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TITOLO TESI

TRANSCATHETER AORTIC VALVE IMPLANTATION

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INDEX

ABBREVIATION LIST

AKI	Acute Kidney Injury
AS	Aortic Stenosis
AV	Atrio-Ventricular
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
CKD	Chronic Kidney Disease
CT	Computed Tomography
CVVH	Continuous Veno-Venous Hemofiltration
EDV	End Diastolic Volume
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
EKG	Elektrocardiogram
ESV	End Systolic Volume
HR	Hazards Ratio
LV	Left Ventricular
NYHA	New York Heart Association
OR	Odds Ratio
PPL	Para-Prosthetic Leaks
PPM	Permanent Pacemaker
SD	Standard Deviation
SE	Self-Expandable
TA	Transapical
TAVI	Transcatheter Aortic Valve Implantation
TF	Transfemoral
VARC	Vascular Academic Research Consortium

SUMMARY

Although surgery with prosthetic valve replacement is the gold standard for severe aortic stenosis (AS) treatment, there are still about one third of patients that are not operated because of inoperability criteria or high surgical risk. 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. This technique, pioneered by Alain Cribier and co-workers in 2002, has been used in more than 20,000 patients throughout the world.

Currently, two transcatheter devices are approved for clinical use and are commercially available in Europe, i.e. the balloon expandable device (Edwards Sapien XT valve, Edwards LifeSciences) and the self-expandable (SE) device (CoreValve Revalving System; Medtronic). The acute success rate of this procedure is now increasing to about 95% in expert hands. In addition, several studies have shown that these prosthetic valves maintain good hemodynamic characteristics over both the short- and medium-term. However, we must await long-term results on potential complications and on the durability of transcatheter valves before this treatment approach can be applied to younger patients or to patients at low surgical risk.

In this study we report our perspective single centre experience about TAVI in a high volume centre, the Department of Cardiac, Thoracic and Vascular Sciences of the University of Padua, using both balloon expandable and SE devices, through all the currently available vascular approaches. We report on early and follow up results, focusing on both clinical outcome and haemodynamic performance of the devices. We also investigated some peculiar fields of application, such as the treatment of bioprosthesis dysfunction, and speculated on the main potential procedural complications, such as the conduction disorders and the periprosthesis leakage.

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.

RIASSUNTO

Sebbene la chirurgia tradizionale sia la tecnica di scelta per il trattamento della stenosi aortica serrata, nella pratica clinica tuttavia circa un terzo dei pazienti non viene sottoposto a chirurgia sostitutiva per inoperabilità o eccessivo rischio chirurgico. Con l'aumentare dell'età media della popolazione, l'entità di questo problema è destinato ad aumentare, per cui vi è una sempre più ampia popolazione di pazienti che potrebbe beneficiare di tecniche operatorie meno invasive.

L'impianto di valvola aortica per via transcatetere (TAVI) consente di applicare una protesi aortica evitando la sternotomia, l'arresto cardioplegico e senza la necessità di circolazione extracorporea. Questa tecnica è stato introdotta nel 2002 da Alain Cribier e dai suoi collaboratori e oggigiorno nel mondo sono stati eseguiti ormai oltre 20.000 interventi di TAVI.

Attualmente esistono due dispositivi transcatetere approvati per uso clinico e disponibili in commercio in Europa, la valvola espandibile su palloncino (Edwards Sapien XT, Edwards Lifesciences) e la valvola auto-espandibile (CoreValve Revalving System, Medtronic). Il tasso di successo procedurale di questa procedura è attualmente in aumento e supera il 95% in mani esperte. Inoltre, diversi studi stanno dimostrando che queste protesi valvolari hanno buone caratteristiche emodinamiche sia a breve che a medio termine. Tuttavia, è necessario attendere risultati più a lungo termine sulle potenziali complicanze e sulla durata di queste valvole transcatetere, prima che questo tecnologia possa essere applicata anche in pazienti più giovani o a minor rischio chirurgico.

In questo studio è riportata la nostra esperienza prospettica monocentrica nell'ambito della TAVI, raccolta in un centro ad alto volume, il Dipartimento di Scienze Cardiache, Toraciche e Vascolari

dell'Università di Padova, utilizzando entrambi i dispositivi, espandibile su pallone ed auto-espandibile, tramite tutti i gli approcci vascolari attualmente disponibili. Sono riportati i risultati immediati ed al follow-up, sia dal punto di vista del miglioramento clinico che della performance emodinamica delle protesi. Sono stati analizzati anche alcuni campi particolari di applicazione della metodica, come ad esempio il trattamento della disfunzione di bioprotesi, e abbiamo discusso sulle principali potenziali complicanze procedurali, come ad esempio i disturbi della conduzione cardiaca e i leak periprotesici.

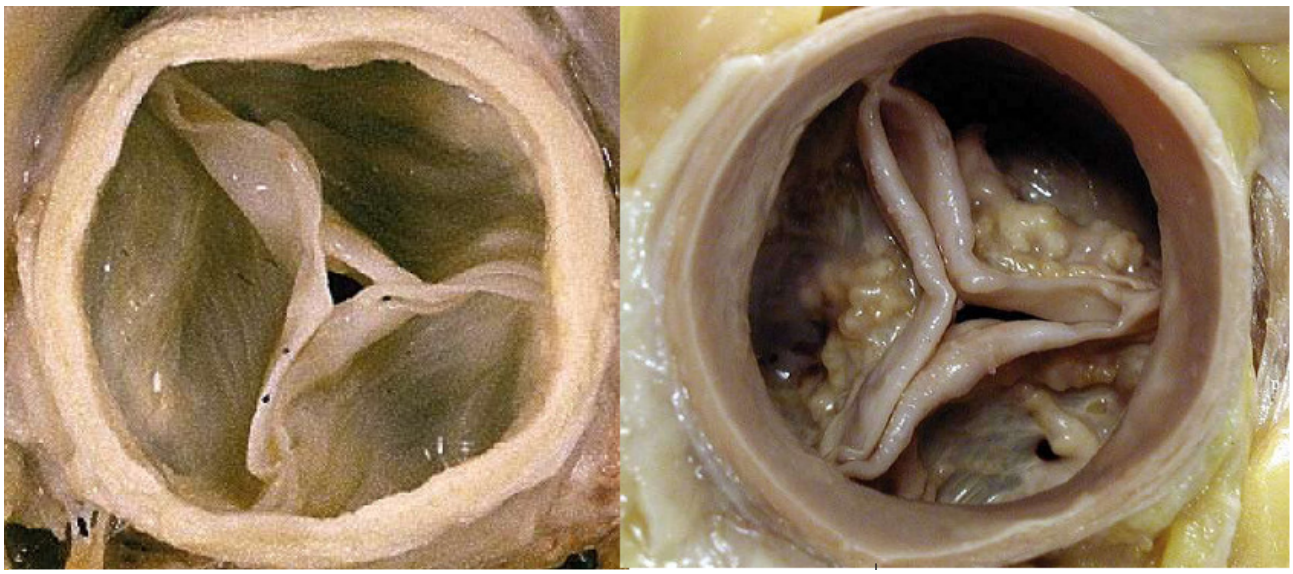
Dall'esperienza fino ad ora maturata, noi siamo fermamente convinti che, non appena alcune attuali limitazioni ed alcune perplessità saranno chiarite, questa tecnica emergente subirà una rapidissima ed ampia diffusione. Tuttavia non bisogna dimenticare che, per continuare a garantire lo straordinario successo di questa nuova metodica, il concetto di heart team, e quindi di una stretta collaborazione fra diversi specialisti, deve rimanere un punto centrale e irrinunciabile, per poter selezionare la miglior protesi ed il più appropriato approccio in ogni paziente, oltre che per garantire un perfetto risultato tecnico e le necessarie cure ed assistenze post-procedurali.

INTRODUCTION

2.1 Epidemiology, aetiology and pathology of degenerative aortic valve disease.

Degenerative AS is an age-related calcific narrowing of the aortic valve creating an obstruction to outflow of blood into the systemic circulation. This pathological condition is typical of the 7^{th} – 8^{th} decade of the human life and it represents the most frequent heart valve disease in Western countries, where its prevalence steadily increases with aging population.[1, 2] 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] (figure 1).

Figure 1. Macroscopic view of an aortic valve. *On the left an example of a normal aortic valve. On the right an aortic valve with degenerative calcification.*



The valvular lesion is characterized by intra- and extracellular lipid accumulation, inflammation and calcification with many similarities to atherosclerosis.[4] Calcific AS is an active disease process, and it is the expression of osteopontin protein metabolism. The calcification process may involve coronary ostia, aortic wall ("porcelain aorta"), anterior mitral leaflet and mitral annulus, and/or

conduction tissue. It has been suggested that the hypercholesterolemia accelerates age-related degenerative changes in the aortic root and valve.[5] More generally, calcific AS is associated with traditional risk factors for atherosclerosis such as cigarette smoking, a history of hypertension, and low high-density-lipoprotein cholesterol values.[6] Moreover, these pathological mechanisms may be accelerated by particular conditions such as end-stage renal disease, homozygous type II hyperlipoproteinemia, Paget disease of bone, radiation exposure.

2.2 Pathophysiology.

Normal aortic orifice area in adults is 3 to 4 cm^2. In adults with AS, the obstruction develops gradually, usually over decades. According to current ACC/AHA Guidelines,[7] AS severity was graded on the basis of a variety of hemodynamic and natural history data (Table 1), using definitions of aortic jet velocity, mean pressure gradient, and valve area as follows:

- Mild (area 1.5 cm^2, mean gradient <25 mmHg, or jet velocity <3.0 m/second);
- Moderate (area 1.0 to 1.5 cm^2, mean gradient 25 to 40 mmHg, or jet velocity 3.0 to 4.0 m/second);
- Severe (area <1.0 cm^2, mean gradient >40 mmHg, or jet velocity >4.0 m/second).

Table 1. Classification of the Severity of Valve Disease in Adults.

	Mild	**Moderate**	**Severe**
Jet velocity (m/second)	<3.0	3.0 – 4.0	>4.0
Mean gradient (mmHg)	<25	25 – 40	>40
Valve area (cm^2)	>1.5	1.0 – 1.5	<1.0
Valve area index (cm^2/m^2)	-	-	<0.6

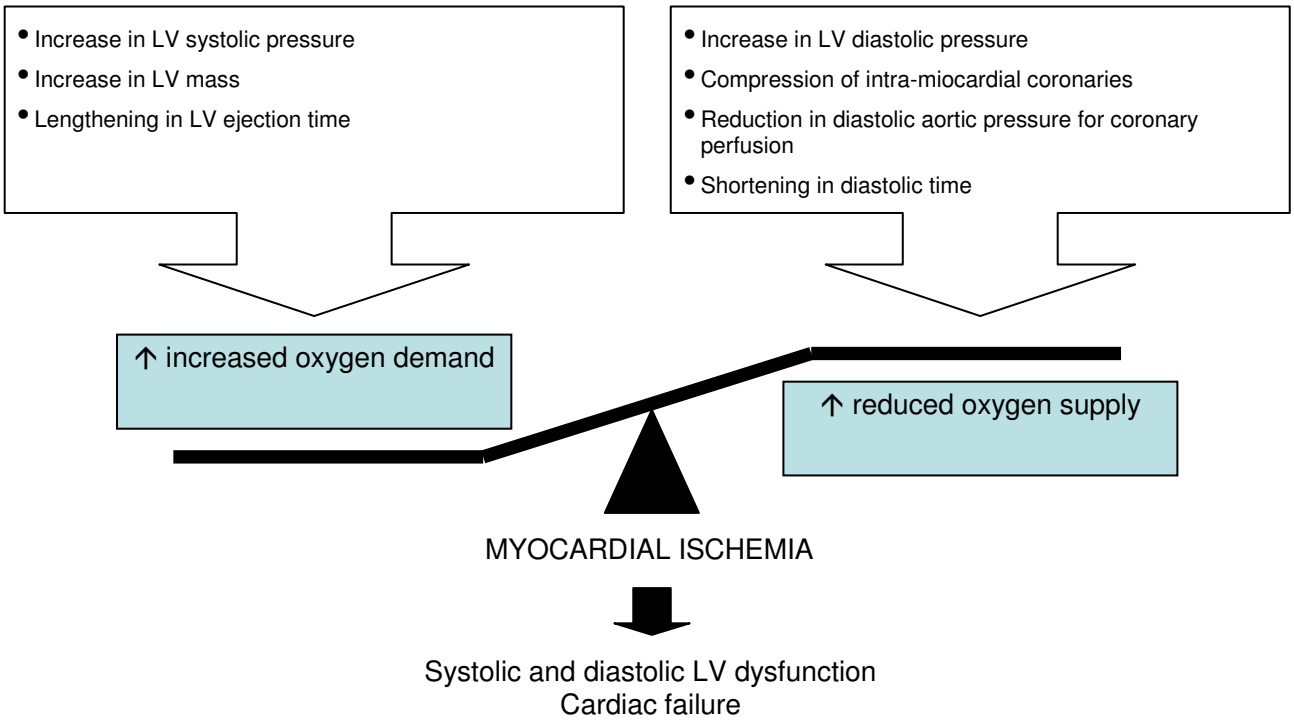
However, valve gradients are flow dependent and when used as estimates of severity of valve stenosis should be assessed with knowledge of cardiac output or forward flow across the valve. In fact, when stenosis is severe and cardiac output is normal, the mean transvalvular pressure gradient

is generally greater than 40 mm Hg. However, when cardiac output is low, severe stenosis may be present with a lower transvalvular gradient and velocity.

As AS worsens, the force the left ventricle must generate to overcome the obstruction increases progressively. Hemodynamically significant AS leads to severe concentric left ventricular (LV) hypertrophy[8]. The development of concentric hypertrophy appears to be an appropriate and beneficial adaptation to compensate for high intracavitary pressures. Unfortunately, this adaptation often carries adverse consequences. The hypertrophied heart may have reduced coronary blood flow and also exhibit a limited coronary vasodilator reserve (figure 2), even in the absence of epicardial coronary artery disease.[9] Although inotropic reserve and the development of LV hypertrophy serve initially to compensate for this increase in demand so that peak systolic wall tension remains normal, when LV failure supervenes, the ventricle dilates the left atrium enlarges, and changes secondary to backward failure occur in the pulmonary vascular bed, the right side of the heart, and the systemic venous bed. Thus, these double-edged swords lead finally to pathologic consequences, the onset of symptoms, morbidity, and mortality.

An inverse correlation between wall stress and ejection fraction (EF) has been described in patients with AS. This suggests that the depressed EF and velocity of fiber shortening that occur in some patients are a consequence of inadequate wall thickening, resulting in “afterload mismatch.[10] In others, the lower EF is secondary to a true depression of contractility.[11] Thus, both increased afterload and altered contractility are operative to varying extents in depressing LV performance.

Figure 2. Determinants of myocardial oxygen consumption in AS. *The major determinants of myocardial oxygen consumption in aortic stenosis. The imbalance between demand and supply of oxygen results in myocardial ischemia with possible impairment of ventricular performance.*



2.3 Clinical manifestations.

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.[12] 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.[13]

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.[9] 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 tachy arrhythmias, or conduction disorders (CD), or abnormal Bezold Jarisch reflex (hypotension, bradycardia).

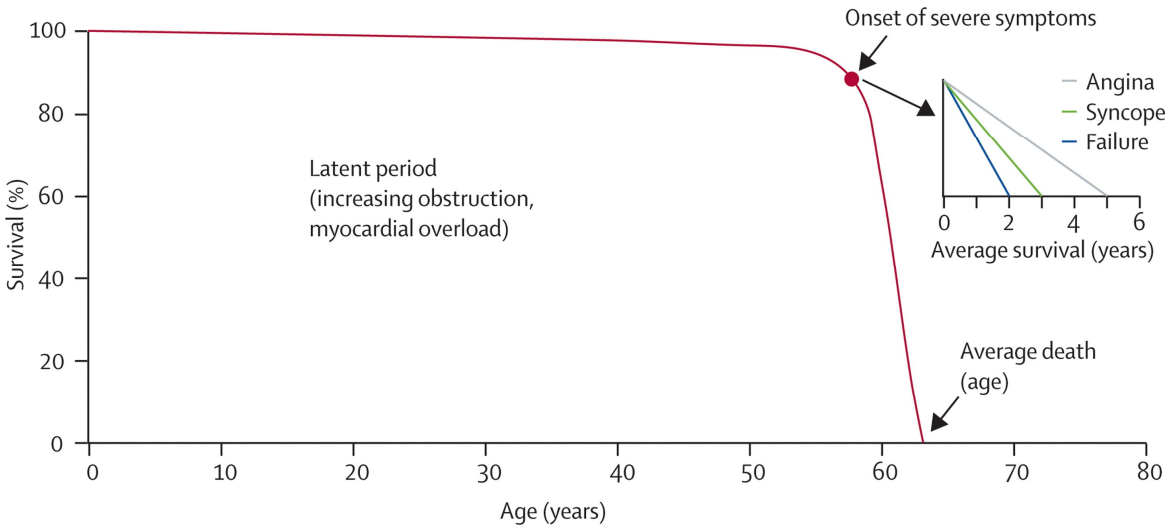
Gastrointestinal bleeding, either idiopathic or due to angiodysplasia (most commonly of the right colon) or other vascular malformations, occurs more often in patients with calcific AS than in persons without this condition; it may cease after aortic valve replacement (AVR).[14]

2.4 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 ≈0.12 cm2 per year.[15] 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.[16] 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).

Figure 3. Natural history of aortic stenosis without operative treatment (from Ross J Jr, Braunwald E: Aortic stenosis. Circulation. 38[Suppl V]:61, 1968). *After onset of symptoms, average survival is <2 to 3 years.*



2.5 Management.

2.5.1 Conventional therapy.

Indications for AVR are well defined in guidelines and there is a consensus that intervention should be advised in patients with severe, symptomatic AS (table 2).[7]

Table 2. Indications for Aortic Valve Replacement according to ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease.

	Indication	Class	Level of Evidence
1	AVR is indicated for symptomatic patients with severe AS.	I	B
2	AVR is indicated for patients with severe AS undergoing coronary artery bypass graft (CABG) surgery.	I	C
3	AVR is indicated for patients with severe AS undergoing surgery on the aorta or other heart valves.	I	C
4	AVR is recommended for patients with severe AS and LV (LV) systolic dysfunction (EF <50%).	I	C
1	AVR is reasonable for patients with moderate AS undergoing CABG or surgery on the aorta or other heart valves.	IIa	B
1	AVR may be considered for asymptomatic patients with severe AS and abnormal response to exercise (e.g., development of symptoms or asymptomatic hypotension).	IIb	C
2	AVR may be considered for adults with severe asymptomatic AS if there is a high likelihood of rapid progression (age, calcification, and coronary artery disease) or if surgery might be delayed at the time of symptom onset.	IIb	C
3	AVR may be considered in patients undergoing CABG who have mild AS when there is evidence, such as moderate to severe valve calcification, that progression may be rapid.	IIb	C
4	AVR may be considered for asymptomatic patients with extremely severe AS (aortic valve area (AVA) <0.6 cm^2, mean gradient >60 mmHg, and jet velocity >5.0 m/second) when the patient's expected operative mortality	IIb	C

	is 1.0% or less.		
1	AVR is not useful for the prevention of sudden death in asymptomatic patients with AS who have none of the findings listed under the class IIa/IIb recommendations.	III	B

In most adults with calcific AS valve replacement is the surgical treatment of choice. 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%[17]. Patient's age should not be a contraindication and, according to current guidelines, "because there is no effective medical therapy and balloon valvotomy is not an acceptable alternative to surgery, AVR must be considered in all elderly patients who have symptoms caused by AS".[7] However, the operative mortality rate for AVR in patients ≥80 years of age is as great as 8% to 15%[18-24]. Furthermore, in the rapidly aging US population, the number of elderly patients with significant comorbidities is steadily increasing, and for many patients, both the natural history of untreated AS and results after the traditional on-pump AVR through a median sternotomy may be worse than conveyed by overall outcomes data[24, 25].

2.5.2 Rationale for new less invasive technique.

Despite surgical AVR is the treatment of choice for symptomatic AS, in the real world surgery was decided against by the attending practitioner in about 33% of patients.[2, 26] The two most striking characteristics of patients who were denied surgery were older age and LV dysfunction. In this scenario, transcatheter minimal invasive beating heart aortic valve therapies (transcatheter aortic valve implantation: TAVI) have been considered as attractive alternatives to the standard AVR for patients carrying an elevated predictable operative risk or in case of peculiar clinical situations that could compromise the patient's outcome after standard open heart surgery. [27-30] In fact TAVI has the advantages of a less invasive technique; it allows for better protection and ensures an improved

recovery of myocardial function, while avoiding (or at least minimizing) ischemic and ischemia/reperfusion injury, inflammatory response, cardioplegia, surgical trauma and oxidative stress which can lead to apoptosis and contractile dysfunction of survivors myocytes.[31]

After long and careful evaluation in vitro and in animal models, the first patient was implanted in 2002 by Cribier and colleagues in Rouen (France)[32] and, after then, more than 30,000 procedures have been performed worldwide.[28, 29, 33-37]

2.5.3 Summary of current outcomes.

The most up-to-date data on the clinical outcomes of TAVI comes from a number of single center reports and multicenter and national registries and from one randomized trial.[27, 37-43] In the light of the current experience, TAVI using both balloon- and SE devices can be said to be feasible. Short- and mid-term haemodynamic results are fair up to 2 years. The overall results can be summarized as follows: procedural success is closely linked to experience and is >95% in experienced centres with a very low on-table mortality rate. Valve function is satisfactory with a final valve area ranging from 1.5 to 1.8 cm^2. Mortality at 30 days ranges from 6 to 10%. Acute myocardial infarction occurs in 2–11%. Valve embolization rates are low (0.3%), as are coronary ostia obstruction rates (0.6%). Stroke risk is 2 to 4%, permanent pacemaker (PPM) requirement is 4% to 8% with the SAPIEN THV and 20% to 40% with the CoreValve. Mild-to-moderate aortic regurgitation, mostly paravalvular, is observed in ≈50% of cases; while the incidence of severe aortic regurgitation up to ≈5%. The most important potential complication of both the transfemoral (TF) and the transapical (TA) approach is major vascular access site complications, with an incidence ranging from 10 to 15%, and they remain a significant cause of mortality and morbidity.

One-year survival is >80% with the TF approach and >70% with the TA approach (the difference mainly being explained by the differences in comorbidities of the patients). with a significant improvement in clinical condition in most cases. The majority of late deaths are non-cardiac, and most likely reflect the comorbidities of the patients. Serial echocardiographic studies have

consistently shown good prosthetic valve function with no structural deterioration of valve tissue. The result of the Partner US randomized trial suggest that TAVI should now be considered the standard of care for patients deemed unsuitable for routine surgical AVR[27] and it is not inferior to surgical intervention in case of high risk patients.[43]

AIMS OF THE THESIS

General assessment:

1) First, to analyze safety and feasibility and long term outcome of TAVI procedure in a single monocentric series, using both SE and balloon expandable devices.
2) Second, to compare the two main approaches, the TF and the TA one, in terms of early results and long term outcome.
3) Third, to analyze the durability over long term, by analyzing echocardiographic variables over time with the self expandable devices.

Special settings:

4) Fourth, to investigate safety and feasibility of alternative approaches, in particular the retrograde transubclavian approach.
5) Fifth, to explore safety and feasibility of a particular indications to TAVI, the treatment of bioprosthesis dysfunction by valve-in-valve technique.
6) Sixth, to demonstrate the safety and feasibility of TAVI in particular setting, such as in patients with prior mitral valve surgery with mechanical prosthesis.

Complications:

7) Seventh, to investigate the incidence and pathophysiology of CD with SE devices.
8) Eighth, to compare CD after SE and balloon-expandable (BE) devices.
9) Ninth, to describe the valve-in-valve technique to overcome severe periprosthesis leakage after first TAVI;
10) Tenth, to analyze incidence, predictive factors and prognostic implications of contrast induced nephropathy after TAVI;
11) Finally, to describe the risk of peri-procedural cerebral embolism during TAVI.

METHODS

4.1 Study population

Between May 2007 and November 2011, 227 patients affected by severe symptomatic AS or aortic bioprosthesis dysfunction and referred to our department for AVR were considered for TAVI because of high surgical risk or inoperability criteria, after discussion by the "Heart Team" (a team including at least one interventional cardiologist and one cardiac surgeon, as well as referring clinical cardiologist and anaesthesiologist).

The patient's surgical risk was estimated using logistic EuroSCORE and STS score, as well as according to clinical judgment and frailty score. Logistic EuroSCORE and STS score of each patient was calculated using the web-based system. In particular, we considered:

1) patients ≥ 80 years old with a logistic EuroSCORE ≥ 15%, or

2) patients aged ≥ 75 years with a logistic EuroSCORE ≥ 20%, or

3) patients aged ≥ 65 years and at least one of the following conditions: marked calcification of the ascending aorta ('porcelain aorta'), previous cerebrovascular event, neurological dysfunction, stage V chronic renal failure, respiratory failure (FEV 1 <70%), liver insufficiency (Child ≥ B / C), severe chest disease or a history of mediastinal radiation therapy.

We excluded patients with bleeding diathesis, significant organic mitral regurgitation (≥ 3+/4), aortic annulus diameter ≤ 19 mm or > 27 mm (according to current valve size available for clinical use). We also excluded 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.[44] Moreover, bicuspid aortic valve disease has generally been an exclusion criterion in major trials of TAVI, and so there is little clinical experience available.

4.2 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 and right heart catheterization, including coronary angiograms, LV angiography, angiograms of ascending and abdominal aorta and iliac-femoral arteries. These angiograms were performed with a 5F marked pigtail catheter for a precise determination of vascular size.
6) A multislice 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 investigation.

In particular, all the variables collected by transthoracic and transesophageal echocardiograms, complete heart catheterization and angiographies and CT scan are listed in the following table 3, 4 and 5, respectively.

Table 3. Echocardiographic variables
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 (cm^2)
Volume (ml/m^2)
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 (color Doppler evaluation and pressure half time)
Mitral valve
Peak transvalvular gradient (mmHg)
Mean transvalvular gradient (mmHg)
Mitral valve area (cm2)
Mitral regurgitation (color Doppler evaluation; vena contracta)
Tricuspid valve
Tricuspid regurgitation
Pulmonary artery systolic pressure (mmHg)
Diastolic function
E and A wave velocity
E/A ratio.

Table 4. Complete heart catheterization: pressure measurements and angiograms
Right atrial (mmHg)
Right ventricle (mmHg)
Pulmonary artery (mmHg)
Pulmonary capillary wedge pressure (mmHg)
Left ventricle (mmHg)
Ascending aorta (mmHg)
Peak-to peak trans-aortic gradient (mmHg)
AVA (cm2)
Cardiac output (l/min)
Cardiac index (l/min/m2)
Pulmonary resistance (UW/m2)

Capillary resistance (UW/m2)
Pulmonary artery oxygen saturation (%)
Aortic oxygen saturation (%)
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 5. 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

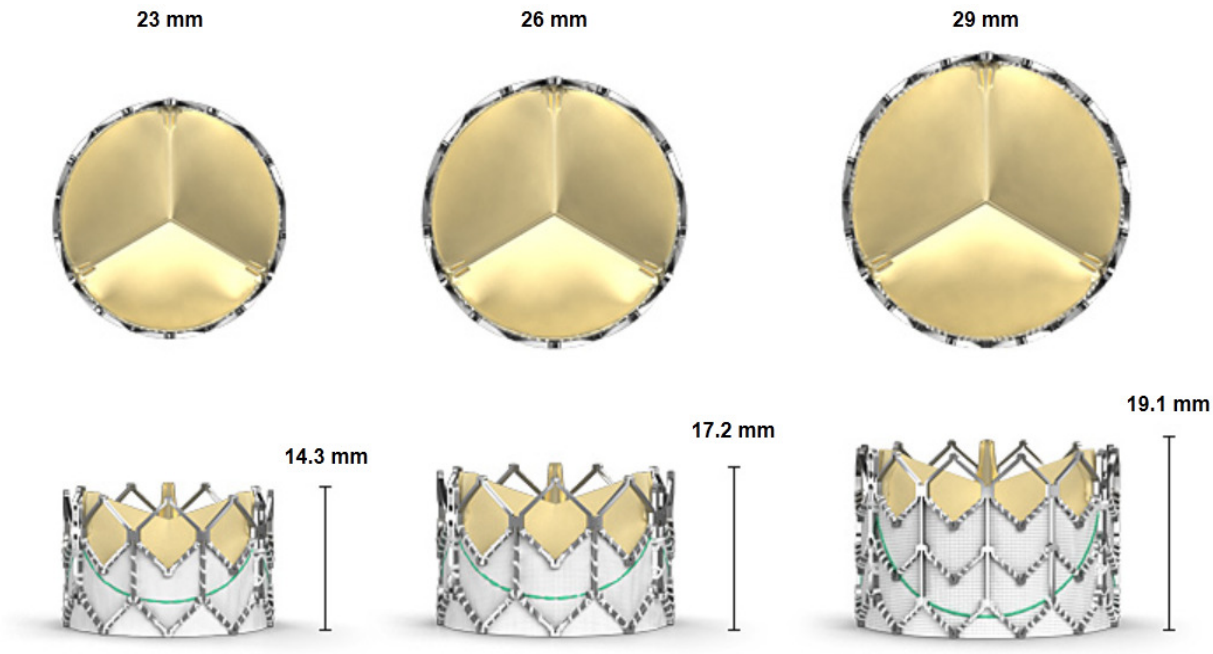
4.3 Description of transcatheter aortic valves

Only two different sutureless transcatheter aortic stent-valves have been developed, tested and, subsequently, introduced into the current clinical practice and have so far achieved the CE mark and are commercially available in Europe: the BE Edwards valve (Edwards Lifesciences, Irvine, CA,

USA) allowing either retrograde TF (or transaortic) or antegrade TA implantation, and the self-expanding CoreValve Revalving system (Medtronic Inc., Minneapolis, MN, USA) designed primarily for the retrograde transarterial (femoral, alternatively subclavian) approach. However, recently, the US Food and Drug Administration advisory panel voted to recommend approval of the Edwards Sapien transcatheter heart valve (Edwards LifeSciences, Irvine, CA, USA) for the treatment of certain inoperable patients. The procedure with both valves seems to be safe and feasible and short and mid term haemodynamic results are very encouraging.[45, 46]

4.3.1 Balloon-expandable valve. The BE valve consists of 3 pericardial cusps, initially equine (Cribier-Edwards) and currently bovine (Edwards-Sapien and Sapien XT) (Edwards Life Sciences Inc, Irving, CA), mounted (sutured) within a tubular, slotted, stainless steel BE stent (or cobalto-chromium in the case of the SAPIEN XT). The cusps undergo a specific process called Carpentier-Edwards ThermaFix process, which is intended to minimize the risk of calcification, helping preserve the performance of the prosthesis. The device is actually available in three different sizes which treats an annulus size range of 18 to 27 mm: the smaller one is 14.1 mm in length and 23 mm in expanded diameter, the medium one has a length of 16.1 mm and an expanded diameter of 26 mm and finally the larger one is 19.1 mm in length and 29 mm in expanded diameter (figure 4). Current devices require either a 18F or 19F sheath for the TF approach (Novaflex) or a 24-26F sheath in case of TA delivery (Ascendra).

Figure 4. Edwards SAPIEN XT Transcatheter Heart Valve Sizes. *The Edwards SAPIEN XT Transcatheter Heart Valve is currently available in three sizes.*



Size	Aortic Annulus Diameter	Valve Height
23 mm	18-22 mm	14.3 mm
26 mm	21-25 mm	17.2 mm
29 mm	24-27 mm	19.1 mm

4.3.2 Self-expandable valve. The SE percutaneous heart valve (CoreValve; CoreValve, Irving, CA) consists of 3 pericardial tissue cusps, initially bovine and currently porcine, mounted and sutured in a SE nitinol stent. The available valve diameters are 26 and 29 mm, covering an annulus size range of 20 to 29 mm (figure 5). The stent frame is composed by three parts:

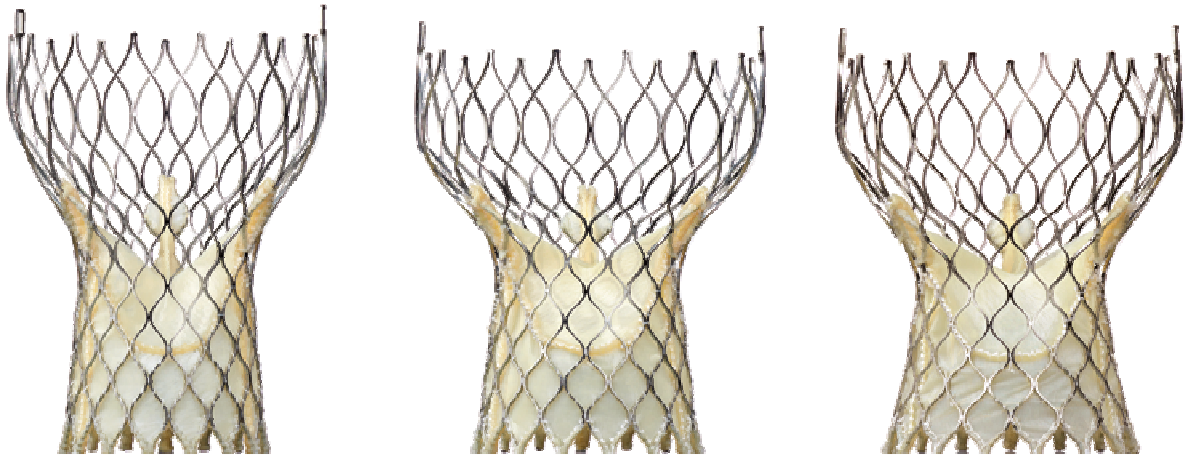
a) the lower (inlet) portion has a high radial force to expand and exclude the calcified aortic leaflets;

b) the middle portion carries the valve and is constrained to avoid obstructing the coronary arteries and is where the coaptation point of the leaflets occur;

c) the upper portion (outlet) is flared to fixate and orient the stent in the ascending aorta.

Early devices required 25F sheaths. Second-generation devices incorporated porcine pericardial tissue that allowed decrease in profile to 21F sheath. The current device was further redesigned in the fixing of the valve tissue onto the stent, decreasing the profile to 18F. The prosthesis can be delivered by TF or transubclavian approach. Recently, a new delivery system called Accutrak is available, allowing a more controlled and accurate deployment.

Figure 5. CoreValve Revalving System. *The CoreValve Revalving System is currently available in three sizes.*



26 mm **29 mm** **31 mm**

Size	Aortic Annulus Diameter	Valve Height
26 mm	20-23 mm	55 mm
29 mm	23-27 mm	53 mm
31 mm	27-29 mm	52 mm

4.4 Description of procedures

In *transfemoral approach*, the device is usually implanted under mild sedation and local anaesthesia, by totally percutaneous TF approach. 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).

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.[47]

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.[48]

The direct *transaortic approach* is generally reserved to patients in which the iliac-femoral arteries and the subclavian arteries are not suitable for large sheath insertion and there is a severe LV dysfunction which contraindicate the TA approach. This approach is conducted under general anesthesia and endotracheal intubation. A 6-cm J-shaped upper ministernotomy is performed and the pericardium is opened to expose the distal part of the ascending aorta. Two purse string sutures are placed after transesophageal echocardiographic and manual examination of the ascending aorta. Preoperative CT must exclude the presence of a diffusely calcified ascending aorta. When the Ascendra device is withdrawn at the end of procedure, the purse string sutures are tied and the sternum is closed with 2 or 3 steel wires.[49]

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 5-F sheath was percutaneously placed in the right radial artery through which a 5-F graduate pigtail was advanced

in the ascending aorta for hemodynamic monitoring and landmark aortic angiography. A catheter for temporary pacing was advanced through the right cephalic 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-2 coronary catheter advanced to the ascending aorta in the LAO 40° projection.

The transvalvular gradient is measured and the AVA is calculated. After then, a 260 cm long, 0.035" Amplatz Super Stiff J Guidewire® (COOK) preshapped into its distal floppy portion is advanced into the left ventricle. An high-pressure and semi-compliant balloon catheter (Cristal Balloon, BALT, Montmorency, France) is introduced over the wire and carefully purged of air in the ascending aorta before valve dilatation. 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.

4.5 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.

4.6 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 was also evaluated using transthoracic echocardiography.

4.7 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.[50] Procedural success was defined as the device success without urgent cardiac surgery and/or intraprocedural death. Periprocedural death was defined as any death within 30 days after the procedure or any death before discharge.

4.8 Statistical analysis

Categorical data are expressed as numbers and percentages and compared by Fisher's or χ^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 (see specific section). 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).

RESULTS

5.1 Safety, feasibility and long term outcome of TAVI in a single monocentric experience using both self-expandable and balloon expandable devices (oral presentation at ESC congress, Paris 2011 and SHVD congress, Barcelona 2011).

This first analysis was conducted on 191 patients who underwent TAVI in our Institution between June 2007 and April 2011. Mean age of total population was 80.5 ± 6.9 years and 81 (42.4%) were male. One hundred and forty-three patients presented a severe AS (74.9%), 44 (23.0%) a combined AS and regurgitation, one a pure aortic regurgitation but with annulus calcification (0.5%) and finally 3 patients (1.6%) were treated because of bioprosthesis dysfunction.

Among them, 87 received a CoreValve prosthesis (82 by TF approach and 5 by transubclavian), while in the other 104 patients an Edwards Sapien/Sapien XT prosthesis was implanted (46 by TF approach and 58 by TA one).

Baseline characteristics of total population are summarized in table 6.

Table 6. Baseline characteristics of total population and according to the prosthesis type.

	All patients n=191	CoreValve n=87	Edwards n=104	p
Logistic EuroSCORE, %	21.43±13.37	22.88±13.78	20.21±12.97	0.17
Hypertension, n	171 (89.5%)	78 (89.7%)	93 (89.4%)	0.96
Diabetes, n	48 (25.3%)	21 (24.1%)	27 (26.2%)	0.74
Coronary Artery Disease, n	113 (59.2%)	57 (65.5%)	56 (53.8%)	0.10
Extracardiac Arteriopathy, n	75 (39.3%)	34 (39.1%)	41 (38.3%)	0.11
Chronic Renal Failure, n	114 (59.7%)	55 (63.2%)	59 (55.7%)	0.36
Chronic Obstructive Pulmonary Disease, n	53 (28.0%)	21 (24.4%)	32 (31.1%)	0.31
Previous stroke, n	25 (13.2%)	14 (16.1%)	11 (10.7%)	0.27
Previous Myocardial Infarction, n	47 (24.7%)	27 (31.0%)	20 (19.4%)	*0.03*
Previous Cardiac Surgery, n	37 (19.4%)	20 (23.0%)	17 (16.3%)	0.25
Previous Percutaneous Coronary Intervention, n	31 (16.2%)	15 (17.2%)	16(15.4%)	0.55
Heart Failure, n	97 (50.8%)	43 (49.4%)	54 (51.9%)	0.73
Porcelain Aorta, n	38 (2.07%)	16 (18.4%)	22 (22.7%)	0.47

Patients who received a CoreValve device, presented lower LV EF and larger LV end-diastolic volume. The main echocardiographic findings are listed in Table 7.

Table 7. Echocardiographic data of total population and according to the prosthesis type.

Echocardiographic Data	All patients n=191	CoreValve n=87	Edwards n=104	P
Maximum aortic gradient, mmHg	74.8 ± 23.5	74.6 ± 25.9	75.1 ± 21.3	0.89
Mean aortic gradient, mmHg	45.6 ± 15.4	44.4 ± 17.3	46.7 ± 13.5	0.31
AVA, cm2	0.77 ± 0.20	0.81 ± 0.22	0.74 ± 0.19	*0.01*
EDV ml/m2	68.5 ± 23.2	75.4 ± 24.9	62.2 ± 19.6	*<0.001*
EF %	54.3± 12.9	51.9 ± 14.0	56.4 ± 11.4	*0.02*

In the majority of patients who received a Corevalve device, the TAVI procedure was performed under local anesthesia and mild sedation; on the other side more than one half of patients who received an Edwards valve had a general anesthesia. Procedural time need to implant an Edwards valve was longer than that required for a CoreValve device (table 8).

Table 8. Procedural detail.

Procedural characteristics	All patients n = 191	CoreValve n= 87	Edwards n=104	P
General anesthesia, n	84 (38.9%)	17 (19.8%)	57 (54.8%)	*<0.001*
Inotropic support drugs, n	62 (33.0%)	37 (42.5%)	25 (24.8%)	*0.010*
Oro-tracheal intubation, n	82 (42.9%)	21 (24.1%)	61 (58.7%)	*<0.001*
Transesophageal echocardiogram, n	106 (55.5%)	28 (32.2%)	78 (75.0%)	*<0.001*
Procedural time, min (mean ± SD)	87.0 ± 37.5	72.5 ± 35.9	100.4 ± 33.9	*< 0.001*
Fluoroscopy time, min (mean ± SD)	22.4 ± 10.1	23.6 ± 9.8	21.4 ± 10.3	0.13
Contrast amount, ml (mean ± SD)	181.4 ± 76.5	186.5 ± 85.5	177.1 ± 68.3	0.39

However, some of these differences could be explained by the fact that in the Edwards group are included both TF but also TA procedures, which require mandatory general anesthesia and orotracheal intubation. In fact, the comparison between CoreValve group and Edwards group in terms of procedural details change if we restrict the analysis only to TF approach (table 9).

Table 9. Procedural details of only TF procedures.

Procedural characteristics	All patients n = 128	CoreValve n= 82	Edwards n=46	P
General anesthesia, n	16 (12.5%)	13 (15.9%)	3 (6.5%)	*0.020*
Inotropic support drugs, n	41 (32.0%)	34 (41.5%)	7 (15.2%)	*0.002*
Oro-tracheal intubation, n	20 (15.6%)	17 (20.7%)	3 (6.5%)	*0.005*
Transesophageal echocardiogram, n	49 (38.3%)	28 (34.1%)	21 (45.6%)	0.089
Procedural time, min (mean ± SD)	78.9 ± 34.2	71.5 ± 35.4	92.3 ± 27.4	*0.001*
Fluoroscopy time, min (mean ± SD)	24.3 ± 9.3	23.2 ± 9.9	26.3 ± 7.9	0.072
Contrast amount, ml (mean ± SD)	186.8 ± 76.9	186.8 ± 85.0	186.8 ± 60.8	0.99

Procedural success was reached in the majority of patients (95.8%), without any differences between CoreValve and Edwards valve. However, device success was lower in CoreValve group, probably because of the more frequent occurrence of significant periprosthesis leakeage and because of the 6 cases of valve-in-valve implantation in this latter group (table 10). No difference was recorded between the two devices about major vascular complications.

Table 10. Procedural outcome.

	All patients n = 191	CoreValve n = 87	Edwards n = 104	P
Procedural Success, n	183 (95.8%)	82 (94.3%)	101(97.1%)	0.53
Device Success, n	179 (93.7%)	78 (89.7%)	100 (96.2%)	*0.03*
Intraprocedural death, n	3 (1.6%)	2 (2.3%)	1 (1.0%)	0.46
Conversion to open heart surgery, n	2 (1.0%)	0	2 (1.9%)	0.19
Device embolization, n	7 (3.7%)	5 (5.7%)	2 (1.9%)	0.16
Post-dilatation, n	31 (16.3%)	27 (31.0%)	4 (3.9%)	*<0.001*
Valve-in-valve implantation, n	7 (3.7%)	6 (6.9%)	1 (1.0%)	*0.03*
Coronary Flow Impairment, n	0	0	0	-
Major vascular complication, n	15 (7.9%)	5 (5.7%)	10 (9.6%)	0.32

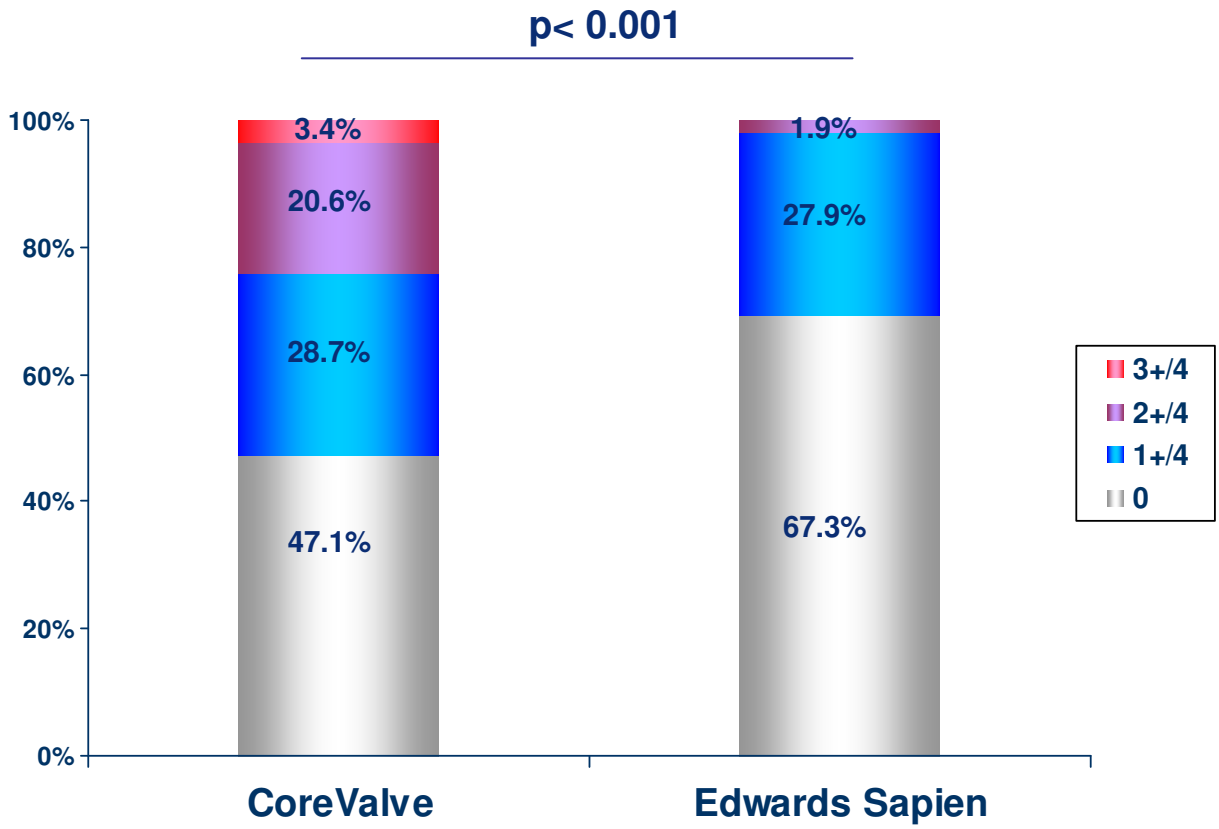
The hemodynamic performance of both devices was good, with some peculiarities: Edwards valve presented, at first echocardiographic examinations, higher transprosthetic gradients and lower

effective orifice area than CoreValve (table 11). On the other side, CoreValve devices had an higher degree of peri-prosthetic leakage (figure 6).

Table 11. Echocardiographic data at 48 hours after TAVI.

Echocardiographic Data	All patients n=191	CoreValve n=87	Edwards n=104	P
Maximum aortic gradient, mmHg	21.1 ± 7.6	19.8 ± 6.5	22.4 ± 8.4	*0.028*
Mean aortic gradient, mmHg	10.9 ± 4.5	10.0 ± 3.9	11.7 ± 4.9	*0.013*
Effective Orifice Area, cm2	1.9 ± 0.39	2.0 ± 0.4	1.8 ± 0.3	*<0.001*

Figure 6. Peri-prosthetic leakage 48-hours after TAVI with CoreValve and Edwards valve. *At 48 hours after TAVI, the incidence of peri-prosthetic leakage is significantly higher with the CoreValve device than with the Edwards Sapien valve.*

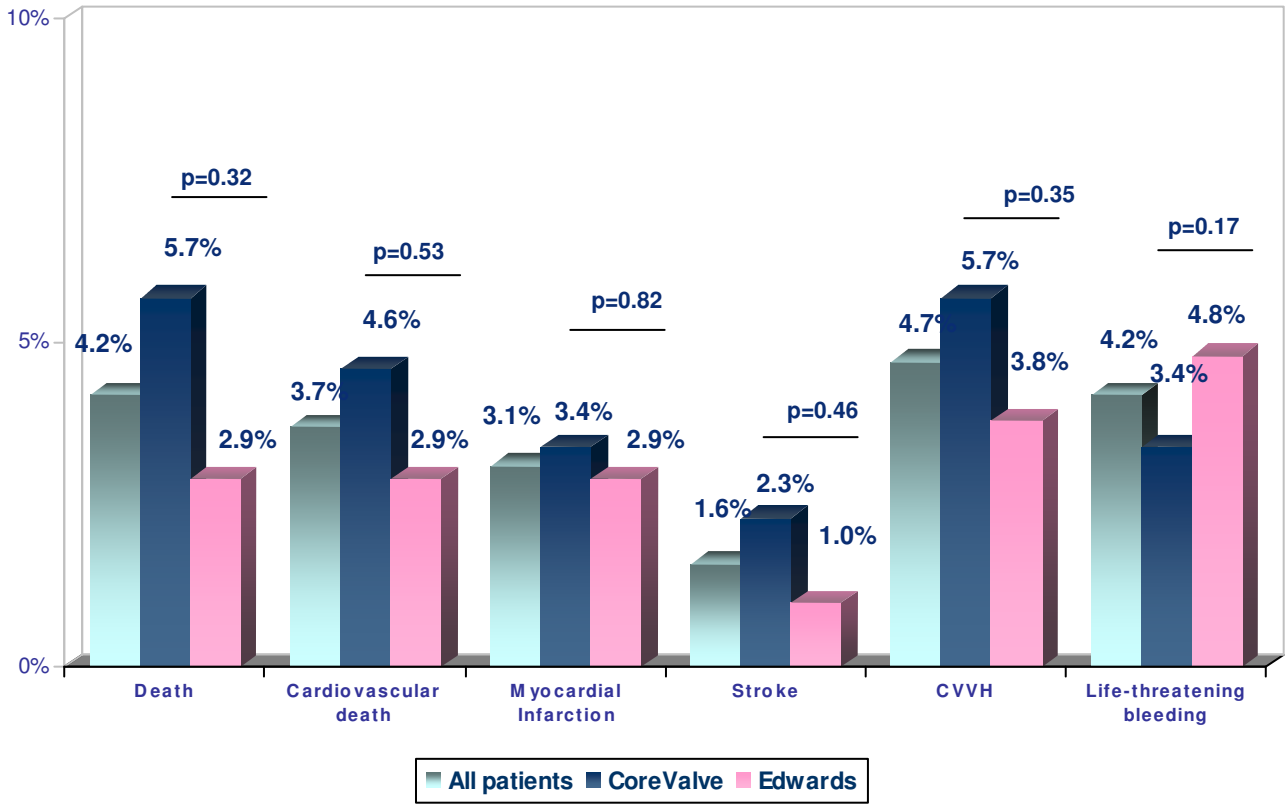


Another important difference between the procedural outcome of the two prosthesis regards the occurrence of complete atrioventricular block and the subsequent need for PPM implantation. In our

series, the need for PPM implantation after TAVI was 40.7% with the CoreValve device and 7.4% with the Edwards valve (*p<0.001*).

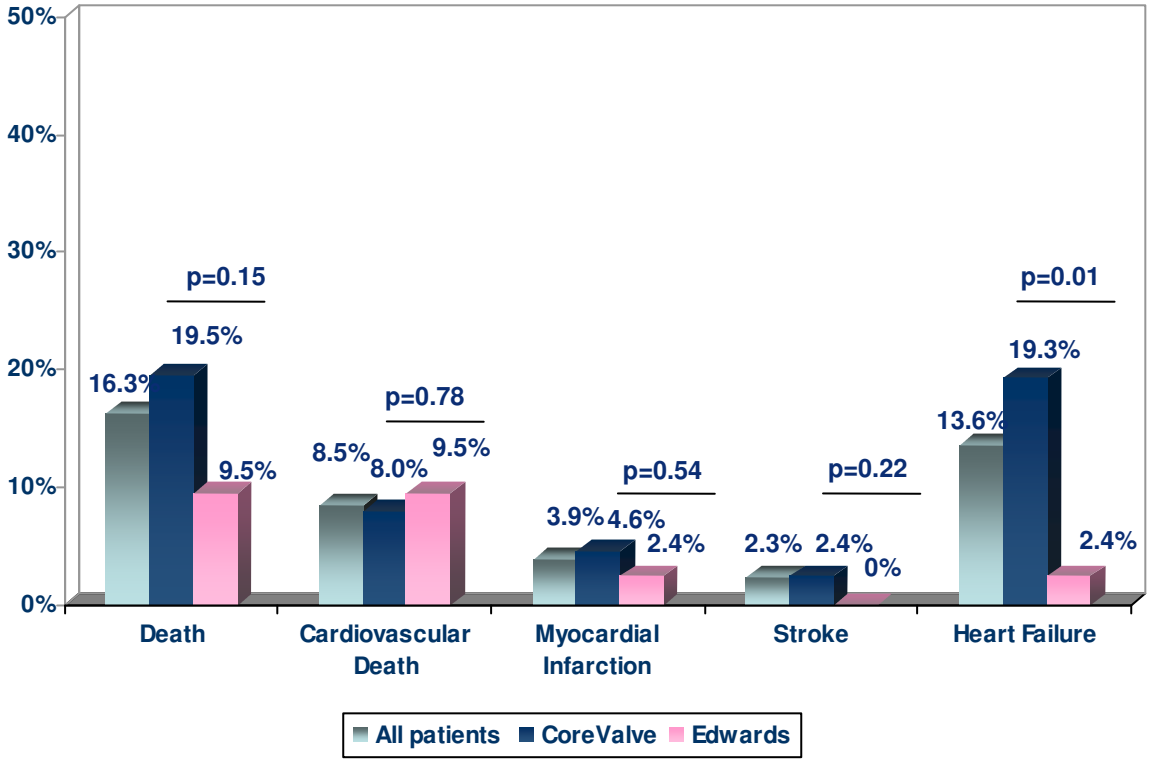
The in-hospital combined safety endpoints attributed according to VARC definitions were 17.3% in total population, without differences between groups (14.9% in CoreValve group and 19.2% in Edwards valve group, p=0.43). They are detailed in the following figure (figure 7).

Figure 7. In-hospital events. *In-hospital events in total population and in patients who received a CoreValve or an Edwards valve.*



At 1-year follow up, the combined efficacy endpoints according to VARC definitions, was in favour of Edwards valve. In fact it was 24.4% in total population, 31.7% in CoreValve group and 9.8% in Edwards group (*p=0.008*). The 1-year events are detailed in figure 8.

Figure 8. One-year events. *One year events in total population and in patients who received a CoreValve or an Edwards valve.*



Predictors of 1-year efficacy at univariate and multivariate analysis are showed in table 12.

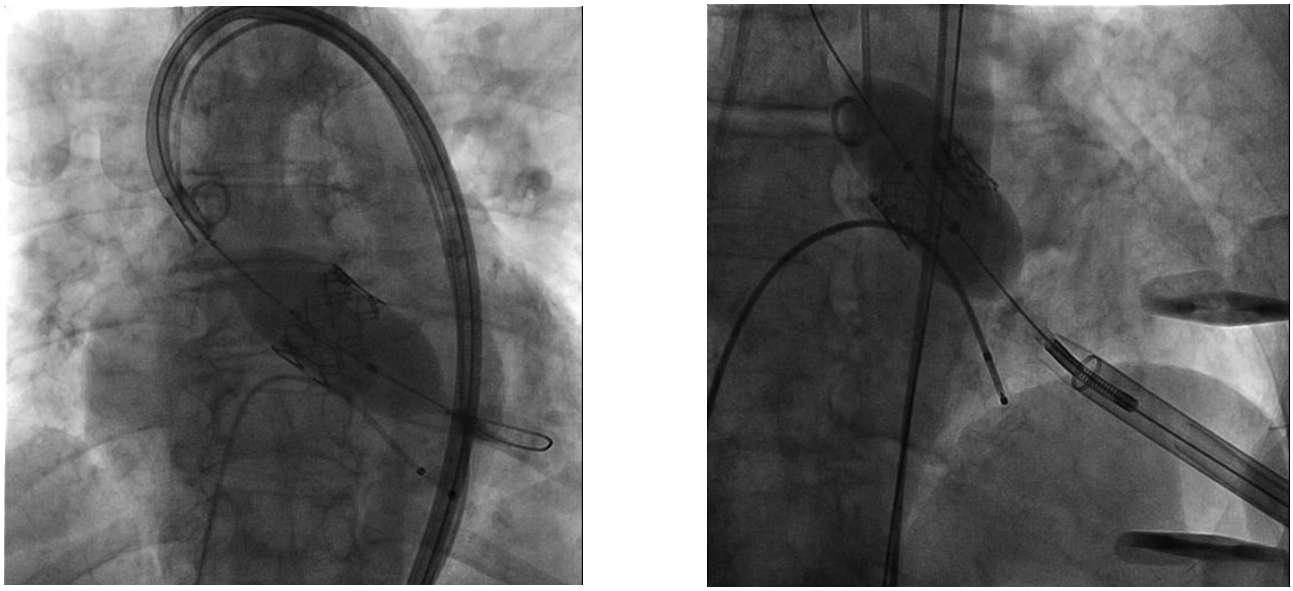
Table 12. Predictors of 1-year efficacy.

	Univariate Analysis			Multivariate Analysis		
	HR	**IC**	**p**	**HR**	**IC**	**P**
Age, 1 year	1.032	0.962 – 1.103	0.38		-	
Previous Congestive heart Failure	0.383	0.163 – 0.896	*0.027*			ns
Coronary Artery Disease	0.622	0.262 – 1.475	0.279		-	
EuroSCORE, %	0.960	0.927 – 0.994	*0.021*	0.965	0.927- 1.005	0.087
TF access	0.580	0.214 – 1.575	0.280		-	
TA access	0.788	0.074 – 8.432	0.844		-	
CoreValve device	0.233	0.075 – 0.722	*0.012*	0.184	0.037 – 0.922	*0.039*
LV EF @48 h	1.069	1.030 – 1.109	*<0.001*	1.066	1.023 – 1.111	*0.002*
Paravalvular leak@48 h	0.406	0.342 – 0.771	*0.006*	0.518	0.244 – 1.102	0.088

5.2 Comparison between transfemoral and transapical approach using balloon-expandable device (oral communication at GISE congress, Genova 2011).

We included in this analysis 104 patients who underwent TAVI with Edwards Sapien or Sapien XT valve at our institution between April 2009 and April 2011. Among them, 46 were treated by TF approach and 58 by TA approach (Figure 9).

Figure 9. Deployment of a balloon expandable valve by different approaches. *Examples of balloon expandable valve positioning by transfemoral approach (on the left) and by transapical approach (on the right).*



The majority of patients was treated because of isolated AS (79), 24 presented a combined AS and regurgitation and one patients presented a degeneration of a previous surgical bioprosthesis. Mean age of total population was 80.2 ± 7.5 and 38.5% were male.

The two groups of patients were similar in baseline characteristics and in particular in logistic EuroSCORE, but patients who were treated by TA approach had lower body mass index and more frequent peripheral vascular disease and previous cardiac surgery for CABG (table 13).

Table 13. Baseline characteristics.

	All patients n=104	**TA n=58**	**TF n=46**	**p**
Logistic EuroSCORE, %	20.21±12.97	19.60±11.40	20.97±14.81	0.59
STS PROM, %	11.8±11.6	12.6±11.2	10,8±12.1	0.44
Body Mass Index, kg/m2	25.6±3.9	24.8±3.9	26.7±3.9	*0.014*
Hypertension, n	93 (89.4%)	53 (91.4%)	40 (87.0%)	0.47
Diabetes, n	27 (26.2%)	15 (25.9%)	12 (26.7%)	0.93
Peripheral Vascular Disease, n	13 (12.5%)	12 (20.7%)	1 (2.2%)	*0.005*
Cerebrovascular Disease, n	31 (29.8%)	17 (29.3%)	14 (30.4%)	0.87
Chronic Renal Failure, n	58 (55.8%)	36 (62.1%)	22 (47.8%)	0.15
Chronic Obstructive pulmonary Disease, n	32 (31.1%)	15 (26.3%)	17 (37.0%)	0.25
Previous stroke, n	11 (10.6%)	6 (10.3%)	5 (10.9%)	0.90
Heart Failure, n	51 (51.9%)	29 (50.0%)	25 (54.3%)	0.66
Porcelain Aorta, n	22 (21.2%)	15 (25.9%)	7 (15.2%)	0.09
Coronary Artery Disease, n	52 (50.0%)	32 (55.2%)	20 (43.8%)	0.20
Previous Myocardial Infarction, n	20 (18.4%)	14 (24.5%)	6 (13.0%)	0.23
Previous Cardiac Surgery, n	17 (16.3%)	12 (20.7%)	5 (10.9%)	0.18
Previous CABG, n	12 (11.5%)	10 (17.2%)	2 (4.3%)	*0.04*
Previous percutaneous Coronary Intervention, n	16 (15.3%)	10 (17.3%)	6(13.1%)	0.76

Echocardiographic characteristics of the two groups were similar with the exception of aortic annulus size which was larger in candidates to TA approach (table 14).

Table 14. Echocardiographic data.

Echocardiographic Data	**All patients** n=104	**TA** n=58	**TF** N=46	**P**
Aortic Annulus, mm	21.9 ± 1.9	22.3 ± 2.1	21.3 ± 1.4	*0.006*
Maximum aortic gradient, mmHg	75.1 ± 21.3	72.7 ± 22.0	78.0 ± 20.1	0.22
Mean aortic gradient, mmHg	46.7 ± 13.5	46.0 ± 13.9	47.6 ± 113.0	0.55
AVA, cm2	0.74 ± 0.19	0.74 ± 0.20	0.72 ± 0.18	0.59
EDV indexed ml/m2	62.2 ± 19.6	62.9 ± 20.6	61.3 ± 18.3	0.69
EF %	56.4 ± 11.4	56.6 ± 10.3	56.3 ± 10.3	0.89

The use of general anaesthesia, orotracheal intubation, transesophageal echocardiogram, was more frequent in TA group, as well as the need for inotropic drug support. Moreover, procedural time, fluoroscopy time were longer in this group (table 15).

Table 15. Procedural details.

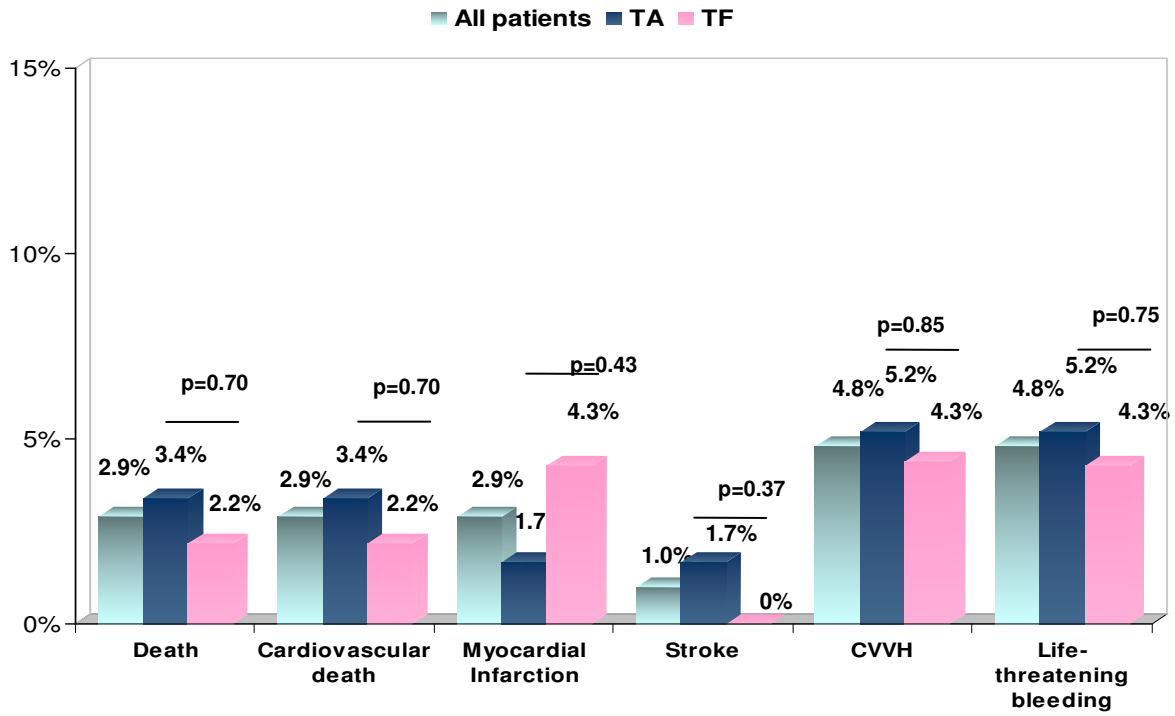
Procedural characteristics	All patients n = 104	TA n= 58	TF N=46	P
General anesthesia, n	57 (54.8%)	54 (93.1%)	3 (6.5%)	*<0.001*
Oro-tracheal intubation, n	61 (58.7%)	58 (100%)	3 (6.5%)	*<0.001*
Inotropic support drugs, n	25 (24.8%)	18 (32.7%)	7 (15.2%)	*0.04*
Extra Corporeal Membrane Oxygenator, n	4 (3.8%)	3 (5.2%)	1 (2.2%)	0.43
Transesophageal echocardiogram, n	78 (75.0%)	57 (98.3%)	21 (45.7%)	*<0.001*
Procedural time, min (mean ± SD)	100.4 ± 33.9	107.9 ± 37.7	92.3 ± 27.4	*0.025*
Fluoroscopy time, min (mean ± SD)	21.4 ± 10.3	17.5± 10.5	26.3 ± 7.9	*<0.001*
Contrast amount, ml (mean ± SD)	177.1 ± 68.3	169.4± 73.3	186.8 ± 60.8	0.20

No differences were recorded between the two groups in procedural outcome (table 16) and in-hospital events (figure 10). In particular combined safety events according to VARC definitions were 19.0% in TA group and 19.% in TF group (p=0.75).

Table 16. Procedural outcome.

	All Patients n = 104	TA n = 58	TF n = 46	P
Procedural Success, n	100 (96.2%)	55 (94.8%)	45 (97.8%)	0.43
Device Success, n	101 (97.4%)	55 (94.8%)	46 (100%)	0.12
Intraprocedural death, n	1 (1.0%)	1 (1.7%)	0	0.37
Conversion to open heart surgery, n	2 (1.9%)	2 (3.4%)	0	0.20
Device embolization, n	2 (1.9%)	2 (3.4)	0	0.20
Post-dilatation, n	4 (3.9%)	2 (3.4%)	2 (4.4%)	0.80
Valve-in-valve implantation, n	1 (1.0%)	1 (1.7%)	0	0.37
Pulseless ventricular tachicardia/fibrillation, n	6 (5.8%)	4 (6.9%)	2 (4.3%)	0.68
Coronary Flow Impairment, n	0	0	0	-
AV Block requiring PPM	7 (7.4%)	5 (9.6%)	2 (4.7%)	0.69
Major vascular complication, n	10 (9.6%)	5 (8.6%)	5 (10.9%)	0.70

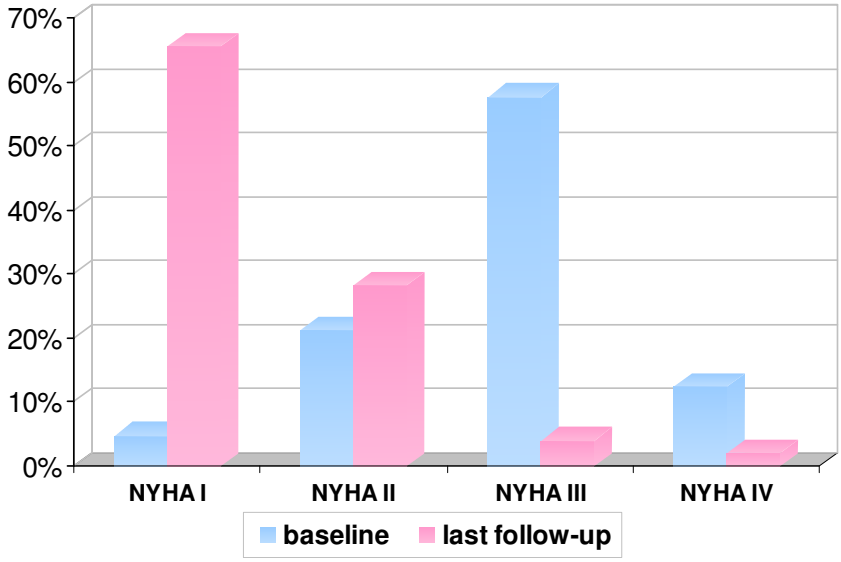
Figure 10. In-hospital events. *In-hospital events in total population and in patients who underwent TAVI by transapical and by transfemoral approach.*



However, even if the need for continuous veno-venous hemofiltration (CVVH) was similar between the two groups, the rate of AKI according to RIFLE criteria (an acronym comprising Risk, Injury, and Failure; and Loss, and End-stage kidney disease) was higher in TA group (24.6% vs 4.3%, *p=0.005*).

At a mean follow up of 9.7 ± 5.9 months, there was a significant improvement in NYHA functional class, with the majority of patients in NYHA I or II (figure 11).

Figure 11. Improvement in NYHA functional class at follow up. *Distribution of NYHA functional class at baseline and at last follow up.*



The rate of combined efficacy at 1-year according to VARC definitions was 9.4% in total population, and it was higher in TA group (TF 3.7% vs TA 13.5%, p=0.18).

At echocardiographic follow up, we recorded good hemodynamic performance of the devices without any case of valve dysfunction.

5.3 Long term hemodynamic performance of SE devices (oral communication, PCR congress, Paris 2011).

This analysis was conducted considering the 87 patients who underwent CoreValve implantation with III generation CoreValve Revalving System in our Department between June 2007 and December 2010. We collected echocardiographic data at baseline, at 48 hours after TAVI and at 1-, 3-, 6- and 12-months follow-up and yearly thereafter, in order to assess the performance of the prosthesis during time and any modification in echocardiographic parameters. Follow up length was 13.5 ± 8.4 months (range 1-36 months).

Mean age of total population was 80.84 ± 6.16 years and the majority were female. About one fourth of total population was affected by diabetes mellitus and the majority presented hypertension, chronic kidney disease (CKD) and coronary artery disease. Mean logistic EuroSCORE was 22.88 ± 13.78. Baseline characteristics are detailed in table 17.

Table 17. Baseline characteristics.

Variables	N=87 (%)
Age, years	80.84±6.16
Male sex	41 (47.2)
Hypertension	78 (89.7)
Diabetes mellitus	21 (24.1)
CKD	51 (58.6)
CerebroVascular Accident	14 (16.1)
Coronary Artery Disease	57 (65.5)
Congestive Heart Failure	43 (49.4)
Previous cardiac surgery	20 (23.0)
Porcelain aorta	16 (18.4)
Logistic EuroScore, %	22.88±13.78

Among total population, 82 were treated by TF approach and the remaining 5 by transubclavian approach. A 26-mm valve and a 29-mm valve was implanted in 48.3% and 51.7% of total population, respectively.

Hemodynamic success was achieved in 96.6% of cases with a in-hospital mortality of 6.9%. Six patients required valve-in-valve implantation. The rate of major vascular complications was 8.0%; 407% of patients required PPM implantation before discharge (table 18).

Table 18. Procedural outcome.

Variables	N=87 (%)
Hemodynamic success	84 (96.6)
Acute procedural success	82 (94.3)
In-hospital death	6 (6.9)
Valve-in-valve	6 (6.9)
Tamponade	1 (1.1)
Coronary flow impairment	0 (0)
Vascular/access site complication	7 (8.0)
Major bleeding	9 (10.3)
PPM	33/81 (40.7)
Intensive Care Unit stay (days)	4.92 ± 5.92
Total hospital stay (days)	14 ± 15.25

Looking at hemodynamic changes over time, TAVI allowed a significant reduction in transvalvular aortic gradient with an improvement in effective orifice area and LV EF in the very early phase. At follow up, there was a trend in further improvement in LV EF, with a slight decrease in effective orifice area and aortic regurgitation (table 19).

Table 19. Haemodynamic changes during time

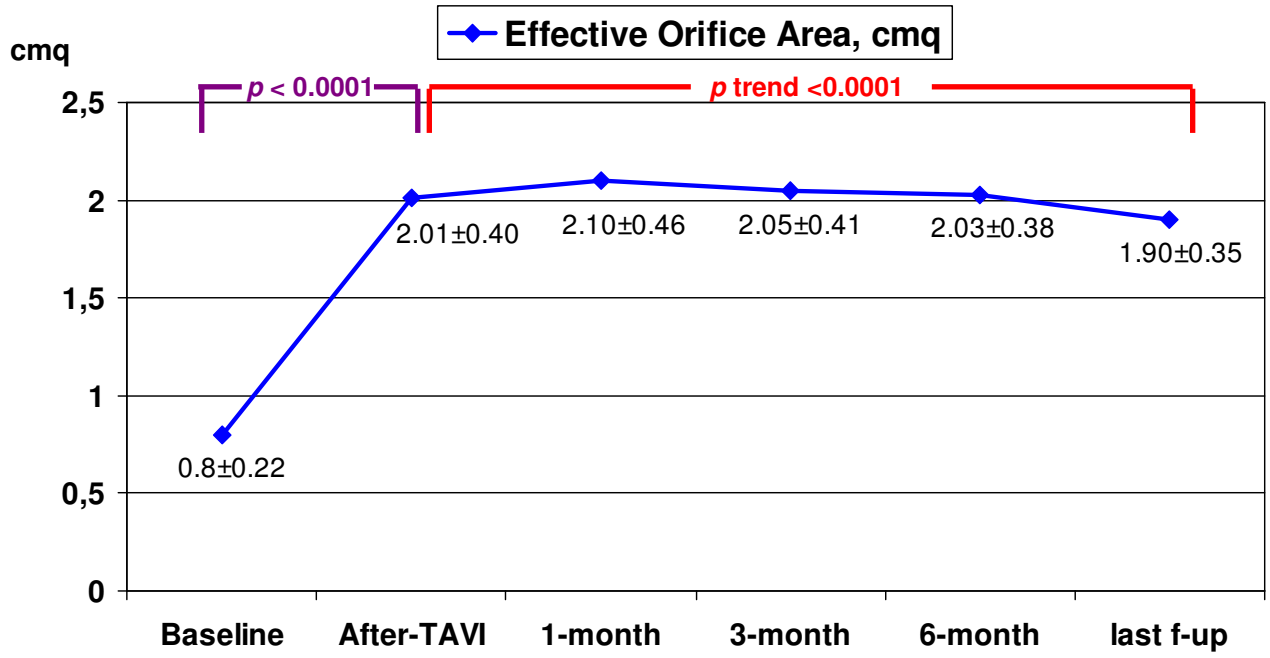
Variable	Before TAVI	48-h after TAVI	1 mo f-up	3 mo f-up	6 mo f-up	Last f-up (6 to 12 mo)
N. of pts	87	84	77	75	68	75
LVEDVi, ml/mq	74.4±22.4	74.8±20.8	75.9±22.9	73.8±24.3	73.1±21.4	70.6±25.4
EF, %	52.4±13.3	54.8±12.8*	57.0±12.0	56.6±14.0	57.8±14.1	57.6±13.1**
LV mass index, gr/mq	102.5±27.5	-	95.8±24.5	95.8±24.6	97.2±24.9	92.6±24.3
Peak Ao grad, mmHg	75.0±26.0	19.8±6.6*	19.0±9.7	17.8±8.1	17.9±8.1	19.4±8.7
Mean Ao grad, mmHg	44.6±17.3	10.0±3.9*	9.5±5.0	8.9±4.3	9.1±4.3	9.9±4.2
Effective Orifice Area, cmq	0.80±0.22	2.01±0.40*	2.10±0.46	2.05±0.41	2.03±0.38	1.90±0.35**
Aortic regurgitation	1.17±0.83	0.89±0.65*	0.95±0.65	0.82±0.71	0.65±0.66	0.80±0.74**
Right Ventricular Systolic Pressure, mmHg	41.8±11.2	39.9±12.7	38.7±12.3	38.2±11.5	37.3±11.6	38.4±11.0
Mitral regurgitation	1.25±0.59	1.20±0.63	1.29±0.63	1.25±0.58	1.20±0.60	1.19±0.60

**p<0.05 versus the value of the same variable before TAVI*
***p for trend <0.05 from "48-h after TAVI" to "last f-up"*

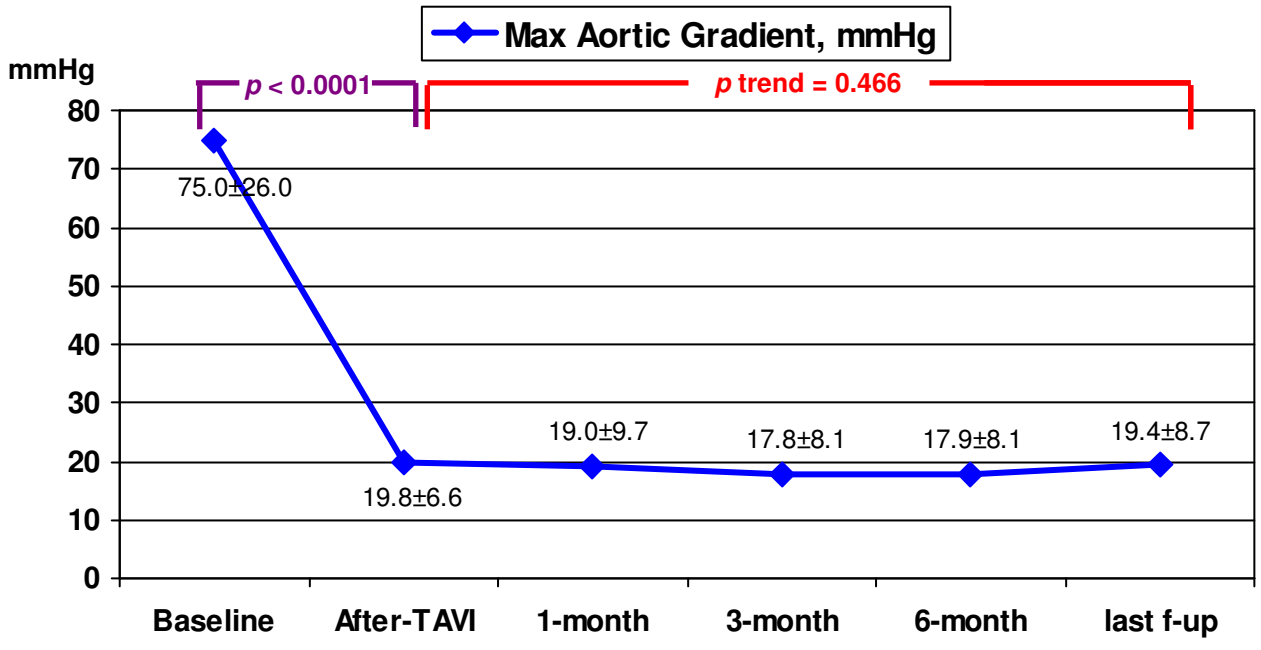
Change over time of each single hemodynamic parameters is visualized in the following graphs (figure 12, A-J).

Figure 12. Hemodynamic changes over time. *The following graphs show the changes immediately after TAVI and over time of effective orifice area (panel A), maximum (panel B) and mean (panel C) aortic gradient, aortic regurgitation (panel D), LV EF (panel E and F), LV EDVi (panel G), LV mass index (panel H), right ventricular systolic pressure (panel I) and mitral regurgitation (panel J).*

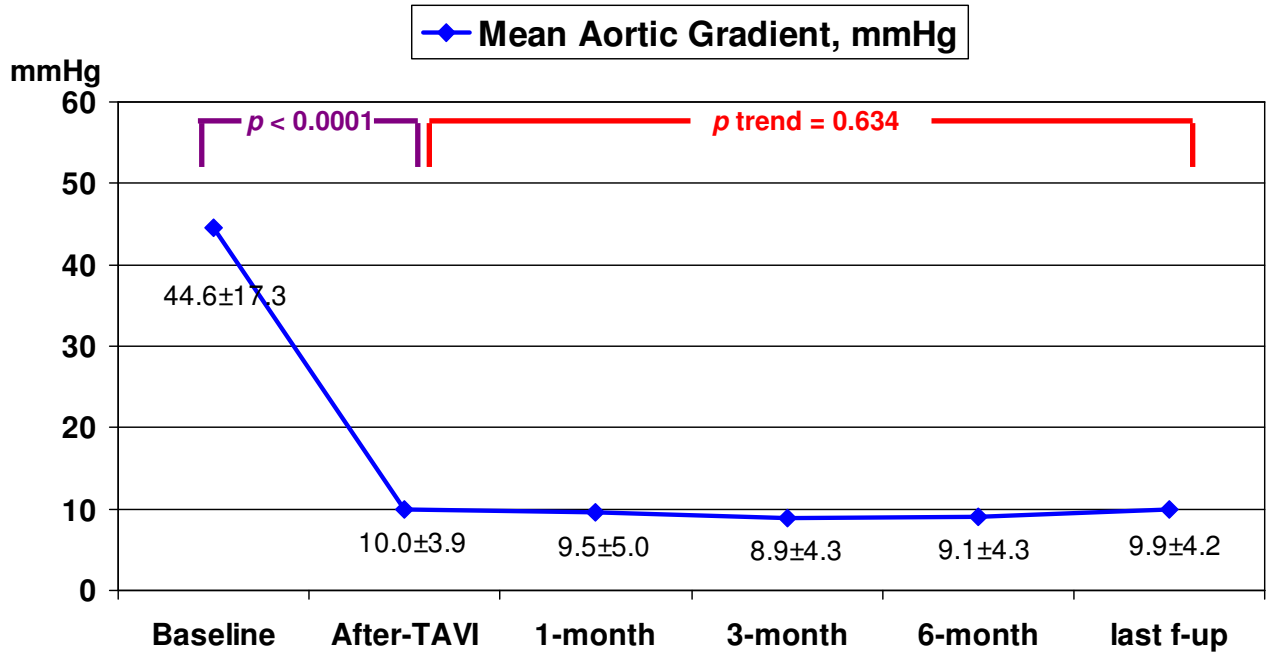
Panel A



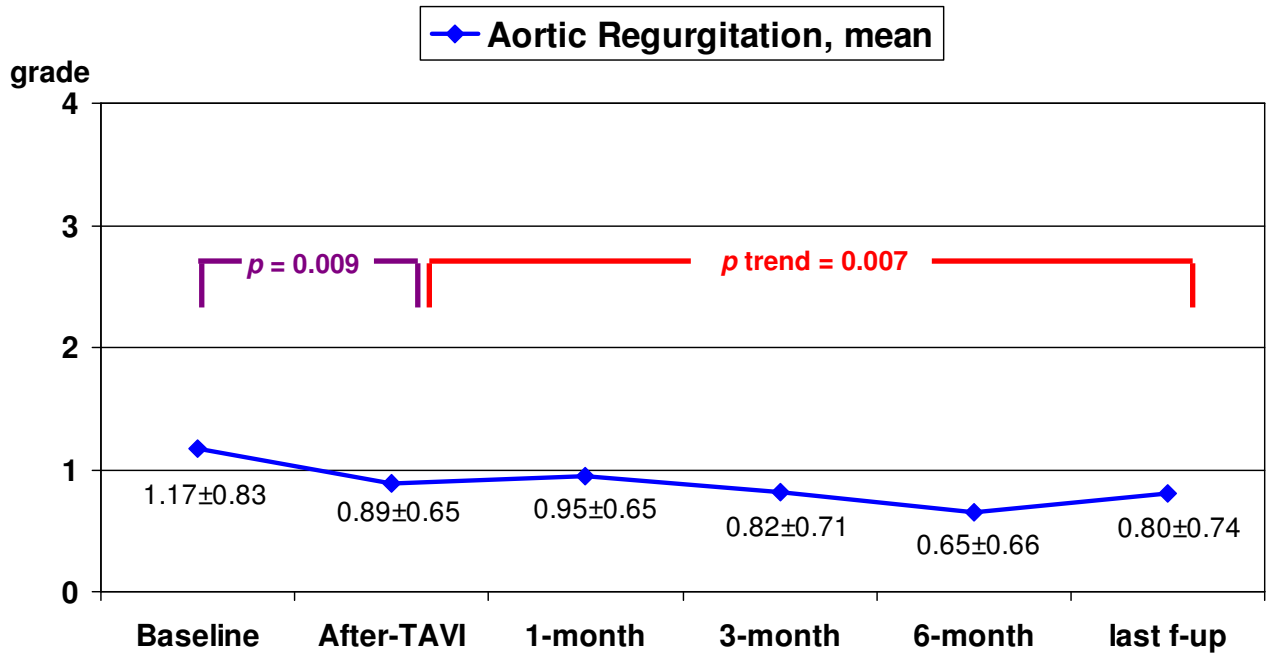
Panel B



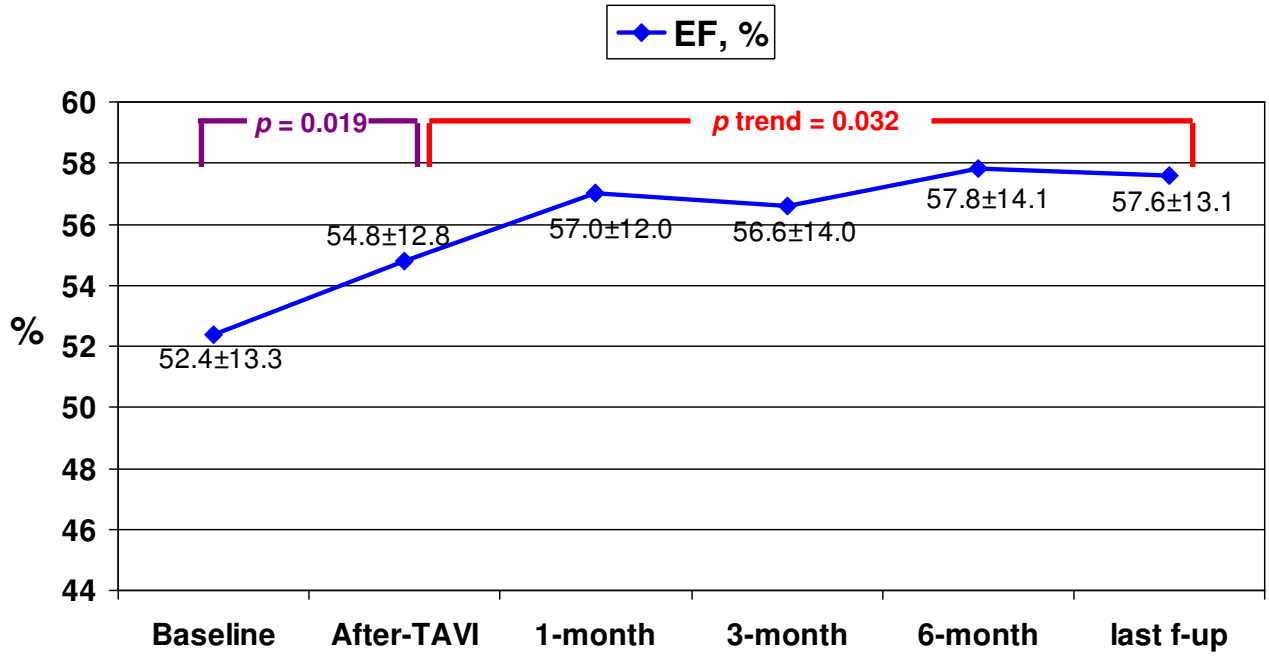
Panel C



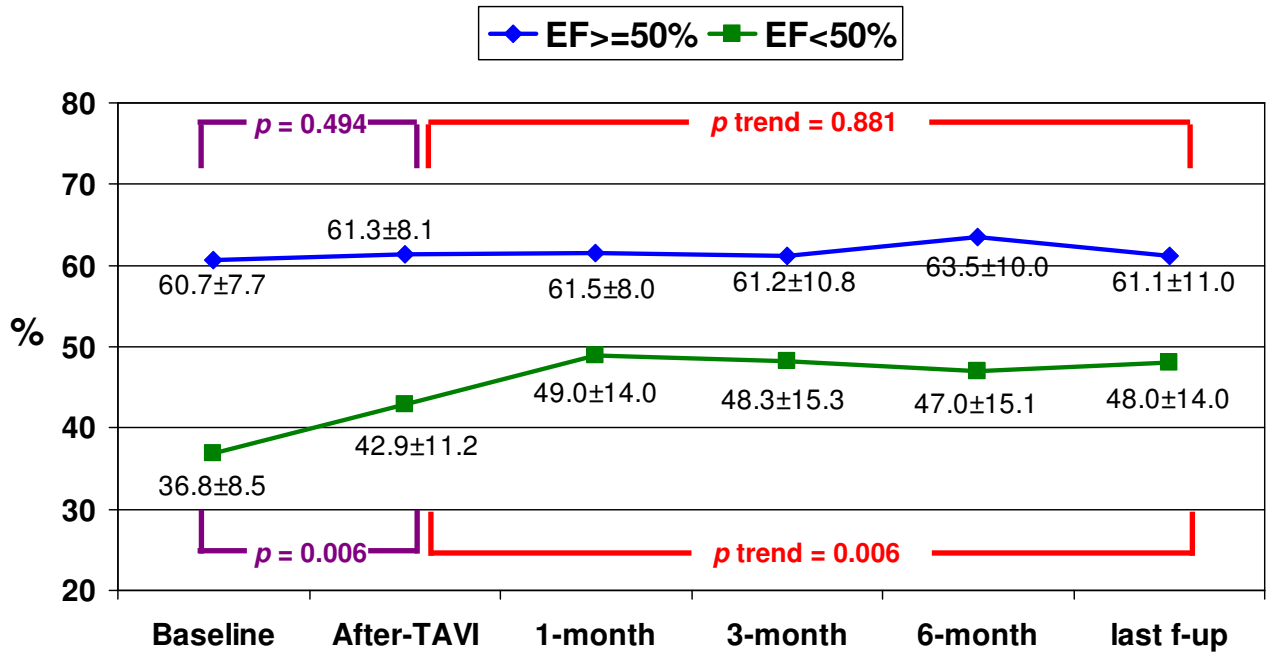
Panel D



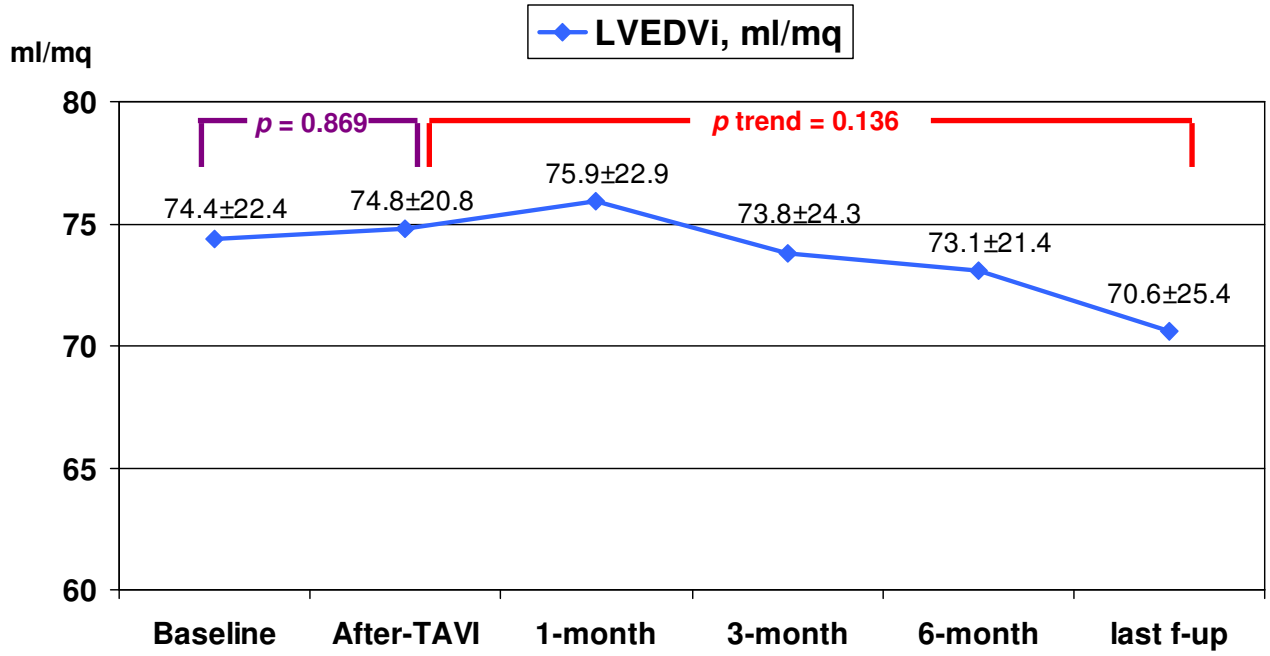
Panel E



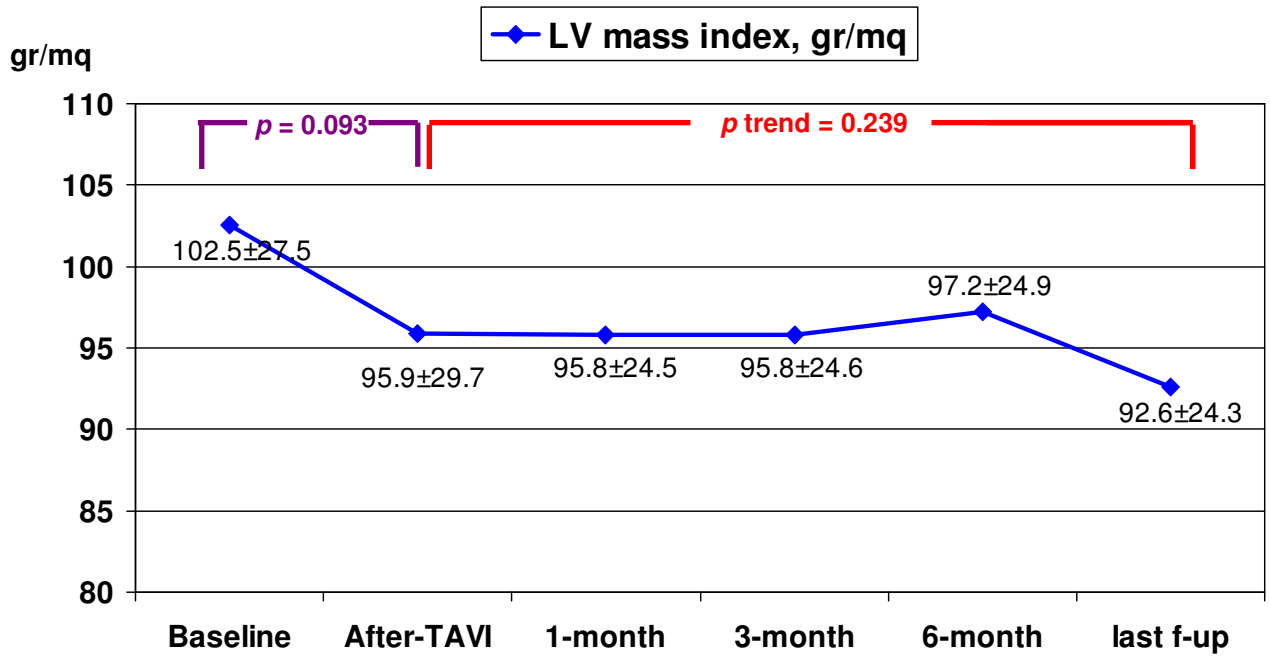
Panel F



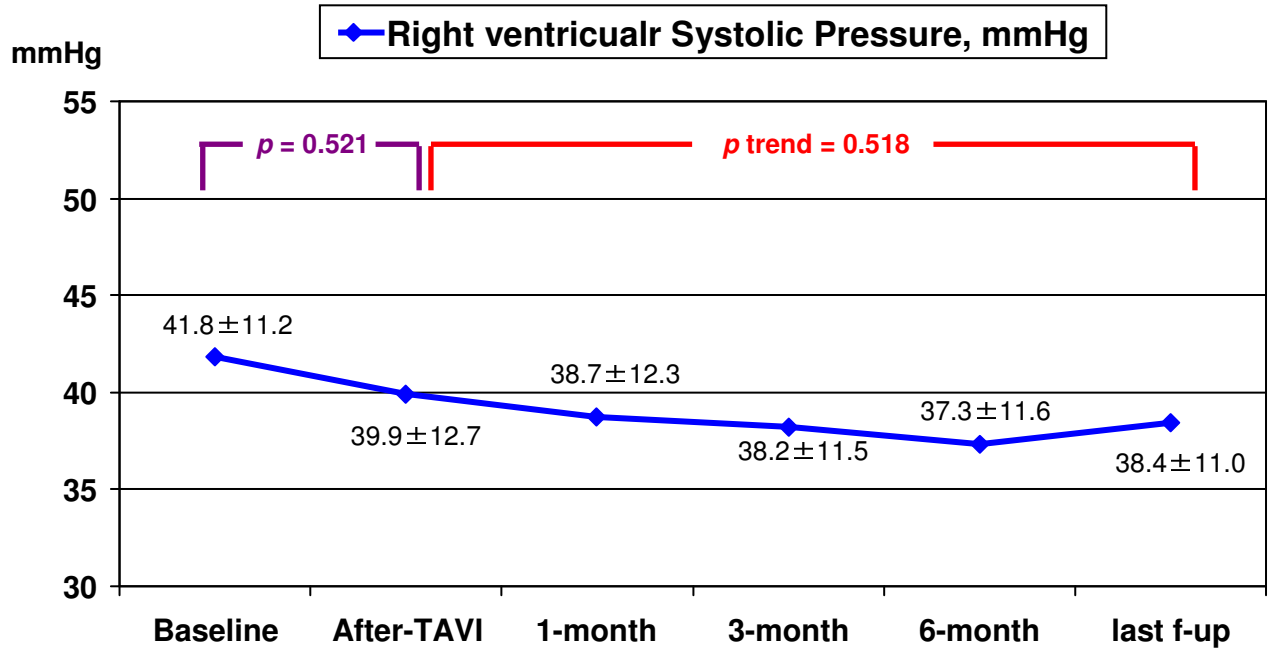
Panel G



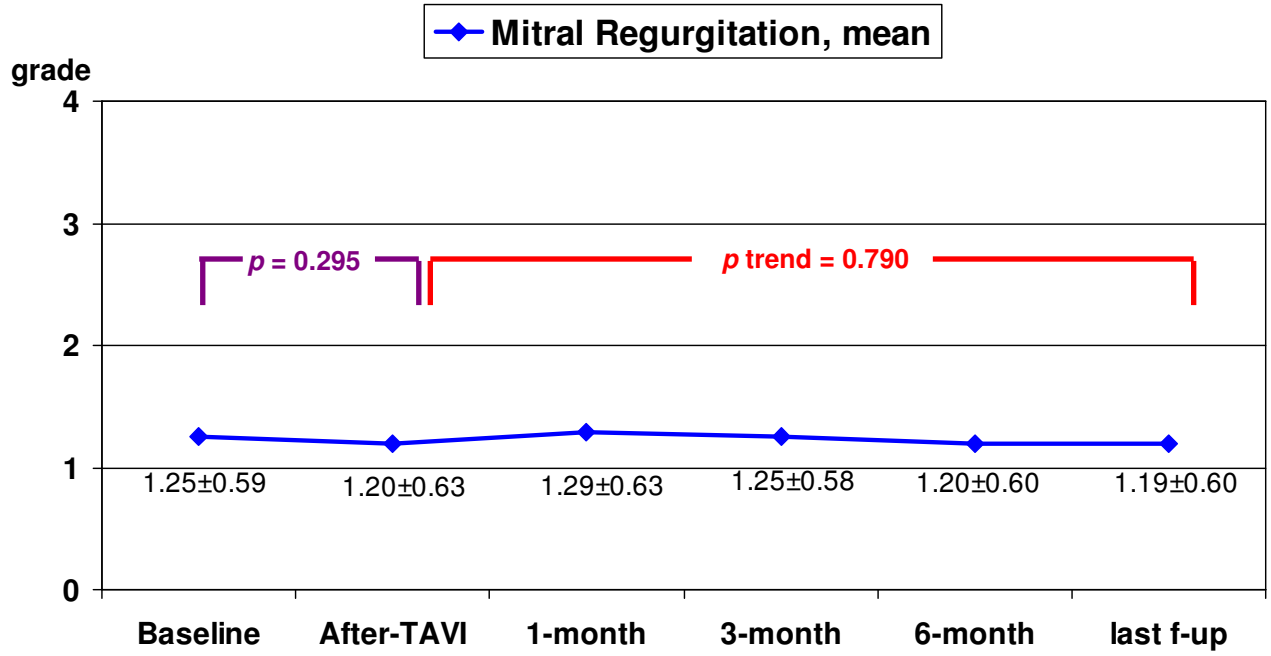
Panel H



Panel I



Panel J

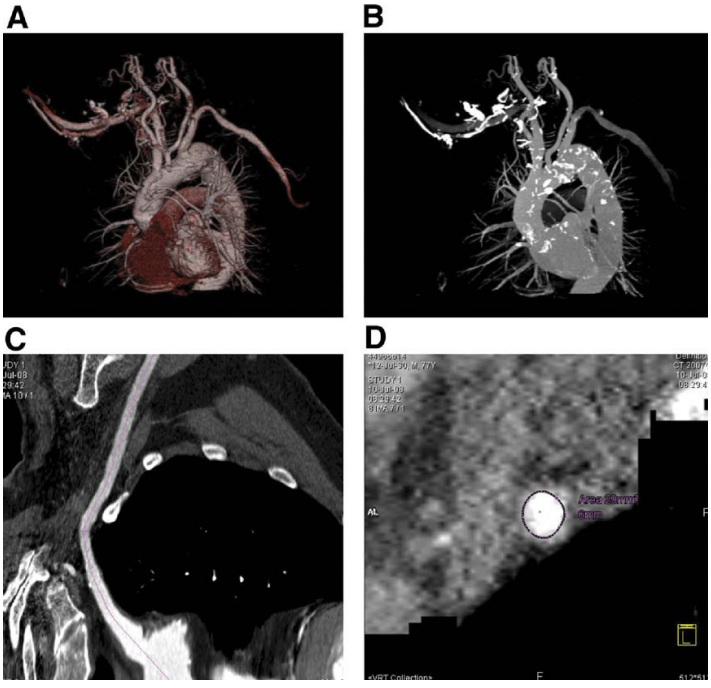


5.4 Expanding the eligibility for transcatheter aortic valve implantation: the trans-subclavian retrograde approach using the III generation CoreValve Revalving System (J Am Coll Cardiol Intv 2009;2:828–33)

In this publication we explore the safety and feasibility of the transubclavian approach for the self expandable prosthesis implantation in high-risk selected patients with AS and severe peripheral vasculopathy. This approach allows to expand the eligibility to TAVI including also patients not eligible to TF approach.

Between May 2007 and December 2008, 5 patients at high risk for conventional surgery were excluded also from TF approach because their iliac-femoral arteries were unsuitable for large sheath insertion (severe arteriopathy, small size, excessive tortuosity, or calcification). Thus they underwent computed tomographic scan of the aorta and supra-aortic vessels in order to assess the size, course, and calcification of the left subclavian artery, as well as aortic arch and ascending aorta anatomy (Figures 13A to 13D).

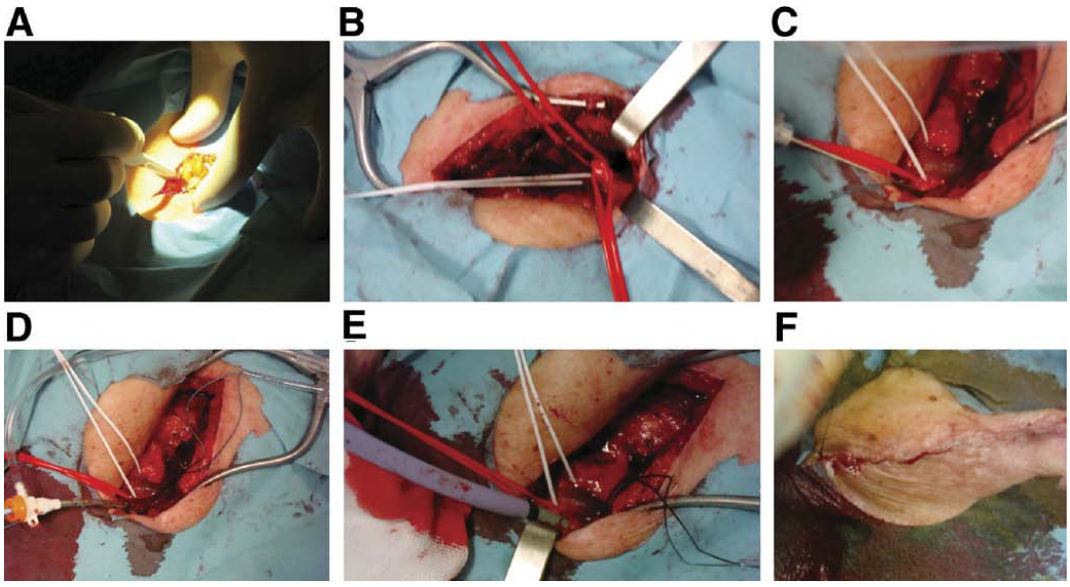
Figure 13. Computed Tomographic Angiography of Left Subclavian Artery. *Computed tomographic angiography performed in order to detect size, course, and calcification of left subclavian artery, aortic arch, and ascending aorta (From Fraccaro et al. J Am Coll Cardiol Intv 2009;2:828–33).*



One of them was excluded from treatment because of severe calcifications and tortuosity of the subclavian artery; another one because of diffuse narrowing of the subclavian artery with a minimal lumen diameter less than 6 mm. By general agreement, 3 of these patients, with a linear course of left subclavian artery and a minimal luminal diameter ≥6 mm, were scheduled for transcatheter implantation of CoreValve by transubclavian retrograde approach. Patients and their relatives consented to the attempted implantation. Logistic Euro-SCORE[51] was calculated using the web-based system.

The transubclavian technique is described in methods section. Briefly, cardiac surgeons performed a surgical cut-down to isolate the left subclavian artery just below the subclavian bone (Figures 14 A and B).

Figure 14. Technical Steps of Left Subclavian Approach. *After incision of cutaneous and subcutaneous tissues **(A)**, a surgical cut-down of left subclavian artery is performed **(B)**. Then the artery is punctured **(C)** and a 7-F sheath is introduced **(D)**. After performing ascending aorta angiogram, crossing the aortic valve and detecting transvalvular gradient, the previously placed sheath is then exchanged for the larger 18-F long sheath **(E)**. After revalving therapy, the subclavian artery is restored by direct suture. Finally, subcutaneous and cutaneous tissues were sutured **(F)** (From Fraccaro et al. J Am Coll Cardiol Intv 2009;2:828–33).*

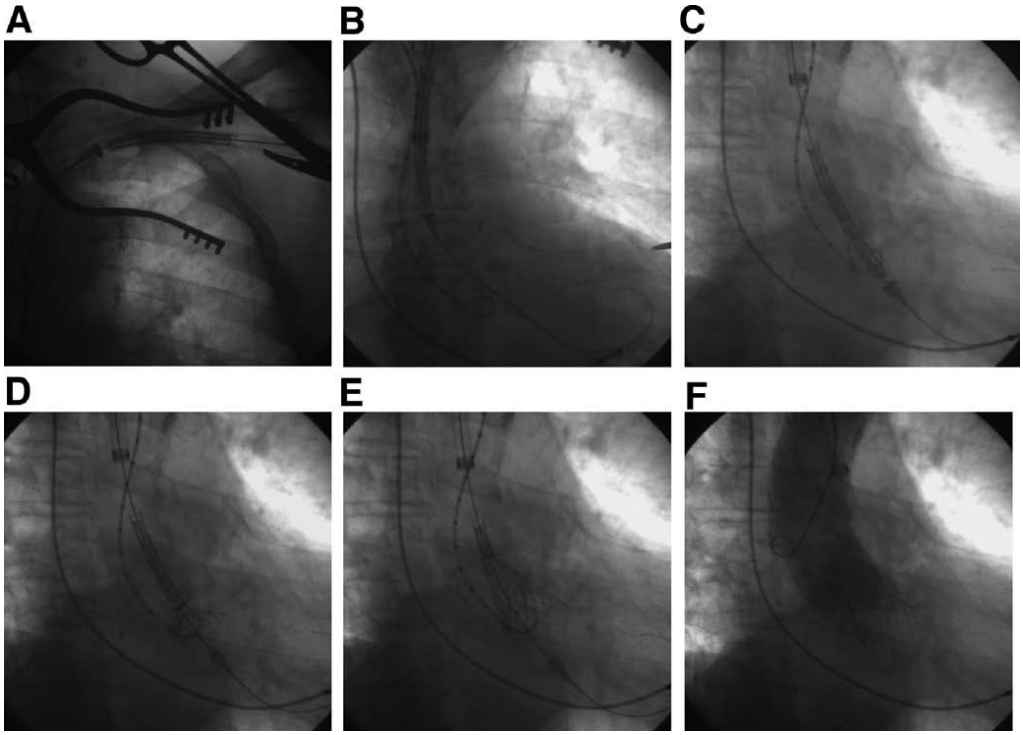


A 7-F sheath was then introduced into the subclavian artery (Figures. 14 C and D) and, using a left Amplatz catheter, a straight 0.035-inch guidewire was advanced across the stenotic aortic valve.

The direct transvalvular aortic gradient was measured. Then, a super-stiff 260-cm long wire (Amplatz Cook, Inc., Bloomington, Indiana) was introduced into the LV, the Amplatz catheter removed, and the 7-F sheath replaced for an 18-F 30-cm long sheath (William Cook Europe, Bjaeverskov, Denmark) advanced into the ascending aorta (Figure 14 E).

At this time, balloon aortic valvuloplasty was performed using a dedicated balloon (Numed Canada Inc., Cornwall, Ontario, Canada) during rapid pacing. The CoreValve Revalving System device was then carefully introduced and retrogradely advanced under fluoroscopic guidance over the stiff wire in the ascending aorta across the aortic valvular plane (Figures 15A to C). After a careful check of valve positioning by angiography, the valve was progressively deployed (Figures 15D and E) and the delivery system retrieved. Immediately after TAVI, angiography of the ascending aorta was performed 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 (Figure 15F).

Figure 15. Aortic Revalving Therapy. *The CoreValve Revalving System device was carefully introduced by the sheath and advanced throughout the aorta into the aortic root* ***(A to C)****. After careful checking by angiography, the valve was released* ***(D to E)****. Post-revalving ascending aorta angiogram demonstrates the correct positioning of the device, without peri-prosthesis regurgitation and with patency of coronary ostia* ***(F)*** *(From Fraccaro et al. J Am Coll Cardiol Intv 2009;2:828–33).*



Transprosthesis pressure gradient was assessed by contemporary pressure trace recording in the ascending aorta and LV. Heparin was administered to maintain an activated clotting time of >250 s throughout the procedure. Patients were pre-medicated with aspirin, clopidogrel, and vancomycin or teicoplanin. After the procedure, the heparin was neutralized by protamine, and the subclavian artery was restored by direct suture. Thereafter, the subcutaneous and cutaneous tissues were also sutured (Figure 14 F). After the procedure, a dual antiplatelet regimen of aspirin 100 mg and clopidogrel 75 mg daily for 6 months, after which 100 mg of aspirin daily was prescribed indefinitely.

Patient characteristics. The first patient was an 89-year-old symptomatic (NYHA functional class II) man with severe AS and LV dysfunction. He was affected by arterial hypertension, chronic obstructive pulmonary disease, and CKD. Logistic Euro- Score was 53.84%; standard EuroScore was 14. He was judged at high surgical risk because of a porcelain aorta. He was also affected by peripheral arteriopathy with multiple severe and calcific stenosis of iliac-femoral arteries, not suitable for large femoral sheath placement.

The second patient was an 83-year-old man affected by severe symptomatic NYHA functional class III AS. He was affected by dyslipidemia, diabetes mellitus, chronic obstructive pulmonary disease, and mild CKD (logistic EuroScore 25.24%; standard EuroScore 11). He had had previous cardiac surgery with 3 CABGs, all patent (left internal mammary on left anterior descending artery, venous jump graft on first diagonal branch, and obtuse marginal branch). He had had subsequent percutaneous coronary revascularization due to reinfarction. Thus, the patient was refused by surgeons because of high surgical risk due to previous cardiac reintervention and comorbidities; he was not eligible for percutaneous aortic replacement by femoral approach because of severe calcification and tortuosity of iliacfemoral arteries. The third patient was a 78-year-old man with severe AS and LV dysfunction (low gradient–low flow AS). Comorbidities included hypertension,

severe chronic obstructive pulmonary disease, and renal failure. He had had CABG surgery 19 years before with venous grafts on the left anterior descending artery and the left circumflex artery, respectively. Four months before TAVI, he suffered from non–ST-segment elevation myocardial infarction: a coronary angiogram showed patency of venous grafts for the left anterior descending artery, chronic total occlusion of the right coronary artery with collateral circulation, occlusion of saphenous vein graft for the left circumflex artery, and severe stenosis of the obtuse marginal branch. The patient was denied surgery because of porcelain aorta and clinical conditions (logistic EuroScore 41.48%; standard EuroScore 13). At that time he underwent stenting of the obtuse marginal branch, and was scheduled for TAVI. The TF approach was not suitable for multiple stenosis of iliac-femoral arteries.

Procedural results. The mean duration of the procedure was 96 ± 40 min (range 67 to 142 min), with a mean fluoroscopy time of 31 ± 4 min and a mean contrast medium amount of 214 ± 129 ml. Implantation success and procedural success were obtained in all 3 cases, leading to a significant reduction in transvalvular gradient without significant para-prosthetic leak. In 1 case, the good performance of bioprosthesis was gained after post-deployment dilation performed to improve prosthesis strut expansion and, as a consequence, to reduce para-prosthetic leak. All 3 patients were extubated within the first 2 h after the end of procedure. At 30 days from the procedure, no major adverse cardiac and cerebrovascular event, no need for blood transfusion, infections, or contrast-induced nephropathy occurred. The second and third patients developed complete atrioventricular block, 3 and 2 days after implantation, respectively, requiring PPM implantation. In both cases, the implantation was planned and performed via right subclavian vein. Hospital stays were 6 days for the first patient who did not need PPM implantation, and 13 and 11 days for the other 2 patients, respectively. Patients #1 and #3 were discharged with double antiplatelet therapy, while Patient #2 was scheduled to warfarin plus clopidogrel therapy because of a pre-existing permanent atrial

fibrillation. All patients were discharged in asymptomatic status with good prosthesis function as assessed by echocardiograph examination.

Follow-up data. At 1 and 3 months follow-up, all patients were alive and experienced remarkable improvement in functional class. Two patients improved to NYHA functional class I; 1 patient improved to NYHA class II (limited by severe lung disease). They have returned to a normal life, limited only by their previous medical conditions. No adverse events occurred. A good prosthesis performance persisted at 3-month follow-up in all patients.

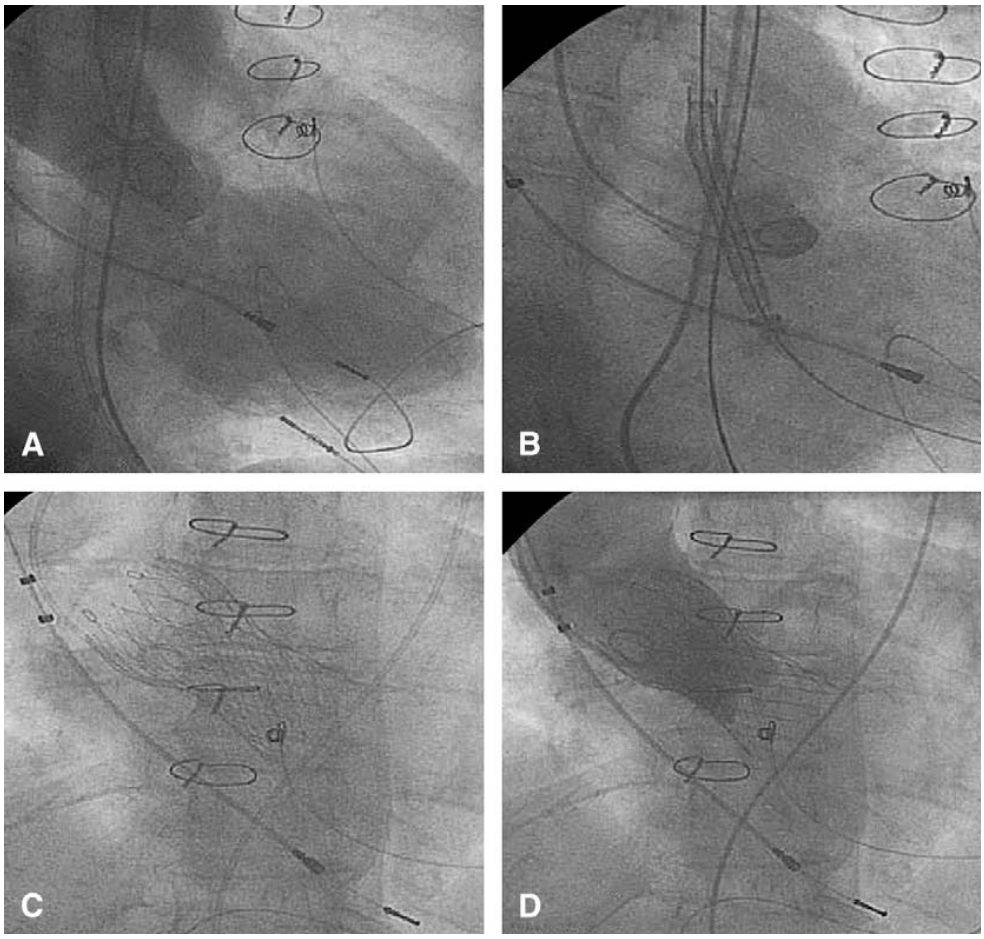
5.5 How to expand the clinical indications to TAVI: the treatment of surgical bioprosthesis dysfunction by valve-in-valve technique using a transcatheter aortic valve. (*Totally percutaneous valve replacement for severe aortic regurgitation in a degenerating bioprosthesis*, J Thorac Cardiovasc Surg. 2009;138:1027-8).

One very promising application of TAVI is the treatment of surgical bioprosthesis dysfunction. We report the case of a patient with severe aortic valve regurgitation owing to bioprosthesis dysfunction who was successfully treated by implantation of a CoreValve (CoreValve Inc, Irvine. Calif) prosthesis with a totally percutaneous approach using the valve-in-valve technique.

Clinical summary. An 84-year-old woman, with previous surgical AVR with a bioprosthesis (Biocor 25 mm stentless; (Biocor Industria e Pesguisa Ltda, Belo Horizonte, Brazil) and cardiac pacemaker implantation for severe AS in 1998, was admitted to a community hospital because of pulmonary edema. Comorbidity included hypertension, chronic renal failure, and previous left hemicolectomy for bowel malignancy. Transthoracic echocardiogram revealed a severe transprosthetic aortic regurgitation caused by leaflet degeneration and prolapse; the left ventricle was enlarged with moderate impairment of systolic function. Despite medical treatment, clinical status rapidly worsened. The case was discussed with two different surgical teams, who deemed the patient at high risk for redoing AVR because of advanced age, the risks of the redo procedure, and comorbidities: the logistic EuroScore was 31.8%. Thus, the patient was transferred to our department to evaluate the feasibility of TAVI. Cardiac catheterization and angiography confirmed the severity of aortic regurgitation with LV dysfunction, increased ventricular filling pressure, pulmonary hypertension, and decreased cardiac index. The computed tomographic scan of the aorta and iliac and femoral arteries showed a moderate degree of wall calcification in the ascending aorta, with aortic root and annular dimensions amenable for TAVI; the femoral and iliac arteries showed a calibre suitable for large sheath insertion. The procedure was performed with the patient under mild sedation and local anaesthesia by a percutaneous retrograde approach. Over an 18F sheath percutaneously inserted in the right femoral artery, the valve (29 mm, third-generation CoreValve

Revalving system) was introduced and retrogradely advanced under fluoroscopic guidance over a stiff wire in the ascending aorta across the pre-existing prosthesis plane. After careful evaluation of prosthesis position by angiography, the prosthesis was progressively deployed and the delivery system retrieved. Aortic angiogram after deployment showed the correct positioning of the prosthesis with a trivial paravalvular leak (Figure 16); no transvalvular gradient was detected.

Figure 16. *Aortic angiogram before (A) prosthesis implantation showing large aortic regurgitation; prosthesis positioning (B) and full deployment (C); aortic angiogram after prosthesis implantation showing no further aortic regurgitation (D) (From Napodano, Fraccaro et al. J Thorac Cardiovasc Surg. 2009;138:1027-8).*



Finally, the 18F sheath was removed and haemostasis of the right femoral artery was successfully obtained by knotting the sutures of a prepositioned suture-based closure device (Prostar XL 10F; Abbott Vascular, Alameda, Calif). The in-hospital course was uneventful and the patient was discharged at home on day 6 after the procedure. Dual antiplateled treatment was prescribed for 6 months. At 6 months' follow-up, the patient remained free of adverse events, with persistent NYHA

functional class I; a transthoracic echocardiogram confirmed good performance of the implanted prosthesis with neither aortic regurgitation nor significant transprosthetic gradient.

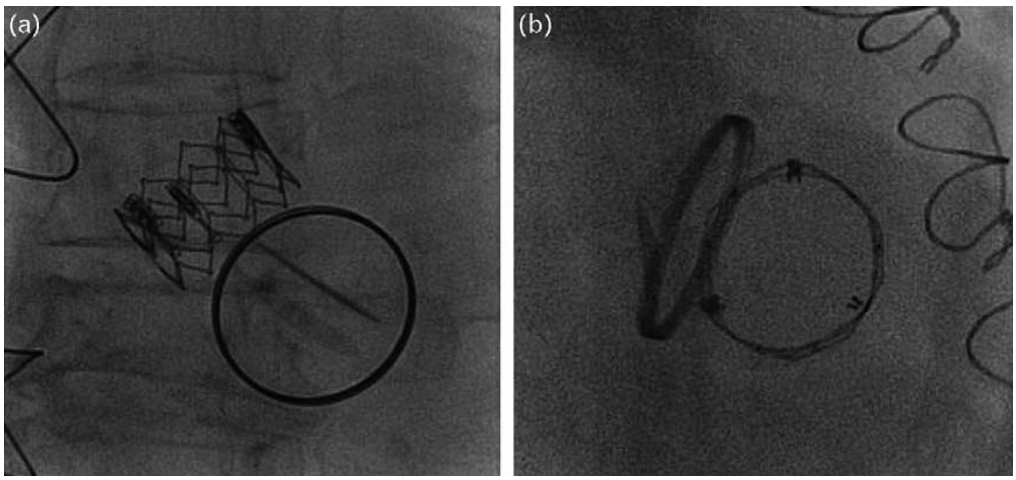
5.6 Safety and feasibility of TAVI in patients with prior mitral valve surgery with mechanical prosthesis (*Transfemoral aortic valve implantation of an Edwards Sapien XT valve in a patient with a mechanical mitral prosthesis*. J Cardiovasc Med (Hagerstown) 2011;12:669-70).

We report the case of a 78-year-old woman who was admitted to our institution because of congestive heart failure. Nine years before current admission, she underwent surgical replacement of the mitral valve (St Jude 29 mm mechanical prosthesis, St Jude Medical Inc., St Paul, Minnesota, USA) because of stenosis.

She had history of CKD, permanent atrial fibrillation and mild restrictive pulmonary disease. On admission, she presented a systolic murmur graded 4/6 irradiated to the neck associated with a diastolic murmur along the right sternal border. Atrial fibrillation was present at ECG. At two-dimensional transthoracic echocardiography, a severe AS (mean trans-aortic valve gradient of 35 mmHg, AVA 0.7 cm^2) along with severe aortic regurgitation was present. Mitral prosthesis had normal function. Haemodynamic examination confirmed the presence of severe AS and regurgitation and the good performance of the mitral prosthesis. Pulmonary artery SBP was 45 mmHg. Left ventricular function was normal (EF 64%) and the coronary arteries were clear. Logistic Euroscore was 17.05% and the STS score 5.10%. The patient was refused by the heart team for surgery and shifted to TF aortic valve implantation.

After multiparametric evaluation of aortic valve and femoral access, a 23-mm Edwards Sapien XT valve (Edwards Lifesciences, Irvine, California, USA) was chosen. The procedure was successfully performed with local anaesthesia and spontaneous breathing without any periprocedural complications. Both the prostheses had a good function (Fig. 17, panel A and B) with a prompt relief of the aortic gradient and regurgitation. The patient was discharged asymptomatic with warfarin along with aspirin at day 8 after the index procedure.

Figure 17. *(a) Left anterior oblique projection showing the anatomical relationship as well as the absence of interference between the two prostheses. (b) Right anterior oblique projection (orthogonal to the previous one) showing the circularity of the Edwards Sapien XT valve and the anatomical continuity of the two prostheses (From Fraccaro et al. J Cardiovasc Med 2011;12:669-70).*



5.7 Incidence, predictors, and outcome of conduction disorders after transcatheter self-expandable aortic valve implantation (Am J Cardiol 2011;107:747–754).

The aim of this analysis is to investigate the incidence and characteristics of CD (CDs) in patients undergoing TAVI and the need for subsequent PPM implantation. In addition, to help identify the clinical, anatomic, and procedural predictors of postoperative PPM implantation and the outcome of CDs over time. In particular, we sought to investigate whether the depth of deployment and other technical aspects of valve implantation might predict the need for PPM implantation after TAVI. Study population included 70 consecutive patients with aortic valve stenosis who underwent TAVI at our Department at Padova University from May 2007 to April 2009. A total of 6 patients were excluded from the analysis because they already had undergone PPM implantation before TAVI. All patients were a part of the multicenter, expanded evaluation registry after conformité européenne mark approval.[34] All procedures were performed using the third-generation self-expanding CoreValve Revalving System (Medtronic, Minneapolis, Minnesota), using a TF or transubclavian approach, according to the anatomy of the iliac and femoral arteries.[48]

For this specific analysis we scored the degree of aortic valve calcium according to the presence and extent of cusp calcification as it appeared on the aortic angiogram. The grading was as follows: grade 1, no calcification; grade 2, mild calcification appearing as a thin marginal rim in one or more cusps; grade 3, moderate calcification characterized by a thick rim occupying the entire surface of one or more cusps; and grade 4, severe calcification, defined as the presence of heavy calcification of all cusps or bulky calcification. The depth of bioprosthesis implantation was measured in the right anterior oblique projection as the distance (in millimeters) of the aortic prosthesis within the LV outflow tract, from the lower edge of the noncoronary cusp (D1) and from the lower edge of the left coronary cusp (D2) to the ventricular end of the prosthesis frame using quantitative angiographic digital techniques (Allura, Philips Medical System, Best, The Netherlands).[52] The difference between D2 and D1 was calculated as the coaxial index. Prosthesis implantation was defined as coaxial when the coaxial index ranged from -1.0 mm to +1.0 mm and noncoaxial when

the coaxial index was > +1.0 mm or < -1.0 mm. The ratio between the prosthesis nominal diameter and native annulus size was calculated as the prosthesis/annulus ratio. The ratio between the diameter of the deployed prosthesis measured at the level of the aortic annulus and the native aortic annulus was calculated as the prosthesis expansion index.

All patients underwent standard 12-lead electrocardiography before the procedure. To assess intraoperative CDs, 3-lead continuous electrocardiographic monitoring was recorded and electronically stored throughout the procedure. After the procedure, continuous monitoring was routinely performed in all patients during the hospital stay. Postoperatively, 12-lead electrocardiography was performed daily during hospitalization and at 1-, 3-, 6-, and 12-month follow-up visits thereafter to detect any modifications in the atrioventricular (AV) and intraventricular conduction.

The analyses of the records were performed by an experienced electrophysiologist. The presence of CDs at any time was defined by the presence of at least one of the following abnormalities: first-, second-, or third-degree atrioventricular (AV) block, left bundle branch block (BBB), right BBB, and/or left anterior or posterior hemiblock. The currently accepted criteria were used to code for each of these CD.[53, 54] The requirement for PPM implantation was determined by the attending cardiologist according to the standardized criteria from the American College of Cardiology/American Heart Association/Heart Rhythm Society 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities.[55] All systems were implanted using a transvenous subclavian approach.

Clinical and echocardiographic follow-up were collected at 1, 3, 6, and 12 months and yearly thereafter. Moreover, at each temporal step, a 12-lead electrocardiogram was collected in all patients, to record modifications in AV and intraventricular conduction. In patients with a PPM, the percentage of ventricular pacing was detected by PPM interrogation. Moreover, to evaluate the PPM dependency in patients with a paced baseline electrocardiogram, the pacemaker was programmed to VVI at the lowest rate possible and the underlying rhythm was obtained.

The patients were considered pacemaker dependent if they continued to be paced or had complete AV block or atrial fibrillation with inadequate ventricular response. The patients were considered as nonpacemaker dependent if they had sinus rhythm or atrial fibrillation with an adequate ventricular response.

The preoperative clinical variables, anatomic characteristics, and procedural data thought likely to influence the conducting system were tested by univariate logistic regression analysis to determine the predictors of postoperative PPM implantation. This model included all the variables with a biologically relevant correlation to the onset of CD: age, gender, anatomic characteristics (e.g., AVA, calcium score, aortic regurgitation, LV mass index), effects of drugs (type of anesthesia), technical aspects that might mechanically effect the conduction system (e.g., valvuloplasty balloon diameter, prosthesis size, prosthesis/annulus diameter ratio, need for postdilation, depth of implantation, prosthesis expansion index, and valve-in-valve), all pre-existing CDs (AV block I, left BBB, anterior hemi block, posterior hemiblock, right BBB, bifascicular block). Multiple stepwise logistic regression analyses of those significant variables ($p < 0.10$) on univariate analysis were performed to identify independent predictors of PPM implantation. Univariate and multivariate analyses were also performed considering the same variables to identify predictors of worsening in CDs.

Results

The baseline characteristics were similar between those patients who required PPM implantation and those who did not (Table 20).

Table 20. Baseline characteristics *(From Fraccaro et al. Am J Cardiol 2011;107:747–754).*

Variable	Total (n=64)	PPM after TAVI (n=25)	No PPM after TAVI (n=39)	*p*
Age, mean±SD	80.97±6.55 (range 55–91)	81.56±5.10	80.59±7.37	0.567
Men	29 (45%)	15 (60%)	14 (36%)	0.058
Logistic EuroSCORE, mean±SD	23.64±14.72 (range 3–71)	25.47±15.70	22.66±14.00	0.464
NYHA I/II	9/19 (14%/30%)	2/8 (8%/32%)	7/11 (18%/28%)	0.719
III/IV	32/4 (50%/6%)	13/2 (52%/8%)	19/2 (49%/5%)	
Canadian Cardiovascular				0.629
Society Angina 0/1/2	39/2/6 (61%/3%/9%)	17/1/3 (68%/4%/12%)	22/1/3 (56%/3%/8%)	
3/4	10/7 (16%/11%)	2/2 (8%/8%)	8/5 (21%/13%)	
Calcium score				0.595
≤2	17 (27%)	8 (32%)	9 (23%)	
3	30 (47%)	10 (40%)	20 (51%)	
4	17 (27%)	17 (28%)	10 (26%)	
Coronary artery disease	40 (63%)	17 (71%)	23 (61%)	0.586
Congestive heart failure	30 (47%)	13 (52%)	17 (44%)	0.511
Cerebral vascular accident	7 (11%)	2 (8%)	5 (13%)	0.547
CKD	35 (55%)	17 (68%)	18 (46%)	0.087
Chronic obstructive pulmonary disease	14 (22%)	7 (29%)	7 (18%)	0.298
Peripheral vascular disease	22 (34.4)	8 (32.0)	14 (35.9)	0.749
Previous cardiac surgery	16 (25.0)	9 (36)	7 (17.9)	0.104
Neurological dysfunction	10 (15.6)	3 (12)	7 (17.9)	0.523
Liver cirrhosis	5 (7.8)	1 (4)	4 (10.3)	0.363
Porcelain aorta*	15 (23.4)	3 (12)	12 (30.8)	0.084
Hostile thorax**	9 (14.1)	3 (12.0)	6 (15.4)	0.704
AVA, (cm^2)	0.78±0.21	0.80±0.20	0.77±0.22	0.544
EF (%), mean±SD	52.32±13.24	51.68±12.95	52.74±13.58	0.759

Implantation success was achieved in 62 (97%) of the 64 patients, with procedural success in 61 (95%) of 64. The procedural data were similar between those who required PPM implantation and those who did not, except for the depth of prosthesis implantation measured from the lower edge of the noncoronary cusp (D1), which was significantly deeper (i.e., more ventricular) in the patients who underwent PPM implantation than in those who did not. Also, the hospital stay was longer in patients who underwent PPM implantation (Table 21).

Table 21. Procedural data *(From Fraccaro et al. Am J Cardiol 2011;107:747–754).*

Variable	Total (n=64)	PPM after TAVI (n=25)	No PPM after TAVI (n=39)	*P*
Procedural success	61 (95%)	23 (92%)	38 (97%)	0.315
General anaesthesia	15 (23%)	8 (33%)	7 (18%)	0.360
Double-lumen intubation	8 (13%)	3 (12%)	5 (13%)	0.419
Trans-esophageal echocardiography	13 (20%)	6 (27%)	7 (21%)	0.604
Access				0.128
TF	60 (94%)	22 (88%)	38 (97%)	
Transubclavian	4 (6%)	3 (12%)	1 (3%)	
Prosthesis size (mm)				0.287
26	36 (56%)	12(48%)	24 (62%)	
29	28 (44%)	13 (52%)	15 (39%)	
Pre-dilatation	62 (97%)	24 (96%)	38 (97%)	0.747
Post-dilatation	19 (30%)	6 (24%)	13 (33%)	0.425
Valve-in-valve	5 (8%)	3 (12%)	2 (5%)	0.318
Prosthesis/annulus diameter ratio	1.21±8.89	1.20±1.05	1.21±7.80	0.561
Depth of implantation (mm), mean ± SD				
D1	10.25±3.39	11.34±3.62	9.50±3.04	*0.031*
D2	11.41±3.27	12.16±3.25	10.89±3.23	0.108
Coaxial index (mm), mean ± SD	1.15±1.59	0.81±1.47	1.39±1.64	0.155
Non-Coaxial Alignment	44 (69%)	15 (58%)	29 (76%)	0.114
Prosthesis expansion index, mean ± SD	0.93±0.11	0.93±0.11	0.93±0.12	0.727
Procedural duration (minutes), mean ± SD	72.7±37.6	72.52±28.33	72.74±42.79	0.982
Hospital stay (days), mean ± SD	12.34±8.37	15.27±11.06	10.24±5.24	*0.022*

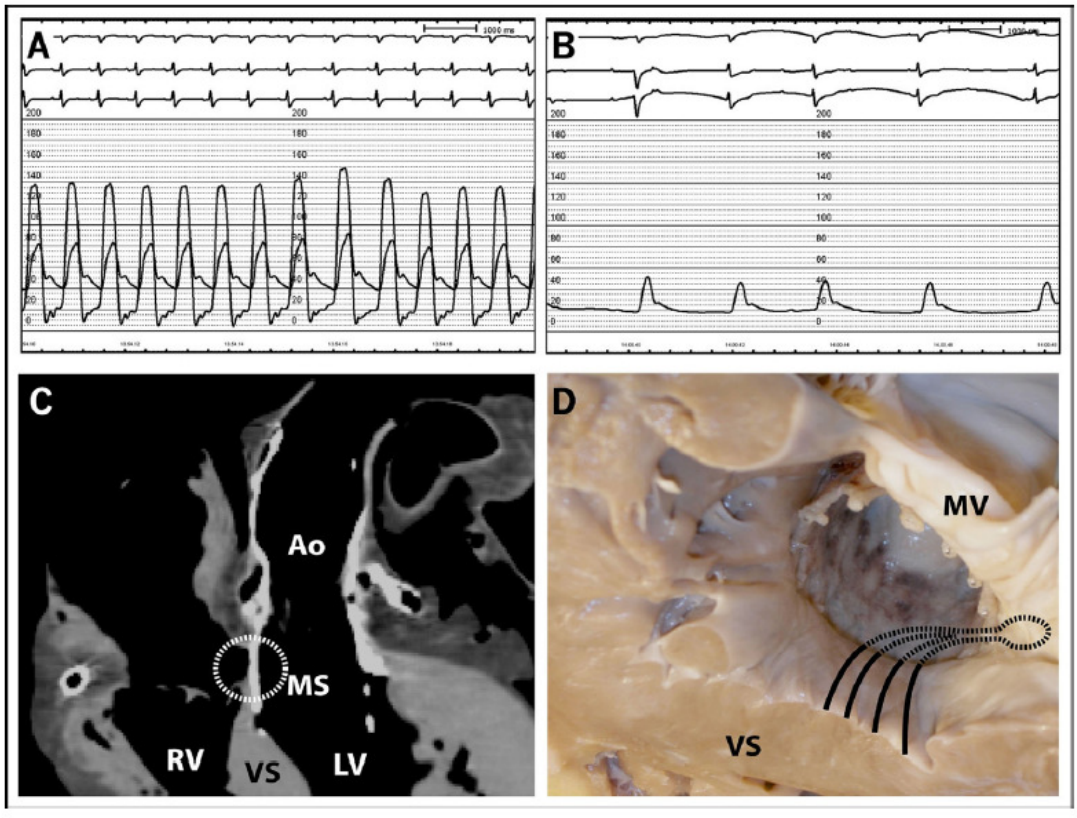
Of the 64 patients, 32 (50%) had one or more degrees of AV-intraventricular CDs before TAVI, including first degree AV block (n =15), complete left BBB (n =9), right BBB (n =8), anterior hemiblock (n =11), and posterior hemiblock (n =2; Table 22). After TAVI, worsening or new-onset CD appeared in most patients (77%). Left BBB was the most frequent new CD, appearing in 28 patients (44%), isolated or associated to new first-degree AV block (Table 22).

Table 22. Changes in conduction parameters over time *(From Fraccaro et al. Am J Cardiol 2011;107:747–754).*

Variable	Pre-TAVI	Post-TAVI	Last follow-up (6.0±4.2 mo)	*p* value		
				pre-TAVI *vs.* post-TAVI	post-TAVI *vs.* last follow-up	pre-TAVI *vs* last follow-up
Atrial fibrillation	10/64 (16%)	11/64 (17%)	10/57* (18%)	0.705	0.655	0.655
Left BBB	9/64 (14%)	37/64 (58%)	25/57* (44%)	*<0.0001*	0.108	*<0.0001*
Right BBB	8/64 (13%)	3/64 (5%)	2/57* (4%)	0.059	0.317	*0.046*
Anterior hemiblock	11/64 (17%)	3/64 (5%)	4/57* (7%)	*0.005*	0.317	*0.034*
Posterior hemiblock	2/64 (3%)	2/64 (3%)	1/57* (2%)	1.000	0.317	1.000
PR interval (msec), mean ± SD	182.9±5.7	211.1±5.5	182.7±29.9	*<0.0001*	*<0.0001*	0.761
QRS width (msec), mean ± SD	103.6±4.1	144.3±3.6	125.3±26.3	*<0.0001*	*<0.0001*	*<0.0001*
QT (msec), mean ± SD	406.2±45.7	424.4±47.7	411.5±30.0	*0.028*	*0.039*	0.486

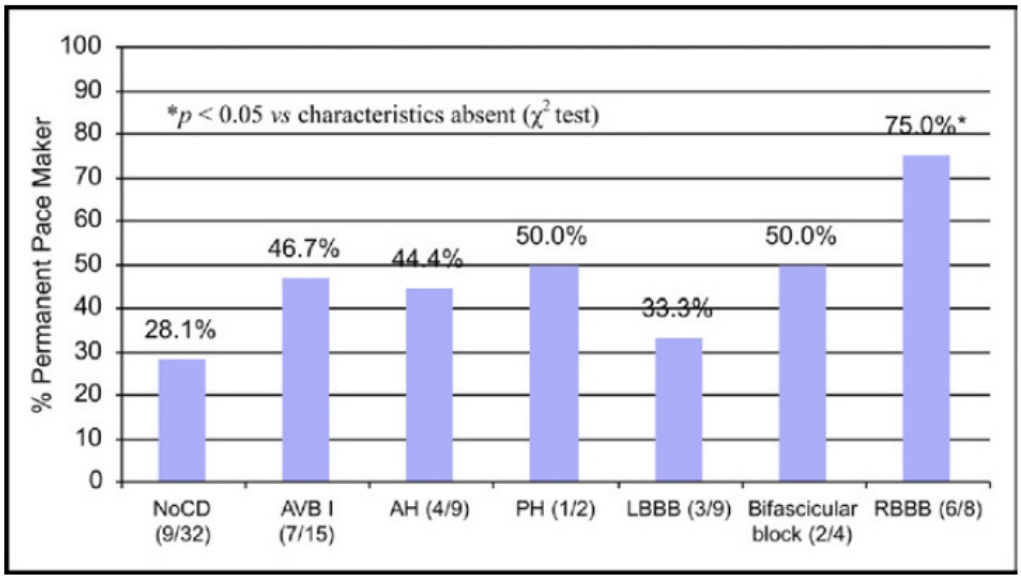
A complete AV block appeared in 19 patients (Figure 18). During the hospitalization, 25 patients (39%) underwent PPM implantation. The indications for PPM implantation were permanent or transient complete AV block in 16, second-degree AV block associated with left BBB in 6, sick sinus syndrome in 1, and trifascicular block in 1 patient. Indeed, 1 patient who did not have any CD before TAVI underwent PPM implantation because of the development of first-degree AV block associated with new left BBB after TAVI, with progressive prolongation of PR and QRS intervals during hospital stay.

Figure 18. *Views of 85-year old woman who had developed complete AV block requiring PPM implantation after TAVI and died 13 days after the procedure. (A) Electrocardiogram showing right BBB and 60 mm Hg transaortic gradient at baseline. (B) Electrocardiogram showing complete AV block immediately after TAVI. (C) CT scan of heart explanted at autopsy. Note, deep positioning of CoreValve within LV outflow tract, overlapping membranous septum (dotted circle) and crest of interventricular septum. (D) Gross anatomic view of LV outflow seen from below. Note, expansion of prosthesis frames in subaortic region compressing ventricular septum and overlapping proximal branching of left bundle branch (dotted lines). Ao, aorta; LV, left ventricle; MS, membranous septum; MV, mitral valve; RV, right ventricle; VS, ventricular septum (From Fraccaro et al. Am J Cardiol 2011;107:747–754).*



Of the 25 patients requiring PPM implantation, 9 had no AV or intraventricular CD before TAVI, and 16 patients showed at least one CD (Figure 19).

Figure 19. *Incidence of PPM implantation according to baseline CD. Right BBB was the only baseline CD significantly related to PPM implantation (From Fraccaro et al. Am J Cardiol 2011;107:747–754).*



On univariate analysis, male gender, right BBB at baseline, and the depth of prosthesis implantation resulted in a greater prevalence of PPM implantation after TAVI (Table 23). After adjustment by multivariate analysis for the baseline clinical, anatomic, and operative characteristics, right BBB at baseline, and the depth of prosthesis implantation remained the only independent predictors of PPM implantation (Table 23). After TAVI, 6 (75%) of 8 patients with right BBB at baseline required PPM implantation versus 19 (34%) of 56 patients, who had not had right BBB before TAVI (*p =0.026*). Right BBB was the only baseline CD that significantly affected the occurrence of PPM implantation after TAVI (Figure 19 and Table 23).

Table 23. Predictors of PPM implantation after TAVI *(From Fraccaro et al. Am J Cardiol 2011;107:747–754).*

Variable	Univariable Analysis			Multivariable Analysis		
	OR	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Age	0.992	0.919-1.070	0.828	-	-	Ns
Male sex	3.077	1.092-8.671	*0.033*	1.182	0.982-1.423	0.127
AVA	2.530	0.226-28.313	0.451	-	-	Ns
Calcium score	0.836	0.433-1.615	0.594	-	-	Ns
Aortic regurgitation	0.773	0.431-1.387	0.388	-	-	Ns
LV mass index	0.992	0.968-1.016	0.507	-	-	Ns
Type of anaesthesia	1.265	0.495-3.230	0.624	-	-	Ns
Valvuloplasty balloon diameter	1.312	0.935-1.840	0.116	-	-	Ns
Prosthesis size	0.500	0.181-1.379	0.180	-	-	Ns
Prosthesis/annulus diameter ratio	0.211	0.001-66.539	0.596	-	-	Ns
Post-dilatation	0.577	0.186-1.790	0.341	-	-	Ns
Depth of implantation	1.200	1.006-1.431	*0.042*	1.210	1.010-1.449	*0.039*
Prosthesis expansion index	1.371	0.015-128.370	0.892	-	-	Ns
Valve-in-valve	6.727	0.706-64.079	0.097	2.768	0.226-33.843	0.425
First degree AV block at baseline	1.968	0.612-6.335	0.256	-	-	Ns
Left BBB at baseline	0.696	0.157-3.074	0.632	-	-	Ns
Anterior hemiblock at baseline	1.230	0.332-4.558	0.757	-	-	Ns
Posterior hemiblock at baseline	1.480	0.088-24.777	0.785	-	-	Ns
Right BBB at baseline	5.400	0.995-29.297	*0.051*	6.132	1.030-36.519	*0.046*
Bifascicular block at baseline	1.522	0.200-11.579	0.685	-	-	Ns

However, considering as a dependent variable the worsening in the CD, rather than the need for PPM implantation, the predictors of CD worsening remained the depth of implantation (OR 1.30, 95% CI 1.00 to 1.69, *p =0.05*) and pre-existing left BBB (OR 0.07, 95% CI 0.01 to 0.49, *p =0.007*). The 30-day mortality rate was 5% (3 of 64), with no difference between those patients who required PPM implantation and those who did not (4% vs 5%; p =0.83).

The causes of death were LV perforation due to stiff guide-wire, pneumonia, and cerebral oedema owing to electrolyte disturbances. During hospitalization, the rate of stroke and myocardial infarction was 2% (1 of 64) and 2% (1 of 64), respectively, with no differences between the groups. At a mean follow-up of 6.0 ± 4.2 months (range 30 days to 13.3 months), the mortality rate was 18% (11 of 61); 29% of patients who needed PPM versus 11% of patients who did not (p =0.07). It was a cardiac death in only 1 case. Of 61 patients, myocardial infarction occurred in 1 (2%), stroke in 1 (2%), heart failure in 7 (12%), with no differences between the 2 groups (p =0.39, p =0.39, and p =0.31, respectively). During the follow-up, the PR, QRS, and QT intervals decreased significantly within the first month after the procedure (Table 23). Two patients, discharged with first-degree AV block plus left BBB and with left BBB alone, respectively, underwent PPM implantation 1 month after TAVI for late onset of complete AV block. In these patients, the prosthesis/annulus was similar to those of patients with early PPM implantation or no PPM implantation (1.10 vs 1.20 and 1.21, respectively). No sudden death occurred. Analyzing the patient's pacemaker dependency at follow-up, of the 17 PPM patients who were alive, 12 presented with a spontaneous rhythm with a mean ventricular pacing percentage of 19% (range 0.2% to 62%; 7 patients <20%). One patient underwent pacing at baseline and had an adequate ventricular response during pacemaker inhibition, with a ventricular pacing percentage of 4%. Finally, 4 patients underwent pacing at baseline electrocardiography and presented with an inadequate ventricular response at the lowest rate programmable (ventricular pacing percentage >95% in all cases).

5.8 Conduction disorders after TAVI: differences between self-expandable and balloon-expandable devices (ESC congress, Paris 2011).

The occurrence of CD is one of the most frequent complications after TAVI. According to the published data, the use of SE rather than BE prostheses seems to confer an increased risk of advanced CD requiring PPM implantation. Aim of the present analysis was to analyze, in our mono-centric experience, the incidence of CD after TAVI, their outcome, and the need for PPM according to the type of implanted device. Patient population included 185 patients who underwent TAVI at our institution between June 2007 and March 2011 with various approaches (TF, TA and transubclavian). Eighty-seven of them received a SE device (SE group), the CoreValve Revalving System, while the other 98 received a BE device (BE group), the Edwards Sapien or Sapien XT valve. In all cases a 12-leads electrocardiogram (EKG) before TAVI and daily after TAVI until discharge was performed, in addition to a continuous EKG monitoring during procedure and a 12-leads EKG at 1 month-follow up. Conduction disorders were defined as the presence of at least one rhythm abnormality including atrioventricular or intraventricular CD such as I°, II° or III° degree of AV block, left or right BBB, left anterior or posterior hemiblock. The requirement for PPM was determined by the attending cardiologist according to the current guidelines.

There was no difference between groups in any of the baseline characteristics here reported (table 24). Fifteen patients (6 of the self expandable group and 9 of the balloon expandable group) were excluded from the following analysis because they already had a PPM before TAVI.

Table 24. baseline characteristics.

Variables	SE (87 pts)	BE (98 pts)	*p*
Age	80.8 ± 6.2	80.6 ± 7.0	0.79
Log EuroScore	22.9 ± 13.8	20.2 ± 13.0	0.30
STS score	10.5 ± 8.4	12.3 ± 11.7	0.25
Female Sex	46 (52.9)	61 (62.2)	0.23
Diabetes	21 (24.1)	26 (26.8)	0.74
Hypertension	78 (89.7)	88 (89.8)	1.00
CKD	50 (57.5)	54 (55.1)	0.77
Coronary Artery Disease	57 (65.5)	51 (52.6)	0.10
Congestive Heart Failure	43 (49.4)	51 (52.0)	0.77
CerebroVascular Accident	14 (16.1)	11 (11.3)	0.39
Chronic Obstructive Pulmonary Disease	21 (24.4)	31 (32.0)	0.33
Carotid Artery Disease	30 (34.5)	28 (30.8)	0.63
Previous Cardiac Surgery	19 (21.8)	16 (16.3)	0.35
Porcelain Aorta	16 (18.4)	19 (20.9)	0.71
PPM	6 (6.9)	9 (9.2)	0.60

Procedural success rate was 94.3% in SE group and 95.9% in BE group and 30 day mortality was 5.7% and 3.1% respectively, without statistical difference between groups. Mean aortic gradient dramatically decreased from 45.6 ± 15.6 to 10.9 ± 4.5 mmHg. AVA increased from 0.78 ± 0.20 to 1.91 ± 0.40 cmq.

At baseline, the incidence of atrial fibrillation was higher in BE group. Any difference was recorded between groups in terms of atrio-ventricular or intraventricular conduction. Notably, the incidence of at least one type of CD was high in these elderly patients affected by calcific degenerative AS (table 25).

Table 25. Baseline CD.

	SE (81 pts)	BE (89 pts)	P
Atrial fibrillation	12 (14.8)	26 (29.2)	*0.03*
AV block I	15 (18.5)	15 (16.9)	0.84
AV block II 2:1	1 (1.2)	0 (0)	0.48
Left BBB	11 (13.6)	8 (9.0)	0.47
Right BBB	11 (13.6)	10 (11.2)	0.65
Left Anterior Hemiblock	14 (17.3)	9 (10.1)	0.19
Left Posterior Hemiblock	2 (2.5)	0 (0)	0.23
Total pts with CD	40 (49.4)	32 (36.0)	0.09

After TAVI, the left BBB was the most frequent CD and its incidence was higher in SE group, with 47.5% of patients in SE group and 17.2% in BE group who develop a new left BBB. Also the incidence of new first degree AV block was higher in SE group. The rate of complete AV block was 21.3% in SE group and only 2.3% in BE group, so at the end total patients with at least one CD was 90.0% in SE group and 57.5% in BE group. Finally, 41.3% of patients who received a CoreValve need for a PPM after TAVI, while only 8.0% of patients who received an Edwards Sapien valve or a Sapien XT do it (table 26).

Table 26. Post-TAVI CD.

	SE (80 pts)	BE (87 pts)	P
Atrial fibrillation	15 (18.8)	26 (29.9)	0.11
AV block I	27 (33.8)	22 (25.3)	0.24
AV block III	17 (21.3)	2 (2.3)	*<0.0001*
Left BBB	48 (60.0)	22 (25.3)	*<0.0001*
Right BBB	3 (3.8)	9 (10.3)	0.14
Left Anterior Hemiblock	5 (6.3)	13 (14.9)	0.08
Left Posterior Hemiblock	1 (1.3)	0 (0)	0.48
Total pts with CD	72 (90.0)	50 (57.5)	*<0.0001*
PPM	33 (41.3)	7 (8.0)	*<0.0001*
New AV block I	18 (22.5)	9 (10.3)	*0.04*
New left BBB	38 (47.5)	15 (17.2)	*<0.0001*

The causes of PPM implantation are summarized in the following table (table 27).

Table 27. Causes of PPM implantation.

Causes	N=40 (%)	
Permanent or transient AV block III	28 (70.0%)	Absolute indications 87.5%
Advanced AV block II + left BBB	4 (10.0%)	
Symptomatic bradicardia	3 (7.5%)	
Atrial fibrillation with pauses + new left BBB	2 (5.0%)	Relative indications 12.5%
AV block I + left BBB	2 (5.0%)	
Atril fibrillation+bifascicular block	1 (2.5%)	

At 30-day follow up, only 1 and 2 patients with the SE device developed a new first degree AV block and a new left BBB, respectively, while no patients with a BE device showed new conduction

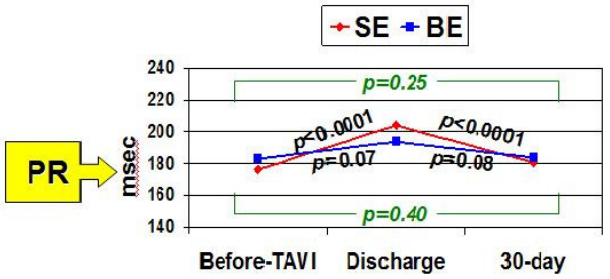
abnormalities. On the other side, first degree AV block disappeared in 10.5% of patients with a CoreValve and in 7.0% of patients with a BE device. Left BBB disappeared in 17.1% of patients with a SE device and in 7.0% of those who received a BE prosthesis. Importantly, 2 patients were urgently readmitted at hospital during the first month of follow up because of late onset of complete atrioventricular block, both of them in the SE group (table 28).

Table 28. Thirty-day follow up.

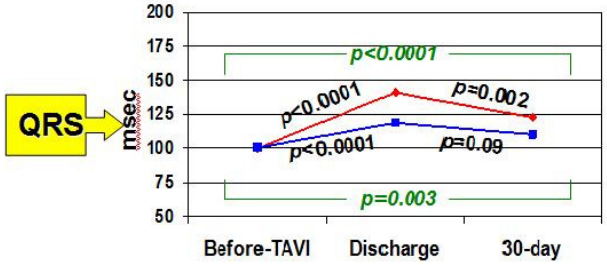
	SE (76 pts)	**BE (86 pts)**	***p***
New AV block I	1 (1.3%)	0	0.47
New left BBB	2 (2.6%)	0	0.22
Regression of AV block I	8 (10.5%)	6 (7.0%)	0.58
Regression of left BBB	13 (17.1%)	6 (7.0%)	*0.05*
New PPM	2 (2.6%)	0	0.22

Further analyzing atrioventricular and intraventricular conduction, we found that PR intervals increased significantly after TAVI only in SE group (red lines), with a quite complete regression to baseline values at 1 month follow up. Looking at QRS intervals, it lengthened significantly in both groups after TAVI and in both cases it shortened significantly at follow up, but the main differences between the two groups is that the QRS interval lengthened more after SE rather BE valve implantation and moreover at follow up it remains longer in CV rather than ES patients (figure 20).

Figure 20. PR and QRS intervals over time according to SE/BE device. *Changes over time of PR and QRS intervals after TAVI with SE (red lines) and BE (blue lines) devices.*



	Before-TAVI	Discharge	30-day
SE	182.1±31.8	211.9±33.0	186.8±25.5
BE	184.1±35.3	194.2±44.9	186.1±37.6
p	0.57	0.02	0.80



	Before-TAVI	Discharge	30-day
SE	104.4±26.9	142.0±24.7	124.9±26.3
BE	100.5±21.9	118.5±37.3	109.8±25.7
p	0.20	<0.0001	0.008

In the first phase of our experience, described in the previous section of this PhD thesis, when we implanted only the self expandable devices, independent predictors of PPM implantation at multivariate analysis were the depth of prosthesis implantation and the presence of a right BBB before procedure. Now, in our wider experience with both SE and balloon expandable devices, putting the self expandable device into a multimodel multivariate analysis, it remains as a strong predictors of PPM implantation in all the models we tested (table 29).

Table 29. SE device as a predictors of PPM after TAVI *(Multimodel multivariate analysis).*

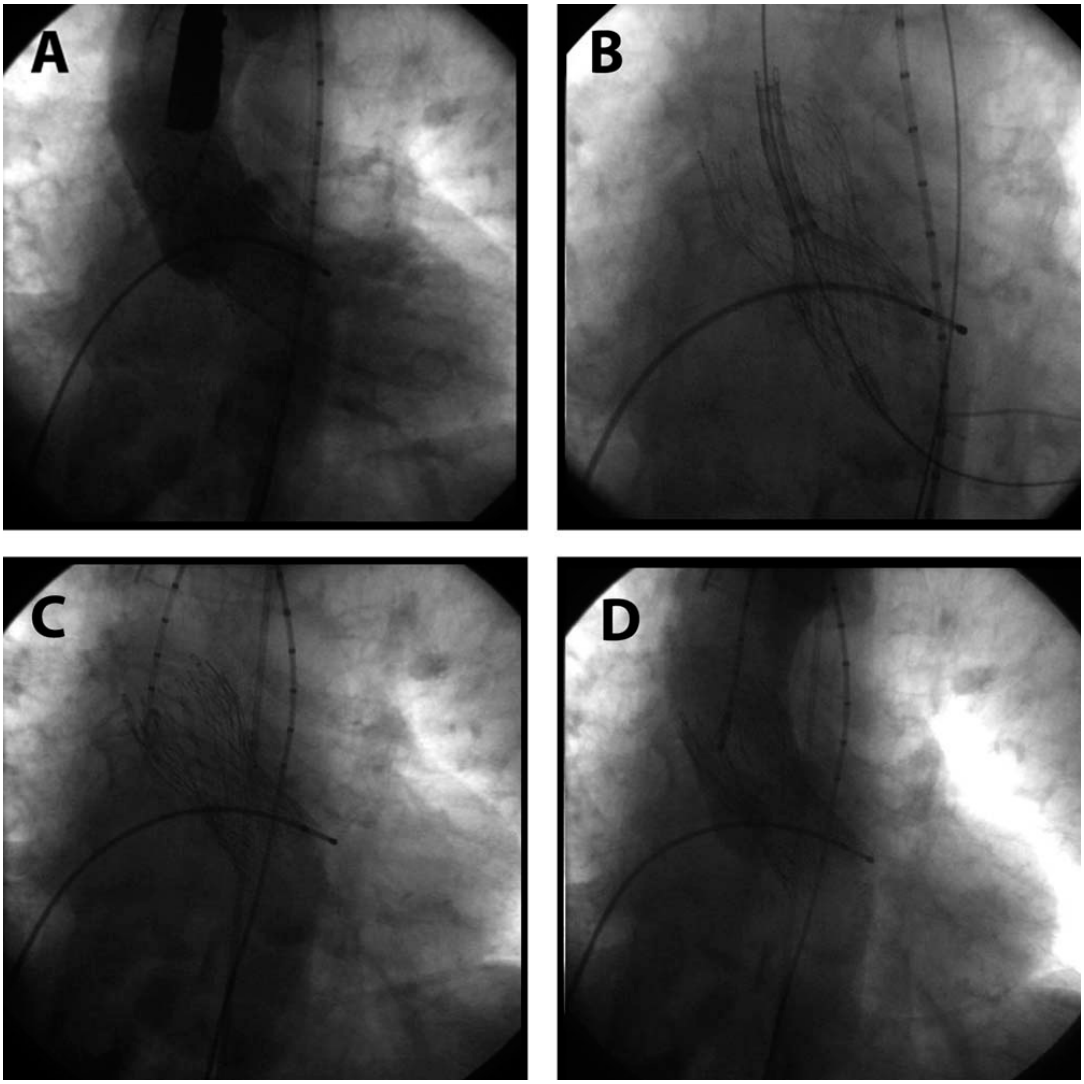
	Hazard ratio	**95% CI**	***P***
Unadjusted model	8.525	3.095-23.483	*<0.0001*
Model adjusted for age	8.878	3.185-24.751	*<0.0001*
Model adjusted for sex	7.825	2.816-21.742	*<0.0001*
Model adjusted for previous I°AV block	8.884	2.905-27.170	*<0.0001*
Model adjusted for previous left BBB	10.049	3.277-30.813	*<0.0001*
Model adjusted for previous right BBB	10.188	3.250-31.931	*<0.0001*
Model adjusted for previous atrial fibrillation	9.430	3.085-28.825	*<0.0001*
Model adjusted for history of syncope	18.229	4.148-80.111	*<0.0001*
Model adjusted for CKD	18.718	4.261-82.214	*<0.0001*
Model adjusted for diabetes mellitus	18.886	4.293-83.091	*<0.0001*
Model adjusted for Logistic EuroSCORE	19.609	4.438-86.639	*<0.0001*

5.9 How to overcome severe periprosthesis leakage after first TAVI: valve-in-valve technique. (Performance of Valve-in-Valve for Severe Para-Prosthetic Leaks due to Inadequate Transcatheter Aortic Valve Implantation. Catheter Cardiovasc Interv. 2011;78:996-1003).

Recently, the feasibility and the safety of TAVI have been reported for the treatment of degenerative aortic valve stenosis. In particular, SE and BE devices have been successfully implanted over the last years with different transcatheter techniques, using both retrograde and antegrade femoral transluminal approach[28-30, 34, 35] or direct TA puncture of the left ventricle.[56, 57] However, despite the high rate of successful implantation, residual para-prosthetic leaks (PPL) of variable degree have been reported in many cases,[28-30, 34, 35, 56, 57] primarily because of stent misdeployment in highly calcified stenotic valves, accounting for variables gaps at commissure level between the stent external surface and the inner surface of native valve.[58] In addition, device malpositioning such as ‘‘too high’’ or ‘‘too deep’’ implantation may also occur, leading to acute failure of bioprosthesis because of extensive leak between the aortic annulus and the prosthetic frames. Recently, Piazza et al. have reported on the feasibility and safety of two self-expanding bioprosthetic valve implantation during the same procedure in a small series to treat the acute failure of TAVI,[59] showing a satisfactory procedural outcome. However, the follow-up outcome of this procedure has been described only anecdotally,[60] and valve-in-valve performance at follow-up is still unknown. This study reports on mid-term safety and performance of valve-in-valve implantation as rescue strategy to overcome severe PPL due to valve malpositioning after TAVI. Out of 87 patients treated in our centre with the SE CoreValve device from June 2007 to November 2009, 31 (35.6%) showed moderate to severe PPL after prosthesis deployment. Overall, of these, 22 showed an under-expanded prosthesis, and a balloon post-dilatation was successfully performed with PPL reduction to mild or moderate degree; one patient had too high prosthesis implantation, and the device was successfully snared in ascending aorta by using the Amplatz GooseNeck (ev3, Plymouth, MN) and a second CoreValve prosthesis was implanted in the correct position. Eight

patients had too deep prosthesis deployment. Of these, two underwent successfully prosthesis snaring with the Amplatz GooseNeck, obtaining an optimal and effective prosthesis position with PPL reduction. Finally, six of 87 (6.9%) patients received a valve-in-valve immediately after the first prosthesis implantation to overcome severe PPL (Figure 21).

Figure 21. Valve-in-valve procedure. *Panel A: severe aortic regurgitation early after CoreValve implantation; Panel B: deployment of a second CoreValve inside and slightly upper the first implanted valve; Panel C: fluoroscopy of valve-in-valve implanted, showing the full expanded frame of second prosthesis; Panel D: aortic angiography after valve-in-valve implantation showing a trivial aortic regurgitation (From Napodano, Fraccaro et al. Catheter Cardiovasc Interv. 2011;78:996-1003).*



Baseline clinical profile and co-morbidities are reported in Table 30.

Table 30. Clinical characteristics *(From Napodano, Fraccaro et al. Catheter Cardiovasc Interv. 2011;78:996-1003).*

Variable	Pt # 1	Pt # 2	Pt # 3	Pt # 4	Pt # 5	Pt # 6
Age (years)	86	76	74	84	72	76
Gender	Female	Male	Male	Male	Male	Female
Logistic EuroSCORE	25.65%	11.89%	24.90%	30.62%	5.90%	17.40%
NYHA class	IV	IV	II	III	III	IV
Coronary artery disease	No	No	Yes	Yes	Yes	Yes
Cerebrovascular disease	No	No	No	Yes	Yes	No
Previous myocardial infarction	Yes	No	Yes	No	Yes	Yes
Previous cardiac surgery	No	No	Yes	Yes	No	No
Severe obstructive pulmonary disease	No	Yes	No	Yes	No	No
Creatinine clearance (ml/min/1.73 m^2)	32.1	46.1	42.4	46.2	72.2	50
Peripheral disease	Yes	No	Yes	No	No	No
Neurological dysfunction	No	No	No	No	No	No
Liver cirrhosis	No	No	No	No	Yes	No
Porcelain aorta	No	No	No	No	No	No

Hemodynamic data are shown in Table 31.

Table 31. Baseline hemodynamic findings *(From Napodano, Fraccaro et al. Catheter Cardiovasc Interv. 2011;78:996-1003).*

Variable	Pt # 1	Pt # 2	Pt # 3	Pt # 4	Pt # 5	Pt # 6
AVA (cm^2/m^2)	0.39	0.55	0.34	0.55	0.56	0.44
Peak-to-peak gradient (mm Hg)	50	30	80	85	30	20
LVEF (%)	57	34	44	58	72	26
AR (+/4)	2	3	0	1	0	2
SPAP (mm Hg)	32	50	30	60	40	45
CI ($L/min/m^2$)	2.8	2.4	2.8	2.1	3.1	2.1

AVA = aortic valve area; AR = aortic regurgitation; CI = cardiac index; LVEF = left ventricular ejection fraction; SPAP = systolic pulmonary artery pressure.

All patients received valve-in-valve because of too deep implantation of the first prosthesis.

Procedural data are detailed in (Table 32).

Table 32. Procedural data *(From Napodano, Fraccaro et al. Catheter Cardiovasc Interv. 2011;78:996-1003).*

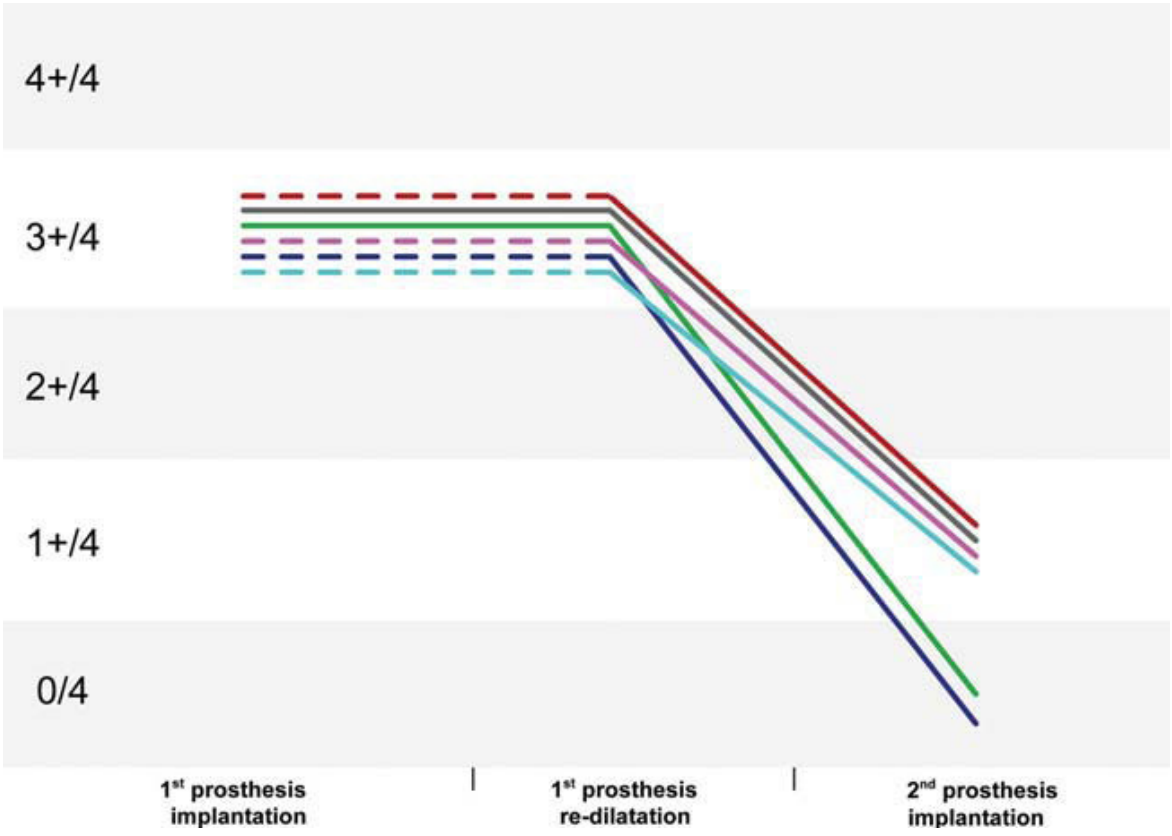
Variable	Pt # 1	Pt # 2	Pt # 3	Pt # 4	Pt # 5	Pt # 6
Aortic annulus[a], mm	22.0	24.0	24.2	23.5	23.6	25.9
Sedation/anaesthesia	GA	GA	S	S	None	S
Oro-tracheal intubation	Yes	Yes	No	No	No	Yes
Transesophageal echo	Yes	Yes	No	No	No	No
BAV	Yes	No	Yes	Yes	Yes	No
1st CoreValve size (mm)	26	26	29	29	29	29
Implantation depth (mm)	14.4	14.9	14.8	12.7	22.3	15.7
Re-dilatation (1st prosthesis)	No	Yes	Yes	No	No	No
2nd CoreValve size (mm)	26	26	29	29	29	29
Re-dilatation (2nd prosthesis)	No	Yes	No	Yes	Yes	No
Procedural time (min)	76	76	97	80	130	152
Contrast amount (ml)	314	313	200	262	300	156
Procedural success	Yes	Yes	Yes	Yes	Yes	Yes

[a]Assesed by transthoracic or transesophageal echocardiogram.BAV = balloon aortic valvuloplasty; GA = general anaesthesia; S = sedation.

In two patients, we did valve-in-valve after unsuccessful prosthesis snaring by using the Amplatz GooseNeck. There was not difference in the occurrence of inadequate prosthesis positioning (4/43 patients vs 5/44patients) neither of valve-in-valve procedure (3/43 patients versus 3/44 patients) between the initial half and the second half of the experience.

After the second prosthesis implantation, in all cases an immediate hemodynamic improvement was observed (Figure 22). In particular, aortic regurgitation was no longer appreciable by aortic angiography in two patients, and it decreased from severe to mild/trivial in the remaining four patients (Figure 22); peak-to-peak transprosthetic gradient was 5 ± 2 mmHg.

Figure 22. Evolution of para-prosthetic leaks (PPL). *Angiographic assessment of aortic regurgitation due to PPL after first prosthesis implantation (on the left); after prosthesis redilatation when performed, and after the second prosthesis implantation (on the right). Dash lines indicate patients who did not received first prosthesis re-dilatation(From Napodano, Fraccaro et al. Catheter Cardiovasc Interv. 2011;78:996-1003).*

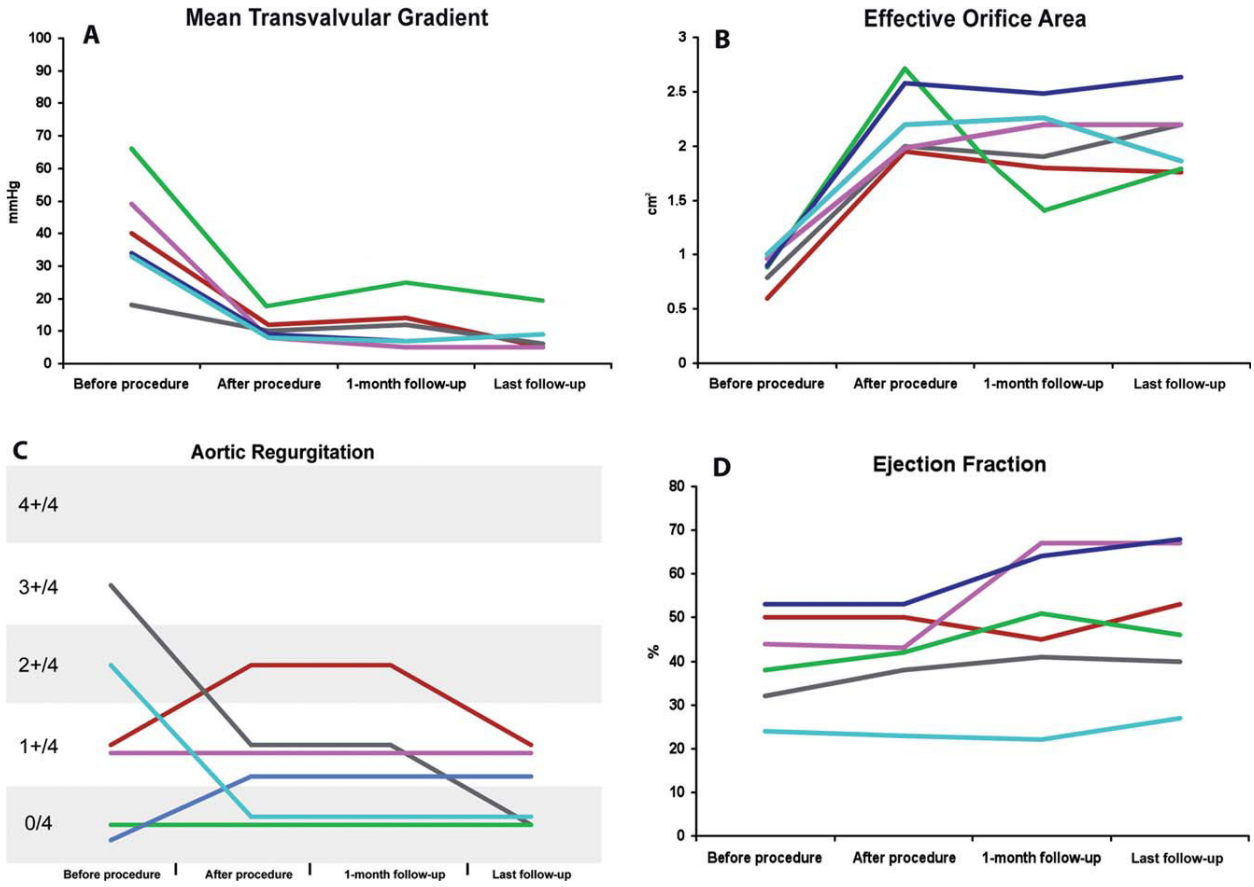


After the release of the second prosthesis no case of early or late prosthesis embolization was observed. Coronary ostia occlusion or myocardial ischemia did not occur. After valve-in-valve implantation procedural success was reached in all patients. During the hospitalization, four patients developed CD requiring in-hospital permanent pace-maker implantation, no other procedure-related adverse events occurred. All patients were discharged alive after 9.7 ± 1.8 days. No death nor cardiovascular and cerebrovascular event occurred at 30-day. One patient had heart failure at 2 months related to chronic anemia/atrial fibrillation and died because of pneumonia complications at day 729; one patient had gastrointestinal bleeding requiring blood transfusions at day 34 and died at day 122 because of pulmonary surgery complications. One patient with severe LV dysfunction had heart failure at 3-months follow-up, and was in NYHA class II at 1 year follow-up. The remaining patients had uneventful follow-up, lasting 1 year in one and 2 years in two patients, and were in NYHA class I.

At 2-d transthoracic echo after the procedure, mean transaortic gradient decreased from 40.6 ± 16.3 mm Hg to 10.7 ± 3.4 mm Hg, while aortic effective orifice area increased from 0.85 ± 0.14 cm2 to 2.24 ± 0.33 cm2, and remained stable throughout the follow-up in all patients (Figure 23A and B). At last follow-up (6 months for one patient, 1-year for two patients, 2-years for three patients), mean transaortic gradient was 9.3 ± 5.8 mm Hg (Figure 22A), aortic effective orifice area 2.07 ± 0.34 cm2 (Figure 23B), aortic regurgitation was absent or mild for all patients (Figure 23C); LV EF improved in four patients and remained unchanged in two (Figure 23D).

Before the procedure, mitral valve regurgitation was trivial in two patients, mild in three patients and moderate in one patient; after valve-in-valve procedure it remained trivial in two patients, mild in three patients and moderate in one patient; and did not change at follow-up.

Figure 23. *Prosthesis performance of valve-in-valve at follow-up echocardiographic assessment before TAVI and at serial follow-up evaluation. Panel A: Mean transvalvular gradient; Panel B: Aortic effective orifice area; Panel C: Aortic regurgitation; Panel D: LV EF (From Napodano, Fraccaro et al. Catheter Cardiovasc Interv. 2011;78:996-1003).*



5.10 Incidence, predictive factors, and prognostic implications of contrast induced nephropathy after TAVI (EuroPCR Congress, Paris 2011).

Older patients that are candidates to TAVI often suffer of CKD or are at very high risk for AKI. Very few data exist on the occurrence of AKI associated with TAVI. Aim of this analysis is to evaluate incidence, predictive factors, and prognostic value of AKI following TAVI.

We analyzed 161 patients affected by inoperable/high risk AS who underwent TAVI between June 2007 and November 2010 at our institution with both self expandable and balloon expandable devices. The procedures were performed by TF, TA or transubclavian approach.

CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2. AKI was defined as a decrease of 25% in eGFR at 48 h following the procedure or the need of haemodialysis during index hospitalization (RIFLE criteria).[61]

Five patients were excluded from the analysis because already in haemodialysis before TAVI, so the final analysis takes into account 156 patients.

Baseline characteristics of study population are shown in table 33. CKD was present in 55.8% of total population and 9.0% had an eGFR < 30.

Table 33. Baseline characteristics

Variables	N=156 (%)
Age, years	81.19 ±6.16
Male sex	61 (39.1)
Hypertension	140 (89.7)
Diabetes mellitus	39 (25.0)
CKD (eGFR <60)	87 (55.8)
eGFR >30 & < 60	73 (46.8)
eGFR < 30	14 (9.0)
CerebroVascular Accident	23 (14.8)
Coronary Artery Disease	93 (60.0)
Congestive Heart Failure	74 (47.4)
Body Surface Area, m2	1.72 ± 0.17
Body Mass Index	25.85 ± 4.20
Logistic EuroScore, %	21.33 ± 12.66

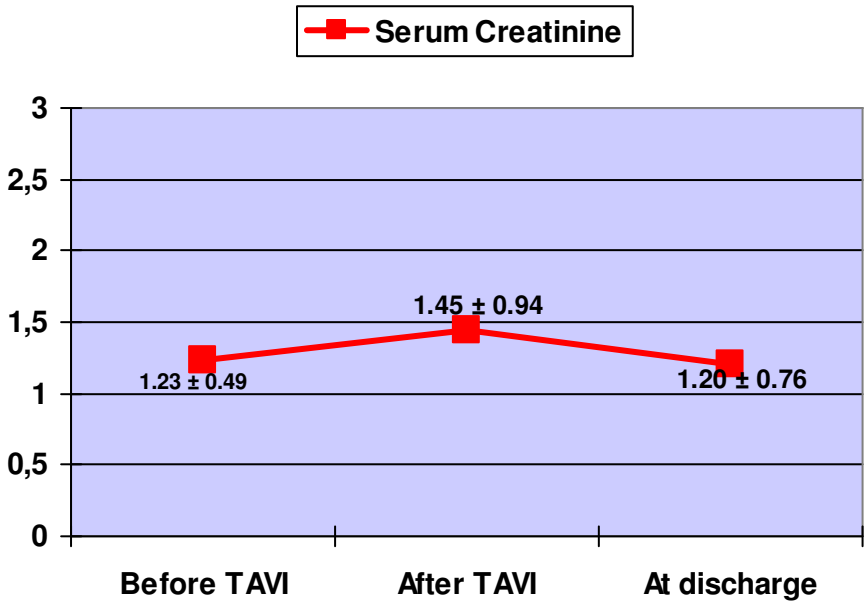
CoreValve device was implanted in 53.8% of total population, while in the remaining we used an Edwards Sapien or Sapien XT device. Mean contrast medium amount was 182.0 ± 74.3 milliliter (range 50 - 450). Other procedural details are listed in table 34.

Table 34. Procedural data

Variables	N= 156 (%)
General anesthesia + Orotracheal intubation	62 (39.7)
Cardiopulmonary bypass	3 (1.9)
Access	
TF	109 (69.9)
TA	42 (26.9)
Transubclavian	5 (3.2)
Device	
CoreValve	84 (53.8)
Edwards Sapien/Sapien XT	72 (46.2)
Procedural time (min)	85.6 ± 39.7
Exposure time (min)	22.2 ± 9.7
Radiation time (gy/cmq)	139.9 ± 86.6
Contrast medium amount (ml)	182.0 ± 74.3 (range 50 - 450)

After TAVI, there was a statistical significant increase in serum creatinine level ($p<0.0001$), with complete recovery at discharge (figure 24).

Figure 24. Serum creatinine level before and after TAVI and at discharge. *The graphs shows the change after TAVI and at discharge of serum creatinine level.*



The procedural outcome is summarized in table 35. Thirty patients (19.2%) experienced AKI after TAVI and 8 of them required haemodialysis during hospitalization. Among them, only one patient with a severe CKD before TAVI (stage IV) required permanent haemodialysis.

Table 35. Procedural outcome.

Variables	N= 156 (%)
Hemodynamic success	153 (98.1)
Acute procedural success	151 (96.8)
In-hospital death	7 (4.5)
Valve-in-valve	6 (3.8)
Tamponade	3 (1.9)
Major vascular complication	17 (10.9)
Major bleeding	11 (7.1)
Blood transfusion >2 Packed Red Cells	13 (8.3)
Major stroke	2 (1.3)
AKI	30 (19.2)
CVVH	8 (5.1)
Intensive Care Unit stay (days)	3.9 ± 4.7
Total hospital stay (days)	13.1 ± 12.6

Univariate analysis identified, as predictive factors of AKI ($p<0.05$), general anaesthesia, TA approach, need of inotropic drugs during procedure, low mean aortic pressure at the end of procedure, haemoglobin nadir level and Troponin I pick level after TAVI, total number of blood transfusions during and after TAVI (table 36).

Table 36. Predictive factors of AKI (univariate analysis).

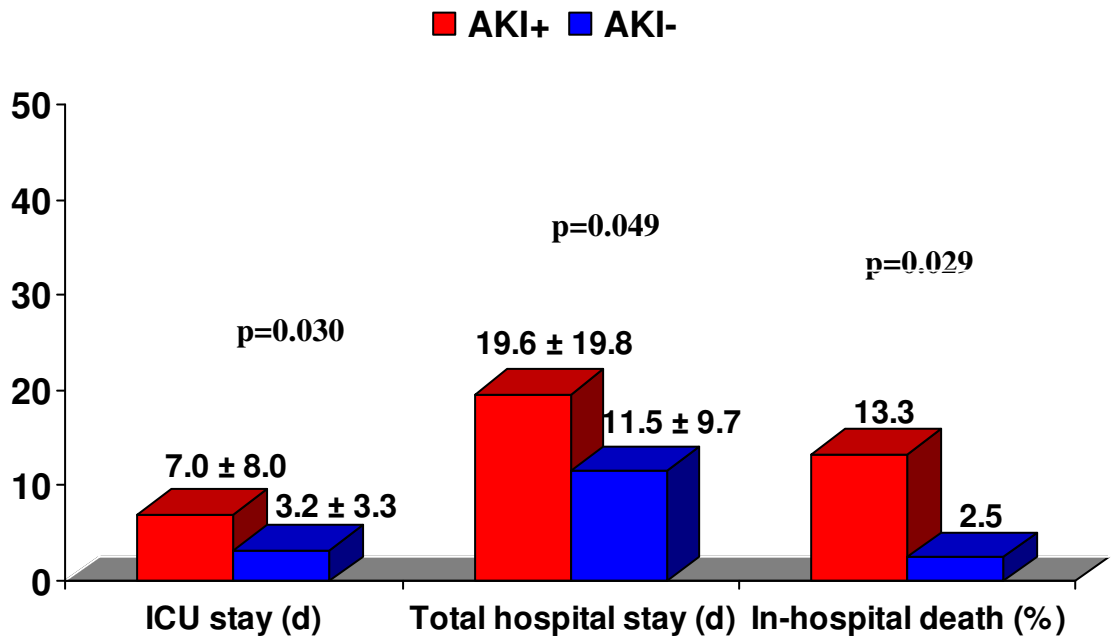
Variables	OR	95% CI	*P*
Age	0.983	0.924-1.045	0.580
Male sex	0.725	0.314-1.678	0.453
Body Mass Index	1.003	0.913-1.103	0.943
Hypertension	1.766	0.379-8.224	0.469
Diabetes Mellitus	0.727	0.273-1.937	0.523
CKD	1.217	0.541-2.739	0.635
eGFR < 30	1.152	0.300-4.414	0.837
Logistic EuroSCORE	1.025	0.996-1.055	0.088
Baseline serum creatinine	1.004	0.996-1.013	0.344
General anestesia	3.892	1.676-9.039	*0.002*
TA approach	3.176	1.379-7.314	*0.007*

Inotropic drug during TAVI	3.000	1.204-7.473	*0.018*
Procedural failure	2.905	0.463-18.212	0.255
Procedural length	1.010	1.000-1.019	0.056
Mean aortic pressure at the end of TAVI	0.965	0.935-0.997	*0.030*
Contrast dye amount	1.000	0.995-1.005	0.970
Hb nadir	0.705	0.512-0.970	*0.032*
TnI peak	1.158	1.043-1.284	*0.006*
Number of blood unit transfusion	1.370	1.038-1.809	*0.026*

At multivariate analysis the only independent predictors of AKI were the need of intraprocedural inotropic drugs (OR: 9.490. 95% CI: 2.195-41.034; *p=0.003*) and the number of blood transfusions (OR: 1.527. 95% CI: 1.035-2.252; *p=0.033*).

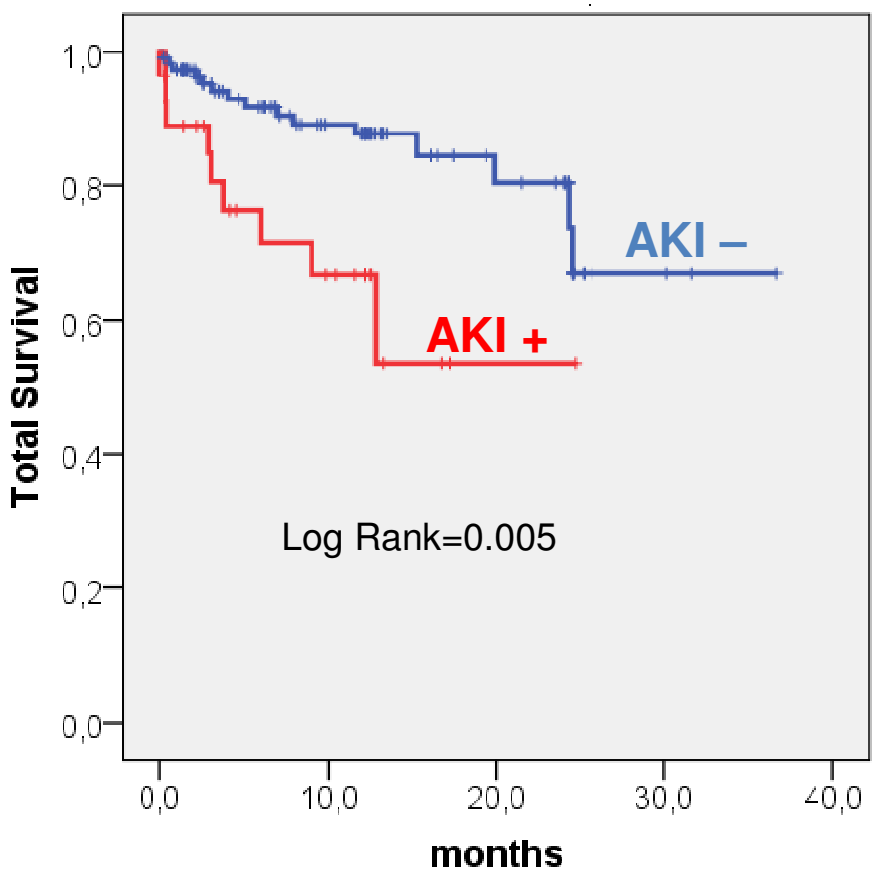
The patients who developed AKI after TAVI had longer intensive care unit stay (7.2±8.0 vs 3.2±3.3; *p<0.0001*) and higher thirty-day mortality (10.7% vs 1.6%; *p=0.014*) than those who did not (figure 25).

Figure 25. Hospital outcome according to AKI. *The graph represents the length of intensive care unit (ICU) stay, total hospital stay and rate of in-hospital death among patients who experienced (red bars) and who did not experience (blue bars) AKI.*



At follow up, one-year survival of patients who had not suffered of AKI during hospitalization was 87.8% while this figure is 53.4% for those who suffered of (figure 26).

Figure 26. Impact of AKI on long term survival. *Total survival according to Kaplan-Meier analysis of patients with (red line) and without (blue line) AKI.*



5.11 Pathological findings of an ischemic stroke after TAVI (oral communication, PCR London Valves congress, London 2011).

This is the case of a 78 years-old female patient affected by severe AS. Her comorbidities included diabetes mellitus, obesity with a body mass index of 37, stage III CKD, restrictive pulmonary disease, severe pulmonary hypertension, moderate LV dysfunction and coronary artery disease. The patient suffered from mild effort dyspnoea, and she had recurrent hospitalization due to congestive heart failure.

The main echocardiographic findings were a pick aortic gradient and a mean aortic gradient of 93 mmHg and 58 mmHg, respectively, the LV EF was 42% and pulmonary artery systolic pressure 100 mmHg. We calculated the logistic EuroScore of this patient which was 54.57%.

The case was discussed by the heart team of our institution and the final decision was to start a screening for transcatheter aortic valve eligibility. The screening included transthoracic and transesophageal echocardiography as well as complete cardiac catheterization. The aortic annulus measured 20 mm by transthoracic and 22 mm by transesophageal echocardiography. There was a moderate impairment in LV function (42%) without regional wall motion abnormalities. The iliac-femoral arteries were at least 6.5 mm. So, we selected for a 26-mm CoreValve implantation by TF approach.

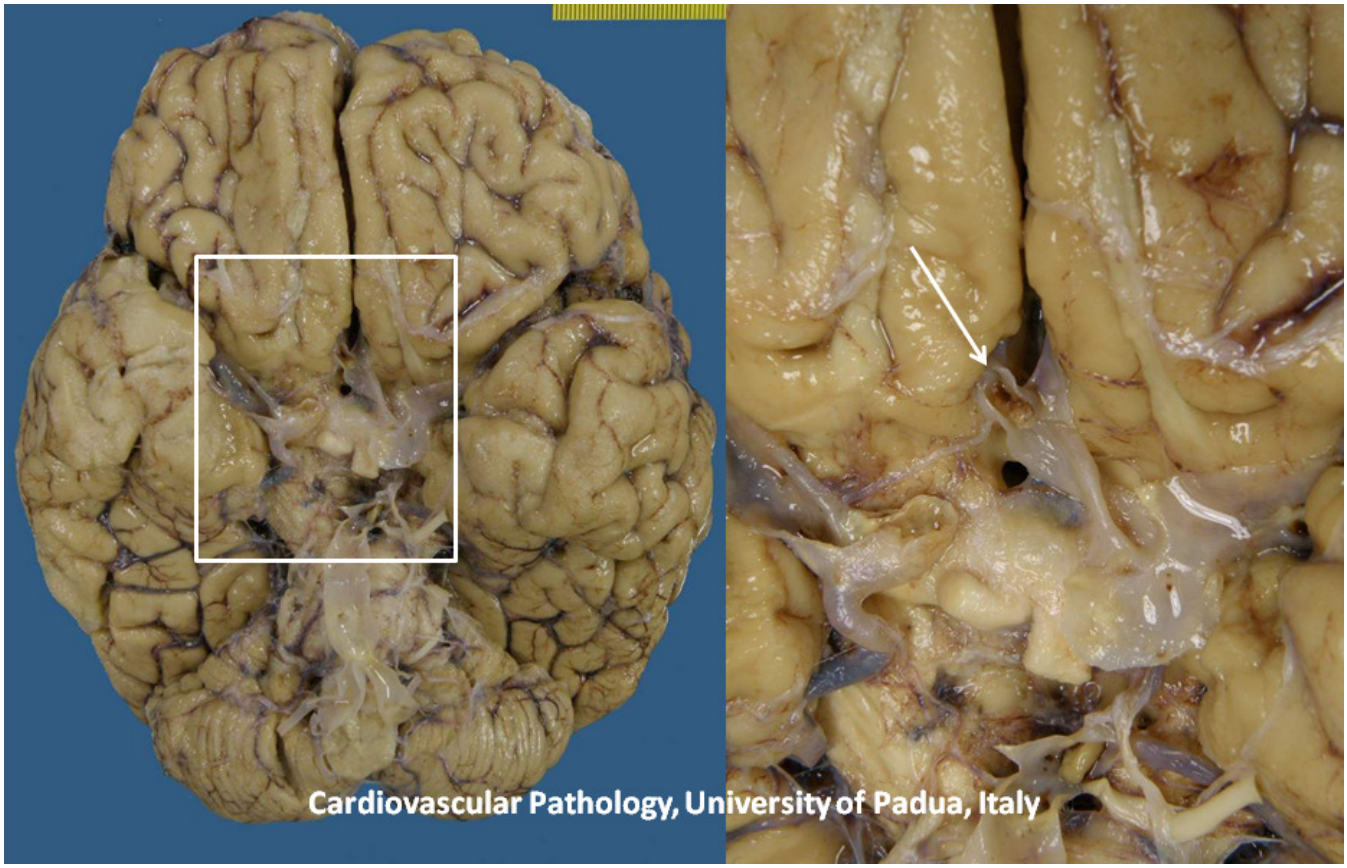
The procedure was performed under local anaesthesia, by totally percutaneous approach. The valve was pre-dilated with a 22-mm Numed balloon. Supra-aortic angiogram after CoreValve deployment showed a relevant regurgitation. Firstly, we decided to post-dilate the valve with a 25-mm balloon and final supra-aortic angiogram demonstrated a reduction in aortic regurgitation with a grade 2+/4 periprosthesis leak at the end of procedure.

The periprocedural outcome was unfavourable and characterized by a series of complications including: new onset left BBB, a minor vascular complication (local pseudoaneurysm) at level of access site medically treated, an embolic stroke 48 hours after TAVI, AKI requiring ultrafiltration,

haemorrhagic shock probably related to retroperitoneal haematoma, and pneumonia. Finally the patient died at day 12 after the index procedure.

The cadaver underwent autopsy which in particular revealed the occlusion of the right anterior cerebral artery by a calcium fragment, as the cause of the embolic stroke (Figure 27).

Figure 27. *Macroscopic anatomical view of the brain of a patient who died due to an ischemic stroke after TAVI. On the right the particular of a calcium fragment (white arrow) occluding the lumen of the right anterior cerebral artery.*



In conclusion, this is an ex-vivo demonstration of a calcium fragment embolization during the hours after TAVI, leading to fatal stroke.

DISCUSSION

6.1 Global population.

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[27] and resulted non inferior to conventional AVR in high surgical risk patients[43].

Our study analyzes the global clinical and echocardiographic outcome of TAVI considering both immediate results and mid term outcome. This monocentric registry takes into account a wide population including patients with native AS, combined AS plus regurgitation and bioprosthesis dysfunction, treated with both commercially available devices, using all the approaches currently adopted: TF, TA, transubclavian and transaortic.

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.

The two different devices and the various approaches present some peculiarities in terms of outcome and complications.

Moreover, some special fields of TAVI application and some more frequent adverse events deserve a particular comment.

6.1.1 Self-expandable versus balloon expandable devices.

In our experience, the two groups of patients, those treated by CoreValve implantation and those who received the Edwards Sapien or Sapien XT valve, presented similar baseline characteristics except for previous myocardial infarction which was more represented in CoreValve patients. This latter group had also low LV EF and more dilated LV end diastolic volumes (EDV).

Notwithstanding, mean logistic Euroscore was similar between groups.

Procedural success was high and statistically similar between groups, with a very low intraprocedural death. However, device success was higher in Edwards patients. This differences is probably related to the higher degree of residual periprosthetic leakage after CoreValve implantation, requiring more often back up strategies such as post-dilation and valve-in-valve implantation. This result is similar to that reported in the United Kingdom TAVI Registry, where the incidence of moderate to severe aortic regurgitation after TAVI was almost two fold higher after CoreValve than after Edwards valve implantation.[62]

In our experience, procedural time was longer and the need for general anaesthesia and oro-tracheal intubation were more frequent in Edwards group, but these differences are mitigated if we exclude from the analysis TA procedures.

Also haemodynamic performance of the two devices are excellent, with CoreValve prosthesis presenting lower gradient and larger effective orifice area.

Looking at procedural complications, the main difference between the two prosthesis is related to the occurrence of complete atrioventricular block and the subsequent need for PPM implantation (40.7% in CoreValve group vs 7.4% in Edwards group). This is probably related to the different geometry of the two devices, with the SE one implanted deeper into the LV outflow tract, causing a direct damage to the conduction system. This particular topic will be subsequently discussed in detail in a dedicated paragraph.

In-hospital death after TAVI is relatively low (4.2%), considering the high risk profile of patients population. The in-hospital combined safety endpoints attributed according to VARC definitions were 17.3% in total population, without differences between groups. However, at 1-year follow up, the combined efficacy endpoints according to VARC definitions, was in favour of Edwards valve. In fact it was 24.4% in total population, 31.7% in CoreValve group and 9.8% in Edwards group ($p=0.008$). In particular, the rate of heart failure was far more frequent in CoreValve group. This could be related to the lower LV EF at baseline in CoreValve patients, but we can not exclude a prognostic implication of the residual aortic regurgitation after SE valve implantation. Interestingly,

at multivariate analysis, the use of Edwards valve remained as independent predictors of 1-year efficacy together with the LV EF after TAVI.

6.1.2 Transfemoral versus transapical approach.

The second main topic that we identified for our discussion is the comparison between the two more frequently used vascular approaches for TAVI: the TF and the TA approach.

First of all, it is important to state that, in our centre, we adopted a strategy whereby patients with femoral arteries suitable for femoral access route underwent TF TAVI as first choice. On the other side, TA approach was reserved as second option for patients with severe peripheral vascular disease not eligible for a TF approach. Currently, there are no randomized trial which directly investigate which is the best strategy for TAVI. However, the TF approach allows to perform TAVI procedure with a totally percutaneous technique, without general anesthesia and orotracheal intubation, and it seems to confer a better myocardial protection with a prompt recovery in LV function.[63] Thus, it seems reasonable in our opinion to chose the less invasive technique as first choice for these inoperable/high risk patients. Similarly, in the study design of the Partner trial Cohort A the TA approach was left as second option.[43]

The comparative analysis of the two approaches, is limited by the fact that this is a prospective (non-randomized) observational study and the two population present some differences. In particular TA patients had a lower body mass index, more frequent peripheral vascular disease and previous CABG. However, the logistic euroscore was similar between groups. TA procedures were longer and required more often general anesthesia, orotracheal intubation and inotropic drug support. On the other side, the fluoroscopy time was shorter in this group, as previously reported by other authors.[64]

Interestingly, using our decision flow algorithm, we obtained a high procedural success and a low complication rate in both groups, without any significant differences between the two approaches. At follow up, the rate of combined efficacy at 1-year according to VARC definitions was 13.5% in

TA group and 3.7% in TF one (p=0.18). Interestingly, in the UK TAVI registry, a non-TF approach conferred a significantly increased risk of death at 30 days and at 1 year and 2 years of follow-up and was a predictor of an adverse outcome in the univariate analysis; however, it was not an independent predictor of mortality at 1 year. The explanation of this phenomenon is probably multifactorial and in particular related to the more adverse risk profile of the non-TF cohort of patients, but it is also possible that aspects of the TA procedure per se may confer an increased risk. On the other side, it is disadvantageous to push the indications for the TF approach when the ilio-femoral vessels are not good enough for this approach, because the occurrence of vascular complications could have serious prognostic implications at short term. In our series, the rate of major vascular complications of 10.9% among TF patients is high, though comparable to other reports.[65] Further studies are required to identify the risk factors for and precise nature of these peripheral vascular complications. It is hoped that improvements in technology and technique and in the selection of the optimal access route for implantation will reduce the rate of this complication in the future.

6.1.3 Long term hemodynamic performance of self-expandable devices.

We decided to restrict the analysis about long term hemodynamic performance only to one prosthesis type, and we chose the CoreValve device because the patients who received this device were treated at the beginning of our experience and so they had longer follow up.

The main finding of our analysis is that TAVI procedure allowed a significant reduction in transvalvular aortic gradient which was absolutely stable over time. Consequently, the effective orifice area improved immediately after TAVI, reaching values which are even better than those obtained with conventional surgical bioprosthesis, both stented and stentless.[66] This optimal hemodynamic performance leads to a reduction in the prosthesis-patient mismatch rate, and it seems advantageous in particular for small aortic valve annulus.[66]

In our analysis, while the transprosthesis gradient is stable over time, on the other side the effective orifice area showed a slight decrease at long term follow up. The explanation of this phenomenon is not so clear; however, it may be justified by the fact that the estimation of effective orifice area of transcatheter prosthesis is not well defined and so there could have been an inter-observer variability during time.[67]

The periprosthesis leakage, which was present in most of patients after TAVI using SE devices, in our experience significantly reduced over time. This phenomenon could have different explanations: perhaps the prolonged SE properties of nitinol stent frame may play a role in this regard.

Interestingly, the LV EF increased in the very early phase and continued to improve over time, especially during the first month after procedure. In particular, the LV function improved in the subgroup of patients with an impaired LV EF at baseline. The improvement in LVEF obtained after TAVI seems even better than that observed after surgical AVR; this may be due, at least in a part, to a superior hemodynamic performance of transcatheter prosthesis in terms of the effective orifice area, transprosthetic gradients and reduction of pressure overload on the left ventricle.[66] In addition, we must consider that TAVI, especially when performed by TF approach, allows for better protection and ensures an improved recovery of myocardial function, while avoiding (or at least minimizing) ischemic and ischemia/reperfusion injury, inflammatory response, cardioplegia, surgical trauma and oxidative stress which can lead to apoptosis and contractile dysfunction of survivors myocytes.[31]

No statistically significant changes were recorded after TAVI in terms of LV volumes and right systolic pulmonary pressures. Moreover, at difference of other series,[68] we did not recorded any significative regression in LV mass.

Finally, we found no impairment in mitral valve function, either stenosis or regurgitation. This is important because it is not excluded that the geometry of the self expandable device and the implantation technique, deep into the LV outflow tract, might lead to a worsening in mitral

regurgitation,[69] development of mitral stenosis especially in patients with heavy calcifications of the anterior leaflet,[69] or damage to the left anterior mitral leaflet itself over long term. Some anecdotic cases are described in literature about this topic.[70]

6.2 Special settings. How to expand the eligibility for TAVI: new candidates.

6.2.1 The trans-subclavian retrograde approach.

Recently, TAVI has emerged as alternative treatment for degenerative AS in inoperable/high-risk surgical patients.[28] However, the amount of patients eligible for transcatheter treatment may be limited for anatomical reasons.[34, 71] In fact, the size and geometry of aortic annulus, aortic root, and ascending aorta may be not suitable for adequate positioning of the current available devices. Moreover, the presence of peripheral artery disease may compromise the retrograde TF arterial approach. The latter condition may be overcome by other transcatheter approaches, such as the antegrade transvenous or the TA one. The antegrade transvenous approach[28, 72] appears more suitable in introducing the large delivery systems reducing the risk of vascular complications. However, trans-septal puncture makes this approach very challenging, and special attention must be given at each step of the procedure not to damage mitral valve apparatus. For these reasons, this approach was completely rejected. Recently, the TA route was widely and successfully performed by using the Edwards-SAPIEN Valve (Edwards LifeSciences Inc., Irvine, California) in patients with severe peripheral vasculopathy.[73, 74] This approach allows the introduction of delivery systems into the heart without limitation in sheath diameter. However, it requires a hybrid operating room, a multidisciplinary team, and it is much more invasive. Moreover, TA valve implantation has some technical limitations, as in the case of severe septal hypertrophy in combination with the angled position of the LV outflow tract in relation to the aortic root.[75] In this scenario, a trans-subclavian retrograde approach could represent an intriguing alternative for TAVI in high-risk aortic patients with associated severe iliac-femoral arteriopathy.

In fact, this approach combines the advantage of overcoming peripheral vascular disease without the invasiveness of the TA technique. As in the TA approach, procedural times are longer than in percutaneous TF implantation, and a multidisciplinary team is needed. However, the trans-subclavian approach enables a more rapid mobilization of patients, and it seems reasonable that, in

the near future, it will require only a local anesthetic and mild sedation with further reduction in periprocedural times. We experienced a simple surgical cut-down for the left subclavian artery, an easy insertion of the sheath with reliable positioning and release of the prosthesis in all attempted cases. No intraprocedural or periprocedural complications occurred. Moreover, the trans-subclavian approach seems to provide a more direct access to the implantation site and an easier delivery of the prosthesis than the TF approach. In fact, in our experience, the manipulation of the device and the positioning of the valve are more precise and reliable by the subclavian approach, probably because of the shorter distance from the subclavian access to the aortic annulus requiring weaker forces of tension and torsion, which bind the delivery catheter. One of our patients previously underwent CABG with the left internal mammary artery. In cases such as these, the subclavian approach may be more challenging, and attention must be paid to introduce the sheath carefully by fluoroscopic guidance. If the subclavian artery is calcified and not too large, it might be safer to completely introduce the sheath only to deliver the prosthesis into the aortic arch, and then slightly retrieve the sheath itself in order to minimize the risk of mammary flow obstruction and/or dissection. This caution should be adopted also in case of right vertebral artery occlusion with a dominant left vertebral artery. In our small series, patients did not experience vascular complications or cerebrovascular accidents. In fact, the proximity of the subclavian access to the implantation site also reduces the likelihood of vascular complications when compared with TF access procedure. In addition, the manipulation of the superstiff wire around a potentially calcified aortic arch, which may cause particulate embolization and subsequent stroke, is more limited in the trans-subclavian procedure than in the TF one. Finally, in our experience, surgical wounds healed quickly in spite of double antiplateled therapy, and patients were discharged within a short period, with good and stable hemodynamic compensation, as assessed at a three-month follow-up.

In conclusion, TAVI by subclavian retrograde approach seems safe and feasible in inoperable/high-risk patients with AS and co-existing peripheral vasculopathy, who are not eligible for surgical valve replacement or TF percutaneous aortic valve implantation. This approach allowed us to

extend the current indications for TAVI and, together with a further reduction in delivery system caliber and the development of a new prosthesis, may increase the percentage of eligibility for TAVI.

6.2.2 The treatment of bioprosthesis dysfunction with the valve-in-valve technique.

Recently, Wenaweser and associates[76] reported the first case of CoreValve implantation for the treatment of aortic regurgitation in a degenerating surgical bioprosthesis using the valve-in-valve technique. They used general anaesthesia with the hemodynamic support of a femoro–femoral bypass with surgical cut-down of arteries. We here reported, to the best of our knowledge, the first case of TAVI to treat a severe aortic regurgitation in bioprosthesis dysfunction. We used the third-generation CoreValve device, avoiding surgical cut-down of femoral arteries and the need for hemodynamic support. We thereby reduced the potential complications related to multiple large sheath placement and to hemodynamic pump use. In agreement with previous reports, our case confirms the feasibility of TAVI in aortic regurgitation caused by bioprosthesis dysfunction, with immediate hemodynamic improvement and persistent clinical benefit. In light of these evidences, it could be argued that stent-based valve implantation in degenerating prostheses may be more effective than in native valves; the latter usually present a higher amount of calcification, responsible for potential coronary ostial obstruction and inadequate stent sealing to the aortic root with subsequent residual paravalvular leak.[58] However, as previously suggested,[77] an accurate evaluation of the aortic root size, of the distance between the bioprosthesis and coronary ostia, and the particular characteristics of the bioprosthesis, is of overwhelming importance, in order to select the correct transcatheter prosthesis size and to avoid procedural complication.[78, 79]

Although neither the CoreValve Revalving System nor the Edwards SAPIEN/SAPIEN XT heart valve have been approved for use in patients with failed aortic bioprostheses, there are reports of successful implantation in patients refused by surgeons for an unacceptable surgical risk.[60, 76, 80-84] We believe that TAVI with both SE and balloon expandable prosthesis may represent in the future

an appropriate therapeutic alternative to surgical reintervention in elderly patients affected by bioprosthesis dysfunction. In fact, since the increase in life expectancy is leading to a huge number of patients undergoing AVR at advanced ages, with increasing use of bioprostheses, an expanding amount of bioprosthesis dysfunction in elderly patients with multiple comorbidities could be expected in the future. Moreover, currently the bioprosthesis are used also in patients younger than 60 years old due to the lower risk of reintervention. This increase even more the rate of expected bioprosthesis dysfunction during the next future. However, data regarding long-term follow-up in a large number of patients are needed to evaluate the real prognostic impact of this treatment.

6.2.3 TAVI in patients with mechanical prosthesis in mitral position.

Few data are available on the effectiveness and safety of TAVI in a patient with an implanted mechanical mitral valve. Concerns exist related to the possible interference between the percutaneous aortic valve and the mechanical mitral prosthesis.

To this regard, the presence of a mitral prosthesis is considered a relative contraindication to TA but not to TF approach. Patients with a pre-existing prosthesis in mitral position should be carefully evaluated for relationship to the aortic annulus to ensure proper

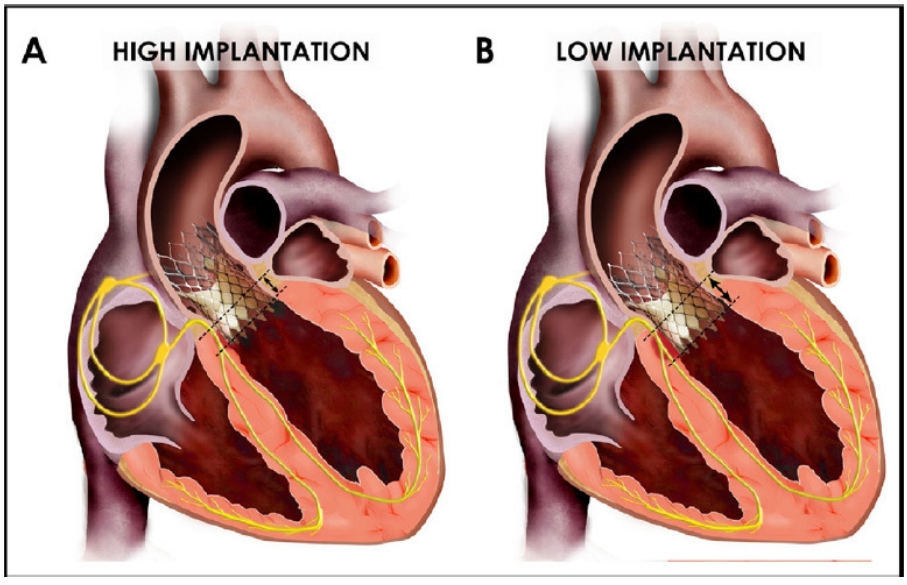
transcatheter heart valve positioning and deployment. Our study confirms and extends the result of a previous report[85] on the feasibility of TAVI in such a situation even without general anaesthesia and trans-oesophageal echocardiography guidance.

6.3 Complications

6.3.1 Conduction disorders after transcatheter self-expandable aortic valve implantation.

Transcatheter revalving therapy has been reported as valuable alternative strategy to AVR in high-risk patients with severe symptomatic aortic valve stenosis.[28, 29, 34] However, TAVI has often been associated with worsening or new-onset CD, particularly when the SE CoreValve device is used,[34, 52] as confirmed by our data showing PPM implantation in more than one third of cases. The geometry and design of this device, based on a 53- to 55-mm-long stent cage extending from ascending aorta to LV outflow, might lead to a variable amount of prosthesis frames, pushing aside the interventricular septum and the underlying conduction tissue. In particular, the lower one third of the prosthesis stent frames, characterized by high radial forces for secure anchoring of the stent against the native annulus and outflow septum, might account for CDs due to compression on the left bundle branch, which runs superficially just below the endocardium in the uppermost part of the leftward ventricular septum (Figures 18 and 28).

Figure 28. Impact of CoreValve positioning on electrical conduction system. *Diagram illustrating anatomic relation between prosthesis across aortic annulus and conduction system. A deeper prosthesis implantation into LV outflow tract might effect electrical conduction system. (From Fraccaro et al. Am J Cardiol 2011;107:747–754).*



In this scenario, it is reasonable that the deeper the prosthesis has been implanted into the LV outflow tract, the greater the risk of compression by the prosthesis against the left bundle branch and, consequently, of the development of severe CD requiring PPM implantation (Figures 18 and 28). These observations are consistent with the greater rate of PPM implantation reported with CoreValve device[52, 86, 87] than with the Edwards Sapien prosthesis (Edwards Lifesciences, Irvine, California), which extends just a few millimeters below the annular plane.[88, 89] Piazza et al[52] described a significant correlation between the depth of prosthesis implantation and new-onset left BBB after CoreValve implantation, suggesting that deploying the prosthesis in a more superior position within the LV outflow tract might limit the risk of AV block and PPM implantation. In light of this hypothesis, we performed a multivariate analysis to identify independent predictors of PPM implantation after TAVI. Our study has confirmed this preliminary hypothesis, identifying the depth of prosthesis implantation into the LV outflow tract as an independent predictor of PPM implantation after CoreValve revalving therapy. In particular, the most relevant measurement predicting PPM implantation was the depth of prosthesis at level of noncoronary cusp, and neither the depth at the level of the left coronary cusp nor the coaxial implantation of prosthesis were related to PPM requirement. Moreover, it is important to emphasize that, as previously reported by Calvi et al,[87] the most frequent CD recorded after TAVI in our series was new-onset left BBB. This CD was likely related to the close anatomic relation between the left bundle branch and the aortic valve apparatus and might favor the development of complete AV block when a right BBB is present before TAVI. Consistent with this assumption, the presence of right BBB before procedure appeared the most powerful predictor of PPM implantation in our analysis, confirming previous observations.[52] A lower rate of PPM was associated with a low prevalence of right BBB at baseline in other series.[90] A greater prevalence of PPM implantation was reported in our study compared to other series.[87] We decided to perform early PPM implantation to minimize the risk related to transvenous temporary pacing support, such as infection and ventricular perforation, coupled with potential problems related to the immobilization and long hospital stay for an elderly patient.

However, our results have confirmed that a recovery in intraventricular conduction (i.e., a decrease in the frequency of left BBB and PPM dependency) can occur over the time. The possible explanations for this include transient inflammation, oedema, ischemia, and mechanical trauma with subsequent recovery of conduction. Postmortem specimens from patients who had developed new AV block after TAVI have demonstrated microscopic evidence of myocardial injury in the interventricular septum, as well as localized hematoma at the site of prosthesis expansion, which might account for mechanical compression of the conduction system coursing in the subendocardium close to the membranous septum.[91] Balloon aortic valvuloplasty itself has been associated in the past with the occurrence of CD.[92] Similarly, the balloon used to predilate the native aortic valve before TAVI could account for reversible mechanical or ischemic effects, explaining the possible conduction recovery with time after TAVI. In contrast, in our series, 2 patients who were discharged with first-degree AV block plus left BBB and with left BBB alone, respectively, experienced late complete AV block. Progressive degeneration of the conduction system, accelerated by mechanical injury and fibrosis in the upper interventricular septum, might have occurred in these patients. Some limitations of our study should be taken into account to place our findings in the proper perspective. First, because we decided to perform early PPM implantation to maximize the patient's safety, the relatively greater rate of PPM resulting from this might have influenced our analyses. However, even though most CDs recovered over time, the PPM dependency was still present in most patients during follow-up. In addition, to understand the relation between prosthesis size and aortic annulus, we assessed the prosthesis dimensions by angiography at the end of the implantation procedure. However, because the full expansion of the nitinol stent frames seems to be reached some days after deployment,[93] this might have led to underestimating the maximal dimensions of the prosthesis and consequently of its effect on annulus stretching.

6.3.2 Conduction disorders after TAVI: differences between self-expandable and balloon-expandable devices.

Although there are no randomized studies comparing Edwards and Corevalve, the available observational data showed that the use of the CoreValve prosthesis rather than Edwards valve confers an increased risk of advanced CD requiring PPM implantation.[94, 95] The different shape, height of the frames of these two devices, their different physical properties account for the different incidence of CD observed with the two types of valves. The SE prosthesis is made by a 53-55 mm high nitinol frame, which gives a continuous radial force for anchoring at the level of LV outflow tract; the balloon expandable prosthesis is made, in its latest generation model, by a cobalt-chromium stent varying in height between 14.3 mm and 19.1 mm (depending on the size of the prosthesis) and it is implanted at intra-annular position through a plastic deformation without continuous radial force.

The left BBB is the most commonly CD observed after TAVI with both devices,[87] with an incidence in our experience of 47.5% in the CoreValve group and of 17.2% in the Edwards group, respectively. In literature, the reported incidence ranges from 7%[88]-18%[90] for the balloon expandable prosthesis and up to 29%[96]-65%[97] for the SE prosthesis.

The need for PPM in our analysis was 41.3% in the CoreValve group and 8.0% in the Edwards group. Similarly, in literature the reported need for PPM varies from 0%[90]-27%[98] after implantation of a balloon expandable prosthesis up to 19%[97, 99]-49%[96] for the self expandable prosthesis, with a significant variability among centers.

In our perspective registry including both SE and balloon expandable devices, putting the self expandable device into a multimodel multivariate analysis, this variable remained as a strong predictors of PPM implantation in all the models we tested.

In our experience the rate of PPM implantation was higher respect to other published series. This is probably related not only to the differences in patients characteristics, but also to the different threshold of PPM implantation. In fact not all the PPM was implanted as an absolute indication

because, in particular at the beginning of our experience, few data existed about the evolution of CD after TAVI.

Currently, data on the progression of CD after TAVI are still scant.

Some authors suggested a spontaneous recovery of CD during follow-up, reduction of PR[86, 97, 100, 101] and QRS intervals,[52, 86, 90, 99-101] and a low stimulation rate in those patients who received PPM.[86, 101, 102] Evidence on this have been mainly described for CoreValve, which is complicated more frequently with CD than Edwards valve.[89, 90] However, a complete recovery of CD is very rare, with a left BBB pattern persisting despite a shortening in QRS duration.[52, 99, 101] On the contrary, cases of late-onset complete atrioventricular block[86, 99, 101] and sudden death[103] are also described in literature for the SE devices.

In our series, we experienced a reduction in PR and QRS intervals which was more evident with SE devices, suggesting in some cases a transient damage of the conduction system with this device. However, the QRS intervals still remained longer in CoreValve patients than in Edwards patients at 30-day follow up. Moreover, even if anecdotic and not statistical significant, no new CD was recorded during the first thirty days after TAVI using balloon expandable device, while after SE valve implantation there was some new first degree AV block, left BBB and need for PPM due to late onset of complete atrioventricular block. This suggests to be extremely cautious in PPM indications especially after CoreValve implantation, at least until more clear evidence will be available.

So, in conclusion, in our study, the left BBB is the most frequent CD after TAVI with both available devices. CD were far more frequent in SE group rather than in BE group, as well as the need for PPM. There seems to be a trend in decreasing of PR and QRS intervals over time after TAVI. However, the risk of late complete atrioventricular block, in particular after SE device, suggests careful evaluation for PPM implantation until clear indications are available.

Data on the prognostic impact of CD after TAVI are anecdotal. Recently, Tzikas and coworkers[104] found, in a small consecutive case-series, that the newly acquired CDs after the CoreValve

implantation were associated with interventricular dyssynchrony and reduced improvement of LV systolic function.

As a consequence, the clear difference in PPM rate after TAVI using the two commercially available devices may suggest to prefer the balloon expandable device in particular subgroup of patients, such as those with pre-existing right BBB (and so probably at higher risk for complete atrioventricular block after CoreValve implantation), and those with baseline LV dysfunction, in order to reduce the probability of interventricular dyssynchrony which negatively impacts on ventricular function.

6.3.3 Periprosthesis leakage after first TAVI: valve-in-valve technique.

We described early and mid-term outcome of valve-in-valve implantation in a small series of patients to overcome acute failure of TAVI. The main finding of our report was that valve-in-valve implantation was feasible in all attempted cases without major procedural complications or adverse events related to double prosthesis implantation. In particular, the deployment of a second device inside an already expanded valve was reliable, since the first implanted prosthesis provided a landmark favoring the correct deployment of a second device, and ensured its firm anchoring, avoiding the risk of early or late embolization or coronary occlusion. Furthermore, the deployment of valve-in-valve was wide and symmetrical enough to guarantee a normal leaflet excursion with an adequate effective orifice area. Indeed, mitral valve function seemed not affected by deep position of the first prosthesis neither by double prostheses implantation. However, the incidence of atrioventricular block and PPM implantation in our patients was higher than those previously reported in TAVI.[52, 86] We guess this might be related to deep positioning of the first prosthesis found in almost all reported cases,[52, 101] rather than to the deployment of two devices. In fact, a deeper implantation of SE prosthesis implies a larger stent-frame surface forcing against the interventricular septum, and may increase the risk of injury of the underlying conduction tissue.[101] Nevertheless, valve-in-valve was highly effective in reducing severe PPL acutely occurred as

consequence of inadequate positioning of transcatheter valve: aortic regurgitation was no longer appreciable or only mild after valve-in-valve in all treated patients. Different mechanisms of PPL have been described, including mainly incomplete stent-frame expansion[58, 105] and prosthesis undersizing.[106] However, PPL may also occur because of bioprosthesis deployment in a suboptimal position across the aortic annulus, particularly too-deep or too-high prosthesis deployment.[107] In fact, during the releasing process, the device ‘‘unloading’’ turns into forces directed forward that may lead to deep implantation. Indeed, the coaxial alignment of the prosthesis in the LV outflow tract as well as the stable position of the device during the step-by-step deployment in some patients is difficult to obtain, especially in very unravelled aortas and in case of angulated aortic arch[107] and very tortuous iliac and femoral arteries. In such situations a careful realignment of prosthesis during the deployment may be useful. Otherwise transubclavian approach may be preferable in this setting, since the manipulation of the device and the positioning of the valve seem more direct and reliable, probably because of the shorter distance from the subclavian access to the aortic annulus and the straighter orientation requiring weaker forces of tension and torsion, which bind the delivery catheter.[48] Recently, Ruiz et al.[60] and Ussia et al.[108] respectively described two cases of valve misplacement successfully treated by valve-in-valve implantation using the SE CoreValve System. Moreover, Piazza et al. have reported in a small series on the effectiveness and safety of two self-expanding bioprosthetic valve implantation during the same procedure to treat the acute failure of TAVI, due to valve malpositioning or valve undersizing.[59] Device repositioning by snaring has been reported by Latib et al. in one case, and by Ussia et al. in four patients respectively, as a feasible and effective solution to PPL due to deep prosthesis implantation.[109, 110] However, as suggested by these authors, this high-risk technique should be performed cautiously, because it might result in prosthesis embolization in the ascending aorta, and only if the operator is concerned about the risk of valve embolization, implanting another valve inside the first with valve-in-valve technique could be considered.[110] In our experience valve snaring was useful in case of low but not very deep implantation. In fact when the valve is very deeply deployed in the left ventricle, it could be of

limited impact, since the snaring does not result in an effective repositioning. Our report confirms the feasibility of valve-in-valve implantation to overcome acute TAVI failure using SE device, due to inadequate valve positioning. In fact, valve misplacement across the aortic annulus (particularly too deep implantation), may lead to large PPL between the not-skirted part of the prosthesis stent frame and the native valve annulus.[59] In this situation, the deployment of a second prosthesis, which overlaps the first one in a slightly upper or deeper position, correctly matching the annulus plane, may ensure effective PPL sealing, without compromising leaflet function.

Valve-in-valve implantation may represent an effective bail-out strategy to overcome acute TAVI failure due to valve misplacement, although a significantly fall in TAVI failure could be expected with increasing operator experience, improvement in releasing system, and more appropriate patients selection. Furthermore, the rate of TAVI success could be improved in the future through development of new transcatheter heart valves, such as retrievable and repositionable devices, and new imaging technologies capable to better locate aortic valve landmark. The other relevant finding of our report is that valve-in-valve deployment seems not to compromise the performance of bioprosthesis leaflets over time. In fact, serial echocardiographic data showed the persistence of low transprosthetic gradient and large effective area, without leaflet incompetence at up to 2-year follow-up. This result, along with the safety of the procedure, could suggest the reliability of redo-TAVI, using SE prosthesis to treat late transcatheter prosthesis failure. In fact, since life expectancy is growing and therefore the prevalence of AS in octogenarians and sicker patients is expected to increase, the use of transcatheter bioprosthesis is likely to expand and a larger number of devices will be implanted in the future.[111] In this scenario, the demonstration of safety and effectiveness of valve-in-valve technique represents a useful acquisition to guide future intervention in late percutaneous bioprosthesis dysfunction.

However, larger studies assessing longterm follow-up, are necessary to further evaluate the clinical impact of this procedure.

6.3.4 Acute kidney injury after TAVI.

Chronic kidney disease is one of the most frequent comorbidities affecting inoperable/high risk patients with severe AS, representing one of the reasons for surgical refusal. In fact, AKI following cardiac surgery is reported to occur in 4% to 30% of the patients[112, 113] and is associated with an increased mortality that is proportional to the severity of AKI.[114, 115]

To date, TAVI seems a viable therapeutic option for these kind of patients and trying to avoid potential deterioration of renal function in patients with CKD has become an important argument for choosing TAVI rather than surgical AVR in those cases. However, information about the impact of TAVI on renal function is scarce. In particular, the use of contrast agents during procedure, the haemodynamic changes during the procedure and the risk of cholesterol embolization when large catheters are manipulated into the diffuse atherosclerotic aorta, deserve particular attention.

The first observation of our analysis is that more than one half (55.8%) of our study population had CKD at baseline. After TAVI there was a statistical significant increase in serum creatinine level, with a complete recovery at discharge.

The incidence of AKI in our experience was about 19%, and was similar to that of other published series,[116] with about 5 per cent of patient requiring dialysis during index hospitalization.

At univariate analysis, the TA approach was more often associated with AKI as compared with the TF technique. Given the small number of patients, we can only speculate on the mechanisms for this difference. The most likely explanation is more prominent generalized arteriosclerosis in TA patients, since peripheral vasculopathy not allowing safe peripheral arterial catheterization, was the reason for choosing the TA approach.

Also the need for inotropic drug support during procedure and a low mean aortic pressure at the end of procedure were more often associated with AKI. To this regard, it is reasonable that a low pressure regimen could explain a transient ischemic impairment in renal function due to inadequate renal perfusion during TAVI.

The need for red blood cell transfusion is a very well recognized predictor of AKI following cardiac surgery.[117, 118]

Consistent with our results, other Authors[116, 119, 120] recently showed that the number of blood transfusions was also associated with an increased risk of AKI following TAVI. In fact, red blood cell transfusions lead to an accumulation of substances which might favour renal dysfunction, such as proinflammatory molecules, free iron, and haemoglobin.[118, 121]

This result suggests that efforts should be made to avoid unnecessary blood transfusions in patients undergoing TAVI.

Interestingly, the amount of contrast media was not associated with AKI following TAVI in our analysis, similarly to previous published studies.[116, 120] Nonetheless, giving the well known association between the contrast amount and the contrast-induced nephropathy following percutaneous coronary intervention,[122, 123] minimization of the use of these agents is warranted.

At multivariate analysis, the need for intraprocedural inotropic drugs and the number of blood transfusions remained as independent predictive factors of AKI.

In our experience, AKI was associated with longer hospital stay, higher in-hospital mortality and worse long-term outcome.

This unfavourable prognostic impact of AKI following TAVI deserve consideration for future preventive strategies.

First of all, contrast media should be used at low doses and continued efforts to minimize the amount of contrast media in these procedures should be made (using for example contrast dilution, contrast hand injections, and echocardiography guiding for valve positioning). A dedicated intravenous pre-hydration protocol to prevent contrast media nephrotoxicity should be applied, even if attention should be paid to avoid an excessive volume overload in these patients.

Finally, the requirement for blood cell transfusions has to be diminished in particular by a strict control of vascular access and haemostasis.

6.3.5 Cerebral embolism after TAVI.

To date, the risk of peri-procedural stroke is a main concern in the field of TAVI.[43, 124]

The rate of all stroke or transient ischemic attack during the first 30-days after procedure ranges from 5.5% (Partner trial Cohort A)[43] to 6.7% (Partner trial Cohort B)[27]. Moreover, at magnetic resonance imaging studies, there seems to be an higher rate of silent cerebral ischemia ranging from 68 to 91%.[125-128] It is uncertain if patients who experience subclinical strokes have a similar prognosis to those who have overt symptoms and in particular we do not know the impact of silent ischemia on neurocognitive function over long term. This is an important point to be clarified before extending the indications of TAVI to a younger and lower risk population.

By the available data, about half of the strokes seems to be intra-procedural,[129] but the remaining are periprocedural.[130, 131] They seem to be related to heavier calcification of the valve.

Potential mechanisms of embolization are[129]:

- Crossing aortic arch;
- Crossing the aortic valve;
- Balloon valvuloplasty;
- Valve positioning and deployment.

In the setting of AVR or TAVI, the presence of a major stroke is undoubtedly associated with a poor overall prognosis. Recent randomized data showed that stroke rates appear to be higher with TAVI compared with AVR, and efforts to reduce the rate of stroke after these procedures are ongoing. Because a significant percentage of these strokes appear to be procedure-related and embolic in nature, some have suggested that active protection of the cerebral circulation from embolic debris might be helpful. The utility of cerebral protection devices is currently in course of validation. A small feasibility study suggested that a deflector device covering the right brachiocephalic trunk and the left carotid arteries may decrease neuroimaging defects post-TAVI.[132]

However, the prevalence of delayed or late strokes after the procedure is not insignificant and should generate active investigation of both devices and adjunctive pharmacotherapy to reduce the frequency and severity of strokes after AVR and TAVI in the future.[131]

CONCLUSIONS

TAVI is maturing as an interventional technique for the treatment of severe symptomatic AS. This technology is undoubtedly considered the biggest advance for patients and the interventional community since the onset of drug-eluting stent technology. The procedural outcome of TAVI is now predictable with optimal early results, a low complication rate and persisting clinical and haemodynamic benefits also at mid term follow up (up to three years). Long term outcome seems to be more "patient-related" than "valve-related", with long term prognosis bound mainly to extra-cardiac comorbidities.

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. A heart team–based selection of devices and access site among patients undergoing TAVI was associated with high device and procedural success. We are strongly convinced that the cooperation between cardiac surgeons, cardiologists, anaesthesiologists, radiologists, nurses and technicians is a key-point of the entire TAVI process.

Recently the indications to TAVI are extending also to particular settings of patients. To this regard, one very promising indication is the treatment of bioprosthesis dysfunction by the so called valve-in-valve technique, allowing to avoid a second sternotomy and giving overwhelming results.

The main concerns about TAVI still regard the risk of embolic complications, CD, periprosthetic leakage and vascular complications.

In the near future, the evolving technology will provide new stent-valves with ameliorated designs and performance, and new smaller delivery systems allowing for less invasive procedures and a lower risk of vascular and cardiac injuries. Moreover, future development of transcatheter valves must focus on improvements in design that facilitate easy and accurate positioning, with avoidance of coronary obstruction and minimization of paravalvular leak. In addition, the ability to retrieve

and redeploy a malpositioned valve would be an invaluable capability that is currently lacking in all devices.

Improvements in intraoperative fluoroscopic, echocardiographic and possibly magnetic resonance imaging will also likely improve the success of these techniques.

It can be presumed that the indications for this emerging procedure will expand towards younger and less risky candidates as soon as ongoing clinical trials provide favourable supporting long-term results.

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APPENDIX A – Personal contribution

Dr. Chiara Fraccaro: Personal contribution during the Ph.D. course (2009-2011):

Papers:

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Lectures:

1. Incontri di Cardiologia del Triveneto. La cardiopatia ischemica riletta alla luce dei nuovi trial randomizzati: luci e ombre. Padova, 21 Novembre 2009
2. Progetto Cardiolive: Stenosi aortica dell'anziano. Padova, 04 Maggio 2010
3. IVUS connection meeting. Padova 30 Settembre 2010
4. Convegno Interventistica Interregionale GISE, 2011, Padova
5. Aggiornamenti in tema di sindromi coronariche acute, Padova 2011
6. Le basi anatomiche dell'impianto transcatetere di protesi valvolare aortica. Il tessuto di conduzione nella TAVI. Padova 2011
7. Incontri SIC Triveneto. Challenges in valvulopatia aortica. Padova, 26 Novembre 2011

Abstracts:

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