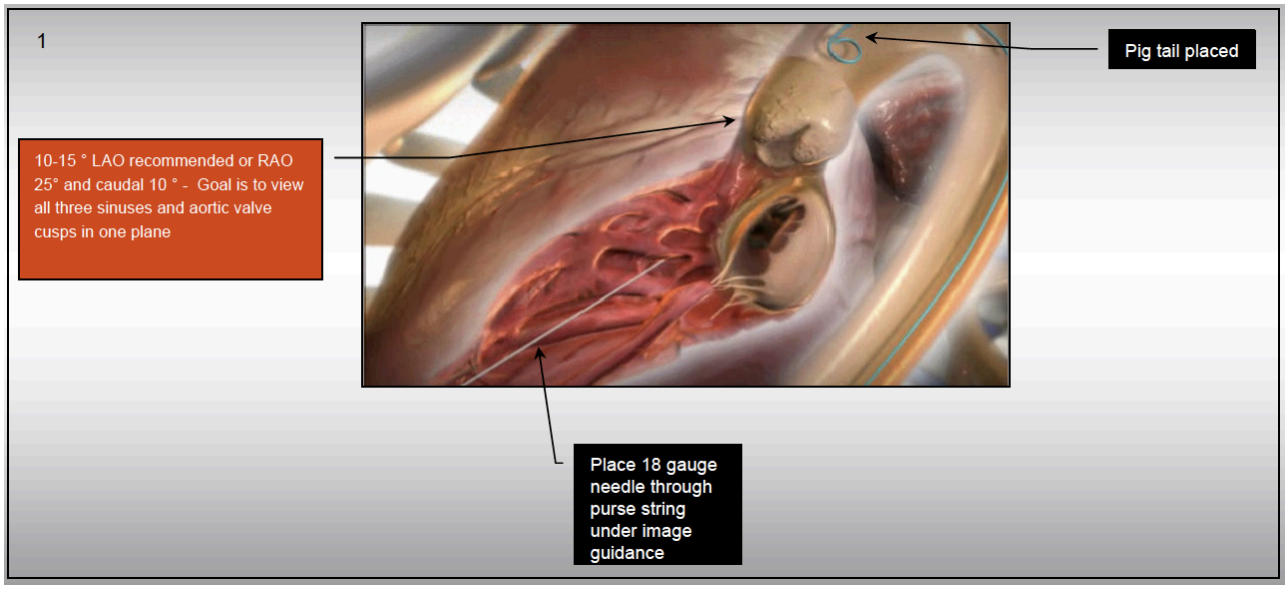



*Source: Edwards Lifesciences*

2. Attach epicardial pacing leads to left ventricle and plug proximal end of leads into pacemaker.
3. Place a reinforced double purse string on the LV apex to access the left ventricle. Ensure the patient is anticoagulated with heparin to obtain an activated clotting time (ACT) of ≥ 250 seconds.
4. Under image guidance, place an 18 gauge (1.2 mm) percutaneous needle through the purse string into the LV cavity and advance a short 0.035" (0.89 mm) stiff guidewire through the needle into the LV. Remove the needle and

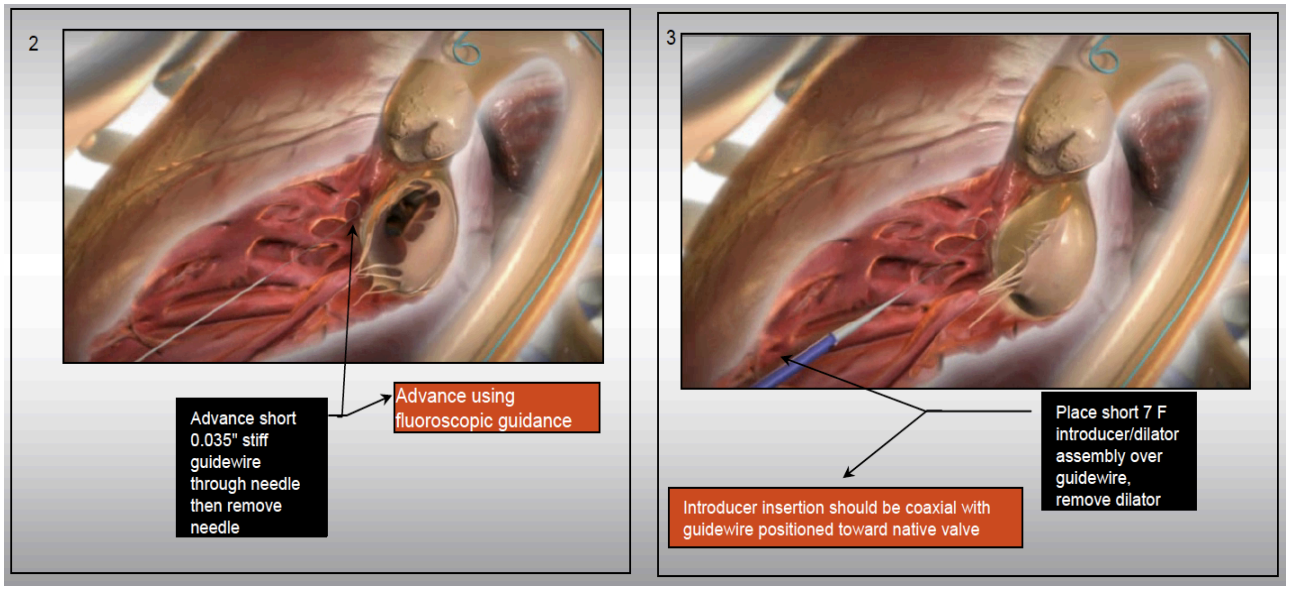
place an 7F (2.7 mm) introducer over the guidewire; then remove the guidewire. Advance an 260 m x 0.035" (0.89 mm) extra-stiff guidewire through the 87F (2.7 mm) introducer and the native valve into the descending aorta (Fig13,14,15).

*Fig.13*



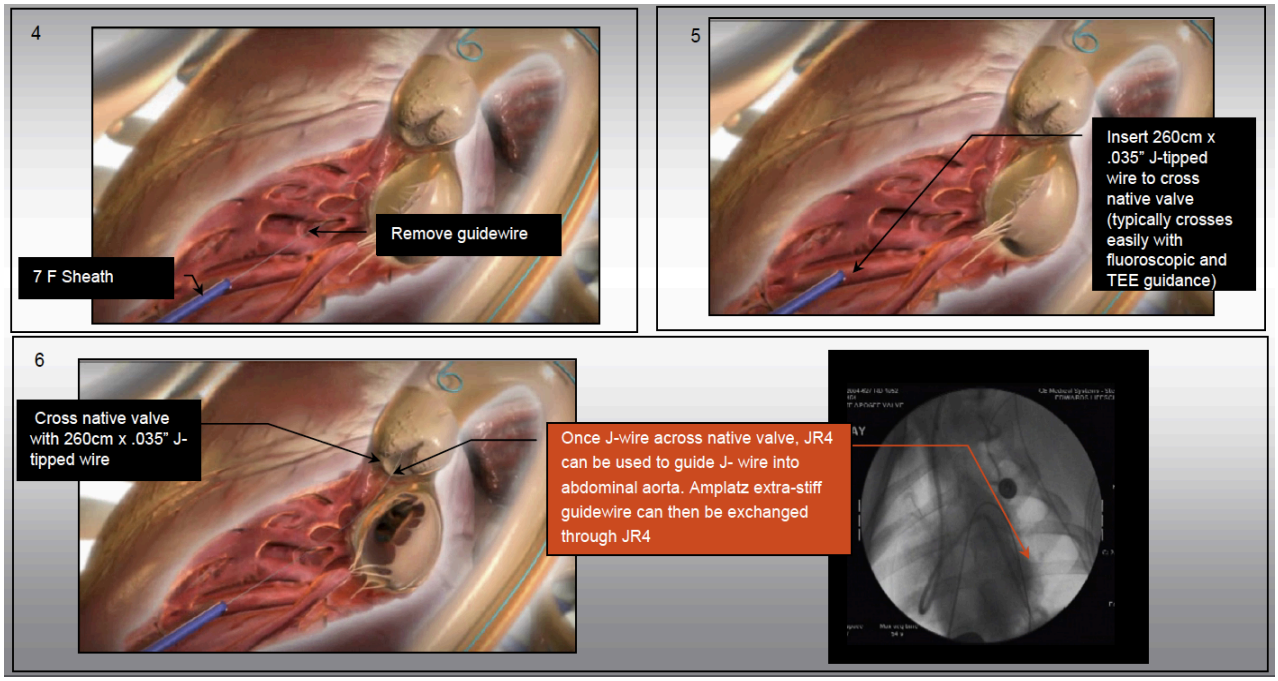

*Source: Edwards Lifesciences*

*Fig14*.




*Source: Edwards Lifesciences*

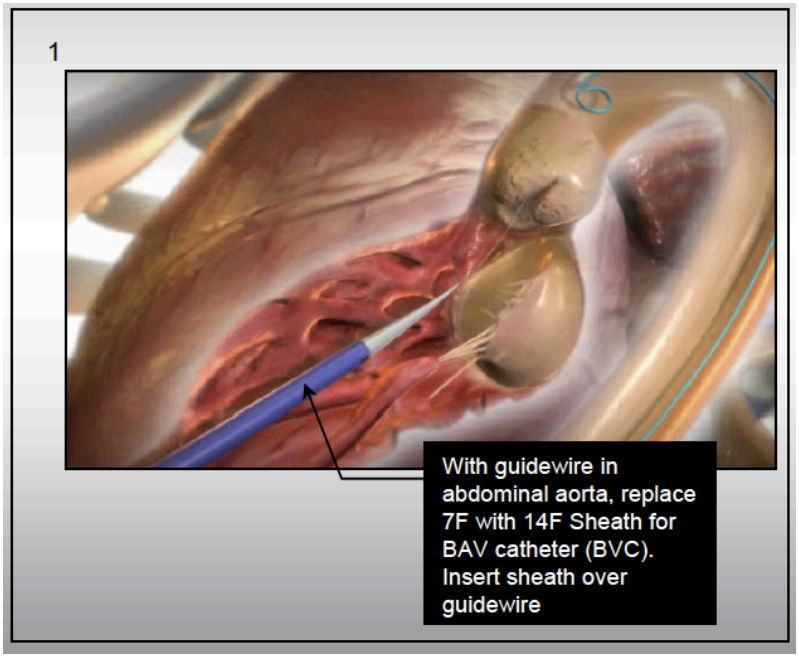
*Fig 15.*




*Source: Edwards Lifesciences*

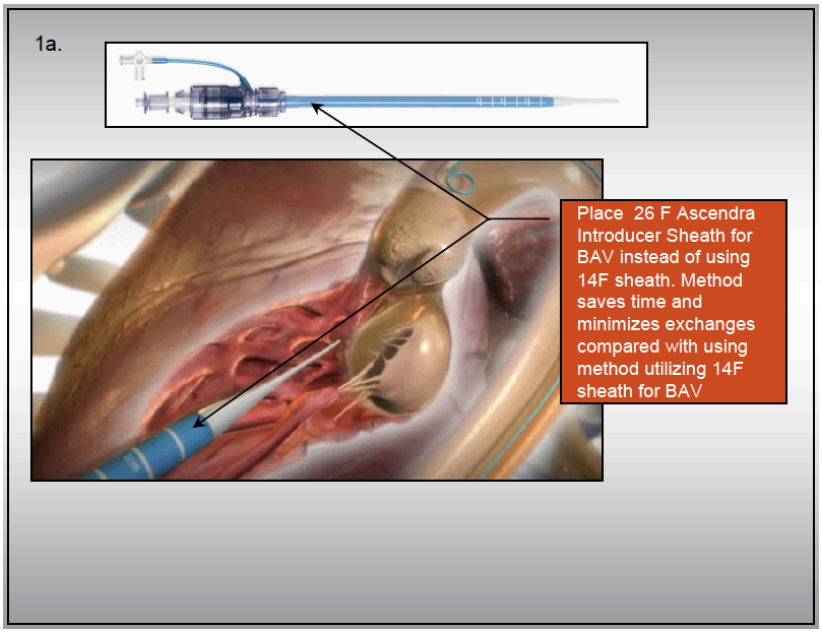
5. Remove the 7F (2.7 mm) sheath and replace with 14F (4.7 mm) sheath or use the Ascendra® (Edwards Lifesciences, Irvine, CA, USA) introducer sheath set, 26F (8.6 mm) x 21 cm. (Fig.15,16,17)

*Fig 16.*



*Source: Edwards Lifesciences*

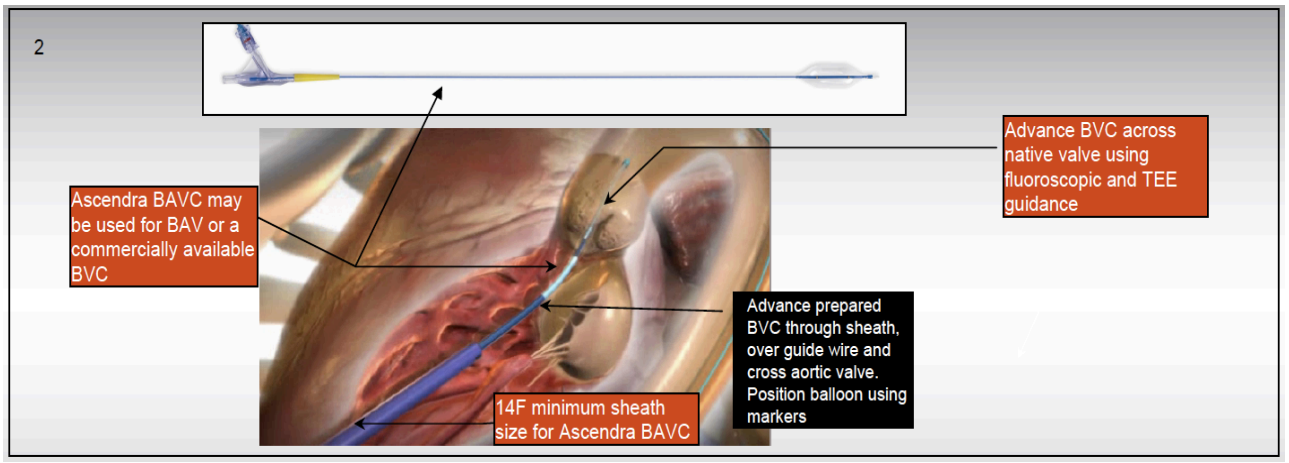
Fig 17.




*Source: Edwards Lifesciences*

6. Prepare a 20 mm commercially available balloon valvuloplasty catheter (BVC), or the Ascendra® (Edwards Lifesciences, Irvine, CA, USA) balloon aortic valvuloplasty catheter.
7. Advance the prepared BVC through the sheath over the guidewire, cross the aortic valve, and position the balloon. (Fig.18)

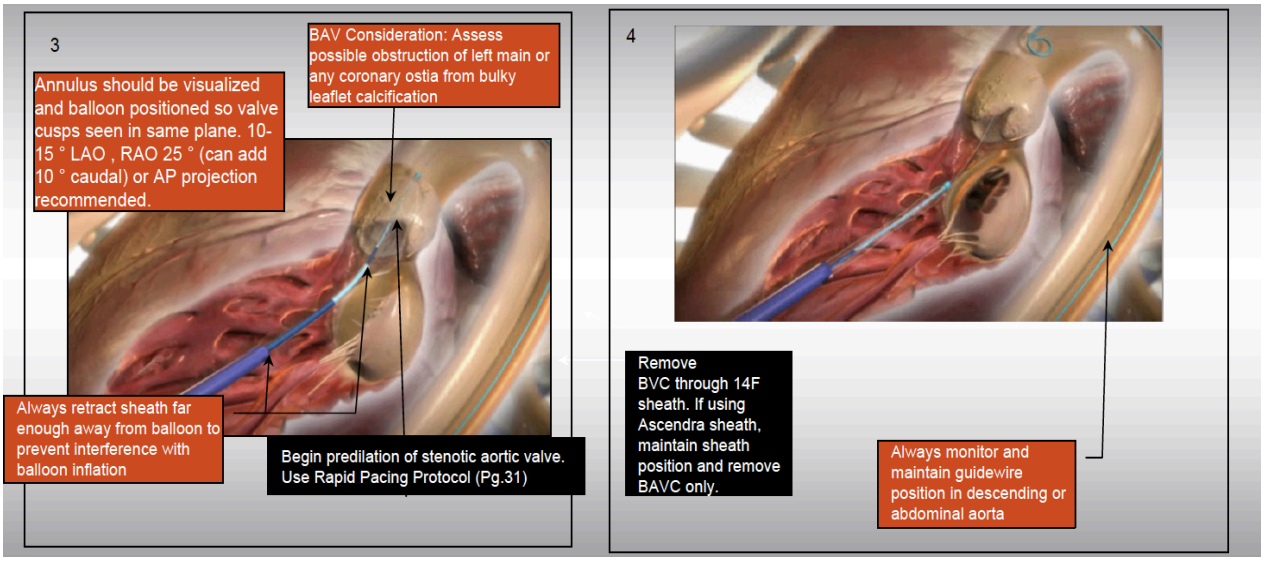
*Fig.18*



*Source: Edwards Lifesciences*

8. Begin predilation (Fig.19):
    - Begin rapid pacing at 200-220 bpm (beats per minute); once arterial blood pressure has decreased to 50 mmHg or below, balloon inflation can commence.
    - Once the desired implantation position is verified, rapidly inflate the BVC.
    - Rapidly deflate the BVC.
    - When the BVC has been completely deflated the pacemaker may be turned off, or returned to 80 b/min, if clinically indicated.
9. Remove the balloon valvuloplasty catheter, leaving the guidewire in place in the descending aorta.

*Fig.19*




*Source: Edwards Lifesciences*

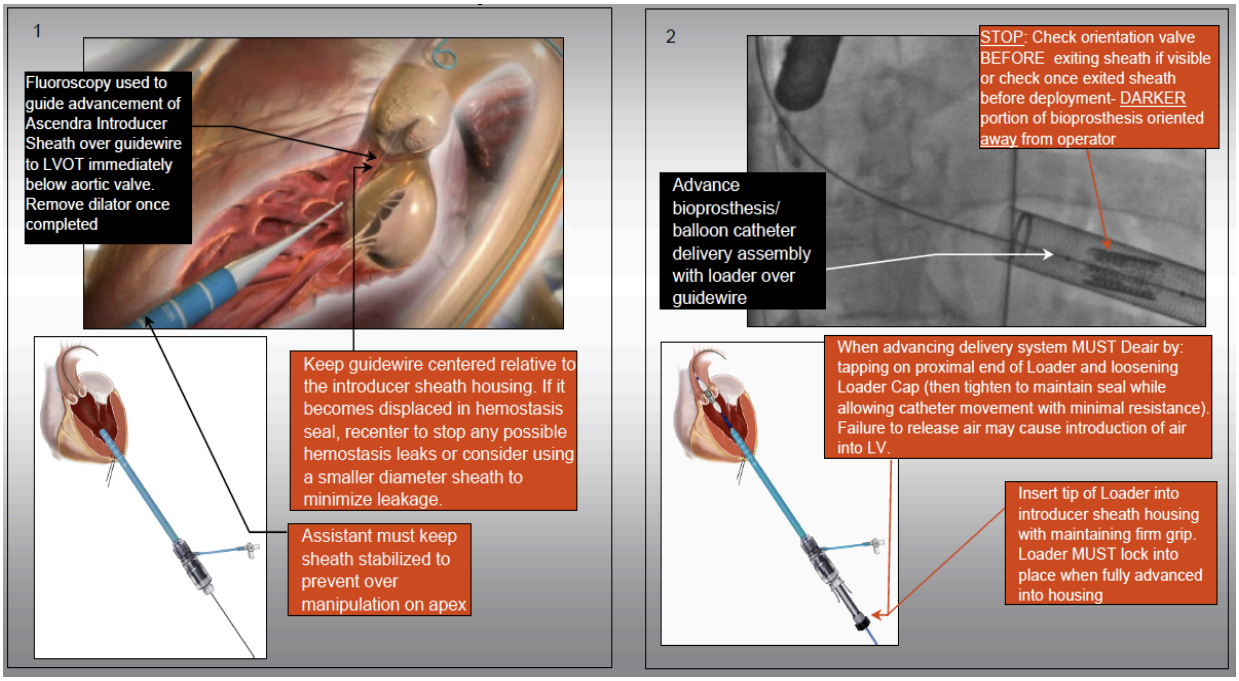
10. If applicable, remove 14F (4.7 mm) sheath and advance the Edwards® (Edwards Lifesciences, Irvine, CA, USA) 26F (8.6 mm) x 21 cm introducer sheath system over the guidewire. Insert the tip of the introducer sheath through the apex of the LV and locate the sheath tip in the LV outflow

immediately below the aortic valve; withdraw the dilator slowly, keeping the introducer sheath in place. Continue to hold the guidewire centered relative to the introducer sheath

***c) Prosthetic valve delivery***

1. Advance the bioprosthesis/balloon catheter delivery assembly with the loader over the guidewire.
2. Insert the tip of the loader into the introducer sheath housing while maintaining a firm grip. The loader will lock into place when it is fully advanced into the housing.
3. Tap lightly on the introducer sheath housing to release air bubbles to the proximal end of the loader. Loosen the loader cap to release the air bubbles from the loader, then tighten the cap until the loader is sealed but the catheter can be moved with minimal resistance. (Fig.20)

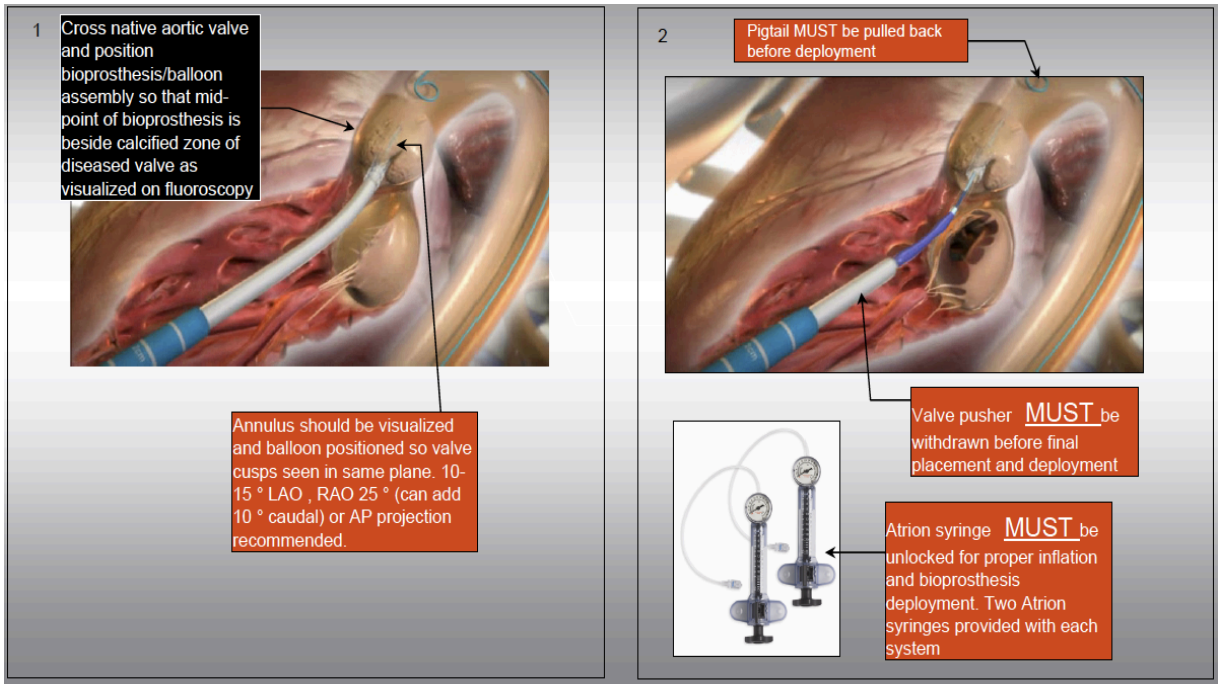
*Fig.20*




*Source: Edwards Lifesciences*

4. Cross the native aortic valve and position the bioprosthesis/balloon assembly so that the mid-point of the bioprosthesis is beside the calcified zone of the diseased valve as visualized on fluoroscopy.
5. Loosen the pusher nut and pull the pusher sleeve as far proximal as possible. Tighten the pusher nut. (Fig.21)

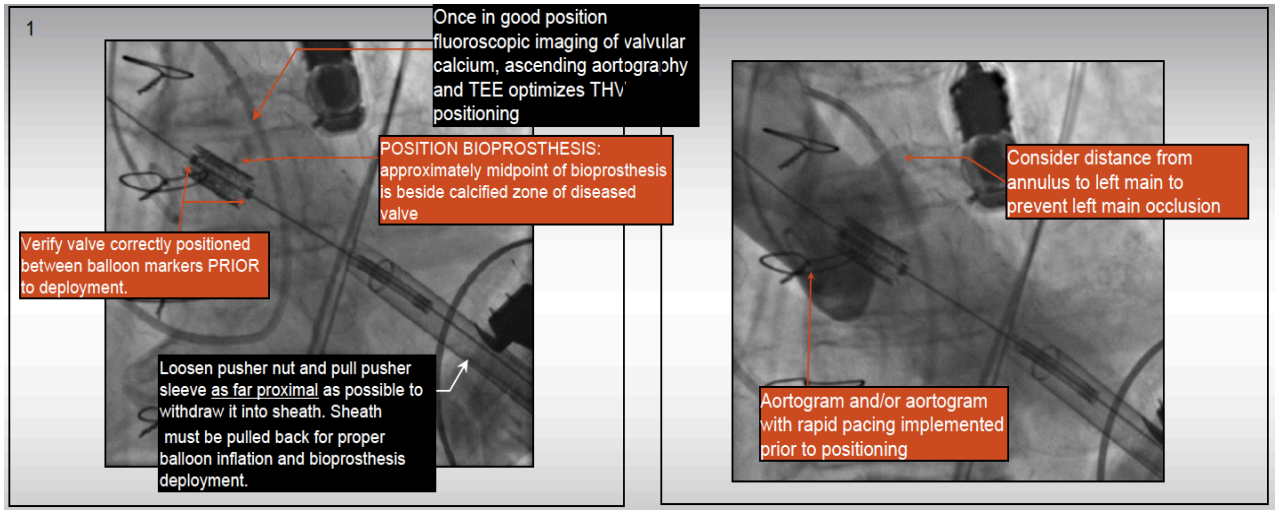
*Fig.21*




*Source: Edwards Lifesciences*

6. The bioprosthesis/balloon assembly position may be adjusted within the annulus by pulling back on the knob on the handle to deflect the catheter tip. The deflection occurs in the same plane as the knob. If deflection is used, the knob must be held until deployment of the bioprosthesis is complete.

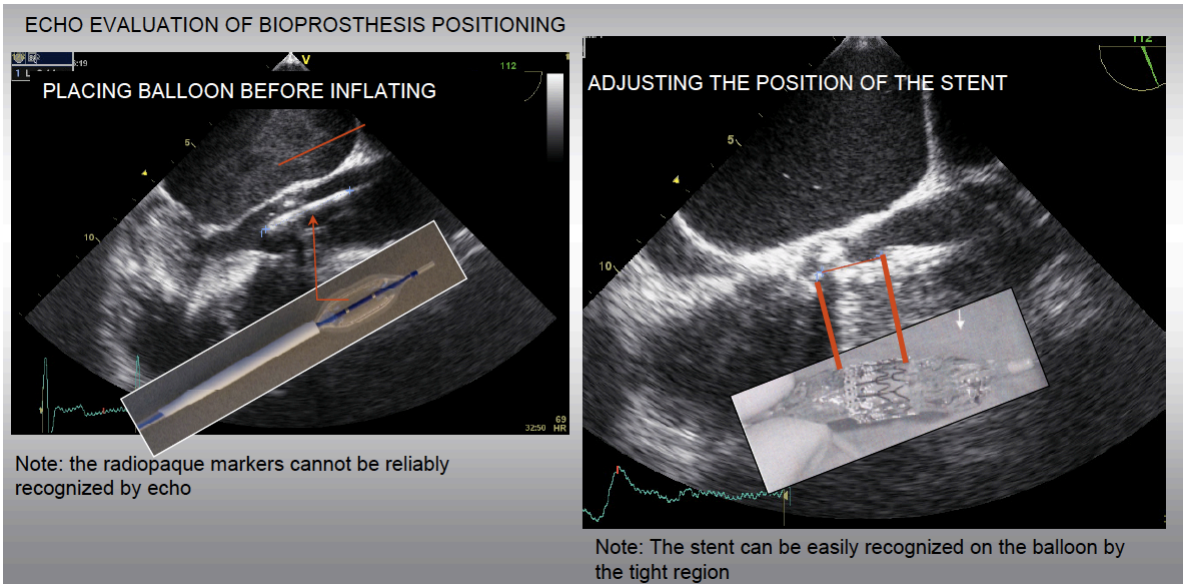
Fig.22




*Source: Edwards Lifesciences*

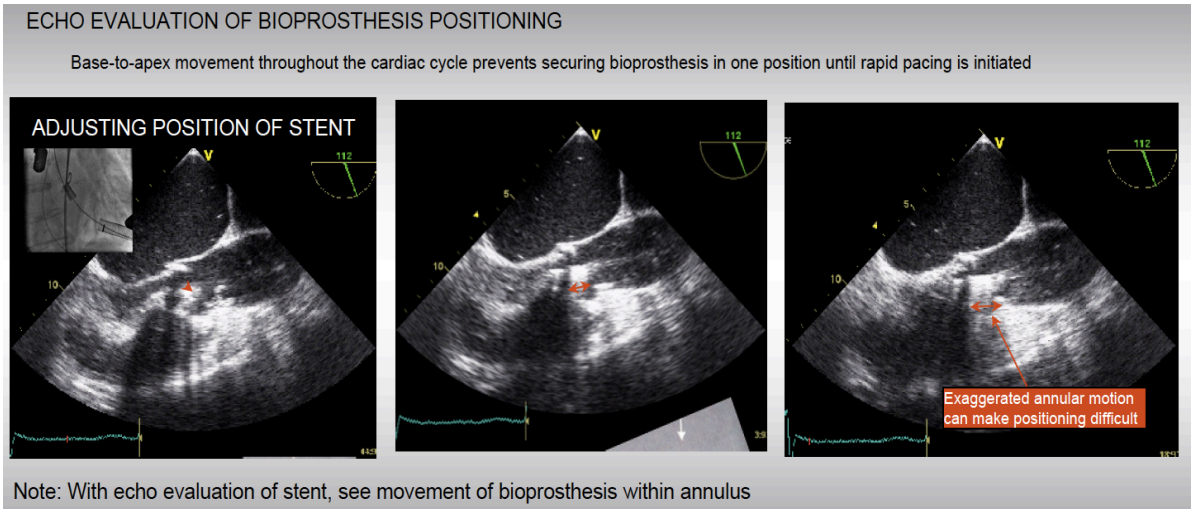
7. Just prior to bioprosthesis/balloon inflation, start rapid pacing by setting the PM to pace at 200-220 b/min. The marked decrease in cardiac output induced by the ventricular tachycardia allows for a more stable balloon inflation.
8. Verify the correct location of the bioprosthesis with respect to the calcified valve using image guidance. (Fig.23,24)

*Fig.23*




*Source: Edwards Lifesciences*

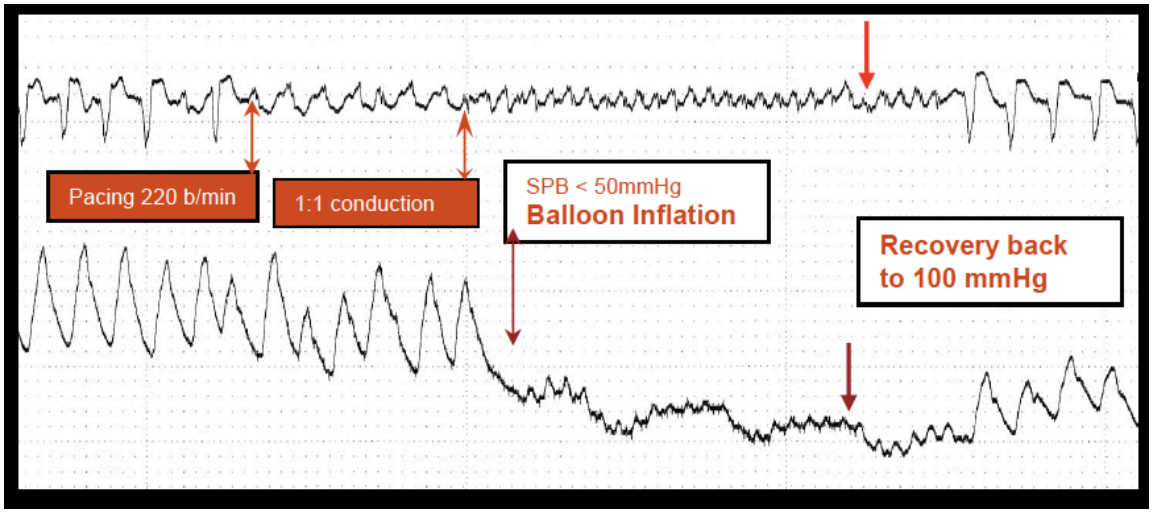
*Fig.24*




*Source: Edwards Lifesciences*

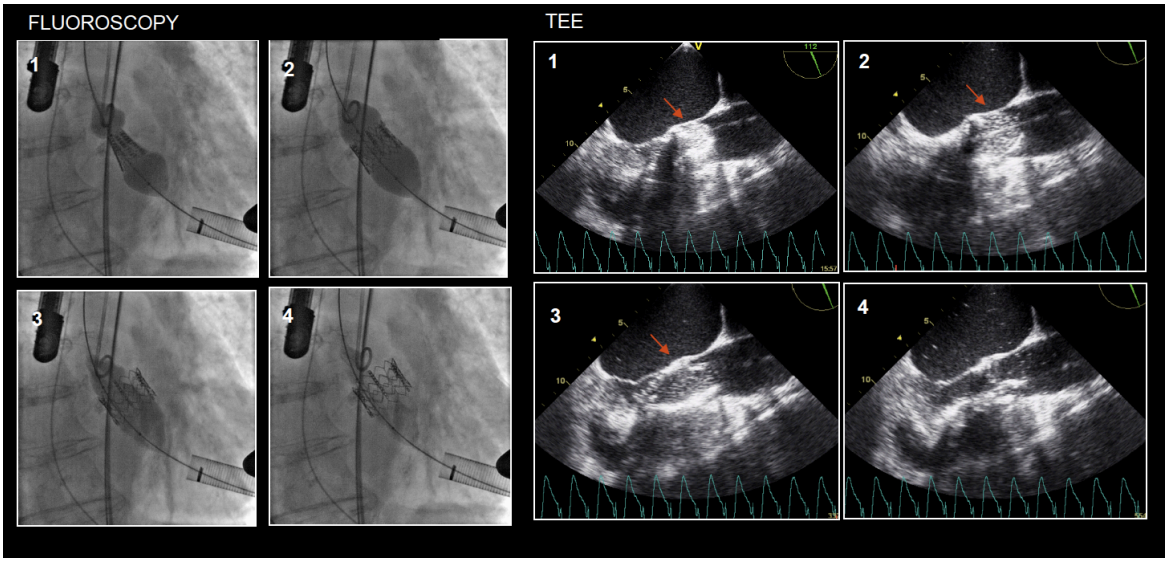
9. Begin bioprosthesis deployment:
    a. Begin rapid pacing at 200-220 bpm; once arterial blood pressure has decreased to 50 mmHg or below, balloon inflation can commence. (Fig.25)
    b. Rapidly inflate the balloon catheter with the entire contents of the inflation syringe to completely deploy the bioprosthesis in the target location. (Fig.26)
    c. Once the bioprosthesis has been deployed, rapidly deflate the balloon catheter.
    d. When the balloon catheter has been completely deflated the pacemaker may be turned off, or returned to 80 b/min, if clinically indicated.

Fig.25




*Source: Edwards Lifesciences*

Fig.26

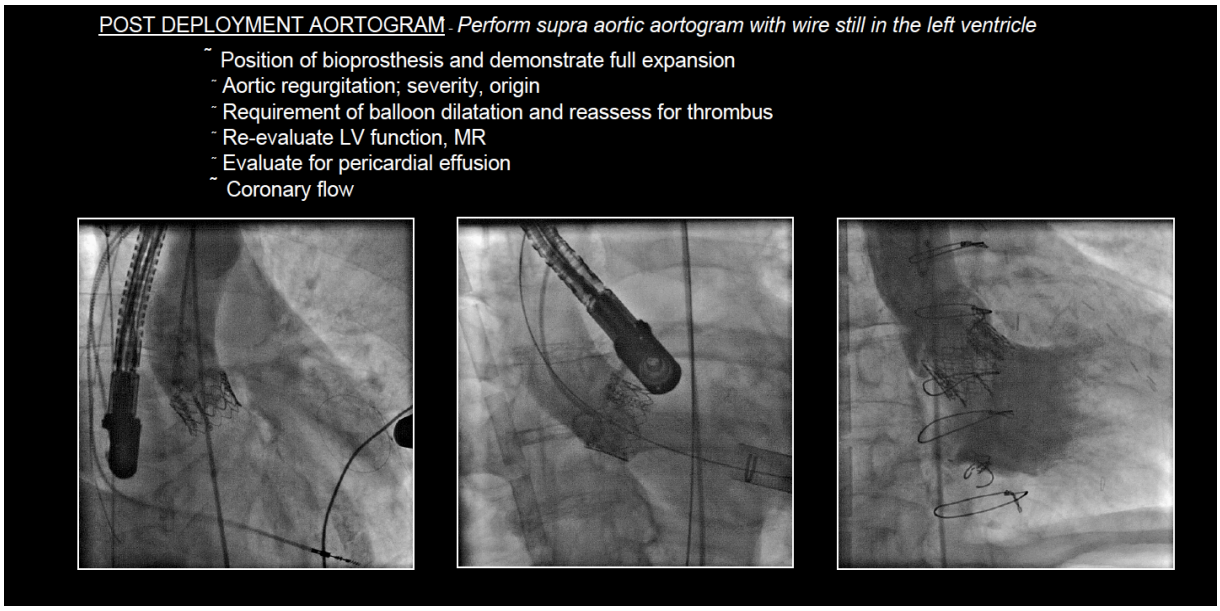



*Source: Edwards Lifesciences*

**d) Verification of prosthetic valve position and measurements**

1. Perform a supra aortic angiogram to evaluate device performance and coronary patency. (Fig.27)

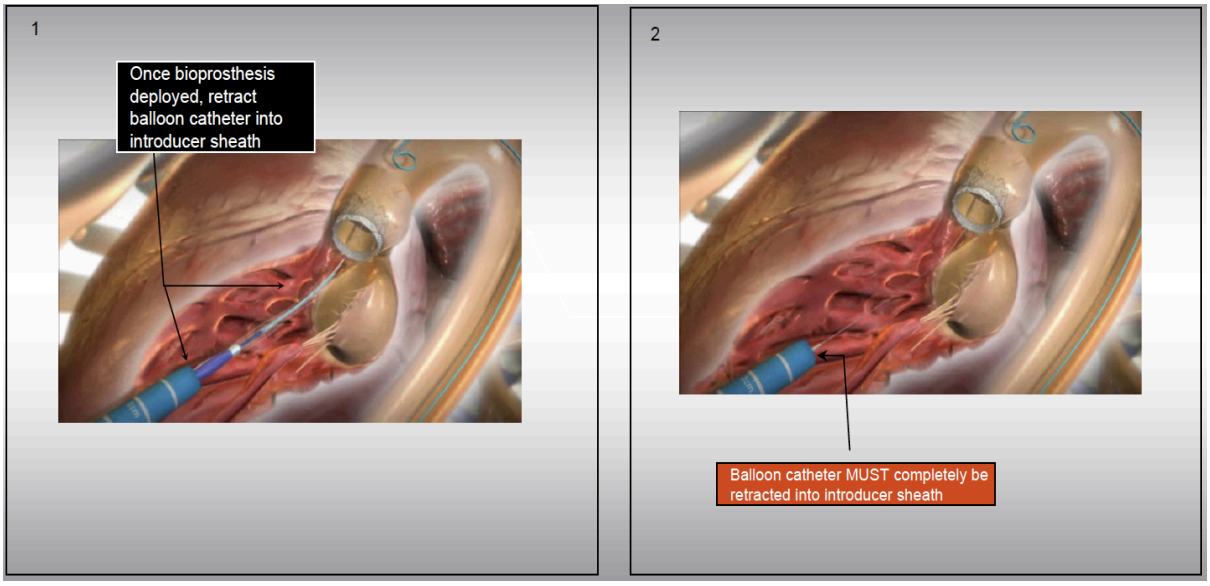
*Fig.27*




*Source: Edwards Lifesciences*

2. Upon satisfactory deployment, remove the sheath, balloon catheter and guidewire. (Fig.28)

Fig.28

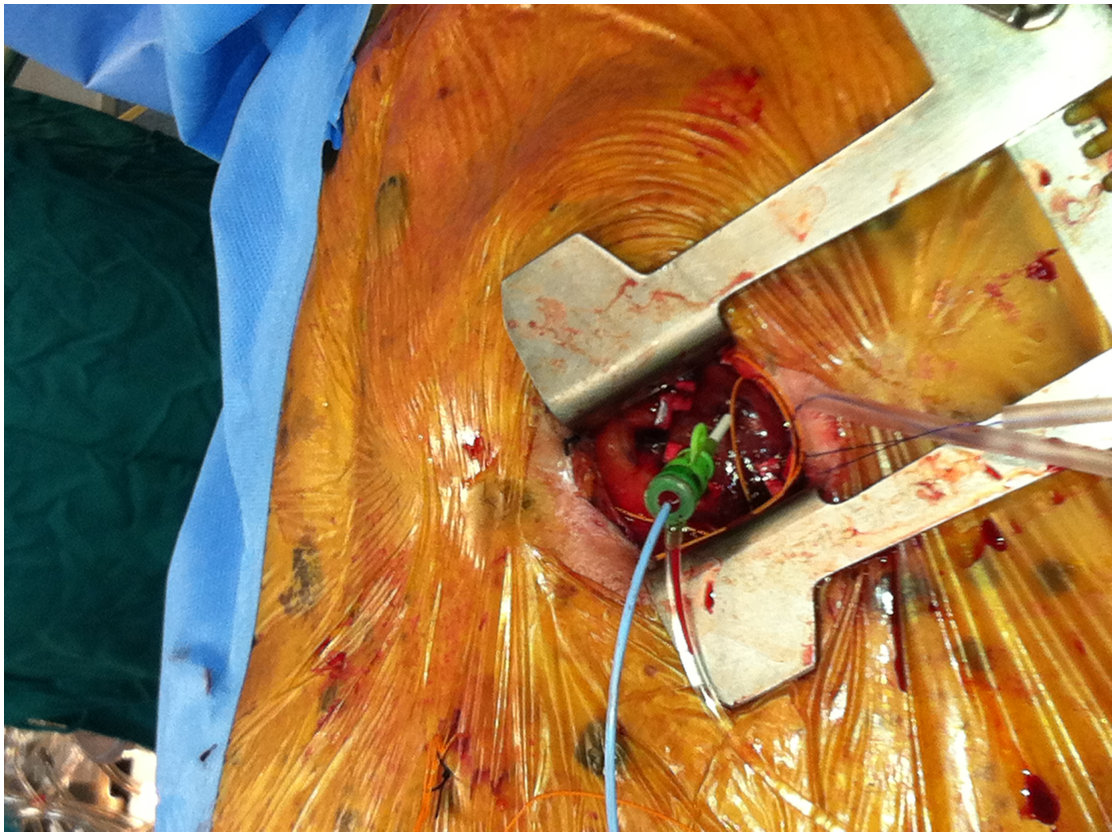



*Source: Edwards Lifesciences*

3. Tie the apical purse string in place and confirm hemostasis.
4. Measure the transvalvular pressure gradients.

5. Remove all catheters and sheaths when the ACT level is appropriate (e.g., reaches < 150 sec).
6. Apply local hemostatic compression on the catheterization puncture sites, or close surgically if clinically indicated. Closure of the incision. (Fig.29)

*Fig.29*



*Source: Consorcio Hospital General Universitario (Valencia, Spain)*

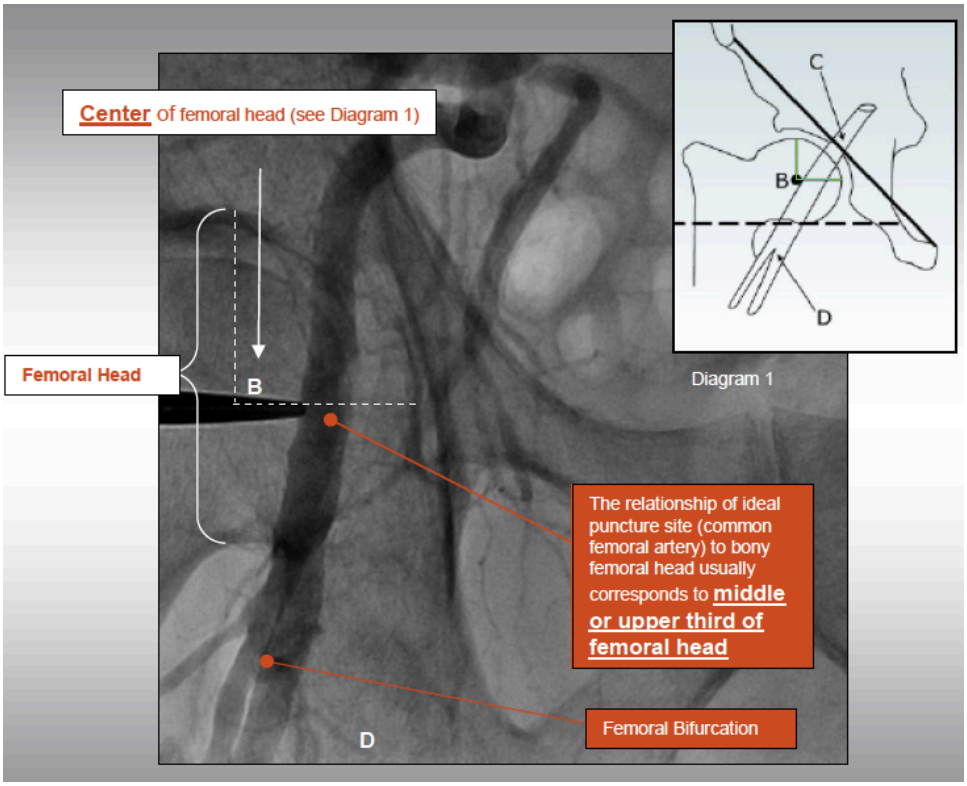
7. The patient should remain on clopidogrel (75 mg/day) for 6 months post procedure and aspirin (75-100 mg/day) for life. Ticlopidine may be used instead of clopidogrel at the physician's discretion.

- TRANSFEMORAL APPROACH

**a) Baseline parameters**

1. Prepare and place a 6F (2.0 mm) sheath into each femoral artery, per standard technique. (Fig.30)
2. Prepare and place an 8F (2.7 mm) sheath into the femoral vein that is contra-lateral to the artery selected for bioprosthesis implantation.
3. In the same leg used in Step 2, introduce a 5F (1.67 mm) or a 6F (2.0 mm) pigtail catheter into the femoral artery and advance the catheter into the aortic root for continuous blood pressure monitoring.
4. Advance an 8F (2.7 mm) PA catheter into the femoral vein sheath to the pulmonary artery. Collect required measurements.
5. If no diagnostic procedure has been performed within one month, perform the following:
    a. Through the femoral artery sheath, sequentially advance right and left coronary artery diagnostic catheters, and perform selective coronary angiograms.
    b. Through the femoral artery sheath, perform a supra-aortic angiogram with the projection of the native aortic valve perpendicular to the screen.
    c. Evaluate the height between the inferior aspect of the annulus and the inferior aspects of the lowest coronary ostium for subsequent prosthetic aortic valve implantation.

*Fig. 30.*




*Source: Edwards Lifesciences*

6. Introduce a 5F (1.67 mm) to 7F (2.3 mm) pacemaker (PM) lead through the 8F (2.7 mm) sheath in the femoral vein and advance the pacemaker lead until its distal end is positioned in the right ventricle.
7. Set the stimulation parameters, test pacing at 200 to 220 b/min and then start pacing on demand, at 80 b/min or as clinically indicated.

***b) Native Valve Predilatation***

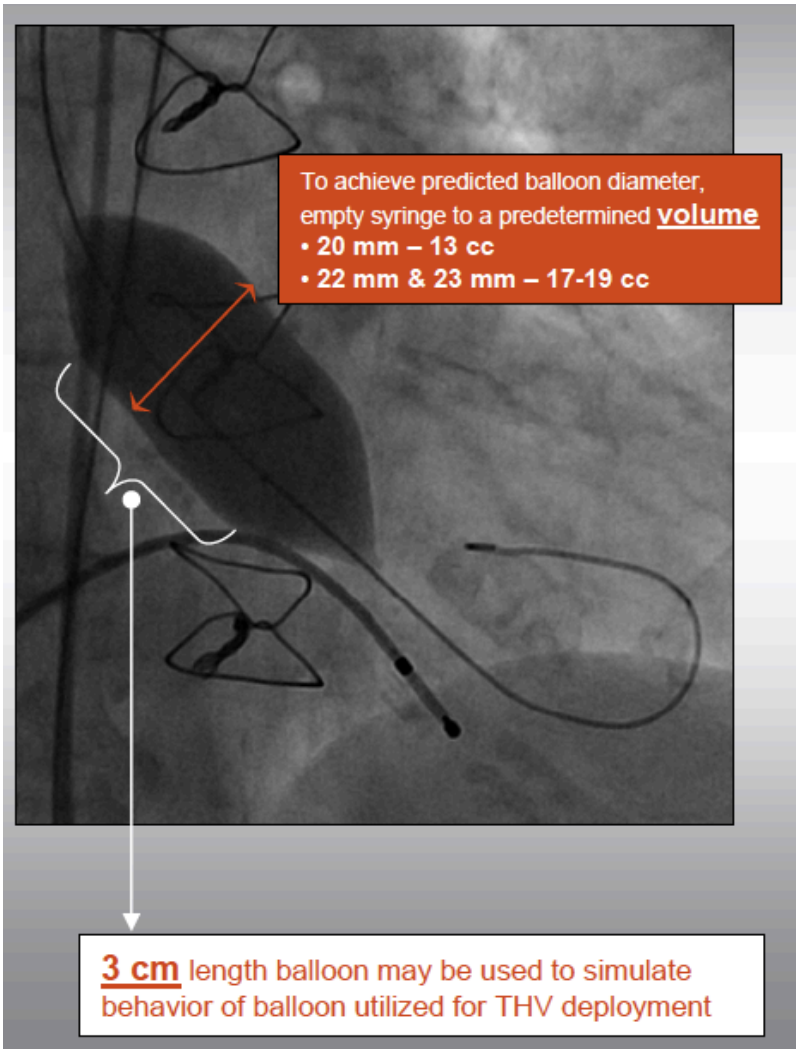
1. Manually pre-shape the tip of the guidewire. Through the 6F (2.0 mm) sheath in the femoral artery selected for bioprosthesis implantation:
    a. Advance a pigtail catheter over a standard guidewire and cross the aortic valve per preferred technique. It is recommended to cross the valve in the 50° LAO position, using a straight guidewire. After the

valve is crossed, advance the selected catheter over the guidewire into the left ventricle.

b. Remove the guidewire and record required hemodynamic information. Measure the cardiac output and assess the valve area.

2. Advance a 260 cm extra-stiff guidewire through the catheter (pigtail) into the left ventricle.
3. Remove the catheter, leaving the guidewire in place in the left ventricle.
4. Over this guidewire, advance a 14F (4.7 mm) sheath into the femoral artery.
5. Advance the prepared balloon through the sheath over the guidewire, cross the aortic valve, and position the balloon
6. Using diluted contrast medium (e.g., 15% contrast medium to heparinized saline) fully and rapidly inflate the balloon with a hand-held syringe until the desired size is reached. In case of balloon instability, repeat balloon inflation while ensuring rapid pacing (200-220 b/min) of the right ventricle. During balloon inflation, measure the aortic blood pressure using the pigtail catheter. Once the blood pressure has decreased to 50 mmHg or below, balloon inflation can commence. (Fig.31)

*Fig.31*




*Source: Edwards Lifesciences*

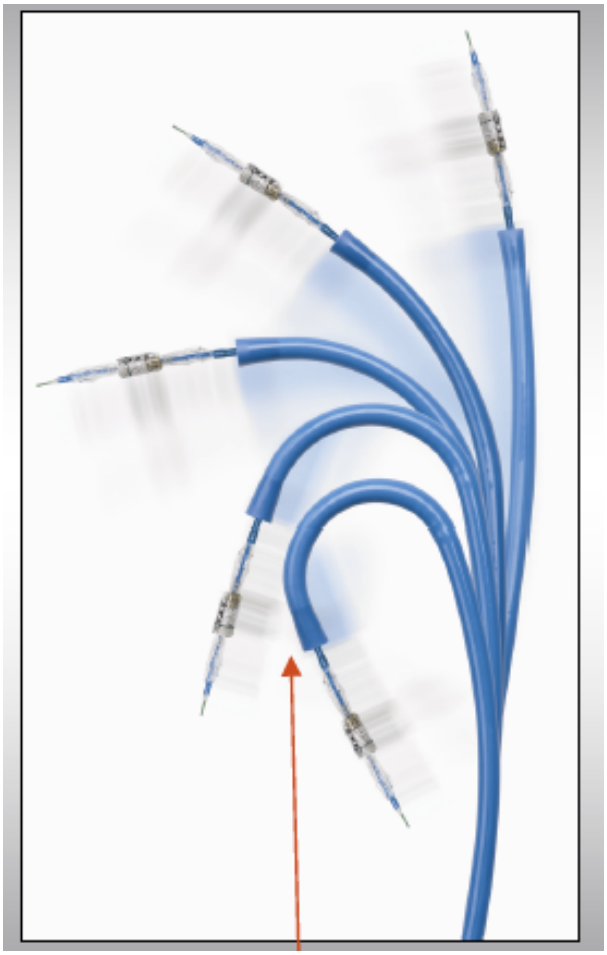
7. Remove the BVC, leaving the guidewire in place in the left ventricle.

**c) Prosthetic Valve Delivery**

1. Predilate the femoro-iliac axis by advancing increasing sized dilators over the guidewire. Advance the maximum possible length of the introducer over the guidewire while following its progression on fluoroscopy. Alternatively, create an arteriotomy in the femoral artery selected for bioprosthesis implantation to allow introduction of the sheath. Use a dilator, if necessary, to expand the puncture site.

2. Pull the bioprosthesis assembly into the delivery RetroFlex® (Edwards Lifesciences Inc., Irvine, CA, USA) or CoreValve® (Medtronic Inc., Minneapolis, MN, USA) catheter until the proximal edge of the bioprosthesis butts up against the distal end of the delivery catheter; be careful to fold the proximal balloon to allow easy advancement of the balloon out of the delivery catheter. Deflect the delivery catheter and advance the balloon catheter out to verify ease of advancement. (Fig.32)

*Fig.32*

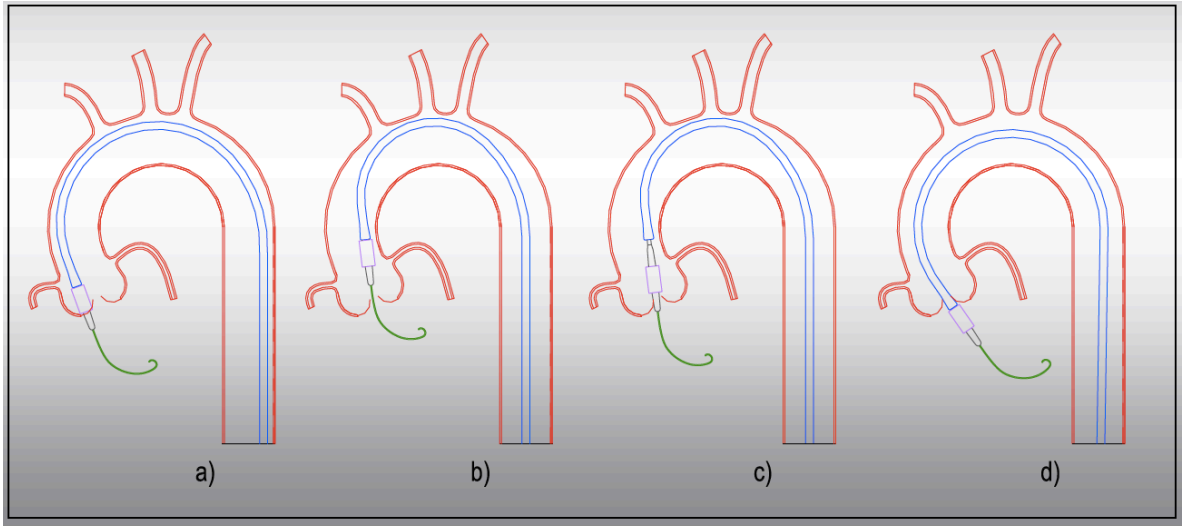


*Source: Edwards Lifesciences*

3. Advance the bioprosthesis assembly into the loader and position the tip of the balloon catheter at the tip of the loader.

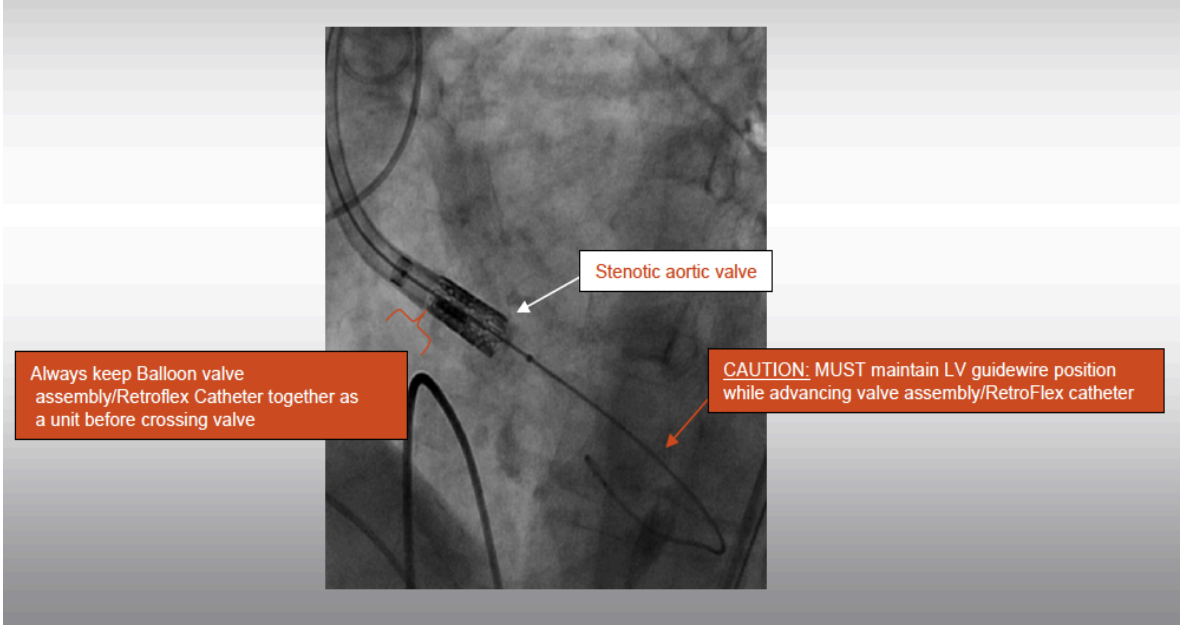
4. Push the RetroFlex catheter up the descending aorta; deflect the tip as needed (by rotating its handle "clockwise" or "counter-clockwise") to track over the guidewire and around the aortic arch. (Fig.33)
5. Cross the native aortic valve and position the bioprosthesis assembly so that the bioprosthesis is beside the calcified zone of the diseased valve as visualized on fluoroscopy. (Fig.34)

Fig. 33




*Source: Edwards Lifesciences*

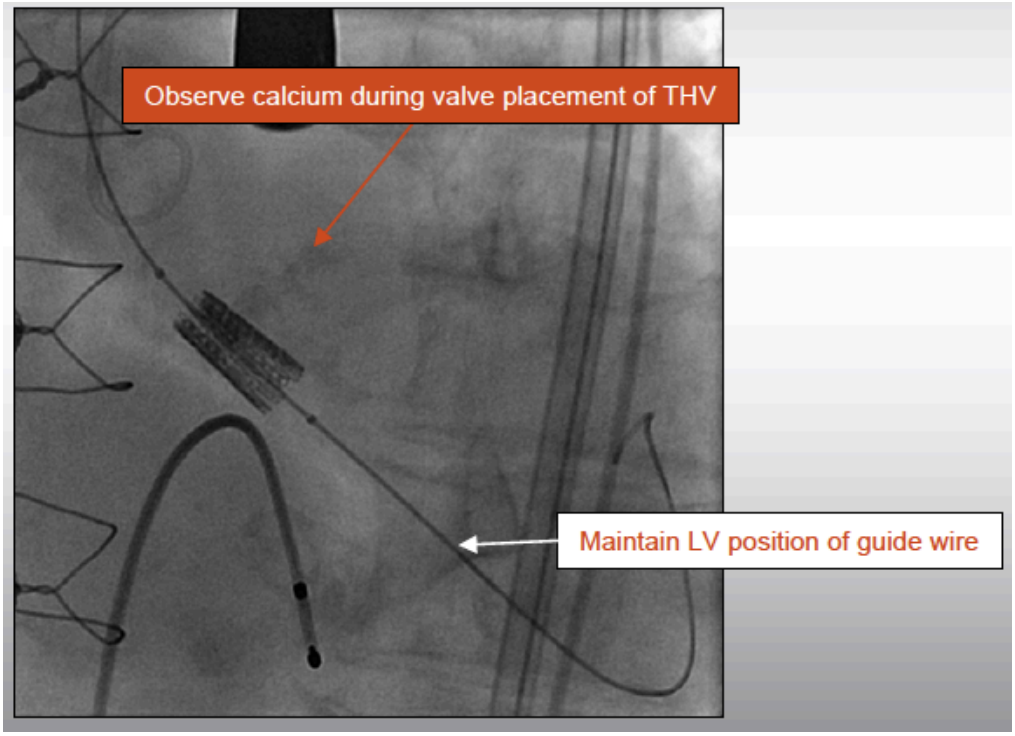
*Fig.34*



*Source: Edwards Lifesciences*

6. Just prior to bioprosthesis inflation, start rapid pacing by setting the pacemaker catheter to pace at 200-220 b/min. The marked decrease in cardiac output induced by the ventricular tachycardia allows for additional stable balloon inflation (Not necessary in self-expanding nitinol valves – CoreValve®)
7. Re-verify the correct location of the bioprosthesis with respect to the calcified valve using fluoroscopy guidance. (Fig.35)

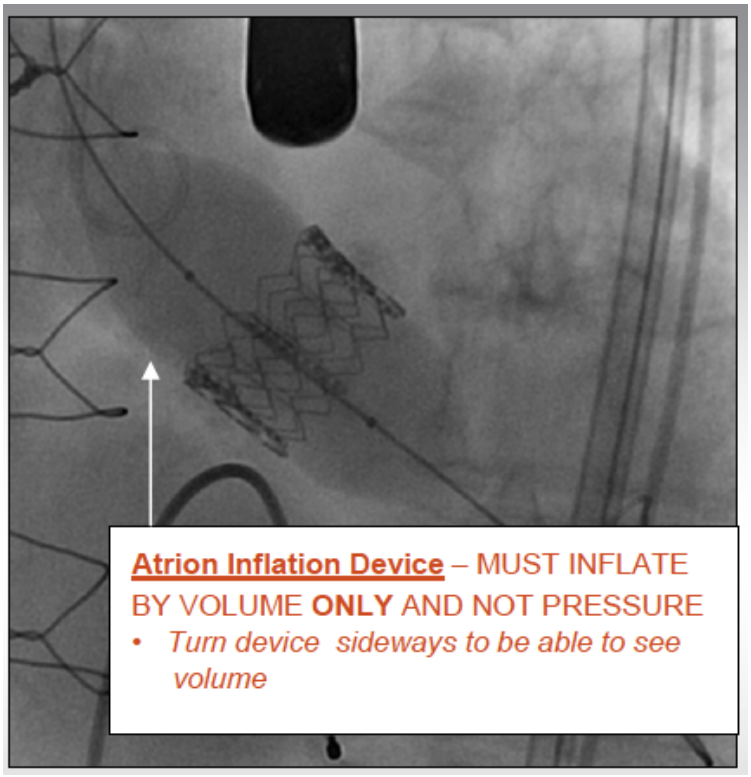
*Fig.35*




*Source: Edwards Lifesciences*

8. Begin bioprosthesis deployment:
    a. Begin rapid pacing at 200-220 bpm; once arterial blood pressure has decreased to 50 mmHg or below, balloon inflation can commence.
    b. Once the desired implantation position is verified, rapidly inflate the balloon catheter with the entire contents of the inflation syringe to completely deploy the bioprosthesis in the target location. (Fig.36)

*Fig.36*




*Source: Edwards Lifesciences*

c. Once the bioprosthesis has been deployed, rapidly deflate the balloon catheter.
d. When the balloon catheter has been completely deflated the pacemaker may be turned off, or returned to 80 b/min if clinically indicated.

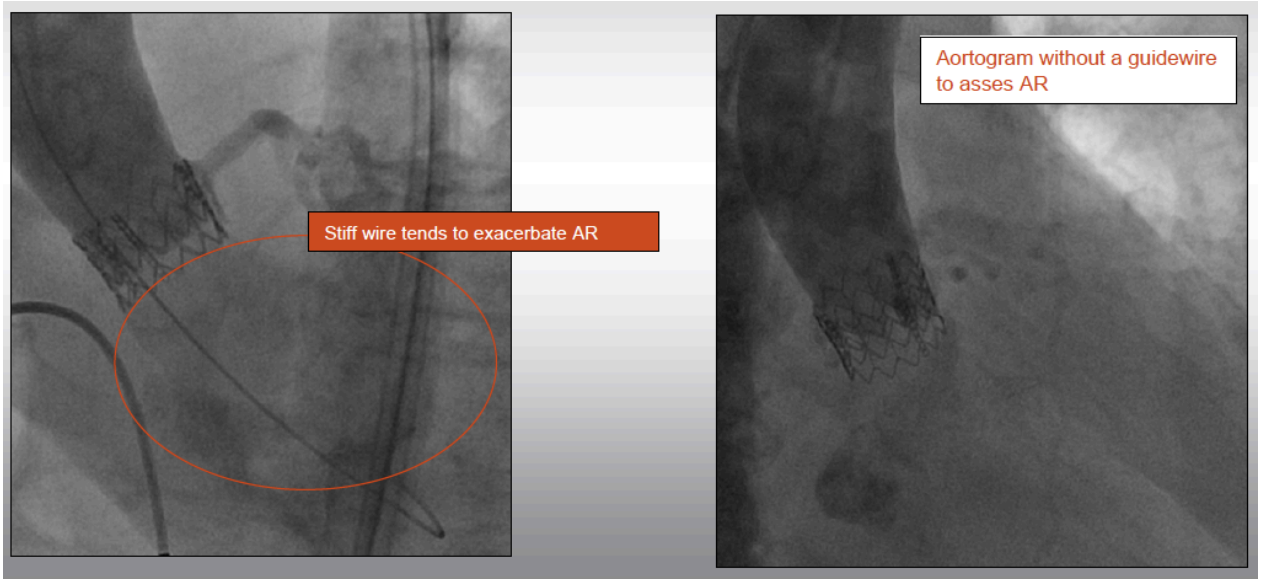
9. For Corevalve® deployment rapid pacing is not necessary. Start releasing the valve when it is correctly positioned.

**d) Verification of Prosthetic Valve Position and Measurements**

Measure and record both the invasive and non-invasive hemodynamic parameters required by the protocol. (Fig.37)

1 Perform a supra aortic angiogram to evaluate device performance and coronary patency.

*Fig.37*



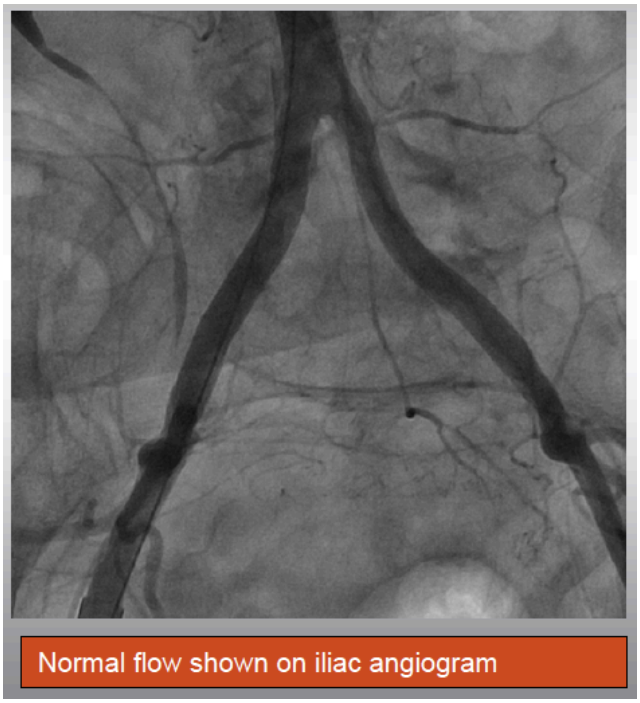

*Source: Edwards Lifesciences*

2 Measure and record the transvalvular pressure gradients.

3 Remove all catheters and sheaths when the ACT level is appropriate (e.g., reaches < 150 sec).

4 Apply local hemostatic compression on the catheterization puncture sites, or close surgically if clinically indicated. (Fig.38)

*Fig.38*



*Source: Edwards Lifesciences*

5 The patient should remain on clopidogrel (75 mg/day) for 6 months post-procedure and aspirin
(75-100 mg/day) for life. Ticlopidine may be used instead of clopidogrel at physician's discretion.

## *CONVENTIONAL AORTIC VALVE REPLACEMENT*

Full median sternotomy is the usual incision for conventional aortic valve replacement, although a partial upper hemisternotomy is also used. After heparinization (ACT>300 sec), the ascending aorta is cannulated in the usual fashion, and the right atrium is cannuated with a two-stage single venous cannula. Anterograde cardioplegia and aortic root vent catheter are placed in the ascending aorta, just distal to the proposed aortotomy site. A pursestring suture is placed on the lateral side of the right atrium for the placement of a retrograde cardioplegia cannula into the coronary sinus if needed.

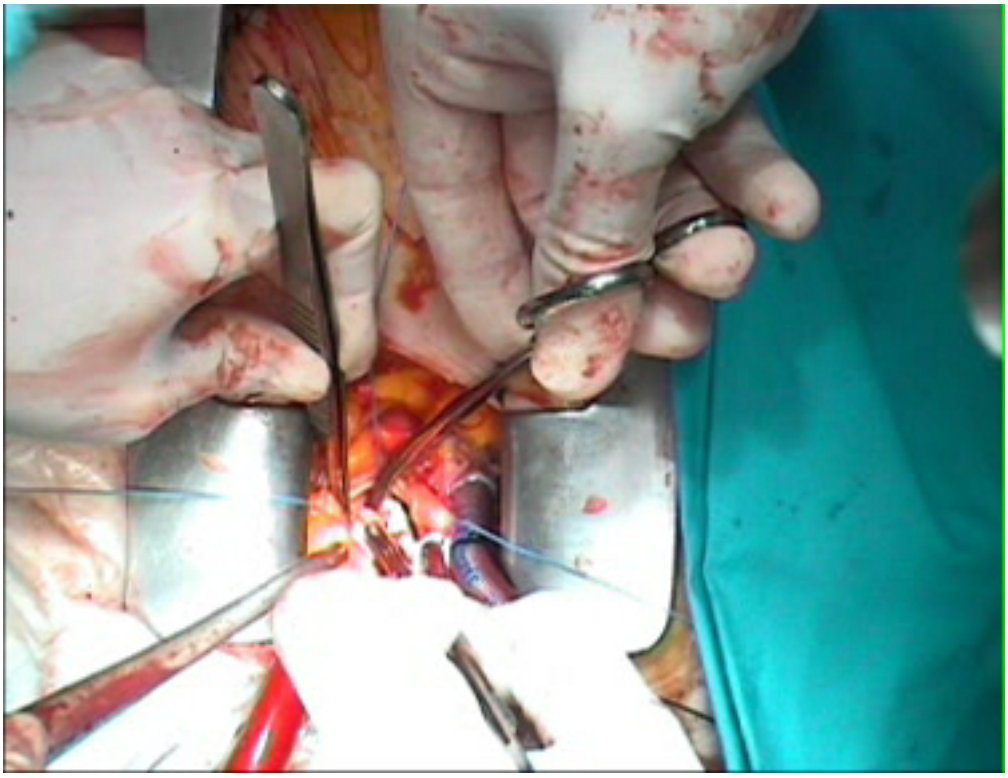
Cardiopulmonary bypass is instituted and the patient is systemically cooled to 34ºC. For patients with pure aortic stenosis without regurgitation, cardioplegic arrest can adequately be achieved in an anterograde fashion. In those with a grade of aortic regurgitation and depending on its severity, the first dose of cardioplegia can be given directly into the coronary ostia via hand-held cannulae after an oblique aortotomy. During the operation, cardioplegic arrest is maintained with intermittent instillation of cardioplegia every 20 minutes. Blood-based cold cardioplegia at 4ºC is used in all cases, as well as topical hypothermia.

An oblique aortotomy is made with the initial incision 2-4 mm above the sinotubular junction and 4-6 mm above the origin of the right coronary artery. The incision extends towards the non-coronary sinus, staying just above the level of the

commissures. Sutures of 3/0 silk or polyester are placed in the aortic wall for retraction and exposure.

The anatomy of the aortic valve, sinuses, sinotubular junction, and anterior leaflet of the mitral valve is assessed. The diseased valve is sharply excised without damage to the aortoventricular junction and the annulus carefully debrided of calcific deposits using small rongeurs. Care should be taken as vigorous decalcification may result in aortic wall injury, injury to the anterior mitral valve leaflet, annular disruption, or left ventricular wall injury. Small calcific debris is evacuated using high vacuum suction and cold saline irrigation of the left ventricle. (Fig.39)

*Fig.39*



*Source: Consorcio Hospital General Univeritario (Valencia, Spain)*

The annulus is sized with a valve sizer and interrupted horizontal mattress sutures of 3/0 with Teflon pledgets are placed in the annulus. Sutures are positioned in a ventricle-to-aorta fashion for supra-valvular placement of the prosthesis. Care is taken in the region of the membranous septum, located inferior to the cupola

formed by the commissure of the noncoronary and right coronary leaflets, so as to avoid injury to the bundle of His.

The sutures are passed through the sewing ring of the valve prosthesis. The valve holder is removed and the valve gently pushed into position. The sutures are tied and cut and the competency of the valve is tested. (Fig 40.)

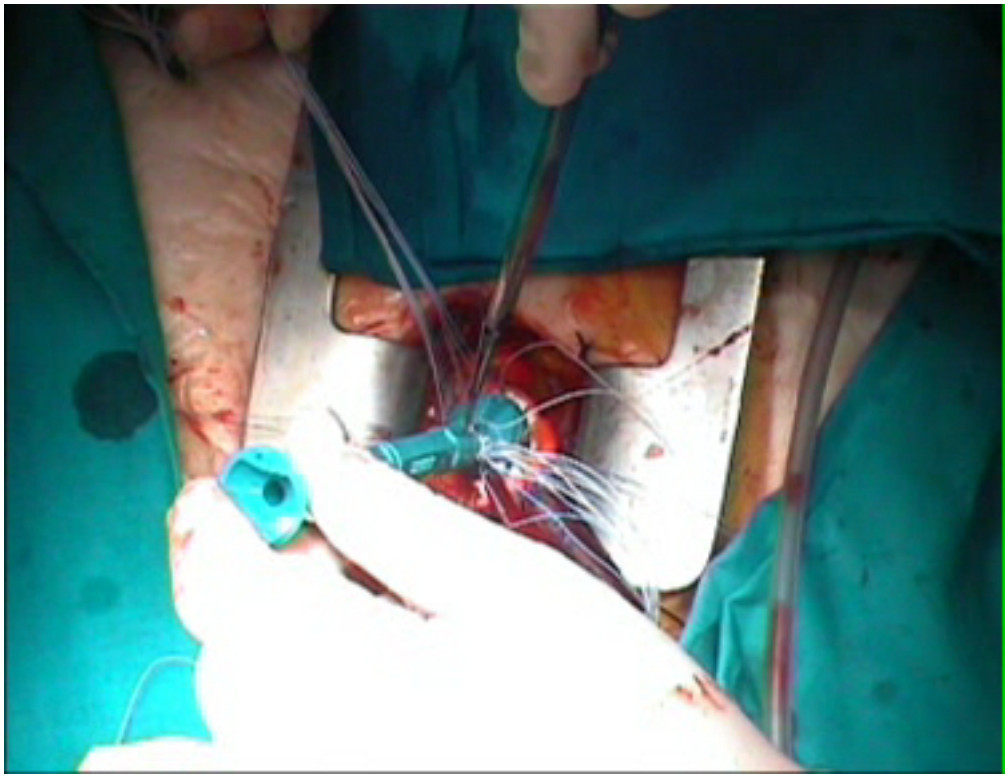
Aortotomy is closed using a 4/0 polypropylene continuous suture placed in an overlapping fashion beginning from the level of the sinus and extending upward, while the patient is rewarming.

After aortotomy closure, the aortic root vent is connected to suction, volume is added to the heart, lungs are gently ventilated and the left ventricle is gently massaged.

The patient is placed in a steed Trendelemburg's position and the aortic cross-clamp is removed. With the heart ejecting the aortotomy is inspected for hemostasis. Additional deairing maneuvers are performed. After adequate rewarming the patient is weaned from cardiopulmonary bypass and then deccanulated. Hemostasis and sternotomy closure are performed in the usual fashion.

In cases of combined aortic valve replacement and coronary artery bypass grafting, the distal coronary anastomoses using vein or free arterial grafts are constructed first before the valve procedure. The distal internal mammary artery graft anastomosis is performed after the valve procedure and closure of the aortotomy. During a combined valve-coronary procedure, cardioplegia can be instilled anterograde via the vein (or free arterial) grafts and retrograde through the coronary sinus.

*Fig.40*



*Source: Consorcio Hospital General Univeritario (Valencia, Spain)*

## *POSTOPERATIVE CARE*

Patients are closely monitored in the intensive care unit postoperatively. A pulmonary artery catheter is often helpful in assessing cardiac performance. Because they experience reduced left ventricular afterload, the majority of patients with aortic stenosis and left ventricular dysfunction have dramatic improvement after aortic valve replacement. Ejection fraction is improved, and the left ventricular end-diastolic volume and capillary wedge pressures are decreased. In those with low transvalvular gradients preoperatively, left ventricular performance may not improve significantly after aortic valve replacement, and intra-aortic balloon pump support may be required in the early postoperative period.

Although myocardial function generally improves relatively rapidly, the hypertrophied ventricle requires and elevated preload to function normally. If the residual transvalvular gradient is low, left ventricular hypertrophy regresses over the

ensuing months. If the patient had a previous significant degree of aortic regurgitation, left ventricular end-diastolic pressure and volume decrease immediately along with a decrease in wall stress; however, regression of left ventricular hypertrophy and dilatation is gradual. Postoperatively, adequate preload is important to fill the dilated left ventricle. Inotropic or intra-aortic balloon pump may be required early postoperatively until left ventricular function improves.

## 5. Variables in the study

The main variables used in the study are presented in Table 3., along with its continuous (CON) or categorical (CAT) condition and its definition. They are classified into preoperative variables, preoperative rhythm, coronary disease, anatomical and morphometric, valve outcomes, primary outcomes, length of stay and discharge rhythm.

*Table 3. Main variables in the study*

| VARIABLES | TYPE | DEFINITION |
|---|---|---|
| | | |
| **PREOPERATIVE** | | |
| **Age (y)** | CON | Age in years |
| **Gender (%male)** | CAT | Gender (male/female) |
| **EuroSCORE** | CON | Additive score for EuroSCORE scale |
| **logEuroSCORE** | CON | Logistic score for EuroSCORE scale |
| **Chronic Pulmonary Disease** | CAT | Long term use of bronchodilators or steroids for lung disease |
| **Extracardiac Arteropathy** | CAT | Any of or more of the following: claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the abdominal aorta, limb arteries or carotids. |
| **Neurological dysfunction** | CAT | Neurologic dysfunction severely affecting ambulation or day-to-day functioning |
| **Previous Cardiac Surgery** | CAT | Cardiac surgery in the past requiring opening of the pericardium |
| **Preoperative Renal Failure** | CAT | Preoperative creatinine level >2.2 mg/d L and/or preoperative hemodyalisis |
| **Active Endocarditis** | CAT | Patient still under antibiotic treatment for endocarditis at the time of surgery |
| **Preoperative Critical Status** | CAT | Any one or more of the following: ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anaesthetic room, preoperative inotropic support, intraaortic balloon counterpulsation, or preoperative acute renal failure (anuria or |

| | | |
|---|---|---|
| | | oliguria <10 mL/h) |
| **Unstable angor** | CAT | Rest angina requiring nitrates until arrival in the anaesthetic room |
| **EF 30/50 %** | CAT | Moderate left ventricle dysfunction (30-50%) as measured by echocardiography |
| **EF < 30%** | CAT | Severe left ventricle dysfunction (<30%) as measured by echocardiography |
| **Recent MI** | CAT | Myocardial infarction within 90 days of surgery |
| **Severe Pulmonary Hypertension** | CAT | Systolic pulmonary artery pressure >60 mmHg |
| **Emergency** | CAT | Suregery carried out on referral before the beggining of the next working day |
| **Other than CABG** | CAT | Major cardiac procedure other than or in addition to coronary artery bypass graft surgery |
| **Surgery on Thoracic Aorta** | CAT | Surgery for disorder of the ascending, arch or descending aorta. |
| **Post MI VSD** | CAT | Post infarction ventricular septal defect. |
| **Significant Mitral Reguritation** | CAT | Moderate or severe mitral valve regurgitation (grades III or IV) as measured by echocardiography |
| **NYHA III/IV** | CAT | New York Heart Association functional class grades III or IV |
| **CHF** | CAT | Clinical or radiologic signs of left heart failure (ortopnea, pulmonary edema, etc) |
| **Calcified Aorta** | CAT | Severe calcification of the ascending, arch or descending aorta identified by preoperative image studies. |
| **Diabetes mellitus** | CAT | Diabetes mellitus under pharmacologic or insulin control |
| | | |
| **RHYTHM (PREOP)** | | Preoperative cardiac rhythm on electrocardiography |
| **sinus rhythm** | CAT | sinus rhythm |
| **AF rhythm** | CAT | atrial fibrillation or flutter rhythms |
| **PCM rhythm** | CAT | pacemaker rhythm |
| | | |
| **CORONARY DISEASE** | | Presence of ischemic coronary disease identified by haemodinamic studies |
| **PTCA** | CAT | Previous preoperative precutaneous transluminal coronary angioplasty |

| | | |
|---|---|---|
| **CABG** | CAT | One or more coronary artery bypass grafts in addition to aortic valve replacement |
| **No vessels** | CON | Number of diseased coronary vessels |
| **No grafts** | CON | Number of coronary artery bypass grafts performed |
| | | |
| **ANATOMICAL & MORPHOMETRIC** | | |
| **Weight (kg)** | CON | Wheight in kilograms |
| **Height (cm)** | CON | Height in centimeters |
| **BSA** | CON | Body Surface Area in m2 |
| **BMI** | CON | Body Mass Index in kg/m2 |
| **Valve area** | CON | Aortic valve area by planimetry on ultrasound studies (cm2) |
| **Mean grad** | CON | Mean transaortic valve gradient on ultrasound studies (mmHg) |
| **Peak grad** | CON | Peak transaortic valve gradient on ultrasound studies (mmHg) |
| **Peak vel** | CON | Peak transaortic blood jet flow velocity (m/s) |
| | | |
| **VALVE OUTCOMES** | | |
| **Success implant rate** | CAT | Rate of successful aortic valve implant |
| **Valve implant size (mm)** | CON | Prosthetic implant diameter in mm |
| **Biological valve (%)** | CAT | Biological protsthetic implant |
| | | |
| **PRIMARY OUTCOMES** | | |
| **30-d mortality (%)** | CAT | Perioperative mortality at 30 days after surgery |
| **MACCE** | CAT | Major Adverse Cardio or Cerebrovascular Event. Composite event of perioperative mortality (30-days mortality) or major cardiovascular or neurological complications |
| **Mortality (cause)** | | Causes of perioperative mortality |
| **cardiac** | CAT | Cardiac-related death (myocardial infarction, malignant arrhythmia, sudden death, etc) |
| **neurological** | CAT | Neurological-related death (stroke, coma, vegetative status, etc) |
| **infective** | CAT | Death related to a non-cardiac infective process (septic shock, etc) |
| **endocarditis** | CAT | Death related to an early prosthetic valve |

| | | |
|---|---|---|
| | | endocarditis |
| **respiratory** | CAT | Respiratory-related death (distress, pneumonia, etc) |
| **renal** | CAT | Death related to a postoperative renal failure |
| **multiorganic** | CAT | Death related to a multiorganic failure |
| **unknown** | CAT | Unknown cause of death |
| **Perioperative morbidity (all)** | | Major postoperative complications |
| **Reintervention** | CAT | Major bleeding or pericardial tamponade that requires reintervention in the early postoperative period |
| **Cardiovascular** | CAT | Major cardiovascular complication excluding rhythm complication (myocardial infarction, aortic or vascular injury, etc) |
| **Respiratory** | CAT | Major respiratory complication (respiratory insufficiency, distress, pneumonia, etc) |
| **Wound** | CAT | Major wound complication (wound infection, sternal dehiscence, mediastinitis, etc) |
| **Renal** | CAT | Major renal complication (acute postoperative renal failure, need for postoperative haemofiltration or dyalisis, etc) |
| **Neurological** | CAT | Major neurological complication (postoperative stroke, coma, transient ischemic attack, etc) |
| **Infective** | CAT | Major infective complication (septic shock, etc) |
| **Other** | CAT | Other major complications (implant-related, etc) |
| | | |
| **LENGTH OF STAY** | | |
| **ICU LOS (days)** | CON | Intensive Care Unit length of stay in days |
| **Hospital LOS (days)** | CON | Hospital length of stay in days |
| | | |
| **RHYTHM (DISCHARGE)** | | Postoperative rhythm in the last ECG prior to discharge |
| **sinus rhythm** | CAT | sinus rhythm |
| **AF rhythm** | CAT | atrial fibrillation |
| **PCM rhythm** | CAT | pacemaker rhythm at discharge (includes pre and postoperative PCM rhythms) |

# 6. Statistical analysis

Statistical software package SPSS® v17.0 for Windows® (SPSS Inc, MN, USA) was used for the data analysis throughout the whole study, considering a level of significance of $p<0.05$. The details for the group configuration and the data obtained are presented as follows:

a) GROUP CONFIGURATION

Results are presented as 'Overall' when referred to the whole population of the study. Grouping of the data concerns the 'TAVI (Transcatheter Aortic Valve Implant)' group and the control 'AVR (conventional Aortic Valve Replacement)' group as separate and independent groups, according to the selected approach for the surgical procedure in each case. Direct statistical comparison between groups is foreseen.

Subgroup analysis is planned in the design of the present study and it considers the following subgroups:

- A so-called 'High-Risk conventional Aortic Valve Replacement (HR-AVR)' group is obtained by means of statistical propensity score matching (described later in the present chapter) and used for direct comparison against the TAVI group. Univariate and multivariate analysis as well as a survival study between TAVI and HR-AVR is also anticipated in this design.

- Preoperative risk profile is measured by the preoperative variable 'Logistic EuroSCORE' and it is used to divide groups with patients scoring 15% or over against those scoring under 15% for direct statistical comparison of the outcome variables '30-days mortality' and 'MACCE'.

- Surgical approach site: transfemoral (TF) or transapical (TA) are subgroups inside the TAVI group. Direct comparison between TF and TA for the previously described study variables is performed. On the other hand, surgical approach site considering median sternotomy (MS), transfemoral approach (TF) or transapical approach (TA) is used for subgroup testing in univariate analysis, multivariate analysis, survival analysis and heart rhythm assessment between TAVI and HR-AVR groups.
- Year in which the procedure is performed is considered for descriptive statistics between TAVI and HR-AVR groups, as well as in multivariate Cox regression analysis for long-term survival to assess the effect of the learning curve for each procedure.

- Prostheses types used inside the TAVI group are presented for descriptive statistics only.

b) DESCRIPTIVE STATISTICS

- Continuous variables are presented as: mean + /- standard deviation or median (minimum – maximum) values. *I .e. Age (years) 71.76 +/- 8.35*. Student t statistic is used for data analysis.
- Categorical (dichotomic) variables are presented as: number of cases (percentage over total of the group). *I.e. Gender (male) 293 (62.6%).* X2 statistic or Fisher's test (when the observed number of cases is below 5) is considered for data testing.

c) PROPENSITY SCORE MATCHING

A propensity score is performed to identify and match appropriate controls inside the AVR group, by building a binary logistic regression model with the following variables: EurosSCORE, body surface area, body mass index, age, gender, chronic pulmonary disease, extracardiac arteropathy, neurological dysfunction, previous cardiac surgery, preoperative renal failure, left ventricular ejection fraction, pulmonary hypertension, mitral regurgitation, NYHA class, preoperative congestive heart failure, calcified aorta, diabetes and presence of concomitant coronary lesions.

The predicted group probability returned by the logistic regression equation, using the enter stepwise method, was saved and used to select proximity controls among the AVR group that matched every experimental case in the TAVI group, to conform the control HR-AVR group. Goodness-of-fit of the model is assessed by a Hosmer-Lemeshow's test and discrimination capacity by building a receptor-operator characteristics (ROC) curve, to contrast the probability of belonging to the TAVI group (returned by the logistic regression model) versus the real allocation to that group for each case and the resulting area under the curve.

TAVI experimental group is tested against HR-AVR control group for descriptive statistics, hospital length of stay, univariate and multivariate analysis for 30-days mortality and MACCE outcome variables, long-term survival analysis as well as for the new preoperative discrimination score build-up.

d) UNIVARIATE ANALYSIS

Univariate logistic regression analysis between TAVI and HR-AVR groups is designed in order to assess significant predictors for the primary outcome variables: 30-days mortality and MACCE. Results are obtained by binary logistic regression equation using the enter stepwise method and expressed as regression coefficient

(B), level of significance for the regression coefficient and predicted odds ratio with 95% confidence interval for each variable subjected to study.

e) MULTIVARIATE ANALYSIS

Multivariate logistic regression analysis between TAVI and HR-AVR groups is performed to identify significant and independent predictors for 30-days mortality and MACCE. A previously level of significance of $p<0.2$ in the univariate analysis is required to enter the model. Results are obtained by binary logistic regression equation using the enter stepwise method and expressed as regression coefficient (B), level of significance for the regression coefficient and predicted odds ratio with 95% confidence interval for each variable subjected to study.

f) SURVIVAL ANALYSIS

Kaplan-Meier survival method and log-rank testing are set to find statistical differences in long-term survival between TAVI and HR-AVR groups. A 1-year after surgery survival analysis is foreseen as an intermediate endpoint. Long-term survival data was retrospectively collected from the ABUCASIS valencian health system database.

On the other hand, planned subgroup analysis considers long-term survival according to surgical approach site: median sternotomy (MS), transfemoral approach (TF) or transapical approach (TA).

This study seeks to ascertain the influence of a learning curve effect among the different surgical approaches on survival. Multivariate Cox regression analysis is designed considering the approach site (MS, TF, TA), the year in which the procedure is performed and the survival status. Results are presented as regression coefficient

(B), level of significance for the regression coefficient and predicted odds ratio with 95% confidence interval.

g) HEART RHYTHM ASSESSMENT

Direct crosstabulation between preoperative and postoperative heart rhythms is planned for TAVI and HR-AVR groups, and X2 of Fisher's tests (if any observation is n < 5) are performed in order to find relevant differences before and after surgery for both groups. Subgroup analysis considers approach site (MS, TF or TA) and direct crosstabulation and X2 or Fisher's tests among them for preoperative and postoperative rhythms.

h) ´REPLACEMENT OR TRANS-CATHETER IMPLANT ODDS' SCORE

The results of the multivariate logistic regression analysis between TAVI and HR-AVR groups are used in the construction of the new score. The non-decimal part of the regression coefficients (B) for each variable are considered as the scoring point and the arithmetic sum of them if the total score for every patient.

Discrimination capacity of the new score is tested in the case-control study (TAVI and HR-AVR) by means of a Receptor-Operator Characteristics (ROC) curve and compared with additive and logistic EuroSCORE scores. The results are presented as Area Under the Curve (AUC) and its 95% confidence interval.

After scoring calculation, patients are conventionally classified into ´Low Profile´ score (between 0 and 2 points) and 'High Profile' score (3 or more points). These two categories (Low Profile, High Profile) are used as a categorical variable and combined with the categorical procedure variable (TAVI or conventional AVR) to construct the Classification and Regression Tree for the case-control study (TAVI vs. HR-AVR) in

order to assess perioperative mortality for every different arm of the tree: Low Profile-TAVI, Low Profile-HR-AVR, High Profile-TAVI, High Profile-HR-AVR.

Internal validation and discrimination capacity of the new score is tested again in the Overall database and afterwards in two subgroups: logistic EuroSCORE < 15 and logistic EuroSCORE > 15. ROC curves and CRT trees are constructed for every one of them and results presented in the same fashion as previously described.

External validation of the new score is intended by modelizing a 'dummy' database with similar characteristics as the PARTNER cohort A trial (see introduction for details). A blank database is constructed and random allocation of dependent variables and perioperative mortality is calculated for each case, intending to obtain identical overall rates as those presented in the PARTNER Cohort A trial for each variable. The new score is tested again in this 'dummy' database in the same fashion: ROC curves are constructed for the new score and logistic EuroSCORE and the AUC is calculated and presented. CRT construction pretends to set discrimination capacity of the new score in the 'dummy' database for Low and High Risk Profiles, the procedure performed (TAVI or AVR) and perioperative mortality rates.

# III. RESULTS

# 1. Overall results

## *DESCRIPTIVE STATISTICS*

This retrospective study presents the data collected between April 2007 and January 2012, and includes a total of 468 patients that received AVR surgery in a single institution (Consorcio Hospital General Universitario, Valencia, Spain). The main demographic, morphometric and echocardiocraphic ultrasound characteristics are presented on Table 1.

*Table 1. Preoperative characteristics*

| | Overall | TAVI | AVR | |
|---|---|---|---|---|
| **n** | 468 | 53 | 415 | |
| **Age (y)** | 71.76+/-8.35 | 80.42+/4.84 | 70.65+/-8.05 | p<0.001 |
| **Gender (%male)** | 293 (62.6%) | 26 (49.1%) | 267 (64.3%) | p<0.05 |
| **Weight (kg)** | 74.42+/-12.66 | 71.65+/-16.51 | 74.68+/-12.06 | ns |
| **Height (cm)** | 160.13+/-9.69 | 155.72+/-15.06 | 160.70+/-8.76 | p<0.05 |
| **BSA (m2)** | 1.81+/-0.17 | 1.74+/-0.17 | 1.82+/-0.17 | ns |
| **BMI (kg/m2)** | 28.93+/-4.67 | 28.19+/-4.46 | 29.02+/-4.69 | ns |
| **Coronary lesions** | 176 (37.6%) | 23 (43.4%) | 153 (36.9%) | ns |
| **No vessels** | 0.72+/-1.08 | 1.74+/-1.18 | 1.95+/-0.84 | ns |
| **PTCA** | 13 (2.8%) | 11 (20.8%) | 2 (0.5%) | ns |
| **CABG** | 142 (30.3%) | 0 | 142 (34.2%) | - |
| **No grafts** | 0.63+/-1.14 | 0 | 1.93+/-1.21 | - |
| **Valve area (cm2)** | 0.68+/-0.19 | 0.61+/-0.13 | 0.72+/-0.21 | ns |
| **Mean Grad (mmHg)** | 52.38+/-16.14 | 52.25+/-16.50 | 53.04+/-14.24 | ns |
| **Peak Grad (mmHg)** | 83.85+/-26.25 | 84.41+/-27.65 | 83.74+/-26.05 | ns |
| **Peak Vel (m/s)** | 4.41+/-0.82 | 4.44+/-0.72 | 4.41+/-0.86 | ns |

*BSA: Body surface area. BMI: body mass index. No. vessels: number of diseased coronary vessels PTCA: percutaneous transluminal coronary angioplasty. CABG: coronary artery bypass graft. No grafts: number of grafts. Mean grad: mean transvalvular gradient. Peak grad: peak transvalvular gradient. Peak vel: peak jet flow velocity.*

- PATIENT CHARACTERISTICS AND DEMOGRAPHICS

Mean age was 80.42+/-4.84 in the TAVI group and 70 +/-8.05 years in AVR ($p<0.001$). Gender distribution was 49.1% and 64.3% male, respectively. ($p<0.05$). Morphometric features were analyzed by weight (71.65+/-16.51 vs. 74.68+/-12.06 Kg, ns.), height (155.72+/-15.06 vs. 160.70+/-8.76 cm, $p<0.05$) and their derivate body surface area (BSA 1.74+/-0.17 vs. 1.82+/-0.17 m2, ns.) and body mass index (BMI 28.19+/-4.46 vs. 29.02+/-4.69 Kg/m2, ns.) (Table 1. Fig. 1,2).

*Fig.1. Age distribution by groups*

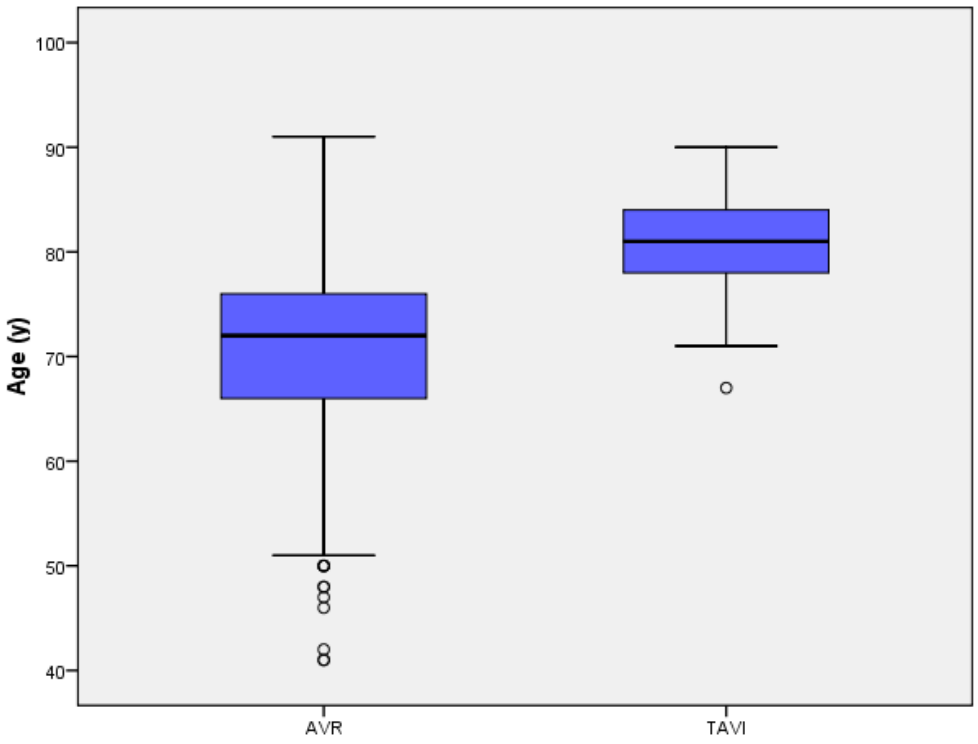
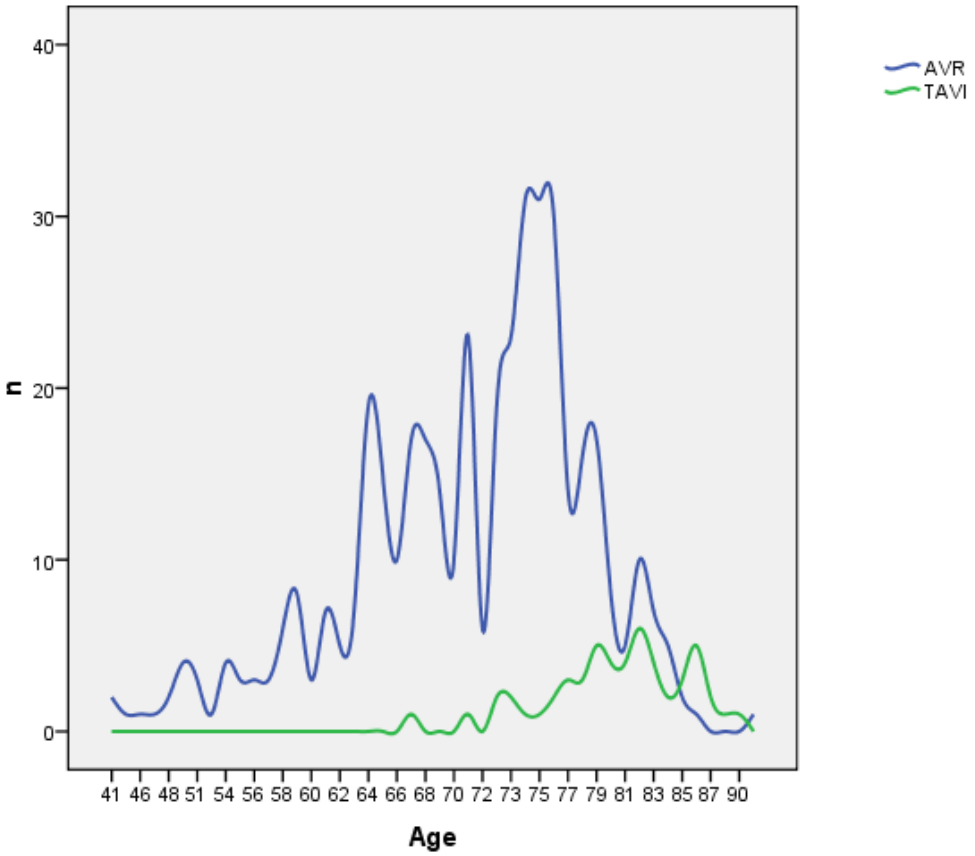


*Fig.2 Age distribution by groups and age.*




- PROCEDURES

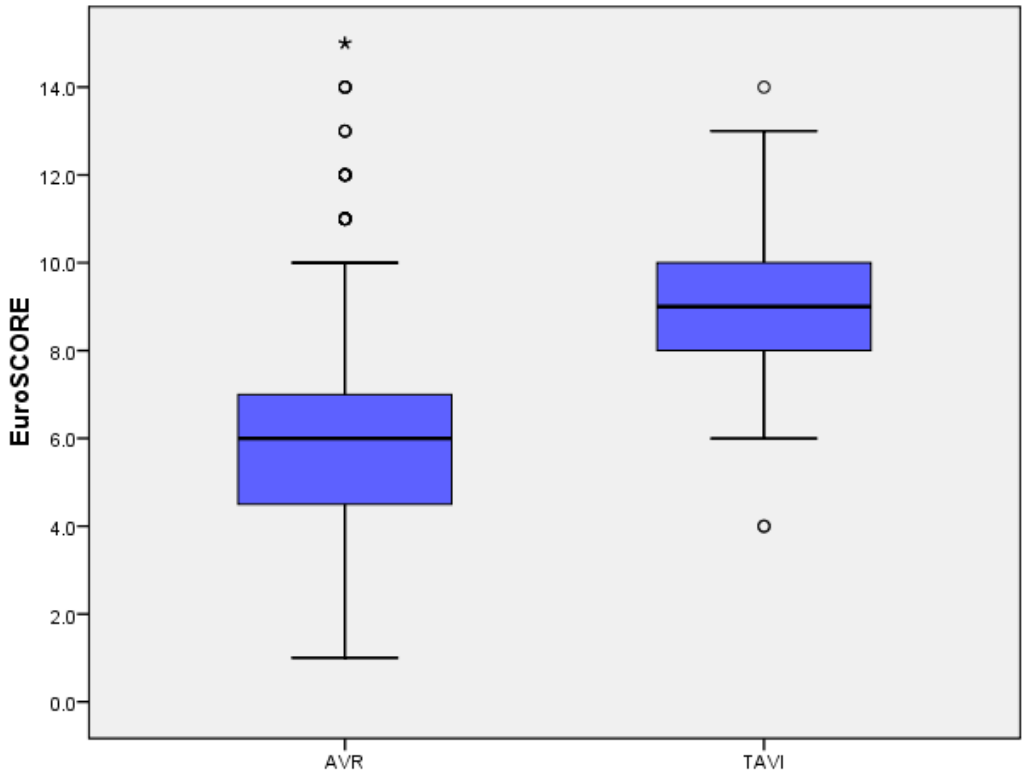
A total of 313 isolated AVR procedures and 155 'mixed' or 'aortic plus coronary' procedures were recorded, as long as they presented with both aortic valve and ischemic coronary disease. Previous surgically or percutaneously revascularized patients were considered as an isolated AVR in a REDO setting. (methods), including 11 (20.8%) previous or concomitant PTCA with the TAVI procedure and 142 (34.2%) concomitant CABG + AVR (Table 1).

21 patients (4.48%) presented in a REDO setting (previous cardiac surgery) regardless their preceding ethiology: 8 (15.1%) in the TAVI group and 13 (3.1%) in the AVR group (Table 2).

- ETHIOLOGIES

All patients (100%) underwent surgery under the diagnosis of severe aortic stenosis (with or without significant aortic regurgitation) of degenerative ethiology (aortic calcific disease) Rheumatic valves, pure aortic regurgitation and surgery of the aortic root were excluded from the analysis by echocardiographic ultrasound studies. The main variables analyzed were aortic valve area by planimetry (0.68+/-0.19 cm2), mean transaortic valve gradient (52.38+/-16.14 mmHg), peak transaortic valve gradient (83.85+/-26.25 mmHg) and peak transaortic blood jet flow velocity (4.41+/-0.82 m/s) (Table 1).

*Fig. 3. Additive EuroSCORE by groups.*



- PREOPERATIVE SURGICAL RISK

Global median additive EuroSCORE was 6 (1-15) and mean logistic 8.90+/-8.57. By groups: 9 (4-14) vs. 6 (1-15), p<0.001; and 16.53+/-10.08 vs. 7.92+/-7.85, p<0.001 in the TAVI and AVR group respectively (Table 2, Fig. 3,4,5).

*Table 2. Preoperative surgical risk and clinical features.*

| | Overall | TAVI | AVR | |
|---|---|---|---|---|
| **n** | 468 | 53 | 415 | |
| **EuroSCORE** | 6 (1-15) | 9 (4-14) | 6 (1-15) | p<0.001 |
| **logEuroSCORE** | 8.90+/-8.57 | 16.53+/-10.08 | 7.92+/-7.85 | p<0.001 |
| **Chronic Pulmonary Disease** | 110 (23.5%) | 21 (39.6%) | 89 (21.4%) | p<0.01 |
| **Extracardiac Arteropathy** | 78 (16.7%) | 9 (17.0%) | 69 (16.6%) | ns |
| **Neurological dysfunction** | 26 (5.6%) | 7 (13.2%) | 19 (4.6%) | p<0.05 |
| **Previous Cardiac Surgery** | 21 (4.5%) | 8 (15.1%) | 13 (3.1%) | p<0.001 |
| **Preoperative Renal Failure** | 20 (4.3%) | 4 (7.5%) | 16 (3.9%) | ns |
| **Active Endocarditis** | 0 | 0 | 0 | - |
| **Preoperative Critical Status** | 11 (2.4%) | 0 | 11 (2.7%) | ns |
| **Unstable angor** | 32 (6.8%) | 3 (5.7%) | 29 (7.0%) | ns |
| **EF 30/50 %** | 85 (18.2%) | 8 (15.1%) | 77 (18.6%) | ns |
| **EF < 30%** | 24 %5.1%) | 5 (9.4%) | 19 (4.6%) | ns |
| **Recent MI** | 8 (1.7%) | 0 | 8 (1.9%) | ns |
| **Severe Pulmonary** | 39 (8.3%) | 11 (20.8%) | 28 (0.7%) | p<0.01 |

| | | | | |
|---|---|---|---|---|
| **Hypertension** | | | | |
| **Emergency** | 78 (16.7%) | 8 (15.1%) | 70 (16.9%) | ns |
| **Other than CABG** | 468 (100%) | 53 (100%) | 415 (100%) | ns |
| **Surgery on Thoracic Aorta** | 0 | 0 | 0 | - |
| **Post MI VSD** | 0 | 0 | 0 | - |
| **Severe Mitral** | | 5 (9.4%) | 21 (5.1%) | ns |
| **Regurgitation** | | | | |
| **NYHA III/IV** | 380 (81.2%) | 48 (90.6%) | 332 (80%) | ns |
| **CHF** | 30 (6.4%) | 5 (9.4%) | 25 (6.0%) | ns |
| **Calcified Aorta** | 45 (9.6%) | 10 (18.9%) | 35 (8.4%) | p<0.05 |
| **Diabetes mellitus** | 153 (32.7%) | 20 (37.7%) | 133 (32.0%) | ns |
| **Rhythm (Preop)** | | | | |
| **sinus** | 410 (87.6) | 31 (58.5%) | 379 (91.3%) | |
| **AF** | 52 (11.1%) | 35 (8.4%) | 17 (32.1%) | |
| **PCM** | 6 (1.3%) | 1 (0.2%) | 5 (9.4%) | p<0.01 |

*EF: ejection fraction (left ventricle). MI: myocardial infarction. CABG: coronary artery bypass graft. VSD: ventricular septal defect. NYHA: New York Heart Association functional class. CHF: congestive heart failure. Rhythm (preop): Preoperative heart rhythm. Sinus: sinus rhythm. AF. Atrial fibrillation. PCM: pacemaker rhythm.*

- CLINICAL PREOPERATIVE FEATURES

Statistically significant differences were found between TAVI and AVR groups for the following clinical preoperative variables: chronic pulmonary disease (39.6% vs. 21.4%), neurological dysfunction (13.2% vs. 4.6%), previous cardiac surgery (15.1% vs. 3.1%), pulmonary hypertension (20.8% vs. 0.7%) calcified aorta (18.9% vs 8.4%) and preoperative sinus rhythm (58.5% vs. 91.3%).

*Fig 4. Additive EuroSCORE distribution*

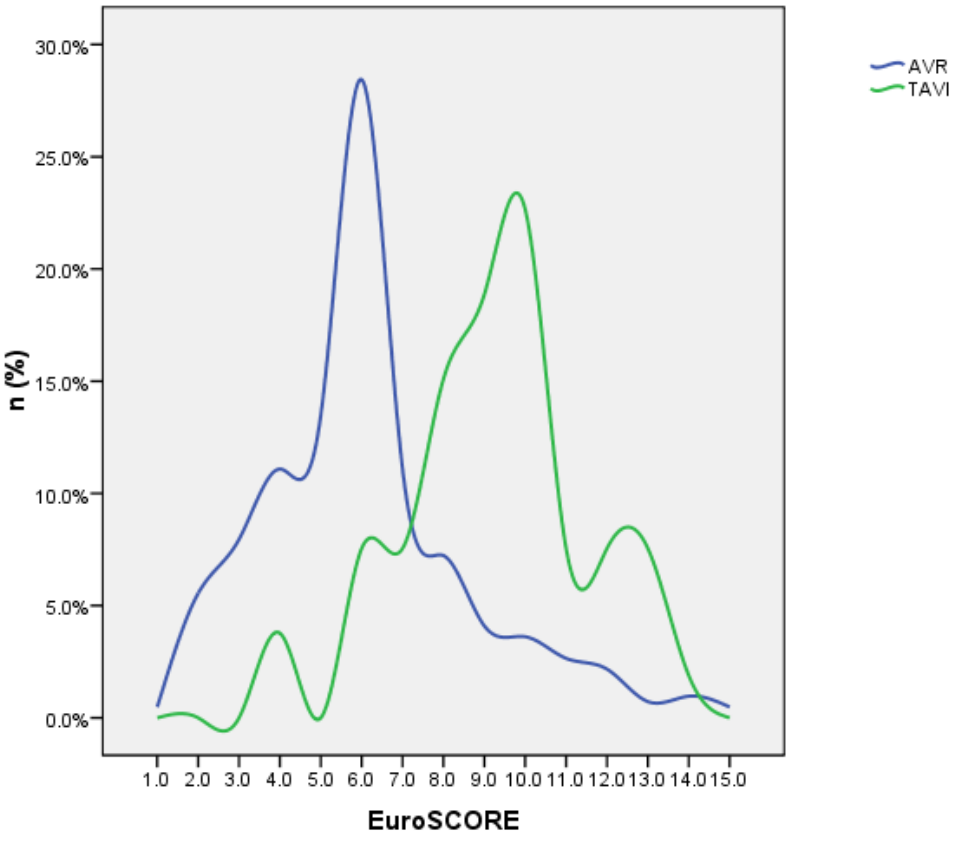
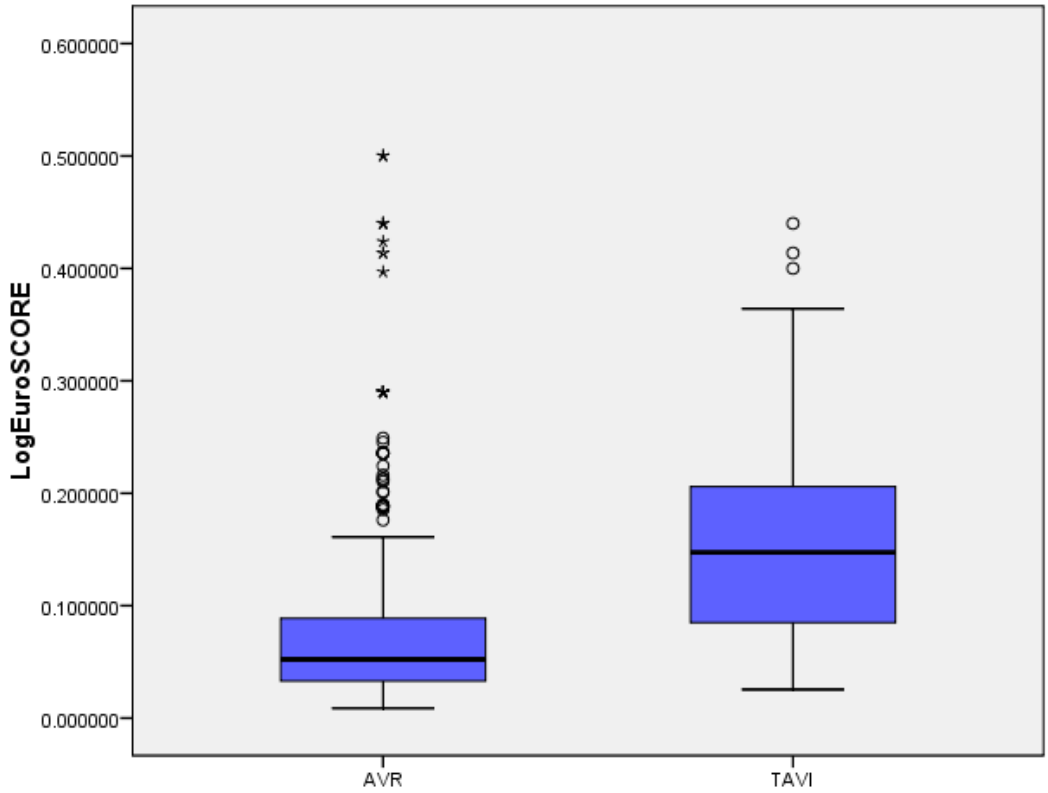


*Fig. 5. Logistic EuroSCORE by groups.*




Extracardiac arteropathy, preoperative renal failure, preoperative critical status, unstable angor, left ventricular ejection fraction, recent myocardial infarction, emergency, mitral regurgitation, NYHA class III/IV, congestive heart failure or diabetes rates differences were non-significant between groups (Table 2, Fig. 6).

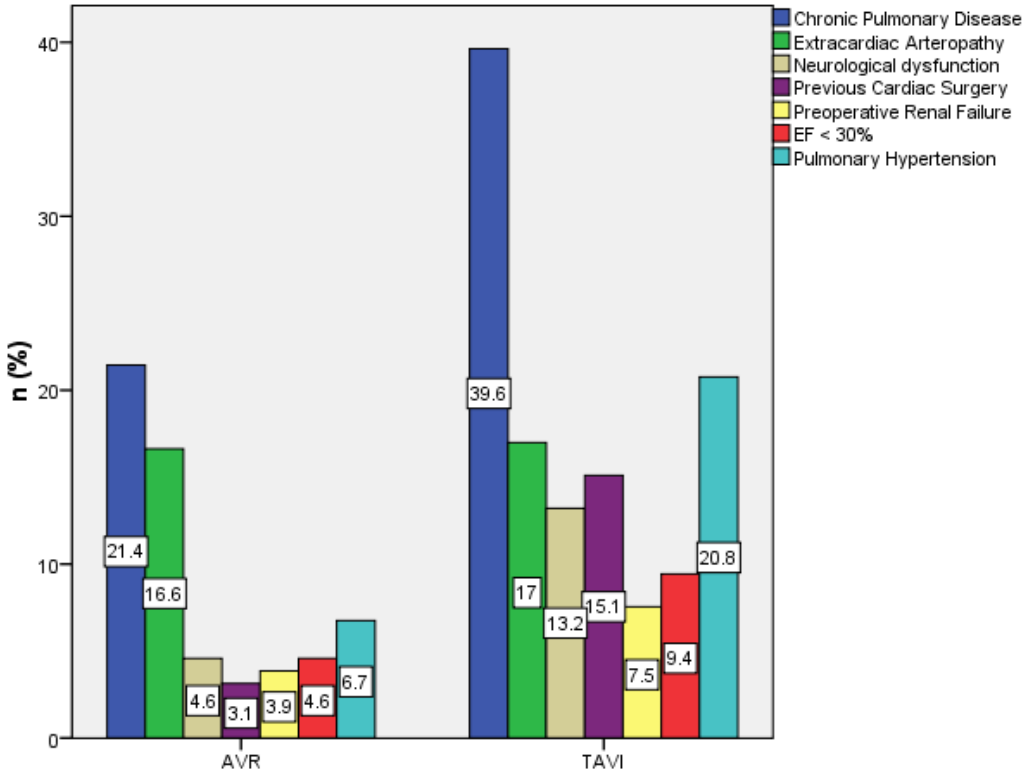
## *OUTCOMES*

- PERIOPERATIVE MORTALITY

30-days operative mortality differences were non-signficant. 4 patients (7.5%) in the TAVI group: 1 cardiac (myocardial infarction), 2 neurological (postoperative stroke) and 1 multiorganic-related; vs. 25 (6.0%) in the control (AVR) group: 7 cardiac, 2 neurological, 4 infective, 1 endocarditis, 3 respiratory, 2 renal, 2

multiorganic-related and 4 of unknown ethiology. Overall mortality of the series was 29/468 (6.2%) (Table 3, Fig. 7).

*Fig 6. Preoperative features by group*




- POSTOPERATIVE COMPLICATIONS

45.3% (24 cases) presented a major postoperative complication in the experimental (TAVI group, vs. 34.5% (143) in AVR. Overall morbidity by any cause was 35.7% (167 cases).

*Table 3. Operative results. Postoperative morbidity and mortality*

| | Overall | TAVI | AVR | |
|---|---|---|---|---|
| **n** | 468 | 53 | 415 | |
| **Biological valve (%)** | 357 (71.2%) | 53 (100%) | 304 (73,3%) | ns |
| **30-d mortality (%)** | 29 (6.2%) | 4 (7.5%) | 25 (6.0%) | ns |
| **log EuroSCORE < 15** | 20 (5.0%) | 1 (3.6%) | 19 (5.1%) | ns |
| **Log EuroSCORE > 15** | 9 (12.7%) | 3 (12.0%) | 6 (13.0%) | ns |
| **Mortality (cause)*** | | | | |
| **cardiac** | 8 (1.71%) | 1 (1.9%) | 7 (1.7%) | |
| **neurological** | 4 (0.85%) | 2 (3.8%) | 2 (0.5%) | |
| **infective** | 4 (0.85%) | 0 | 4 (1.0%) | |
| **endocarditis** | 1 (0.21%) | 0 | 1 (0.2%) | |
| **respiratory** | 3 (0.64%) | 0 | 3 (0.7%) | |
| **renal** | 2 (0.43%) | 0 | 2 (0.5%) | |
| **multiorganic** | 2 (0.43%) | 1 (1.9%) | 2 (0.5%) | |
| **Unknown** | 4 (0.85%) | 0 | 4 (1.0%) | |
| **Perioperative morbidity (all)*** | 167 (35.7%) | 24 (45.3%) | 143 (34.5%) | ns |
| **Reintervention** | 33 (7.1%) | 3 (5.7%) | 30 (5.2%) | ns |
| **Cardiovascular** | 6 (1.3%) | 4 (7.5%) | 2 (0.2%) | p<0.01 |
| **Respiratory** | 35 (7.5%) | 3 (5.7%) | 32 (7.7%) | ns |
| **Wound** | 7 (1.5%) | 3 (5.7%) | 4 (1.0%) | p<0.05 |
| **Renal** | 32 (6.8%) | 4 (7.5%) | 28 (6.7%) | ns |
| **Neurological** | 15 (3.2%) | 5 (9.4%) | 10 (2.4%) | p<0.05 |
| **Infective** | 19 (4.1%) | 0 | 19 (4.6%) | ns |
| **Other** | 22 (4.71%) | 4 (7.5%) | 18 (4.34%) | ns |
| **MACCE** | 41 (8.8%) | 9 (17.0%) | 32 (7.7%) | p<0.05 |
| **Rhythm (discharge)** | | | | |
| **sinus** | 391 (83.5%) | 34 (64.2%) | 357 (86.0%) | |

| | | | | |
|---|---|---|---|---|
| **AF** | 64 (13.7%) | 8 (15.1%) | 56 (13.5%) | |
| **PCM** | 13 (2.8%) | 11 (20.8%) | 2 (0.5%) | p<0.001 |

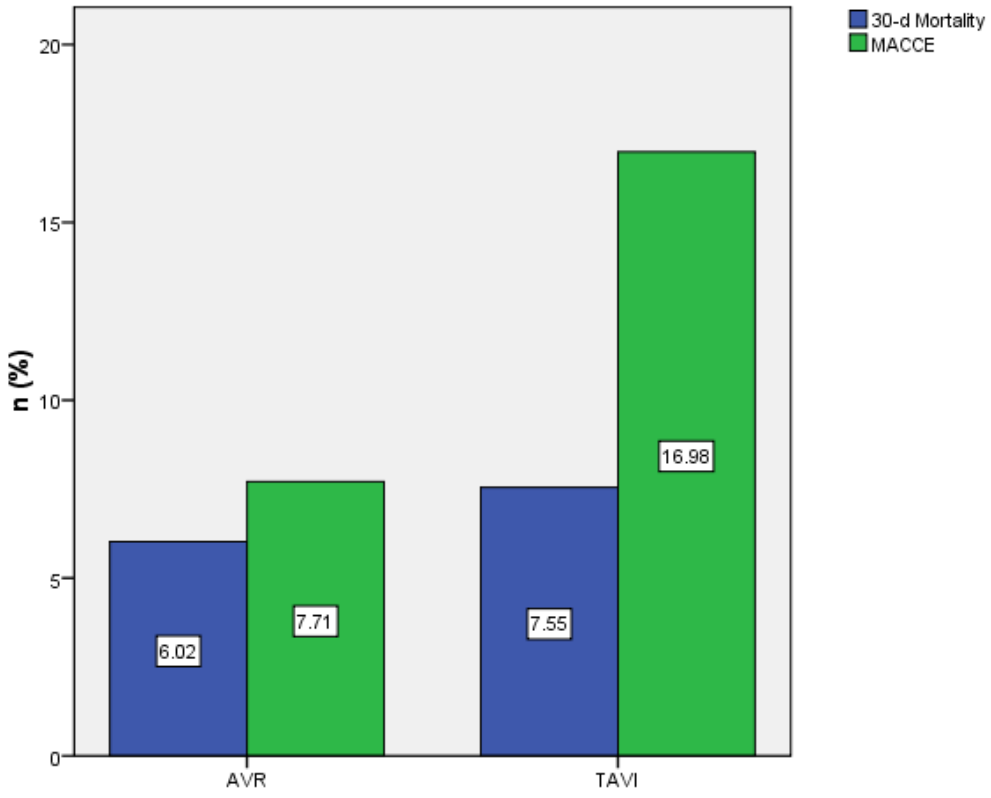
*30-d mortality: thirty-day mortality. MACCE: major adverse cardio or cerebral events. AF: atrial fibrillation. PCM: pacemaker.*

** See Annex for definitions*

Respiratory morbidity (pleural effusion, prolonged ventilation, pneumonia) represented the main and most frequent source of morbidity: 7.5% (5.7% TAVI vs. 7.7% AVR, ns.), followed by early reintervention caused by excessive postoperative bleeding or cardiac tamponade: 7.1% (5.7% vs. 5.2%, ns.). The most significant differences by morbidity source were: cardiovascular (postoperative myocardial infarction or major vascular injury) 7.5% TAVI vs. 0.2 AVR, p<0.05; wound complications (superficial or deep incision site infection) 5.7 TAVI vs. 1.0% AVR, p<0.05; and neurological events (permanent stroke or transitory ischemic attack) 9.4% TAVI vs. 2.4% AVR (Table 3, Fig.8).

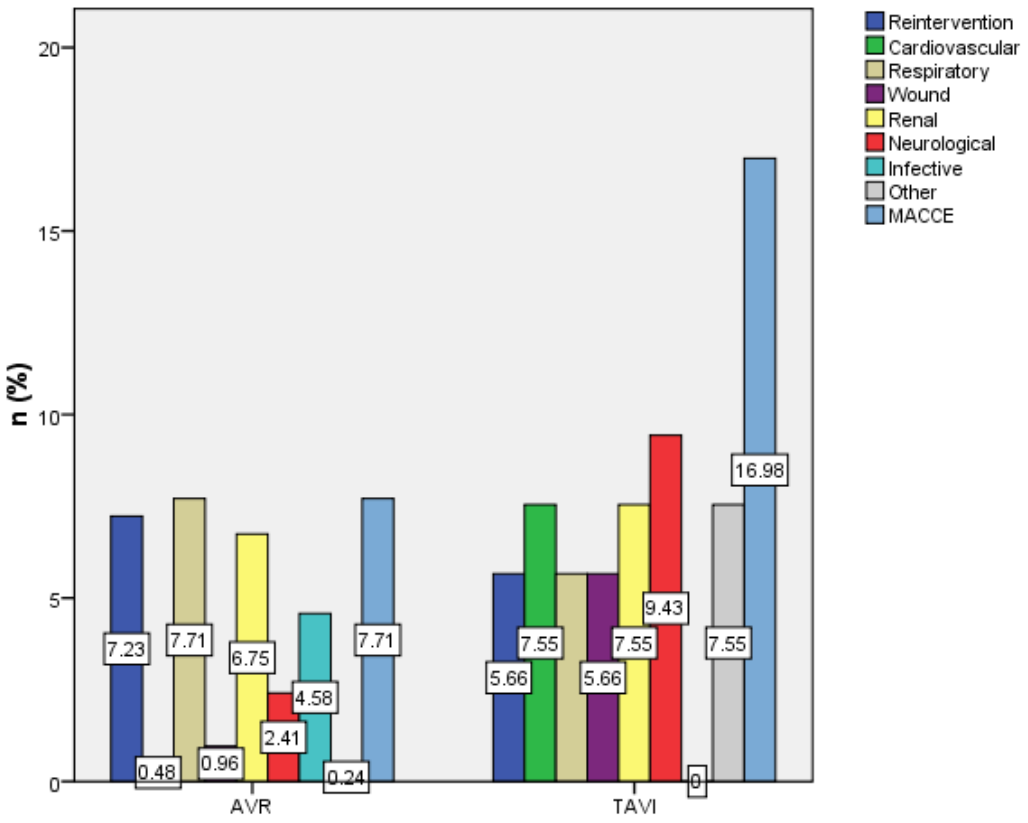
Overall MACCE rate (composite event of death, cardiovascular or neurological morbidity) was 8.8% (17.0% TAVI vs. 7.7% AVR, p<0.05) (Table 3, Fig. 7).

*Fig. 7. Perioperative mortality and MACCE rates by group.*




*30-d mortality: thirty-days mortality. MACCE: perioperative death or major adverse cardio or cerebral events. p= ns. For both 30-days mortality and MACCE analysis of TAVI vs. AVR*

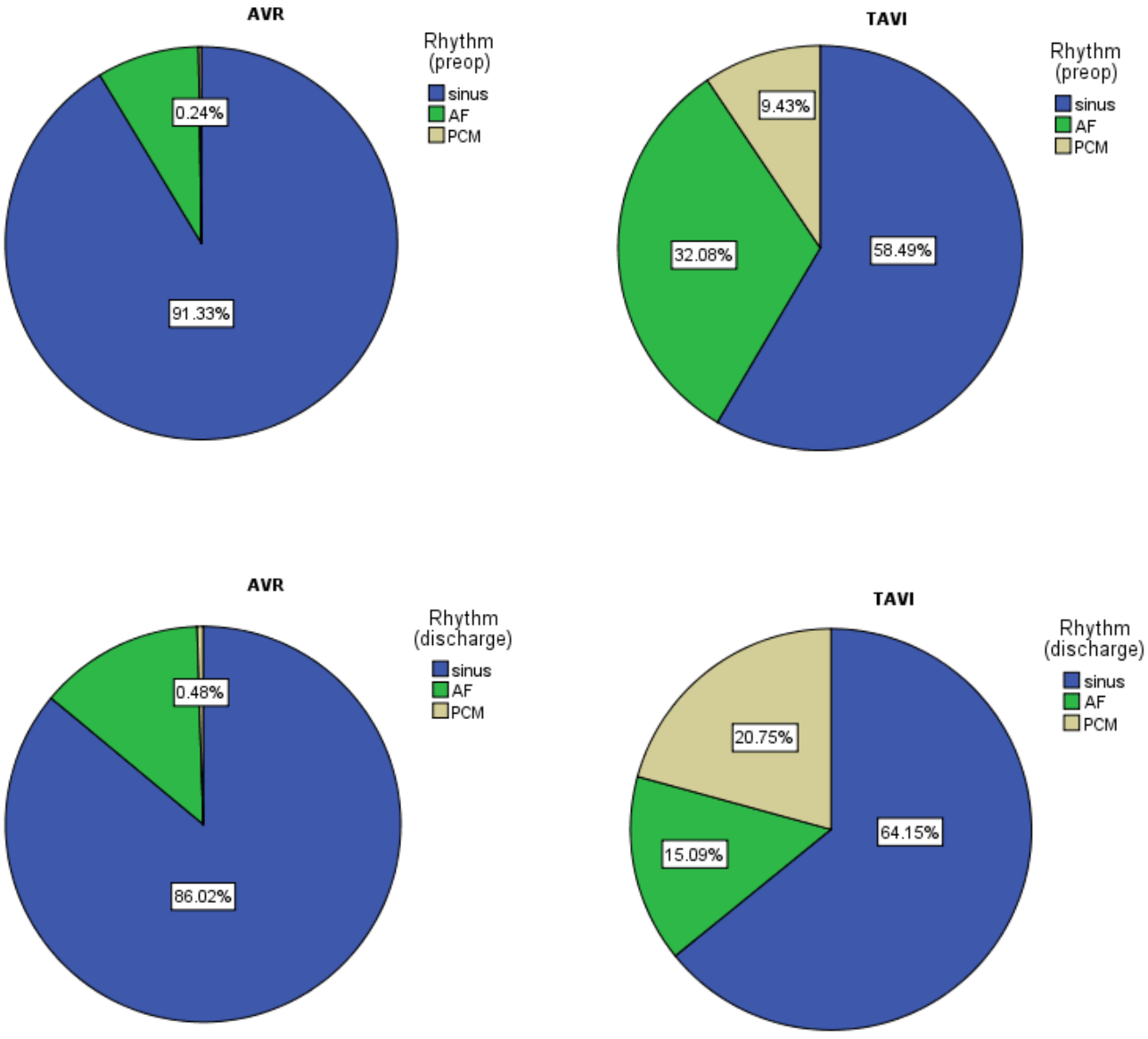
*Fig 8. Postoperative complications rate by group.*




## *HEART RHYTHM*

Statistically significant differences among the different ECG rhythms preoperatively and at the time of discharge were found. Rhythm rates found before surgery were 58.5% TAVI vs. 91.3% AVR for sinus rhythm; 32.1% vs. 8.4% for AF; 9.4% vs. 0.2% for PCM rhythm ($p<0.01$); and before discharge: 64.2% vs. 86.0%, 15.1% vs. 13.5% and 20.8% vs. 0.5%, respectively ($p<0.001$) (Fig 9).

*Fig. 9. Preoperative and postoperative rhythm rates by group*




*Rhythm (preop): Preoperative heart rhythm. Rhythm (discharge): Postoperative heart rhythm at the time of discharge. Sinus: sinus rhythm. AF: atrial fibrillation. PCM: pacemaker rhythm.*

Subgroup crosstabulation analysis for preoperative *versus* postoperative heart rhythm was performed for TAVI and AVR groups, finding significant changes in the rhythm patterns before and after surgery in the experimental group (rates of AF rhythm of 32.1% vs. 15.1% and PCM rhythm of 9.4% vs. 20.8%) The distribution of cases for preoperative and postoperative rhythm for each group are shown on Fig. 10.

*Fig. 10. Crosstabulation analysis of heart rhythm (before vs. after surgery) for each group.*

**AVR: Rhythm (preop) vs. Rhythm (discharge)[a]**

| No. patients | | Rhythm (discharge) | | | |
|---|---|---|---|---|---|
| | | sinus | AF | PCM | Total |
| Rhythm (preop) | Sinus | 328 | 49 | 2 | 379 |
| | AF | 28 | 7 | 0 | 35 |
| | PCM | 1 | 0 | 0 | 1 |
| Total | | 357 | 56 | 2 | 415 |

a. p = ns.

**TAVI: Rhythm (preop) vs. Rhythm (discharge)[a]**

| No. patients | | Rhythm (discharge) | | | Total |
|---|---|---|---|---|---|
| | | sinus | AF | PCM | |
| Rhythm (preop) | sinus | 25 | 1 | 5 | 31 |
| | AF | 5 | 7 | 5 | 17 |
| | PCM | 4 | 0 | 1 | 5 |
| Total | | 34 | 8 | 11 | 53 |

a. p< 0.01

*Rhythm (preop): Preoperative heart rhythm. Rhythm (discharge): Postoperative heart rhythm at the time of discharge. Sinus: sinus rhythm. AF: atrial fibrillation. PCM: pacemaker rhythm.*

## 2. Case-control analysis by propensity score matching

A propensity score was performed to identify appropriate controls inside the AVR group, by building a binary logistic regression model with the following variables: age, gender, body surface area, body mass index, logistic EuroSCORE, chronic pulmonary disease, extracardiac arteropathy, neurological dysfunction, previous cardiac surgery, preoperative renal failure, left ventricular ejection fraction, severe pulmonary hypertension, severe mitral regurgitation, NYHA class, preoperative congestive heart failure, calcified aorta, diabetes and presence of concomitant coronary lesions. The predicted group probability returned by the logistic regression equation, using the enter stepwise method, was saved and used to select 67 controls among the AVR group to conform the so-called HR-AVR group (High-Risk Aortic Valve Replacement group), and match them with the 53 cases in the TAVI group. Goodness-of-fit was assessed by a non-significant Hosmer-Lemeshow's test. Discrimination capacity of the model was evaluated by a receptor-operator characteristics curve, contrasting the probability of belonging to the TAVI group returned by the logistic regression model versus the real allocation to that group in each case; and resulted in an area under the curve of 0.925 (95% CI 0.893 – 0.957) (Fig.11).

Distribution of cases and the selected controls according to the year when surgery was performed is shown on Fig.12.

### *DESCRIPTIVE STATISTICS*

- PREOPERATIVE CHARACTERISTICS

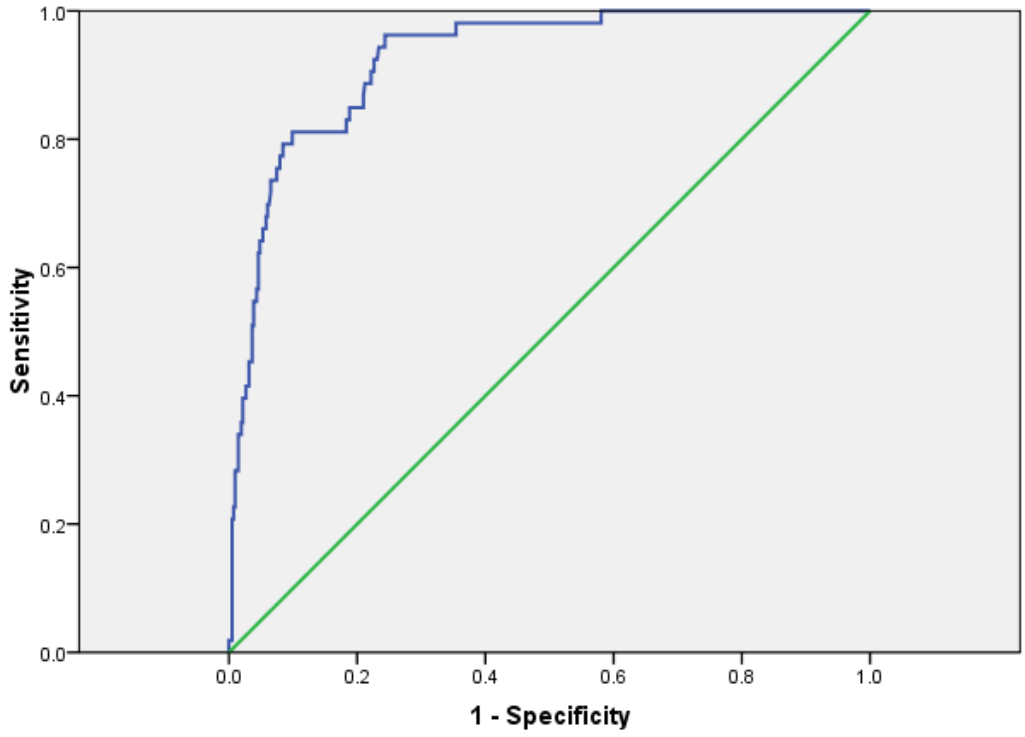
No differences in terms of isolated valve replacement or combined valve plus coronary procedures (43.4% TAVI vs. 46.3% HR-AVR) were found. Neither concerning demographic (80.42+/-4.84 vs. 79.13+/-4.22 years; 49.1% vs. 56.7% male) or echocardiographic features (0.61+/-0.13 vs. 0.64+/-0.17 cm2 valve area, 52.25+/-

16.50 vs. 54.02+/-16.23 mmHg mean transaortic gradient, 4.44+/-0.72 vs. 4.23+/-0.74 m/s peak jet flow velocity. (Table 4). Age distribution is shown on Fig. 13.

- RISK PROFILE

Both case (TAVI) and control (HR-AVR) groups were statistically comparable in terms of preoperative risk profile: Additive EuroSCORE 9 (4-14) vs. 8 (3-15) and Logistic EuroSCORE 16.53+/-10.08 vs. 14.82+/-11.73 (Fig.14); as well as regarding the main clinical preoperative variables: chronic pulmonary disease 39.6% vs. 35.8%, extracardiac arteropathy 17.0% vs. 16.4%, neurological dysfunction 13.2% vs. 9.0%, previous cardiac surgery 15.1% vs. 10.4%, preoperative renal failure 7.5% vs. 6.9% , severe ventricular function impairment (<30%) 9.4% vs. 9.0%, recent myocardial infarction 0% vs. 3.0%, pulmonary hypertension 20.8% vs. 11.9%, Emergency 15.1% vs. 22.4%, NYHA class III or IV 90.6% vs. 92.5% , congestive left heart failure 9.4% vs. 6.0% calcified aorta 18.9% vs. 19.4% or diabetes 37.7% vs. 35.8% (Fig 15).

*Fig.11. Receptor-operator characteristics curve.*



**Area Under the Curve**

| | 95% Confidence Interval | |
|---|---|---|
| Area | Lower Bound | Upper Bound |
| .925 | .893 | .957 |

*Fig.12. Distribution of cases (TAVI) and selected controls (HR-AVR) by year.*

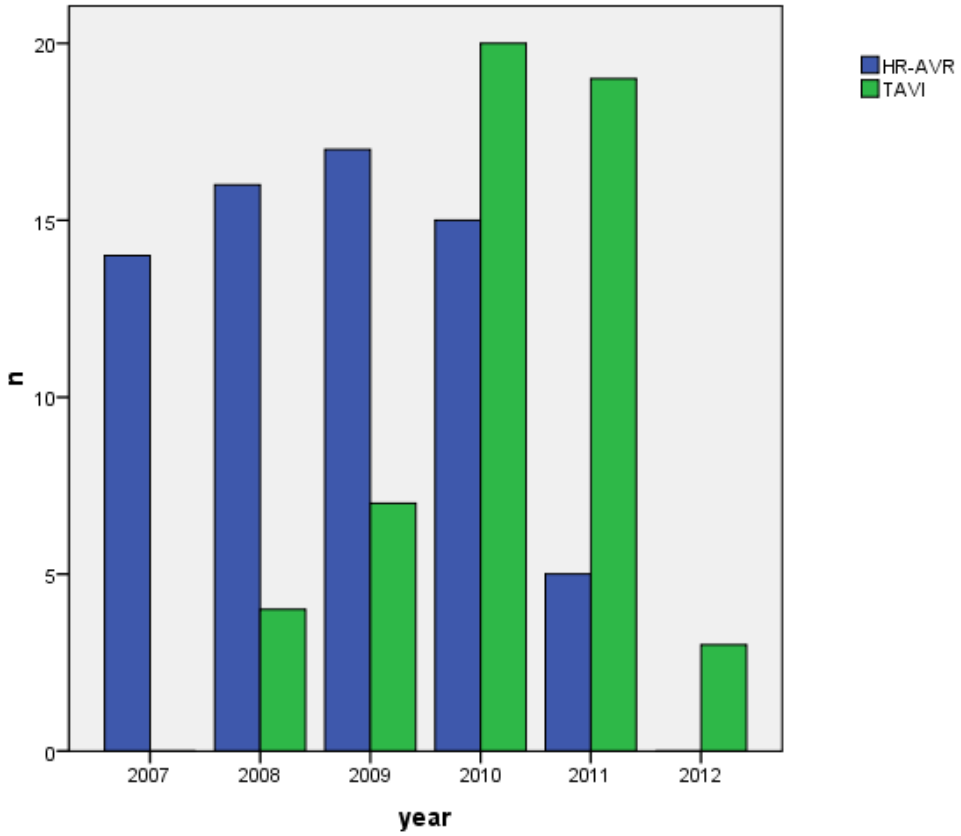
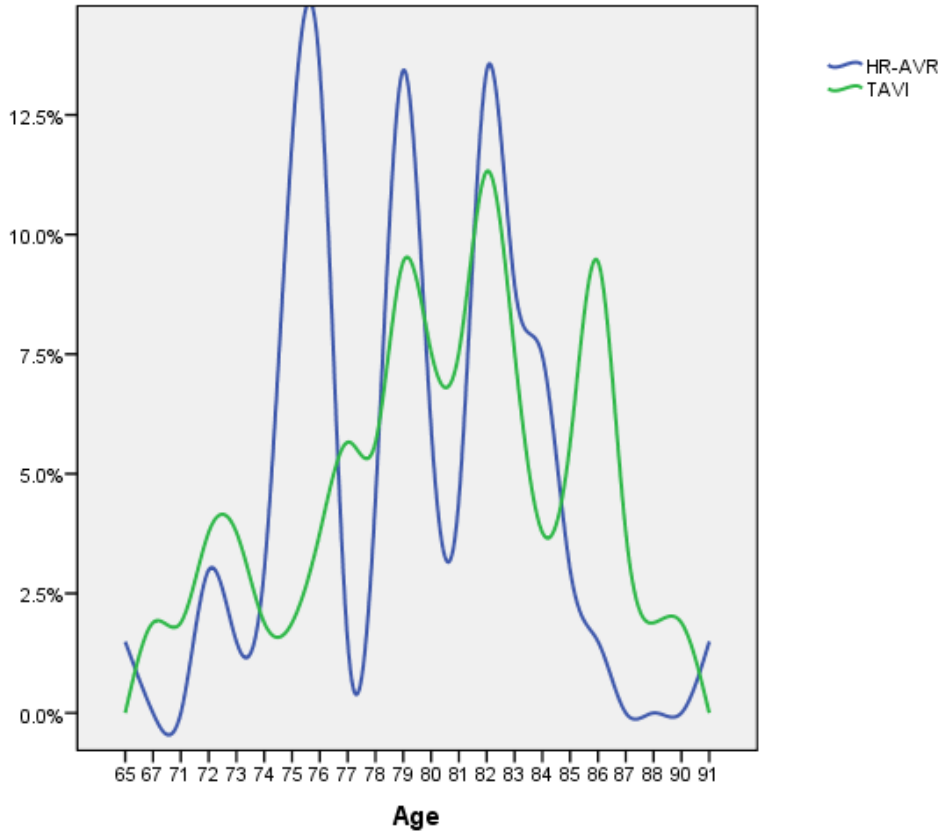


*Table 4. Main preoperative charcteristics*

| | TAVI | HR-AVR | |
|---|---|---|---|
| **N** | 53 | 67 | |
| **Age (y)** | 80.42+/4.84 | 79.13+/-4.22 | ns |
| **Gender (%male)** | 26 (49.1%) | 38 (56.7%) | ns |
| **Weight (kg)** | 71.65+/-16.51 | 71.18+/-11.45 | ns |
| **Height (cm)** | 155.72+/-15.06 | 157.15+/-8.81 | ns |
| **BSA (m2)** | 1.74+/-0.17 | 1.76+/-0.17 | ns |
| **BMI (kg/m2)** | 28.19+/-4.46 | 28.77+/-4.69 | ns |
| **Coronary lesions** | 23 (43.4%) | 31 (46.3%) | ns |
| **No vessels** | 1.74+/-1.18 | 2.03+/-0.79 | ns |
| **PTCA** | 11 (20.8%) | 0 | ns |
| **CABG** | 0 | 27 (40.3%) | ns |
| **No grafts** | 0 | 1.81+/-1.11 | ns |
| **Valve area (cm2)** | 0.61+/-0.13 | 0.64+/-0.17 | ns |
| **Mean Grad (mmHg)** | 52.25+/-16.50 | 54.02+/-16.23 | ns |
| **Peak Grad (mmHg)** | 84.41+/-27.65 | 81.43+/-27.80 | ns |
| **Peak Vel (m/s)** | 4.44+/-0.72 | 4.23+/-0.74 | ns |

*BSA: Body surface area. BMI: body mass index. No. Vessels: numer of diseased coronary vessels. PTCA: percutaneous transluminal coronary angioplasty. CABG: coronary artery bypass graft. No grafts: number of grafts. Mean grad: mean transvalvular gradient. Peak grad: peak transvalvular gradient. Peak vel: peak jet flow velocity.*

*Fig,13, Age distribution by year and age for TAVI and HR-AVR groups.*




However, different rates of preoperative ECG rhythms were found: 58.5% sinus, 32.1% AF and 9.4% PCM rhythm for TAVI vs. 83.6%, 14,9% and 1.5% for HR-AVR, respectively (Table 5.).

*Table 5. Preoperative risk profile and clinical variables.*

| | TAVI | HR-AVR | |
|---|---|---|---|
| **n** | 53 | 67 | |
| **EuroSCORE** | 9 (4-14) | 8 (3-15) | ns |
| **logEuroSCORE** | 16.53+/-10.08 | 14.82+/-11.73 | ns |
| | | | |
| **Chronic Pulmonary Disease** | 21 (39.6%) | 24 (35.8%) | ns |
| **Extracardiac Arteropathy** | 9 (17.0%) | 11 (16.4%) | ns |

| | | | |
|---|---|---|---|
| **Neurological dysfunction** | 7 (13.2%) | 6 (9.0%) | ns |
| **Previous Cardiac Surgery** | 8 (15.1%) | 7 (10.4%) | ns |
| **Preoperative Renal Failure** | 4 (7.5%) | 4 (6.9%) | ns |
| | | | |
| **Active Endocarditis** | 0 | 0 | ns |
| **Preoperative Critical Status** | 0 | 3 (4.5%) | ns |
| | | | |
| **Unstable angor** | 3 (5.7%) | 6 (9.0%) | ns |
| **EF 30/50 %** | 8 (15.1%) | 12 (17.9%) | ns |
| **EF < 30%** | 5 (9.4%) | 6 (9.0%) | ns |
| **Recent MI** | 0 | 2 (3.0%) | ns |
| **Severe Pulmonary Hypertension** | 11 (20.8%) | 8 (11.9%) | ns |
| **Emergency** | 8 (15.1%) | 11 (22.4%) | ns |
| **Other than CABG** | 53 (100%) | 67 (100%) | ns |
| **Surgery on Thoracic Aorta** | 0 | 0 | ns |
| | | | |
| **Post MI VSD** | 0 | 0 | ns |
| **Severe Mitral Regurgitation** | 5 (9.4%) | 5 (7.5%) | ns |
| | | | |
| **NYHA III/IV** | 48 (90.6%) | 62 (92.5%) | ns |
| **CHF** | 5 (9.4%) | 4 (6.0%) | ns |
| **Calcified Aorta** | 10 (18.9%) | 13 (19.4%) | ns |
| **Diabetes** | 20 (37.7%) | 24 (35.8%) | ns |
| **Rhythm (Preop)** | | | |
| **sinus** | 31 (58.5%) | 56 (83.6%) | |
| **AF** | 17 (32.1%) | 10 (14.9%) | |
| **PCM** | 5 (9.4%) | 1 (1.5%) | p<0.05 |

*EF: ejection fraction (left ventricle). MI: myocardial infarction. CABG: coronary artery bypass graft. VSD: ventricular septal defect. NYHA: New York Heart Association functional class. Rhythm (preop): Preoperative heart rhythm. Sinus: sinus rhythm. AF. Atrial fibrillation. PCM: pacemaker rhythm.*

*Fig. 14. Logistic Euroscore by groups (TAVI and HR-AVR)*

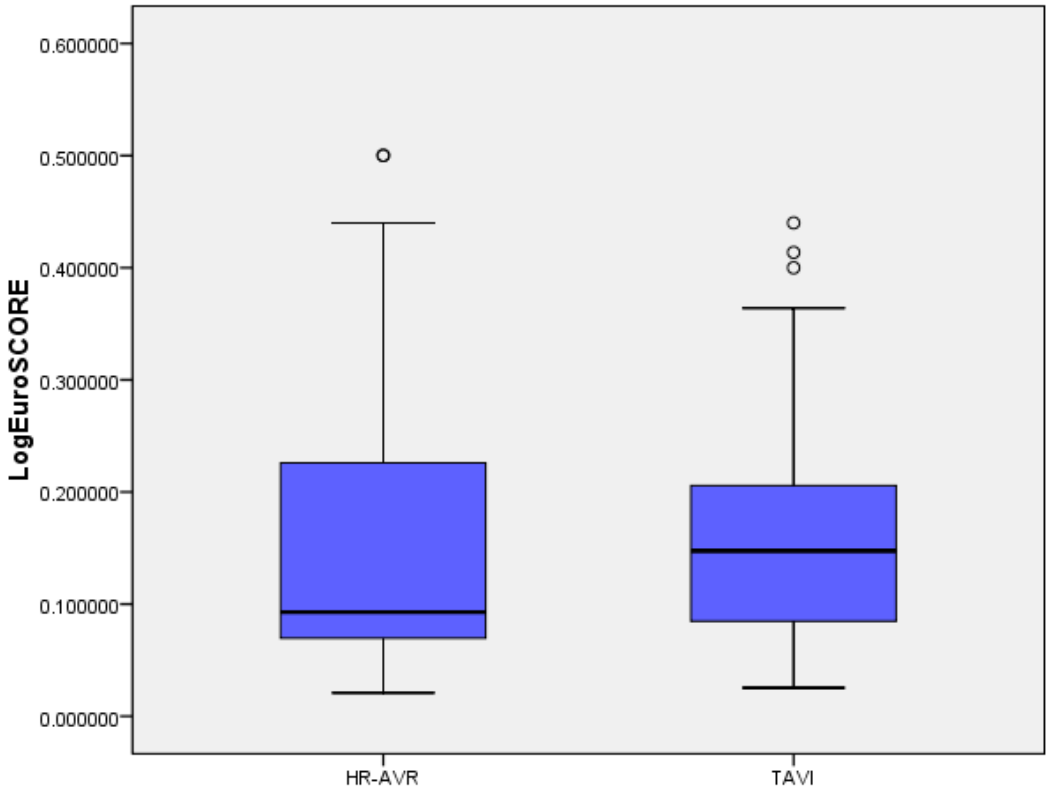
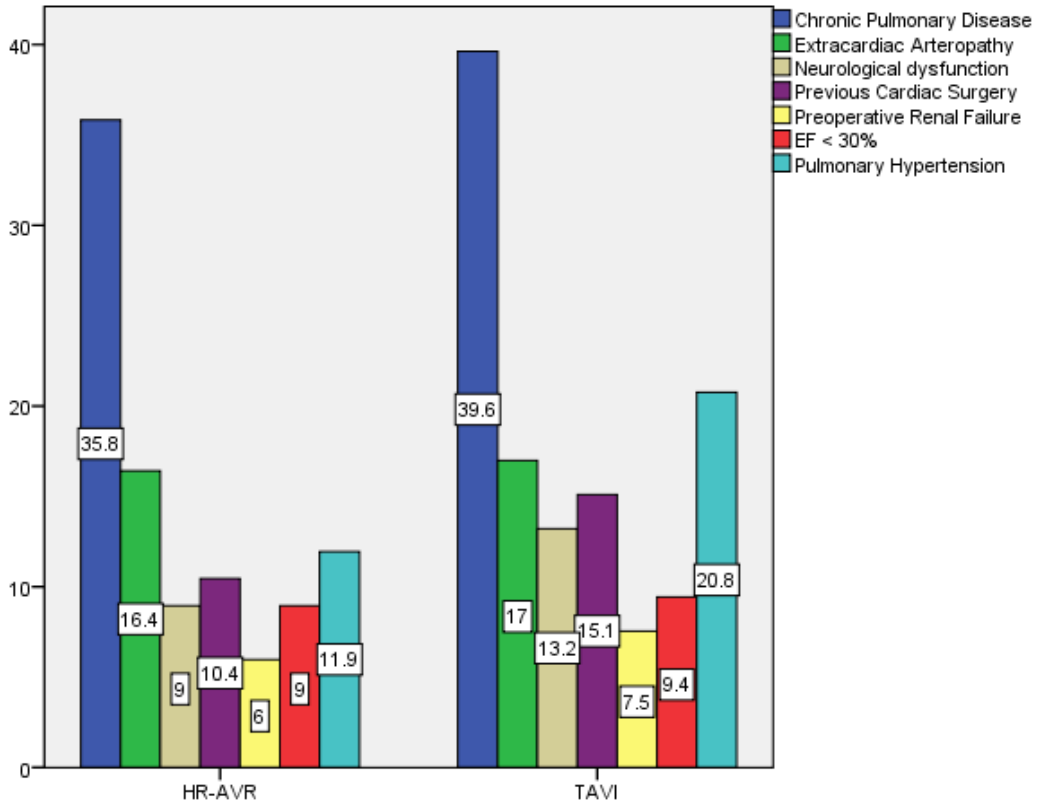


*Fig. 15. Main preoperative variables by group.*




## *OUTCOMES*

- OPERATIVE OUTCOMES

Operative outcomes resulted in different median prosthetic implant diameters 26 (23-29) for TAVI and 21 (18-25) for HR-AVR ($p<0.01$). 30-days mortality (7.5% vs. 4.5%, ns) and global perioperative morbidity (45.3% vs. 32.8%, ns) were comparable (Table 6). Nevertheless, a significant level was reached for cardiovascular (7.5% TAVI vs. 0% HR-AVR) and neurological (9.4% vs. 0%) major postoperative complications. The differences in the composite event MACCE (perioperative mortality or major adverse cardiac or cerebral events) were also found to be relevant: 17.0% TAVI vs. 4.5% HR-AVR Table 6, Figs. 16-17).

*Table 6. Operative outcomes.*

| | TAVI | HR-AVR | |
|---|---|---|---|
| **n** | 53 | 67 | |
| **Biological valve (%)** | 53 (100%) | 63 (94.0%) | ns |
| **30-d mortality (%)** | 4 (7.5%) | 3 (4.5%) | ns |
| **LogEuroSCORE < 15** | 1 (3.6%) | 1 (2.3%) | ns |
| **LogEuroSCORE > 15** | 3 (12.0%) | 2 (8.7%) | ns |
| | | | |
| **Mortality (cause)*** | | | |
| **cardiac** | 1 (1.9%) | 1 (1.5%) | |
| **neurological** | 2 (3.8%) | 0 | |
| **infective** | 0 | 1 (1.5%) | |
| **endocarditis** | 0 | 0 | |
| **respiratory** | 0 | 1 (1.5%) | |
| **renal** | 0 | 0 | |
| **multiorganic** | 1 (1.9%) | 0 | |
| **unknown** | 0 | 0 | |
| **Perioperative morbidity (all)*** | 24 (45.3%) | 22 (32.8%) | ns |
| | | | |
| **Reintervention** | 3 (5.7%) | 5 (7.5%) | ns |
| **Cardiovascular** | 4 (7.5%) | 0 | p<0.05 |
| **Respiratory** | 3 (5.7%) | 8 (11.9%) | ns |
| **Wound** | 3 (5.7%) | 0 | ns |
| **Renal** | 4 (7.5%) | 8 (11.9%) | ns |
| **Neurological** | 5 (9.4%) | 0 | p<0.05 |
| **Infective** | 0 | 3 (4.5%) | ns |
| **Other** | 4 (7.5%) | 0 | p<0.05 |
| **MACCE** | 9 (17.0%) | 3 (4.5%) | p<0.05 |
| **Rhythm (discharge)** | | | |
| **sinus** | 34 (64.2%) | 58 (86.6%) | |
| | | | |
| **AF** | 8 (15.1%) | 9 (13.4%) | |
| **PCM** | 11 (20.8%) | 0 | p<0.001 |

*30-d mortality: thirty-day mortality. MACCE: death or major adverse cardio or cerebral events. AF: atrial fibrillation. PCM: pacemaker.*

** See Annex for definitions*

Fig.16. 30-days mortality (p=ns) and MACCE rates (p<0.05) by group .

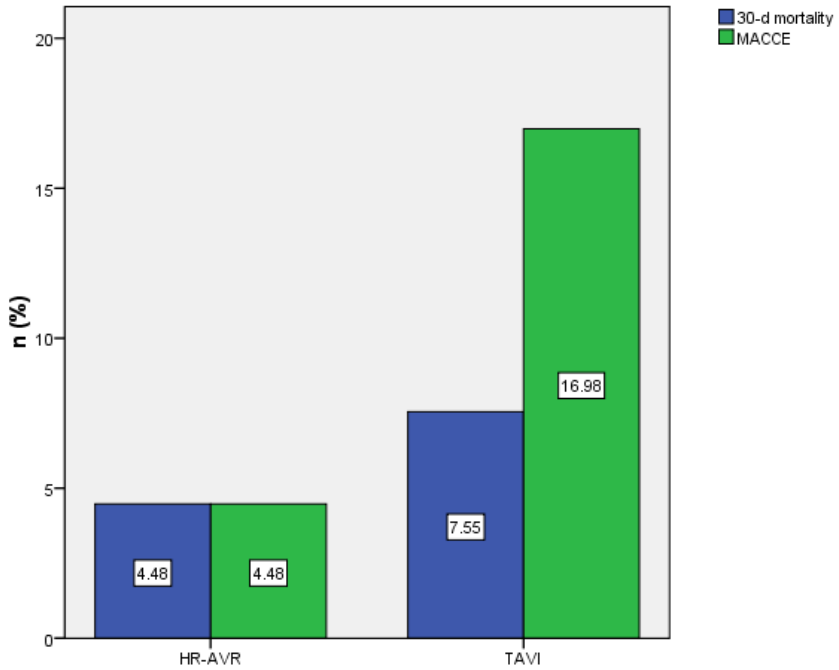



*Fig 17. Main postoperative morbidity by group.*

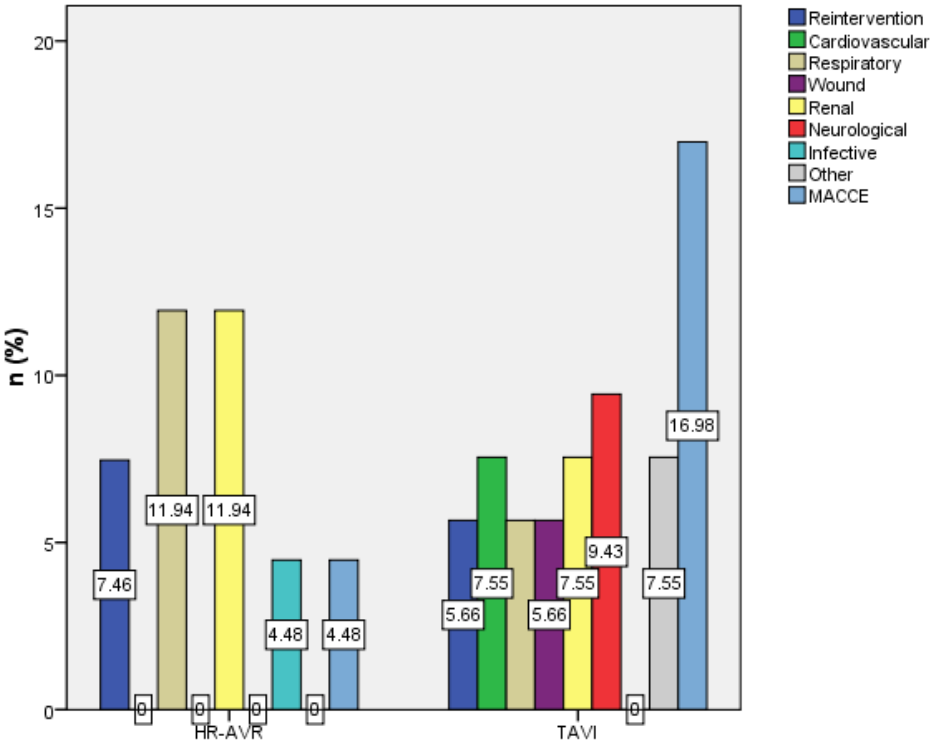
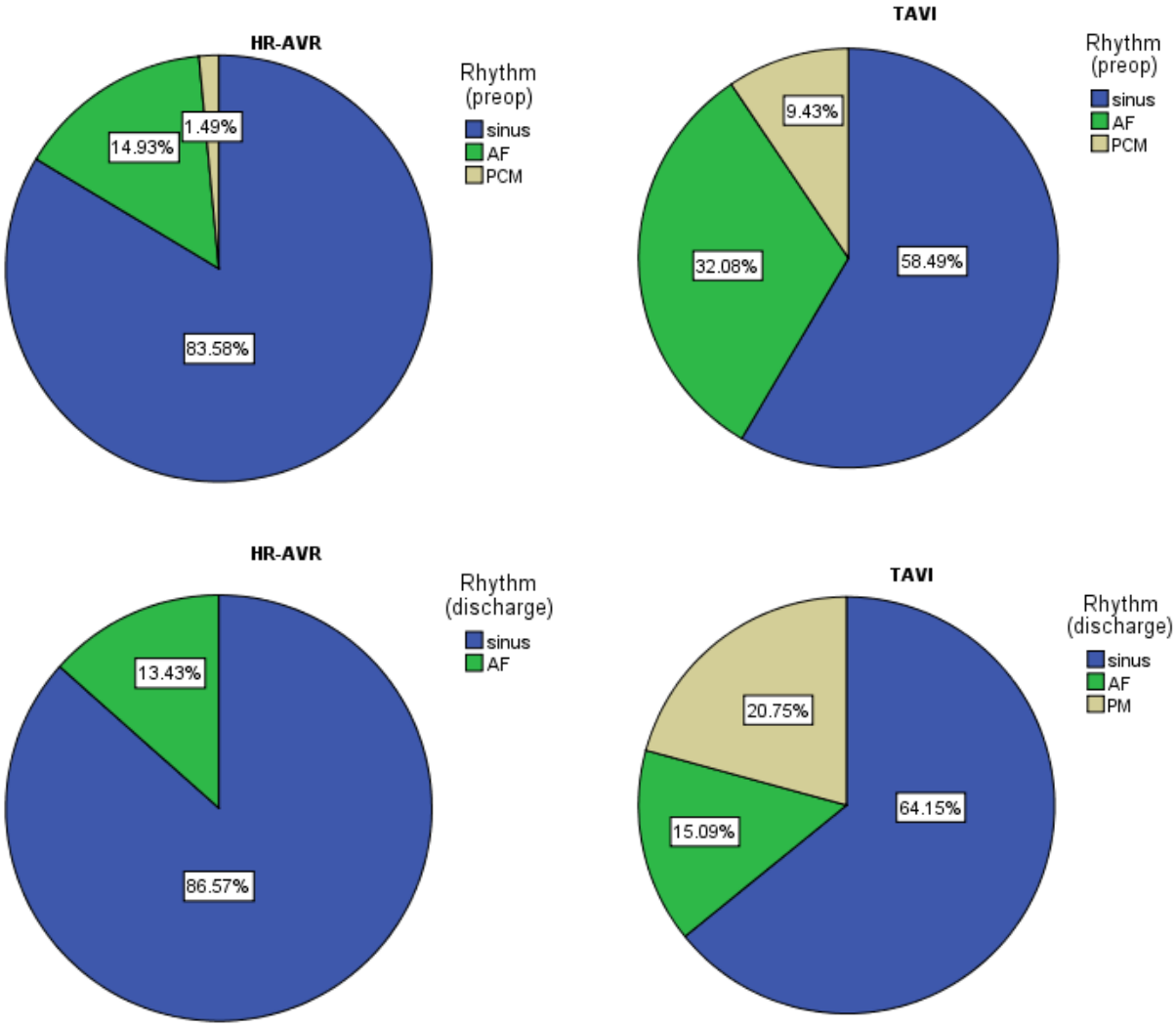


*Fig. 18. Preoperative and postoperative rhythm rates by group*




*Rhythm (preop): Preoperative heart rhythm. Rhythm (discharge): Postoperative heart rhythm at the time of discharge. Sinus: sinus rhythm. AF: atrial fibrillation. PCM: pacemaker rhythm*

## *HEART RHYTHM*

Pearson Chi-Square test returned a significant result ($p<0.001$) in the Preoperative vs. Dischargre Rhythm crosstabulation in the TAVI group. 10 new

pacemaker implants were reported (5 in previous sinus rhythm and 5 in previous AF) against 0 in the HR-AVR group. Postoperative AF was 15.09% (TAVI) vs. 13.43% (HR-AVR), although there was only 1 new AF case in the experimental group versus 8 among the HR-AVR controls; and discharge sinus rhythm rates 64.15% (34 cases) vs. 86.57% (58 cases), respectively (Fig.18-19).

*Fig. 19. Crosstabulation analysis of heart rhythm (before vs. after surgery) for each group.*

**TAVI: Rhythm (preop) vs. Rhythm (discharge)[a]**

| No. patients | | Rhythm (discharge) | | | Total |
|---|---|---|---|---|---|
| | | sinus | AF | PCM | |
| Rhythm (preop) | sinus | 25 | 1 | 5 | 31 |
| | AF | 5 | 7 | 5 | 17 |
| | PCM | 4 | 0 | 1 | 5 |
| Total | | 34 | 8 | 11 | 53 |

a. p< 0.01

**HR-AVR: Rhythm (preop) * Rhythm (discharge)[a]**

| No. patients | | Rhythm (discharge) | | Total |
|---|---|---|---|---|
| | | sinus | AF | |
| Rhythm (preop) | sinus | 48 | 8 | 56 |
| | AF | 9 | 1 | 10 |
| | PCM | 1 | 0 | 1 |
| Total | | 58 | 9 | 67 |

a. p= ns.

*Rhythm (preop): Preoperative heart rhythm. Rhythm (discharge): Postoperative heart rhythm at the time of discharge. Sinus: sinus rhythm.AF: atrial fibrillation. PCM: pacemaker rhythm.*

## *LENGTH OF STAY*

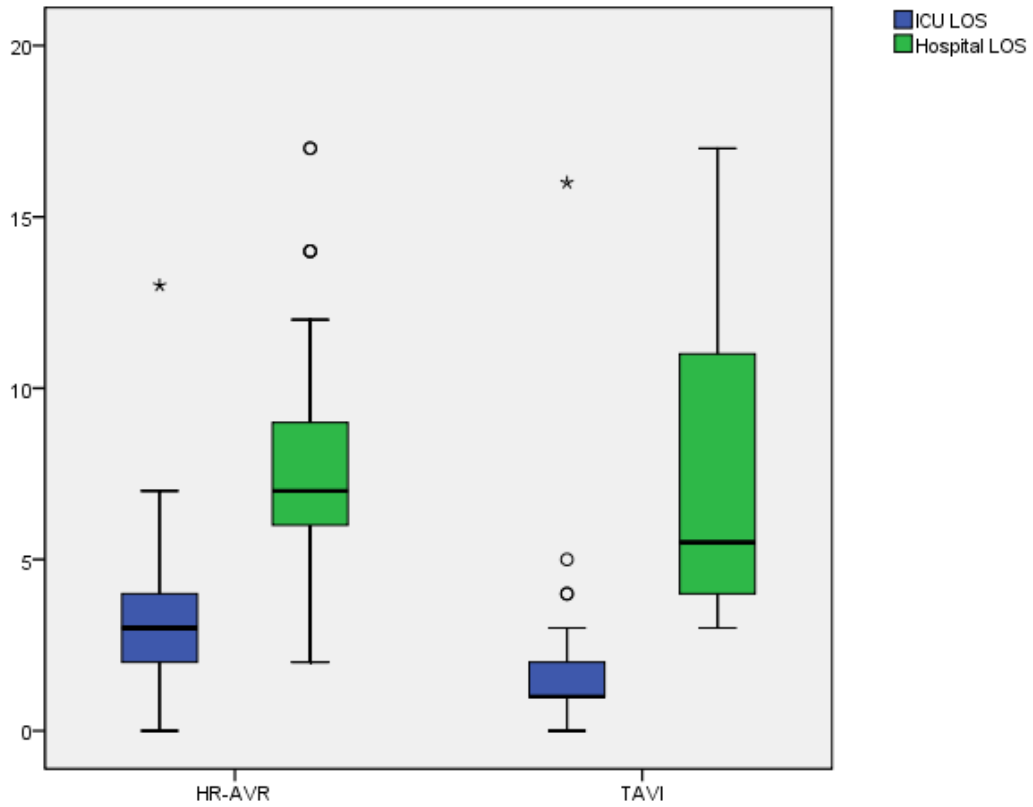
Mean intensive care unit (ICU) and Hospital length of stay (LOS) were computed concluding statistical evidence between TAVI and HR-AVR groups for ICU LOS (2.03+/-2.58 vs. 3.33+/-1.80) but not for total in hospital LOS (7.25+/-4.35 vs. 8.00+/-3.10). Table 7. Fig. 20.

*Table 7. ICU and Hospital length of stay by group.*

| | TAVI | HR-AVR | |
|---|---|---|---|
| **ICU LOS (days)** | 2.03+/-2.58 | 3.33+/-1.80 | p<0.01 |
| **EuroSCORE < 15** | 1.61+/-1.12 | 3.29+/-1.90 | p<0.001 |
| **EuroSCORE > 15** | 2.67+/-3.87 | 3.38+/-1.69 | ns |
| **Hospital LOS (days)** | 7.25+/-4.35 | 8.00+/-3.10 | Ns |
| **EuroSCORE < 15** | 5.46+/-2.81 | 7.90+/-3.19 | P<0.01 |
| **EuroSCORE > 15** | 9.94+/-4.93 | 8.24+/-2.95 | ns |

ICU LOS: Intensive care unit length of stay. Hospital LOS: Total hospital length of stay

*Fig. 20. ICU and Hospital length of stay (days) by group.*




*ICU LOS: Intensive care unit length of stay. Hospital LOS: Total hospital length of stay*

## *UNIVARIATE ANALYSIS*

Univariate logistic regression analysis to assess significant predictors of 30-days perioperative mortality and MACCE (composite event of death, cardio or cerebrovascular major adverse events) among 120 patients (53 TAVI and 67 HR-AVR) using the enter method was performed. The results are shown on Tables 8-9.

*Table 8. Univariate analysis for 30-days mortality endopoint.*

| **30-d mortality** | | | |
|---|---|---|---|
| | B | (Sig.) | OR (95% CI) |
| **TAVI procedure** | 0.555 | 0.481 | 1.741 (0.372-8.144) |
| **Surgical Approach** | | | |
| **MS** | n/a | n/a | n/a |
| **TF** | -0.026 | 0.978 | 0.974 (0.156-6.104) |
| **TA** | 1.335 | 0.271 | 3.800 (0.562-25.693) |
| **Age (y)** | 0.141 | 0.243 | 1.151 (0.953-1.390) |
| **Gender (female)** | 0.477 | 0.570 | 1.564 (0.335-7.310) |
| **Coronary disease** | 0.519 | 0.510 | 1.680 (0.359-7.854) |
| **Chronic Pulmonary Disease** | 0.237 | 0.763 | 1.268 (0.271-5.943) |
| **Extracardiac Arteropathy** | 2.090 | 0.010 | 8.083 (1.652-39.545) |
| **Neurological dysfunction** | 0.338 | 0.763 | 1.403 (0.155-12.660) |
| **Previous Cardiac Surgery** | -18.564 | 0.999 | 0 (0 - ) |
| **Preoperative Renal Failure** | 0.926 | 0.420 | 2.524 (0.266-23.968) |
| **Active Endocarditis** | n/a | n/a | n/a |
| **Preoperative Critical Status** | -18.448 | 0.999 | 0 (0 - ) |
| **Unstable angor** | -18.504 | 0.999 | 0 (0 - ) |
| **EF 30/50 %** | 1.443 | 0.074 | 4.235 (0.869-20.630) |
| **EF < 30%** | -18.524 | 0.999 | 0 (0 - ) |
| **Recent MI** | -18.439 | 0.999 | 0 (0 - ) |

| | | | |
|---|---|---|---|
| **Severe Pulmonary Hypertension** | 1.514 | 0.062 | 4.547 (0.929-22.244) |
| **Emergency** | 1.249 | 0.220 | 3.487 (0.723-16.813) |
| **Other than CABG** | n/a | n/a | n/a |
| **Surgery on Thoracic Aorta** | n/a | n/a | n/a |
| **Post MI VSD** | n/a | n/a | n/a |
| **Severe Mitral Regurgitation** | -18.514 | 0.999 | 0 (0 - ) |
| **CHF** | -18.504 | 0.999 | 0 (0 - ) |
| **Calcified Aorta** | 0.561 | 0.519 | 1.752 (0.318-9.59) |
| **Diabetes mellitus** | 0.275 | 0.727 | 1.317 (0.261-6.176) |
| **Rhythm (Preop)** | | | |
| **sinus** | n/a | n/a | n/a |

| | | | |
|---|---|---|---|
| **AF** | 0.507 | 0.571 | 1.660 (0.287-9.603) |
| **PCM** | 1.423 | 0.239 | 4.150 (0.388-44.389) |

*TAVI: Transcatheter Aortic Valve Implant group.. MS: median sternotomy approach. TF: transfemoral approach. TA: Transapical approach. EF: left ventricular ejection fraction. MI myocardial infarction. CHF. Congestive heart failure. . sinus: sinus rhythm. AF. Atrial fibrillation. PCM: pacemaker rhythm*

*Table 9. Univariate analysis for MACCE endpoint*

| **MACCE** | | | |
|---|---|---|---|
| | B | (Sig.) | OR (95% CI) |
| **TAVI procedure** | 1.473 | 0.034 | 4.364 (1.118-17.033) |
| **Surgical Approach** | | | |
| **MS** | n/a | n/a | n/a |
| **TF** | 1.181 | 0.110 | 3.257 (0.765-13.863) |
| **TA** | 1.846 | 0.038 | 6.333 (1.103-36.370) |
| **Age (y)** | 0.215 | 0.010 | 1.240 (1.052-1.460) |
| **Gender (female)** | 0.522 | 0.397 | 1.686 (0.503-5.645) |
| **Coronary disease** | -0.545 | 0.396 | 0.580 (0.165-2.042) |
| **Chronic Pulmonary Disease** | -0.202 | 0.754 | 0.817 (0.231-2.885) |

| | | | |
|---|---|---|---|
| **Extracardiac Arteropathy** | 1.056 | 0.115 | 2.875 (0.774-10.681) |
| **Neurological dysfunction** | -0.318 | 0.770 | 0.727 (0.086-6.140) |
| **Previous Cardiac Surgery** | -19.155 | 0.999 | 0 (0- ) |
| **Preoperative Renal Failure** | 0.271 | 0.808 | 1.312 (0.147-11.670) |
| **Active Endocarditis** | n/a | n/a | n/a |
| **Preoperative Critical Status** | -19.034 | 0.999 | 0 (0- ) |
| **Unstable angor** | -19.093 | 0.999 | 0 (0- ) |
| **EF 30/50 %** | 1.056 | 0.115 | 2.875 (0.774-10.681) |
| **EF < 30%** | -19.113 | 0.999 | 0 (0- ) |
| **Recent MI** | -19.024 | 0.999 | 0 (0- ) |
| **Severe Pulmonary Hypertension** | 1.131 | 0.093 | 3.100 (0.830-11.585) |
| **Emergency** | 0.851 | 0.299 | 2.342 (0.639-8.580) |
| **Other than CABG** | n/a | n/a | n/a |
| **Surgery on Thoracic Aorta** | n/a | n/a | n/a |
| **Post MI VSD** | n/a | n/a | n/a |
| **Severe Mitral Regurgitation** | -19.103 | 0.999 | 0 (0- ) |
| **CHF** | 0.128 | 0.908 | 1.136 (0.130-9.953) |
| **Calcified Aorta** | 0.383 | 0.590 | 1.467 (0.364-5.912) |
| **Diabetes** | -0.607 | 0.382 | 0.545 (0.139-2.129) |

| **Rhythm (Preop)** | | | |
|---|---|---|---|
| **sinus** | n/a | n/a | n/a |
| **AF** | 1.545 | 0.018 | 4.686 (1.303-33.683) |
| **PCM** | 1.188 | 0.318 | 3.280 (0.319-33.683) |

*TAVI: Transcatheter Aortic Valve Implant group. MS: median sternotomy approach. TF: transfemoral approach. TA: Transapical approach. EF: left ventricular ejection fraction. MI myocardial infarction. CHF. Congestive heart failure. sinus: sinus rhythm. AF. Atrial fibrillation. PCM: pacemaker rhythm*

TAVI procedures, neither when as a whole nor when the surgical approach (TF or TA) was detached showed a significant association with perioperative mortality with the resulting odds ratios (95% CI) against conventional aortic valve replacement (HR-AVR): 1.741 (0.372-8.144) for the whole TAVI group, 0.974 (0.156-6.104) for the TF approach and 3.800 (0.562-25.693) for the TA approach.

However, these results reached significance for TAVI as well as for TA when the MACCE endpoint was considered, but not for the TF approach alone; with 4.364 (1.118-17.033), 6.333 (1.103-36.370) and 3.257 (0.765-13.863) respective odds ratios.

Other predictors for 30-days mortality endpoint were (OR, 95% CI): extracardiac arteropathy (8.803, 1.652-39.545), impaired left ventricular ejection fraction or EF 30/50 (4.235, 0.869-20.630), severe pulmonary hypertension (4.547, 0.929-22.244) and urgent nature of the intervention or Emergency (3.487, 0.723-16.813); although these last three variables were in the limits of significance.

Back to the MACCE endpoint, age (1.240, 1.052-1.460), as well as preoperative atrial fibrillation (4.686, 1.303-16.852), were also found to be

significant predictors of an event; and pulmonary hypertension showed a strong but non-significant association (3.100, 0.830-11.585).

Univariate analysis for main postoperative complications was performed for the 30-days mortality endpoint exclusively: cardiovascular (22.200, 2.573-191.554), respiratory (9.884, 1.871-51.803) and neurological postoperative complications (14.667, 1.983-108.493) had a strong and significant association with early mortality (Table 10).

*Table 10. Univariate analysis for postoperative complications and 30-days mortality endpoint.*

| **30-d mortality** | | | |
|---|---|---|---|
| | B | (Sig.) | OR (95% CI) |
| **Perioperative morbidity (all)*** | | | |
| **Reintervention** | 0.926 | 0.420 | 2.524 (0.266-23.968) |
| **Cardiovascular** | 3.100 | 0.005 | 22.200 (2.573-191.554) |
| **Respiratory** | 2.287 | 0.007 | 9.884 (1.871-51.803) |
| **Wound** | -18.448 | 0.999 | 0 (0 - ) |
| **Renal** | 1.416 | 0.116 | 4.120 (0.706-24.035) |
| **Neurological** | 2.686 | 0.009 | 14.667 (1.983-108.493) |
| **Infective** | 2.225 | 0.086 | 9.250 (0.732-116.951) |
| **Other** | 1.810 | 0.141 | 6.111 (0.550-67.886) |

| | | | |
|---|---|---|---|
| **MACCE** | n/a | n/a | n/a |
| **Rhythm (discharge)** | | | |
| **sinus** | n/a | n/a | n/a |
| **AF** | 0.110 | 0.921 | 0.896 (0.101-7.950) |
| **PCM** | -18.540 | 0.999 | 0 (0 - ) |

*MACCE: death or major adverse cardio or cerebrovascular events. sinus: sinus rhythm. AF. Atrial fibrillation. PCM: pacemaker rhythm*

** See Annex for definitions*

## MULTIVARIATE ANALYSIS

As previously stated in the Methods section, an agreed level of significance of 0.2 in the univariate analysis was required to enter the multivariate logistic regression model for both 30-days mortality and MACCE endpoints. Results of the equation computed by enter method are presented on Tables 11-12.

*Table 11. Multivariate analysis for 30-days mortality endpoint*

| **30-d mortality** | | | |
|---|---|---|---|
| | B | (Sig.) | OR (95% CI) |
| **Extracardiac Arteropathy** | 2.080 | 0.009 | 21.766 (2.189-216.418) |
| **EF 30/50 %** | 1.083 | 0.215 | 2.953 (0.534-16.332) |
| **Pulmonary Hypertension** | 1.622 | 0.028 | 13.766 (1.318-143.742) |

*EF: left ventricular ejection fraction*

Both extracardiac arteropathy (21.766, 2.189-216.418) and pulmonary hypertension (13.766, 1.318-143.742) variables were found to be independent

predictors for the 30-days mortality endpoint. Left ventricular function dysfunction or EF 30/50 (2.953, 0.534-16.332) did not reach enough statistical power.

*Table 12. Multivariate analysis for MACCE endpoint*

| **MACCE** | | | |
|---|---|---|---|
| | B | (Sig.) | OR (95% CI) |
| **Surgical Approach** | | | |
| **MS** | n/a | n/a | n/a |
| **TF** | 1.307 | 0.178 | 3.694 (0.551-24.767) |
| **TA** | 1.182 | 0.278 | 3.262 (0.386-27.574) |
| **Age (y)** | 0.182 | 0.036 | 1.199 (1.011-1.422) |
| **Extracardiac Arteropathy** | 1.108 | 0.231 | 3.027 (0.494-18.534) |
| **EF 30/50 %** | 0.971 | 0.259 | 2.640 (0.488-14.274) |
| **Pulmonary Hypertension** | 0.958 | 0.253 | 2.606 (0.505-13.446) |
| **Rhythm (Preop)** | | | |
| **sinus** | n/a | n/a | n/a |
| **AF** | 0.991 | 0.181 | 2.695 (0.630-11.535) |
| **PCM** | 0.222 | 0.873 | 1.248 (0.082-18.907) |

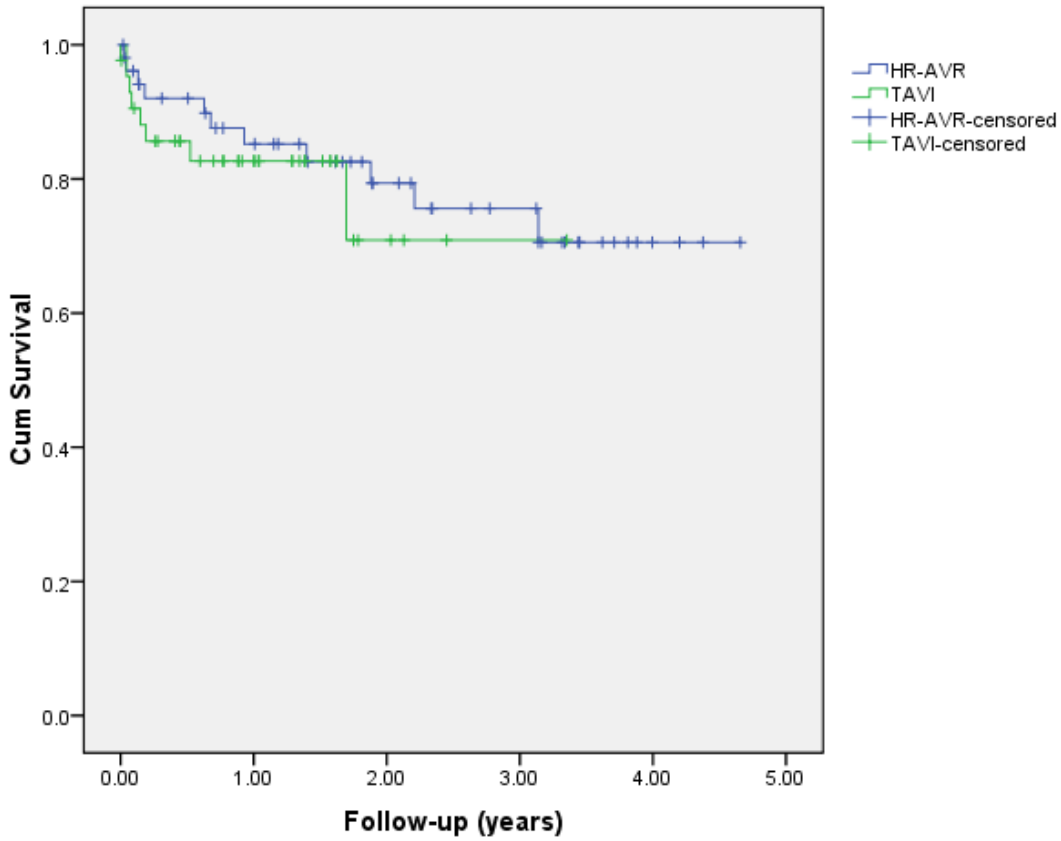
*MS: median sternotomy. TF. Transfemoral. TA: transapical. EF: left ventricular ejection fraction. Sinus: sinus rhythm. AF: atrial fibrillation. PCM: pacemaker rhythm.*

With regard to the MACCE endpoint, Age was the only significant independent predictor of event in the multivariate analysis although presenting a weak association with the independent variable (1.199,1.011-1.422). Neither extracardiac artheropathy (3.027, 0.494-18.534), pulmonary hypertension (2.606, 0.505-13.446), nor previous AF (2.695, 0.630-11.535), TF (3.694, 0.551-24.767), TA approaches (3.262, 0.386-27.574) reached signification.

## *SURVIVAL ANALYSIS*

Mean long-term follow-up was 1.49+/-1.22 years (range 0-4.66 years) in the whole 120 cases series. 0.99+/-0.75 years (range 0-3.35 years) in the TAVI group and 1.90+/-1.38 years (range 0.02-4.66 years) in the HR-AVR group. Cumulative survival was 83.0% and 81.4% for each group, respectively (global survival 82.1%). Log-rank test (Mantel-Cox) resulted non significant between both groups (Fig 21.).

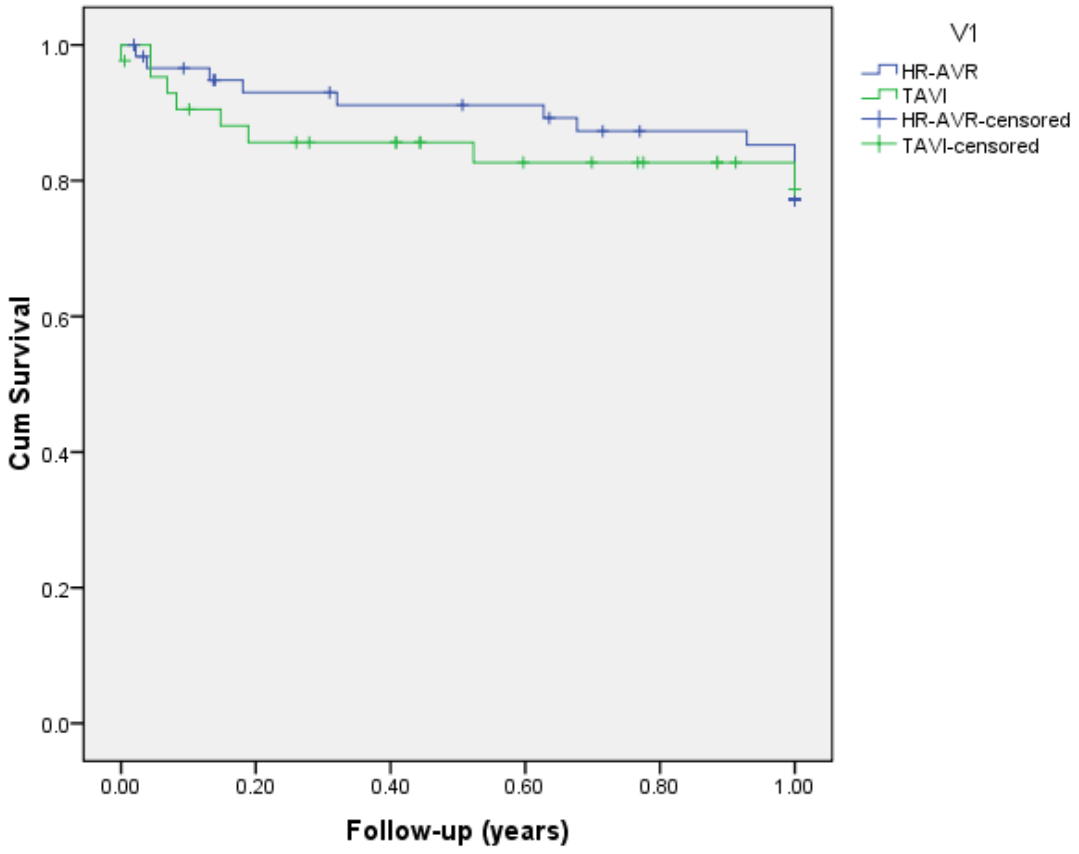
*Fig. 21. Long-term cumulative survival by groups*



| | Chi-Square | df | Sig. |
|---|---|---|---|
| Log Rank (Mantel-Cox) | .364 | 1 | .547 |

We also performed a 1-year after surgery survival as an intermediate endpoint in the survival analysis with an estimated overall survival of 88.6% (95% CI 82.8-94.4), 85.5% (74.9-96.1) for TAVI and 90.9% (84.1-97.8) for HR-AVR groups, with a non-relevant log-rank test result (Fig. 22).

*Fig. 22. 1-year cumulative survival by groups.*



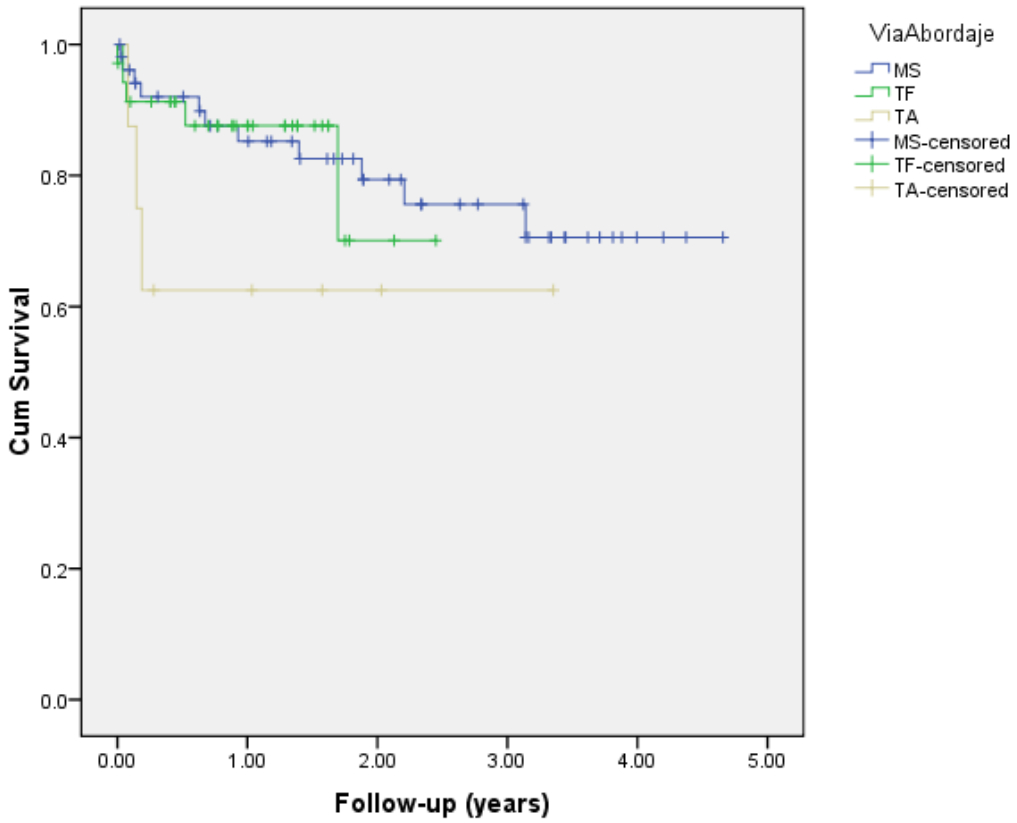

| | Chi-Square | df | Sig. |
|---|---|---|---|
| Log Rank (Mantel-Cox) | .029 | 1 | .865 |

| | Chi-Square | df | Sig. |
|---|---|---|---|
| Log Rank (Mantel-Cox) | .029 | 1 | .865 |

Considering the different surgical approaches, transapical presented a 66.7% long-term overall survival (mean follow-up of 1.08+/-1.17) and transfemoral a 87.8% (0.97+/-0.64) versus the 81.4% for median sternotomy in the HR-AVR (1.90+/-1.38 years) group. Log-rank test was non-significant (Fig. 23).

In order to assess the hypothetical learning curve effect for each approach in the survival analysis a Cox multivariate logistic regression test was performed, including long-term survival as an independent variables; and the surgical approach used and the year in which surgery was performed as dependent variables. MS and 2007 were chosen as references. TA showed an OR 2.880 (95% CI 0.733-11.315) and TF 1.361 (0.367-5.041) though none of them reached a significant result. Year in which surgery was performed presented a progressive, mild non-relevant protective effect represented by the negative regression coefficients in the logistic regression equation (Table 13.)

*Fig. 23. Long-term cumulative survival by surgical approach*




| | Chi-Square | df | Sig. |
|---|---|---|---|
| Log Rank (Mantel-Cox) | 2.042 | 2 | .360 |

*Table 13. Multivariate Cox Regression analysis for long-term survival.*

| **long-term survival** | | | |
|---|---|---|---|
| | B | (Sig) | OR (95% CI) |
| **Surgical Approach** | | | |
| **MS** | n/a | n/a | n/a |
| **TF** | 0.308 | 0.645 | 1.261 (0.367-5.041) |
| **TA** | 1.058 | 0.130 | 2.880 (0.733-11.315) |
| **year of surgery** | | | |
| **2007** | n/a | n/a | n/a |
| **2008** | -0.313 | 0.669 | 0.731 (0.174-3.069) |
| **2009** | 0.102 | 0.888 | 1.107 (0.268-4.577) |
| **2010** | -0.886 | 0.336 | 0.412 (0.068-2.505) |
| **2011** | -0.323 | 0.756 | 0.724 (0.094-5.562) |
| **2012** | -8.553 | 0.998 | 0 (0- ) |

MS: Median sternotomy. TF: transfemoral. TA: transapical.

## 3. Transfemoral vs. Transapical approach subgroup analysis

Subgroup analysis as foreseen in the Methods section sets the descriptive statistics (Table 14-15), operative outcomes (Table 16) and heart rhythm analysis (Fig.24) of TF vs. TA subgroups.

No differences in preoperative demographics or risk data were found, apart from a higher rate of extracardiac arteropathy in the TA group (50% vs 7.3% p<0.01). Operative outcomes differences were also non-significant, although a higher incidence of renal failure for the TA approach (33.3% vs. 0%).

*Table 14. Descriptive statistics for TF and TA subgroups*

| | TF | TA | |
|---|---|---|---|
| **n** | 41 | 12 | |
| **Age (y)** | 80.71+/-4.70 | 79.42+/-5.40 | ns |
| **Gender (%male)** | 20 (48.8%) | 6 (50.0%) | ns |
| **Weight (kg)** | 72.16+/-17.84 | 69.94+/-11.27 | ns |
| **Height (cm)** | 154.82+/-16.13 | 158.78+/-10.75 | ns |
| **BSA (m2)** | 1.74+/-0.17 | 1.75+/-0.19 | ns |
| **BMI (kg/m2)** | 28.33+/-4.71 | 27.71+/-3.59 | ns |
| **Coronary disease** | 18 (43.9%) | 5 (41.7%) | ns |
| **No vessels** | 0.71+/-1.10 | 0.92+/-1.38 | ns |
| **PTCA** | 8 (19.5%) | 3 (25.0%) | ns |
| **CABG** | 0 | 0 | - |
| **No grafts** | 0 | 0 | - |
| **Valve area (cm2)** | 0.59+/-0.10 | 0.69+/-0.18 | ns |
| **Mean Grad (mmHg)** | 54.62+/-14.25 | 47.85+/-13.55 | ns |
| **Peak Grad (mmHg)** | 80.33+/-38.56 | 85.71+/-23.91 | ns |

| | | | |
|---|---|---|---|
| **Peak Vel (m/s)** | 4.46+/-0.78 | 4.27+/-0.11 | ns |

*BSA: Body surface area. BMI: body mass index. No. Vessels: numer of diseased coronary vessels. PTCA: percutaneous transluminal coronary angioplasty. CABG: coronary artery bypass graft. No grafts: number of grafts. Mean grad: mean transvalvular gradient. Peak grad: peak transvalvular gradient. Peak vel: peak jet flow velocity.*

*Table 15. Preoperative features for TF and TA subgroups.*

| | TF | TA | |
|---|---|---|---|
| **n** | 41 | 12 | |
| **EuroSCORE** | 9 (4-14) | 10 (6-13) | ns |
| **logEuroSCORE** | 15.76+/-10.10 | 19.20+/-10.00 | ns |
| | | | |
| **Chronic Pulmonary Disease** | 17 (41.5%) | 4 (33.3%) | ns |
| **Extracardiac Arteropathy** | 3 (7.3%) | 6 (50.0%) | p<0.01 |
| **Neurological dysfunction** | 5 (12.2%) | 2 (16.7%) | ns |
| **Previous Cardiac Surgery** | 5 (12.2%) | 3 (25.0%) | ns |
| **Preoperative Renal Failure** | 4 (9.8%) | 0 | ns |
| **Active Endocarditis** | 0 | 0 | - |
| **Preoperative Critical Status** | 0 | 0 | - |
| **Unstable angor** | 2 (4.9%) | 1 (8.3%) | ns |
| **EF 30/50 %** | 5 (12.2%) | 3 (25.0%) | ns |
| **EF < 30%** | 5 (12.2%) | 0 | ns |
| **Recent MI** | 0 | 0 | - |
| **Pulmonary Hypertension** | 8 (19.5%) | 3 (25.0%) | ns |
| **Emergency** | 5 (12.2%) | 3 (25.0%) | ns |
| **Other than CABG** | 41 (100%) | 12 (100%) | ns |
| **Surgery on Thoracic Aorta** | 0 | 0 | - |
| **Post MI VSD** | 0 | 0 | - |
| **Mitral Regurgitation** | 5 (12.2%) | 0 | ns |
| **NYHA III/IV** | 37 (90.2%) | 11 (91.7%) | ns |

| | | | |
|---|---|---|---|
| **CHF** | 5 (12.2%) | 0 | ns |
| **Calcified Aorta** | 6 (14.6%) | 4 (33.3%) | ns |
| **Diabetes** | 15 (36.6%) | 5 (41.7%) | ns |
| **Rhythm (Preop)** | | | |
| **sinus** | 24 (58.5%) | 7 (58.3%) | |
| **AF** | 12 (29.3%) | 5 (41.7%) | |
| **PCM** | 5 (12.2%) | 0 | ns |

*EF: ejection fraction (left ventricle). MI: myocardial infarction. CABG: coronary artery bypass graft. VSD: ventricular septal defect. NYHA: New York Heart Association functional class. Rhythm (preop): Preoperative heart rhythm. Sinus: sinus rhythm. AF. Atrial fibrillation. PCM: pacemaker rhythm.*

*Table 16. Operative outcomes for TF and TA subgroups*

| | **TF** | **TA** | |
|---|---|---|---|
| **n** | 41 | 12 | |
| **Valve implant size (mm)** | 26 (23-29) | 26 (23-29) | ns |
| **Biological valve (%)** | 41 (100%) | 12(100%) | ns |
| **30-d mortality (%)** | 2 (4.9%) | 2 (16.7%) | ns |
| **Mortality (cause)*** | | | |
| **cardiac** | 1 (2.4%) | 0 | |
| **neurological** | 1 (2.4%) | 1 (8.3%) | |
| **infective** | 0 | 0 | |
| **endocarditis** | 0 | 0 | |
| **respiratory** | 0 | 0 | |
| **renal** | 0 | 0 | |
| **multiorganic** | 0 | 1 (8.3%) | |
| **unknown** | 0 | 0 | |
| **Perioperative morbidity (all)*** | 18 (43.9%) | 6 (50.0%) | ns |
| **Reintervention** | 2 (4.9%) | 1 (8.3%) | ns |

| | | | |
|---|---|---|---|
| **Cardiovascular** | 4 (9.8%) | 0 | ns |
| **Respiratory** | 1 (2.4%) | 2 (16.7%) | ns |
| **Wound** | 3 (7.3%) | 0 | ns |
| **Renal** | 0 | 4 (33.3%) | p<0.01 |
| **Neurological** | 3 (7.3%) | 2 (16.7%) | ns |
| **Infective** | 0 | 0 | - |
| **Other** | 4 (9.8%) | 0 | ns |
| **MACCE** | 6 (14.6%) | 3 (25.0%) | ns |
| **Rhythm (discharge)** | | | |
| **sinus** | 27 (65.9%) | 7 (58.3%) | |
| **AF** | 4 (9.8%) | 4 (33.3%) | |
| **PCM** | 10 (24.4%) | 1 (8.3%) | ns |
| **ICU LOS (days)** | 1.97+/-2.76 | 2.33+/-1.37 | ns |
| **Hospital LOS (days)** | 7.36+/-4.59 | 6.71+/-3.25 | ns |

*30-d mortality: thirty-day mortality. MACCE: death or major adverse cardio or cerebral events. AF: atrial fibrillation. PCM: pacemaker. ICU LOS: intensive care unit length of stay. Hospital LOS: Hospital length of stay*

** See Annex for definitions*

Differences in ICU and hospital length of stay (1.97+/-2.76 vs. 2.33+/-1.37 and 7.36+/-4.59 vs. 6.71+/-3.25 days for TF and TA approaches respectively) as well as postoperative PCM rhythm (24.4% for TF and 8.3% for TA) were also statistically non-relevant.

Fig. 24. Pacemaker (PCM) rhythm at discharge by surgical approach (p=ns)

**Surgical approach vs. PCM Rhythm Crosstabulation**

| | | PCM | | |
|---|---|---|---|---|
| | | No | Yes | Total |
| approach | MS | 67 | 0 | 67 |
| | | 100.0% | .0% | 100.0% |
| | TF | 31 | 10 | 41 |
| | | 75.6% | 24.4% | 100.0% |
| | TA | 11 | 1 | 12 |
| | | 91.7% | 8.3% | 100.0% |
| Total | | 109 | 11 | 120 |
| | | 90.8% | 9.2% | 100.0% |

# 4. 'Replacement Or trans-Catheter Implant Odds'. A new discrimination score for preoperative assessment in high-risk aortic valve replacement surgery.

## *CONSTRUCTION OF THE NEW SCORE*

The first step to construct a new scoring system for the preoperative discrimination of the best aortic valve surgery procedure in high-risk patients was to select the multivariate logistic regression analysis dependent variables for the 30-days mortality endpoint (Table 17.).

*Table 17. Multivariate logistic regression analysis for 30-days mortality endpoint.*

| **30-d mortality** | | | |
|---|---|---|---|
| | B | (Sig.) | OR (95% CI) |
| **Extracardiac Arteropathy** | 2.080 | 0.009 | 21.766 (2.189-216.418) |
| **EF 30/50 %** | 1.083 | 0.215 | 2.953 (0.534-16.332) |
| **Pulmonary Hypertension** | 1.622 | 0.028 | 13.766 (1.318-143.742) |

Secondly, the round number for the regression coefficient for each variable was chosen as the punctuation score and the additive punctuation of all three variables was calculated for each patient (Table 18.).

*Table 18.*

| | |
|---|---|
| | points |
| **Extracardiac Arteropathy** | 2 |
| **EF 30/50 %** | 1 |
| **Pulmonary Hypertension** | 1 |

Subsequently a consensus two different scoring profiles were created: Low profile (total sum between 0 and 2 points), and High profile (scoring 3 or more points). The descriptive results of the punctuation and the distribution of the new score profile groups are shown on Table 19.

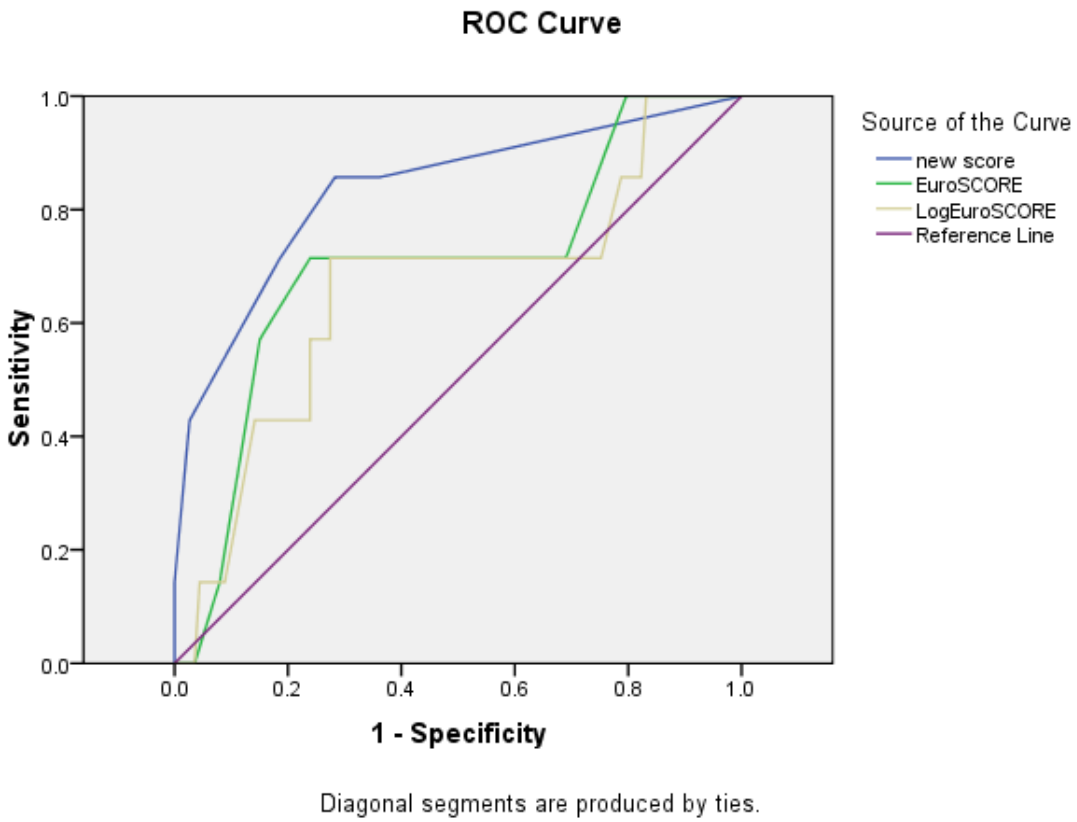
*Table 19.*

| **Score** | **Overall** | **TAVI** | **HR-AVR** |
|---|---|---|---|
| **N** | 120 | 53 | 67 |
| **risk groups** | | | |
| **Low profile** | 102 (85.0%) | 44 (83.02%) | 58 (86.57%) |
| **High profile** | 18 (15.0%) | 9 (16.98%) | 9 (13.43%) |

30-days mortality discrimination capacity of the score was tested against additive EuroSCORE and logistic EuroSCORE in the 120 cases group by the construction of specific receptor-operator curves (ROC curve) for each scoring punctuation system and assessing the area under the curve (AUC) for every one of

them (0.835 for the New Score, 0.702 for additive EuroSCORE and 0.660 for logistic EuroSCORE).

*Fig. 25. Receptor-operator carachteristics curve for perioperative mortality by discrimination score in the 120 patients matched case-control group.*




**Area Under the Curve**

| Test Result Variable(s) | Area | Std. Error[a] | Asymptotic 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| new score | .835 | .091 | .638 | 1.000 |
| EuroSCORE | .702 | .111 | .485 | .920 |
| LogEuroSCORE | .660 | .116 | .432 | .888 |

a. a. standard error

And finally, a discrimination tree by the Classification and Regression Tree (CRT) method was constructed using the categorical classification of the new scoring system (low-profile versus high-profile), the procedure to select (TAVI versus conventional AVR) when considering 30-days mortality as the dependent (outcome) variable in the 120 patients 'high-risk' group. (Fig. 26)

Discrimination Tree shows a 2.9% perioperative mortality in the ´Low Profile´group and a 22.2% in the ´High Profile´ group. Differences between both procedures were found: in the ´Low Profile´group, 30-days mortality was 6.8% for TAVI, higher than the 0% for conventional AVR; whether in the ´High Profile´ group results was 11.1% for TAVI, lower than the 33.3% rate for conventional AVR (Fig. 26).

### *INTERNAL VALIDATION*

We sought to assess internal validation of the new scoring system by applying the punctuation to the overall 468 patients' database and subsequently to the logistic EuroSCORE < 15 and over 15 subgroups. Construction of ROC curves for the new score, additive and logistic EuroSCORE as well as Classification and Regression Trees (CRT) for the new score were calculated for the overall database and the mentioned subgroups.

*Fig 26. Classification and Regression Tree for 30-days mortality for Low and High Profile groups and the procedure (TAVI or conventional AVR) performed in the 120 patients case-control study.*

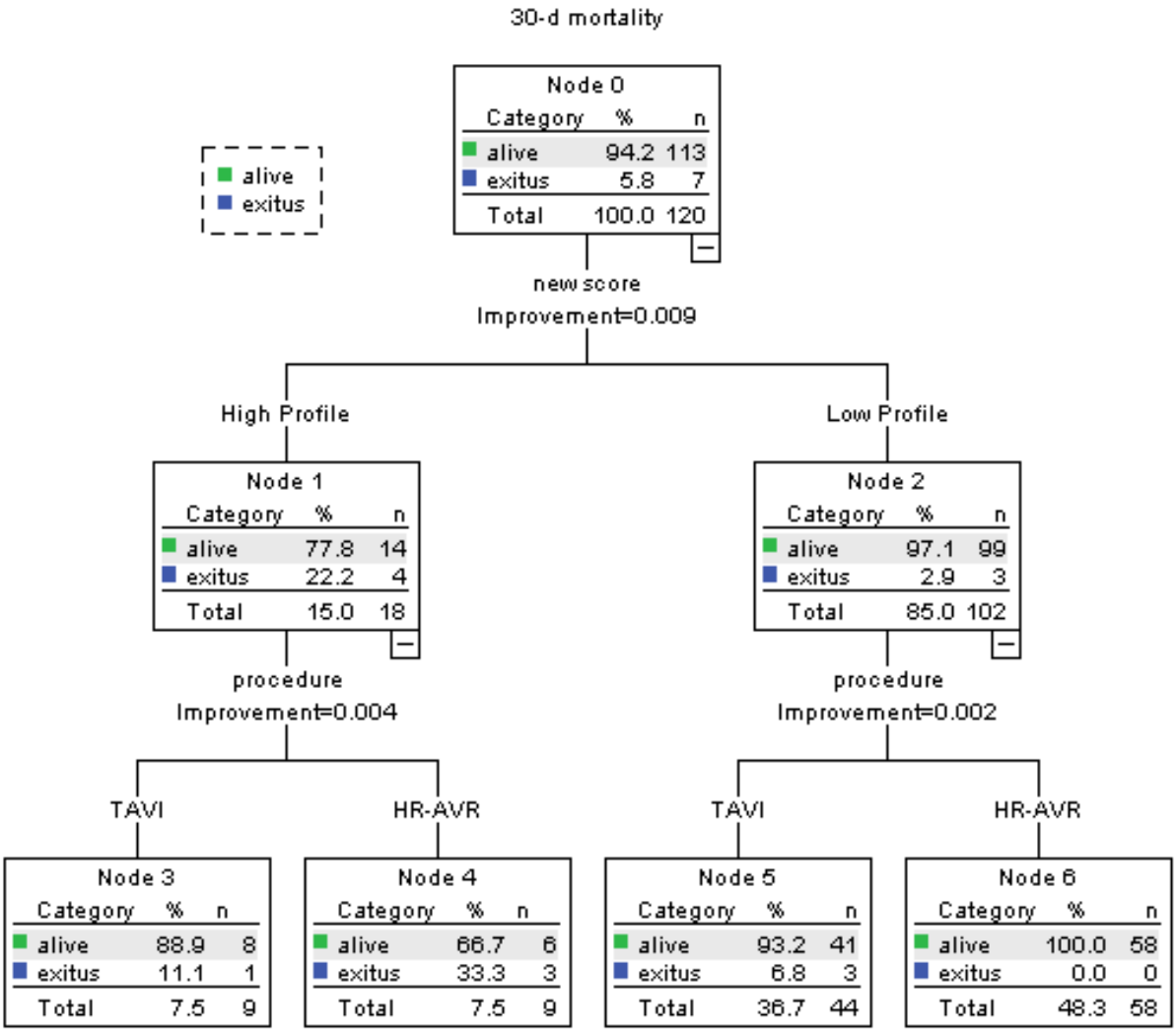
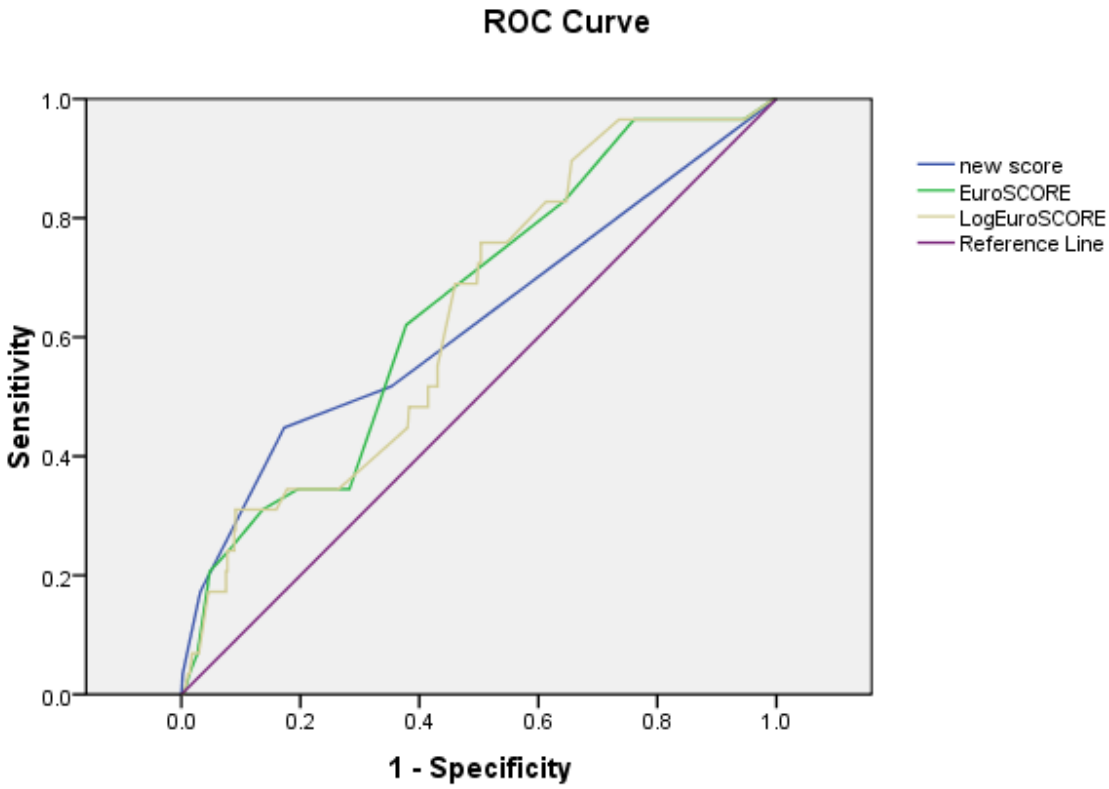


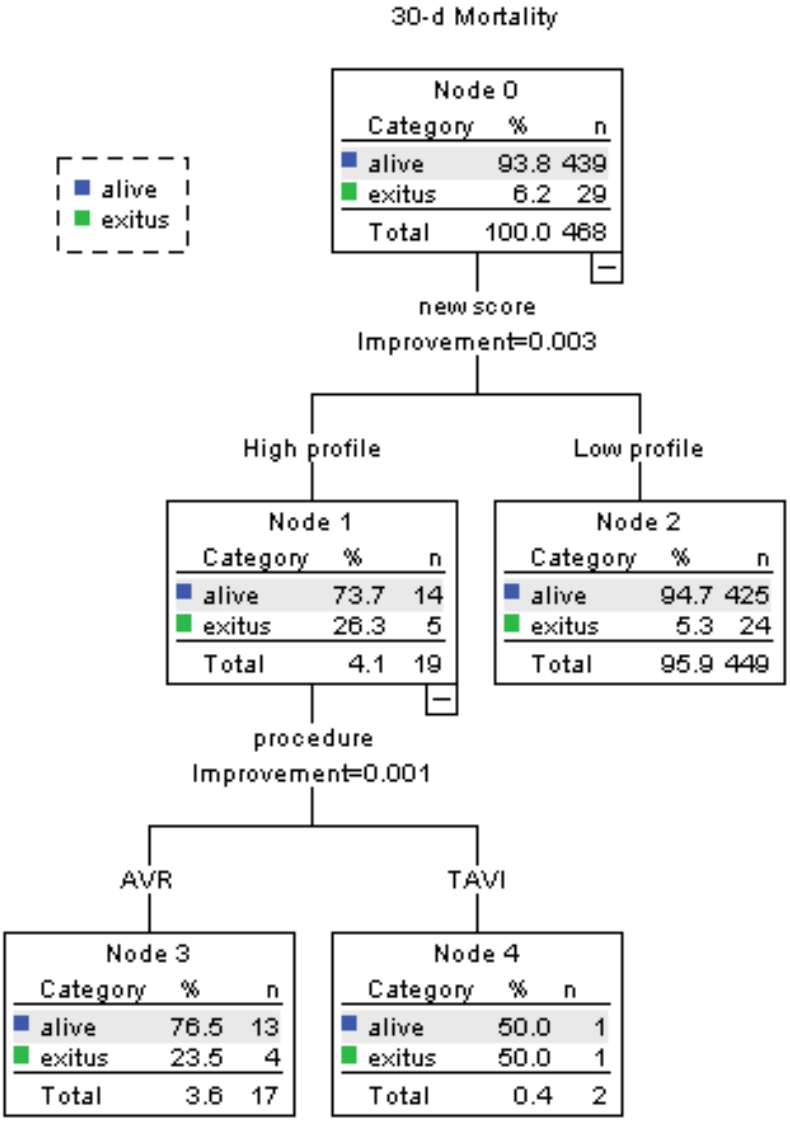
*Fig. 27 Receptor-operator characteristics curve for perioperative mortality by the new score, additive EuroSCORE, logistic EuroSCORE in the overall 468 patients database*




**Area Under the Curve**

| Test Result Variable(s) | Area | Std. Error | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| new score | .625 | .061 | .505 | .745 |
| EuroSCORE | .651 | .050 | .554 | .749 |
| LogEuroSCORE | .640 | .049 | .544 | .736 |

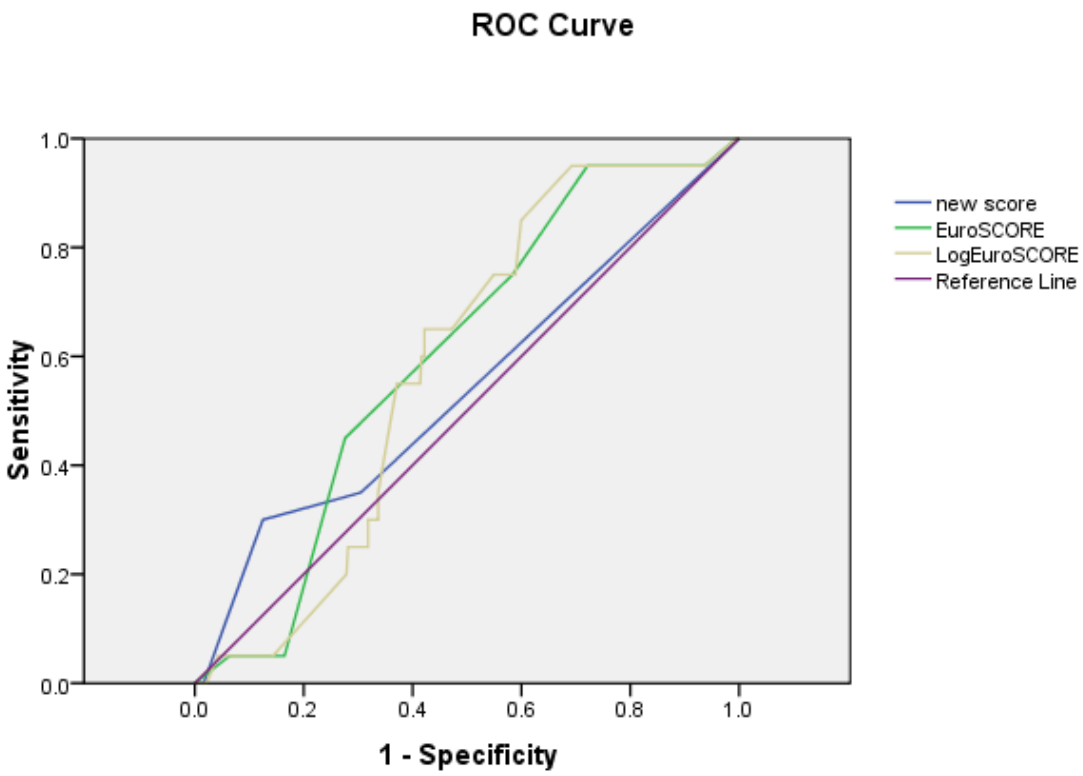
*Fig. 28. Classification and Regression Tree for 30-days mortality for Low and High Profile groups and the procedure (TAVI or conventional AVR) performed in the 468 patients overall database*




ROC curve returned 0.625, 0651 and 0.640 AUC for the new score, additive EuroSCORE and logistic EuroSCORE respectively. CRT was able to discriminate in the high-risk profile group (showing 50% perioperative mortality for TAVI and 23.5% for conventional AVR) but not in the Low Profile group (Fig 27-28).

When considering the logistic EuroSCORE < 15 subgroup, ROC curve returned 0.544,0.603 and 0.584 AUC for the new score, additive EuroSCORE and logistic EuroSCORE respectively. CRT was unable to discriminate by procedure neither in the Low Profile (5.1% perioperative mortality) nor in the High Profile (0% perioperative mortality) (Fig. 29-30).

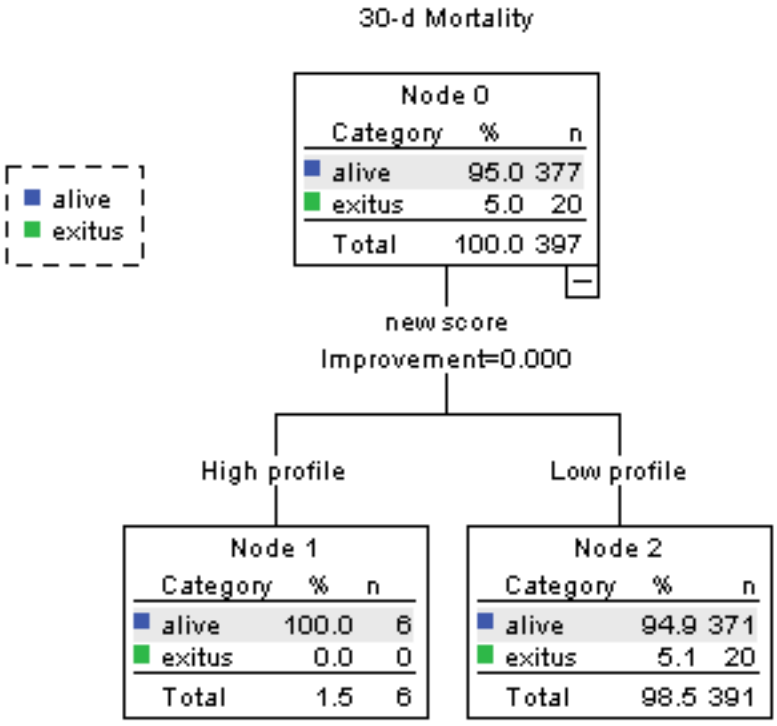
*Fig. 29 Receptor-operator characteristics curve for perioperative mortality by the new score, additive EuroSCORE, logistic EuroSCORE in the logistic EuroSCORE < 15 subgroup.*



**Area Under the Curve**

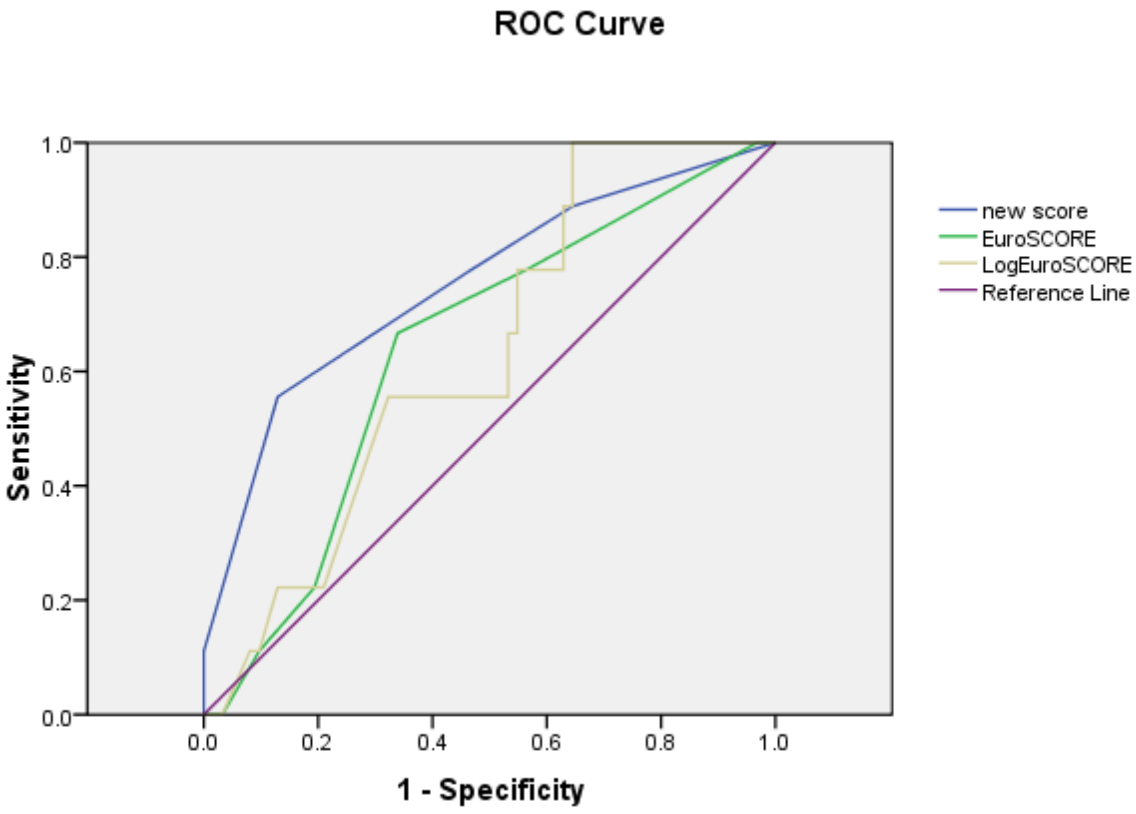
| Test Result Variable(s) | Area | Std. Error | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| new score | .544 | .072 | .403 | .685 |
| EuroSCORE | .603 | .054 | .497 | .708 |
| LogEuroSCORE | .584 | .049 | .488 | .680 |

*Fig. 30 Classification and Regression Tree for 30-days mortality for Low and High Profile groups and the procedure (TAVI or conventional AVR) performed in logistic EuroSCORE < 15 subgroup.*



In the same fashion, ROC curves and CRT were tested for the EuroSCORE > 15 subgroup. Returned AUC were 0.752, 0.638 and 0.631 for the new score, additive EuroSCORE and logistic EuroSCORE respectively. CRT was able to discriminate in both Low and High Profile, showing a perioperative mortality of 100% (1 case) for TAVi and 33.3% for conventional AVR in the first and 8.3% for TAVI vs. 5.9% for AVR in the second one (Fig. 31-32).

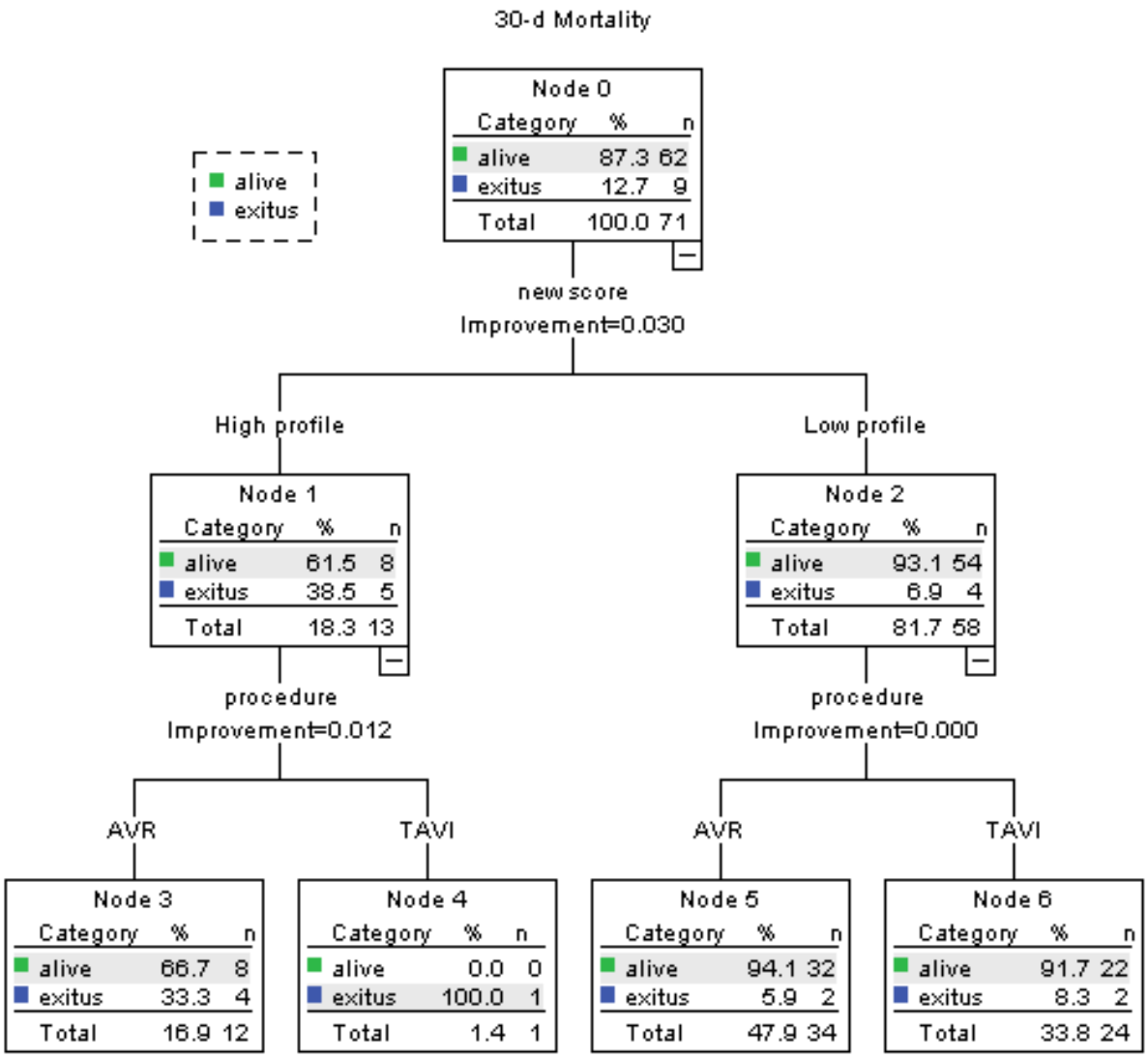
*Fig. 31. Receptor-operator characteristics curve for the new score, additive EuroSCORE, logistic EuroSCORE in the logistic EuroSCORE > 15 subgroup.*



**Area Under the Curve**

| Test Result Variable(s) | Area | Std. Error | 95%Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| new score | .752 | .095 | .566 | .938 |
| EuroSCORE | .638 | .092 | .458 | .818 |
| LogEuroSCORE | .631 | .083 | .468 | .794 |

*Fig. 31 Classification and Regression Tree for 30-days mortality for Low and High Profile groups and the procedure (TAVI or conventional AVR) performed in logistic EuroSCORE > 15 subgroup.*




## *EXTERNAL VALIDATION*

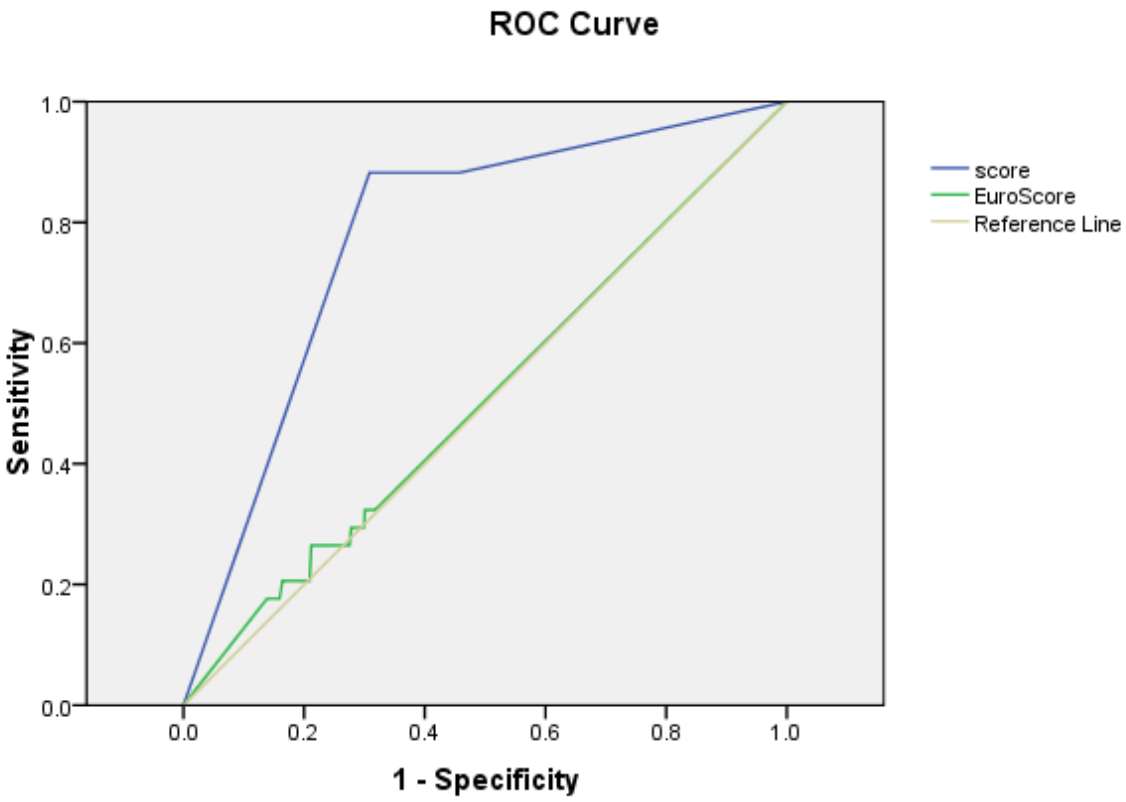
As described in the Methods section, external validation was modelized by constructing a ´dummy´ database with similar characteristics as those presented with Cohort A in the PARTNER trial. The variables and data used for building the

´dummy database´ are presented again in figure 32. ROC curves for the new score and logistic EuroSCORE (Fig. 33) and CRT for perioperative mortality (Fig. 34) were tested in this ´dummy´database.

*Fig. 32. PARTNER Cohort A Dummy Database Characteristics (89)*

| Characteristic | Transcatheter Replacement (N=348) | Surgical Replacement (N=351) | P Value |
|---|---|---|---|
| Age — yr | 83.6±6.8 | 84.5±6.4 | 0.07 |
| Male sex — no./total no. (%) | 201/348 (57.8) | 198/349 (56.7) | 0.82 |
| Society of Thoracic Surgeons score† | 11.8±3.3 | 11.7±3.5 | 0.61 |
| Logistic EuroSCORE† | 29.3±16.5 | 29.2±15.6 | 0.93 |
| New York Heart Association class — no./total no. (%) | | | 0.79 |
| II | 20/348 (5.7) | 21/349 (6.0) | |
| III or IV | 328/348 (94.3) | 328/349 (94.0) | |
| Coronary artery disease — no./total no. (%) | 260/347 (74.9) | 266/346 (76.9) | 0.59 |
| Previous myocardial infarction — no./total no. (%) | 92/343 (26.8) | 103/343 (30.0) | 0.40 |
| Previous CABG — no./total no. (%) | 147/345 (42.6) | 152/344 (44.2) | 0.70 |
| Previous PCI — no./total no. (%) | 116/341 (34.0) | 110/338 (32.5) | 0.68 |
| Previous balloon aortic valvuloplasty — no./total no. (%) | 46/344 (13.4) | 35/344 (10.2) | 0.24 |
| Cerebral vascular disease — no./total no. (%) | 95/324 (29.3) | 87/317 (27.4) | 0.60 |
| Peripheral vascular disease — no./total no. (%) | 148/344 (43.0) | 142/341 (41.6) | 0.76 |
| COPD — no./total no. (%) | | | |
| Any | 151/348 (43.4) | 151/351 (43.0) | 0.94 |
| Oxygen-dependent | 32/348 (9.2) | 25/351 (7.1) | 0.34 |
| Creatinine level >2 mg/dl (177 μmol/liter) — no./total no. (%) | 38/343 (11.1) | 24/344 (7.0) | 0.06 |
| Atrial fibrillation — no./total no. (%) | 80/196 (40.8) | 73/171 (42.7) | 0.75 |
| Permanent pacemaker — no./total no. (%) | 69/345 (20.0) | 76/347 (21.9) | 0.58 |
| Pulmonary hypertension — no./total no. (%) | 125/295 (42.4) | 110/302 (36.4) | 0.15 |
| Frail condition — no./total no. (%) | 46/295 (15.6) | 53/301 (17.6) | 0.58 |
| Extensively calcified aorta — no./total no. (%) | 2/348 (0.6) | 4/351 (1.1) | 0.69 |
| Deleterious effects of chest-wall irradiation — no./total no. (%) | 3/348 (0.9) | 3/351 (0.9) | 1.00 |
| Chest-wall deformity — no./total no. (%) | 0 | 1/351 (0.3) | 1.00 |
| Liver disease — no./total no. (%) | 7/344 (2.0) | 9/346 (2.6) | 0.80 |
| Aortic-valve area — $cm^2$ | 0.7±0.2 | 0.6±0.2 | 0.13 |
| Aortic-valve gradient — mm Hg | 42.7±14.6 | 43.5±14.3 | 0.45 |
| Left ventricular ejection fraction — % | 52.5±13.5 | 53.3±12.8 | 0.45 |
| Moderate or severe mitral regurgitation — no./total no. (%) | 66/334 (19.8) | 71/333 (21.3) | 0.63 |

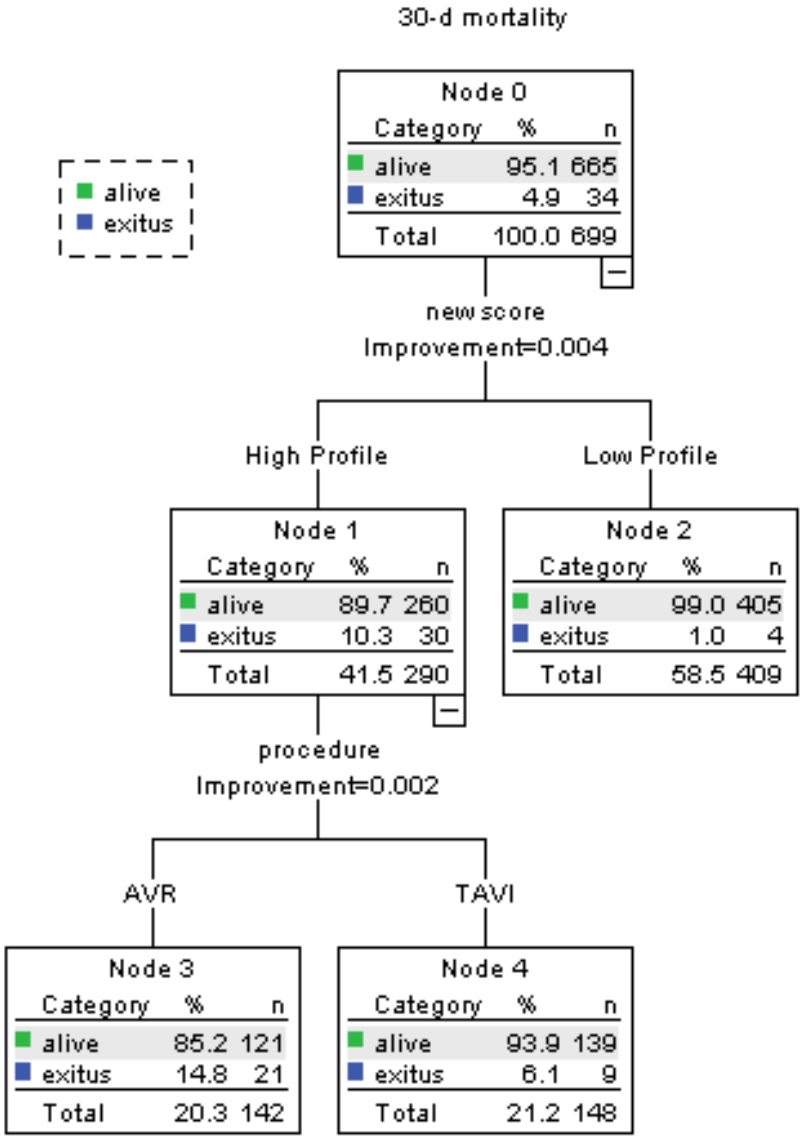
*Fig. 33. Receptor-operator characteristics curve for perioperative mortality by the new score and logistic EuroSCORE in the PARTNER cohort A ´dummy´database.*




**Area Under the Curve**

| Test Result Variable(s) | Area | Std. Error | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| new score | .778 | .038 | .705 | .852 |
| logistic EuroScore | .508 | .052 | .407 | .610 |

*Fig. 34. Classification and Regression Tree for 30-days mortality for Low and High Profile groups and the procedure (TAVI or conventional AVR) performed in the PARTNER Cohort A ´dummy´database.*



ROC curve was tested for the new score and logistic EuroSCORE in the PARTNER cohort A ´dummy´database, obtaining 0.778 AUC for the new score and 0.508 for logistic EuroSCORE. CRT showed discrimination in the High Profile arm (6.1% 30-days mortality for TAVI vs. 14.8% for AVR) exclusively.

# IV. DISCUSSION

# 1. Impact of new technology

Aortic stenosis (AS) is the most common valvular heart disease in adults (112). The disorder is becoming more frequent as the age of the population increases, representing a growing public health issue. Severe AS is universally fatal if left untreated, with three-quarters of patients dying within 3 years of symptom onset. No medical treatment improves survival in chronic disease, as the obstruction to outflow tract requires mechanical relief. Mortality rates are significantly reduced in symptomatic patients with AS by aortic valve replacement (AVR). Thus, AVR can be withheld in such patients only when compelling contraindications exist. A recent prospective survey of patients with valvular heart disease throughout Europe suggests that almost one-third of patients over the age of 75 with severe AS do not undergo AVR, due to risks arising from age and comorbidities (112). These findings have stimulated tremendous interest in reducing patient morbidity and mortality and motivated the development of a less-invasive transcatheter aortic valve (TAV) procedure (92).

The emergence of new technologies for the treatment of aortic valve disorders has brought with it a host of medical and ethical challenges regarding patient selection and choice of treatment. Because of the uncertainty around the safety of new transcatheter aortic valve implantation (TAVI) technologies, early device trials have focused on enrolling and treating patients at high surgical risk who are ‘‘non-operative’’ candidates. Although outcomes for open surgical repair of critical aortic stenosis are improving, early results with TAVI are encouraging and have led to expanded patient selection criteria.

Consequently, transformational technology is defined as one that when introduced radically changes markets, creates wholly new markets, or could even eliminate existing markets for older technology. The field of medicine is replete with examples of such therapies that have radically altered the treatment of disease, including sterile techniques in surgery, vaccines to cure polio, penicillin and

sulfamide drugs for infectious diseases, and cortisone. Physicians, scientists, and industry partners have developed all these therapies in concert.

Catheter-based therapies present new and potentially transformational technology for valvular and structural heart disease (117). The associated issues are complex, with multiple actors: first and foremost, the patients receiving this therapy, but also including clinicians, inventors, industry, regulatory agencies, governments and professional societies.

Several issues emerge with the introduction of this new technology.

1. How will this technology be regulated and by whom?
2. Will the technology be available in all centers by all physicians or only in selected regional centers; if the latter, how will those centers be selected?
3. How will training of physicians and centers be accomplished? What will the training paradigms be and what experience is necessary for credentialing to be deemed proficient? Will the training be the same for cardiologists and surgeons?
4. Will clinical databases be linked to administrative databases facilitating long-term outcome assessment, comparative effectiveness research, and cost-effectiveness analysis? Will data collection be required using standardized definitions in harmonized national clinical and administrative databases and registries, and if so, from where will the resources come to accomplish this? Can these standardized registries be used worldwide?
5. What will be the rational diffusion of the new technology to other patient groups not originally studied in randomized clinical trials?
6. How will patient cohorts be identified that will benefit the most and provide the most cost-effective and clinically effective treatment?

Transcatheter valve therapy is a transformational technology with the potential to significantly impact the clinical management of patients with valvular heart disease in a less invasive manner. Although the initial experience is positive, evidence exists from only 1 randomized clinical trial in patients with aortic stenosis. In order to address the challenges ahead for the responsible diffusion of this innovative transformational technology, it is critical that the professional societies, industry, payers, and regulatory agencies work together to optimize benefits for the patient and society (118,119).

## 2. Current state of the evidence

- REGISTRY EXPERIENCE

Registry data provide important information for assessing the role of TAVI in a large number of patients who are not eligible for randomized controlled trials because of strict selection criteria. Several multicenter registries, including Edwards Lifesciences and Medtronic CoreValve (tables 1 and 2), have reported early and late outcomes with TAVI. However, patient selection criteria varied amongst the different registries; standardized definitions for clinical events were not used; and endpoints were not prospectively adjudicated using a blinded clinical event committee. This study is not an exception and data was retrospectively collected. Selection criteria have been widely explained in previous sections, but basically were based upon experts committee criteria.

CoreValve system real-world clinical experience to date is comprised of multiple registries from several participating national sites (97,120–126). These study sizes range from 61 to 663 patients, with a combined clinical patient experience of nearly 2,350 patients that includes follow-up of up to 2 years (Table 2). Our study comprises a single-center experience of 468 patients eligible for aortic valve replacement, out of whom 53 underwent a TAVI procedure and the rest a conventional AVR.

The early and late major outcomes with Sapien and CoreValve registries are summarized in Tables 1 and 2 respectively. The early morbidity of TAVI includes stroke, coronary occlusion, pacemaker implantation, vascular complications, renal failure, cardiac rupture and tamponade, bleeding, aortic dissection, and death. The overall risk of any 30-day major complication ranges from 20% to over 40%, whereas we present a 45.3% for overall perioperative mortality in TAVI and 32.8% in the HR-AVR group. Early mortality ranges from an in-hospital rate of 5% to 8% and a 30-day mortality rate from 8% to 10%, similar to the 7.5% for TAVI presented in this study but somewhat higher than for HR-AVR (4.5%) although these differences were non-significant.

In the SOURCE registry, the incidence of a major bleeding event was significantly greater among patients undergoing transapical versus transfemoral TAVI (3.9% vs. 2.3%), whereas the incidence of vascular access related complications was significantly higher among patients having transfemoral TAVI (major—11.3% vs. 2.0%; minor—10.4% vs. 1.0%) (125,127–129). In our results reintervention for bleeding in TA group is increased almost by two-fold when compared to TF (8.3% vs. 4.9%). In consonance, vascular related complications were absent in TA (0%) while 9.8% in TF. This has an important impact in the overall TAVI cardiovascular morbidity in our study, which results significantly higher than in HR-AVR (7.5% vs. 0%, $p<0.05$). Likewise stroke rates differ between 7.3% for TA and 16.7% for TF, causing an overall TAVI neurological complications rate of 9.4%, between two and tree-fold higher to those reported in the main registries and statistically significant different than for the HR-AVR group (0%).

Permanent pacemaker placement is reported in between 1.8% up to 8.5% of patients with Sapien and 19.1% to 42.5% with the CoreValve (90,125). Our study did not differenciate between prosthetic implant type, but TF pacemaker rhythm at discharge was 24.4% whereas in the TA group only 8.3% (p=ns). In the same direction overall pacemaker rhythm at discharge was 20.8% for TAVI vs. 0% for HR-AVR ($p<0.001$).

- RESULTS OF CLINICAL TRIALS

A robust knowledge of the current scientific literature is mandatory to place this technology in perspective. Data from multiple single-center series, and national and commercial registries are available for both transcatheter aortic and mitral procedures. Randomized clinical trials represent the highest form of evidence-based medicine and form the backbone of regulatory approval and instructions for use. Up to the present date, only the results of one trial of transcatheter aortic valves have been published: the PARTNER trial has received a great deal of interest. Specific

details about patient selection, protocols used, endpoints, and statistical evaluation are crucial.

*Table 1. Main registries for Sapien Valve.*

| Characteristic | REVIVE, REVIVAL, PARTNER EU (N=222) | SOURCE Registry (TF) (N=920) | France Registry (N=1,137) | Belgium Registry (N=303) | Canada Registry (TF) (N=162) |
|---|---|---|---|---|---|
| **Demographics** | | | | | |
| Age (y) | 83 | 82 | 83 | 83 | 83 |
| Female (%) | 55 | 56 | 49 | 46 | 44 |
| EuroSCORE (mean, %) | 26 | 24 | 23 | 29 | 26 |
| NYHA functional class III/IV (%) | 89 | 76 | 75 | 80 | 93 |
| Aortic valve area ($cm^2$) | 0.59 | 0.70 | 0.67 | 0.60 | 0.63 |
| Mean gradient (mm Hg) | 45 | 49 | 48 | 47 | 48 |
| Prior CABG (%) | 26 | 15 | 19 | 20 | 30 |
| Ejection fraction (%) | 51 | 52 | 53 | 50 | 55 |
| **Outcomes** | | | | | |
| 30-day mortality (%) | 10.4 | 7.5 | 7.8 | 8 | 9.5 |
| 1-y mortality (%) | 24 | 18.9 | NR | NR | NR |
| Stroke (%) | 3.3 | 3.5 | 3.5 | 5.0 | 3.0 |
| Major vascular complications (%) | 27.9 | 11.3 | 11.3 | NR | 13.1 |
| Permanent pacemaker (%) | 1.8 | 6.7 | 8.5 | 4.0 | 3.6 |

CABG = coronary artery bypass graft; NR = not reported; NYHA = New York Heart Association; TF = transfemoral.

*Table 2. Main registries for CoreValve.*

| Characteristic | Tamburino et al. [109] (N=663) | Milan [107] (N=61) | French [106] (N=66) | Spanish [97] (N=108) | UK/Ireland [108] (N=288) | UK [115] (N=452) | German [110] (N=588) | Buellesfeld et al. [105] (N=126) |
|---|---|---|---|---|---|---|---|---|
| **Demographics** | | | | | | | | |
| Age (y) | 82 | 79 | 82.5 | 78.6 | 81 | 81.3 | 81.4 | 81.9 |
| Female (%) | 56 | 47 | 51.5 | 54.6 | NR | 48 | 55.8 | 57.1 |
| EuroSCORE (mean, %) | 23 | 26.6 | 24.7 | 16 | 22 | 18.1 | 20.8 | 23.4 |
| NYHA functional class III/IV (%) | 71.5 | 69 | 74.6 | 58.4 | 74 | 73.9 | 88.2 | 74.6 |
| Mean gradient (mm Hg) | 52 | 54 | 46 | 55 | NR | NR | 48.7 | 46.8 |
| **Outcomes** | | | | | | | | |
| Procedural success (%) | 98 | 98.4 | 92.6 | 98.1 | 97.5 | 98.2 | NR | 72.6 |
| 30-day mortality (%) | 5.9 | 2.2 | 15.1 | 7.4 | 4.7 | 5.8 | 12.4 | 15.2 |
| 1-y mortality (%) | 15 | 18.4* | NR | 17.7 | NR | 21.7 | NR | 38.1** |
| Stroke (%) | 2.5 | 2.2 | 4.5 | 0.0 | 4.2 | 4.0 | 2.8 | NR |
| Major vascular complications (%) | 2.0 | 21.3 | 7.5 | 5.6 | 9.0 | 6.2 | 4.0 | NR |
| Permanent pacemaker (%) | 19.1 | 26.1 | 25.7 | 35.2 | 26 | 24.4 | 42.5 | 26.2 |

* 6-month survival. ** 2-year survival.

N = number; NR = not reported; NYHA = New York Heart Association.

The PARTNER trial was basically 2 parallel trials that enrolled the highest-risk patients ever seen in any cardiovascular trial by virtue of their age and severity of comorbid conditions: 1) PARTNER Cohort A, which randomized high-risk surgical patients to either traditional aortic valve replacement or to TAVI by either a

transfemoral or transapical approach; and 2) PARTNER Cohort B in which patients who were inoperable were randomized to either a TAVI by a transfemoral approach or to conventional medical therapy, which typically con- sisted of balloon aortic valvuloplasty. Screening required an evaluation by 2 experienced cardiac surgeons to agree on the surgical risk using the STS Predicted Risk of Mortality score (20) and was rigorous, with approximately one quarter to one third of screened patients subsequently enrolled. The primary endpoint was death from any cause at 1 year.

The results of PARTNER Cohort B have recently been published (9) and included 358 patients deemed unsuitable for conventional aortic valve replacement because of predicted probability of >50% mortality or at risk for a serious irreversible complication by 30 days. At 1 year, all-cause mortality with TAVI was 30.7% versus 50.7% with medical therapy (hazard ratio: 0.55, 95% confidence interval: 0.40 to 0.74). Despite the marked improvement in survival and event-free survival, there were some significant safety hazards, particularly a higher incidence of major strokes (5.0% versus 1.1%) as well as increased major vascular complications (16.2% versus 1.1%) with TAVI, both of which may impact early and longer-term outcome adversely.

The preliminary results of the PARTNER Cohort A trial were presented and, the primary endpoint of the trial was met, with TAVI found to be non-inferior to aortic valve replacement for all-cause mortality at 1 year (TAVI versus aortic valve replacement, 24.2% versus 26.8%, respectively, $p<0.001$ for non-inferiority). Death at 30 days was lower than expected in both arms of the trial: TAVI mortality (3.4%) was the lowest reported in any series, despite an early generation device and limited previous operator experience. Aortic valve replacement mortality (6.5%) was lower than the expected operative mortality (11.8%).

In our study, mean long-term follow-up was 1.49+/-1.22 years (range 0-4.66 years) in the whole 120 cases series. 0.99+/-0.75 years (range 0-3.35 years) in the TAVI group and 1.90+/-1.38 years (range 0.02-4.66 years) in the HR-AVR group. Cumulative survival was 83.0% and 81.4% for each group, respectively (global

survival 82.1%). Log-rank test resulted non significant between both groups. Intermediate 1-year survival analysis was also performed with an estimated overall survival of 88.6% (95% CI 82.8-94.4), 85.5% (74.9-96.1) for TAVI and 90.9% (84.1-97.8) for HR-AVR groups, with a non-relevant log-rank test result and in consonance with the PARTNER results.

Furthermore, in PARTNER Cohort A both TAVI and aortic valve replacement were associated with important but different periprocedural hazards: major strokes at 30 days (3.8% versus 2.1%, p=0.20) and 1 year (5.1% versus 2.4%, p=0.07), and major vascular complications were more frequent with TAVI (11.0% versus 3.2%, p<0.001). Major bleeding (9.3% versus 19.5%, p<0.001) and new onset atrial fibrillation (8.6% versus 16.0%, p<0.001) were more frequent with aortic valve replacement. We present a relatively high 30-days stroke rate in TAVI of 9.4% significantly higher than 0% for selected matched controls (HR-AVR). Reintervention for major bleeding rates and atrial fibrillation rhythms on discharge were similar in our TAVI and HR-AVR series (5.7% vs. 7.5% and 15.1% vs. 13.4% respectively).

The 30-day mortality in PARTNER Cohort A (3.4%) and PARTNER Cohort B (5.2%) is better than published European registry mortality (8.5%) (21–23) as well as for our series (7.5% for TAVI). This raises questions about the “generalizability” of these trial results after commercialization. Responsible diffusion of this technology with close monitoring of outcomes after commercialization will be critical to maintain these results. The incidence of neurologic events (5.5% at 30 days, 8.3% at 1 year) and major vascular complications (11%) that occur in patients undergoing TAVI also needs to be addressed. The results presented in this work also support this evidence.

In conclusion**,** the approval of TAVI represents a fundamental change in the management of aortic valvular heart disease by offering an alternative to traditional surgical aortic valve replacement in carefully selected patients. The penetration of this technology in the broad group of patients with AS remains to be determined and will depend on the continued evolution of the technology and the results of clinical

trials conducted in these patients. At the present time, several observations and recommendations can be extracted from the review of the current literature (Table 3) (119).

*Table 3. Present recommendations for the treatment of aortic stenosis*

| Treatment | Indication | Major Complications |
|---|---|---|
| Surgical Aortic Valve Replacement | • Symptomatic severe AS (Class I, LOE: B)<br>• Severe AS undergoing CABG, aortic surgery or other valve surgery (Class I, LOE: C)<br>• Symptomatic moderate AS undergoing CABG, aortic surgery or other valve surgery (Class IIa, LOE: C)<br>• Asymptomatic severe AS with hypotensive response to exercise (Class IIb; LOE: C)<br>• Asymptomatic extremely severe AS (AVA <0.6 $cm^2$, mean gradient >50 mm Hg, or jet velocity >5 m/s) (Class IIb, LOE: C) | • Mortality (3%)<br>• Stroke (2%)<br>• Prolonged ventilation (11%)<br>• Thromboembolism and bleeding<br>• Prosthetic dysfunction<br>• Perioperative complications are higher when surgical AVR is combined with CABG |
| Transcatheter Aortic Valve Replacement | • TAVR is recommended in patients with severe, symptomatic, calcific stenosis of a trileaflet aortic valve who have aortic and vascular anatomy suitable for TAVR and a predicted survival >12 months, and who have a prohibitive surgical risk as defined by an estimated 50% or greater risk of mortality or irreversible morbidity at 30 days or other factors such as frailty, prior radiation therapy, porcelain aorta, and severe hepatic or pulmonary disease.<br>• TAVR is a reasonable alternative to surgical AVR in patients at high surgical risk (PARTNER Trial Criteria: STS≥8%.*) | • Mortality (3% to 5%)<br>• Stroke (6% to 7%)<br>• Access complications (17%)<br>• Pacemaker insertion<br>○ 2% to 9% (Sapien)<br>○ 19% to 43% (CoreValve)<br>• Bleeding<br>• Prosthetic dysfunction<br>• Paravalvular AR<br>• Acute kidney injury<br>• Other<br>○ Coronary occlusion<br>○ Valve embolization<br>○ Aortic rupture |
| Balloon Aortic Valvuloplasty | • Reasonable for palliation in adult patients with AS in whom surgical AVR cannot be performed because of serious comorbid conditions (Class IIb, LOE: C)<br>• Bridge to surgical AVR (Class IIb, LOE: C) | • Mortality<br>• Stroke<br>• Access complications<br>• Restenosis |
| Medical Therapy | • No specific therapy for asymptomatic AS<br>• Medical therapy not indicated for symptomatic severe AS<br>• Appropriate control of blood pressure and other risk factors as indicated<br>• Statins not indicated for preventing progression of AS<br>• Diuretics, vasodilators and positive inotropes should be avoided in patients awaiting surgery because of risk of destabilization | • Hemodynamic instability |

* The original PARTNER protocol specified inclusion criteria as a minimum STS-predicted risk of mortality of ≥10. During the trial enrollment phase, the minimum STS-predicted risk of mortality was changed to ≥8. In both instances, 2 surgeons had to document that the true predicted risk of mortality was ≥15.

Class I: Conditions for which there is evidence for and/or general agreement that the procedure or treatment is beneficial, useful, and effective; Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment; Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy; Class IIb: Usefulness/efficacy is less well established by evidence/opinion; LOE B: Data derived from a single randomized trial or nonrandomized studies; LOE C: Only consensus opinion of experts, case studies, or standard-of-care.

AR = aortic regurgitation; AS = aortic stenosis; AVR = aortic valve replacement; CABG = coronary artery bypass graft; LOE = level of evidence; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement.

## 3. Health care costs and effectiveness

With the population aging, AS is becoming a more prevalent public health issue. Medical therapy is unlikely to modify the course of the disease, especially once symptoms or left ventricular dysfunction become manifest. Percutaneous balloon aortic valvuloplasty has only a limited role in the treatment of AS, as the results are not durable. Surgical AVR remains the mainstay of definitive treatment. Although surgical therapy is effective, it entails the risks and morbidity associated with cardiopulmonary bypass and median sternotomy. When a frail and elderly patient with significant comorbidities presents with severe AS, he or she may be precluded from surgical AVR due to potentially high operative risks. TAV implantation with its less invasive nature is believed to offer a safer treatment solution for these patients.

According to the 2010 EACTS Database Report, over 40.000 isolated AVR and over 25.000 combined AVR plus coronary surgery procedures were performed during 2008 in the Europe. Heart valve replacement has long been proven to be clinically effective in extending life expectancy and improving quality of life. It is increasingly performed in older patients, including those aged more than 80 years or even more than 90 years. The clinical effectiveness of this technique has been well documented, but only few studies focus on cost-effectiveness, especially when considering the modern TAVI techniques. New technologies are often cited as a major contributor to increasing healthcare costs. Before a new technology or clinical strategy is widely adopted, it is therefore important to understand the clinical and economic benefits that any increased upfront expenditures may yield. Given the advanced age and multiple comorbid conditions that characterize patients with high surgical risk for surgical valve replacement, the question of whether TAVI can provide meaningful health benefits to the population at an acceptable cost is particularly appropriate.

Cost-effective analysis has long been used to compare 2 treatments on the basis of their economic and clinical outcomes (130). The results of a cost-effective

analysis are summarized as a cost-effective ratio (CER), of which the numerator is the difference of the costs of the 2 treatments and the denominator is the difference of the Quality Adjusted Life Years (QALYs). Thus, the CER provides the cost for gaining 1 additional QALY and is commonly used to judge whether a treatment is worth its costs compared with an alternative treatment. Wu and colleagues published that concerning conventional AVR, the CER increased according to age at surgery. Still, the CER was less than €16,000 per QALY for all but the nonagenarians, and it was only €21,000 per QALY for them. There are generally accepted thresholds: A treatment costing less than €15,000/QALY is considered very cost- effective, between €15,000 and €75,000/QALY is acceptable, and more than €75,000/QALY is not cost-effective (131). Despite the limitations, this is well within generally accepted thresholds, making AVR very cost-effective(130).

Reynolds and colleagues (132) have set the CER for TAVI versus standard care of €38,500 per year of life gained. The cost-effectiveness of TAVI for patients with inoperable aortic stenosis is also well within the range of other cardiovascular technologies commonly used (133), including implantable defibrillators for the primary prevention of sudden cardiac death (134,135) and catheter ablation for atrial fibrillation (136), and far below recent estimates of the cost-effectiveness of percutaneous coronary intervention versus medical therapy for patients with stable coronary artery disease (137) or left ventricular assist devices (138).

Despite providing substantial cost offsets during the first year of follow-up, among the highly complex, inoperable patients enrolled in the PARTNER trial (Cohort B), TAVI did not result in long-term cost savings. In fact, empirically derived projections (132) suggest that the cost difference between TAVI and standard therapy actually increased beyond the first year of follow-up as a result of the greater life-expectancy for the TAVI group coupled with the high cost of ongoing medical care even after successful valve replacement in this patient population. Given the very large survival benefit observed in the PARTNER trial (cohort B), it appears unlikely that such a study will be repeated, and the control group from our study will remain the benchmark for future clinical and economic evaluations of this technique among inoperable patients.

## 4. Rationale of indication and discrimination for TAVI

The evolution of transcatheter valve therapy raises important questions for practitioners, patients, and government agencies on the appropriate treatment strategy for patients who could be eligible for this procedure or whether it results inappropriate or futile.

Therapeutic futility may be determined based upon: 1) lack of medical efficacy, as judged by the patient's physician; or 2) lack of a meaningful survival, as judged by the personal values of the patient. Although therapeutic futility may be invoked to justify denial, limitation, or withdrawal of care, the threshold for defining it is unclear, controversial, and often viewed differently among interested parts. In the PARTNER trial, the criterion for inoperability—used as a surrogate for futility with regards to surgical intervention—was an estimate of probability of death or serious, irreversible morbidity >50% by a cardiologist and 2 experienced cardiothoracic surgeons (7). Despite successful correction of AS leading to an absolute 20% survival advantage, there was still 30% mortality in the TAVI treatment arm at 1 year, mainly due to non-cardiac causes. The key to treatment in this group of "inoperable" patients is to define the "futility versus utility" treatment paradigm. Clearer definition of comorbid conditions that adversely affect survival despite successful valve implementation as well as quality of life and health economic assessment in those "inoperable" patients is crucial so that this therapy is appropriately used in patients likely to benefit (utility) compared with those unlikely to benefit despite successful therapy (futility). Although some might argue that it is inappropriate and misleading to say that treatment is futile simply because the probability that it will succeed is small, especially given the substantial uncertainty in our ability to prognosticate in individual patients and lack of validated tools that universally discriminate survivors from non-survivors, it is nonetheless important to define meaningful cutoff points.

Ethical frameworks can offer a different point of view: it would look simply at the patient and the feasibility of implanting a percutaneous aortic valve. If the patient were deemed a suitable candidate, he or she would be offered this intervention. If the patient is an appropriate candidate for TAVI, it should be offered to the patient to improve his or her quality of life and to relieve suffering. A majority of clinicians would follow this principle of justice (139).

However, as previously described, In terms of the possibility of rationing TAVI procedures, the costs of this procedure need to be compared with other existing technologies and treatments. Wu and colleagues (130) have looked at the cost-effective ratio (CER or monetarily costs per life year gained) of standard aortic valve replacement and shown that for a 75-year-old patient the average CER is €13,000. This is compared with a CER of €38,500 for TAVI procedures (132). These costs take into consideration the quality of life, hospital costs, and need for extended care. Although this difference is substantial, TAVI has already proven to be a successful and useful technology for high-risk surgical patients with critical aortic stenosis. The increased procedural and device costs of TAVI compared with a surgical aortic valve prosthesis and replacement surgery put TAVI procedures at risk for future health care rationing as part of health care reform to minimize growing health care costs in the western world. Nevertheless, it needs to be considered that the CER of TAVI procedures is in line with other existing technologies (like hemodialysis) and therefore should not be singled out as an 'expensive'' new technology. The principles of justice in health care rationing also support continued use of TAVI procedures in high-risk patients.

The real world experience shows that uncontrolled diffusion of new medical technology has been a major source of the current crisis in funding for medical care. Given the growing elderly population in this country and the incidence of aortic valve sclerosis in this aging population, there is a significant likelihood that use of TAVI for all elderly patients with aortic valve disease could add significantly to the health expenditures for cardiovascular disease.

It is important to differenciate between efficacy and effectiveness, indeed. The efficacy assessment is typically based on randomized clinical trials, such as the PARTNER trial, in carefully defined clinical populations. Effectiveness has been described as the outcome when this same device is deployed in the general population by the medical profession. The assessments of effectiveness involve the medical profession's obligations to society to self-regulate and to wisely allocate what is now becoming a scarce societal resource. Mayer and others (140) have argued that if the medical profession does not actively engage in this effectiveness assessment, then major resource allocation decisions will be made by those who o not take care of patients, and then the medical profession will have forfeited an important role and responsibility in society. If physicians and surgeons indiscriminately apply a new and expensive technology to any patient who might benefit, even if it will minimally prolong life or marginally reduce suffering, can the medical profession argue that there has been a wise use of society's health care? (141,142).

The current direction in the study of TAVI moves towards providing directions to cardiologists and surgeons involved in this therapy to identify subgroups of patients for whom this therapy will provide superior or little benefit; or whether it could result in significant harm. In our study we identified preoperative risk factors that act as independent predictors for perioperative mortality by multivariate logistic regression analysis: extracardiac arteropathy, left ventricular impairment and significant pulmonary hypertension. We demonstrated that these factors not only play an important role on 30-days outcome, but also that its relative impact for each procedure group (TAVI or conventional AVR) is different. Hence our new scoring system acts as an easy preoperative clinical decision making tool, by discriminating high-risk considered patients candidates for either TAVI or conventional AVR. By classifying them in the ´Low Profile´ or ´High Profile´ score groups one can easy decide towards TAVI or conventional AVR, as our Classification and Regression Trees (CRT) show important differences in perioperative mortality between them (see Results section for details).

Internal validation of the new score was tested. Discrimination capacity was addressed by means of ROC curve analysis and CRT construction. As expected, the performance and discrimination of the new score was better than EuroSCORE when high-risk profile patients (EuroSCORE > 15 or HR-AVR matched controls) were considered, but not when the overall database neither when the low-risk profile (logistic EuroSCORE < 15) group were evaulated. This brings up an important consideration, which is that the score seems only applicable to high-risk patients whereas low-risk patients would probably be straightforwardly be addressed towards conventional AVR, the current gold-standard. On the other hand, clearly inoperable patients as described in PARTNER Cohort B are widely accepted to be directly addressed for TAVI. In the in-between PARTNER cohort B and low-risk profile patients lays a huge ´grey zone´ of elderly, high-risk considered, comorbid patients with aortic stenosis, were our score seems to appropriately discriminate and hence it should be used.

External validation is a crucial issue that still needs to be addressed. We hypothesized by modeling a random ´dummy´ database with identical preoperative and outcome characteristics as in PARTNER Cohort A trial, by random allocation of variables for 699 ´dummy´ patients in the database. Therefore our new score was tested and CRT showed discrimination capacity for High-Profile group, favoring TAVI by two-fold, but was non-discriminant in the 'Low-Profile' arm of the tree. ROC curves also returned a better performance of the new score when compared to logistic EuroSCORE (see Results section for details). These results are based upon statistical modeling, but if they are confirmed in further studies they will provide an important step forward preoperative management of a especially controversial group of patients, and perhaps help in better decision-making to improve outcomes and cost-effectiveness of high-risk aortic valve replacement surgery.

# 5. Conclusions

TAVI represents a milestone in the treatment of calcific aortic stenosis and probably the most important advance in cardiac surgery in the last decade. It has transformed the general overview of valve disease and forced surgeons, interventional and clinical cardiologists to closely work together for the benefit of the patient. Up to the present date, no objective discrimination tool has been described for preoperative decision-making in high-risk aortic valve replacement surgery, causing heterogeneous eligibility and selection criteria among the different studies published in medical literature, that are mainly based upon expert consensus or commercial recommendations.

This work proposes for the first time in medical literature a clinical tool for preoperative decision-making in high-risk aortic valve replacement candidates for TAVI or conventional AVR, based in commonly known and easily determined preoperative variables. Primary and secondary endpoints (as described in the Methods section) were achieved and our work hypothesis confirmated, for which the following conclusions can be extracted:

1. The current direction in the study of TAVI moves towards providing guidelines to cardiologists and surgeons involved in this therapy to identify subgroups of patients for whom this therapy will provide superior or little benefit; or whether it could result in significant harm. In our study we identified preoperative risk factors that act as independent predictors for perioperative mortality by multivariate logistic regression analysis: extracardiac arteropathy, left ventricular impairment and significant pulmonary hypertension. We demonstrated that these factors not only play an important role on 30-days outcome, but also that the relative impact for each procedure group (TAVI or conventional AVR) is different.

2. Extracardiac arteropathy, severe pulmonary hypertension and left ventricular dysfunction were identified as independent predictors for perioperative

mortality in the multivariate logistic regression analysis (B regression coefficients of 2.080, 1.662 and 1.083 respectively). Patients were classified into Low Profile or High Profile according to the presence or absence of these variables and a Classification and Regression Tree was built to discriminate between TAVI and AVR for 30-days mortality in each group. TAVI mortality was significantly lower than AVR in the High Profile group (11.1% vs. 33.3%) whereas it was higher in the Low Profile group (6.8% vs. 0%), evidencing the discrimination capacity of the model. Returned receptor-operator characteristics area under the curve was 0.835 (0.638-1.000). Hence our new scoring system acts as an easy preoperative clinical decision making tool, discriminating high-risk considered patients candidates for either TAVI or conventional AVR. By means of classifying them in the ´Low Profile´ or ´High Profile´ score groups one can easy decide towards TAVI or conventional AVR.

3. Internal validation of the new score was tested in the overall 468 patients' series and in the logistic EuroSCORE <15 and > 15 subgroups. Acceptable discrimination was achieved in the high-risk subgroup (logistic EuroSCORE>15) exclusively, whereas in the low-risk subgroup (logistic EuroSCORE < 15) or in the overall series it resulted to be non-discriminant. Consequently its application seems to be limited to the operable high-risk profile group of patients that could be suitable for both techniques (TAVI or conventional AVR) where decision-making is still controversial.

4. External validation of the new score needs to be properly addressed. We statistically modelized a random 'dummy' database with similar characteristics in terms of preoperative risk, comorbidities and perioperative mortality than in the PARTNER Cohort A series, and tested the new score in it, with acceptable discrimination capacity. However, it needs to be tested in larger and different series in the real world yet. Weighting of the variables included might change as well as different new variables might come into scene with its application. It should be a dynamic tool that would need to be periodically reviewed and updated.

5. According to our results, TAVI seems non-inferior to conventional AVR for operable high-risk patients, although stroke and postoperative pacemaker rates (specially for TF approach) and learning curve effect (specially for TA approach) are still crucial issues for this novel procedure.

6. No differences in terms of preoperative risk variables or comorbidities nor perioperative mortality and long-term survival between TAVI and matched HR-AVR groups were found. MACCE was significantly higher in TAVI (17.0% vs. 4.5%, $p<0.05$) than in matched HR-AVR as well as pacemaker rhythm at patients' discharge (20.8% vs. 0%, $p<0.001$). Relevant intensive care unit length-of-stay differences in TAVI (2.03+/-2.58 days) vs. matched HR-AVR (3.33+/-1.80 days) were appreciable, although these disappeared when a subgroup analysis using a logistic EuroSCORE cutoff value of 15% was performed.

7. In the same direction, we found that additive EuroSCORE seems to have a better correlation with perioperative mortality in the high-risk series whereas logistic EuroSCORE has similarities with MACCE. However, this hypothesis is out of the purpose of the present study and it should be addressed separately.

8. Extracardiac arteropathy (OR 8.083, 95% CI 1.652-39.545) was found to be the only predictor of 30-days mortality after univariate logistic regression analysis in the TAVI vs. matched HR-AVR high-risk series. Interestingly, different variables resulted significant predictors for MACCE composite event: TAVI approach (OR 4.364, 95% CI 1.118-17.033), especially TA approach (OR 6.333, 95% CI 1.103-36.370), age (OR 1.240, 95% CI 1.052-1.460) and preoperative AF (OR 4.686, 95% CI 1.303-33.683).

9. Multivariate Cox regression analysis was performed in order to ascertain the impact of the different approaches (MS, TF or TA) and the year in which

surgery was performed in long-term survival. No statistical differences were found among those variables, although negative B regression coefficients in the year timeline advocate a 'protective' effect and evidence a certain degree of learning curve effect in mortality. To sum up, non-significant odds ratios for the different approaches suggest that the worse performance of TA when compared to TF or MS is not attributable to the technique itself.

## 6. Limitations of the study

This study is based on non-randomized retrospective data from a single institution. Although it addresses important issues for the first time (like objective clinical preoperative decision-making), it is provides limited number of observations and their results might non be applicable to different populations than the one intended.

In the same direction, external validation of the results provided by the new scoring system, although it has been satistically modellized, it has not been tested in the real world yet. Furthermore, applying the score to larger and different populations may result in changes in the current score variables and proportions. Like in the Heisenberg's uncertainty principle for quantum physics, application of the score can result in group reclassification and therefore different risk variables might appear and be added or modified to the score. Subsequently it certainly will need frequent review and update.

# References


1. Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. Circulation. 2005 feb 22;111(7):920–5.

2. Selzer A. Changing aspects of the natural history of valvular aortic stenosis. N. Engl. J. Med. 1987 jul 9;317(2):91–8.

3. Spann JF, Bove AA, Natarajan G, Kreulen T. Ventricular performance, pump function and compensatory mechanisms in patients with aortic stenosis. Circulation. 1980 sep;62(3):576–82.

4. Carabello BA, Paulus WJ. Aortic stenosis. Lancet. 2009 mar 14;373(9667):956–66.

5. Carabello BA, Green LH, Grossman W, Cohn LH, Koster JK, Collins JJ Jr. Hemodynamic determinants of prognosis of aortic valve replacement in critical aortic stenosis and advanced congestive heart failure. Circulation. 1980 jul;62(1):42–8.

6. Gardin JM, Kaplan KJ, Meyers SN, Talano JV. Aortic stenosis: can severity be reliably estimated noninvasively? Chest. 1980 feb;77(2):130–1.

7. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010 oct;363(17):1597–607.

8. Chizner MA, Pearle DL, deLeon AC Jr. The natural history of aortic stenosis in adults. Am. Heart J. 1980 abr;99(4):419–24.

9. Ross J Jr, Braunwald E. Aortic stenosis. Circulation. 1968 jul;38(1 Suppl):61–7.

10. Schwarz F, Baumann P, Manthey J, Hoffmann M, Schuler G, Mehmel HC, et al. The effect of aortic valve replacement on survival. Circulation. 1982 nov;66(5):1105–10.

11. Kitai T, Honda S, Okada Y, Tani T, Kim K, Kaji S, et al. Clinical outcomes in non-surgically managed patients with very severe versus severe aortic stenosis. Heart. 2011 dic;97(24):2029–32.

12. Ben-Dor I, Pichard AD, Gonzalez MA, Weissman G, Li Y, Goldstein SA, et al. Correlates and causes of death in patients with severe symptomatic aortic stenosis who are not eligible to participate in a clinical trial of transcatheter aortic valve implantation. Circulation. 2010 sep 14;122(11 Suppl):S37–42.

13. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, et al. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2008 oct 7;118(15):e523–661.

14. Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, et al. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Eur Heart J. 2007 ene;28(2):230–68.

15. Davies SW, Gershlick AH, Balcon R. Progression of valvar aortic stenosis: a long-term retrospective study. Eur. Heart J. 1991 ene;12(1):10–4.

16. Cheitlin MD, Gertz EW, Brundage BH, Carlson CJ, Quash JA, Bode RS Jr. Rate of progression of severity of valvular aortic stenosis in the adult. Am. Heart J. 1979 dic;98(6):689–700.

17. Faggiano P, Aurigemma GP, Rusconi C, Gaasch WH. Progression of valvular aortic stenosis in adults: literature review and clinical implications. Am. Heart J. 1996 ago;132(2 Pt 1):408–17.

18. Otto CM, Burwash IG, Legget ME, Munt BI, Fujioka M, Healy NL, et al. Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. Circulation. 1997 may 6;95(9):2262–70.

19. Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. N. Engl. J. Med. 2000 ago 31;343(9):611–7.

20. Rosenhek R, Zilberszac R, Schemper M, Czerny M, Mundigler G, Graf S, et al. Natural history of very severe aortic stenosis. Circulation. 2010 ene;121(1):151–6.

21. Palta S, Pai AM, Gill KS, Pai RG. New insights into the progression of aortic stenosis: implications for secondary prevention. Circulation. 2000 may 30;101(21):2497–502.

22. Otto CM, Pearlman AS, Gardner CL. Hemodynamic progression of aortic stenosis in adults assessed by Doppler echocardiography. J. Am. Coll. Cardiol. 1989 mar 1;13(3):545–50.

23. Roger VL, Tajik AJ, Bailey KR, Oh JK, Taylor CL, Seward JB. Progression of aortic stenosis in adults: new appraisal using Doppler echocardiography. Am. Heart J. 1990 feb;119(2 Pt 1):331–8.

24. Faggiano P, Ghizzoni G, Sorgato A, Sabatini T, Simoncelli U, Gardini A, et al. Rate of progression of valvular aortic stenosis in adults. Am. J. Cardiol. 1992 jul 15;70(2):229–33.

25. Pellikka PA, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG, et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. Circulation. 2005 jun 21;111(24):3290–5.

26. Bahler RC, Desser DR, Finkelhor RS, Brener SJ, Youssefi M. Factors leading to progression of valvular aortic stenosis. Am. J. Cardiol. 1999 nov 1;84(9):1044–8.

27. Pohle K, Mäffert R, Ropers D, Moshage W, Stilianakis N, Daniel WG, et al. Progression of aortic valve calcification: association with coronary atherosclerosis and cardiovascular risk factors. Circulation. 2001 oct 16;104(16):1927–32.

28. Cosmi JE, Kort S, Tunick PA, Rosenzweig BP, Freedberg RS, Katz ES, et al. The risk of the development of aortic stenosis in patients with «benign» aortic valve thickening. Arch. Intern. Med. 2002 nov 11;162(20):2345–7.

29. Turina J, Hess O, Sepulcri F, Krayenbuehl HP. Spontaneous course of aortic valve disease. Eur. Heart J. 1987 may;8(5):471–83.

30. Faggiano P, Antonini-Canterin F, Ribichini F, D'Aloia A, Ferrero V, Cervesato E, et al. Pulmonary artery hypertension in adult patients with symptomatic valvular aortic stenosis. Am. J. Cardiol. 2000 ene 15;85(2):204–8.

31. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. J Am Soc Echocardiogr. 2009 ene;22(1):1–23; quiz 101–102.

32. Popović AD, Thomas JD, Nesković AN, Cosgrove DM 3rd, Stewart WJ, Lauer MS. Time-related trends in the preoperative evaluation of patients with valvular stenosis. Am. J. Cardiol. 1997 dic 1;80(11):1464–8.

33. Blais C, Burwash IG, Mundigler G, Dumesnil JG, Loho N, Rader F, et al. Projected valve area at normal flow rate improves the assessment of stenosis severity in patients with low-flow, low-gradient aortic stenosis: the multicenter TOPAS (Truly or Pseudo-Severe Aortic Stenosis) study. Circulation. 2006 feb 7;113(5):711–21.

34. Grayburn PA. Assessment of low-gradient aortic stenosis with dobutamine. Circulation. 2006 feb 7;113(5):604–6.

35. Monin JL, Monchi M, Gest V, Duval-Moulin AM, Dubois-Rande JL, Gueret P. Aortic stenosis with severe left ventricular dysfunction and low transvalvular pressure gradients: risk stratification by low-dose dobutamine echocardiography. J. Am. Coll. Cardiol. 2001 jun 15;37(8):2101–7.

36. Nishimura RA, Grantham JA, Connolly HM, Schaff HV, Higano ST, Holmes DR Jr. Low-output, low-gradient aortic stenosis in patients with depressed left ventricular systolic function: the clinical utility of the dobutamine challenge in the catheterization laboratory. Circulation. 2002 ago 13;106(7):809–13.

37. Shanewise JS, Cheung AT, Aronson S, Stewart WJ, Weiss RL, Mark JB, et al. ASE/SCA guidelines for performing a comprehensive intraoperative multiplane transesophageal echocardiography examination: recommendations of the American Society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists Task Force for Certification in Perioperative Transesophageal Echocardiography. Anesth. Analg. 1999 oct;89(4):870–84.

38. Greenland P, Bonow RO, Brundage BH, Budoff MJ, Eisenberg MJ, Grundy SM, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography). Circulation. 2007 ene 23;115(3):402–26.

39. Hundley WG, Bluemke DA, Finn JP, Flamm SD, Fogel MA, Friedrich MG, et al. ACCF/ACR/AHA/NASCI/SCMR 2010 expert consensus document on cardiovascular magnetic resonance: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. J. Am. Coll. Cardiol. 2010 jun 8;55(23):2614–62.

40. Lancellotti P, Lebois F, Simon M, Tombeux C, Chauvel C, Pierard LA. Prognostic importance of quantitative exercise Doppler echocardiography in asymptomatic valvular aortic stenosis. Circulation. 2005 ago 30;112(9 Suppl):I377–382.

41. Connolly HM, Oh JK, Orszulak TA, Osborn SL, Roger VL, Hodge DO, et al. Aortic valve replacement for aortic stenosis with severe left ventricular dysfunction. Prognostic indicators. Circulation. 1997 may 20;95(10):2395–400.

42. Kvidal P, Bergström R, Hörte LG, Ståhle E. Observed and relative survival after aortic valve replacement. J. Am. Coll. Cardiol. 2000 mar 1;35(3):747–56.

43. Kolh P, Kerzmann A, Honore C, Comte L, Limet R. Aortic valve surgery in octogenarians: predictive factors for operative and long-term results. Eur J Cardiothorac Surg. 2007 abr;31(4):600–6.

44. Litmathe J, Feindt P, Kurt M, Gams E, Boeken U. Aortic valve replacement in octogenarians: outcome and predictors of complications. Hellenic J Cardiol. 2011 jun;52(3):211–5.

45. Pereira JJ, Balaban K, Lauer MS, Lytle B, Thomas JD, Garcia MJ. Aortic valve replacement in patients with mild or moderate aortic stenosis and coronary bypass surgery. Am. J. Med. 2005 jul;118(7):735–42.

46. Smith WT 4th, Ferguson TB Jr, Ryan T, Landolfo CK, Peterson ED. Should coronary artery bypass graft surgery patients with mild or moderate aortic stenosis undergo concomitant aortic valve replacement? A decision analysis approach to the surgical dilemma. J. Am. Coll. Cardiol. 2004 sep 15;44(6):1241–7.

47. He GW, Acuff TE, Ryan WH, Douthit MB, Bowman RT, He YH, et al. Aortic valve replacement: determinants of operative mortality. Ann. Thorac. Surg. 1994 may;57(5):1140–6.

48. Pai RG, Varadarajan P, Kapoor N, Bansal RC. Aortic valve replacement improves survival in severe aortic stenosis associated with severe pulmonary hypertension. Ann. Thorac. Surg. 2007 jul;84(1):80–5.

49. Kapoor N, Varadarajan P, Pai RG. Echocardiographic predictors of pulmonary hypertension in patients with severe aortic stenosis. Eur J Echocardiogr. 2008 ene;9(1):31–3.

50. McHenry MM, Rice J, Matlof HJ, Flamm MD Jr. Pulmonary hypertension and sudden death in aortic stenosis. Br Heart J. 1979 abr;41(4):463–7.

51. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J. Am. Coll. Cardiol. 2009 abr 28;53(17):1573–619.

52. Trachte AL, Lobato EB, Urdaneta F, Hess PJ, Klodell CT, Martin TD, et al. Oral sildenafil reduces pulmonary hypertension after cardiac surgery. Ann. Thorac. Surg. 2005 ene;79(1):194–197; discussion 194–197.

53. Herrmann S, Störk S, Niemann M, Lange V, Strotmann JM, Frantz S, et al. Low-gradient aortic valve stenosis myocardial fibrosis and its influence on function and outcome. J. Am. Coll. Cardiol. 2011 jul 19;58(4):402–12.

54. Tribouilloy C, Lévy F, Rusinaru D, Guéret P, Petit-Eisenmann H, Baleynaud S, et al. Outcome after aortic valve replacement for low-flow/low-gradient aortic stenosis without contractile reserve on dobutamine stress echocardiography. J. Am. Coll. Cardiol. 2009 may 19;53(20):1865–73.

55. Quere J-P, Monin J-L, Levy F, Petit H, Baleynaud S, Chauvel C, et al. Influence of preoperative left ventricular contractile reserve on postoperative ejection fraction in low-gradient aortic stenosis. Circulation. 2006 abr 11;113(14):1738–44.

56. Horstkotte D, Loogen F. The natural history of aortic valve stenosis. Eur. Heart J. 1988 abr;9 Suppl E:57–64.

57. Murphy ES, Lawson RM, Starr A, Rahimtoola SH. Severe aortic stenosis in patients 60 years of age or older: left ventricular function and 10-year survival after valve replacement. Circulation. 1981 ago;64(2 Pt 2):II184–188.

58. O'Brien SM, Shahian DM, Filardo G, Ferraris VA, Haan CK, Rich JB, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2–isolated valve surgery. The Annals of Thoracic Surgery. 2009 jul;88(1 Suppl):S23–42.

59. Ambler G, Omar RZ, Royston P, Kinsman R, Keogh BE, Taylor KM. Generic, simple risk stratification model for heart valve surgery. Circulation. 2005 jul 12;112(2):224–31.

60. Birkmeyer JD, Siewers AE, Finlayson EVA, Stukel TA, Lucas FL, Batista I, et al. Hospital volume and surgical mortality in the United States. N. Engl. J. Med. 2002 abr 11;346(15):1128–37.

61. Asimakopoulos G, Edwards MB, Taylor KM. Aortic valve replacement in patients 80 years of age and older: survival and cause of death based on 1100 cases: collective results from the UK Heart Valve Registry. Circulation. 1997 nov 18;96(10):3403–8.

62. Lund O, Flø C, Jensen FT, Emmertsen K, Nielsen TT, Rasmussen BS, et al. Left ventricular systolic and diastolic function in aortic stenosis. Prognostic value after valve replacement and underlying mechanisms. Eur. Heart J. 1997 dic;18(12):1977–87.

63. Villari B, Vassalli G, Betocchi S, Briguori C, Chiariello M, Hess OM. Normalization of left ventricular nonuniformity late after valve replacement for aortic stenosis. Am. J. Cardiol. 1996 jul 1;78(1):66–71.

64. Kang D-H, Park S-J, Rim JH, Yun S-C, Kim D-H, Song J-M, et al. Early surgery versus conventional treatment in asymptomatic very severe aortic stenosis. Circulation. 2010 abr 6;121(13):1502–9.

65. Föppl M, Hoffmann A, Amann FW, Roth J, Stulz P, Hasse J, et al. Sudden cardiac death after aortic valve surgery: incidence and concomitant factors. Clin Cardiol. 1989 abr;12(4):202–7.

66. Toole JM, Stroud MR, Kratz JM, Crumbley AJ 3rd, Bradley SM, Crawford FA Jr, et al. Twenty-five year experience with the St. Jude medical mechanical valve prosthesis. Ann. Thorac. Surg. 2010 may;89(5):1402–9.

67. Braunwald E. Aortic valve replacement: an update at the turn of the millennium. Eur. Heart J. 2000 jul;21(13):1032–3.

68. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. J. Am. Coll. Cardiol. 2000 oct;36(4):1152–8.

69. Rahimtoola SH. Choice of prosthetic heart valve for adult patients. J. Am. Coll. Cardiol. 2003 mar 19;41(6):893–904.

70. Verhoye JP, Merlicco F, Sami IM, Cappabianca G, Lecouls H, Corbineau H, et al. Aortic valve replacement for aortic stenosis after previous coronary artery bypass grafting: could early reoperation be prevented? J. Heart Valve Dis. 2006 jul;15(4):474–8.

71. Ross D, Jackson M, Davies J. The pulmonary autograft--a permanent aortic valve. Eur J Cardiothorac Surg. 1992;6(3):113–116; discussion 117.

72. Oury JH. Clinical aspects of the Ross procedure: indications and contraindications. Semin. Thorac. Cardiovasc. Surg. 1996 oct;8(4):328–35.

73. Pibarot P, Dumesnil JG, Briand M, Laforest I, Cartier P. Hemodynamic performance during maximum exercise in adult patients with the ross operation and comparison with normal controls and patients with aortic bioprostheses. Am. J. Cardiol. 2000 nov 1;86(9):982–8.

74. Takkenberg JJM, Klieverik LMA, Schoof PH, van Suylen R-J, van Herwerden LA, Zondervan PE, et al. The Ross procedure: a systematic review and meta-analysis. Circulation. 2009 ene 20;119(2):222–8.

75. Klieverik LMA, Takkenberg JJM, Bekkers JA, Roos-Hesselink JW, Witsenburg M, Bogers AJJC. The Ross operation: a Trojan horse? Eur. Heart J. 2007 ago;28(16):1993–2000.

76. Elkins RC, Thompson DM, Lane MM, Elkins CC, Peyton MD. Ross operation: 16-year experience. J. Thorac. Cardiovasc. Surg. 2008 sep;136(3):623–630, 630.e1–5.

77. Chambers JC, Somerville J, Stone S, Ross DN. Pulmonary autograft procedure for aortic valve disease: long-term results of the pioneer series. Circulation. 1997 oct 7;96(7):2206–14.

78. Nishimura RA, Holmes DR Jr, Reeder GS. Percutaneous balloon valvuloplasty. Mayo Clin. Proc. 1990 feb;65(2):198–220.

79. Lieberman EB, Bashore TM, Hermiller JB, Wilson JS, Pieper KS, Keeler GP, et al. Balloon aortic valvuloplasty in adults: failure of procedure to improve long-term survival. J. Am. Coll. Cardiol. 1995 nov 15;26(6):1522–8.

80. Klein A, Lee K, Gera A, Ports TA, Michaels AD. Long-term mortality, cause of death, and temporal trends in complications after percutaneous aortic balloon valvuloplasty for calcific aortic stenosis. J Interv Cardiol. 2006 jun;19(3):269–75.

81. Nietlispach F, Wijesinghe N, Wood D, Carere RG, Webb JG. Current balloon-expandable transcatheter heart valve and delivery systems. Catheter Cardiovasc Interv. 2010 feb 1;75(2):295–300.

82. Moreno PR, Jang IK, Newell JB, Block PC, Palacios IF. The role of percutaneous aortic balloon valvuloplasty in patients with cardiogenic shock and critical aortic stenosis. J. Am. Coll. Cardiol. 1994 abr;23(5):1071–5.

83. Chiam PTL, Ruiz CE. Percutaneous transcatheter aortic valve implantation: Evolution of the technology. Am. Heart J. 2009 feb;157(2):229–42.

84. Liang M, Devlin G, Pasupati S. The Incidence of Transcatheter Aortic Valve Implantation-Related Heart Block in Self-Expandable Medtronic CoreValve and Balloon-Expandable Edwards Valves. J Invasive Cardiol. 2012 abr;24(4):173–6.

85. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, et al. Two-Year Outcomes after Transcatheter or Surgical Aortic-Valve Replacement. The New England Journal of Medicine [Internet]. 2012 mar 26 [citado 2012 abr 16]; Available a partir de: http://www.ncbi.nlm.nih.gov/pubmed/22443479

86. Miller DC, Blackstone EH, Mack MJ, Svensson LG, Kodali SK, Kapadia S, et al. Transcatheter (TAVR) versus surgical (AVR) aortic valve replacement: Occurrence, hazard, risk factors, and consequences of neurologic events in the PARTNER trial. The Journal of Thoracic and Cardiovascular Surgery. 2012 abr;143(4):832–843.e13.

87. Zajarias A, Cribier AG. Outcomes and safety of percutaneous aortic valve replacement. J. Am. Coll. Cardiol. 2009 may 19;53(20):1829–36.

88. Petronio AS, De Carlo M, Bedogni F, Marzocchi A, Klugmann S, Maisano F, et al. Safety and efficacy of the subclavian approach for transcatheter aortic valve implantation with the CoreValve revalving system. Circ Cardiovasc Interv. 2010 ago;3(4):359–66.

89. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011 jun;364(23):2187–98.

90. Thomas M, Schymik G, Walther T, Himbert D, Lefèvre T, Treede H, et al. Thirty-day results of the SAPIEN aortic Bioprosthesis European Outcome (SOURCE) Registry: A European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. Circulation. 2010 jul 6;122(1):62–9.

91. Bauer F, Lemercier M, Zajarias A, Tron C, Eltchaninoff H, Cribier A. Immediate and long-term echocardiographic findings after transcatheter aortic valve implantation for the treatment of aortic stenosis: the Cribier-Edwards/Edwards-Sapien valve experience. J Am Soc Echocardiogr. 2010 abr;23(4):370–6.

92. Piazza N, Grube E, Gerckens U, den Heijer P, Linke A, Luha O, et al. Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 Fr) corevalve revalving system: results from the multicentre, expanded evaluation registry 1-year following CE mark approval. EuroIntervention. 2008 ago;4(2):242–9.

93. Wendler O, Walther T, Nataf P, Rubino P, Schroefel H, Thielmann M, et al. Trans-apical aortic valve implantation: univariate and multivariate analyses of the early results from the SOURCE registry. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2010 ago;38(2):119–27.

94. Wendler O, Walther T, Schroefel H, Lange R, Treede H, Fusari M, et al. The SOURCE Registry: what is the learning curve in trans-apical aortic valve implantation? European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2011 jun;39(6):853–9; discussion 859–60.

95. Thomas M, Schymik G, Walther T, Himbert D, Lefèvre T, Treede H, et al. One-Year Outcomes of Cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) Registry: The European Registry of Transcatheter Aortic Valve Implantation Using the Edwards SAPIEN Valve. Circulation. 2011 jul;124(4):425–33.

96. Walther T, Schuler G, Borger MA, Kempfert J, Seeburger J, Rückert Y, et al. Transapical aortic valve implantation in 100 consecutive patients: comparison to propensity-matched conventional aortic valve replacement. Eur. Heart J. 2010 jun;31(11):1398–403.

97. Buellesfeld L, Gerckens U, Schuler G, Bonan R, Kovac J, Serruys PW, et al. 2-year follow-up of patients undergoing transcatheter aortic valve implantation using a self-expanding valve prosthesis. J. Am. Coll. Cardiol. 2011 abr 19;57(16):1650–7.

98. Webb JG, Wood DA, Ye J, Gurvitch R, Masson J-B, Rodés-Cabau J, et al. Transcatheter valve-in-valve implantation for failed bioprosthetic heart valves. Circulation. 2010 abr 27;121(16):1848–57.

99. Webb J, Cribier A. Percutaneous transarterial aortic valve implantation: what do we know? Eur. Heart J. 2011 ene;32(2):140–7.

100. Lutter G, Kuklinski D, Berg G, Von Samson P, Martin J, Handke M, et al. Percutaneous aortic valve replacement: an experimental study. I. Studies on implantation. J. Thorac. Cardiovasc. Surg. 2002 abr;123(4):768–76.

101. Levi DS, Kusnezov N, Carman GP. Smart materials applications for pediatric cardiovascular devices. Pediatr. Res. 2008 may;63(5):552–8.

102. Melby SJ, Moon MR, Lindman BR, Bailey MS, Hill LL, Damiano RJ Jr. Impact of pulmonary hypertension on outcomes after aortic valve replacement for aortic valve stenosis. J. Thorac. Cardiovasc. Surg. 2011 jun;141(6):1424–30.

103. Sündermann S, Dademasch A, Praetorius J, Kempfert J, Dewey T, Falk V, et al. Comprehensive assessment of frailty for elderly high-risk patients undergoing cardiac surgery. Eur J Cardiothorac Surg. 2011 ene;39(1):33–7.

104. van Gameren M, Kappetein AP, Steyerberg EW, Venema AC, Berenschot EAJ, Hannan EL, et al. Do we need separate risk stratification models for hospital mortality after heart valve surgery? Ann. Thorac. Surg. 2008 mar;85(3):921–30.

105. Nissinen J, Biancari F, Wistbacka J-O, Loponen P, Teittinen K, Tarkiainen P, et al. Is it possible to improve the accuracy of EuroSCORE? Eur J Cardiothorac Surg. 2009 nov;36(5):799–804.

106. Bhatti F, Grayson AD, Grotte G, Fabri BM, Au J, Jones M, et al. The logistic EuroSCORE in cardiac surgery: how well does it predict operative risk? Heart. 2006 dic;92(12):1817–20.

107. Grossi EA, Schwartz CF, Yu P-J, Jorde UP, Crooke GA, Grau JB, et al. High-risk aortic valve replacement: are the outcomes as bad as predicted? The Annals of Thoracic Surgery. 2008 ene;85(1):102–6; discussion 107.

108. Wendt D, Osswald BR, Kayser K, Thielmann M, Tossios P, Massoudy P, et al. Society of Thoracic Surgeons score is superior to the EuroSCORE determining mortality in high risk patients undergoing isolated aortic valve replacement. Ann. Thorac. Surg. 2009 ago;88(2):468–474; discussion 474–475.

109. Osswald BR, Gegouskov V, Badowski-Zyla D, Tochtermann U, Thomas G, Hagl S, et al. Overestimation of aortic valve replacement risk by EuroSCORE: implications for percutaneous valve replacement. European Heart Journal. 2009 ene;30(1):74–80.

110. Dewey TM, Brown D, Ryan WH, Herbert MA, Prince SL, Mack MJ. Reliability of risk algorithms in predicting early and late operative outcomes in high-risk patients undergoing aortic valve replacement. The Journal of Thoracic and Cardiovascular Surgery. 2008 ene;135(1):180–7.

111. Dua A, Dang P, Shaker R, Varadarajan P, Pai RG. Barriers to surgery in severe aortic stenosis patients with Class I indications for aortic valve replacement. J. Heart Valve Dis. 2011 jul;20(4):396–400.

112. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. Eur. Heart J. 2003 jul;24(13):1231–43.

113. Iung B, Cachier A, Baron G, Messika-Zeitoun D, Delahaye F, Tornos P, et al. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? Eur. Heart J. 2005 dic;26(24):2714–20.

114. Mihaljevic T, Nowicki ER, Rajeswaran J, Blackstone EH, Lagazzi L, Thomas J, et al. Survival after valve replacement for aortic stenosis: implications for decision making. J. Thorac. Cardiovasc. Surg. 2008 jun;135(6):1270–1278; discussion 1278–1279.

115. Gammie JS, Brown JW, Brown JM, Poston RS, Pierson RN 3rd, Odonkor PN, et al. Aortic valve bypass for the high-risk patient with aortic stenosis. Ann. Thorac. Surg. 2006 may;81(5):1605–10.

116. Vahanian A, Alfieri OR, Al-Attar N, Antunes MJ, Bax J, Cormier B, et al. Transcatheter valve implantation for patients with aortic stenosis: a position statement from the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI). European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2008 jul;34(1):1–8.

117. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. N. Engl. J. Med. 2011 jun 2;364(22):2128–37.

118. Holmes DR Jr, Mack MJ. Transcatheter valve therapy: a professional society overview from the American College of Cardiology Foundation and the Society of Thoracic Surgeons. Ann. Thorac. Surg. 2011 jul;92(1):380–9.

119. Holmes DR Jr, Mack MJ, Kaul S, Agnihotri A, Alexander KP, Bailey SR, et al. 2012 ACCF/AATS/SCAI/STS Expert Consensus Document on Transcatheter Aortic Valve Replacement: Developed in collaboration with the American Heart Association, American Society of Echocardiography, European Association for Cardio-Thoracic Surgery, Heart Failure Society of America, Mended Hearts, Society of Cardiovascular Anesthesiologists, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. Ann. Thorac. Surg. 2012 abr;93(4):1340–95.

120. Avanzas P, Muñoz-García AJ, Segura J, Pan M, Alonso-Briales JH, Lozano I, et al. Percutaneous implantation of the CoreValve self-expanding aortic valve

prosthesis in patients with severe aortic stenosis: early experience in Spain. Rev Esp Cardiol. 2010 feb;63(2):141–8.

121. Eltchaninoff H, Prat A, Gilard M, Leguerrier A, Blanchard D, Fournial G, et al. Transcatheter aortic valve implantation: early results of the FRANCE (FRench Aortic National CoreValve and Edwards) registry. Eur. Heart J. 2011 ene;32(2):191–7.

122. Godino C, Maisano F, Montorfano M, Latib A, Chieffo A, Michev I, et al. Outcomes after transcatheter aortic valve implantation with both Edwards-SAPIEN and CoreValve devices in a single center: the Milan experience. JACC Cardiovasc Interv. 2010 nov;3(11):1110–21.

123. Moynagh AM, Scott DJA, Baumbach A, Khavandi A, Brecker SJ, Laborde J-C, et al. CoreValve transcatheter aortic valve implantation via the subclavian artery: comparison with the transfemoral approach. J. Am. Coll. Cardiol. 2011 feb 1;57(5):634–5.

124. Tamburino C, Capodanno D, Ramondo A, Petronio AS, Ettori F, Santoro G, et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. Circulation. 2011 ene 25;123(3):299–308.

125. Zahn R, Gerckens U, Grube E, Linke A, Sievert H, Eggebrecht H, et al. Transcatheter aortic valve implantation: first results from a multi-centre real-world registry. Eur. Heart J. 2011 ene;32(2):198–204.

126. Moat NE, Ludman P, de Belder MA, Bridgewater B, Cunningham AD, Young CP, et al. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. J. Am. Coll. Cardiol. 2011 nov 8;58(20):2130–8.

127. di Marco F, Gerosa G. Percutaneous aortic valve replacement: which patients are suitable for it? A quest for a controlled use. J. Thorac. Cardiovasc. Surg. 2007 feb;133(2):294–8.

128. ElBardissi AW, Shekar P, Couper GS, Cohn LH. Minimally invasive aortic valve replacement in octogenarian, high-risk, transcatheter aortic valve implantation candidates. J. Thorac. Cardiovasc. Surg. 2011 feb;141(2):328–35.

129. Higgins J, Ye J, Humphries KH, Cheung A, Wood DA, Webb JG, et al. Early clinical outcomes after transapical aortic valve implantation: a propensity-matched comparison with conventional aortic valve replacement. J. Thorac. Cardiovasc. Surg. 2011 ago;142(2):e47–52.

130. Wu Y, Jin R, Gao G, Grunkemeier GL, Starr A. Cost-effectiveness of aortic valve replacement in the elderly: an introductory study. J. Thorac. Cardiovasc. Surg. 2007 mar;133(3):608–13.

131. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. CMAJ. 1992 feb 15;146(4):473–81.

132. Reynolds MR, Magnuson EA, Wang K, Lei Y, Vilain K, Walczak J, et al. Cost-effectiveness of transcatheter aortic valve replacement compared with standard care among inoperable patients with severe aortic stenosis: results from the placement of aortic transcatheter valves (PARTNER) trial (Cohort B). Circulation. 2012 mar 6;125(9):1102–9.

133. Mark DB, Hlatky MA. Medical economics and the assessment of value in cardiovascular medicine: Part II. Circulation. 2002 jul 30;106(5):626–30.

134. Mark DB, Nelson CL, Anstrom KJ, Al-Khatib SM, Tsiatis AA, Cowper PA, et al. Cost-effectiveness of defibrillator therapy or amiodarone in chronic stable heart failure: results from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). Circulation. 2006 jul 11;114(2):135–42.

135. Sanders GD, Hlatky MA, Owens DK. Cost-effectiveness of implantable cardioverter-defibrillators. N. Engl. J. Med. 2005 oct 6;353(14):1471–80.

136. Reynolds MR, Zimetbaum P, Josephson ME, Ellis E, Danilov T, Cohen DJ. Cost-effectiveness of radiofrequency catheter ablation compared with antiarrhythmic drug therapy for paroxysmal atrial fibrillation. Circ Arrhythm Electrophysiol. 2009 ago;2(4):362–9.

137. Weintraub WS, Spertus JA, Kolm P, Maron DJ, Zhang Z, Jurkovitz C, et al. Effect of PCI on quality of life in patients with stable coronary disease. N. Engl. J. Med. 2008 ago 14;359(7):677–87.

138. Clegg AJ, Scott DA, Loveman E, Colquitt JL, Royle P, Bryant J. Clinical and cost-effectiveness of left ventricular assist devices as a bridge to heart transplantation for people with end-stage heart failure: a systematic review and economic evaluation. Eur. Heart J. 2006 dic;27(24):2929–38.

139. Wheatley GH 3rd. Use of transcatheter valve should not be rationed. J. Thorac. Cardiovasc. Surg. 2012 abr;143(4):774–5.

140. Mayer JE Jr. Transcatheter aortic valve implantation should be controlled and monitored by the medical profession. J. Thorac. Cardiovasc. Surg. 2012 abr;143(4):771–3.

141. Mayer JE Jr. Is there a role for the medical profession in solving the problems of the American health care system? Ann. Thorac. Surg. 2009 jun;87(6):1655–61.

142. Mayer J. The American health care system and the role of the medical profession in solving its problems. Ann. Thorac. Surg. 2007 nov;84(5):1432–4.

# Annex

*Annex 1. Variable definitions*

| VARIABLES | DEFINITION |
|---|---|
| | |
| **PREOPERATIVE** | |
| **Age (y)** | Age in years |
| **Gender (%male)** | Gender (male/female) |
| **EuroSCORE** | Additive score for EuroSCORE scale |
| **logEuroSCORE** | Logistic score for EuroSCORE scale |
| **Chronic Pulmonary Disease** | Long term use of bronchodilators or steroids for lung disease |
| **Extracardiac Arteropathy** | Any of or more of the following: claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the abdominal aorta, limb arteries or carotids. |
| **Neurological dysfunction** | Neurologic dysfunction severely affecting ambulation or day-to-day functioning |
| **Previous Cardiac Surgery** | Cardiac surgery in the past requiring opening of the pericardium |
| **Preoperative Renal Failure** | Preoperative creatinine level >2.2 mg/dL |
| **Active Endocarditis** | Patient still under antibiotic treatment for endocarditis at the time of surgery |
| **Preoperative Critical Status** | Any one or more of the following: ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anaesthetic room, preoperative inotropic support, intraaortic balloon counterpulsation, or preoperative acute renal failure (anuria or oliguria <10 mL/h) |
| **Unstable angor** | Rest angina requiring nitrates until arrival in the anaesthetic room |
| **EF 30/50 %** | Moderate left ventricle dysfunction (30-50%) as measured by echocardiography |
| **EF < 30%** | Severe left ventricle dysfunction (<30%) as measured by echocardiography |
| **Recent MI** | Myocardial infarction within 90 days of surgery |
| **Pulmonary Hypertension** | Systolic pulmonary artery pressure >60 mmHg |
| **Emergency** | Suregery carried out on referral before the beggining of the next working day |
| **Other than CABG** | Major cardiac procedure other than or in addition to coronary artery bypass graft surgery |
| **Surgery on Thoracic Aorta** | Surgery for disorder of the ascending, arch or descending aorta. |
| **Post MI VSD** | Post infarction ventricular septal defect. |
| **Mitral Reguritation** | Moderate or severe mitral valve regurgitation (grades III or IV) |

| | |
|---|---|
| | as measured by echocardiography |
| **NYHA III/IV** | New York Heart Association functional class grades III or IV |
| **CHF** | Clinical or radiologic signs of left heart failure (ortopnea, pulmonary edema, etc) |
| **Calcified Aorta** | Severe calcification of the ascending, arch or descending aorta identified by preoperative image studies. |
| **Diabetes** | Diabetes mellitus under pharmacologic or insulin control |
| | |
| **RHYTHM (PREOP)** | Preoperative cardiac rhythm on electrocardiography |
| **sinus rhythm** | sinus rhythm |
| **AF rhythm** | atrial fibrillation |
| **PCM rhythm** | pacemaker rhythm |
| | |
| **CORONARY DISEASE** | Presence of ischemic coronary disease identified by haemodinamic studies |
| **PTCA** | Previous preoperative precutaneous transluminal coronary angioplasty |
| **CABG** | One or more coronary artery bypass grafts in addition to aortic valve replacement |
| **No vessels** | Number of diseased coronary vessels |
| **No grafts** | Number of coronary artery bypass grafts performed |
| | |
| **ANATOMICAL & MORPHOMETRIC** | |
| **Weight (kg)** | Wheight in kilograms |
| **Height (cm)** | Height in centimeters |
| **BSA** | Body Surface Area in m2 |
| **BMI** | Body Mass Index in kg/m2 |
| **Valve area** | Aortic valve area by planimetry on ultrasound studies (cm2) |
| **Mean grad** | Mean transaortic valve gradient on ultrasound studies (mmHg) |
| **Peak grad** | Peak transaortic valve gradient on ultrasound studies (mmHg) |
| **Peak vel** | Peak transaortic blood jet flow velocity (m/s) |
| | |
| **VALVE OUTCOMES** | |
| **Succes implant rate** | Rate of successful aortic valve implant |
| **Valve implant size (mm)** | Prosthetic implant diameter in mm |
| **Biological valve (%)** | Biological protsthetic implant |
| | |
| **PRIMARY OUTCOMES** | |
| **30-d mortality (%)** | Perioperative mortality at 30 days after surgery |
| **MACCE** | Major Adverse Cardio or Cerebrovascular Event. Composite event of perioperative mortality (30-days mortality ) or major |

| | |
|---|---|
| | cardio or neurological complications |
| **Mortality (cause)** | Causes of perioperative mortality |
| **cardiac** | Cardiac-related death (myocardial infarction, malignant arrhythmia, sudden death, etc) |
| **neurological** | Neurological-related death (stroke, coma, vegetative status, etc) |
| **infective** | Death related to a non-cardiac infective process (septic shock, etc) |
| **endocarditis** | Death related to an early prosthetic valve endocarditis |
| **respiratory** | Respiratory-related death (distress, pneumonia, etc) |
| **renal** | Death related to a postoperative renal failure |
| **multiorganic** | Death related to a multiorganic failure |
| **unknown** | Unknown cause of death |
| **Perioperative morbidity (all)** | Major postoperative complications |
| **Reintervention** | Major bleeding or pericardial tamponade that requires reintervention in the early postoperative period |
| **Cardiovascular** | Major cardiovascular complication excluding rhythm complication (myocardial infarction, aortic or vascular injury, etc) |
| **Respiratory** | Major respiratory complication (respiratory insufficiency, distress, pneumonia, etc) |
| **Wound** | Major wound complication (wound infection, sternal dehiscence, mediastinitis, etc) |
| **Renal** | Major renal complication (acute postoperative renal failure, need for postoperative haemofiltration or dyalisis, etc) |
| **Neurological** | Major neurological complication (postoperative stroke, coma, transient ischemic attack, etc) |
| **Infective** | Major infective complication (septic shock, etc) |
| **Other** | Other major complications (implant-related, etc) |
| | |
| **LENGTH OF STAY** | |
| **ICU LOS (days)** | Intensive Care Unit length of stay in days |
| **Hospital LOS (days)** | Hospital length of stay in days |
| | |
| **RHYTHM (DISCHARGE)** | Postoperative rhythm in the last ECG prior to discharge |
| **sinus rhythm** | sinus rhythm |
| **AF rhythm** | atrial fibrillation |
| **PCM rhythm** | pacemaker rhythm |

*Annex 2. List of abbreviations*

| | |
|---|---|
| **AF** | Atrial Fibrillation |
| **AR** | aortic regurgitation |
| **AS** | aortic stenosis |
| **AUC** | Area under the curve |
| **AVA** | aortic valve area |
| **AVR** | Aortic Valve Replacement |
| **BMI** | Body Mass Index (kg/m2) |
| **BSA** | Body Surface Area (m2) |
| **CABG** | Coronary Artery Bypass Graft |
| **CAD** | coronary artery disease |
| **CHF** | congestive heart failure |
| **CRT** | Classification and Regression Tree |
| **ECG** | Electrocardiography |
| **EF** | ejection fraction (left ventricle) |
| **LV** | left ventricle |
| **LVH** | left ventricular hypertrophy |
| **LVOT** | left ventricular outflow tract |
| **MACCE** | combined event of perioperative death or Major Adverse Cardio or Cerebrovascular Events |
| **MR** | mitral regurgitation |
| **MS** | median sternotomy approach |
| **n/a** | non applicable |
| **ns** | non significant |
| **PCM** | pacemaker |
| **PH** | pulmonary hypertension |
| **PTCA** | Percutaneous Transluminal Coronary Angioplasty |
| **REDO** | Previous Cardiac Surgery |
| **ROC** | Receptor-operator characteristics |
| **RV** | right ventricle |
| **TA** | transapical approach |
| **TAVI** | transcatheter aortic valve implant |
| **TEE** | transesophageal echocardiography |
| **TF** | transfemoral approach |
| **THV** | trancatheter heart valve |
| **TR** | tricuspid regurgitation |
| **US** | ultrasound (echocardiographic) |
| **VSD** | ventricular septal defect |