UNIVERSITY OF VERONA

GRADUATE SCHOOL FOR LIFE AND HEALTH SCINCES

DOCTORAL PROGRAM

CARDIOVASCULAR SCINCES

Director- Prof. Alessandro Mazzucco

XXV BATCH

TRANSCATHETER AORTIC VALVE IMPLANTATION- NEW INNOVATION IN AORTIC VALVE Replacement

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Dedicated to my beloved family!!!

TABLE OF CONTENTS

STATEMENT OF ORIGINALITY

The series of patients presented within this thesis was primarily performed by Heart Team composite of Cardiologist, cardiac surgeon, anesthesiologist and echocardiographist at University Hospital (Borgo Trento) Verona, Italy.

The prospective collection of patient data was performed by me under supervision of Prof. Giuseppe Faggian and Prof. Flavio Ribichini.

Aside from where due reference is made, this work has not previously been submitted for a degree or a diploma in any university, been previously published or written by another person.

Dandale Rajesh Madhukar

March 2013

ABBREVIATION LIST

AKI	Acute Kidney Injury
AS	Aortic Stenosis
AV	aortic valve
AVA	Aortic Valve Area
AVR	Aortic Valve Replacement
BBB	Bundle Branch Block
BE	Balloon-Expandable
CABG	Coronary Artery Bypass Graft
CD	Conduction Disorders
CI	Confidence Interval
CFA	common femoral artery
CKD	Chronic Kidney Disease
CT	Computed Tomography
ECG	Electrocardiogram
EDV	End Diastolic Volume
EF	Ejection Fraction

eGFR	Estimated Glomerular Filtration Rate
LVESV	Left Ventricular End Systolic Volume
HR	Hazards Ratio
LV	Left Ventricular
NYHA	New York Heart Association
OR	Odds Ratio
PPM	Permanent Pacemaker
PVD	Peripheral arterial disease
SD	Standard Deviation
SE	Self-Expandable
SFA	superficial femoral artery
TA	Transapical
TAVI	Transcatheter Aortic Valve Implantation
TF	Transfemoral
TTE	Transthorasic echocardiography
TEE	Transesophageal echocardiography
VARC	Vascular Academic Research Consortium

Summary

Aortic valve stenosis is the commonest valvular heart disease in western world. An incidence of aortic valve stenosis is increasing as ageing of population. In spite of several option for management of this disorder like observation, medical treatment, balloon valvuloplasty, surgical aortic valve replacement is consider as the gold standard. However, there are 2/3 of patients are consider as high risk for surgical treatment and refused by surgeon for open heart surgery. Therefore, with the ageing of global population, the lengthening in life-expectancy and the consequent growing need to treat elderly patients with severe AS, there is a wide population who would benefit from a less invasive way of replacing the aortic valve. Transcatheter aortic valve implantation (TAVI) allows the aortic valve to be implanted without a sternotomy, with beating heart and without the need for routine cardiopulmonary support.

In the present series, we reported our prospective single centre experience about TAVI in a the Department of Cardiovascular Sciences, at the University of Verona, using both balloon expandable Edward-Sapien and self expanding Core-Valve devices, through trans-femoral, trans-apical and sub-clavian approaches. We report on early (30days) and long term follow up results, focusing on both clinical outcome and hemodynamic performance of the devices. We also investigated some peculiar fields of application, such as the treatment of severe aortic insufficiency in Heart Mate II patient, and speculated on the main potential procedural complications, such as the vascular complication and the periprosthesis leakage.

In present series we found that procedural success was high. Hemodynamic function of prosthesis was well maintained up to long term follow up. Moreover, neither patient needed emergency conversion to open heart surgery nor underwent aortic valve replacement on long term follow up. Non-cardiac mortality was higher than cardiac causes on both short term and long term follow up. Euroscore II is more predictor of operative mortality then logistic Euroscore. High EuroScore II and heart failure patients are predictor of long term mortality. Vascular complication was most common immediately after procedure. Proper patients screening and selection of proper approach is key to success. Recent improvements in the introducer and delivery system increase the procedural success and decrease complications.

We strongly believe that, once some current limitations and concerns are overcome, this emerging technique will have a very fast and wide spread. However, it should not be forgotten that, in order to guarantee the extraordinary success of this new minimally invasive procedure, the heart team approach should remain a key-point. This will allow to select the best device and the most appropriate vascular access for each patient, as well as to guarantee the best technical result and the necessary post-procedural care.

1. Introduction

1.1 Epidemiology and aetiology of Aortic valve stenosis

Aortic stenosis (AS) is the most commonly acquired valvular heart disease in the Western world (2–7% of the population aged >65 years), mostly related to the significant increase in the average life span of the population **[1]**. Moreover, in the coming decades, there will be a tremendous aging of the population in developed countries with a unique increase of inhabitants older than 80 years **[2]**. Hence, AS will become more frequent and constitute a growing burden for public health.

1.2 Pathophysiology of Aortic Stenosis

The aortic valve stenosis is defined as an obstacle to the flow of blood through the aortic valve during left ventricular (LV) ejection. In AS there is a reduction in cusp motion and effective valve area: the stenosis is caused by deposits of calcium from the base to the distal tip of the cusps, without commissural fusion **[3]** as showed in **Figure 1**.

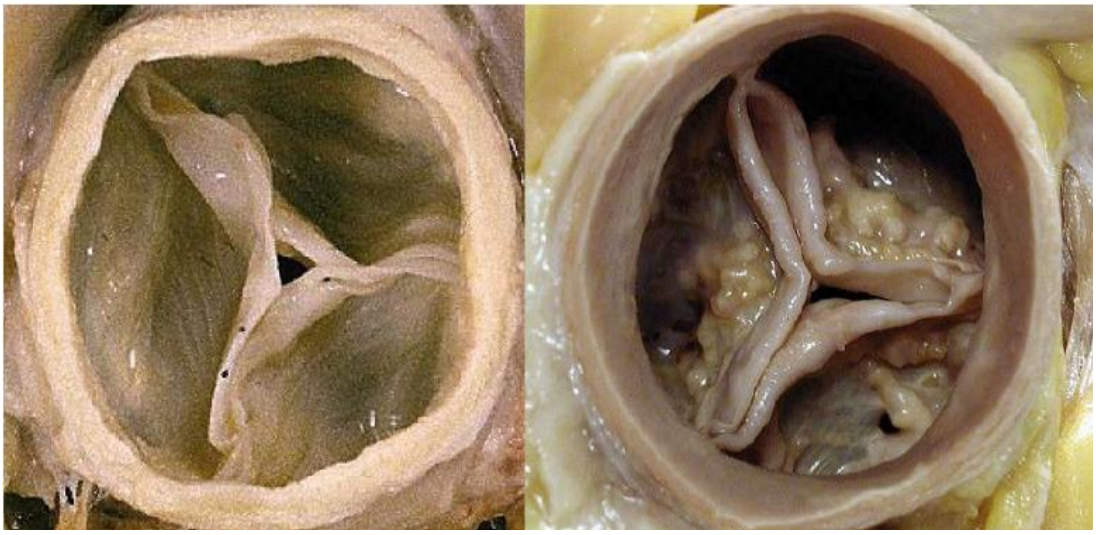


Figure 1 *showed a macroscopic view of aortic valve: normal aortic valve (left side), severely calcified aortic valve (right side)*

The aetiology of aortic valve stenosis is varied with age of patient. The bicuspid aortic valve is most prevalent cause of aortic stenosis in young, however, degenerative aortic valve disease in elderly patients **[4]** as demonstrated in **Figure 2**.

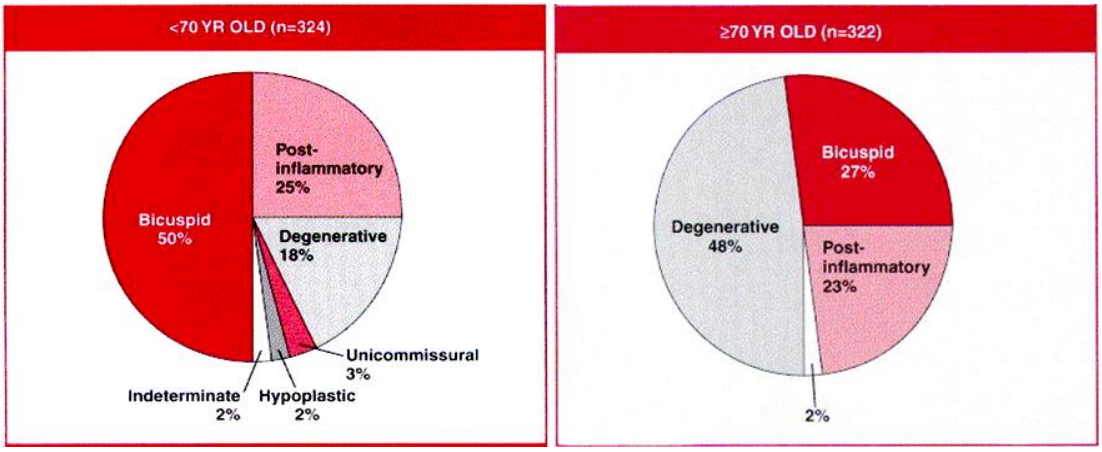


Figure 2 *showing aetiology of aortic valve stenosis according to the age of patients*

Alterations in hemodynamic of aortic valve are established when the valve area is reduced by at least 50% [5]. Severity of aortic valve stenosis is classified according to aortic valve area; peak gradient; mean gradient and jet velocity measured by echocardiography (**Table 1)**.

Table 1*- classification of aortic valve stenosis*

AS/echo	Area (cm^2)	Mean gradient(mmHg)	Jet Velocity (m/s)
Mild	1.5	<25	<3
Moderate	1-1.5	25-40	3-4
Severe	<1	>40	>4

The pressure overload, established with AS, is initially compensated by the development of myocardial hypertrophy without dilatation of the left ventricular chamber (concentric hypertrophy) that is able to maintain for many years normal systolic function. However, the increases in systolic blood pressure, ventricular mass and ejection time lead to increased consumption of oxygen by the myocardium. The increase in oxygen consumption and its contributing to decreased myocardial ischemia cause further deterioration of LV function **[6]**.

In more advanced disease, the disappearance of effective compensatory mechanisms is associated with an imbalance between pump function and LV afterload (afterload mismatch). At this stage, the ventricular chamber dilates, the ejection fraction (EF) is reduced and both the ventricular filling pressure and pulmonary pressure increase. This stage usually coincides with the occurrence of severe stenosis and the onset of symptoms. Usually, the symptoms in patients with AS appear around the 6^{th} decade of life after a long latency period, characterized by progressive thickening and calcification of the aortic valve or progressive myocardial dysfunction, or both as showed in **Figure 3 [7]**.

1.3 Clinical manifestation of aortic stenosis

In the natural history of adults with AS, a long latent period exists during which there is gradually increasing obstruction while the patient remains asymptomatic **[8]**. The cardinal manifestations of acquired AS, which commence most commonly in the fifth

or sixth decades of life, are angina pectoris, syncope, exertional dyspnea, and ultimately heart failure **[9]**.

Angina occurs in approximately two-thirds of patients with critical AS (about half of whom have associated significant coronary artery obstruction). In patients without coronary artery disease, angina results from the combination of the increased oxygen needs of the hypertrophied myocardium and the reduction of oxygen delivery secondary to the excessive compression of intramural coronary vessels **[10]**. In patients with coronary artery disease, angina is caused by a combination of the epicardial coronary artery obstruction and the earlier-described oxygen imbalance characteristic of AS.

Syncope is most commonly due to the reduced cerebral perfusion that occurs during exertion when arterial pressure declines consequent to systemic vasodilation in the presence of a fixed cardiac output. Syncope has also been attributed to malfunction of the baroreceptor mechanism in severe AS, as well as to a vasodepressor response to a greatly elevated LV systolic pressure during exercise. Premonitory symptoms of syncope are common.

Exertional dyspnea: orthopnea, paroxysmal nocturnal dyspnea, and pulmonary edema reflect varying degrees of pulmonary venous hypertension.

Sudden death: In asymptomatic AS and in the absence of coronary artery disease the incidence of sudden death is low and not significantly different from that of the general population. However, in symptomatic patients, sudden death is reported

between 13-34%, in relation to ventricular tachyarrhythmias, or conduction disorders (CD) or abnormal Bezold Jarisch reflex (hypotension, bradycardia).

Gastrointestinal bleeding, either idiopathic or due to angiodysplasia (most commonly of the right colon) or other vascular malformations, occurs more often in patients with calcific AS than in persons without this condition; it may cease after aortic valve replacement (AVR) **[11]**.

1.4 Natural history of aortic stenosis

The natural history of AS in the adult consists of a prolonged latent period in which morbidity and mortality are very low. The rate of progression of the stenotic lesion has been estimated in a variety of hemodynamic studies performed largely in patients with moderate AS. Cardiac catheterization and Doppler echocardiographic studies indicate that some patients exhibit a decrease in valve area of 0.1 to 0.3 cm2 per year; the average rate of change is approximately 0.12 cm2 per year **[12]**. The systolic pressure gradient across the valve may increase by as much as 10 to 15 mm Hg per year. However, more than half of the reported patients showed little or no progression over a 3 to 9-year period and it is not possible to predict the rate of progression in an individual patient.

Eventually, symptoms of angina, syncope, or heart failure develop after a long latent period, and the outlook changes dramatically. After onset of symptoms, average survival is <2 to 3 years **[13]**. Thus, the development of symptoms identifies a critical point in the natural history of AS and patients with severe AS require careful monitoring in order to identify the more appropriate timing for surgery. In fact, in

patients in whom the obstruction remains unrelieved, the prognosis is poor once these symptoms are manifested. Survival curves show that the interval from the onset of symptoms to the time of death is approximately 2 years in patients with heart failure, 3 years in those with syncope, and 5 years in those with angina (**Figure 3**).

1.5 Management of aortic stenosis

The course of symptomatic severe AS under medical treatment has high mortality rates. After the onset of heart failure, syncope and angina a median survival is only 11, 27 and 45 months, respectively, as shown in **Figure 3 [14]**. The balloon aortic valvuloplasty (BAV) can only be considered as a palliative treatment method for patients with a good quality of life (QoL) who are not eligible for surgical aortic valve replacement (sAVR). However, it has high risk of restenosis [**15-18]**.

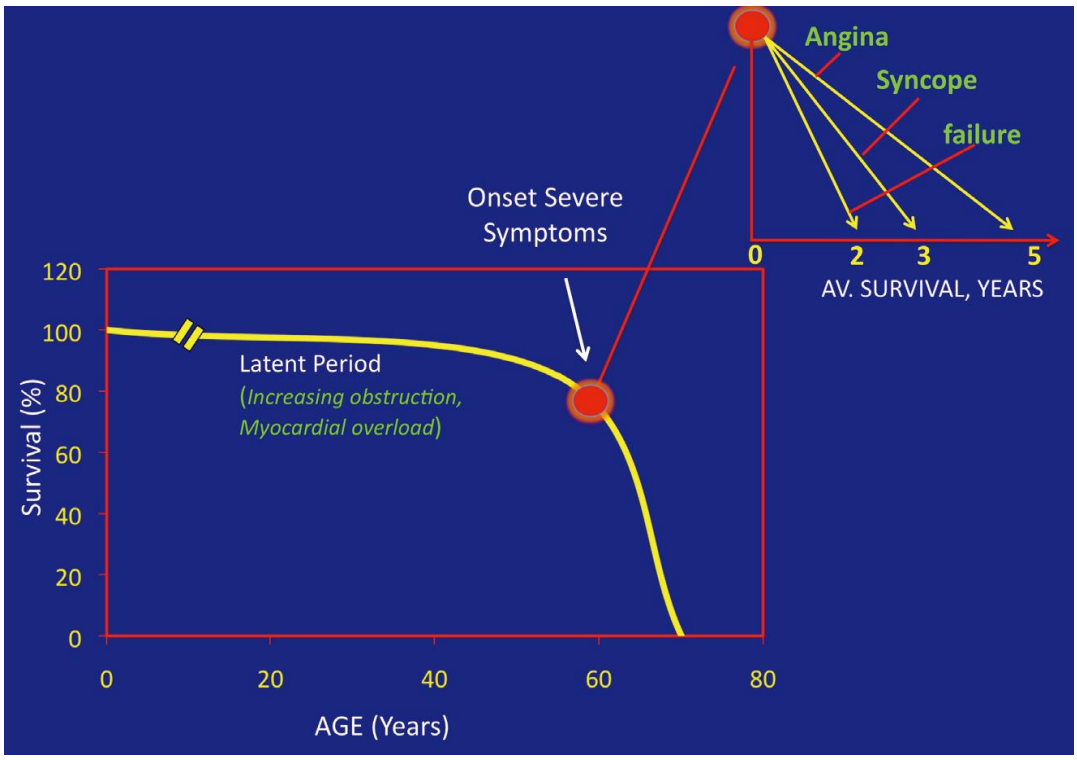


Figure 3 . *Symptoms in patients with aortic stenosis begin around the 6th decade of life, after a long latency period, and are characterized by progressive thickening and calcification of the aortic valve or progressive myocardial dysfunction, or both. Without aortic valve replacement or transcatheter aortic valve implantation the prognosis of patients with aortic stenosis after the onset of severe symtoms is extremely poor. (Branwald E.**6**)*

Up to date the surgical aortic valve replacement (sAVR) is considered as the gold-standard treatment for patients with severe symptomatic AS. This is typically a well-tolerated and durable intervention. Clinical outcomes after AVR have been quite good, with an overall operative mortality rate for isolated AVR of 4% **[19]**. Without surgery, the prognosis is extremely poor, with a 3-year survival rate less than 30% **[4]**. However, the operative mortality rate for AVR in patients >80 years of age is as great as 8% to 15% **[20-26]**.

2. Criteria for aortic valve replacement in aortic stenosis

2.1 For symptomatic aortic stenosis

In patients in whom symptomatic severe AS is not treated, the prognosis is poor. For this reason, the ACC/AHA guidelines **[7]** recommend valve replacement in patients with severe symptomatic AS. According to the latest update of the ACC/AHA guidelines 2008 the indications for AVR are as follows.

Table 2 Class I

Aortic Valve Replacement	Level of evidence
Symptomatic patients with severe AS	B
Patients with severe AS undergoing coronary artery bypass graft surgery (CABG)	C
Patients with severe AS undergoing surgery on the aorta or other heart valves	C
Patients with severe AS and LV systolic dysfunction (EF <0.50)	C

There are two important considerations in elderly patients with AS: the absence of symptoms despite severe AS, and patients with low-flow/low-gradient AS.

2.2 For asymptomatic Patients with Severe AS

Asymptomatic patients with AS have outcomes similar to age-matched normal adults. However, disease progression with symptom onset is common. There is a high probability that these patients will need to undergo surgery within the 5 years

after symptom onset. The assessment should only be done by a high-quality cardiology group and the procedure by a high-quality surgical group where the risk is 1% or less **[7]**.

Table 3 Class IIb

Aortic Valve Replacement	Level of evidence
Asymptomatic patients with severe AS and abnormal response to exercise	C
Adults with severe asymptomatic AS if there is a high likelihood of rapid progression or if surgery might be delayed at the time of symptom onset	C
Patients undergoing CABG who have mild AS when there is evidence, such as moderate to severe valve calcification, that progression may be rapid	C
Asymptomatic patients with extremely severe AS (aortic valve area <0.6 cm2, mean gradient> 60 mmHg and jet velocity >5.0 m/s) when the patient's expected operative mortality is 1.0% or less	C

In asymptomatic patients, symptoms such as heavy calcification or very severe AS are important. A recent study by Rosenhek et al pointed out that patients with a valve peak velocity greater than 4 m/s have a high likelihood of requiring surgery over the course of the next 3–4 years **[27].** If the velocity is greater than 4.5 or greater than 5, the attrition rate is even more important, so a very severe degree of AS may be enough to consider surgery as long as it is performed by a high-quality surgical group.

2.3 What is different in the European guidelines?

However, the European guidelines **[1]** recommend surgery in asymptomatic patients with AS as follows.

Class I Asymptomatic patients with severe AS and abnormal exercise test showing symptoms on exercise (level of evidence: C).

Class IIa Asymptomatic patients with severe AS and abnormal exercise test showing a fall in blood pressure below baseline (level of evidence: C).

Flow chart 1 demonstrated a treatment algorithm in patients with severe AS.

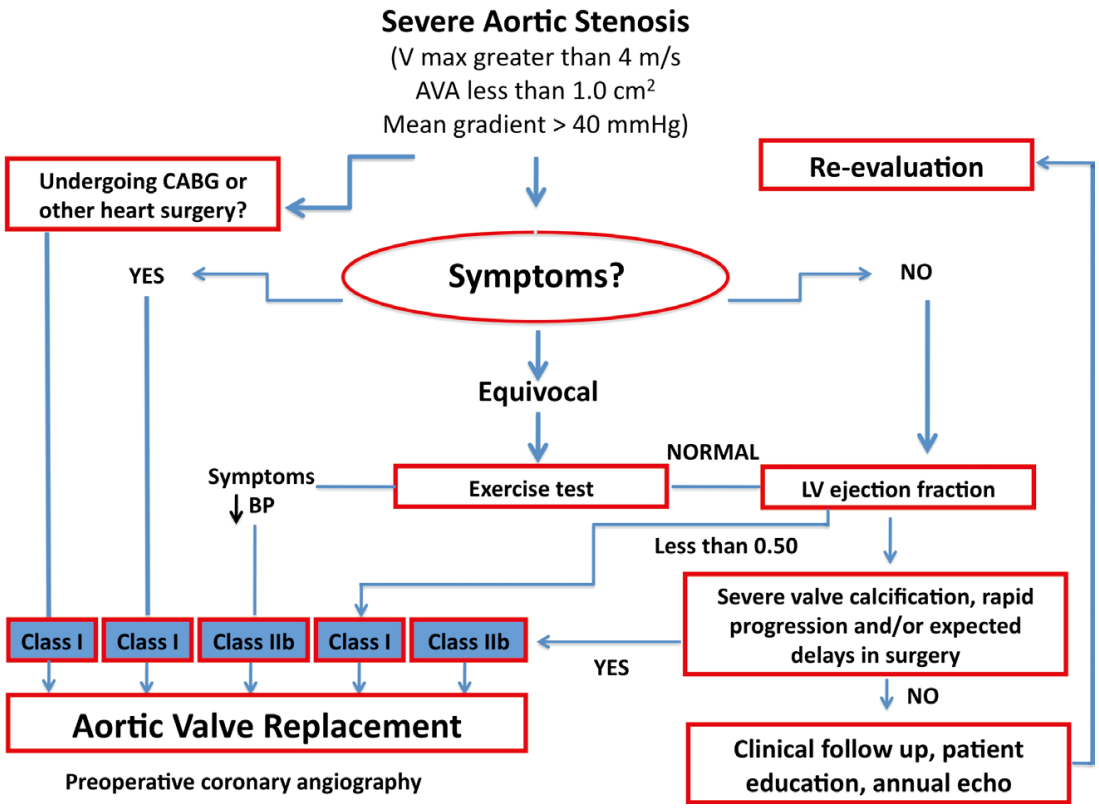


Figure 3 *Management strategies for patients with severe aortic stenosis. (AVA-aortic valvular area; BP-blood pressure; CABG-coronary artery bypass graft surgery; echo-echocardiography; LV-left ventricular; Vmax-maximal velocity across the aortic valve by Doppler echocardiography)*

A study by Pai et al **[28]** reveals how complex asymptomatic patients with AS can be. Patients with no symptoms can still have a high mortality rate, especially the older group. In addition, it is can sometimes be difficult to establish the presence of symptoms, for a variety of reasons. A study by Otto et al confirmed the findings of previous studies showing importance of aortic valve velocity, found that patients with a peak velocity >4 m/s, which is how severe AS is being defined, either underwent surgery or had a bad outcome over the course of the subsequent 5 years **[12].**

2.4 For patients with Low-Flow/Low-Gradient AS

Patients with severe AS (<1 cm2) and low cardiac output often present with a relatively low transvalvular pressure gradient (ie, mean gradient <30 mmHg). Such patients can be difficult to distinguish from those with low cardiac output and only mild to moderate AS. In the former (true, anatomically severe AS), the stenotic lesion contributes to an elevated afterload, decreased EF, and low stroke volume (SV) **[7]**. In the latter, primary contractile dysfunction is responsible for the decreased EF and low SV. The problem is further complicated by a reduction in the valvular opening forces that contributes to limited valve mobility and apparent stenosis. Therefore, it may be useful to determine the transvalvular pressure gradient and to calculate

valvular area during a baseline state and again during exercise or low-dose pharmacological (ie, dobutamine infusion) stress, with the goal of determining whether the stenosis is severe or only moderate. Thus, if a dobutamine infusion produces an increment in SV and an increase in valve area greater than 0.2 cm2 and little change in gradient, it is likely that the baseline evaluation overestimated the severity of the stenosis. In contrast, patients with true severe AS will have a fixed valvular area with an increase in SV and an increase in gradient during dobutamine infusion. These patients are likely to respond favorably to surgery and perhaps to TAVI.

2.5 Why we need new technique for management of aortic stenosis

Although surgical AVR is regarded to be the mainstay for improved survival and symptom relief, not all patients, especially the elderly, are able to profit from this technique **[29,30]**. The European Heart Survey of patients with valvular heart disease suggests that up to 33% of subjects over the age of 75 are not considered for surgical AVR because of age and comorbidities **[31]**. Moreover, Vardarajan P et al demonstrated that the mortality for untreated symptomatic severe AS is up to 50–60% at 2 years in high-risk patients, and among such patients those who ultimately undergo surgical valve replacement, a proportion is at high risk of morbidity/mortality from the procedure(**Figure 2) [30]**.

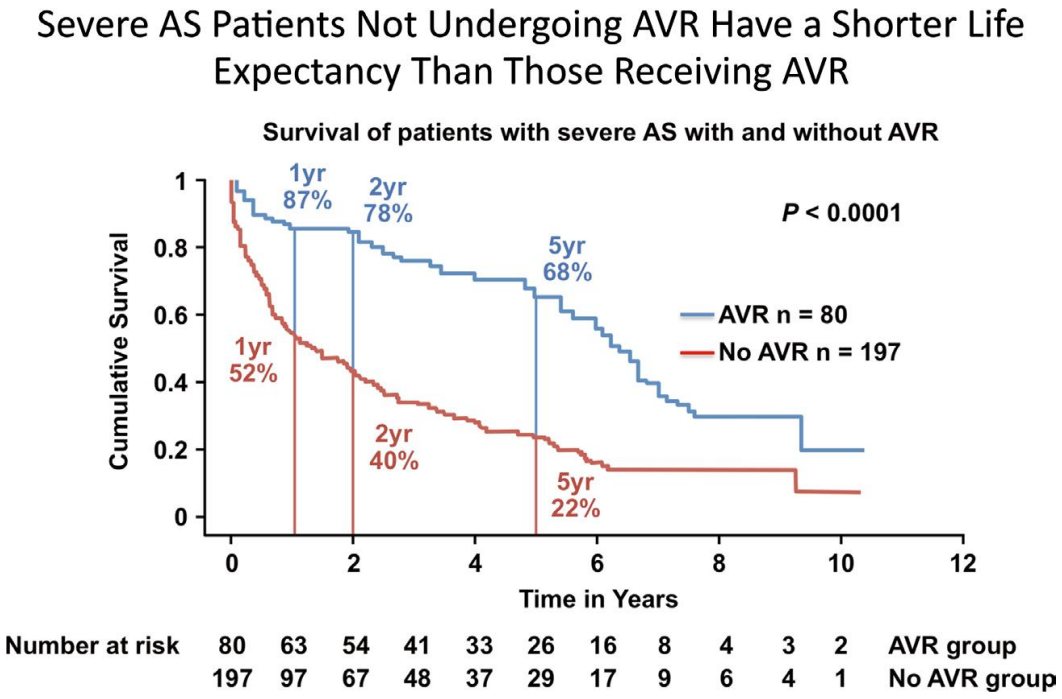


Figure 4 *demonstrated that33% of all patients aged >75 years with severe aortic stenosis (AS) are declined for surgery. The mortality for untreated symptomatic severe AS is up to 50–60% at 2 years in high-risk patients (red line). Of these patients, among those who ultimately undergo surgical valve replacement, a proportion is at high risk of morbidity/mortality from the procedure. AVR, aortic valve replacement. (Modified from Varadarajan P et al.Speccarotella 20122,3)*

However, recently introduced transcatheter aortic valve implantation (TAVI) is a new, innovative invasive procedure that promises effective treatment for high-risk patients which are not suitable for surgical AVR.

3. Trans-catheter Aortic Valve Implantation (TAVI)

3.1 Birth of concept "TAVI"

Actually, the concept of transcatheter heart valve implantation was not new. In the 1970s, several projects aimed at treating aortic regurgitation **[32-34]**. remained experimental. In 1989, Henning-Rud Andersen first implanted an original model of a balloon-expandable catheter-mounted stented valve within the aorta of pigs, using a handmade mesh containing a porcine valve. The results, published in 1992 **[35]**, were not followed by human application. Other experimental concepts emerged thereafter **[36-38]**. In 2000, Philip Bonhoeffer developed a stented valve made of a bovine jugular vein conduit inserted in a platinum-iridium stent, which was implanted in the pulmonary artery of lambs **[39]**. Followed by this animal model he performed the first human implantation of same device in a right ventricle to pulmonary artery conduit in 2000 **[40]**. Success of this followed by intensive technical development in this indication.

3.2. Tribute to Prof. Alian Cribier

The idea of percutaneous treatment of aortic stenosis was first put into clinical practice in 1985, when Cribier performed an aortic balloon valvuloplasty for non-operable severe calcified aortic stenosis **[41]**. Concept of having stented aortic valve was put forward by him. After lots of heard effort, Edward group accepted proposal to produce device. In the 2002, "golden year" of TAVI, the first in human successful

percutaneous aortic valve implantation performed by Alain Cribier, via trans-venous antigrade approach, with septal puncture **[42]**. This was a very complex technique with high incidence of complication. At same time John Webb performed retrograde implantation aortic prosthesis via femoral artery access **[43]**. Initial series has several complications mainly vascular which stimulate need for improvement in TAVI technique, prosthesis and delivery system. Up to date, more than 50,000 patients have been treated with this novel technique worldwide.

There are several prosthesis devices. However, in Europe, the Edwards SAPIEN valve (Edwards Lifesciences, Irvine, CA) and the CoreValve ReValving System (Medtronic, Minneapolis, MN) are used most frequently and both devices have received the CE (European Conformity) mark, based on the clinical trials.

3.3 Anatomy of aortic-root for TAVI

The aortic root is the direct continuation of the left ventricular outflow tract (LVOT). Its components are the sinuses of Valsalva, the fibrous interleaflet triangles, and the valvular leaflets themselves. When defined literally, an “annulus” is no more than a little ring **[44].**

Aortic Valvar Leaflets-The normal aortic valve is tricuspid, and proper functioning of the valve depends on the proper relationship between the leaflets within the aortic root. In the majority of cases, the orifices of the coronary arteries arise within the 2 anterior sinuses of Valsalva, usually positioned just below the sinotubular junction **[43].** Knowledge of the location of the coronary arteries, of course, is essential for appropriate percutaneous replacement of the aortic valve. The combination of a

relatively low-lying coronary artery ostium and a large native aortic valvular leaflet can therefore obstruct the flow into the coronary arteries during valvular deployment **[42-44].** The presence of a significant subaortic bulge or a hypertrophied septum has been considered a relative contraindication to implantation, mainly for the CoreValve aortic prosthesis. The atrioventricular node is located just inferior to the apex of the triangle adjacent to the membranous septum, and therefore the atrioventricular node is in fact in close proximity to the subaortic region and the membranous septum of the LVOT.

3.4 Role of Heart Team

First of all, it should be stressed that today and in the future, the TAVI Heart Team approach is and will remain, essential for the management of patients with severe aortic stenosis. [44, 45] This will apply at each step of the procedure: patient selection, performance of the procedure, post-procedural care and evaluation of the results. The Heart Team is comprised of clinical cardiologists, interventionists, surgeons, anaesthetists and imaging specialists, all with expertise in the treatment of valve disease. Heart team approach is the key to success of this new technique.

4. Screening for TAVI

Patient selection plays a crucial role in the success of transcatheter aortic valve implantation (TAVI). It requires meticulous attention to the smallest of details and needs to be performed in a systematic manner for every patient. In addition to patient risk evaluation, anatomical selection criteria need to be considered. Multimodality imaging, using a combination of angiography, echocardiography and multislice computed tomography (MSCT), is necessary to determine the anatomical suitability for the procedure. In particular, assessment of the peripheral vasculature and aortic valvar complex will allow selection of the access route and prosthesis type and size, respectively **[46]**.

Following variable to be assessed during assessment of TAVI candidate-

4.1 Patients risk evaluation

The logistic EuroSCORE I and the STS (Society of Thoracic Surgeons) are mostly commonly used as Predicted Risk of Mortality score. These scores have guided enrolment of ‘‘high surgical risk’’ patients into TAVI trials. Because low-to-intermediate surgical risk patients characterized the development of these risk models, their reliability when applied to high or prohibitive surgical risk patients has been rightfully questioned. Furthermore, models may not take into account important comorbidities (e.g. porcelain aorta, chest wall radiation, liver cirrhosis, pulmonary hypertension) and frailty variables that may impact clinical outcomes.

The newly updated logistic EuroSCORE II and STS score, however, are expected to incorporate frailty variables. In high surgical risk patients, the logistic EuroSCORE I tend to overestimate the observed mortality risk by a factor of 2 to 3; the new logistic EuroSCORE II appears to provide significantly lower mortality estimates than the logistic EuroSCORE I. The STS score has been found to be more reliable than the logistic EuroSCORE I or the Ambler Risk Score for the prediction of operative and long-term mortality in high-risk patients undergoing surgical aortic valve replacement. Risk scores should guide but not dictate clinical decision-making **[47]**.

4.2 Anatomical patient selection

The most important aspect of anatomical screening involves assessment of the arterial vasculature and aortic valvar complex (left ventricular outflow tract, aortic annulus, sinus of Valsalva, sinutubular junction and ascending aorta.

4.2.1 Access selection: This information will guide physicians to select the most appropriate access route (i.e. transfemoral, subclavian, apical or direct aortic) and transcatheter valve size. Furthermore, it will alert physicians to potential complications that may arise during the procedure. Following imaging technique used:

1. Peripheral contrast angiography- practical, low cost, less contrast and radiation exposure.
2. MSCT- greater appreciation of vessel size, tortuosity and calcification.

   Acceptable minimal ilio-femoral diameters for implantation of the 23, 26 and 29 mm Edwards SAPIEN XT prostheses are 6.0, 6.5 and 7.0 mm, respectively. Although in case of self-expandable Medtronic Core Valve prosthesis the

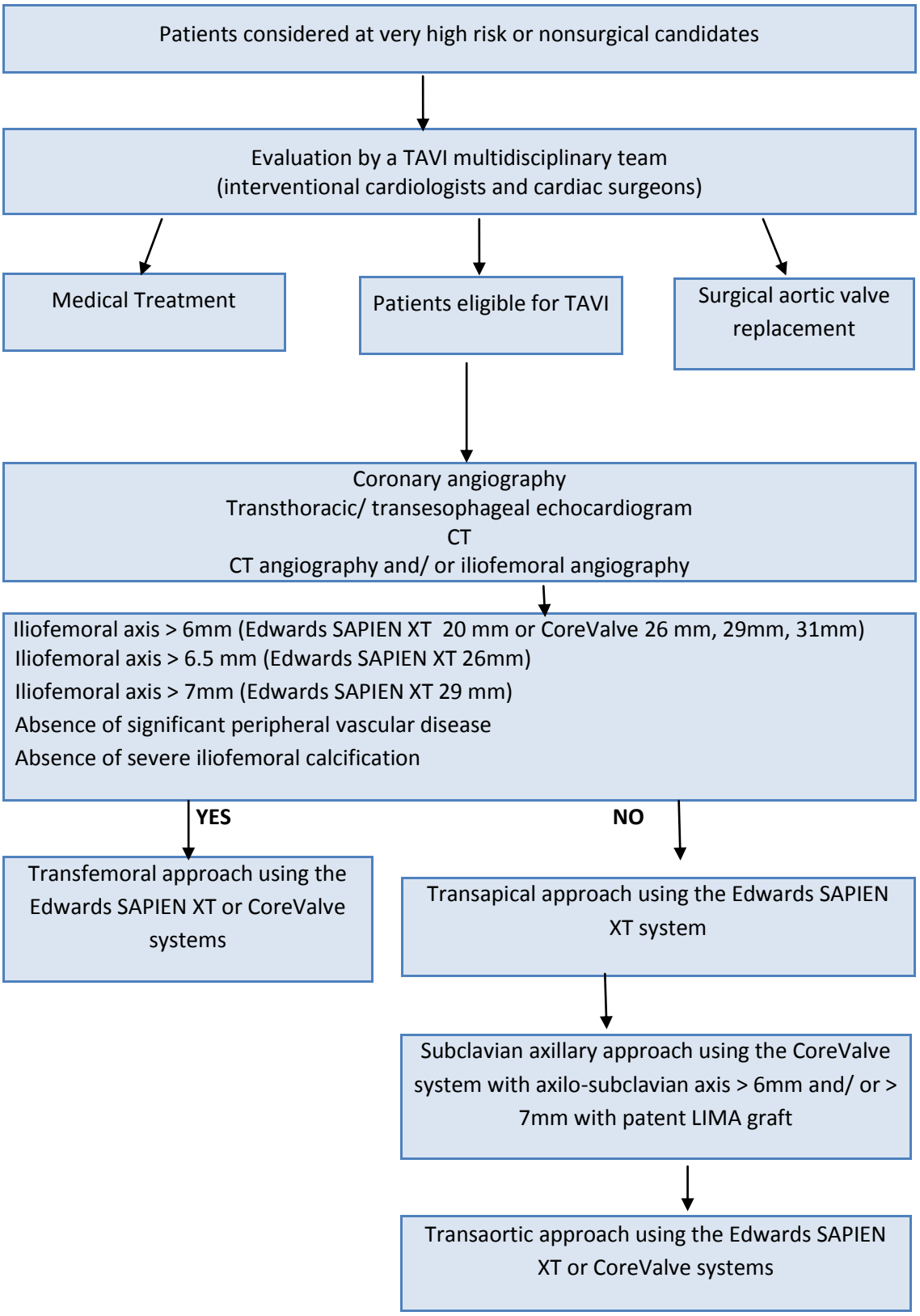
acceptable minimal iliofemoral diameter for implantation of the 26, 29 and 31 mm is 6.0 mm.

Alternative routes to the transfemoral include the sub-clavian artery, apex of heart, trans-aortic, brachial and recently introduced axillary artery approach **[48]**.

4.2.2 Measurement of aortic valve annulus- The aortic valve annulus diameter can be measured using various imaging modalities. These include transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), MSCT, contrast aortography and magnetic resonance imaging **[49]**.

Every patient must be screened thoroughly using proper investigation tool before performing TAVI. Rodés-Cabau in his recent review gives focus on pre-TAVI screening protocol, as showed in **flowchart 2**.

Flow chart 2 for screening in TAVI candidate



5. TAVI Devices

5.1 Which are the most commonly used TAVI device?

There are currently two TAVI devices in widespread use for the treatment of AS in Europe with the CE mark **(Tables 4)**. The current generation Edwards SAPIEN XT valve (Edwards Lifesciences, Irvine, CA) is constructed on balloon expandable cobalt chromium frame to which are sewn bovine pericardial leaflets and a fabric sealing cuff **(Figure 5a & 5b)**. The CoreValve device (Medtronic, Irvine, CA) consists of a self-expanding nitinol frame to which are sewn porcine pericardial leaflets and a porcine pericardial sealing cuff **(Figure 5c)**. Both valves are available with delivery catheters compatible with arterial sheaths with inner diameters of around 18Fr **(Figure 6).** The SAPIEN XT valve is also available with a delivery catheter designed to facilitate transapical implantation **[50-52].**

5.2 Comparison of Edward SAPIEN XT and Medronic CoreValve Prosthesis

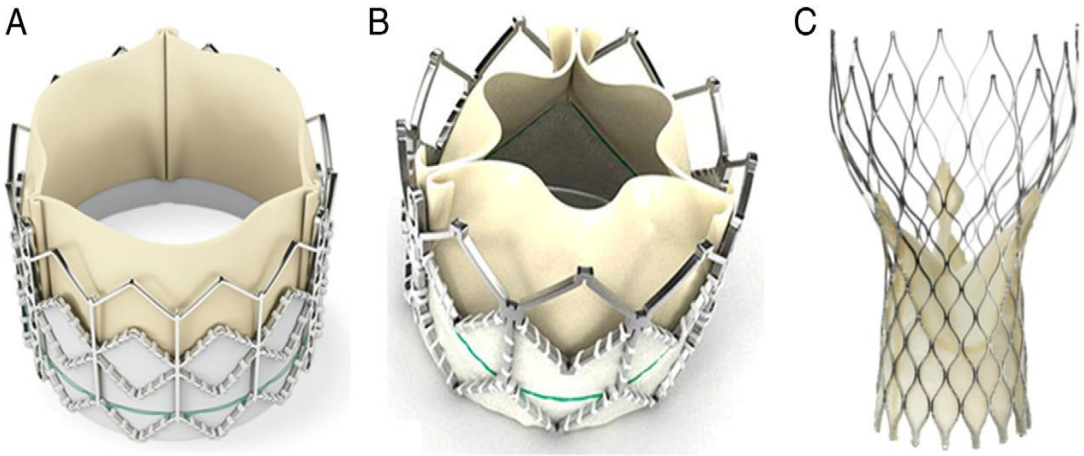
Edward SAPIEN XT and Medtronic CoreValve prosthesis are most frequently used in clinical practice, so necessary to understand their features, which helps in proper prosthesis selection. Comparisons of both devices are showed in **table 4**.

Table 4 Comparison of the Edwards SAPIEN XT and Medronic CoreValve Prostheses

Characteristics	Edwards SAPIEN XT	Medronic CoreValve
Frame	Cobalt chromium	Nitinol
Leaflets	Bovine pericardial	Porcine pericardial
Seal	Synthetic	Porcine pericardial
Expansion	Balloon expandable	Self-expandable
Repositionable	No	Yes
Retrievable	No	Yes
Annular/valvular fixation	Yes	Yes
Ascending aorta fixation	No	Yes
Manufacturers diameter	23,26 mm	26, 29 mm
Treatable annulus diameter	18-25 mm	20-27 mm
Length	15-17 mm	53-55 mm
Sheath internal diameter	18F, 19F	18F
Sheath external diameter	7 mm	7 mm
Minimal arterial diameter	6 mm	6 mm
Suitable for		
Aortic stenosis	Yes	Yes
Aortic regurgitation	If calcified stenosis present	If size appropriate
Dilated ascending aorta	Yes	No
Pulmonary position	Yes	No
Valve-in-Valve	All 4 valve positions	Aortic only
Transapical access	Yes	No
Transaxillary access	Yes, limited experience	Yes
Transaortic access	Yes	Yes
Largest published follow-up	>6 yrs	>4 yrs
Pacemaker requirement	3%-8%	14%-40%
CE mark approval	Yes (2007)	Yes (2007)
FDA approval	Sapien transfemoral only	No
Randomized trials results	PARTNER A and B	Results anticipated 2013

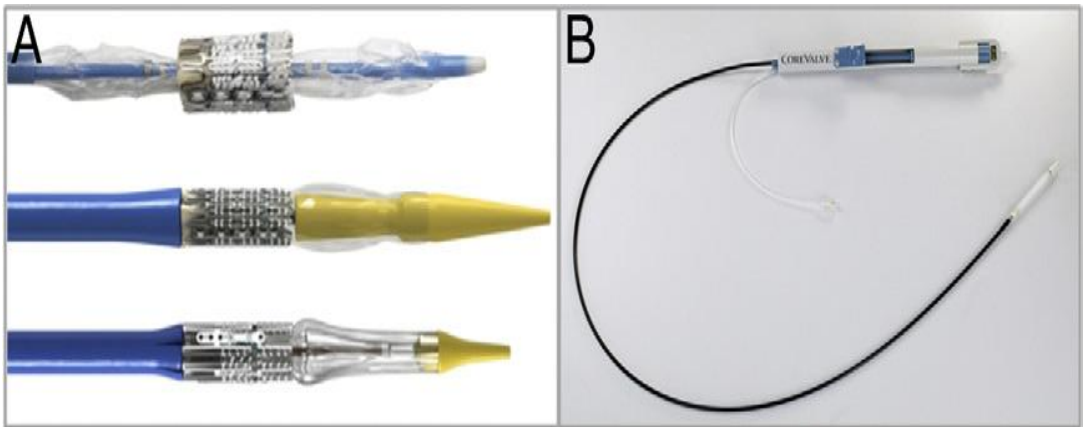
**SAPIEN XT 20, 29 mm (Edwards Lifesciences, Irvine, California); and CoreValve 31(Medtronic, Minneapollis, Minnesota) device are available in some countries.*

Figure 5 Currently widely available Transcatheter Valves



A) The Edwards SAPIEN THV balloon-expandable valve (Edwards Lifesciences, Irvine, California) incorporates a stainless steel frame, bovine pericardial leaflets, x and a fabric sealing cuff. (B) The SAPIEN XT THV (Edwards Lifesciences) utilizes a cobalt chromium alloy frame and is compatible with lower profile delivery catheters.(C) The Medtronic CoreValve (Medtronic, Minneapolis, Minnesota) incorporates a self-expandable frame, porcine pericardial leaflets, and a pericardial seal.

Figure 6 Valve delivery system

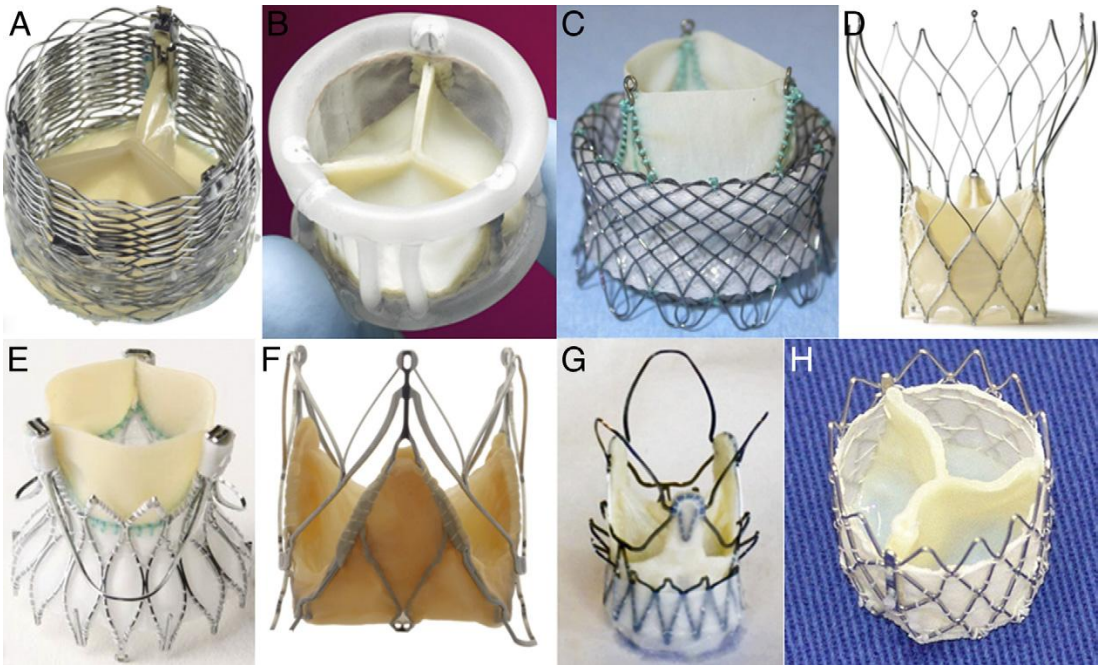


*(**A, top**) The RetroFlex 1 delivery system for the Edwards SAPIEN THV (Edwards Lifesciences, Irvine, California) as used in the PARTNER 1 (Placement of AoRTic TraNscathetER Valve 1) trials (8 mm diameter). (**A, Middle**) The RetroFlex 3 system (Edwards Lifesciences). (**A, Bottom**) The NovaFlex/SAPIEN XT system (6 mm diameter; Edwards Lifesciences). (**B**) The Accutrak delivery system with the Medtronic CoreValve (6 mm diameter, also with a tapered nosecone; Medtronic, Minneapolis, Minnesota). The prosthesis is enclosed within an outer sheath.*

5.3 New generation prosthesis devices

Several newer valves are currently in early clinical trials; including the Engager (Medtronic Inc.), Lotus (Boston Scientific Inc.,), Direct Flow (Direct Flow Medical Inc.,) JenaClip (JenaValve Inc.,) and the Accurate (Symetis Inc.,) valves as showed in **figure 7**. These newer valves offer the potential of lower diameter and less traumatic catheters, features which facilitate accurate positioning, improve paravalvular sealing or allow retrieval and repositioning **[50-54]**.

Figure 7 Valve undergoing early evaluation



*(**A**) Lotus (Boston Scientific Inc., Natick, Massachusetts), (**B**) Direct Flow (Direct Flow Medical Inc., Santa Rosa, California), (**C**) HLT (Bracco Inc., Princeton, New Jersey), (**D**) Portico (St. Jude Medical Inc., St. Paul, Minnesota), (**E**) Engager (Medtronic Inc., Minneapolis Minnesota), (**F**) JenaClip (JenaValve Inc., Munich, Germany), (**G**) Acurate valve (Symetis Inc., Ecublens, Switzerland), and (**H**) Inovare (Braile Biomedica Inc., São José do Rio Preto, Brazil) valves.*

5.4 Advantages of New generation device over first generation devices

Although these newer valves offer many desirable features, there are concerns with respect to radial strength, symmetric expansion, and late fracture with nitinol. Experience with newer leaflet technology is limited. Repositionable valves may be associated with aortic injury, atheroembolism, or reduced durability. Whether clinical outcomes will be equivalent or superior to currently available THVs will need to be evaluated **[50-54]**.

6. Endovascular Access

6.1 Transfemoral artery

The femoral artery has been the most popular access site. Although originally requiring a surgical cutdown most experienced groups now utilize a percutaneous puncture and suture pre-closure technique avoiding the need for open surgical access. Current consensus, with some exceptions, strongly favours transfemoral arterial access as the preferred, default approach for TAVR **(Figure 8)**.

Current transcatheter valve systems utilize vascular access sheaths, which are typically described in terms of their inner diameter in French size (3 x internal diameter in millimeters). Sheath external diameters are slightly larger. The only approved device in the United States (SAPIEN valve) requires a 22-F or 24-F sheath with outer diameters of just over 8 or 9 mm, respectively. However, current generation systems generally utilized outside the United States utilize smaller sheaths ($\leq$ 18-F with outer diameters of 7 mm). A relatively compliant non diseased artery can generally accommodate a sheath slightly larger than its internal diameter. In the absence of severe calcification, tortuosity, or atheroma an arterial diameter <6 mm might be adequate for an 18-F system, while an arterial diameter of >8 mm might be required for a 24-F system. Assessing this minimal arterial diameter is fundamental to patient selection. However, many patients have small or diseased femoral arteries. On occasion an open surgical retroperitoneal approach is utilized to gain access to the larger iliac artery in patients with femoral disease. Recently, transaxillary (sometimes referred to as subclavian) access has gained popularity as

an alternative to femoral access, although a surgical cutdown is generally utilized **[51,53,55,56]**.

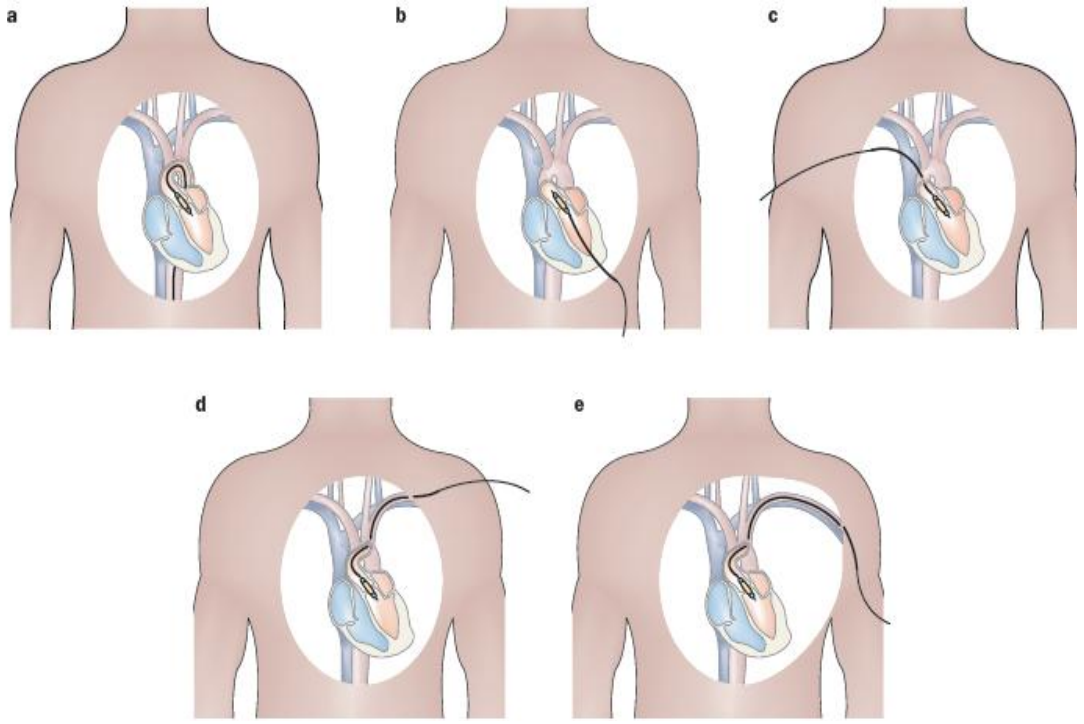
6.2 Trans-apical approach

A transapical approach, with direct access to the left ventricle through an intercostal thoracotomy, has several potential advantages: a low risk of peripheral vascular injury, a direct pathway to the aortic valve, and easier antegrade crossing of the diseased aortic valve. Concerns relate to direct myocardial injury, bleeding, mitral injury, hemodynamic instability, and post-operative respiratory compromise and thoracotomy pain. The transapical procedure is generally associated with the Edwards SAPIEN valve, although a number of newer valves (e.g., JenaClip, Engager, Portico, Acurate) have been developed for this application **[52]**. **Figure 8** showed most commonly used TAVI access.

6.3 Newer approaches for aortic valve implantation

Most recently, a transaortic approach with direct access to the ascending aorta has been advocated. Although requiring a mini-thoracotomy and aortotomy, potential advantages over the transapical approach include a reduced risk of myocardial injury and bleeding and an access route more familiar to cardiac surgeons **[52]**. Moreover, in coming future, as new innovations are coming with prosthesis and delivery system, we are expecting even trans-brachial, trans-axillary approach.

Figure 8 showing different approaches for TAVI procedure



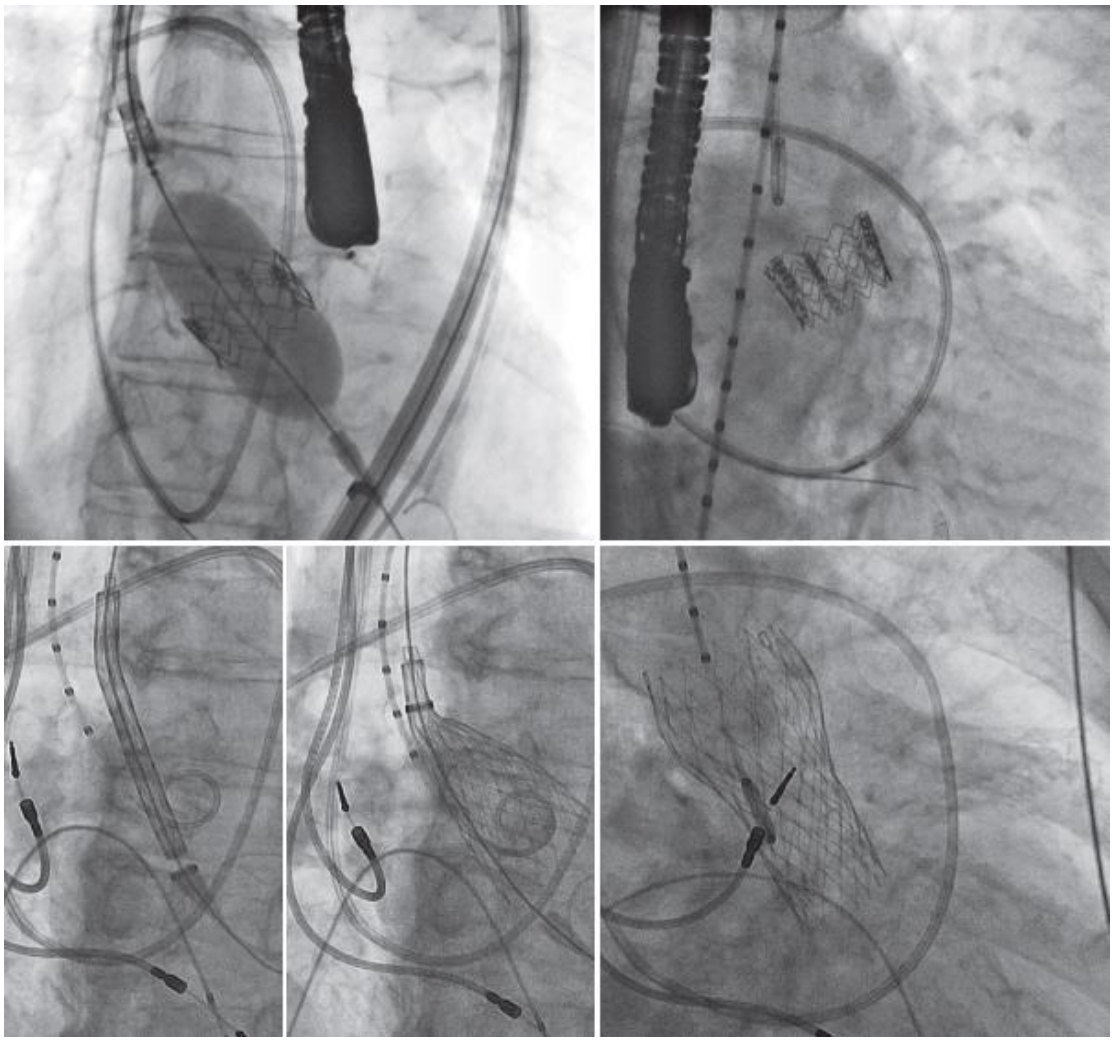
a) *The transfemoral approach. The delivery catheter for implantation of the valve prosthesis is advanced through the right or left femoral arteries.* ***b)*** *The transapical approach. After left lateral minithoracotomy (usually between the fifth and sixth intercostal spaces), the delivery catheter for implantation of the valve prosthesis is advanced through the left ventricular apex.* ***c)*** *The transaortic approach. After right or mid ministernotomy, the delivery catheter for implantation of the valve prosthesis is advanced directly through the ascending aorta.* ***d)*** *The subclavian approach. The delivery catheter for implantation of the valve prosthesis is advanced through the subclavian artery (usually the left vessel).* ***e)*** *The transaxillary approach. The delivery catheter for implantation of the valve prosthesis is advanced through the axillary artery (usually the left vessel).*

7. Valve Implantation

7.1 Basic of valve implantation

Balloon aortic valvuloplasty is systematically performed before valve implantation for both types of prosthetic valves currently used in TAVI, although Grube *et al.* have suggested direct implantation of the CoreValve system with no prior balloon valvuloplasty **[51-53]**. The Edwards valve is positioned using fluoroscopy, angiography, and transesophageal echocardiography, and valve expansion is achieved by balloon inflation under rapid pacing (180–220 bpm) to minimize cardiac output and avoid valve embolization during valve implantation **(Figure 9a,b)**. CoreValve positioning is usually performed by fluoroscopy and angiography, and the valve is deployed without rapid pacing, by retracting the outer sheath of the delivery catheter **(Figure 9c–e)**.

Figure 9 Valve implantation of balloon-expandable and self-expandable transcatheter valve



a) *Deployment of a balloon-expandable Edwards SAPIEN XT® (Edwards Lifesciences Corporation, Irvine, CA, USA) valve. The white arrow indicates the balloon during maximal expansion.* ***b)*** *Fluoroscopic image of an Edwards SAPIEN XT® valve (white arrow) after valve implantation.* ***c,d)*** *Deployment of a self-expandable CoreValve® (Medtronic CV Luxembourg S.a.r.l., Luxembourg) system. The white arrows indicate the outer sheath that is being retracted to allow the expansion of the valve.* ***e)*** *Fluoroscopic image of a third-generation CoreValve® system (white arrow) after valve implantation.*

8. Scopes of thesis

8.1 General assessment:

1) To analyze safety and feasibility and 30 days outcome of TAVI procedure in a single centre series, using both Self expandable and balloon expandable devices.

2) To analyze safety and feasibility and long term outcome of TAVI procedure in a single centre series, using both SE and balloon expandable devices.

3) To analyze the durability over long term, by analyzing echocardiographic variables over time, using both SE and balloon expandable devices.

4) To evaluate incidence, predictor and prognostic impact of acute kidney injury after TAVI.

8.2 Special settings:

5) To explore safety and feasibility of particular indications to TAVI, the treatment of severe aortic regurgitation in Heart Mate-II and bioprosthesis dysfunction by valve-in-valve technique.

6) To evaluate feasibility and safety of using “Limb-saving” contra-lateral implantation of a protection guide-wire in femoral access during TAVI.

7) To evaluate feasibility and safety of trans-femoral TAVI in patient with aorto-iliac endoprosthesis and severely tortuous and atherosclerotic accesses-“Railing tract” technique.

8) To evaluate the safety and feasibility of Core-Valve insertion without introducer sheath.

9) To evaluate the safety and feasibility of the Subclavian approach in the TAVI

8.3 Special cases

10) How to manage patient accidental finding of left atrial thrombus in TAVI suite? Whether to quite the play or we have some option?

11) How to overcome coronary occlusion found during balloon valvuloplasty: Challenges from the coronary arteries take off. Is it safe to put protection guide wire in high risk coronary? Is there possibility for introduction of angioplasty catheter on wire?

12) To evaluate the feasibility and safety of TAVI without contrast medium, in severe renal failure. Is an expert transesophageal echocardiography is alternative?

13) Step by step approach for a case of severe multi-level vascular disease waiting for TAVI- complex TAVI candidate.

14) Safety and feasibility of TAVI in the patient of AVS with associated severe mitral regurgitation, coronary artery disease, and heart failure.

8.4 Complications and their management:

15) Challenges from the femoral vascular access

16) “Tunnelling” of femoral arteries

17) Sessile thrombus in aortic root after transapical aortic valve implantation.

9. Methodology

9.1 Study population

We prospectively enrolled all patients of severe symptomatic aortic valve stenosis with high risk for conventional valve surgery who are planned to trans-apical and trans-femoral aortic valve implantation between February 2010 and February 2013. An inclusion and exclusion criteria are as follow:

9.1.1 Inclusion criteria

1. Age >75 years
2. Severe aortic stenosis from degenerative origin
    - Symptomatic
    - Valve area < 0.7 cm2 (1 cm2)*
    - Aortic valve gradient- > 40 mmHg*
3. Surgical mortality predicted by the logistic
    - EuroSCORE >20% for age >75year
    - EuroSCORE- 10-20% for age >85 years
4. Alternative criteria
    - Porcelain aorta
    - Radiation of the sternum or chest deformities
    - Precluding an open chest surgery
    - Severe chronic obstructive pulmonary disease

Patients referred for surgery and rejected by the surgeon

5. Adequate diameters

Aortic annulus >18 mm and ≤ 25 mm.

Ilio-femoral axes >8 mm or 9mm.

9.1.2 Exclusion criteria

1. Left main stenosis ≥ 70%, as assessed by coronary angiogram;
2. Aortic annulus diameter<17 mm or >25 mm, as measured from the echocardiographic parasternal long axis view at the level of the leaflet attachment.
3. Ilio-femoral disease or diameters <7 or 8mm, according to the diameter of the sheath (22 or 24F), as obtained by conventional angiography and computed tomography.
4. Any condition that made the quality or duration of life unlikely, despite AVR.
5. Hypersensitivity or contraindication to any study medication.
6. Sepsis or active endocarditis
7. Bleeding diathesis; or coagulopathy
8. Patients with significant mitral valve regurgitation (3+/4+)
9. Patients with clear bicuspid aortic valve, because of the presumed risk of poor seating or paravalvular regurgitation due to severe distortion of the native valve leaflets

9.1.3 Criteria for Transapical TAVI-

1. Severe calcification and/ or tortuosity of iliac- femoral arteries with minimal internal diameter less than 6-8mm.
2. Aortic aneurism with thrombus
3. Chronic aortic dissection
4. Co-arctation of aorta
5. Previous aorto-femoral bypass
6. Severe aortic angulations
7. Severe atherosclerosis of ascending, descending aorta and aortic arch

9.2 TAVI screening

In all potential candidates to TAVI, we performed a diagnostic screening in order to evaluate the eligibility to transcatheter procedure and to choose the most appropriate vascular access. Patient screening included:

1) Blood tests;

2) Chest radiography;

3) Electrocardiogram;

4) Transthoracic and transesophageal echocardiogram,

5) Complete left heart catheterization, including coronary angiograms, LV angiography, angiograms of ascending and abdominal aorta and iliac-femoral

arteries. These angiograms were performed with a 5F pigtail catheter for a precise determination of vascular size.

6) A multi-slice computed tomography (CT)-scan of aortic root, ascending and abdominal aorta, and iliac-femoral axis was performed for patients without contraindications.

7) Doppler ultrasound evaluation of carotid and vertebral arteries;

8) Pulmonary function test.

In particular, all the variables collected by transthoracic and sometime transesophageal echocardiograms, complete heart catheterization and angiographies and CT-scan are listed in the following **table 5, 6 and 7**, respectively.

Table 5 Echocardiographic parameters
Aortic dimensions
Aortic annulus (mm)
Aortic root, height, depth (mm)
Sino-tubular junction (mm)
Tubular aorta (mm)
Valve characteristics
Calcium score (1-4+/4)
Anatomic valve area (cm2)
Left and right atrium
Cranial – caudal diameter (mm)
Antero-posterior diameter (mm)
Transverse diameter (mm)
Area (cm2)
Volume (ml/m2)
Left ventricle

		End-diastolic diameter (mm)
		End-systolic diameter (mm)
		End-diastolic volume (EDV) (ml)
		EDV indexed (ml/m2)
		End-systolic volume (ESV) (ml)
		End-systolic volume indexed (ml/m2)
		EF (%)
Right ventricle		
		End-diastolic area (mm)
		End-systolic area (mm)
		Tricuspid annular plane systolic excursion (mm)
		Shortening fraction (%)
Doppler		
	Aortic valve	
		Peak transvalvular gradient (mmHg)
		Mean transvalvular gradient (mmHg)
		AVA (cm2)
		Aortic regurgitation
	Mitral valve	
		Peak transvalvular gradient (mmHg)
		Mean transvalvular gradient (mmHg)
		Mitral valve area (cm2)
		Mitral regurgitation
	Tricuspid valve	
		Tricuspid regurgitation
		Pulmonary artery systolic pressure (mmHg)
Diastolic function		
		E and A wave velocity
		E/A ratio.

Table 6 Angiographic parameters
Left ventricle angiography (RAO 30°)
EDV index (ml/m2)
ESV index (ml/m2)
Stroke volume (ml)
EF (%)
Mitral regurgitation (0-4+/4)
Supra-aortic angiogram (RAO 30° and LAO 60°)
Aortic annulus (mm)
Aortic root (height and depth, mm)
Sino-tubular junction (mm)
Ascending aorta (tubular, mm)
Abdominal aorta – iliac-femoral arteries
Size of common iliac arteries, external iliac arteries,
Common femoral arteries (mm)
Calcium score (0-4+/4)
Degree of tortuosity (0-4+/4)
Minimal luminal diameter and degree of stenosis
Subclavian arteries: diameter, tortuosity and
calcification
Selective coronary angiograms:
Minimal luminal diameter and degree of stenosis

Table 7 MultiSlice CT scan
Ascending aorta dimensions and degree of calcifications
Aortic annulus (mm)
Aortic root (height, depth, mm)
Sino-tubular junction (mm)
Ascending aorta (tubular, mm)
Aortic arch (mm)

Valve characteristics
Calcium score (1-4+/4)
Anatomic AVA (cm2)
Coronary ostia height respect to annular plane
Abdominal aorta and iliac-femoral arteries
Size (mm)
Calcium score (0-4+/4)
Degree of tortuosity (0-4+/4)
Degree of stenosis
Subclavian arteries: size, tortuosity and degree of calcifications and stenosis

9.3 Description of procedure

In *transfemoral approach*, in beginning we have started the device implantation with surgical exploration of femoral artery. However, in majority of patients, totally percutaneous TF closure was performed under mild sedation and local anaesthesia. A pre-closure of the common femoral artery puncture site is done before introduction of the sheath using the Prostar XL devices (Abbott Vascular Devices, Redwood City, California) **[52]**.

Transapical approach is usually performed under general anaesthesia and endotracheal intubation. An anterolateral minithoracotomy, usually in the fifth or eventually in the sixth intercostal space, is performed. Two circular purse-string sutures are placed on the cardiac apex. The procedure itself starts with an apical puncture. At the end of procedure, the apical puncture site usually can be safely secured by tying the purse-string sutures **[58]**.

With the *transubclavian approach,* procedures are generally performed under general anaesthesia with double-lumen intubation in the catheterization laboratory. Cardiac surgeons perform a surgical cut-down to isolate the left subclavian artery just below the subclavian bone. After the procedure, the subclavian artery is restored by direct suture **[56,59]**.

For all the described approaches, a supra-aortic angiogram is always performed in LAO 40° projection to evaluate the presence and degree of aortic regurgitation. A 6-F sheath was percutaneously placed in the opposite femoral artery through which a 6-F pigtail was advanced in the ascending aorta for hemodynamic monitoring and landmark aortic angiography. A catheter for temporary pacing was advanced through the opposite site femoral vein in the right ventricle.

For the more commonly used TF retrograde approach, the native aortic valve is then crossed with a straight 0.035-inch guide wire using an Amplatz Left-1 or 2 coronary catheter advanced to the ascending aorta in the LAO 40° projection.

The transvalvular gradient is measured. After then, a 260 cm long, 0.035" Amplatz Super Stiff J Guidewire® (COOK) pre-shaped into its distal floppy portion is advanced into the left ventricle. A high-pressure and semi-compliant balloon catheter (Cristal Balloon, BALT, Montmorency, France) is introduced over the wire. A valve dilatation is performed using manual injection with a regular Luer-lock syringe during rapid ventricular pacing (200 to 220 stimulations/min). Pacing is achieved using a temporary lead placed into the right ventricle through the femoral vein.

After inflation, the balloon is removed maintaining the guide in place. The valve, crimped onto his catheter, is introduced on the same guide-wire by retrograde

approach till the native aortic valve. The supra-aortic angiogram and native valve calcifications are used as anatomical landmarks for valve placement. SE valves are deployed step-by-step during normal heart beating while balloon expandable valves are deployed during rapid pacing. Hemodynamic improvement is measured immediately afterwards, and a supra-aortic angiogram is performed in patients without renal insufficiency to assess the presence, location, and degree of aortic regurgitation and the patency of the coronary arteries, as well as to rule out complications, such as aortic dissection. Heparin at a dose of 100 IU/kg body weight is administered to yield an activated clotting time of 250-300 seconds throughout the procedure and after the procedure, the heparin was neutralized by protamine. Patients were pre-medicated with aspirin, clopidogrel, and vancomycin or teicoplanin.

9.4 Post-TAVI monitoring and management

After TAVI, patients remained in the cardiac intensive care unit for at least 24 hours and are closely monitored for 48-72 hours with particular attention to hemodynamic balance, vascular access, renal function, infections and eventual onset of cardiac conduction disturbances (especially late atrioventricular block). A transthoracic echocardiography was performed 24-48 hours after the procedure and pre-discharge. Twelve-lead electrocardiography was performed daily during hospitalization. A chest X-ray was performed during the first 24 hours after TAVI and according to clinical need after then. Blood tests were carried out every 8 hours the first day, then every 12-24 hours (troponin I, blood count, LDH, haptoglobin, total

and fractional bilirubin, BUN, creatinine, PT, PTT, INR, AT III). After the procedure, a dual antiplateled regimen of aspirin 100 mg and clopidogrel 75 mg daily for 3 to 6 months, after which 100 mg of aspirin daily was prescribed indefinitely.

9.5 Follow up

Clinical and echocardiographic follow-up was data were collected at 1, 3, 6, and 12 months and yearly thereafter. The clinical follow-up events included death from all causes, cardiac death (including all unexplained deaths), acute myocardial infarction, stroke, cardiac heart failure requiring rehospitalization, and PPM implantation. Functional status was evaluated according to New York Heart Association (NYHA) classification. At each temporal step, a 12-lead electrocardiogram was collected in all patients, to record modifications in atrioventricular and intraventricular conduction. Prosthesis function (peak and mean transvalvular gradient, peri- or intra-prosthetic leakage) as well as chamber size and function and other valvulopathies were also evaluated using transthoracic echocardiography.

9.6 Definitions

Device success, cardiovascular mortality, myocardial infarction, stroke, life-threatening or disabling bleeding, acute kidney injury (AKI) and vascular complications were defined according to Vascular Academic Research Consortium (VARC) definitions [60]. Procedural success was defined as the device success without urgent cardiac surgery and/or intraprocedural death. Peri-procedural death was defined as any death within 30 days after the procedure or any death before discharge.

10. Statistical analysis

Categorical data are expressed as numbers and percentages and compared by Fisher's or X^2 exact test as appropriate; continuous variables are expressed as mean ± standard deviation (SD). Differences between means of continuous variables were tested by one way analysis of variance. Repeated measures of continuous variables at different time points were compared by repeated measures analysis of variance. Multiple stepwise logistic regression analyses of significant variables at univariate analysis were performed to identify independent predictors of events. Odds ratios (ORs), hazards ratios (HR) and their corresponding 95% confidence intervals (CIs) are provided. Cumulative survival curves were drawn using the Kaplan-Meier method, and the log-rank test was used to compare differences between groups. A p value <0.05 with a 2-tailed test was considered statistically significant. Other specific tests are described in each section of results. Statistical analysis was carried out using the statistical software SPSS version 17.0 for Windows (SPSS, Inc., Chicago, Illinois).

11. Results

11.1 Global population

We prospectively enrolled 72 patients affected by severe symptomatic AS or aortic bio-prosthesis dysfunction referred to university hospital, Verona between March 2010 and March 2013 for TAVI, because of high surgical risk or inoperability criteria, after discussion with the Heart Team. Clinical and demographic characteristic of the study population was showed in **Table 8**. Mean age of population was 81.9 $\pm$ 6.3 year with range of 53 - 91 year. Among them 37 (51.4%) were female, 34 (47%) were overweight (BMI 25-29.9) and 6 (8.3%) were obese (BMI>30%). Majority of patients suffered from chronic arterial hypertension 60 (83.3%). Diabetes, dyslipidemia and chronic obstructive pulmonary disease was present in 19(26.4%), 68 (94.4%) and 18(25%) respectively.

According to EuroSCORE I, 34 (47.2%) patients were labelled as high surgical risk (logistic euroSCORE >20%). However, with EuroSCORE II only 10 (13.9%) of patients were consider high risk for surgical treatment (euroSCORE II >20%). There was statically significant difference in calculation of mean euroSCORE II and mean euroSCORE I (11.40 $\pm$ 11.38 % vs 26.86 $\pm$ 18.42 %; $p<0.001$) for the overall population. EuroSCORE I was overestimated risk of intervention in general population.

Table 8 showing clinical and demographic parameters of general population

Variables	Total population(n=72)
Age, years ± SD	81.9 ± 6.3
Female gender, *n* (%)	37 (51.4%)
Weight, mean ± SD	69.2 ± 11.8
BMI, mean ± SD	25.37 ± 3.93
Normal weight (BMI ≤ 24.9), n (%)	32 (44.4%)
Overweight (BMI 25-29.9); n (%)	34 (47%)
Obese (BMI ≥30), n (%)	6 (8.3%)
Height(m), mean ± SD	1.65 ± 0.09
Systolic Blood Pressure (mmHg), mean ± SD	129 + 20
Hypertension, *n* (%)	60 (83.3)
Diabetes, *n* (%)	19 (26.4)
Dyslipidemia, *n* (%)	68 (94.4)
COPD, *n* (%)	18 (25)
Previous CAD, *n* (%)	43 (59.7)
History of PCI, *n* (%)	31 (43.1)
History of CABG, *n* (%)	17 (23.6)
Atrial fibrillation, *n* (%)	29 (40.3)
Previous stroke, *n* (%)	6 (8.3)
Peripheral artery disease, *n* (%)	37 (51)
Porcelain Aorta, n (%)	5 (6.9)
Serum Creatinine, mean ± SD	1.49 + 0.98
Creatinine clearance(mL/min), mean + SD	41.04 + 14.20
Euroscore I, % ± SD	26.86 ± 18.42
Euroscore II, % ± SD	11.40 ± 11.38

In this series of patients, most common presentation for aortic valve disease was stable angina 43 (55.6%). Second most common presentation was syncope 38 (52.8%) which was followed by cardiac failure 27 (37.5%) and nearly 60% patients has NYHA class III/IV as demonstrated in **table 9**.

Table 9 Symptoms before TAVI

Variables	Total population (n=72)
Syncope, n (%)	38 (52.8)
Unstable angina, n (%)	2 (2.8)
Stable angina, n (%)	43 (59.7)
NYHA class	
I, n(%)	1 (1.4)
II, n (%)	28 (38.9)
III, n (%)	40 (55.6)
IV, n (%)	3 (4.2)
Cardiac failure, n (%)	27 (37.5)

Four (5.6%) patients were undergoes balloon aortic valvuloplasty (BAV) before TAVI as bridge to TAVI, majority of them presented in emergency as critically ill clinical condition. Staged TAVI was performed after clinical and hemodynamic stabilization of patient. In three (4.2%) patients, percutaneous coronary artery intervention performed along with BAV for critically coronary artery disease. Even two (2.8%) patients underwent carotid artery stenting for critical carotid artery disease before TAVI.

Every patient underwent thorough baseline trans-thoracic echocardiographic to evaluate severity of stenosis, measurement of aortic valve annulus and left ventricular systolic and diastolic dysfunction. Baseline echocardiographic finding are presented in **Table 10**.

Table 10 Baseline echocardiography

Variables	Total population (n=72)
Aortic annulus (mm) mean ± SD	21.30 ± 1.73
Aortic valve area (cm^2/m^2), mean ± SD	0.56 ± 0.23
Peak gradient (mmHg), mean ± SD	68.61 ± 23.13
Mean gradient (mmHg), mean ± SD	42.1 ± 16.2
Inter-ventricular septum thickness (cm), mean + SD	1.6 ± 0.24
LVEF, % ± SD	52.4 ± 14
Good (EF >50%), n (%)	43 (59.7)
Detoriated (EF <50%), n (%)	29 (40.3)
Mean pulmonary artery pressure, mean ± SD	45.53 ± 16.23
Normal/mild PHT (<30 mmHg), n (%)	15 (20.8)
Moderate PHT (31-55mmHg), n (%)	37 (51.4)
Severe PHT (>55mmHg), n (%)	20 (27.8)
Aortic valve insufficiency	
No, n (%)	24 (33.3)
Grade-1, n (%)	37 (51.4)
Grade-2, n (%)	8 (11.1)
Grade-3, n (%)	2 (2.8)
Grade-4, n (%)	1 (1.4)

Mitral Valve insufficiency	
No, n (%)	10 (13.9)
Grade-1, n (%)	52 (72.2)
Grade-2, n (%)	9 (12.5)
Grade-3, n (%)	1 (1.4)

TAVI was performed in fifty eight (80.6%) patients for the severe, symptomatic aortic valve stenosis, in four (5.6%) patients for aortic valve insufficiency and ten patients (13.9%) have both stenosis-insufficiency complex but stenosis component was more severe than insufficiency. **Table 11** demonstrated procedural detail. At our centre, transfemoral approach was used more frequently 60 (83.3%) as compare to transapical 11 (15.3%), because has low surgical risk and periprocedural complications. Trans-apical approach was preferred in patients with severely calcified ilio-femoral axis, aortic tortousity and calcification. Sub-clavian approach was used only in single patient who was presented with severe calcified, tortuous ilio-femoral axis along with deformities of thoracic cage.

Among the patient with trans-femoral approach, initially, we started with surgical exploration followed by closure with surgical purse string suture of femoral artery, however, after performing 10 (17.8%) patients, we have started to apply suture mediated percutaneous closure device (Prostare XL) in almost all patients and surgical exploration remained for the patients with severely calcified, tortuous and small femoral arteries. Among a 40 (65.6%) trans-femoral approach closed with suture mediated device, four (10%) patients showed significant stenosis at device

closure site which was treated with peripheral angioplasty balloon dilatation. Single patient needed stent implantation. However, three (7.5%) showed small leak at device closure site two of them was treated with manual compression of femoral artery and one patient needed covered stent implantation.

An Edward- Sapien was most commonly used device at our centre 59 (81.9%), Core-Valve was implanted exceptional in 13 (18.1%) patients mostly with aortic insufficiency, big aortic annulus or vascular and aortic root anatomy which not suitable for Edward- Sapien device. Size of prosthesis and other details were showed in **table 11**. Pre-prosthesis implantation valvuloplasty was performed in most of the patient to remove the aortic valve stenosis and break the calcified aortic leaflet ring, however, in four patients balloon valvuloplasty was not performed; due to severe aortic valve insufficiency without calcification (2 patients), one with malfunctioning aortic valve prosthesis and another with big aortic annulus without calcification.

According to VARC, first prosthesis implantation was unsuccessful in 5(6.9%). The most common causes of failure was severe aortic insufficiency; due to small prosthesis [However, it was only largest prosthesis available for clinical use (1 patient)]; low implantation (1 patient); high implantation (2 patients) and finally, implantation of prosthesis in thoracic aorta due to difficulty in passing device through severely tortuous and calcified aortic arch which leads to dislodgement of the prosthesis. In case of moderate to severe aortic insufficiency after prosthesis implantation, post-dilatation of prosthesis was performed with valvuloplasty balloon with appropriate size in 9 (12.7%).

Table 11 TAVI procedural details

Variables	Total population (n=72)
Aortic valve etiology for TAVI	
Aortic stenosis, n (%)	58 (80.6)
Aortic insufficiency, n (%)	4 (5.6)
Aortic stenosis + Aortic insufficiency, n (%)	10 (13.9)
Approach for TAVI	
Trans-femoral, n (%)	60 (83.3)
Trans-apical, n (%)	11 (15.3)
Sub-clavian, n (%)	1 (1.4)
Closure used for Trans-femoral and sub-clavian approach	
Surgical, n (%)	21 (34.4)
Suture mediated closing device, n (%)	40 (65.6)
Type of Valve prosthesis	
Edward- Sapien, n (%)	59 (81.9)
Core-Valve, n (%)	13 (18.1)
Size of aortic prosthesis	
23mm, n (%)	26 (36.1)
26mm, n (%)	33(45.8)
29mm, n (%)	10(13.9)
31mm, n (%)	3(4.2)
Valvuloplasty done before deployment of prosthesis, n (%)	68(94.4)
First Valve implantation successful, n (%)	67(93.1)
First Valve implantation unsuccessful, n (%)	5(6.9)
Causes of unsuccessful valve implnatation	
Severe Aortic insufficiency (small size of prosthesis), n	1
Severe Aortic insufficiency (low deployment of prosthesis), n	1
Severe Aortic insufficiency (high deployment of prosthesis), n	2
Valve implanted in thoracic aorta, n	1
Post-dilatation after prosthesis implantation, n (%)	9 (12.7)
Amount of contrast (ml), mean $\pm$ SD	143.54 $\pm$ 60.29
Fluoroscopy time (min), mean $\pm$ SD	20.8 $\pm$ 11.2
Procedure time (min), mean + SD	111.3 $\pm$ 39.6

11.2 Immediate peri-procedural outcome

Immediate peri-procedural all cause complications found in 35 (48.6%), among them vascular complications were most frequent 14 (41.2%), moderate to severe aortic valve insufficiency found in 7 (20.6%), conduction blockage in 4 (11.8%) and finally most important complication noted in our series is thrombus like structure around the implanted prosthesis 4(11.8%). These special cases were managed with infusion of intravenous heparin, controlled echocardiography every 24 hours. In almost all patients thrombus resolves spontaneously after few days. However, one patient showed persistence of thrombus which complicated as cerebral stroke at 3 month follow up. One patient died during procedure. After deployment of prosthesis, ventricular fibrillation started, which change to asystole even after cardio-pulmonary resuscitation. Post-mortem report showed occlusion of right coronary ostium with thrombus. Occlusion of right coronary artery with ruptured calcified tissue during balloon valvuloplasty and prosthesis deployment which leads to acute myocardial infarction manifesting as arrhythmia is reasonable explanation. Other peri-complications are showed in **Table 12**.

Table 12 peri-procedural immediate complications

Variables	Total population (n=72)
All-cause immediate complications, n (%)	35 (48.6)
Vascular complications, n (%)	14 (41.2)
Aortic insufficiency (Moderate-severe), n(%)	7 (20.6)
Bundle branch block, n	4 (11.8)
Thrombus around implanted prosthesis, n (%)	4 (11.8)
Death, n(%)	1(2.9)
Stroke, n (%)	1 (2.9)
Ventricular fibrillation, n (%)	1 (2.9)
Hypotension, n (%)	1(2.9)
Prosthesis implantation in thoracic aorta, n (%)	1(2.9)
Thrombus in left atrium, n (%)	1 (2.9)

Every patient after TAVI was monitored in intensive care unit for minimum six hours. Mean ventilation time was 277.8 $\pm$ 1004.7 min (range= 70-8640 min). In trans-femoral setting, on table extubation was performed in almost all patients. 24 hour mean blood loss was 184.2 $\pm$ 188.5 ml. Moreover, 29 (40.3%) patients needed red blood cell transfusion in peri-procedural period. Mean recovery in intensive therapy unit was 2.3 $\pm$ 1.7 days (range=1-10 days) and total hospital recovery was 14.4 $\pm$ 9.7 days (range=4-59 days).

11.3 Outcome at 30days

All patients were followed with routine ECG, echocardiography and laboratory investigation at 30 days after procedure. All cause mortality was 3 (4.2%) among these cardiovascular mortality was one (33.3%) and non-cardiac mortality was 2 (66.7%). One patient died due to acute myocardial infarction which leads to ventricular fibrillation, another one with severe bleeding form apical puncture site which was worsened even after apical puncture site revision and last one was died due to massive cerebral haemorrhage and non responsive hypertension.

Vascular access site hematoma was found in 15 (20.8%) of patients. Vascular complications like major bleeding and hematoma, limb ischemia were most commons 29 (40.1%) like other multicentre series. Three (4.2%) patients suffered from cerebral stroke. One cerebral stroke resolve spontaneously remaining two complicated with disability. Five (6.9%) patients needed permanent pacemaker implantation due to conduction abnormality after prosthesis deployment. Among them majority were with Core-Valve 60%.

Transthoracic echocardiography at 30 days was performed in remaining 69 patients which showed marked decrease in peak gradient from 68.6 $\pm$ 23.1 mmHg to 16.3 $\pm$ 7.2 mmHg ($p<0.001$), mean gradient decrease from 42.2 $\pm$ 16.2 mmHg to 8.7 + 3.9 mmHg ($p<0.001$) and mild improvement in left ventricular function from 52.4 $\pm$ 14 % to 53.75 $\pm$ 13.35% which was not significant ($p=0.10$) as showed in **table 13** and **figure 10 and 11**.

Table 13 Trans-thoracic echocardiography at 30 days post-TAVI

Echo parameters	Total Baseline population (n=72)	Total population at 30 days FU (n=69)	*P* Value
Aortic valve area(cm^2/m^2), mean ± SD	0.56 + 0.23	1.82 ± 0.30	<0.0001
Peak gradient(mmHg), mean ± SD	68.61 + 23.13	16.3 ± 7.15	<0.0001
Mean gradient(mmHg), mean ± SD	42.1 + 16.2	8.71 ± 3.87	<0.0001
Inter-ventricular septum thickness(cm), mean ± SD	1.6 + 0.24	1.54 ± 0.22	<0.001
Left Ventricular ejection fraction(%), mean ± SD	52.4 + 14.1	53.75 ± 13.35	0.103
Aortic valve insufficiency			
No, n (%)	24(33.3)	9(12.5)	
Grade-1, n (%)	37(51.4)	56(77.8)	0.54
Grade-2, n (%)	8(11.1)	4(5.6)	
Grade-3, n (%)	2(2.8)	0(0)	
Grade-4, n (%)	1(1.4)	0(0)	
Mitral valve insufficiency			
No, n (%)	10(13.9)	7(9.7)	
Grade-1, n (%)	52(72.2)	50(69.4)	0.32
Grade-2, n (%)	9(12.5)	12(16.7)	
Grade-3, n (%)	1(1.4)	0	

Figure 10 showing marked decrease in peak gradient

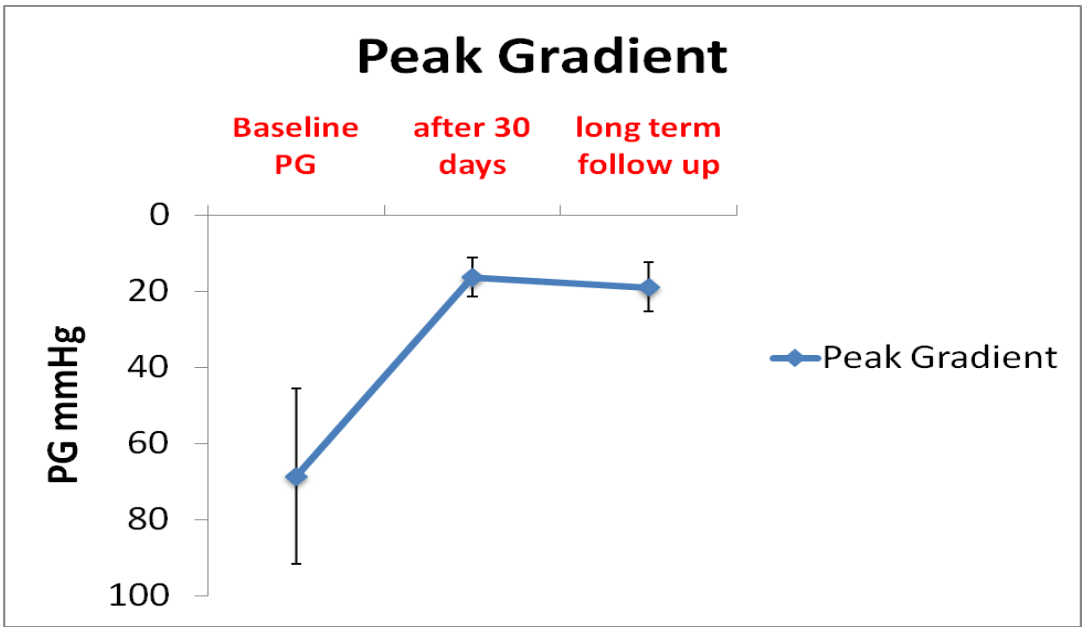
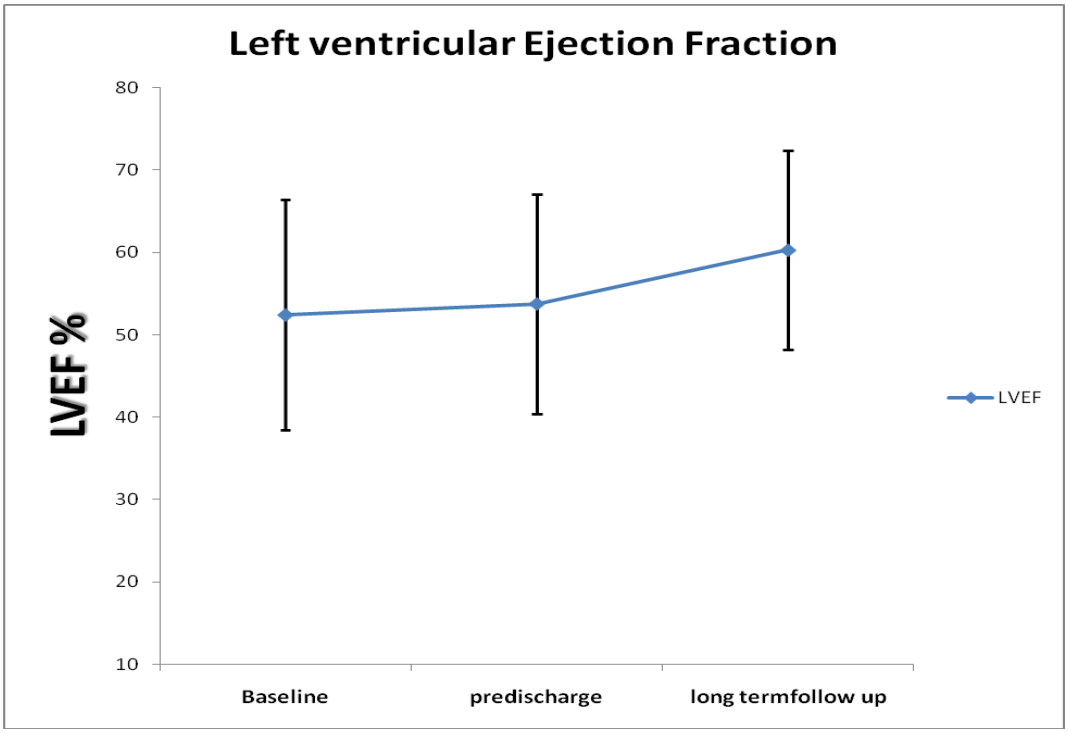


Figure 11 showing small improvement in left ventricular function



11.4 Long term follow up

Recently long term follow up was performed in all 69 (100%) patients remained alive after 30 days follow up. Mean duration of follow up was 13.19 ± 9.7 month (range 3-35 months). All cause mortality was found in 11 (15.9%), among them cardiovascular and non-cardiovascular mortality was found in 4 (36.36%) and 7 (63.63%) patients respectively. One patient (1.45%) underwent heart transplantation which was on heart transplantation list for severe left ventricular failure. A composite outcome (death and re-hospitalization) was found in 32 (44.4%). Bleeding complication, cerebral stoke and re-hospitalization in the patients alive at follow up was showed in **table 14**.

Table 14 Re-hospitalization

Variable	Population (n=77)
Re-hospitalization	18(31.6)
Cardiac causes, n (%)	4(22)
Non-cardiac causes, n (%)	14(78)
Cardiac failure, n (%)	3(16.67)
Cardiac and renal failure, n (%)	1(5.5)
Cerebral stroke, n (%)	3(16.67)
Respiratory insufficiency, n (%)	4(22.22)
Respiratory tract infection, n (%)	2(11.11)
Hepatic failure, n (%)	1(5.5)
Septicaemia, intestinal ischemia, n (%)	1(5.5)
Anaemia, n (%)	1(5.5)
Intervention of carotid end-arteriotomy, n (%)	1(5.5)
Constipation, n (%)	1(5.5)

Table 15 Long term follow up

Variables	Total population (n=57)
Bleeding complications, n (%)	12(21)
Cerebral stroke, n (%)	3 (5.3)
NYHA class	
I, n (%)	10(17.5)
II, n (%)	28(49.1)
III, n (%)	18(31.6)
IV, n (%)	1(1.8)
Frality Scale	
0, n (%)	22(38.6)
1, n (%)	2(3.5)
2, n (%)	27(47.4)
3, n (%)	6(10.5)

There was marked improvement in NYHA class as showed in **table 15** and **figure 12 and 13** on long term follow up. Most of patients shifted to lower NYHA class than baseline NYHA class.

Figure 12 showed decrease in NYHA class on long term follow up

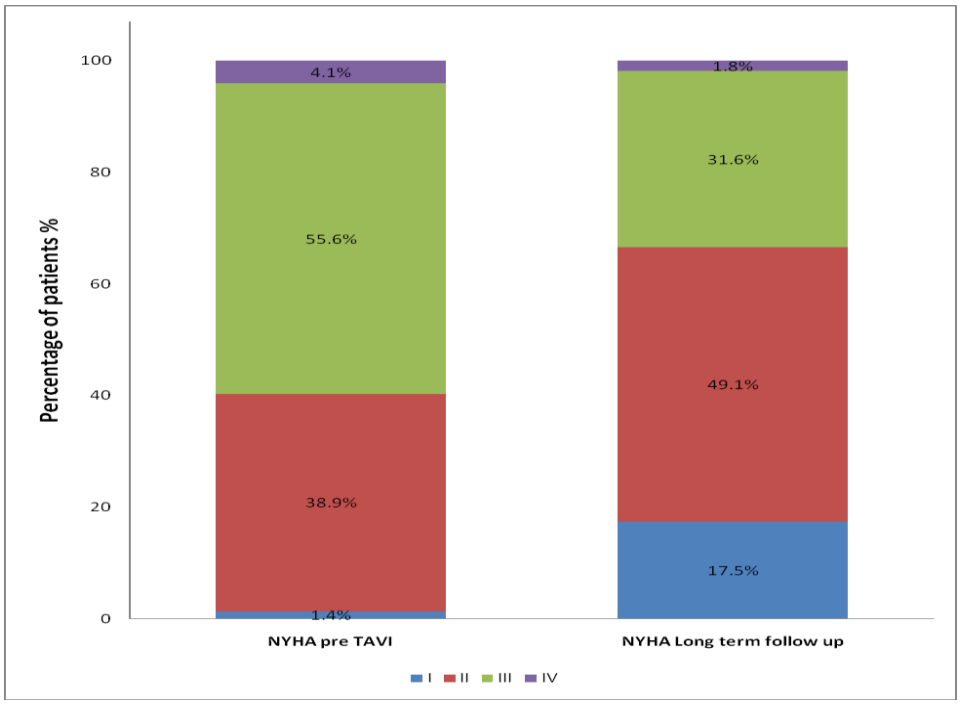
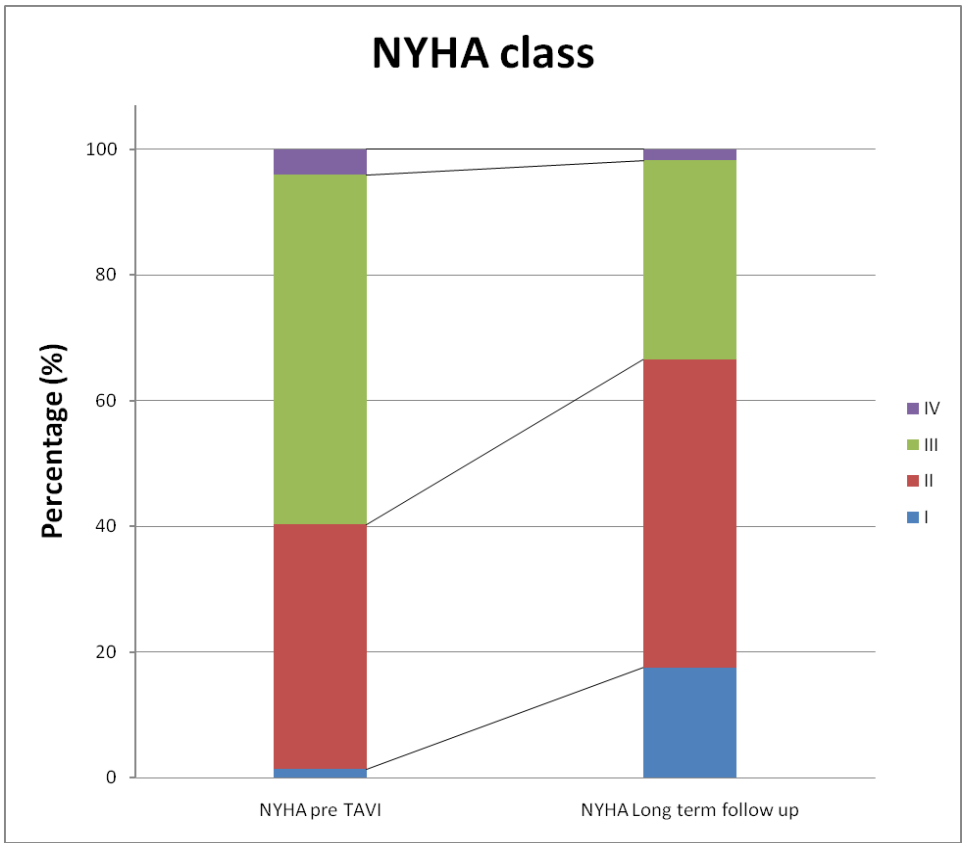


Figure 13 showed how the NYHA class shifted from higher class to lower class



11.5 Survival analysis

Figure 14 and 15 showed survival analysis performed using Kaplan-Meier curve stratifying with heart failure and high euroSCORE.

Figure 14 shows KM curve stratified with heart failure

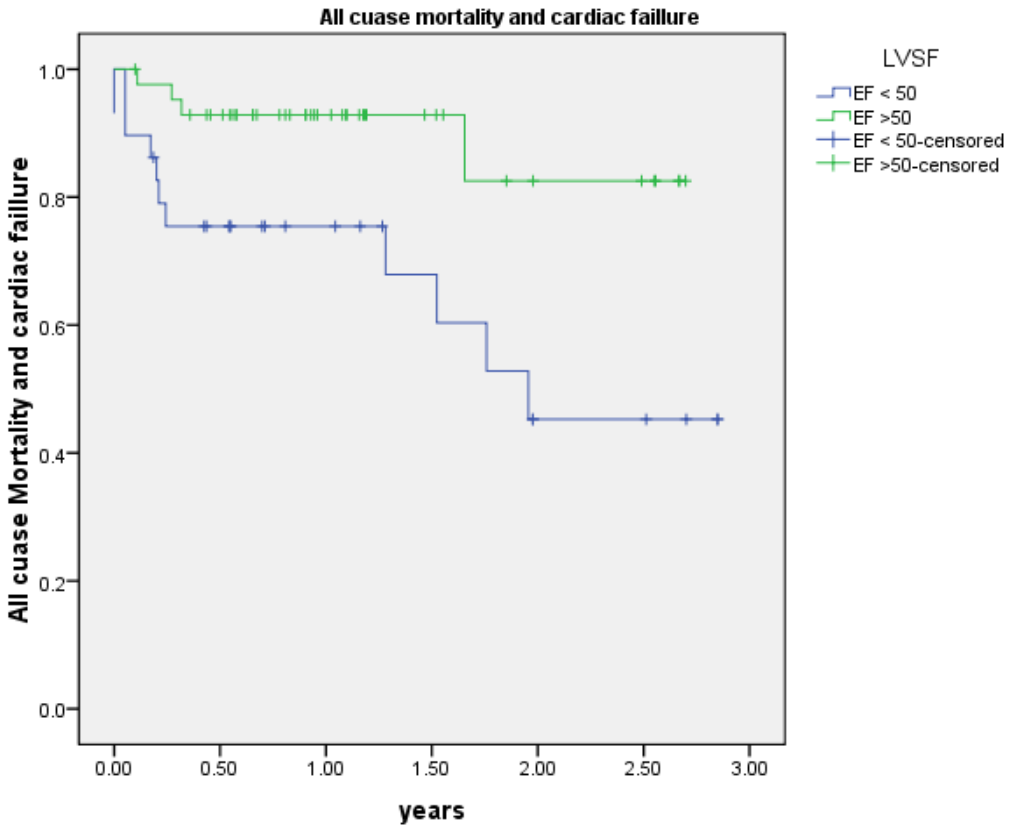
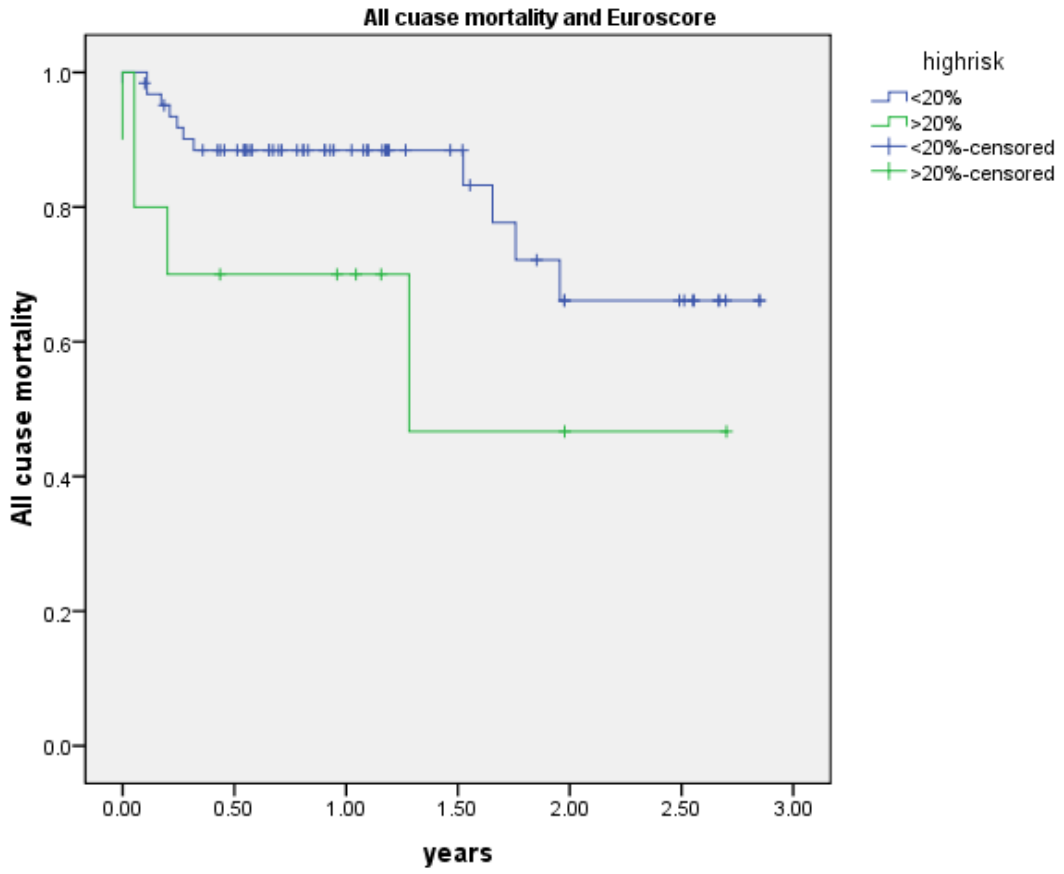


Figure 15 demonstrated nature of KM curve for all cause mortality with high euroscore II on long term follow up



Moreover, high Euroscore-II predict more accurately mortality as compare to high logistic Euroscore I ($p<0.002$; CC= 0.375) showed by Kaplan-meier hazard curve as showed in **figure 16** and **figure 17**.

Figure 16 showing hazard curve stratified with high logistic euroscore

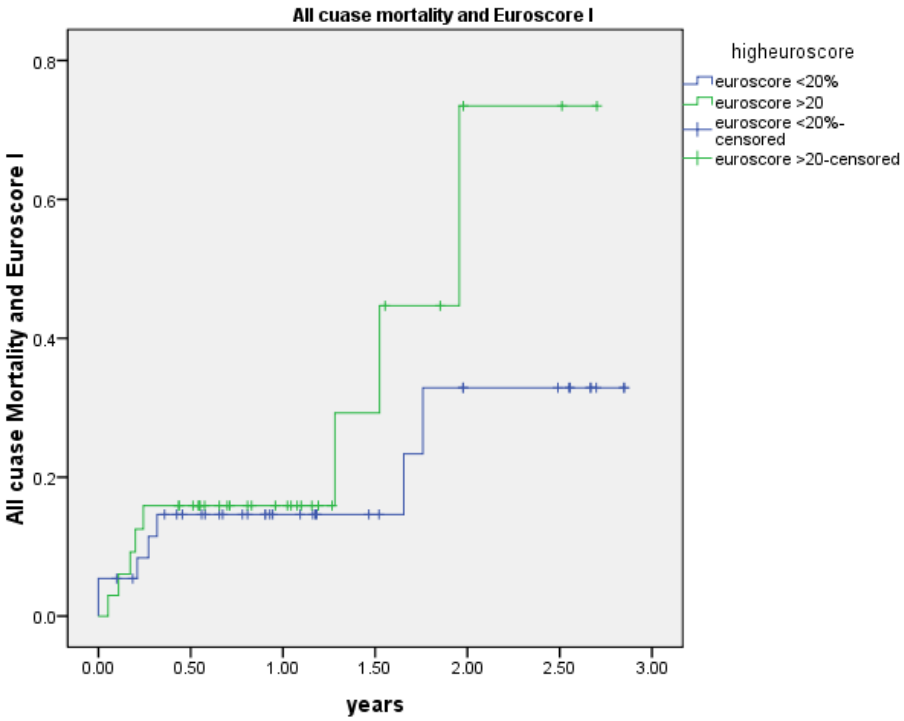
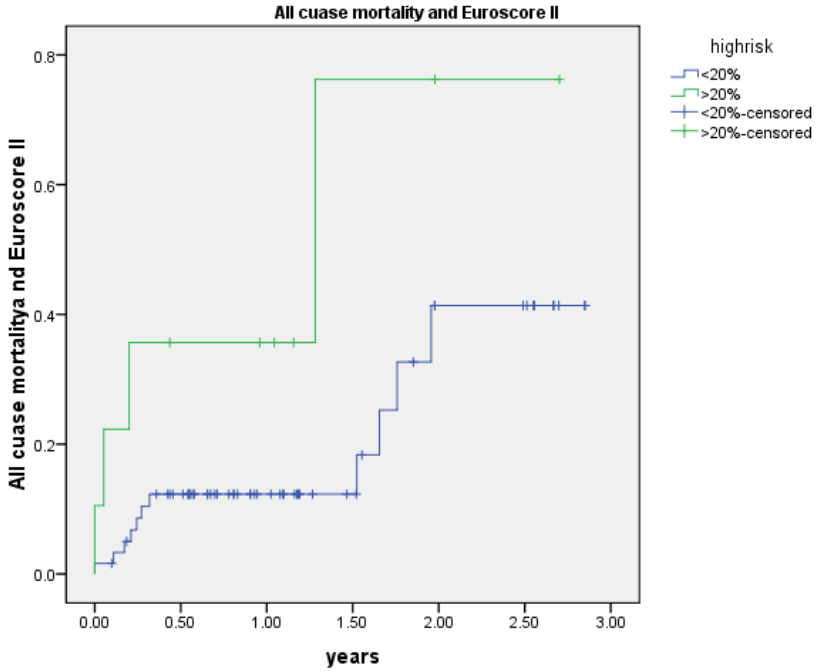


Figure 17 showing hazard curve for mortality stratified with high euroscore II



11.6 Long term performance of prosthesis

Echocardiographical follow up was present in all 57 patients alive at long term follow up. Peak gradient remained decrease from 68.61 ± 23.13 mmHg at baseline to 18.9 ± 6.4 mmHg at follow up ($p<0.001$); even mean gradient remained decrease from 42.1 ± 16.2 mmHg to 9.9 ± 3.4 mmHg ($p<0.001$), improvement in left ventricular ejection fraction from baseline 52.4 ± 14 % to 60.3 ± 12.12 %($p<0.001$) was significant as compare to 30 days follow up. Pulmonary artery mean pressure was decrease from 45.33 ± 16.23 mmHg at baseline to 37.4 ± 14.3 mmHg ($p=0.01$) significantly than 30 days follow up. There was mild increase in PG and mean gradient as compare to parameter at 30 days follow up but was not statistically significant. Other parameters are showed in **table 16** and **figure 18**.

Table 16 Echocardiographic performance of prosthesis

Echocardiography parameter	Baseline population (n=72)	Population at 30 days FU (69)	Population at long term FU (n=57)	*P* for baseline and LTFU
Peak gradient(mmHg), mean ± SD	68.61 ± 23.13	16.3 + 7.2	18.9 ± 6.4	<0.0001
Mean gradient(mmHg), mean ± SD	42.1 + 16.2	8.71 + 3.87	9.9 ± 3.4	<0.0001
PAP (mmHg), mean ± SD	45.33 + 16.23	42.28 + 14.20	37.4 ± 14.3	0.001
LVEF (%), mean ± SD	52.4 + 14	53.75 + 13.35	60.3 ± 12.12	<0.001
EF >50%, n (%)	43(59.7)	44(63.8)	46(80.7)	0.001
EF <50%, n (%)	29(40.3)	25(36.2)	11(19.3)	0.001
Aortic Valve insufficiency				
No, n (%)	24(33.3)	9(12.5)	19(33.3)	
Grade-1, n (%)	37(51.4)	56(77.8)	31(54.4)	0.44
Grade-2, n (%)	8(11.1)	4(5.6)	7(12.3)	
Grade-3, n (%)	2(2.8)	0(0)	0(0)	
Grade-4, n (%)	1(1.4)	0(0)	0(0)	
Mitral Valve insufficiency				
No, n (%)	10 (13.9)	7(9.7)	1 (1.8)	
Grade-1, n (%)	52 (72.2)	50(69.4)	40 (70.2)	0.004
Grade-2, n (%)	9 (12.5)	12(16.7)	12 (21.1)	
Grade-3, n (%)	1 (1.4)	0(0)	4 (7)	

Figure 18 showed improvement in trans-aortic gradient, LVEF and PAP

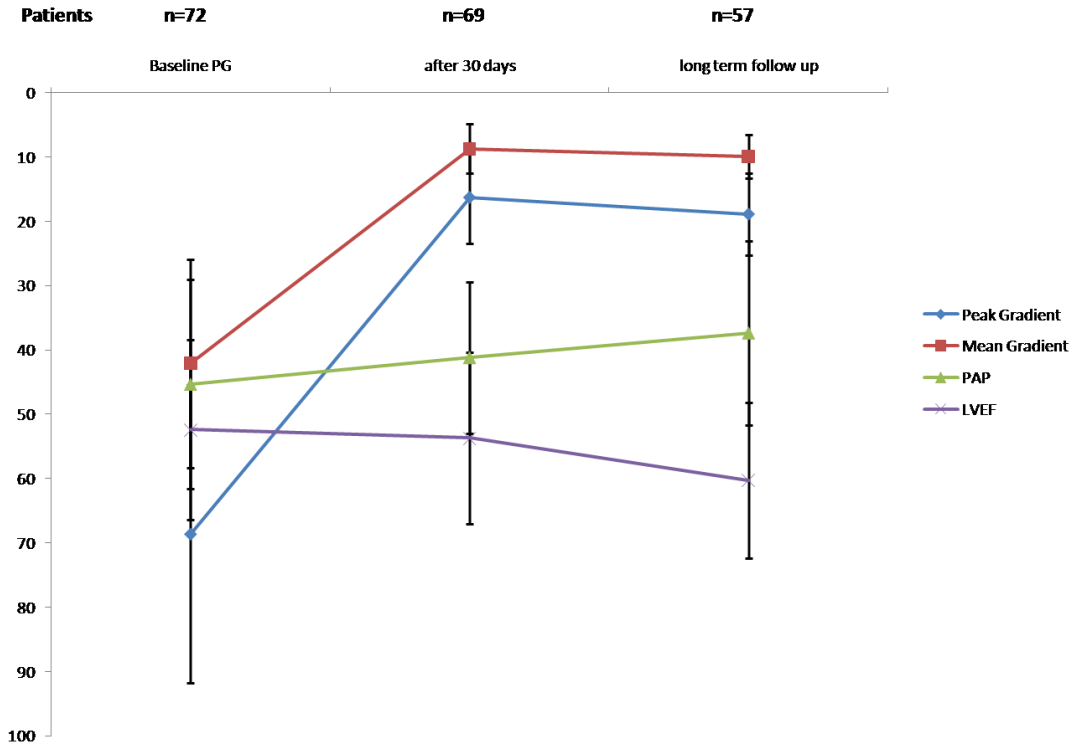


Figure 19 showed changes in aortic valve insufficiency at baseline, 30 days and long term follow up

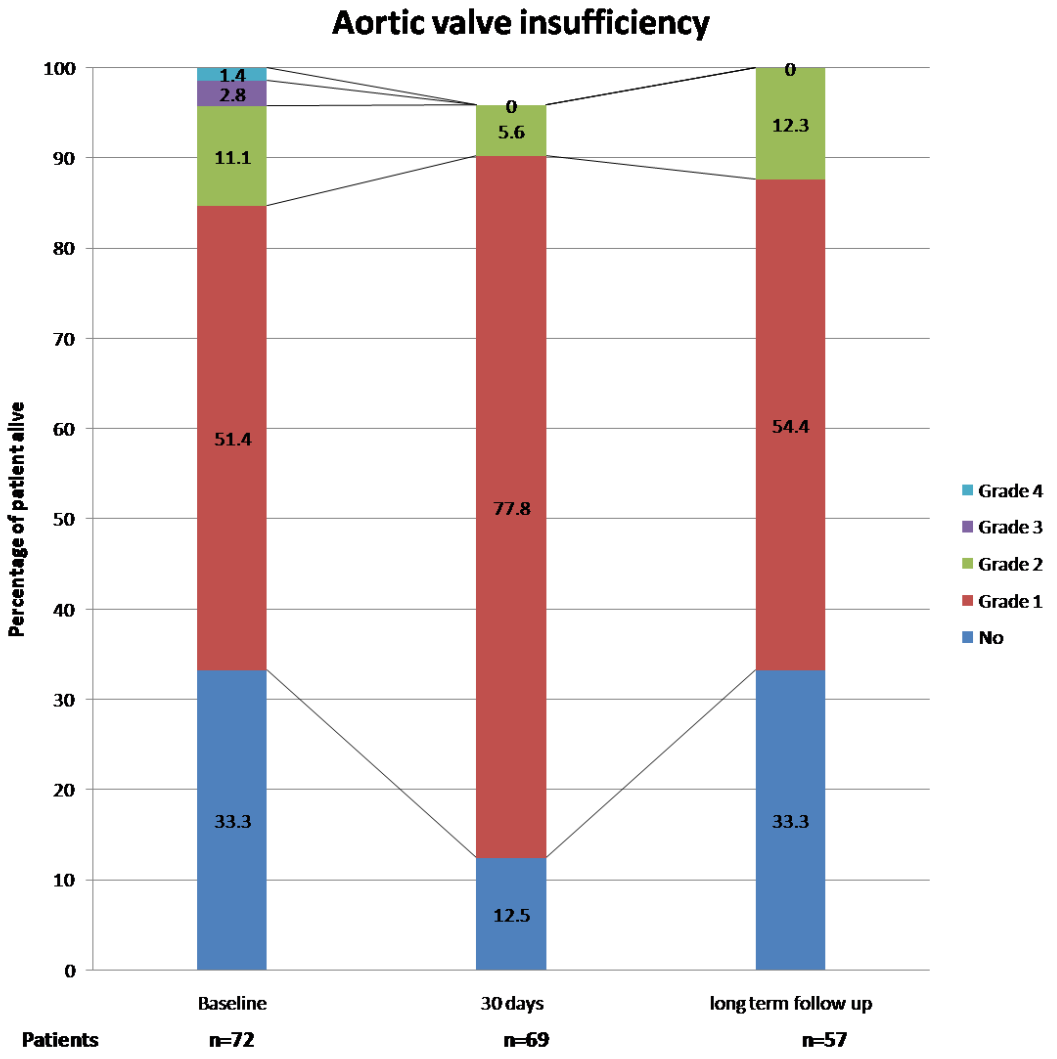
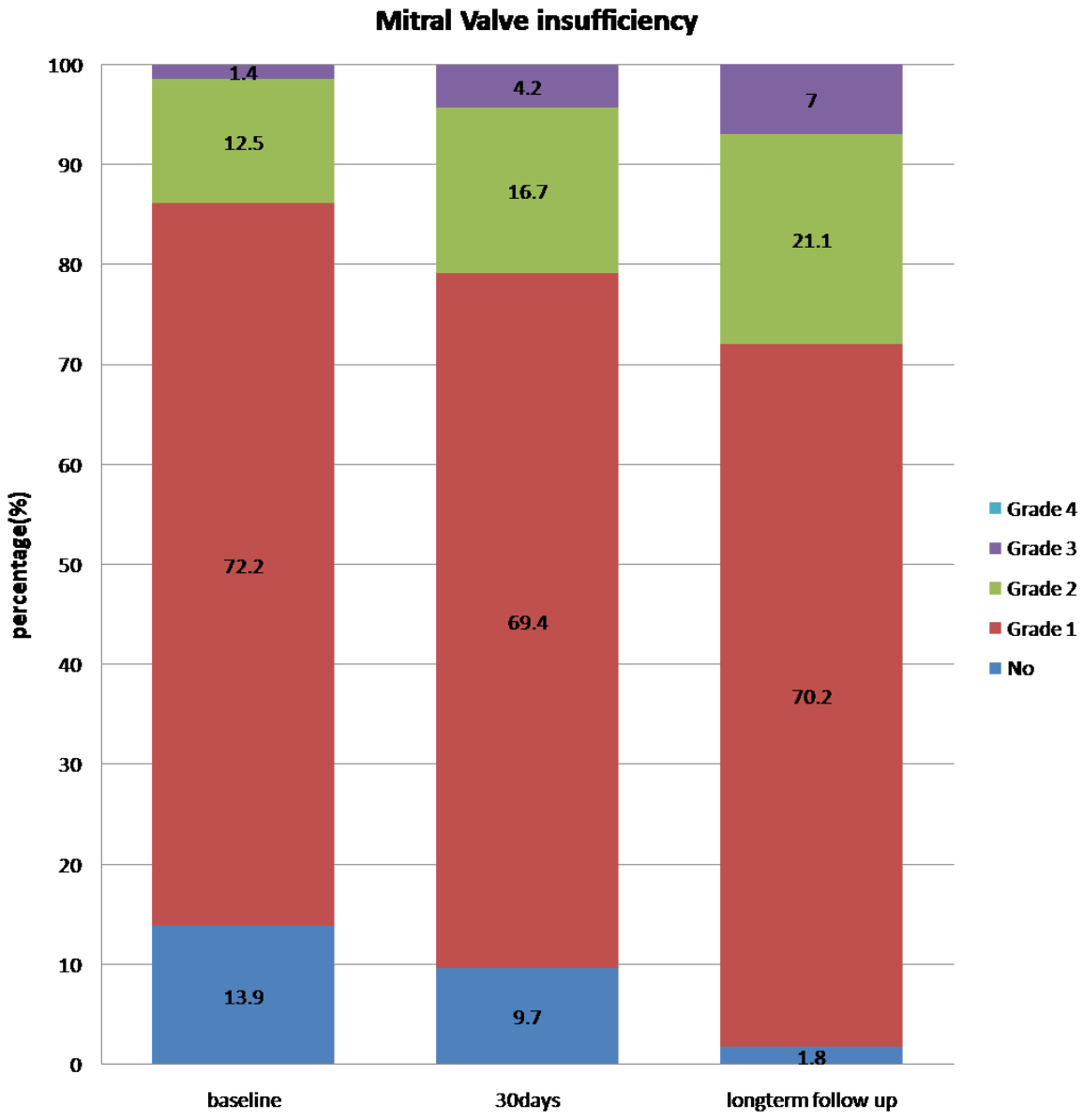


Figure 20 showed changes in mitral valve insufficiency at baseline, 30days and long term



Predictor of mortality at long term was found to be high Euroscore II OR= 6.15 (CI 1.1-34.1); p<0.04, obesity(BMI>30) OR=22(3.34-150); p<0.001.

11.7 Incidence, predictor factors and prognostic implication of acute kidney injury (AKI) produced after TAVI procedure

TAVI candidates are mostly elder patients suffering from chronic kidney disease. Kidney function may be worsened after use of contrast during the TAVI. Aim of this analysis is to evaluate the incidence of AKI, predictors and prognostic value of same in long term follow up.

PreTAVI serum creatinine was defined as value of serum creatinine immediately before TAVI. Highest level of creatinine in first week after TAVI was considered as the post-TAVI serum creatinine. Creatinine clearance was calculated according to the Cockgroft-Gault equation, based on s. creatinine, age, sex and weight of the patient. In this analysis more than 20 % decline in creatinine clearance value or need for haemodialysis after procedure was considered as AKI (RIFLE criteria) **[61]**.

We analysed 69 patients operated for severe aortic valve disease during Febraury 2010- Febraury 2013 at our centre. According to development of acute kidney injury, population is divided into two groups; AKI present and AKI absent. Clinical and demographic characteristics of both groups are showed in **table 10**.

Incidence of AKI was 21.7% in this small group of population. There was no difference in the clinical presentation, demographic characteristic, co-morbidities and other peri-operative parameters. Amount of contrast used during procedure was higher in group with AKI than without AKI (156 $\pm$ 65 vs 143.3 $\pm$ 58.2; p=0.34).

Table 17 clinical and demographic characteristic of AKI present and AKI absent group

Variables	AKI present (n=15)	AKI absent (n=54)	P value	Univariate analysis	
				OR	95% CI
Gender male, n (%)	5 (33.3)	28 (51.9)	0.16	1.16	0.72-3.3
Age, mean ± SD	83.5 + 5.2	81.9 + 6.2	0.99	0.01	-0.01-0.02
BMI, mean ± SD	24.7 + 3.2	25.6 + 3.8	0.51	-0.01	-0.04-0.02
Overweight (BMI 25-29.9), n (%)	9 (60)	24 (44)	0.21	0.91	0.83-0.99
Hypertension, n (%)	13 (86.7)	45 (83.3)	0.75	0.96	0.76-1.2
Diabetes, n (%)	2 (13.3)	14 (25.9)	0.30	1.9	0.50-7.6
COPD, n (%)	2(13.3)	15 (27.8)	0.25	2.1	0.53-8.1
Baseline S. Creatinine , mean + SD	1.04 + 0.11	1.55 + 1.07	**0.01**	-0.1	-0.2-0.01
Baseline Creatinine clearance, mean + SD	44.5 + 9.6	41.1 + 14.9	0.15	0.00	-0.00-0.01
Coronary artery disease, n (%)	9 (60)	31 (59.3)	0.96	0.98	0.62-1.6
Prior PCI, n (%)	6 (40)	23 (42.6)	0.86	1.1	0.53-2.1
Prior CABG, n (%)	2 (13.3)	14 (25.9)	0.31	1.9	0.50-7.6
Atrial fibrillation, n (%)	7 (46.7)	21 (38.9)	0.59	0.83	0.44-1.6
Peripheral vascular disease, n (%)	6 (40)	28 (51.9)	0.41	1.3	0.66-2.5
LVEF%, mean + SD	51.4 + 14.3	53.4 + 13.8	0.73	-0.02	-0.01-0.01
Cardiac dysfunction (EF<50%), n (%)	7 (46.7)	20 (37)	0.50	0.8	0.42-1.5
NYHA III, n (%) IV, n (%)	 10(71.4) 0(0)	 29(53.7) 3(5.6)	0.40		
Euroscore logistic % + SD	25.28 + 14.5	27.5 + 19.7	0.08	-0.00	-0.01-0.00
Euroscore II % + SD	8.4 + 4.4	12.2 + 12.7	0.05	-0.01	-0.01-0.04
Peak gradient, mean + SD	66.3 + 25.14	69.45 + 23.3	0.97	0.00	-0.01-0.00
Pulmonary artery pressure, mean + SD	44.33 + 12.24	45.44 + 17.44	0.03	0.00	-0.01-0.00

On univariate analysis only pre-TAVI s. creatinine, euroscore II and pulmonary artery pressure was predictor of development of acute kidney injury after TAVI procedure. On long term follow mortality was higher in patient group without AKI after TAVI (22% vs 0%; p=0.04). However, rehospitalisation for any cause was higher in AKI developed group (53.3 % vs 23.8%; p=0.03) as showed in **table 18**.

Table 18 peri-procedural, 30days and long term FU parameter in AKI present and AKI absent group

Variables	AKI present (n=15)	AKI absent (n=54)	P value	Univariate analysis	
				OR	95% CI
Amount of constrast used, mean ± SD	156.7 + 65	143.2 + 58.2	0.34	0.001	-0.00-0.00
Procedural time, mean + SD	101 + 29	113 + 42.3	0.25	-0.00	-0.00-0.00
Stay in intensive therapy unit, day ± SD	2.3 +2.5	2.3 + 1.34	**0.05**	0.002	-0.06-0.06
Stay in hospital, days ± SD	13.8 + 10.4	15.1 + 9.5	0.80	-0.00	-0.01-0.00
Immediate post TAVI complications, n (%)	7 (46.7)	25(46.3)	0.98	1.0	0.54-1.8
Long term outcome					
All cause mortality, n(%)	0(0)	12(22.2)	**0.04**	0.45	0.22-0.9
Rehospitalisation, n (%)	8(53.3)	10(23.8)	**0.03**		
NYHA III, n (%)	6(40)	12(28.6)	0.28		
NYHA IV, N (%)	1(6.7)	0(0)			
Frality					
0, n (%)	4(26.7)	18(42.9)			
1, n (%)	0(0)	2(4.8)	0.34		
2, n (%)	8(53.3)	19 (45.2)			
3, n (%)	3(20)	3 (7.1)			

Among the 57 patients remained alive at long term follow up, 16 (28%) showed the improvement in creatinine clearance after TAVI procedure. Improvement in renal function is considered as increase in > 20% of creatinine clearance on long term follow up. Insufficient renal perfusion in setting of severe aortic stenosis may be reason for this.

11.8 Feasibility and safety of TAVI in treatment of severe aortic regurgitation in patients with HEART MATE II

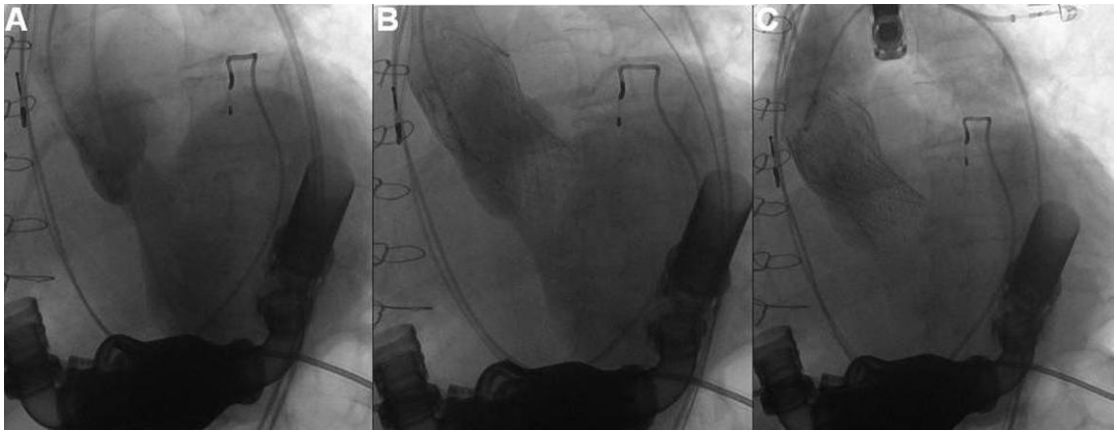
TAVI has enhanced the therapeutic spectrum far beyond expected, and as stated before, with growing experience of the heart team, patients in difficult conditions and perhaps no other option, may benefit from “off label” use of transcatheter valves. In particular the versatility of the CoreValve allows the treatment of difficult cases of aortic regurgitation as the one presented below.

A 53-year-old male patient with end-stage dilated cardiomyopathy was uneventfully implanted with a Thoracic HeartMate II left ventricular assistance device intended as a bridge to transplantation. Ten months post-operatively, he showed progressively worsening of symptoms. In view of the unfavourable anthropometric characteristics, any attempt to anticipate transplantation was unsuccessful for lack of appropriate donors. Ineffective ventricular assistance output enssued due to severe aortic regurgitation [Fig. 21A]. Pulmonary edema with desaturation, and major arrhythmias ultimately required endotracheal intubation and cardiopulmonary resuscitation. Since neither optimal medical therapy nor ventricular assistance adjustments provided hemodynamic stability, the Heart Team decided for emergency trans-catheter aortic valve implantation.

Procedure: through an 18-F introducer, an extra-stiff guidewire was positioned in the left ventricle, and a 29-mm CoreValve (Medtronic, Milwaukee, Wisconsin) was implanted under fluoroscopy and echo control. Due to a moderate residual periprosthetic regurgitation [Fig. 21B], a second 29-mm CoreValve was deployed

within the previous valve prosthesis with minimal residual leak [Fig. 21C], and no complications. (of note, at the time of this procedure, the 31mm CoreVale was not yet available). The femoral access was repaired by the Prostar XL Closure device. The patient's hemodynamics improved immediately after procedure. On discharge, echocardiography showed mild periprosthestic regurgitation. The patient was transplanted 6 months later.

Figure 21. Life saving TAVI for aortic insufficiency in Heart Mate II



A) preTAVI severe aortic insufficiency, B) after first device implantation, C) after second device implantation

Use of TAVI technique for severe aortic regurgitation in Heart Mate II resulted in a life-saving procedure that allowed management of an acutely occurred hemodynamic instability. Being the first, ever reported case of this nature, it has been published elsewhere **[62]**.

11.9 Feasabilty and safety of using "Limb-saving" contra-lateral implantation of a protection guide-wire in femoral access during TAVI

The use of a totally percutaneous technique for trans-femoral TAVI has several advantages over the surgical exploration **[52]**. First is the spared time compared to the surgical preparation of the vascular access that requires, even for expert teams, more than 60 to 90 minutes to open and close the vascular access as compared to percutaneous the technique. Furthermore, it can be performed with local anesthesia, and allows rapid patient mobilisation after 2 or 3 days of the procedure, depending on the patinet's general conditions. However, a totally percutaneous management of the femoral access route requires accurate pre-intervention screening, confidence with the use of the Prostar closure device, experience with peripheral vascular interventions, and the availability of a wide array of dedicated material. We believe that all cases performed percutaneously with the pre-implantation of the Prostar device must be prepared with a contralateral implantation of a safety guide-wire before the implantation of the introducing sheath. This wire warrants a rapid access to the true lumen of the iliac-femoral vessels in case of occlusion or vascular rupture before or after TAVI **[Figure 22A]**.A present case below is one of example of such alternative.

An 87-year old obese female with medical history of hypertension, type II diabetes mellitus and CKD was admitted in hospital with heart failure. A TTE showed severe aortic valve stenosis (PG-56mmHg, MG-38mmHg, AVA-0.3cm^2/m^2) with important left ventricular dysfunction (LVEF=35%). Coronary angiography showed mild

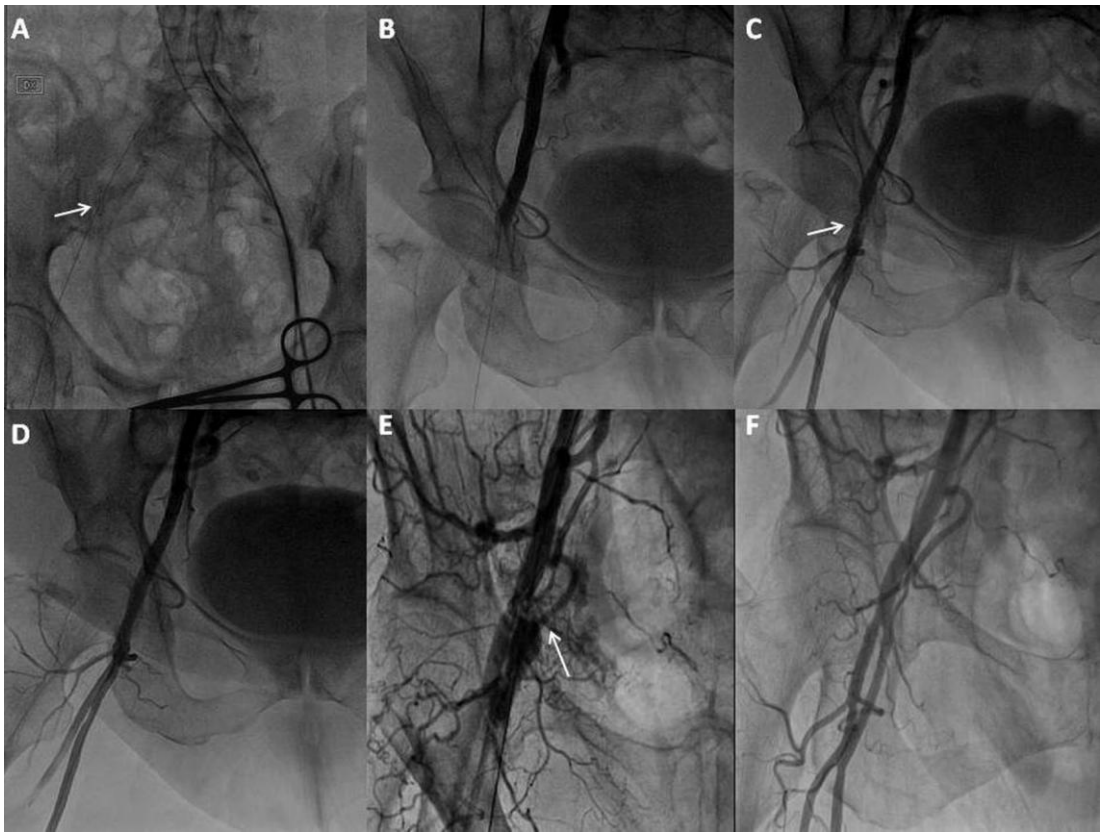
atherosclerotic disease, peripheral angiography visualized moderate atherosclerotic stenosis with severe degree of calcification. Logistic EuroScore was 45%. PreTAVI screening with TTE and CTscan showed the following measurement: aortic annulus-21mm, CFA diameter 7mm and 8mm on right and left side respectively. Implantation of 26mm Edward Sapien XT prosthesis was planned.

Procedure: The procedure was performed under general anaesthesia. The Prostar suture mediated closing device was implanted on the right CFA after positioning a 0.018" extra-support, 200mm length guide wire (Control V, *Boston Scientific* Corp*., Natick, Massachusetts*) from the contralateral CFA. Due to the impossibility of advancing the 20F introducer sheath through the extra-stiff 0.035 wire, several balloon dilatations of increased diameters were performed on the external and common iliac arteries. The Edward Sapien XT prosthesis was then successfully deployed under rapid pacing. The delivery system was retrieved and puncture site was closed with Prostar device. The final angiographic control showed the total occlusion of the right iliac artery **[Figure 22B].** A peripheral angioplasty balloon 9x60mm was inflated at the occluded site over the contralateral "limb saving" guide wire with rapid recovery of blood flow along the right femoral artery **[Figure 22C]**. Due to the presence of dissection and residual stenosis, a 9x40mm self-expandable Wallstent (*Boston Scientific* Corp., Natick, MA) was inserted which resulted in normal flow **[Figure 22D]**. Further clinical evolution was un-eventful.

The rapid access to the vascular entry site of the large introducer sheath from a contralateral "safety wire" allows relatively simple management of complications that, otherwise, may prove life threatening, or that may require emergency major

vascular surgery with potentially severe post-operation complications **[63,64]**. The positioning of a balloon at the point of the percutaneous access site for a trans-femoral TAVI procedure from the contralateral vascular access allows for example the rapid interruption of bleeding in case of arterial rupture or failure of the Prostar suture, or the resolution of stenosis created by the closing device itself **[Figure 22C]**. When simple balloon inflations are not sufficient, naked stent implantation may become necessary (like in the previously described case, **Figure 22D**), or even in some more dramatic situations covered stents may be required like in the case of a 95-year old lady that, despite apparently excellent vascular conditions, experimented a large rupture of the CFA after removal of the introducer sheath and Prostar closure **[Figure 22E]**. This potentially severe complication was easily managed with the rapid implantation of an 8x40mm self-expandable covered stent that permitted a rapid recover and uneventful hospital course **[Figure 22F]**.

Figure 22 Safety guide-wire from contralateral side for rescue peripheral artery angioplasty



A) 0.0018" guide wire in the rigth femoral artery advanced from the left femoral puncture (arrow); B) Occlusion of right external iliac artery; C) Angiography after balloon dilatation. Residual stenosis and dissection at puncture site (arrow); D) Angiography after implantation of self-expandable stent; E) Rupture of right common femoral artery. Constrast media is evident outside the artery (arrow);F) Final angio after positioning a covered self expandable stent in ruptured right CFA.

Vascular complications are common with calcified, atherosclerotic iliac-femoral arteries **[63-67]**. However, proper selection of patient and access route, and adequate preventive measures reduce the risk. Apparently "normal" iliac-femoral arteries may give rise to severe complications in the elderly. Insertion of a safety wire from the contralateral artery is a "must" when planning a totally percutaneous trans-femoral TAVI.

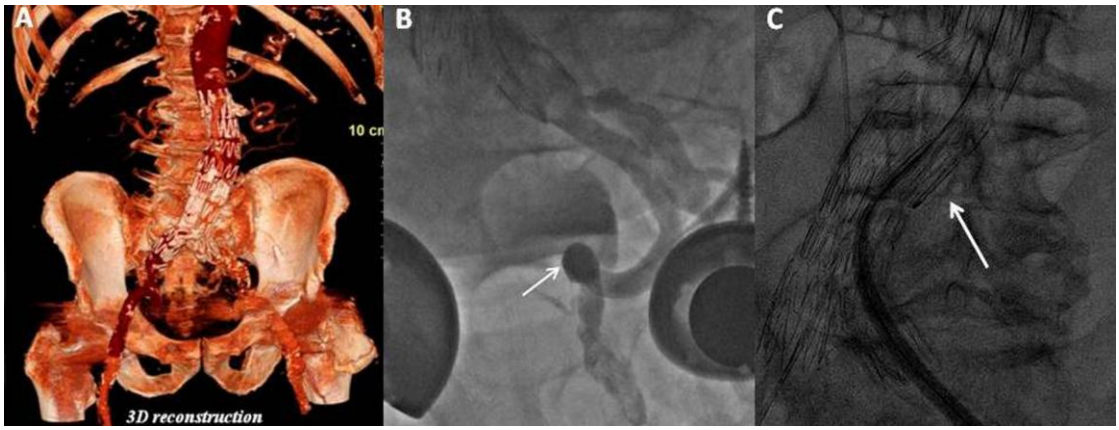
11.10 Feasabilty and safety of trans-femoral TAVI in patient with aorto-iliac endoprosthesis and severely tortuous and atherosclerotic accesses-"Railing tract" technique

A symptomatic 82-year old male with a known severe AVS was admitted in emergency with episodes of syncope and overt heart failure. He was rejected for SAVR in view of a severe pulmonary disease with bilateral emphysematous lungs (GOLD classification stage III), left anterior descending coronary artery disease, moderate CKD and high EuroScore (43%). He had also severe PVD with previous implantation of an aortic-bi-iliac endo-prosthesis. Heart Team opted for a trans-femoral approach because of the severe lung disease despite presence of an aortic-bi-iliac endo-prosthesis and severe tortuosity of the ilio-femoral axes, determining an approximately 360° loop on the right external iliac artery and a 260° loop on the left side, respectively **[Figure 23A and 23B]**.

Procedure: TAVI was undertaken with surgical exposure of left CFA. An extra-stiff wire was inserted upwards through the CFA to straighten the left iliac tortuosity. The 22F Edward introducer however, could not advance beyond the endoprosthetic part of left common iliac. After several attempts the introducer was removed, its tip was found damaged likely because of friction against the calcium and the struts of the endoprosthesis. Another extra-stiff wire was therefore advanced from the right brachial artery to the left SFA through a multipurpose catheter for additional support. A new 22F Edward introducer was finally advanced as "railing track" with

two extra-stiff wires **[Figure 23C]**. After conventional balloon valvuloplasty, a 23mm Edward-Sapien XT aortic valve was successfully implanted. The femoral access was surgically repaired without complications.

Figure 23 Railing tract technique



A) CT Scan showing aortic-bi-iliac endoprosthesis and severe tortuosity of the ilio-femoral axes; B) Angiography showing severely tortuous left ilio-femoral axis (arrow); C) Insertion of introducer over the extrastiffs guidewires, one from right brachial artery up to left common femoral artery, and one from the SFA (arrow).

This case is a successful example of an extremely challenging trans-femoral TAVI, managed with a special technique in a patient with clear contra-indications to the femoral access, but with no alternative options. The technique of inserting a second extra stiff wire down from the right brachial artery up to the femoral artery together with an ascending extra stiff wire from the femoral access to the ascending aorta which acts as “railing track” may be useful in specific TAVI candidate **[69]**.

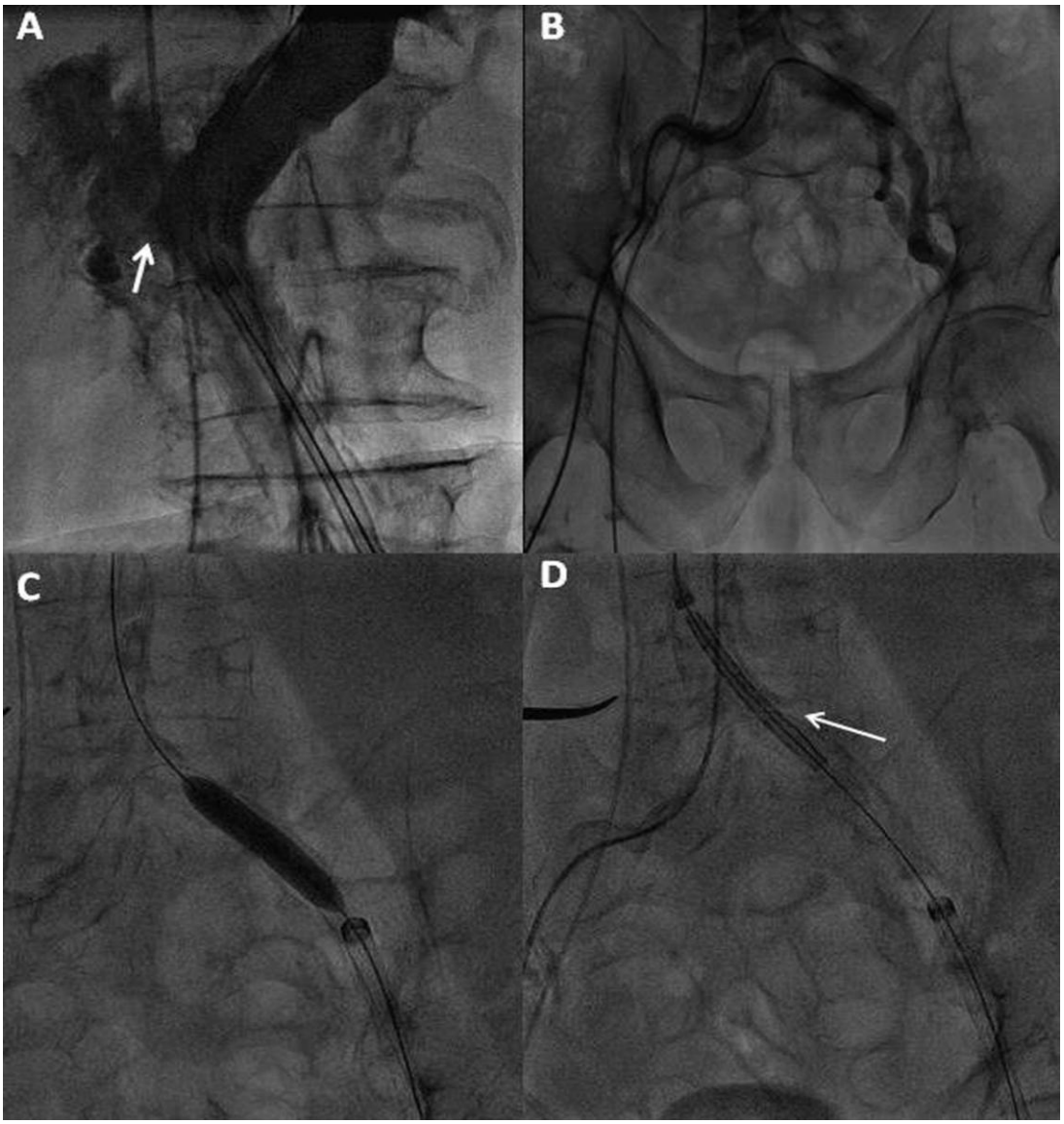
11.11 Safety and feasibilty of Core-Valve insertion without introducer sheath

Positioning the large introducing sheath from the CFA to the aorta in patients with severe PVD is the most challenging step of the trans-femoral procedure in these patients.Technically,theEdwards-Sapien prosthesis should not be pushed out of the introducer sheath, if it has not been fully advanced up to the thoracic-abdominal aortic segment **[52]**. Indeed, the rigidity of the catheter and valve device unit may cause aortic wall rupture if strongly pushed in direct contact to the vessel without the protection of the sheath **[Figure24A]**. The CoreValve system instead, due to its particularly flexible structure and self-expanding stent, can “cautiously navigate” into the iliac arteries even without the protection of the introducer sheath, that being larger than the valve itself, may not advance into a severely calcified and stenotic iliac axe. This was the case of a 79-year old man with medical history of hypertension, dyslipidemia and smoking habit, with previous coronary artery bypass grafts (CABG) and aortic valve replacement with a Toronto 25mm biological prosthesis implanted 13 years before. He presented with heart failure due to severe aortic regurgitation, moderate AVS and well preserved LVEF (63%). Pre-TAVI screening showed important athero-calcific iliac-femoral vascular disease **[Figure 24B]**. Logistic Euro Score was 30%, and he was scheduled for a 26mm trans-femoral CoreValve implantation.

Procedure: TAVI was performed by surgical exploration of left CFA under general anaesthesia. The difficulty encountered was, as expected, to insert the 18F introducer through the left common iliac artery due to severe calcifications and diffuse stenoses. Aggressive balloon angioplasty was performed with 8x30mm and

10x40mm peripheral balloons [Fig. 24C] but no further advancement of the 18Fr was possible. Considering the low profile of the CoreValve, the device was carefully advanced through the iliac artery without introducer **[Figure 24D]**. A 26mm CoreValve was successfully implanted within the previous aortic valve prosthesis (valve in valve). The access site was repaired surgically without complications.

Figure 24 Valve insertion without introducer



A) Fluoroscopic view showing ruptured abdominal aorta (arrow); B) Angiography showing tortuous and severely calcified ilio-femoral axis; C) Fluroscopic view showing iliac artery balloon dilatation; D) Fluroscopic view showing insertion of CoreValve delivery system without introducer (arrow)

Treating patients with previous cardiac surgery is challenging, and in this particular case with a patent left internal thoracic bypass graft and a degenerated aortic bio-prosthesis and important PVD the access site requires cautious evaluation. The CoreValve device offers an excellent alternative allowing negotiation of severely diseased iliac arteries without the need for fully implanting the large introducer sheath. This may be a valuable alternative to the more complex subclavian access, in particular in patients with a patent mammary bypass graft that may contraindicate the use of such vascular route.

11.12 How to manage patient accidental finding of left atrial thrombus in TAVI suite? whether to quite the play or we have some option?

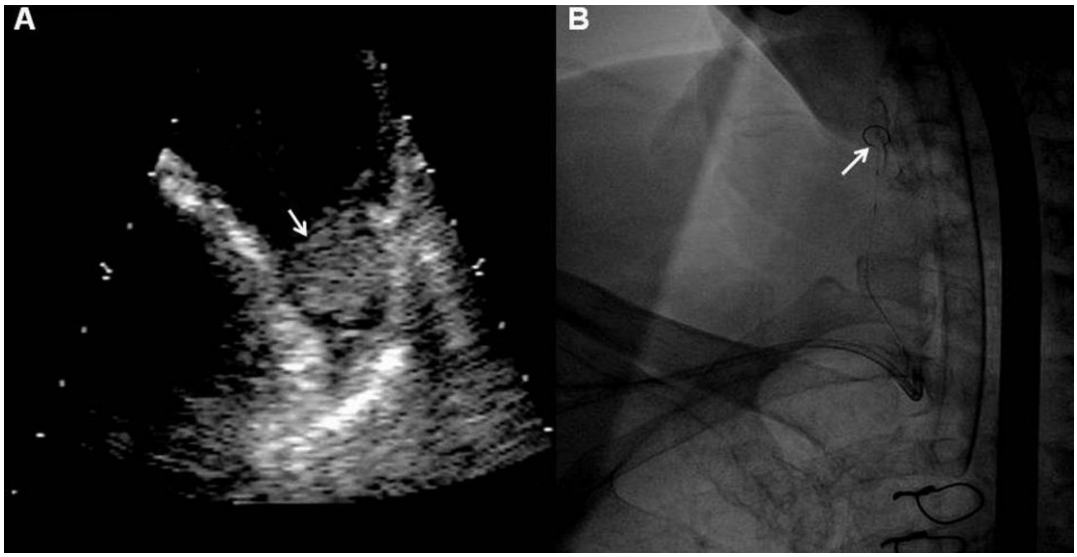
Cerebral stroke is the most dreadful complication of aortic valve interventions, either surgical or trans-catheter **[51,55,63-68]**. So far, dedicated devices to protect the cerebral circulation of TAVI patients are under development but still not available. Intra-cardiac thrombosis is a major contra-indication to TAVI due to the risk of thrombus embolization during rapid pacing and during energic post-arrhythmic beats **[46,52]**.

An afrail 84-year old woman with hypertension, diabetes, chronic hepatic disease, chronic atrial fibrillation in oral anticoagulation and a previous CABG surgery was admitted for a recurrent episode of heart failure. TTE showed severe AS (MG-45mmHg, AVA- 0.4cmq/mq) and pulmonary hypertension. Coronary angiography showed patent bypass grafts, peripheral angiography showed 50% stenosis in severely tortuous left common iliac artery, however right iliac and femoral axis was free of significant stenosis. Euroscore was 59% and a trans-femoral TAVI with 23mm Edward- Sapien valve was scheduled.

Procedure: the procedure was started with general anaesthesia.TEE examination revealed a large thrombus of 5x10mm in the left atrium **[Figure 25A]**. Due to the high risk of cerebral emobilization during TAVI, two carotid embolic protection devices (*EPI EZ. FilterWire*, *Boston Scientific Corp.*) were placed into the right and left common carotid arteries through the right and left brachial arteries respectively **[Figure 25B]**. After implantation of a 23mm Edward- Sapien XT prosthesis, the intra-

operative TEE showed properly positioned and well functioning aortic prosthesis and a persisting left atrial thrombosis. After closure of the femoral access site, the two carotid artery filters were retrieved without clear images of embolic debris. The patient was discharged in optimal clinical and hemodynamic conditions.

Figure 25 Accidental left atrial thrombus detection in TAVI suite



A) TEE showing thrombus in left atrium; B) Insertion of filter device in right carotid artery

Cerebral stroke is the most severe complication of TAVI, a persistent data that emerges from either randomized studies and large Registries **[51,55,63-68].** An Intra-cardiac thrombus is an absolute contra-indication for TAVI **[52]**. Usually during TAVI screening, transthoracic echocardiography is not sensitive for intracardiac thrombus detection. The reported case is an example of accidental left atrial thrombus detection and its management in the catheterization suite. Placing two embolic protection filters is technically challenging and time consuming. A dedicated device to protect the brain from embolic debris is still an unmet need of TAVI that requires urgent development from the Industry to further enhance safety of TAVI.

11.13 How to overcome coronary oclusion found during balloon valvuloplasty: Challenges from the coronary arteries take off. Is it safe to put protection guide wire in high risk coronary? is there possibilty for introduction of angioplasty catheter on wire?

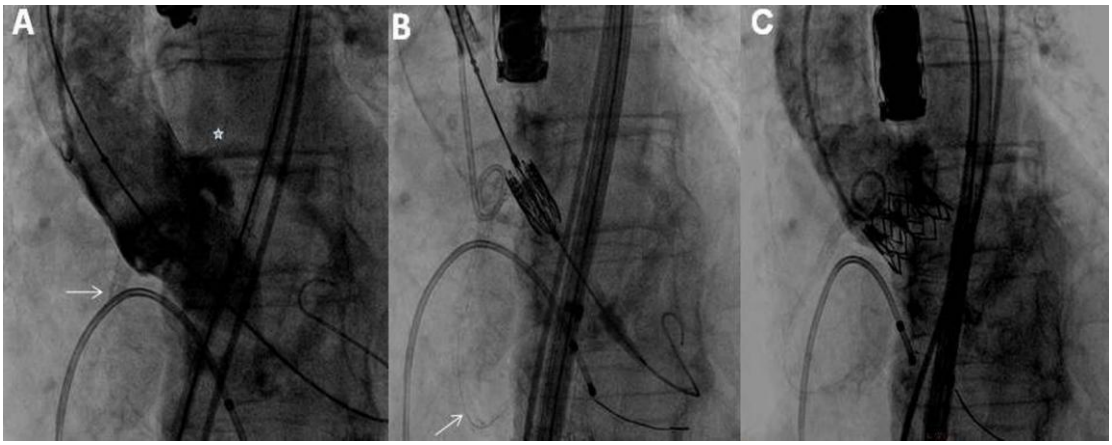
Coronary artery occlusion is a dreadful complication of TAVI and it has been reported in 0.4% to 1% of cases with either Edwards-Sapien and CoreValve systems **[46,51,55,63-68].** Accurate pre-TAVI diagnostic screening is, again, a crucial step to avoid this complication. In particular, CT scan measurements from the aortic annulus to the coronary take off should be performed in all cases before considering a patient for TAVI. A safe distance rom the lower part of left main coronary artery to the aortic annular ring is 14mm an at least 10mm is the minimum recommended space. However, coronary occlusion may ensue even when these safety distances are preserved. This may happen because of the presence of redundant aortic leaflet that, after being apposed between the prosthetic valve and the aortic wall in fully opened position may reach e coronary ostium causing its occlusion. Similarly, a tight sino-tubular junction diameter may not fully accommodate the crashed leaflets of the native valve that may reach with its more distal segment the origin of the coronaries. A practical trick before deciding whether to implant a valve in doubtful cases is performing an aortic angiogram while the balloon for aortic valvuloplasty is fully inflated in the aortic root. **Figure 26A** shows a case of a widely patent left coronary artery during balloon inflation and a complete occlusion of the right coronary artery. In cases with no other therapeutic options, and with the developing of growing experience, TAVI in such cases can be afforded with reasonable safety. It

is absolutely recommended hawever, to place a long (300cm) 0.0014" coronary guide-wire along the coronary at risk of occlusion. The guide-wire alone can be introduced through the diagnostic femoral access using an 8 or 9F sheath and a 6F guiding catheter that is then removed **[Figure 26B]**, leaving the wire alone as a rapid access to advance a coronary balloon in case of coronary occlusion to rapidly restore the flow in the artery. If further intervention is need a guiding catheter can be advanced through the wire to complete the job. Alternatively, both, the wire and a guiding catheter can be left in place using a different vascular access, preferable through the radial route.

Procedure: an 89-year old female with medical history of hypertension, dyslipidemia, and severe AVS had several episodes of syncope in last 3 month. Six months before, she had been admitted to another hospital with an acute coronary syndrome that required emergent angioplasty of the right coronary artery with implantation of a stent at the right coronary artery ostium. TTE during hospitalization showed severe AVS (PG-70mmHg, MG-44mmHg, AVA-0.6cm^2/m^2, AA-18mm) with moderate aortic and mitral regurgitation and a well preserved left ventricular function (LVEF=60%). TAVI screening with angio-CT showed good femoral artery diameters, but a rather low right coronary artery take-off (7-8mm). After implantation of a Prostar XL 10F closure device, balloon valvuloplasty with a 20x40mm balloon was performed, and the aortography during balloon inflation demonstrated a totally occluded right coronary artery **[Figure 26A]**. Due to the ostial lesion, the stent, and the risk of coronary occlusion, a 300cm coronary angioplasty guide-wire was placed along the right coronary artery **[Figure 26B]**. The aortic

prosthesic valve was properly positioned under fluoroscopic and TEE monitoring without apparent coronary complication and normal ECG. The guide wire was removed and angiography showed normal flow in the coronary arteries **[Figure 26C]**.

Figure 26 Bailout guidewire in coronary artery



A) aortography during balloon valvuloplasty showing occluded right coronary artery along with normal flow in left coronary artery; B) guide-wire in right coronary artery during device placement; C) aortography after device deployment showing normal coronary flow

Coronary artery occlusion is an infrequent but serious complication of TAVI **[46,51,55,63-68]**. Similar cases as the one described above are regularly performed in our center using protection wires when there is any suspicion of a possible acute coronary occlusion after valve deployment. This awareness prolongs the procedure by only a few minutes, but permits a rapid management of the massive ischemia caused by coronary occlusion that may rapidly evolve into irreversible haemodynamic impairment or arrhythmic storm in these old and fragile patients.

11.14 How to overcome renal faillure obstacle for TAVI? feasibilty and safety of TAVI without constrast medium. Is expert transesophageal echocardiography is alternative?

Renal function is one of the most important predictors of long-term outcome of patients with cardiovascular disease **[70]**. Transcatheter interventions and contrast media administration can both exert deleterious effects on renal function and the risk is in direct relationship with the baseline renal function. Accordingto recent guidelines, general preventive measures must be applied as in any catheter-based intervention **[71]**. However, some additional precautions may help to avoid or reduce the risk of renal impairment in patients with diffuse atherosclerosis of the aorta needing contrast media administration to implant the trans-catheter valves **[72-74]**. Intense saline hydration during the procedure can be better managed in patients treated under general anaesthesia, since mechanical ventilation can facilitate the management of peri-operative volumes overload that, in patients with severe AVS, impaired left ventricular function, and often secondary mitral insufficiency, may otherwise ensue pulmonary edema of difficult management without the assistance of well monitorized mechanical ventilation. Of utmost importance remains however, the limited administration of contrast media. In cases of severe renal dysfunction, performing a successful TAVI without the use of contrast media may be an ideal goal, but this requires a great experience of the heart team.

TAVI without contrast media in severe renal failure

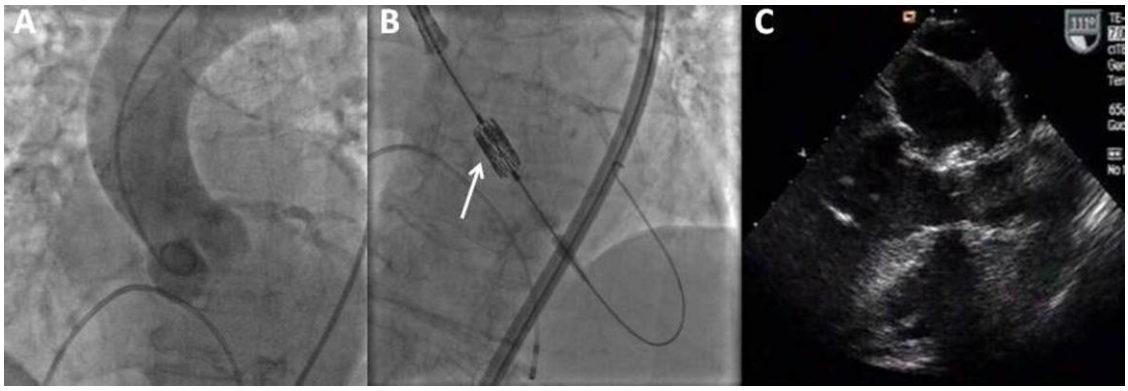
A 77 year-old female with a known history of severe AVS (AVA 0.6 cm^2/ m^2, PG 45mmHg), severe coronary artery disease with previous stent implantation and a recent anterior myocardial infarction, diabetes, severe CKD-class IV (without dialysis), and liver failure as a consequence of profound cardiogenic shock was transported by the Emergency Service to our Intensive Care Unit. During transportation the Emergency Medical Services reverted several episodes of sustained ventricular tachycardia with DC shocks. On admission blood pressure was 65/40mmHg with atrial fibrillation; LVEF was 14%, serum creatinine-4.7mg/dl, total plasma-bilirubin-44.3umol/L [N-(1-17)] and serum alkaline phosphatase-1900 U/L [N-(5-40)].

Procedure: an emergency aortic balloon-valvuloplasty was performed through the left CFA with a 25mm balloon. The trans-valvular gradient was reduced from 33 to 5mmHg, blood pressure raised immediately to 95/60mmHg. Subsequently, coronary angiography showed a patent left circumflex and right coronary artery and a thrombotic sub-occlusion of a previously implanted drug eluting stent in the mid left anterior descending artery with TIMI flow grade 1. Aortic-iliac angiography showed moderately tortuouse and calcified arteries with non significant stenosis. Coronary angioplasty was not performed as the amount of contrast media given was near to the 4mL/kg limit. Three days later although signs of renal and liver failure persisted, balloon angioplasty of left anterior descending artery was performed. During a 2-week hospital stay, left ventricular function improved up to 40% and serum creatinine dropped to 1.9 mg/dl. Aortic gradient however increased from 5mmHg

after valvuloplasty to 20mmHg suggesting both a partial valve recoil and left ventricular function recovery. Due to the high operative risk (Euro SCORE 68%) she was disqualified for conventional aortic valve surgery and the patient accepted a TAVI attempt.

The procedure was performed under general anesthesia through a surgically explored right femoral artery. A 12° cranial 10° left anterior oblique projection obtained by angiography at the time of the emergency valvuloplasty was selected to properly visualize the severely calcified aortic valve **[Figure 27A]**. A "stand by" pig-tail catheter was placed in the ascending aorta (in case of need for contrast injection). A 23mm Edwards SAPIEN XT transcatheter valve was successfuly implanted under fluoroscopy control only, using the calcifications of the aortic annulus as landmarks **[Figure 27B]** and TEE imaging **[Figure 27C]**. Intraoperative TEE confirmed the good position and functioning of the prosthesis valve. The patient had a favorable clinical evolution and was discharged one month later.

Figure 27 Severe renal failure



A) Projection selected for prosthesis implantation; B) Fluoroscopic guided device deployment; C) TEE guided device deployment

The present case demonstrates the feasibility of guiding a trans-femoral TAVI with fluoroscopy and TEE without administration of contrast media, and may represent a step further on the possibilities offered by TAVI in patients with severe renal insufficiency. Due to the extraordinary setting of this procedure, the case has been published elsewhere **[75]**.

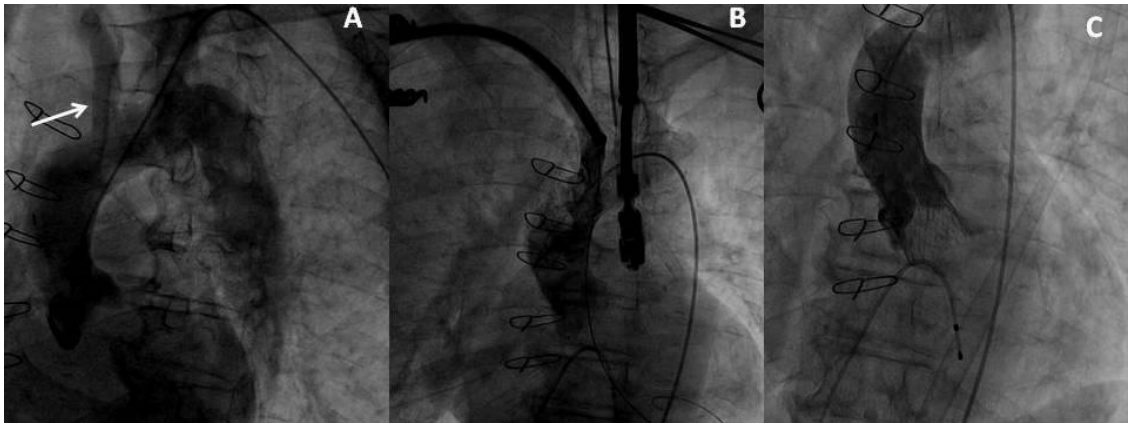
11.15 Safety and feasibilty of the Subclavian approach in the TAVI

This vascular access may prove useful in some selected cases and when operators have developed high levels of expertise with TAVI **[59,76]**.

We report as an example, the case of an 82-year old man with symptomatic AVS admitted for heart failure. He had two previous cardiac coronary bypass surgeries in 1979 and 1999 and severe PVD, with multiple iliac-femoral artery stenosis including a previous stenting of the left external iliac artery and right SFA angioplasty in 2005, a totally occluded right internal carotid artery, and a previous left carotid artery endoartheriectomy. The right subclavian artery was deemed to be the only possible vascular access due to its acceptable diameter (6.2mm at angio CT scan) despite moderate tortuosity **[Figure 28A]**, in a patient with a logistic EuroScore 59%. A trans-succlavian implantation of 29mm CoreValve prosthesis was planned.

Procedure: the procedure was performed in general anesthesia with surgical exploration of the right suclavian artery. An 18F introducer sheath was passed over an extra-stiff 0.035" wire **[Figure 28B]**, and the 29mm CoreValve delivery system was successfully implanted under fluoroscopic control and rapid ventricular pacing **[Figure 28C]**. Intra-operative post implant TEE showed a properly placed and well functioning valve. The subclavian artery access site was closed surgically without complication and the patient was discharged uneventfully 7 days later.

Figure 28 Subclavian approach



A) PreTAVI angiography of right subclavian artery; B) Fluoroscopic view showing introduction of sheath through right SCA; C) Insertion of device through right SCA

The subclavian artery approach may be an option in patients with no other alternatives. Severe complications have been reported with the subclavian access as well **[76]**, and therefore it should not be proposed as a routine alterative to the simpler femoral route; furthermore, no dedicated material is available to be used though the subclavian access and its use is recommended only after an extensive TAVI experience.

11.16 Step by step approach for a case of severe multi-level vascular disease waiting for TAVI

A 79-year old lady with medical history of hypertension, dyslipidemia, CKD class III with a known severe AVS was referred to our Laboratory for pre-operative catheterization. She was symptomatic for angina during daily activities, had a previous history of TIA, and was recently admitted for syncope. TTE confirmed the severe AVS (MG-55mmHg with preserved LVEF=65%). Angiograms revealed a severe left main stenosis at the ostium **[Figure 29A]** and severe bilateral internal carotid artery stenosis **[Figure 29C]**.

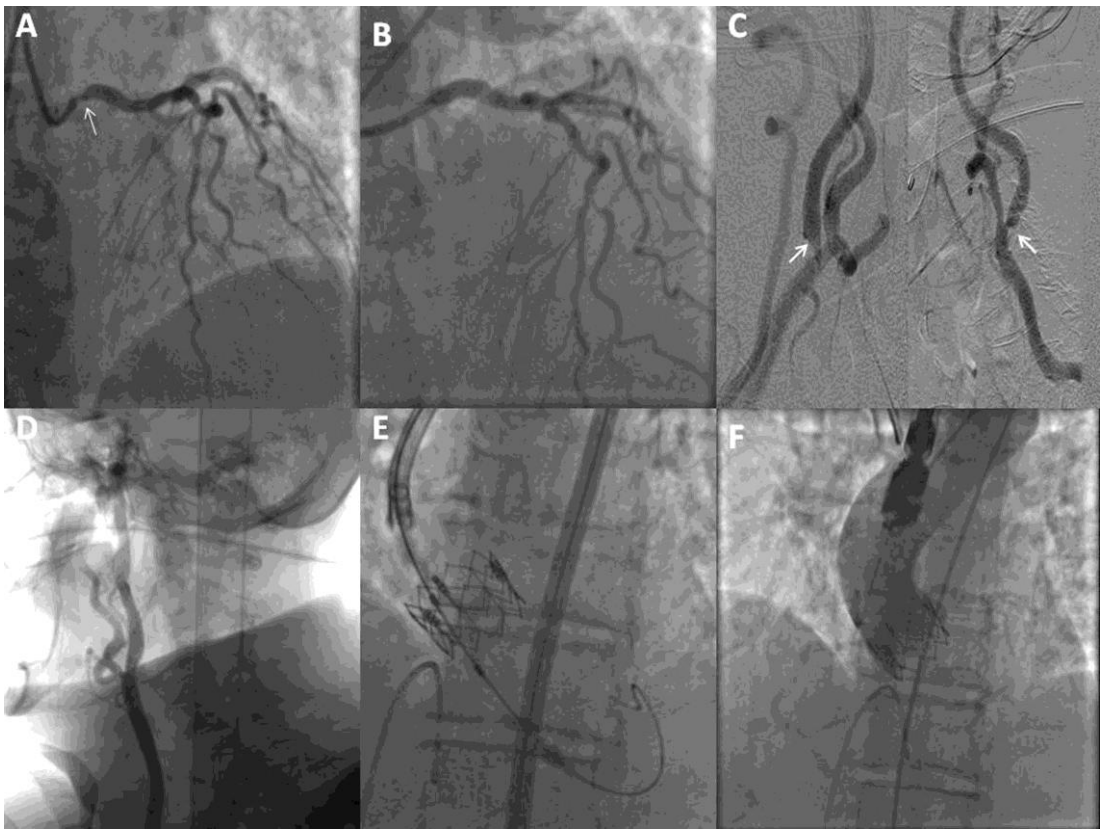
After discussion within the Heart Team, the decision was made of treating the left main stenosis with a relatively simple angioplasty to avoid combined CABG and SAVR. Logistic EuroScore was 45%.

Procedure: the coronary procedure was performed by the radial route with optimal result **[Figure 29B]**. One week after coronary angioplasty, the right internal carotid artery was treated with a 7x40mm self expandable meshed stent implanted after positioning an EPI EZ filterwire embolic protection device (*Boston Scientific Corp., Natick, Massachusetts*) **[Figure 29D]**.

After these multi-level endovascular treatments, and considering the good quality of the aorto-iliac and femoral vessels, a staged TAVI was considered as a rapid and less invasive alternative to SVAR. Indeed, some days later a 26mm Edward- Sapien prosthesis was implanted under rapid pacing with a good immediate result **[Figure**

29E-F] confirmed by the intra-operative TEE. Post-operative course was uneventful and the patient was discharged one week later.

Figure 29 complex TAVI candidate



A) Severe left main stenosis (arrow); B) Angiography after left main stenting; C) Right and left internal carotid artery stenosis (arrows); D) Right internal carotid artery after stenting; E) Aortic prosthesis at aortic root level; F) Angiography after deployment of prosthesis

Treatment of the elderly patient with multi-level vascular disease is complex and needs thorough evaluation by a multi-disciplinary team. This case shows the feasibility, safety, and reduced invasiveness of staged endovascular procedures that may be particularly appropriate in old and fragile patients with multi-level vascular disease and severe symptomatic AVS.

11.17 Safety and feasibilty of TAVI in the patient of AVS with associated severe mitral regurgitation, coronary artery disease, and heart failure

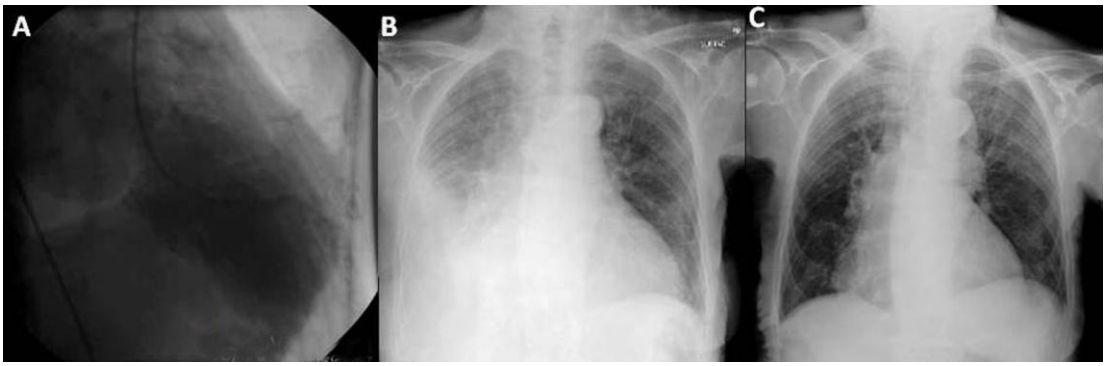
Severe mitral regurgitation associated to AVS has been considered a contra-indication for TAVI **[52,65]**. In particular, patients with impaired LVEF and severe mitral disease may not improve their long-term prognosis even after aortic valve replacement. However, mitral regurgitation itself does not pose technical difficulties to the TAVI, and releasing the left ventricle from the outflow obstruction caused by the AVS may result in a significant reduction of the mitral regurgitant volume with subsequent clinical improvement **[77]**.

This is the case of an 83-year old lady with a previous large anterior myocardial infarction and severe secondary mitral regurgitation that later developed severe AVS. She was admitted with refractory heart failure, in NYHA class IV despite continuous i.v. infusion of furosemide, and inotropes, with no clinical improvement after two months of hospitalization in the Geriatric Department. She was transferred to our Center for coronary angiogram and eventually balloon aortic valvuloplasty. Left ventriculography showed severe mitral valve regurgitation **[Figure 30A]**. LVEF was 23%, the mitral regurgitant volume was 60ml and the pulmonary artery systolic pressure was 56mmHg.

Procedure: during a single catheterization suite the patient underwent coronary artery angioplasty of a co-dominant left circumflex; the left anterior descendent artery was chronically occluded. After angioplasty, aortic valve valvuloplasty was

performed with a 23mm balloon under rapid pacing. PG was reduced from 38mmHg to 10mmHg and the subsequent clinical evolution was impressive, with rapid weaning from inotropes and i.v. diuretics and resolution of the chronic bilateral pleural effusions in about two weeks **[Figure 30B-30C]**. She had rapid clinical improvement and returned to walk after several months of bed resting, and was discharged. After two months she had returned to her previous activities. The mitral regurgitant volume was reduced to 48ml, and the EF increased to 36% after aortic valvuloplasty. The case was considered for TAVI and the procedure was performed successfully with the implantation of 23mm Edwards-Sapien prosthesis through the femoral route by using a totally percutaneous approach and on local anesthesia. At 3 months follow up the patient was in functional class I, EF was 40%, pulmonary artery pressure was 28mmHg and mitral regurgitation was further reduced to 38ml in the left atrium. After 2 years of follow-up the patient is still doing well.

Figure 30 TAVI in severe mitral regurgitation



30A) Ventriculography showing severe regurgitation in left atrium; 30B) chest X-ray showing bilateral pleural effusion before balloon valvuloplasty; 30C)chest X-ray showing resolution of pleural effusion 2 weeks after balloon valvuloplasty

This is a case of end-stage heart failure due to major cardiac contra-indications to TAVI and extremely fragile clinical conditions: severe mitral regurgitation and severe left ventricular impairment, associated to severe coronary artery disease. In such a case, percutaneous myocardial revascularization and aortic balloon valvuloplasty may serve as an effective atempt to improve the general clinical conditions and offer a bridge to a definitive treatment.

12. Discussion

TAVI is now a viable option in the treatment of inoperable/high-risk severe symptomatic AS. It has been shown to reduce mortality compared with a conservative strategy among patients deemed inoperable **[64-68]** and resulted non inferior to conventional AVR in high surgical risk patients **[65]**.

Present series of patients, we have analyzed the global clinical and echocardiographic outcome of TAVI considering both immediate and long-term outcome. This monocentric registry takes into account a wide population including patients with native AS, combined AS plus regurgitation and bioprosthesis dysfunction, and treated with both commercially available devices, using all the approaches currently adopted: TF, TA and subclavian.

The main finding of our analysis is that TAVI is a safe and effective procedure leading to early clinical and hemodynamic improvement and persisting benefits over time. Periprocedural mortality and procedural complications are extremely low and long term outcome seems related more often to extracardiac comorbidities of this kind of patients.

In the present series almost all patients are elderly with mean age of 81.9 + 6.3 year along with several co-morbid conditions like hypertension, diabetes, coronary artery disease and more. In spite all these procedural success was 93.1 %. Prosthesis was hemodynamicaly well functioning even on long term follow up. However, complexity of the patient at presentation affects the short term and long term outcome. As per our opinion special care should be given to achieve success. Balloon valvuloplasty,

bridge to TAVI, is reasonable option for critically ill patients which is followed by step TAVI. In special category of patients which are presented with multiple vascular pathologies, as we have mentioned in complication section, may be treated by sequential manner.

As per prosthesis concerned, Edward-Sapien is most commonly used at our centre which has high success rate. Core-Valve was used in specific aortic valve pathology like severe aortic insufficiency, dysfunctioning aortic valve prosthesis, large annulus and difficult vascular access for Edward delivery system. Conduction difficulty after aortic valve replacement is well known from era of surgical replacement due to anatomically close relation. Recetly published studies showed increase incidence of conduction problem, mostly with CoreValve prosthesis **[78-81]**. In our small series of patients conduction problem was found in 10(13.89%). Among them 5 patients comes to normal rhythm with 24 hours, however, 5 needed permanent pacemaker implantation. Incidence of permanent pacemaker implantation was high with CoreValve (23.1% of all CoreValve), however, in Edward-sapine was only 3.4%.

Amount of constrast, ventilation time and procedure time varies with every patient. However as per our experience, ventilation time and procedure time was longer with trans-apical TAVI than transfemoral TAVI. On table extubation and early immobilisation are advantages of transfemoral approach.

Complication immediately after procedure was not uncommon found in 34 (47.2%) of patients. Detailed of these complications and their management was mentioned in special title below. As in most TAVI registries vascular complications were most common; among them 14 (41.2%) which was treated with our experience in

peripheral artery interventions **[63-67]**. Moderate to severe aortic prosthesic regurgitation attributed to 7 (20.6%) which was managed with post-dilatation of prosthesis with valvuloplasty balloon of appropriate size or implantation of another prosthesis. Interesting finding in this series was presence of thrombus like echographic shadow around the implanted prosthesis 4(11.8%) which was treated with control echocardiography and heparin infusion. We think that may be disrupted native aortic valve leaflet gives these type of images. However, we are afraid that whether this structure may acts as nidus for the future thrombus formation which may gives rise to cerebral stroke which we found in 2(50%) of these patients.

Thirty days clinical and hemodynamic function of prosthesis has promising results. Prosthesis was functioning properly with significant increase in aortic valve area ($P<0.001$), decrease in peak gradient ($P<0.0001$), mean gradient ($P<0.0001$) along with trivial-mild degree of periprosthesis regurgitation. All cause mortality was relatively low 3(4.2%) considering high risk profile of patients. Mortality was found to be higher in patients undergoing trans-apical approach. Complexity of intervention and high operative risk was reasonable explanation. Incidence of cerebral stroke events was comparably low 3(4.2) as in other studies [dggd]. Vascular complications like puncture site hematoma was even common at 30 days follow up (20.8%).

Long term follow up was performed up to maximum of 2.9 year in all 69 patients remained alive at 30 days. All cause mortality was relatively low 11(15.9%) considering high co-morbidities. Mortality was with the non-cardiac reasons in 7(63.64%) of all died, only 4(36.36%) died with cardiac causes. Cardiac mortality was

earlier with mean duration of 190 ± 304 days as compare to non-cardiac death at 271 ± 278 days. Single patient on heart transplant list with Heart Mate II was treated for aortic valve insufficiency with Core-Valve was transplanted after 6 months.

In the 57 patient remained alive at long term follow up most of them are without symptom for aortic valve stenosis. Clinical status assessed with NYHA class which was improved in most of patients as compared to baseline. Only 33.4% of patients were in class III/Iv functional NYHA class as compare to 59.8% at baseline. A frality scale was improved and most of them are autonomous with their daily activities.

Incidence of rehospitalisation was 18 (31.6%) in this series of patients mostly for non cardiac reason 14 (77.8%) than cardiac 4 (22.2%). Incidence of composite outcome of mortality and rehospitalisation was higher up to 32(44.4%). Bleeding complications like was found in 12 (21%). Incidence of cerebral stroke was maintained as short term follow up 3 (5.3%) even in long term.

In almost all patient prosthesis was functioning properly with maintaining significant increase in aortic valve area, decreasing peak gradient, and mean gradient as found in short term follow up. Re-intervention for aortic valve prosthesis was not needed in single patient. We found marked decrease in grade of aortic prosthesis regurgitation as compare to 30 days follow up. Moreover, left ventricular systolic function was improved on long term follow up. Only 11(19.3%) of patients has poor left ventricular function (<50%) as compare to 29(40%) before TAVI. Most of patients with poor left ventricular function were died. On multivariate logistic analysis we

found that poor left ventricular function (EF<50%) is strong predictor of short term and long term mortality (P<0.01).

13. special cases, complications and their management

13.1 Challenges from the femoral vascular access

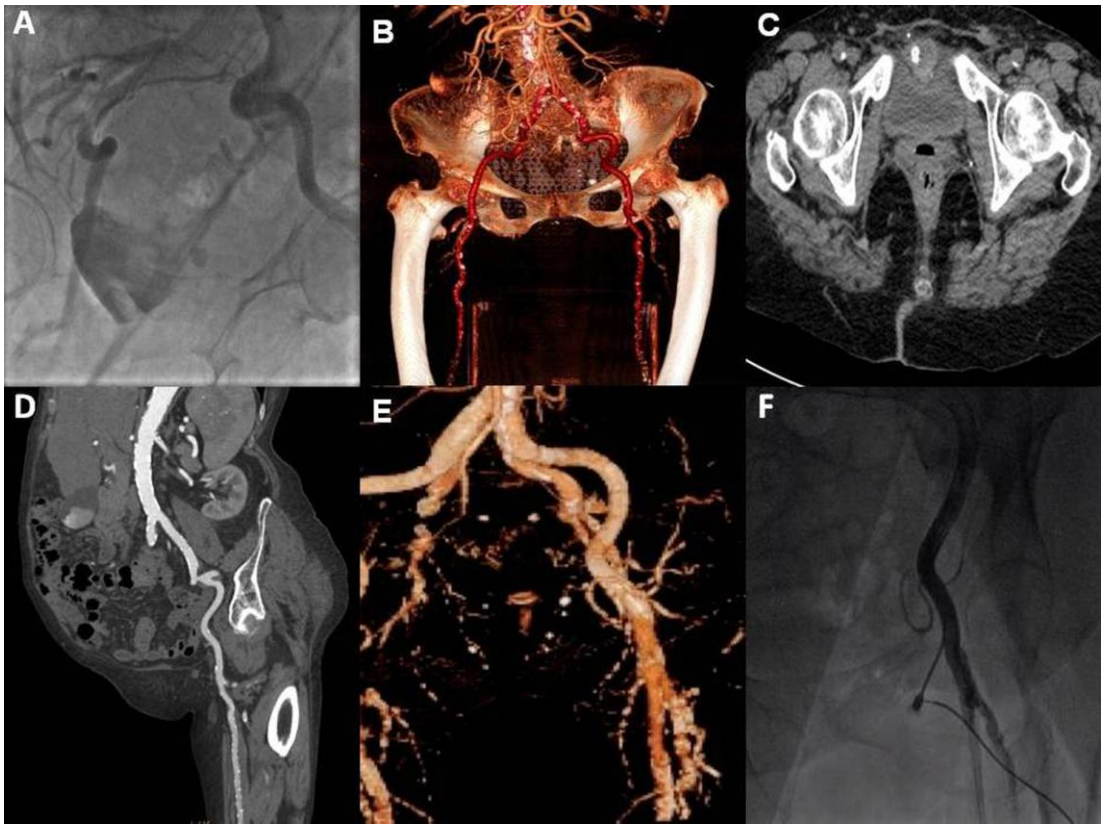
TAVI can be achieved by several accesses, such as the trans-femoral, trans-apical, trans-aortic, sub-clavian and trans-axillary **[46,52]**. Among these, the trans-femoral is the most preferable route as it is the less invasive. We believe that during the initial phase of a "TAVI learning curve" the femoral access should be managed surgically so that interventional cardiologists could concerte in learning tips and tricks of the valve implantation exclusively, without adding complexity to the procedure related to the percutaneous management of the vascular access with the Prostar XL closure device. It is obvious that such recommendation does not apply to operators that are already proficient with the use of this closing device.

Before selectingthe femoral approach, the operator should well analyse diameter, tortuosity, and calcification of the common femoral artery (CFA), external, and common iliac arteries **[46,52]**. Furthermore, the exact location of the calcium with respect to the anterior wall of the CFA is crucial during implantation of a closure device. The operator must know the vascular situation of the inferior limbs, in particular patency of the superficial femoral artery (SFA), or collateral circulation, and the quality of the infra-renal aortic wall.

To this aim, both, computerized tomography (CT) scan and contrast angiography are essential pre-TAVI examinations. CT scan offers accurate information about the vessels anatomy and disposition, the severity and localisation

of calcifications, it offers reliable measurements in non-calcified tracts, but tends to under-estimate vessel diameter in calcified segments **[46,52]** Contrast angiography as a screening for potential TAVI candidates should be ideally performed by the radial access to avoid complications at the femoral puncture site during the diagnostic examination. Angiography adds an important perception to the estimations of the vessels diameter, and being a dynamic imaging, shows the degree of rigidity or flexibility of the aortic-iliac-femoral axe by analysing its systolic-diastolic excursions. The more flexible the vascular axe, the more likely it will accommodate the large introducer sheath despite relatively small diameters, or marked tortuosity. Apparently challenging tortuosity as shown in **[Figure 31A-B]**, can be easily afforded when the vessel is elastic and not severely calcified. Also small arteries (less than 5.5mm) can safely accommodate the 18 or 19F sheath when are not calcified **[Figure 31C-D]**. However, much caution is required in these cases with delicate advancement of the dilators and introducer, avoiding energic pushing that may cause arterial rupture. Angiography provides also valuable information about the run off of the contrast media along the SFA and the dynamic of collateral circulations when important vessels are occluded. Knowledge of the SFA angiographic anatomy is essential for the positioning of a contralateral safety guide-wire, as discussed later in this article. Last, accurate selection of the exact point for the puncture of the CFA (well above the bifurcation of the SFA and the profunda) is clue, avoiding sites with calcium in the anterior arterial wall where the introducer and then the Prostar needles will be implanted **[Figure 31E-F]**.

Figure 31 vessel anatomy



31A) Angiography showing bilateral tortuous ilio-femoral arteries; 31B) CT Scan showing bilateral tortuous ilio-femoral arteries. Despite marked tortuosity a 21 F introducer sheath was advanced into the right iliac axe without dificulties; 31C) CT Scan showing relatively small iliac arteries without calcification (arrows). The maximum diameter measured in the comon iliac was 5.5mm. However, a 21 F introducer sheath was advanced without complications; 31D) CT Scan sagittal section showing relatively small iliac arteries without calcification (arrow); 31E) CT Scan reconstruction showed severe calcification on left CFA with a small area withou calcification (arrow); 31F) The fluoroscopic view shows the accurate position of the puncture site taking account of the CT Scan in the same patient shown in figure 1E.

The most challenging situations for the femoral vascular access are dictated by the presence of severely calcified stenosis in the iliac-femoral axe. These may be a

contra-indication to the femoral route, but with the continuos improvement in delivery systems and skills in peripheral artery interventions, the success without serious complications can be achieved in most cases as shown in the following examples.

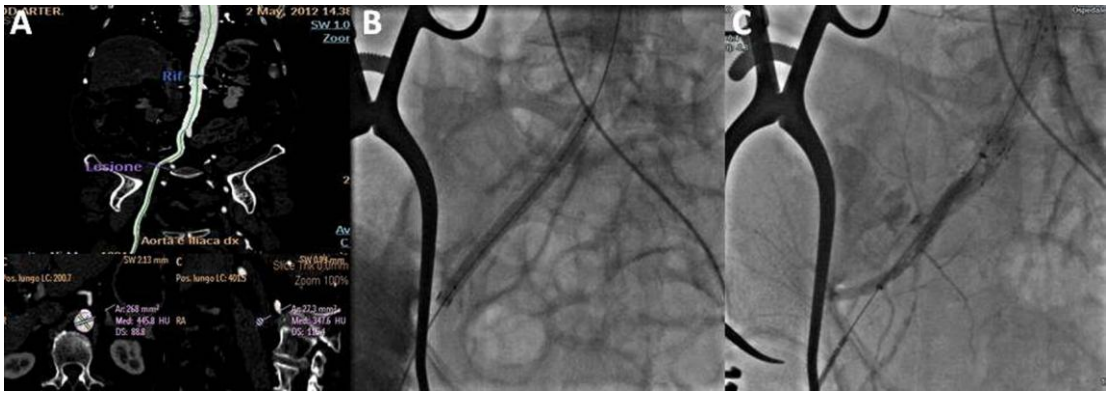
13.2 "Tunnelling" of femoral arteries

An 85-year old man with severe aortic stenosis was repeatedly admitted in hospital with syncope and heart failure. He had previous cardiac bypass surgery and a severe impairment of the LV function and chronic atrial fibrillation, hypertension, diabetes mellitus, moderate chronic kidney disease (CKD) (calculated clearance 35ml/h/m2) and severe PVD. The logistic Euroscore was 55%. Pre-TAVI transthoracic echocardiography (TTE) showed aortic annulus 23mm, EF=27%, pulmonary artery pressure (PAP)-65mmHg and CT scan and angiography showed adequate iliac-femoral diameters with multiple calcified plaques. A 26mm Edward prosthesis was scheduled by trans-femoral route.

Procedure: Anaorto femoral angiography showed apparently suitable vasculature for femoral access (left and right common iliac artery diameter was 9.5mm and 10mm respectively; CFA diameter was 6mm and 6.5mm on left and right side respectively) **[Figure 32A]**.The procedure was performed under general anaesthesia and with surgical exploration of right CFA. Due to the extensive calcifications, and the extreme vascular rigidity, it was not possible to introduce the 14F dilator in the era of retroflex 22F sheath. The right femoral artery was dilated using 8mm and 10mm balloons over the extra-stiff wire **[Figure 32B]** but without success in introducing the

dilator. After several dilations, there was a clear evidence of bleeding due to vascular rupture, therefore, despite the fact that implantation of stents before passing the large 22F sheath may cause stent dislodgement and embolization in aorta, two self-expandable covered stents of 10mm each were rapidly implanted through the same extra-stiff wire to control bleeding **[Figure 32C]**. Additional high-pressure balloon dilatations were needed to allow the 22F sheath pass into the common iliac artery. A 26mm Edward-Sapien prosthesis was implanted after balloon valvuloplasty without difficulties. The vascular access site was repaired surgically with the need of a short vascular Teflon prosthesis to reconstruct the anterior wall of the CFA. Post-operative course was uneventful.

Figure 32 Femoral artery tunnelling



A) AngioCT showing measurement of right iliac-femoral arteries; B) Fluroscopic view showing balloon dilatation of ilic-femoral axis; C)Fluroscopic view showing stented iliac-femoral axis (segment between asterisks) and contrast media that exits the vessel lumen due to a perforation (arrow)

Although the diameter of ilio-femoral axis by angiography and CTscan were adequate, the diffuse atherosclerotic disease, and the use of a “first generation” introducer sheath created a serious obstacle to the TAVI procedure. Tunnelling the vascular axe with aggressive balloon angioplasty and implanting self-expanding covered stents allowed both, to solve the bleeding complication, and to implant the prosthesic valve successfully. However, implanting stents before placing the introducing sheath is not recommended, and should be reserved for emergency to avoid life threatening bleeding. This technique is an option when a surgical cut down of the artery is used as vascular access, but as described later in this article, a different technique is recommended if a totally percutaneous approach is selected.

13.3 Sessile thrombus in aortic root after transapical aortic valve implantation

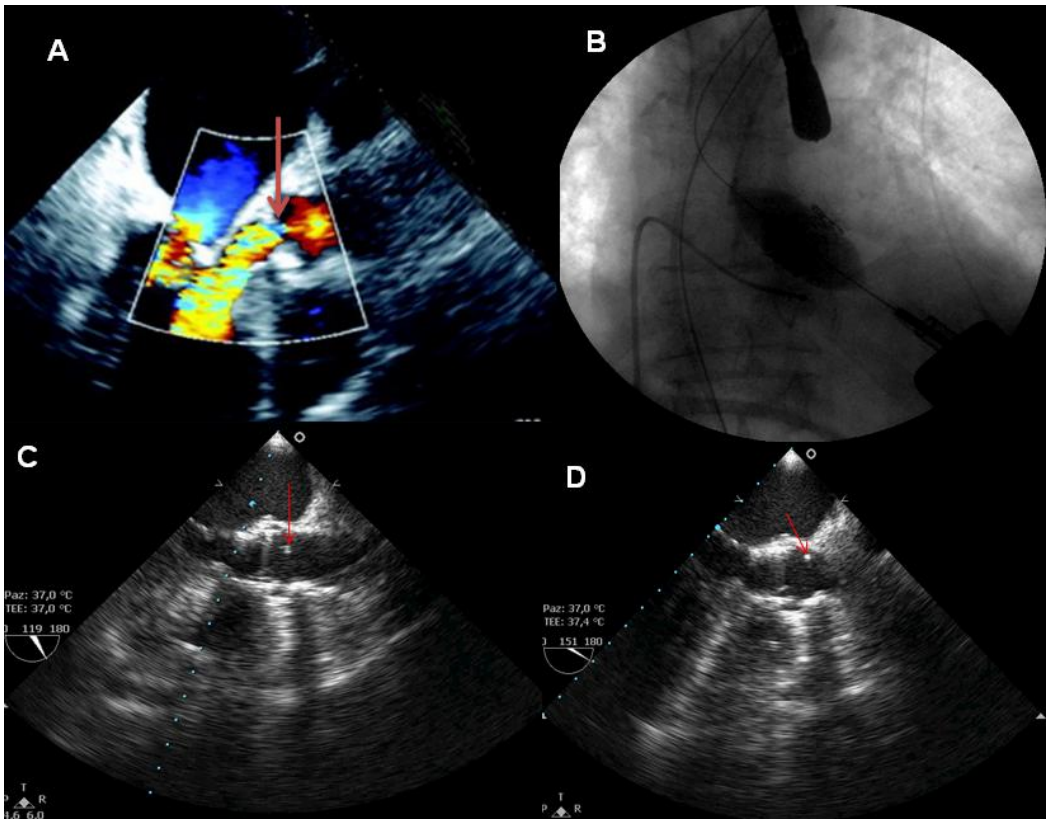
The occurrence of cerebrovascular events has a major concern from the very beginning of the transcatheter aortic valve implantation (TAVI) era. Transapical TAVI was first reported as an alternative to the transfemoral in 2006 **[82]**. Although more invasive, it has the potential to avoid the use of large catheters through the atherosclerotic iliofemoral system, aortic arch and ascending aorta, thus contributing to reduce cerebrovascular events **[83]**.

A 72 year old male with severe aortic stenosis (peak gradient- 80mmHg; mean gradient- 55mmHg; aortic valve area-0.50 cm^2/m^2, arotic annulus-26mm), hypertension, insulin-dependent diabetes, and chronic renal failure was admitted with syncope and cardiogenic shock. He had previously undergone bilateral carotid endartectomy and CABG. PreTAVI screening confirmed normally functioning bypass-

grafts, non significant carotid arteries. Transapical TAVI with 29mm Edward Sapien prosthesis was therefore proposed to the patient by the heart team.

Transapical TAVI was performed at our centre under general anesthesia through a left lateral minithoracotomy **[84]**. The activated coagulation time was maintained ≥ 250 sec with heparin. Transesophageal echocardiography immediately after balloon valvuloplasty showed moderate aortic valve insufficiency **[Figure 33A]**. A 29mm Edward Sapien XT (Edwards Lifesciences, Irvine, CA, USA) was then successfully deployed by the Ascendra delivery system **[Figure 33B]**. Post-deployment aortography showed trivial prosthetic regurgitation whereas TEE showed a properly placed and functioning device (MG-8mmHg; AVA-2.4mm2) with only mild periprosthetic leak, but a sessile thrombus like structure (2X4 mm size) was attached along the non coronary leaflet **[Figure 33C]**.

Figure 33 sessile thrombus around implanted prosthesis



A) TEE showing aortic regurgitation after balloon valvuloplasty; B) Fluoroscopy showing deployment of 29mm Edward Sapien XT prosthesis; C) TEE showing sessile thrombotic mass along non coronary leaflet; D) TEE showing persistent thrombus around prosthesis

Continuous TEE monitoring performed until closure of minithoracotomy incision. Thrombus was still present **[Figure 4D]**. Neurological examination at 1,6,12,24 and 48 hours after procedure showed normal sensory and motor function. Cranial CT Scan before discharge showed small multiple ischemic focuses in left cerebral hemisphere without neurological abnormality. Follow up visit after 2 month showed normally functioning valve prosthesis without any neurological problem.

The occurrence of cerebral embolism and stroke are most worrisome complications which associated with TAVI. The 30-day stroke rate was approximately 3.5% (1.2%-6.7%) in multicentre registries and the PARTNER trial. Stroke seems to be affected by TAVI approach, TF vs TA; Canadian study (3% vs 1.7%); France registry (4.2 % vs 2.8%); SOURCE registry (2.4% vs 7.19) **[51,63-68]**.

We here reported a case of tranapical TAVI, as per our knowledge first reported which presented with sessile, floating thrombus in aortic root immediately after prosthesis implant which may act as “nidus” for further development of thromboembolic phenomena in postoperative TAVI. The mechanism of stroke during TAVI needs to study before wide use of cerebral embolic protection device.

14. Conclusion

TAVI represents a less invasive strategy than SVAR. It offers an extraordinary option for symptomatic patients with severe AVS who are either, no candidates to SAVR, or present an unacceptable surgical risk. The rapid development of the technique is making of TAVI a “routine” practice in high-volume centres. By now, all efforts should be made to improve procedural success by reducing peri-procedural complications. Along with other important factors, patient’s selection is clue. Procedure planning, using proper approach, interventional materials, and application of coronary, structural and peripheral interventional skills, in the context of an accurate clinical management will certainly help to obtain optimal results.

Transapical and TF approaches are the most frequent established techniques to perform a TAVI, with others new approaches such as the transubclavian and the transaortic ones leading to further expansion of current eligibility criteria. Nonetheless, a fundamental key for the success of a TAVI program remains the effective and respectful cooperation between cardiologists and surgeons, and the observation of the available evidence-based indications. TAVI procedures beyond this context, imposes thoughtful discussion within the Heart Team and a great deal of experience.

Recently the indications to TAVI are extending also to particular settings of patients. To this regard, one very promising indication is the treatment of severe aortic valve regurgitation in Heart Mate II patient. In these patients valve prosthesis may be act

as bridge to heart transplatation. Second important application is treatment of bioprosthesis dysfunction by the so called valvein-valve technique, allowing to avoid a second sternotomy and giving overwhelming results.

The main concerns about TAVI still regard the risk of embolic complications, conduction defect, periprosthetic leakage and vascular complications. There is no doubt that with technology development and learning experience these complications rates are much lower nowadays and will likely continue to drop.

Cost effectiveness of this procedure is currently a topic of criticism. Moreover, recently transarterial AVR has arguably become the standard of care for patients for whom surgical risk is prohibitive and an increasingly reasonable alternative for selected operable patients in whom the high-risk of either mortality or of morbidity is “high.” Broader application will require further refinement as well as more rigorous and longer follow-up. It is possible that, with time, TAVR will become a preferred option for a much broader group of patients. A major concern may well be the following: When are patients too ill, frail, or old to gain significant benefit in terms of duration or quality of life?

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16. Acknowledgement

This project work would not have been possible without the guidance and the help of several individuals who in one way or another contributed and extended their valuable assistance in the preparation and completion of this study. The contributions of many different people, in their different ways, have made this possible. I would like to Thank **God** for the wisdom and perseverance that he has been bestowed upon me during this research project, and indeed, throughout my life: "I can do nothing through him who give me strength. I extend my appreciation especially to the following.

First and foremost, my utmost gratitude to **Prof. Giuseppe Faggian**, whose sincerity and encouragement I will never forget. He has been my inspiration as I hurdle all his support, guidance, advice throughout the research project, are greatly appreciated.

Prof. Flavio Ribichini, for his unselfish and unfailing support as my thesis co-relator; He is one of most skilled interventonal cardiologist I ever seen.

Dr Anrea Rossi, for his patience and steadfast encouragement to guide in scientific activities, I will forget his sincerity and valuable guidance. I learned lots from him.

The useful suggestion of **Prof. Francesco Santini and Dr. Francesco Onorati**, helped me in taking valuable decisions.

I would really like to thanks my colleagues and friends **Gabriele Pessarini** and **Maddalena Tessari** for their support in all issues.

The Administrators of the Faculty of the University of Verona, for their untiring effort and painstakingly e-mailed the information I needed.

I am really thankful, to my colleagues and administration staff of cardio-vascular sciences department, for making this research project possible. Their supports, guidance, advice throughout the research project, make things easier.

Last but not the least, **my family** without their support and patients, I am sure, even I can't stand in this competitive World. In particular, the patience and understanding shown by my family during the honors' year is greatly appreciated.