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Impact of asymptomatic carotid artery stenosis on short and mid term outcome of transcatheter aortic valve implantation.

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Alla mia famiglia

INTRODUCTION

Aortic valve stenosis (AS) is the most common degenerative valve disease in western countries, its socio-economic impact is an emerging issue caused by the close link between the degenerative etiology and an aging population.

Recent epidemiological data from Europe and US show a prevalence of aortic stenosis of 3% in the population older than 75 years and of of 8.1% in those over the 85 years old.

The degenerative aortic valve stenosis, in its most severe form, is a highly debilitating chronic condition, characterized by a survival of 2-3 years after the onset of the symtoms.

The surgical valve replacement with mechanical or biological prosthesis is the gold standard because it is able to change the prognosis and significantly improve the quality of life.

Cardiac surgery, with extracorporeal circulation performed by sternotomy or thoracotomy, under general anesthesia, in general population is associated with a low risk (about 2-3% in elective patients), but it is not a viable therapeutic option in a group of patients considered at high surgical risk or inoperable.

In 2003, the Euro Heart Survey showed that about 30% of patients were not elegible to surgery due to significant comorbidities with a high risk.

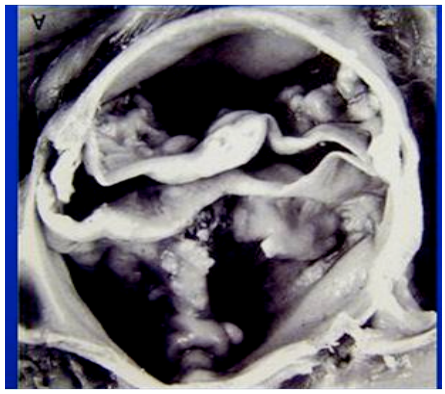
Since the 80s, it has been searched an alternative therapeutic option to traditional surgical valve replacement, which led in 1985 to the first percutaneous aortic valvuloplasty performed by Alain Cribier, this technique was soon abandoned for the high recurrence of AS in few weeks. In 2002 Cribiere opened a new era with the first trans-catheter aortic valve implantation (TAVI) in a human, this technique become in few years the current standard of care in inoperable patients with a severe aortic valve stenosis.

AORTIC STENOSIS

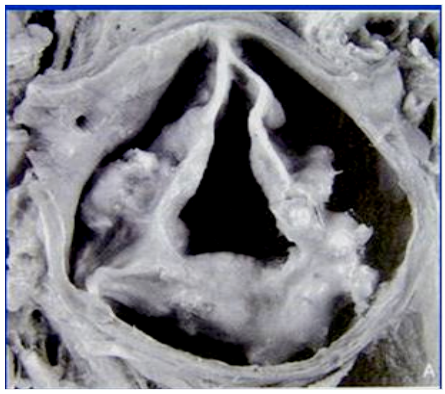
The aortic stenosis (AS) is a valvular heart disease due to three main aetiological categories:

- congenital,
- rheumatic
- degenerative (or senile).

Degenerative aortic valve disease



Bicuspid Aortic valve



Rheumatic diseased aortic valve

In the past, AS was most frequently found as a rheumatic disease characterized by adhesions and fusions of cusps, vascularization of cusps and valve ring, the presence of calcified nodules on the cusps surface, with retraction and stiffening of the free edges of the cusps and a crucial reduction of valve orifice often associated with aortic regurgitation.

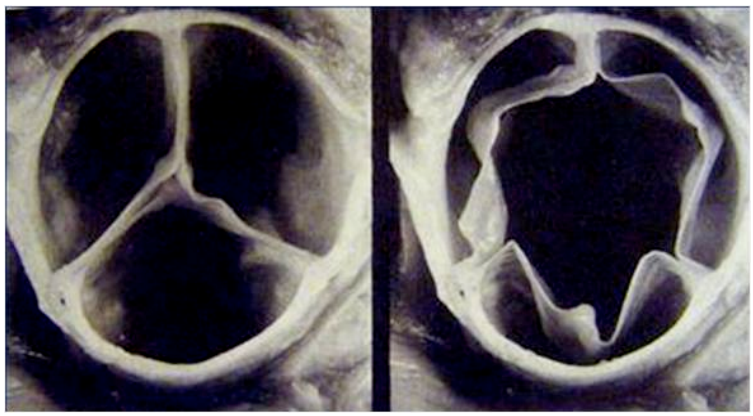
Congenital malformations of the aortic valve are classified as unicuspid, bicuspid or tricuspid depending on the valve morphology. The unicuspid form cause serious obstruction since childhood and are the most frequent among the fatal AS in children under one year.

Bicuspid aortic valve disease presents a congenital fusion of the commissures at birth, but more often it causes severe aortic orifice narrowing in young adults, bicuspid aortic valve is often a congenital disese with autosomal dominant inheritance with incomplete penetrance. The third type of congenital AS is characterized by triscuspid valves, with leaflet of different sizes and different degrees of congenital commissures fusion.

The degenerative aetiology is currently the most common cause of AS in adults. Recent epidemiological data from Europe and the United States show a moderate-severe aortic stenosis prevalence in 4.6% of the population aged more than 75 years old raising to 8.1% in subjects older than 85 years.

Risk factors develope an aortic stenosis are similar to those of atherosclerotic vascular disease: elevated serum levels of LDL cholesterol and Lp (a), diabetes mellitus, smoke and hypertension.

According to the most recent hypothesis the degenerative process that affects the aortic valve is secondary to inflammatory and proliferative changes, with lipid accumulation and infiltration of macrophages and T lymphocytes, that leads to a buildup of calcium which initially involve the bending lines of cusps commissures and progressively extend over the entire valve surface causing valve stenosis. 3



Normal aortic valve

PATHOPHYSIOLOGY

The main hemodynamic characteristic of AS is constituted by the obstruction of the left ventricular outflow tract, which determines a pressure gradient between the left ventricle and the aorta. In adults the obstruction gradually worsens, allowing the maintenance of a normal cardiac output through the development of a compensatory mecha left ventricular hypertrophy which tends to normalize the systolic stress of the myocardium.

AS is an insidious disease with a long latency period, patients develops progressively a high trans-aortic pressure gradient that may remain asymptomatic for many years, however, leading to cardiac output reduction and left ventricle remodeling in end-stage disease.

When the heart faces an hemodynamic burden, it can do the following to compensate:

1 use the Frank-Starling mechanism to increase crossbridge formation;
2 augment muscle mass to bear the extra load;
3 recruit neurohormonal mechanisms to increase contractility.

The first mechanism is limited in its scope, and the third is deleterious

as a chronic adjustment. Thus, increasing mass assumes a key role in the compensation for hemodynamic overload. This increase in mass is due to the hypertrophy of existing myocytes rather than hyperplasia, because cardiomyocytes become terminally differentiated soon after birth. In response to pressure overload the parallel addition of sarcomeres causes an increase in myocyte width, which in turn increases wall thickness. This remodeling results in concentric hypertrophy (increase in ratio of wall thickness/chamber dimension).

According to LaPlace's Law, the load on any region of the myocardium is given as follows: (pressure×radius)/(2×wall thickness); thus, an increase in pressure can be offset by an increase in wall thickness. Because systolic stress (afterload) is a major determinant of ejection performance, the normalization of systolic stress helps maintain a normal ejection fraction even when needing to generate high levels of systolic pressure.1

Thanks to these mechanisms the ventricle is able to maintain a normal performance at least at rest but the compensatory mechanism represented hypertrophy, however, has disadvantages:

- increase of myocardial O_2 consumption due to the increased muscle mass.

- increase of systolic period and of intracavitary pressure, determining a reduced coronary perfusion flow inducing myocardial ischemia even in the absence of coronary artery disease.
- reduced compliance of the left ventricle that alters the ventricular relaxation and makes crucial the atrial contribution to ventricular diastolic filling

In patients with left ventricular hipertrophy due to sustained pressure overload (hypertension and aortic stenosis), a hemodynamic hallmark is the elevation of LV end-diastolic pressure relative to a normal or small LV diastolic cavity volume. This decrease in diastolic chamber distensibility is predominantly related to altered passive properties causing an increase in myocardial stiffness, which is described formally by the mechanical stress/strain relationship. Dynamic abnormalities of slowed isovolumic LV pressure decay, as well as slowed early diastolic mitral inflow velocity and ventricular filling with enhanced reliance on atrial transport (decreased E/A ratio), have been described in multiple studies using both invasive and noninvasive technologies; in some patients with advanced hypertrophy, this pattern may evolve to the more severe abnormality of a restrictive pattern of diastolic filling.

In patients with aortic stenosis, senescence profoundly influences the pattern of hypertrophic growth and diastolic function. Using hemodynamic studies complemented by morphometric analyses of ventricular biopsies, Villari et al[85] compared younger (<60 years) and elderly (>65 years) patients with comparable severities of aortic stenosis and showed that elderly patients with pressure overload were characterized by more severe hypertrophy and interstitial fibrosis, as well as more severe impairment of relaxation, myocardial stiffness, and filling indices.

In pressure-overload hypertrophy, the increase in collagen production occurs as an adaptation to overload; autopsy and biopsy studies of patients with severe aortic stenosis frequently show changes in collagen architecture, as well as severe increases in the percentage of fibrosis occupying the myocardium; this fibrosis reaches a maximum at ≈30%.

SYMPTOMS

The symptom triad of aortic stenosis is represented by:

- Exertional and rest angina: discrepancy between increased myocardial O_2 consumption and reduced coronary perfusion;
- Syncope or fainting: by reduced cardiac output associated with low blood pressure due to vasodilation triggered from the abnormal baroreflex in response to increased ventricular pressure;
- Exertional dyspnea, paroxysmal nocturnal dyspnea and pulmonary edema: reflect different degrees of increase in pulmonary capillary pressure secondary to increased end-diastolic pressure in the left ventricle garbling the dynamic balance between hydrostatic and osmotic pressures in pulmunary capillary circulation.

NATURAL HISTORY

Many patients with aortic stenosis will not have any symptoms, and the diagnosis is made on the basis of a heart murmur heard on examination. Patients with AS tend not to manifest cardiovascular symptoms until a relatively advanced stage of the disease when heart failure develops. The clinical history of aortic stenosis is characterized by a long latency period during which the mortality and morbidity are quite low.

In most cases the first symptom is exertional dyspnea while others appear later when the left ventricular failure is going on (orthopnea, paroxysmal nocturnal dyspnea, pulmonary edema). The breathlessness often accompany episodes of angina. Syncope is the rarest and latest symptom and occurs usually under stress.

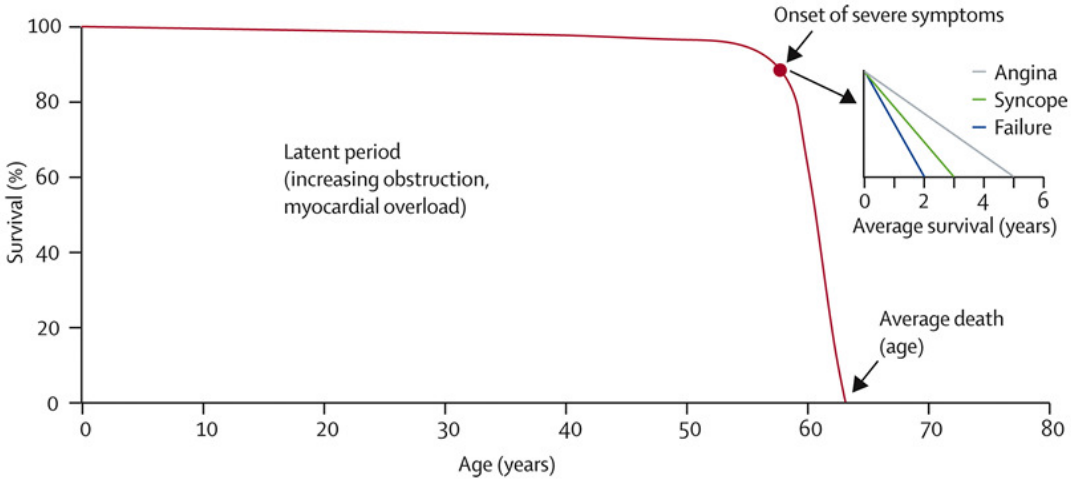
Usually asthenia, peripheral cyanosis and low flow events characterizethe end stages of the disease. Even the symptoms of left ventricular failure as orthopnea, paroxysmal nocturnal dyspnea and pulmonary edema are characteristic of an advanced aortic stenosis.

It is critical for proper patient management and must be taken into account the possibility that patients may deny symptoms as they subconsciously reduce their activities.

The appearance of symptoms is followed by rapid progression, resulting in a high rate of death among untreated patients; since

patients experienced angina pectoris or syncope mean survival is 1-3 years; after the onset of heart failure symptoms the mean survival rate drops to 1.5 years (Fig. 1.3). Among symptomatic patients with severe AS, the prognosis is even worse when reduced left ventricular function is associated with reduced cardiac output and low trans-valvular gradient (a condition known as low flow low-gradient aortic stenosis).

Sudden death can occur in advanced disease and is mainly related to the onset of acute pulmonary edema, cerebral hypoperfusion and malignant ventricular arrhythmias.



The course of aortic valve disease (Source: Ross et al, 1968)[2]

Diagnosis of Aortic Stenosis

Medical and interventional approaches to the management of patients with valvular AS depend on accurate diagnosis of the cause and stage of the disease process. Each stage of disease is defined by valve anatomy, valve hemodynamics, the consequences of valve obstruction on the left ventricle and vasculature, as well as by patient symptoms. Hemodynamic severity is best characterized by the transaortic maximum velocity (or mean pressure gradient) when the transaortic volume flow rate is normal. However, some patients with AS have a low transaortic volume flow rate due to either left venricle (LV) systolic dysfunction with a low LV ejection fraction (LVEF) or due to a small hypertrophied left ventricle with a low stroke volume.

The definition of severe AS is based on natural history studies of patients with unoperated AS, which show that the prognosis is poor once there is a peak aortic valve velocity of >4 m per second, corresponding to a mean aortic valve gradient >40 mm Hg. In patients with low forward flow, severe AS can be present with lower aortic valve velocities and lower aortic valve gradients. Thus, an aortic valve area should be calculated in these patients. The prognosis of patients with AS is poorer when the aortic valve area is <1.0 cm2. At normal flow rates, an aortic valve area of <0.8 cm2 correlates with a mean aortic valve gradient >40 mm Hg. However,

symptomatic patients who have a calcified aortic valve with reduced opening and an aortic valve area between 0.8 cm2 and 1.0 cm2 should be closely evaluated to determine whether they would benefit from valve intervention. Meticulous attention to detail is required when assessing aortic valve hemodynamics, either with Doppler echocardiography or cardiac catheterization, and the inherent variability of the measurements and calculations should always be considered in clinical-decision making.

As told most patients with AS are first diagnosed when cardiac auscultation reveals a systolic murmur or after a review of trans thoracic echocariography (TTE) requested for other indications. Physical examination findings are specific but not sensitive for evaluation of stenosis severity. The classic findings of a loud (grade ≥3/6), late-peaking systolic murmur that radiates to the carotid arteries, a single or paradoxically split second heart sound, and a delayed and diminished carotid upstroke confirm the presence of severe AS. However, carotid upstroke may be normal in elderly patients because of the effects of aging on the vasculature, and the murmur may be soft or may radiate to the apex. The only physical examination finding that is reliable in excluding the possibility of severe AS is a normally split second heart sound.

TTE is indicated when there is an unexplained systolic murmur, a

single second heart sound, a history of a bicuspid aortic valve, or symptoms that might be due to AS. Echocardiographic imaging allows reliable identification of the number of valve leaflets along with qualitative assessment of valve motion and leaflet calcification. In nearly all patients, the hemodynamic severity of the stenotic lesion can be defined with Doppler echocardiographic measurements of maximum transvalvular velocity, mean pressure gradient, and continuity equation valve area, as discussed in the European Association of Echocardiography (EAE)/ASE guidelines for evaluation of valve stenosis. Doppler evaluation of severity of AS has been well validated in experimental and human studies compared with direct measurements of intracardiac pressure and cardiac output. In addition, Doppler measures of severity of AS are potent predictors of clinical outcome. However, Doppler may underestimate or overestimate aortic velocity and disease severity in some patients, so clinical evaluation should include symptoms, physical examination findings, and results of other diagnostic testing such as cardiac catheterization, exercise testing, low dose dobutamine stress testing using TTE or invasive hemodynamic measurements.

Echocardiographic assessment of aortic valve stenosis

Echocardiography has become the standard means for evaluation of aortic stenosis (AS) severity

The most common causes of valvular AS are calcific stenosis of a tfrileaflet valve, a bicuspid aortic valve with superimposed calcific changes, and rheumatic valve disease.

Anatomic evaluation of the aortic valve is based on a combination of short- and long-axis images to identify the number of leaflets, and to describe leaflet mobility, thickness, and calcification. In addition, the combination of imaging and Doppler allows the determination of the level of obstruction; subvalvular, valvular, or supravalvular. Transthoracic imaging usually is adequate, although transesophageal echocardiography (TEE) may be helpful when image quality is suboptimal.

The primary haemodynamic parameters recommended for clinical evaluation of AS severity are:

- AS jet velocity
- Mean transaortic gradient
- Valve area by continuity equation.

Jet velocity

The antegrade systolic velocity across the narrowed aortic valve, or aortic jet velocity, is measured using continuous-wave (CW) Doppler ultrasound. AS jet velocity is defined as the highest velocity signal obtained from any window after a careful examination. The shape of the CW Doppler velocity curve is helpful in distinguishing the level and severity of obstruction. Although the time course of the velocity curve is similar for fixed obstruction at any level (valvular, subvalvular, or supravalvular), the maximum velocity occurs later in systole and the curve is more rounded in shape with more severe obstruction. The shape of the CW velocity curve also can be helpful in determining whether the obstruction is fixed or dynamic. Dynamic subaortic obstruction shows a characteristic late-peaking velocity curve, often with a concave upward curve in early systole. Severe aortic stenosis is defined when AS jet velocity is more than 4m/sec.

Mean transaortic gradient

The difference in pressure between the left ventricular (LV) and aorta in systole, or transvalvular aortic gradient, is another standard measure of stenosis severity. Transaortic pressure gradient is calculated from velocity (v) using the Bernoulli equation as: □

$\Delta P = 4v2$

The maximum gradient is calculated from maximum velocity: □Pmax= 4 vmax ²

and the mean gradient is calculated by averaging the instantaneous gradients over the ejection period, a function included in most clinical instrument measurement packages using the traced velocity curve. Severe aortic stenosis is defined as mean gradient more than 40 mmHg.

Valve area.

Doppler velocity and pressure gradients are flow dependent; for a given orifice area, velocity and gradient increase with an increase in transaortic flow rate, and decrease with a decrease in flow rate. Calculation of the stenotic orifice area or aortic valve area (AVA) is helpful when flow rates are very low or very high, although even the degree of valve opening varies to some degree with flow rate. Aortic valve area is calculated based on the continuity-equation concept that the stroke volume (SV) ejected through the LV outflow tract (LVOT) all passes through the stenotic orifice (AVA) and thus SV is equal at both sites:

SVAV =SVLVOT

Because volume flow rate through any CSA (cross sectional area) is equal to the CSA times flow velocity over the ejection period (the VTI of the systolic velocity curve), this equation can be rewritten as:

$$AVA \times VTI_{AV} = CSA_{LVOT} \times VTI_{LVOT}$$

Solving for AVA yields the continuity equation

$$AVA = CSA_{LVOT} \times VTI_{LVOT} / VTI_{AV}$$

Severe aortic stenosis is suggested by

- AS jet >4 m/sec
- mean gradient >40 mmHg
- valve area < 1.0 cm2 at any flow rate

Exercise stress echocardiography.

When LV systolic dysfunction co-exists with severe AS, the AS velocity and gradient may be low, despite a small valve area; a condition termed 'low-flow low-gradient AS'. A widely used definition of low-flow low-gradient AS includes the following conditions:

- Effective orifice area < 1.0 cm2 ;
- LV ejection fraction <40%; and
- Mean pressure gradient < 30 – 40 mmHg

Dobutamine stress echocardiography is applied to assess contractile reserve and AS severity in the setting of LV dysfunction.

Dobutamine stress provides information on the changes in aortic velocity, mean gradient, and valve area as flow rate increases, and also provides a measure of the contractile response to dobutamine, measured by the change in SV or ejection fraction. These data may be helpful to differentiate two clinical situations:

- Severe AS causing LV systolic dysfunction. The transaortic velocity is flow dependent; so, LV failure can lead to a patient with severe AS having an apparently moderate transaortic peak velocity and mean pressure gradient associated with a small effective orifice area. In this situation, aortic valve replacement will relieve afterload and may allow the LV ejection fraction to increase towards normal.
- Moderate AS with another cause of LV dysfunction (e.g. myocardial infarct or a primary cardiomyopathy). The effective orifice area is then low because the LV does not generate sufficient energy to overcome the inertia required to open the aortic valve to its maximum possible extent. In this situation, aortic valve replacement may not lead to a significant improvement in LV systolic function.

The role of dobutamine stress echocardiography in decision-making in adults with AS is controversial; the findings recommend as reliable are:

- An increase in valve area to a final valve area >1.0 cm2 suggests that stenosis is not severe.
- Severe stenosis is suggested by an AS jet > 4.0m/sec or a mean gradient >40 mmHg provided that valve area does not exceed 1.0 cm2 at any flow rate.
- Absence of contractile reserve is a predictor of a high surgical mortality and poor long-term outcome although valve replacement may improve LV function and outcome even in this subgroup

Current standard of care for Aortic Stenosis

The goals of treatment for patients with AS include delaying disease progression, avoid congestive heart failure, improving symptoms and prolonging life. According to ESC/EACT and AHA/ACC guidelines, the following criteria for severe AS should be satisfied: aortic-valve area of less than 1 cm2, a mean aortic-valve gradient of 40 mm Hg or more, or a peak aortic-jet velocity of 4.0 m per second or more. [11] The currently treatment options for severe AS are:

1. Medical therapy
2. Balloon valvuloplasty
3. Aortic valve replacement surgery (AVR)
4. Transcatheter aortic valve implantation (TAVI)

The only definitive treatment are AVR and TAVI. The development of symptoms due to severe AS and the evidence of an impaired left ventricular function (EF <50%) provide a clear indication for valve replacement [11]

For patients who are not candidates for surgical intervention, percutaneous aortic balloon valvuloplasty may provide some symptom relief. It may be considered as a bridge to surgery or transcatheter aortic-valve implantation (TAVI) in haemodynamically unstable patients or in patients with symptomatic severe AS who

require urgent major non-cardiac surgery. When used in isolation its efficacy is low and it is associated with a high rate of complication (10%) and the occurrence of restenosis and clinical deterioration within 6–12 months in most patients results in a mid- and longterm outcome similar to natural history. [12]

Medical treatment in aortic stenosis may provide temporary symptom relief but is generally not effective in long term as it does not modify the natural history. [10,11]

Transcatheter aortic-valve implantation (TAVI) is a procedure in which a bioprosthetic valve is inserted through a catheter and implanted within the diseased native aortic valve. Since 2002, when the procedure was first performed [13], there has been a rapid growth in its use and it is now widely practiced, and the technique has been recommended as an alternative strategy for patients in high-risk surgical groups. [10,14,15]

Transcatheter Aortic Valve Implantation

Usefulness of TAVI

Many patients with severe AS and cardiac symptoms are not candidates for AVR because of a high risk for operative complications or death on the basis of coexisting conditions. Risk of AVR is increased by a number of factors, including increasing age and comorbidities, such as heart failure, respiratory and renal

disease, prior cardiac surgery, and need for concomitant coronary revascularization. [16] Many studies have suggested that TAVI is a less invasive option for these high-risk patients. It has been demonstrated that TAVI, as compared with standard therapy, significantly reduced the rates of death from any cause, the composite end point of death from any cause or repeated hospitalization and cardiac symptoms.[10,14,15]

In the Placement of Aortic Transcatheter Valves (PARTNER) trial, inoperable patients with severe aortic stenosis had improved survival with transcatheter aortic valve implantation compared with standard medical therapy. Survival was similar with TAVI and surgical aortic valve replacement in high risk patients.[14,17]

However, important differences in periprocedural risks were observed. Major vascular complications and stroke were more frequent with TAVI, whereas major bleeding and new-onset atrial fibrillation were more frequent with surgical valve replacement. [18]

In another randomized study, TAVI using a self-expanding transcatheter aortic-valve bioprosthesis (CoreValve, Medtronic) was associated with a significantly higher survival rate at one year follow-up than surgical aortic-valve replacement in high surgical risk patients. The rate of death from any cause was 14.2% in the TAVI group and 19.1% in the surgical group ($P = 0.04$). The occurrence of major adverse cardiovascular and cerebrovascular events was

significantly lower through one year in the TAVI group than in the surgical group and the data did not show an increased risk of stroke with TAVI, as compared with surgery. [19]

Indications for TAVI

TAVI should only be performed in hospitals with cardiac surgery on-site. A 'multidisciplinary heart team' assesses individual patient's risks, as well as the technical suitability of TAVI and access issues. Eligible patients should have a life expectancy of more than 1 year and should also be likely to gain improvement in their quality of life, taking into account their comorbidities. Based on current data, according to the guidelines of the European Society of Cardiology, TAVI is recommended in patients with severe symptomatic AS who are considered unsuitable for conventional surgery because of severe comorbidities. TAVI should be considered as an alternative to surgery in those patients for whom the 'heart team' favours it. [10] A logistic Euro-SCORE ≥20% has been suggested as an indication for TAVI therapy but EuroSCORE is known to markedly overestimate operative mortality. Use of the STS scoring system >10% may result in a more realistic assessment of operative risk. [20] On the other hand, frailty and conditions such as porcelain aorta, history of chest radiation or patent coronary bypass grafts may make patients less

suitable for AVR despite low or intermediate predicted mortality by risk scores. Therefore, according to european guidelines the risk assessment should mostly rely on the clinical judgement of the 'heart team', in addition to the combination of scores. [10]

Current Principles and Technique

The procedure is best performed in an interdisciplinary setting involving cardiovascular surgeons, interventional cardiologists, anaesthesiologists, and cardiac imaging specialists. Depending on the local environment, the procedure may be performed in a standard catheterization laboratory, an operating theatre, or a dedicated hybrid room. Although the implantation of a transcatheter heart valve is less invasive than surgical aortic valve replacement, a sterile environment is mandatory to avoid complications such as wound infections and endocarditis [20]

There are many possible accesses:

I. retrograde transfemoral
II. transapical
III. subclavian or axillary
IV. transaortic

The transfemoral route allows minimally invasive vascular access through a percutaneous approach or surgical arterial exposure. This route shortens the length of hospital stay and has higher 1-year

survival rates than the transapical route; however, this may be due to higher rates of comorbidity in the transapical group. [21,22] The transaxillary/subclavian approach was introduced as an alternative route in patients with difficult transfemoral access for implantation of the CoreValve. Initial studies reported excellent procedural success rates that suggest that this technique may provide a safer alternative to the transapical route in patients in whom the transfemoral route is contraindicated. [23]

Devices

In clinical application there were 2 first-generation percutaneous valves, the self-expanding CoreValve ReValving system (Medtronic Inc; Minneapolis, MN) and the balloon-expandable Edwards SAPIEN prosthesis (Edward Lifesciences Inc; Irvine, CA), which is now available as the new generation, smaller profile, balloon-expandable Edwards SAPIEN XT prosthesis.

The CoreValve is available in 4 inflow diameter sizes, 23, 26, 29 and 31 mm, whereas the Edwards SAPIEN and Edwards SAPIEN XT valves are available in 23- , 26- and 29-mm diameters. The transfemoral route is the first choice for both prostheses in the majority of patients; however, in patients in whom the transfemoral route is contraindicated, the transapical route can be considered for Edwards SAPIEN or Edwards SAPIEN XT valve implantation, and the

transaxillary/subclavian route is an alternative for implantation of the CoreValve. The transaortic approach has emerged as an alternative access feasible with both devices, most of the time preferred by caridac surgeons because technically closer to their standard surgical practice.

The CHOICE trial found that procedural success was more frequent with a balloon-expandable valve compared to a self-expanding valve, due to a lower frequency of greater than mild aortic regurgitation and less need for implanting more than one valve in the balloon-expandable group; cardiovascular mortality at 30 days was similar (4.1 vs 4.3%); permanent pacemaker placement was less frequent in the balloon-expandable group (17.3 versus 37.6 %). [24]

Despite highly favourable outcomes with these devices, several issues remain, including, non-exhaustively, paravalvular regurgitation, valve malpositioning, vascular complications and conduction disorders. [25] New TAVI devices are now CE marked or under evaluation for CE mark. These new-generation devices incorporate features to address the limitations of the first-generation devices. Table 1 illustrates the key features of the second-generation devices that are entering clinical practice.

Complications

The consensus document of Valve Academic Research Consortium (VARC) and the VARC 2 criteria may help to standardize documentation of postoperative complications. [26,27]

A meta-analysis performed by Genereux et al. including 3,519 patients from 16 unique studies, describes the incidence of TAVI related complication according to the VARC 1 and 2 definitions. The most frequent complication observed is *bleeding*. In the meta analysis of Genereux life-threatening and major bleeding after TAVI occurred in 15.6% (95% CI: 11.7% to 20.7%) and 22.3% (95% CI: 17.8% to 28.3%), respectively. The total incidence of bleeding (life-threatening, major and minor) was 41.4%.

The *permanent pacemaker insertion* reported in literature is about 14% resulting from data of both devices (Medtronic CoreValve system and Edwards Lifesciences device). It is generally accepted that the self-expandable CoreValve, because of its higher and longer lasting radial force as well as the deeper implantation site in the left ventricular outflow tract, has a higher rate of pacemaker requirement than the Edwards valve. Current evidences show that 20% and 30% of patients after CoreValve implantation and 3% to 5% of patients after Edwards valve placement will require a new permanent pacemaker. [28, 29]

Acute Kidney Injury (AKI) in literature has been reported according to the VARC definition in a percentage of about 20%, including stage I,II and III. [28]

Major vascular complications has been reported in about the 12% of patients. The TA approach has been associated with a lower rate of vascular complications than the TF route.

Periprocedural myocardial infarction (<72 h after TAVI) occurred at a rate of about 1.1%. Although coronary obstruction is a potential cause, other factors such as global ischemia due to hypotension, rapid pacing, microembolism induced by device delivery or implantation, myocardial tissue compression by the device expansion, and direct trauma of the apex during transapical access must also be considered. [28]

Cerebrovascular events (CVEs) are one of the most serious complications, potentially affecting patient survival, autonomy, and quality of life. CVEs before and after TAVI may be multifactorial and include embolic debris or thrombus, aortic dissection, hemodynamic instability, and bleeding. The major stroke rate reported in literature is of about 4%. [28,30]

Our Study

Aim of the study

Increased neurologic events associated with TAVI have raised concerns. Stroke is a potential major complication of AVR, TAVI, and balloon aortic valvuloplasty. Although its occurrence is rare, stroke significantly affects survival and quality of life. [14,18,32]

The risk of stroke after TAVI may be due to dislodgement and subsequent embolization of debris from aortic arch atheroma or from the calcified valve itself during the intravascular manipulation. [31,32]

The impact of comorbidity and preoperative risk factors in valve replacement operations has been reported in detail since 1985.

Peripheral vascular disease and carotid artery disease are independent risk factors that have been identified as predictors of operative death according to surgical risk scores. The presence of a significant carotid stenosis may increase the surgical risk leading to the choice of a percutaneous transaortic valve implantation rather than a surgical AVR. [33,34]

Patients with high grade carotid stenosis, who have undergone cardiac surgery, are at increased risk for perioperative stroke. Surgical treatment of carotid stenosis before heart surgery is

indicated only in patients with a high risk for perioperative stroke in whom it is expected that the risk of cerebral embolism is mostly related to carotid atherosclerosis. A staged surgical approach is recommended. Stenting of carotid arteries represents a less invasive alternative for high-risk surgical patients.

Data from brain MRI performed in patients with AS before and 3 months after TAVI documented that TAVI is associated with a high rate of clinically silent cerebral embolism (72.7%), in contrast, the clinical symptoms of neurological deficits persist only in 3.6% of patients examined three months after TAVI; these works were conducted on a small population so further research are needed to determine the clinical relevance of these findings in a larger population of patients.

In the Western world, ischaemic stroke has a major public health impact as the first cause of long-term disability and the third leading cause of death. At present there is no evidence that describes the impact of asymptomatic significant carotid stenosis detected accidentally during preoperative evaluation on the onset of cerebrovascular periprocedural events after TAVI. The aim of our study is to assess the impact of these stenosis on the incidence of cerebrovascular accidents at short and mid term after TAVI.

Methods

Population

From July 2008 through December 2015, we enrolled 1523 patients with severe AS and cardiac symptoms (New York Heart Association [NYHA] class II function or worse) at Centre Hospitalier Universitaire de Toulouse and at Clinique Pasteur in Toulouse. Severe aortic stenosis was defined as an aortic-valve area of less than 1 cm^2 plus either a mean valve gradient of at least 40 mm Hg or a peak velocity of at least 4.0 m per second. Patients were deemed to be at high risk for operative complications or death on the basis of coexisting conditions. The final determination of high operative risk was made by a multidisciplinary Heart Team, composed by a clinical cardiologist, interventional cardiologist, cardiovascular surgeon, anesthesiologist and geriatrician, according to the guidelines of the European Society of Cardiology. [10]

We used a score of at least 20 % on the EuroSCORE (European System for Cardiac Operative Risk Evaluation) and 10% on the risk model developed by the Society for Thoracic Surgeons (STS), which uses an algorithm based on the presence of coexisting illnesses in order to estimate the 30-day operative mortality. [33,34] Exclusion criteria were an extreme frailty, life expectancy of less than one year, sepsis including active endocarditis, recent neurologic event

(less than 30 days), active digestive bleeding, acute coronary syndrome and recent STEMI (less than 30 days).

All patients, during preoperative assessment, underwent clinical examination, electrocardiogram (ECG) and biochemical tests. The comprehensive preprocedural imaging assessment consisted of transthoracic echocardiography (TTE), multidetector computer tomography (MDCT), invasive coronary angiography and Doppler ultrasonography.

Significant asymptomatic carotid stenosis was defined as a narrowing of at least 60% according to the guidelines on peripheral artery disease of the European Society of Cardiology. [35] In the Asymptomatic Carotid Atherosclerosis Study (ACAS) patients with asymptomatic carotid artery stenosis of 60% or greater reduction in diameter and whose general health makes them good candidates for elective surgery will have a reduced 5-year risk of ipsilateral stroke if carotid endarterectomy performed with less than 3% perioperative morbidity and mortality is added to aggressive management of modifiable risk factors. JAMA. 1995 May 10;273(18):1421-8.

All periprocedural events during follow-up were collected in a prospective registry. The outcomes were evaluated according to the standardized endpoint definitions for transcatheter aortic valve

implantation: The Valve Academic Research Consortium consensus document VARC and VARC 2. [27,28]

Regarding the new onset atrial fibrillation (AF) after TAVI, it has been defined as an episode of AF > 30 seconds with no history of chronic or paroxysmal arrhythmia. The heart rhythm was assessed by pre and post operative ECG and by ECG telemetry system during 24 hours after the procedure. ECG was also performed daily until discharge and at follow-up control.

Baseline clinical and therapeutic characteristics are provided in Table 1 and 2.

Baseline electrocardiographic and echocardiography characteristics are provided in Table 3.

Outcomes

The primary outcome combined mortality and incidence of cerebrovascular events (stroke/transient ischemic attack) at one year.

The secondary outcomes combined cardiovascular mortality and incidence of cerebrovascular events (stroke/transient ischemic attack) at 30 days and one year, as well as usual VARC 2 defined endpoints

	n	%
Sténose carotide	216	14,2
Pas de sténose carot.	1307	85,8
Total	1523	

Table 1

	Sténose carotide		Pas de sténose carot.		Tous		p
	n	%	n	%	n	%	
Centre							NS (0,16)
Pasteur	133	61,6	869	66,5	1 002	65,8	
Rangueil	83	38,4	438	33,5	521	34,2	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
Sexe							NS (0,16)
Hommes	118	54,6	646	49,4	764	50,2	
Femmes	98	45,4	661	50,6	759	49,8	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
Age minimum	62,8		43,6		43,6		
Age moyen *	83,9	+/- 6,1	83,9	+/- 6,5	83,9	+/- 6,5	NS
Age maximum	93,7		100,1		100,1		p=0,86
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
ATCD de maladie coronarienne							S (0,0000)
Oui	147	68,1	675	51,6	822	54,0	
Non	69	31,9	632	48,4	701	46,0	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
ATCD d'IDM							S (0,0000)
Oui	29	17,4	82	7,6	111	8,9	
Non	138	82,6	1 000	92,4	1 138	91,1	
Non disponible	*49*	*22,7*	*225*	*17,2*	*274*	*18,0*	
Total donnée disponible	*167*		*1 082*		*1 249*		
ATCD de pontage coronarien							S (0,0039)
Oui	44	20,4	170	13,0	214	14,1	
Non	172	79,6	1 137	87,0	1 309	85,9	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
ATCD d'ATC							S (0,0000)
Oui	109	50,5	448	34,3	557	36,6	
Non	107	49,5	859	65,7	966	63,4	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
ATCD AVC/AIT							S (0,0082)
Oui	32	14,8	118	9,0	150	9,8	
Non	184	85,2	1 189	91,0	1 373	90,2	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		

	Sténose carotide		Pas de sténose carot.		Tous		p
	n	%	n	%	n	%	
ATCD AOMI							S (0,0000)
Oui	90	41,7	205	15,7	295	19,4	
Non	126	58,3	1 102	84,3	1 228	80,6	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
ATCD sténose carotidienne							S (0,0000)
Oui	59	71,1	19	4,3	78	15,0	
Non	24	28,9	419	95,7	443	85,0	
Non disponible	*133*	*61,6*	*869*	*66,5*	*1 002*	*65,8*	
Total donnée disponible	*83*		*438*		*521*		
ATCD anévrisme aortique (thoracique ou abdominal)							NS (0,68)
Oui	4	1,9	30	2,3	34	2,2	
Non	212	98,1	1 277	97,7	1 489	97,8	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
ATCD aorte porcelaine							S (0,0308)
Oui	17	7,9	58	4,4	75	4,9	
Non	199	92,1	1 249	95,6	1 448	95,1	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
ATCD hémodialyse							NS (0,28)
Oui	3	1,4	34	2,6	37	2,4	
Non	213	98,6	1 273	97,4	1 486	97,6	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
ATCD valvuloplastie au ballon							NS (0,30)
Oui	43	19,9	302	23,1	345	22,7	
Non	173	80,1	1 005	76,9	1 178	77,3	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
ATCD chirurgie valvulaire							NS (0,53)
Oui	8	3,7	61	4,7	69	4,5	
Non	208	96,3	1 246	95,3	1 454	95,5	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
ATCD dégénérescence bioprothèse aortique							NS (0,92)
Oui	6	2,8	38	2,9	44	2,9	
Non	210	97,2	1 269	97,1	1 479	97,1	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
ATCD diabète							NS (0,92)
Oui	56	25,9	343	26,2	399	26,2	
Non	160	74,1	964	73,8	1 124	73,8	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
ATCD HTA							NS (0,46)
Oui	157	72,7	981	75,1	1 138	74,7	
Non	59	27,3	326	24,9	385	25,3	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
ATCD dyslipidémie							S (0,0349)
Oui	110	50,9	565	43,2	675	44,3	
Non	106	49,1	742	56,8	848	55,7	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		

	Sténose carotide		Pas de sténose carot.		Tous		p
	n	%	n	%	n	%	
Tabagisme actif ou sevré < 1 an							NS (0,30)
Oui	42	19,4	217	16,6	259	17,0	
Non	174	80,6	1 090	83,4	1 264	83,0	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
Maladie cognitive							NS (0,21)
Oui	14	6,5	59	4,5	73	4,8	
Non	202	93,5	1 248	95,5	1 450	95,2	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
Maladie respiratoire							NS (0,11)
Oui	57	26,4	415	31,8	472	31,0	
Non	159	73,6	892	68,2	1 051	69,0	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		

TRAITEMENTS EN COURS AVANT LA PROCEDURE - SYMPTOMES INITIAUX

	n	%
Sténose carotide	216	14,2
Pas de sténose carot.	1307	85,8
Total	1523	

Table 2

		Sténose carotide		Pas de sténose carot.		Tous		p
		n	%	n	%	n	%	
TRAITEMENTS EN COURS AVANT	**Aspirine**							NS (0,37)
	Oui	178	82,4	1 043	79,8	1 221	80,2	
	Non	38	17,6	264	20,2	302	19,8	
	Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
	Total donnée disponible	*216*		*1 307*		*1 523*		
	Clopidogrel							NS (0,07)
	Oui	106	49,1	554	42,4	660	43,3	
	Non	110	50,9	753	57,6	863	56,7	
	Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
	Total donnée disponible	*216*		*1 307*		*1 523*		
	Prasugrel							
	Oui	0	0,0	0	0,0	0	0,0	
	Non	216	100,0	1 307	100,0	1 523	100,0	
	Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
	Total donnée disponible	*216*		*1 307*		*1 523*		
	Anti-coagulant oral							S (0,0184)
	Oui	43	19,9	360	27,5	403	26,5	
	Non	173	80,1	947	72,5	1 120	73,5	
	Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
	Total donnée disponible	*216*		*1 307*		*1 523*		
	Statine							S (0,0054)
	Oui	129	59,7	647	49,5	776	51,0	
	Non	87	40,3	660	50,5	747	49,0	
	Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
	Total donnée disponible	*216*		*1 307*		*1 523*		
	Amiodarone							NS (0,42)
	Oui	40	18,5	213	16,3	253	16,6	
	Non	176	81,5	1 094	83,7	1 270	83,4	
	Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
	Total donnée disponible	*216*		*1 307*		*1 523*		
	Digoxine							NS (0,19)
	Oui	6	2,8	62	4,7	68	4,5	
	Non	210	97,2	1 245	95,3	1 455	95,5	
	Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
	Total donnée disponible	*216*		*1 307*		*1 523*		
SYMPTOMES INITIAUX	**Classe NYHA initiale**							NS (0,66)
	I ou II	44	20,4	246	18,8	290	19,0	
	III	137	63,4	870	66,6	1 007	66,1	
	IV	35	16,2	191	14,6	226	14,8	
	Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
	Total donnée disponible	*216*		*1 307*		*1 523*		
	Oedeme pulmonaire							NS (0,99)
	Oui	45	54,2	237	54,1	282	54,1	
	Non	38	45,8	201	45,9	239	45,9	
	Non disponible	*133*	*61,6*	*869*	*66,5*	*1 002*	*65,8*	
	Total donnée disponible	*83*		*438*		*521*		
	Angor							NS (0,64)
	Oui	16	19,3	75	17,1	91	17,5	
	Non	67	80,7	363	82,9	430	82,5	
	Non disponible	*133*	*61,6*	*869*	*66,5*	*1 002*	*65,8*	
	Total donnée disponible	*83*		*438*		*521*		

		Sténose carotide		Pas de sténose carot.		Tous		p
		n	%	n	%	n	%	
SYMPTOMES INITIAUX	**Syncope**							NS (0,67)
	Oui	8	9,6	36	8,2	44	8,4	
	Non	75	90,4	402	91,8	477	91,6	
	Non disponible	*133*	*61,6*	*869*	*66,5*	*1 002*	*65,8*	
	Total donnée disponible	*83*		*438*		*521*		
	Hospitalisation <1 an pour AS							NS (0,68)
	Oui	135	62,5	836	64,0	971	63,8	
	Non	81	37,5	471	36,0	552	36,2	
	Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
	Total donnée disponible	*216*		*1 307*		*1 523*		
SCORES	**Logistic Euroscore minimum**	4,5		4,5		4,5		
	Logistic Euroscore moyen *	26,0	+/- 11,1	21,9	+/- 11,0	22,5	+/- 11,1	S
	Logistic Euroscore maximum	67,4		74,2		74,2		p<0,001
	Non disponible	*4*	*1,9*	*36*	*2,8*	*40*	*2,6*	
	Total donnée disponible	*212*		*1 271*		*1 483*		
	STS minimum	2,1		0,8		0,8		
	STS moyen *	10,3	+/- 5,9	9,6	+/- 6,7	9,7	+/- 6,6	NS
	STS médiane (IQ)	9,0	(6,3 - 12,6)	7,8	(5,3 - 11,7)	8,0	(5,5 - 11,8)	p=0,0074
	STS maximum	36,5		54,4		54,4		*(Test Mann & Whitney)*
	Non disponible	*6*	*2,8*	*47*	*3,6*	*53*	*3,5*	*non paramétrique*
	Total donnée disponible	*210*		*1 260*		*1 470*		
	BMI minimum	17,5		15,2		15,2		
	BMI moyen *	25,5	+/- 4,7	25,8	+/- 4,7	25,8	+/- 4,7	NS
	BMI maximum	50,0		52,9		52,9		p=0,36
	Non disponible	*2*	*0,9*	*18*	*1,4*	*20*	*1,3*	
	Total donnée disponible	*214*		*1 289*		*1 503*		
	Cl. Créatinine MDRD minimum	8,1		4,2		4,2		
	Cl. Créatinine MDRD moyenne *	48,5	+/- 21,6	51,2	+/- 26,2	26,2	+/- 4,2	NS
	Cl. Créatinine MDRD maximum	119,9		239,5		239,5		p=0,15
	Non disponible	*2*	*0,9*	*13*	*1,0*	*15*	*1,0*	
	Total donnée disponible	*214*		*1 294*		*1 508*		
	Clairance MDRD							NS (0,43)
	< 30	38	17,8	260	20,1	298	19,8	
	30 et +	176	82,2	1 034	79,9	1 210	80,2	
	Non disponible	*2*	*0,9*	*13*	*1,0*	*15*	*1,0*	
	Total donnée disponible	*214*		*1 294*		*1 508*		

	n	%
Sténose carotide	216	14,2
Pas de sténose carot.	1307	85,8
Total	1523	

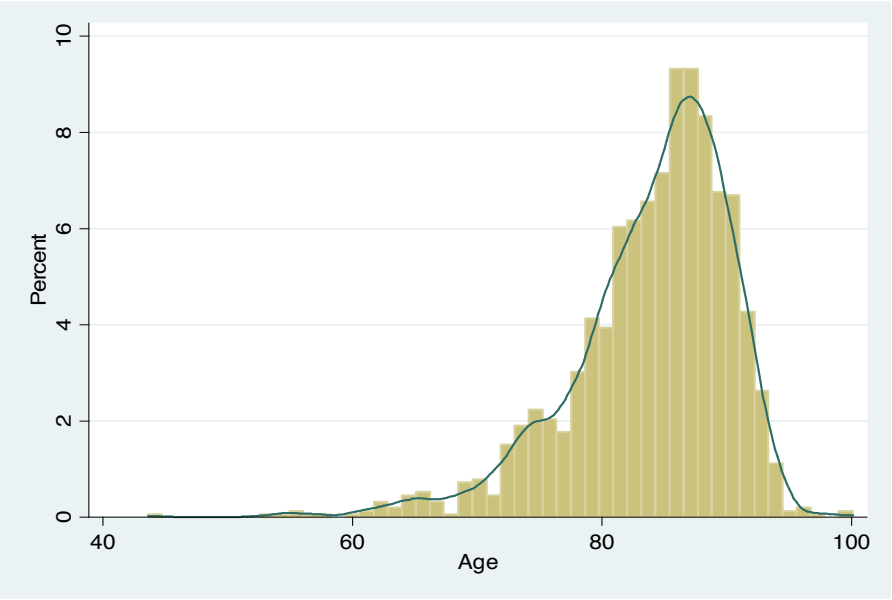
Table 3

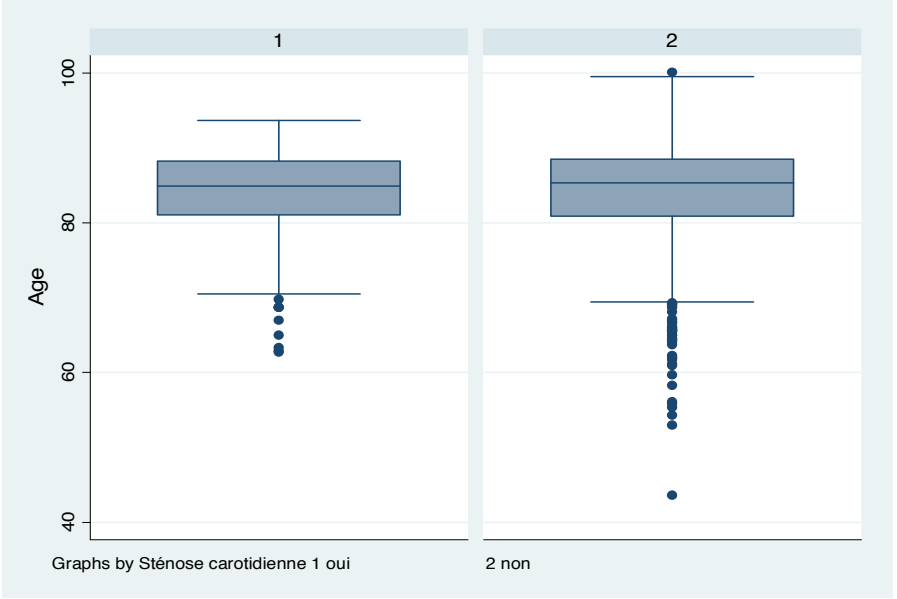
		Sténose carotide		Pas de sténose carot.		Tous		p
		n	%	n	%	n	%	
ECG INITIAL	**Rythme sinusal**							NS (0,22)
	Oui	173	80,1	997	76,3	1 170	76,8	
	Non	43	19,9	310	23,7	353	23,2	
	Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
	Total donnée disponible	*216*		*1 307*		*1 523*		
	FA							NS (0,20)
	Perm ou Parox	40	18,5	293	22,4	333	21,9	
	Non	176	81,5	1 014	77,6	1 190	78,1	
	Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
	Total donnée disponible	*216*		*1 307*		*1 523*		
	BAV							NS (0,30)
	I, II ou III	42	19,4	217	16,6	259	17,0	
	Non	174	80,6	1 090	83,4	1 264	83,0	
	Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
	Total donnée disponible	*216*		*1 307*		*1 523*		
	BBD							NS (0,52)
	Oui	30	13,9	204	15,6	234	15,4	
	Non	186	86,1	1 103	84,4	1 289	84,6	
	Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
	Total donnée disponible	*216*		*1 307*		*1 523*		
	BBG							S (0,0132)
	Oui	29	13,4	270	20,7	299	19,6	
	Non	187	86,6	1 037	79,3	1 224	80,4	
	Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
	Total donnée disponible	*216*		*1 307*		*1 523*		
	Présence d'un Pace-Maker							NS (0,75)
	Oui	29	13,4	186	14,2	215	14,1	
	Non	187	86,6	1 121	85,8	1 308	85,9	
	Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
	Total donnée disponible	*216*		*1 307*		*1 523*		
ECHOCARDIO	**FEVG minimum**	17,0		18,0		17,0		
	FEVG moyenne	54,4	+/- 13,2	53,5	+/- 13,8	53,6	+/- 13,7	NS
	FEVG maximum	80,0		83,0		83,0		p=0,37
	Non disponible	*1*	*0,5*	*4*	*0,3*	*5*	*0,3*	
	Total donnée disponible	*215*		*1 303*		*1 518*		
	Aire Valve Aortique minimum	0,31		0,29		0,29		
	Aire Valve Aortique moyenne *	0,75	+/- 0,18	0,75	+/- 0,19	0,75	+/- 0,19	NS
	Aire Valve Aortique maximum	1,20		2,21		2,21		p=0,78
	Non disponible	*4*	*1,9*	*21*	*1,6*	*25*	*1,6*	
	Total donnée disponible	*212*		*1 286*		*1 498*		
	Gradient moyen minimum	10,0		4,0		4,0		
	Gradient moyen moyenne *	45,6	+/- 15,1	45,5	+/- 15,5	45,5	+/- 15,5	NS
	Gradient moyen maximum	110,0		115,0		115,0		p=0,90
	Non disponible	*1*	*0,5*	*23*	*1,8*	*24*	*1,6*	
	Total donnée disponible	*215*		*1 284*		*1 499*		

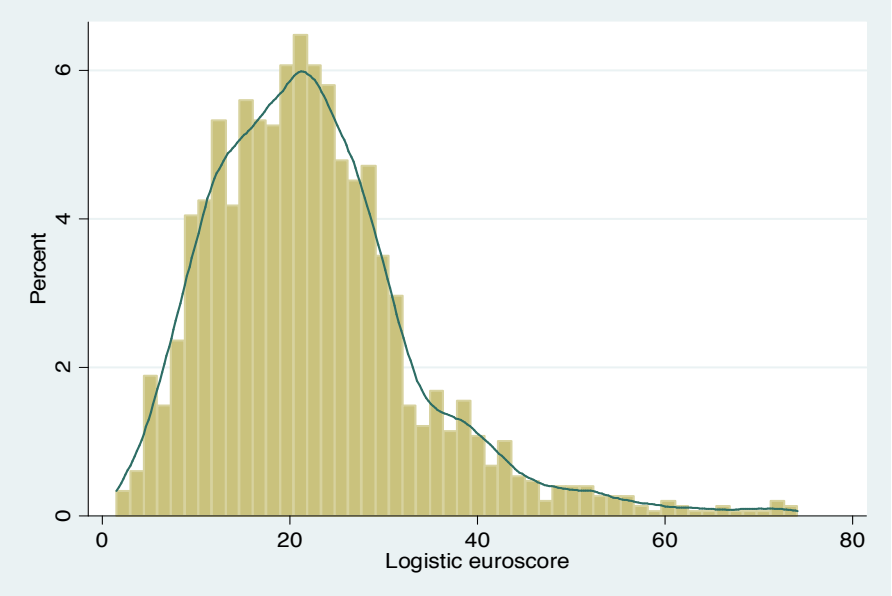
		Sténose carotide		Pas de sténose carot.		Tous		p
		n	%	n	%	n	%	
ECHOCARDIO	**Diamètre TTE minimum**	18,0		17,0		17,0		
	Diamètre TTE moyenne *	22,0	+/- 1,9	22,3	+/- 2,1	22,2	+/- 2,1	NS
	Diamètre TTE maximum	27,0		36,0		36,0		p=0,06
	Non disponible	*36*	*16,7*	*174*	*13,3*	*210*	*13,8*	*(K&W p=0,13)*
	Total donnée disponible	*180*		*1 133*		*1 313*		
	Fuite aortique							NS (0,21)
	Non	70	32,7	490	38,1	560	37,4	
	Grade 1	120	56,1	637	49,6	757	50,5	
	Grades 2 à 4	24	11,2	158	12,3	182	12,1	
	Non disponible	*2*	*0,9*	*22*	*1,7*	*24*	*1,6*	
	Total donnée disponible	*214*		*1 285*		*1 499*		
AORTO-CORO	**Aorto-coro (attention bcp de données manquantes)**							S (0,0003)
	Lésion>50%	96	44,4	415	31,8	511	33,6	
	Pas de lésion>50%	120	55,6	892	68,2	1 012	66,4	
	Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
	Total donnée disponible	*216*		*1 307*		*1 523*		
	Calcification valve aortique							S (0,0135)
	Sévère	178	82,8	980	75,0	1 158	76,1	
	Aucune ou modérée	37	17,2	326	25,0	363	23,9	
	Non disponible	*1*	*0,5*	*1*	*0,1*	*2*	*0,1*	
	Total donnée disponible	*215*		*1 306*		*1 521*		

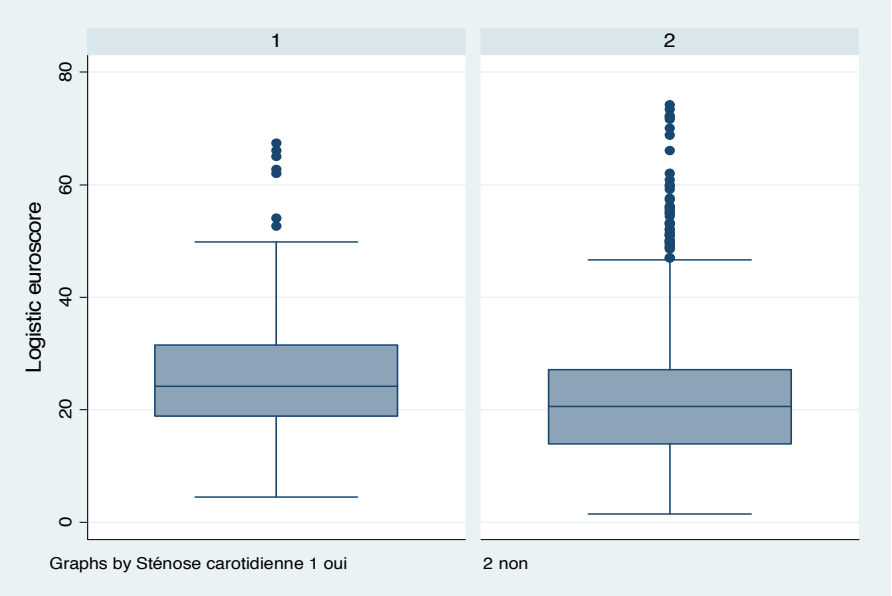
DISTRIBUTIONS DES VARIABLES QUANTITATIVES

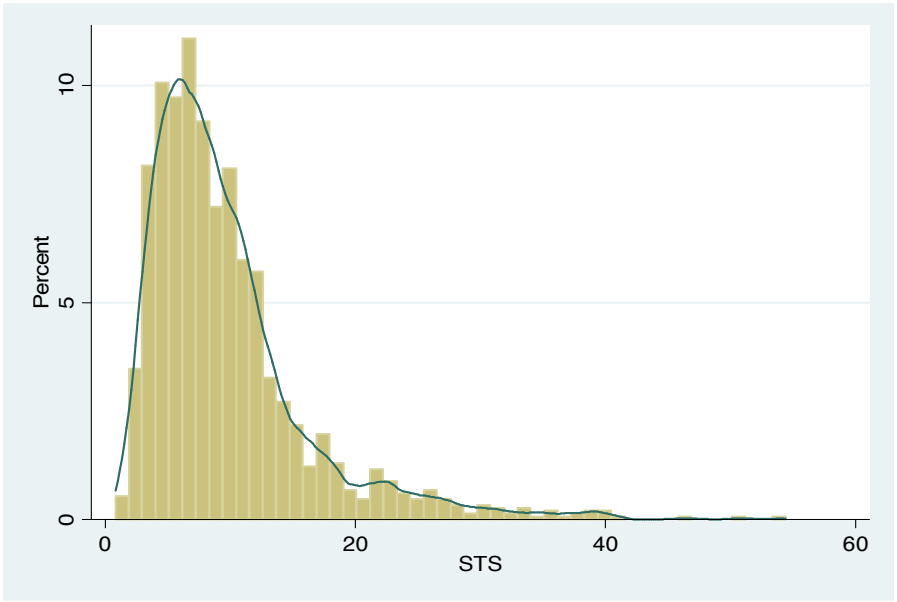
Baseline and demographic data distribution

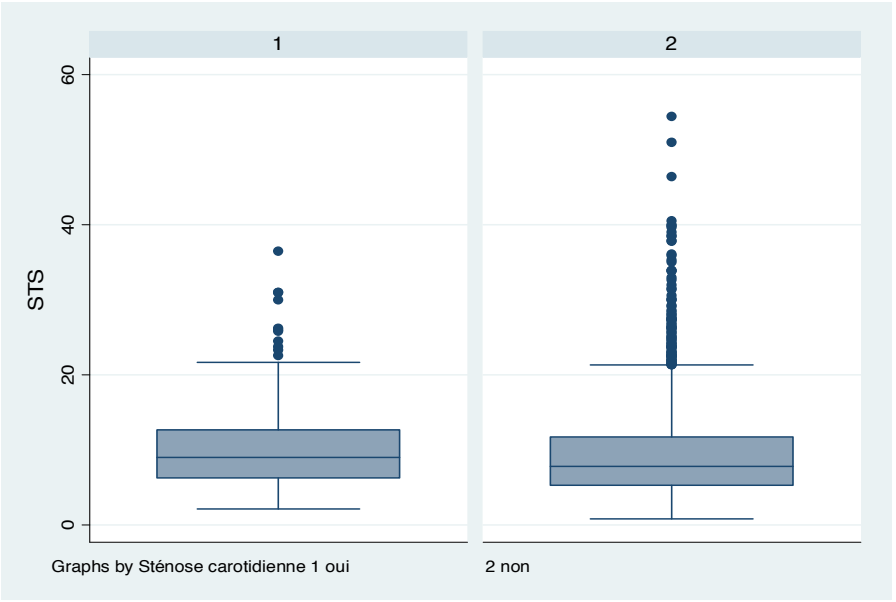


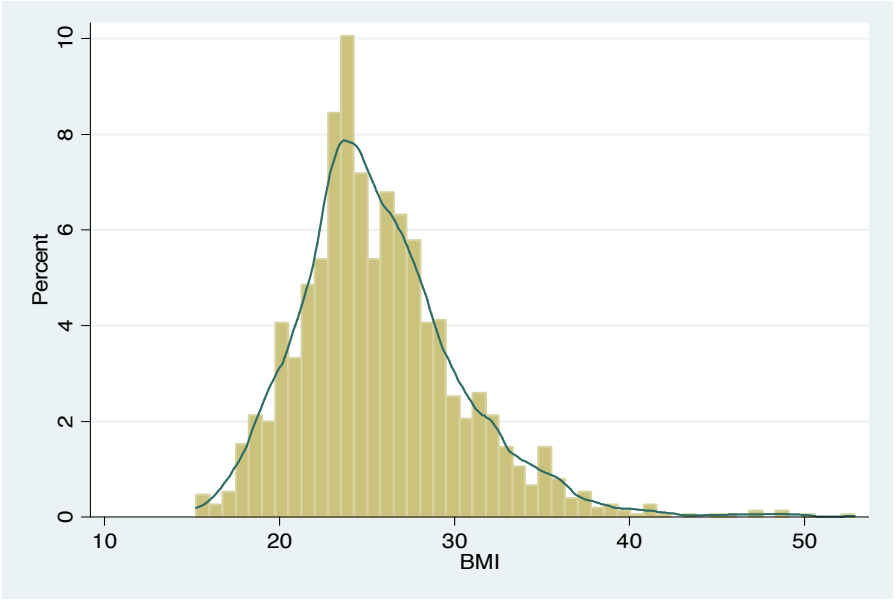







Percent
0
5
10
0
20
40
60
STS


1
2
STS
0
20
40
60
Graphs by Sténose carotidienne 1 oui
2 non


Percent
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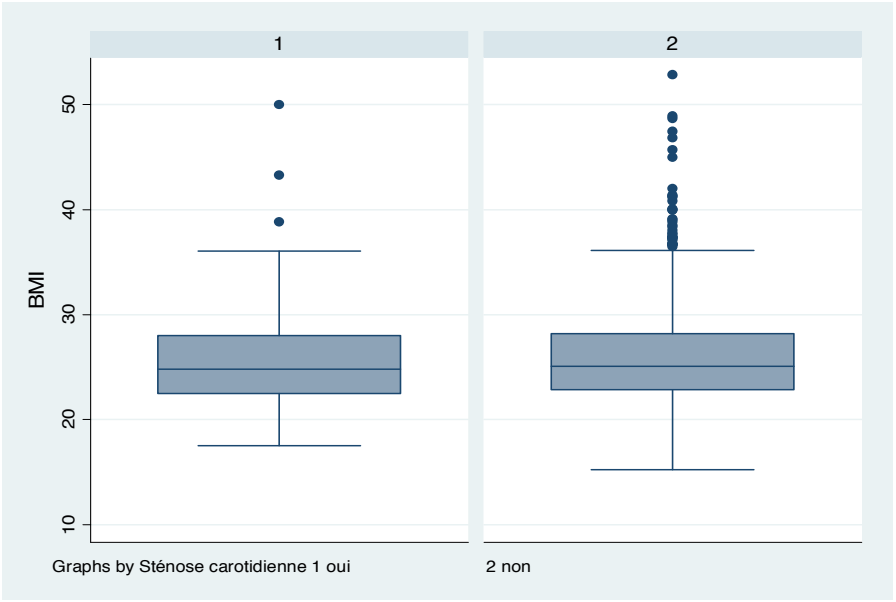
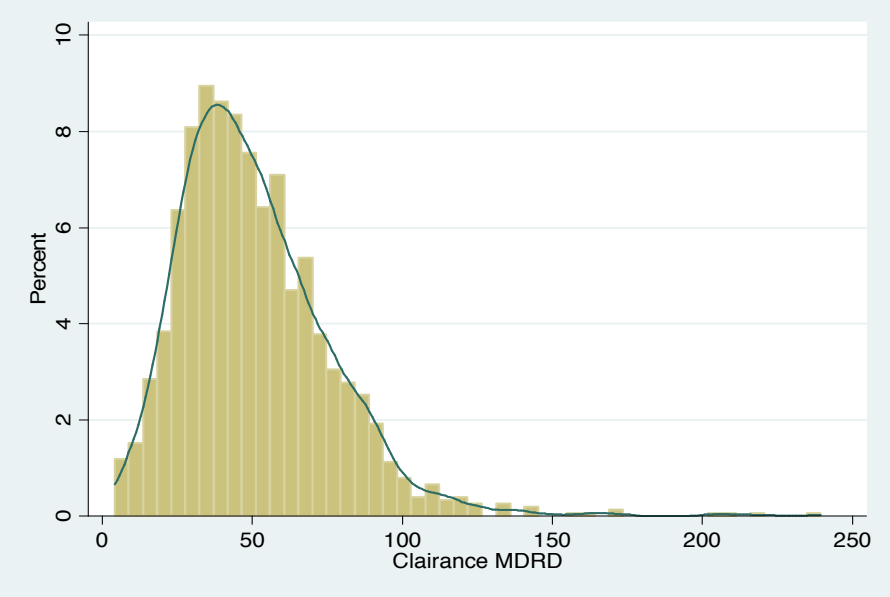
2
4
6
8
10
10
20
30
40
50
BMI


1
2
BMI
10
20
30
40
50
Graphs by Sténose carotidienne 1 oui
2 non


Percent
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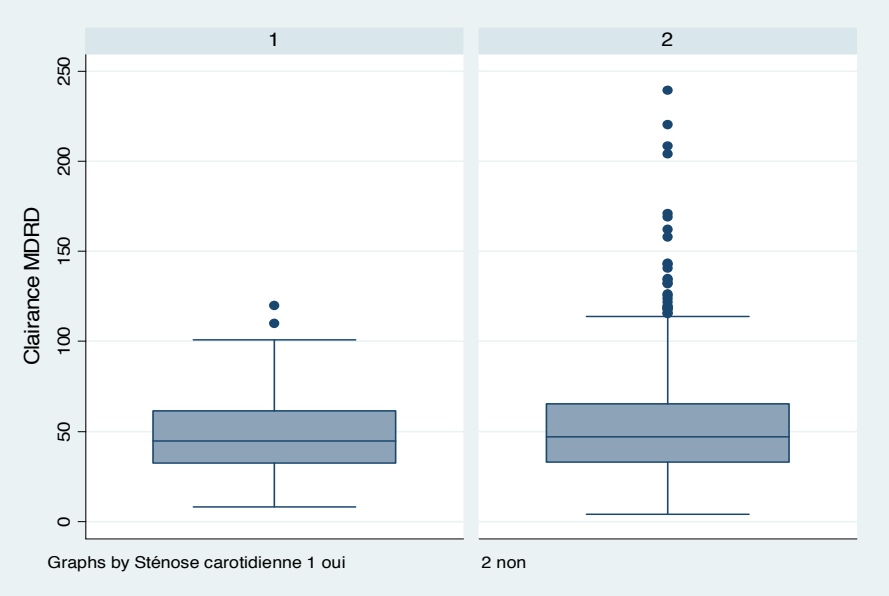
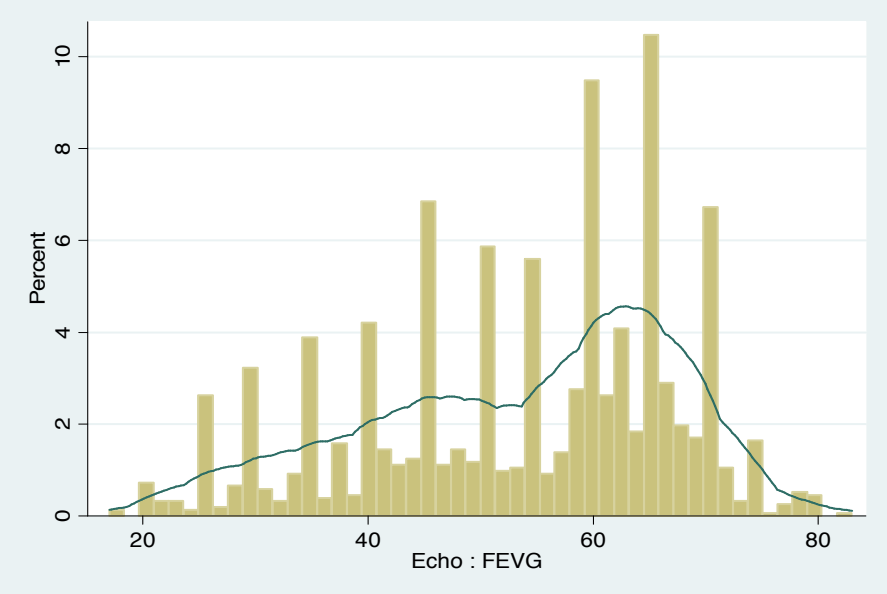
2
4
6
8
10
0
50
100
150
200
250
Clairance MDRD


1
2
Clairance MDRD
0
50
100
150
200
250
Graphs by Sténose carotidienne 1 oui
2 non


Percent
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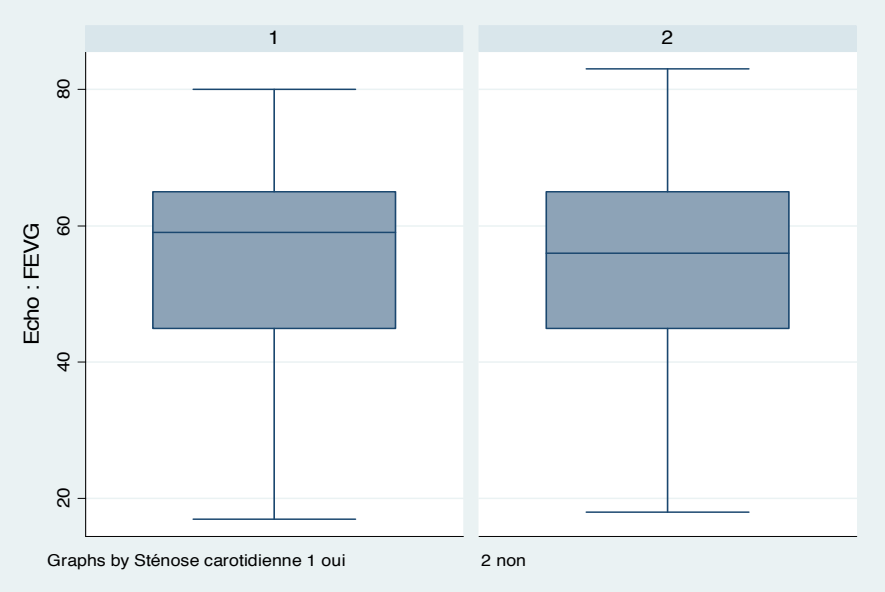
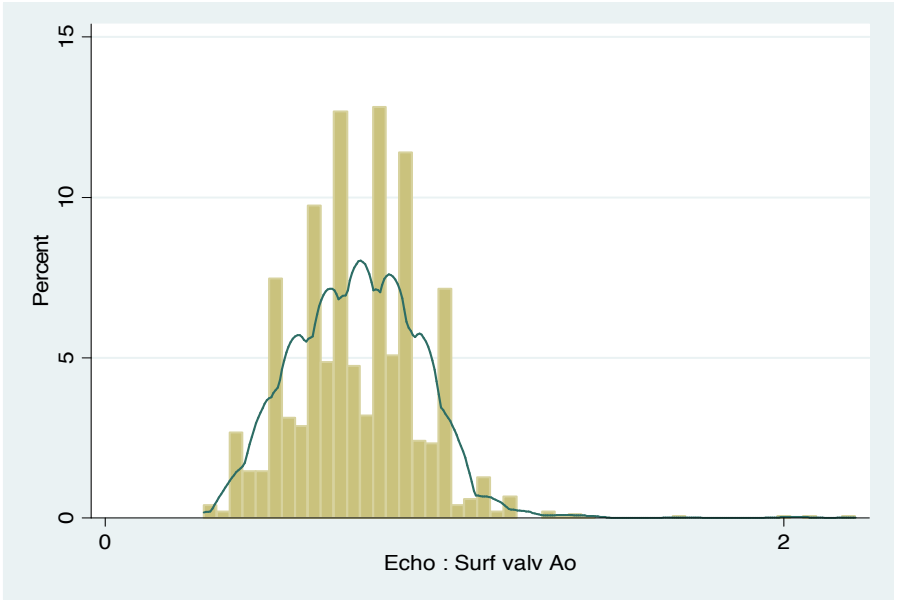
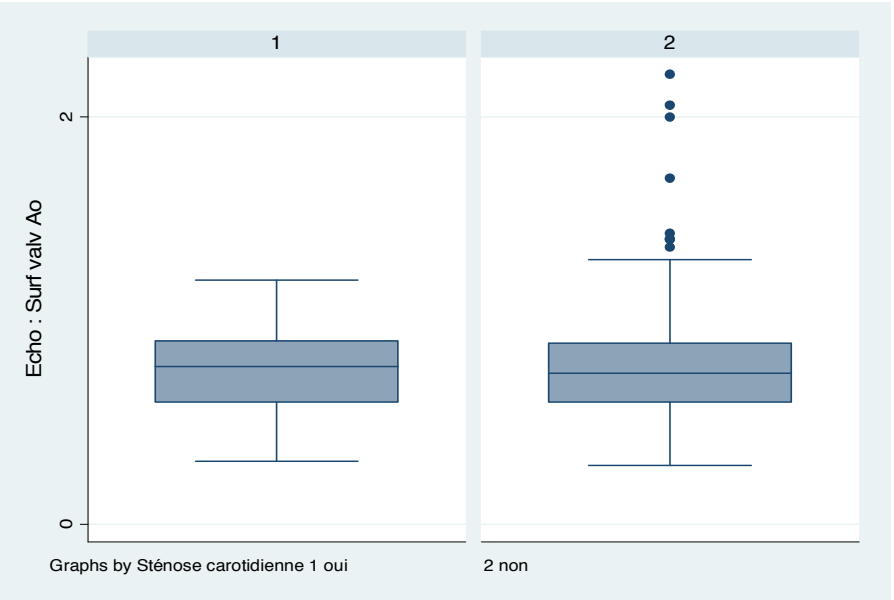
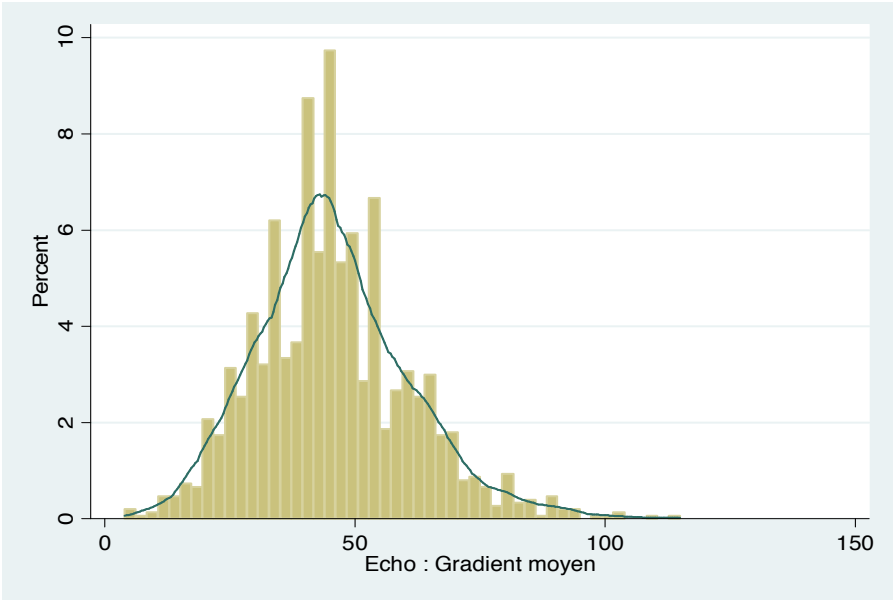
4
6
8
10
20
40
60
80
Echo : FEVG


1
2
Echo : FEVG
20
40
60
80
Graphs by Sténose carotidienne 1 oui
2 non


Percent
0
5
10
15
0
2
Echo : Surf valv Ao


1
2
Echo : Surf valv Ao
0
2
Graphs by Sténose carotidienne 1 oui
2 non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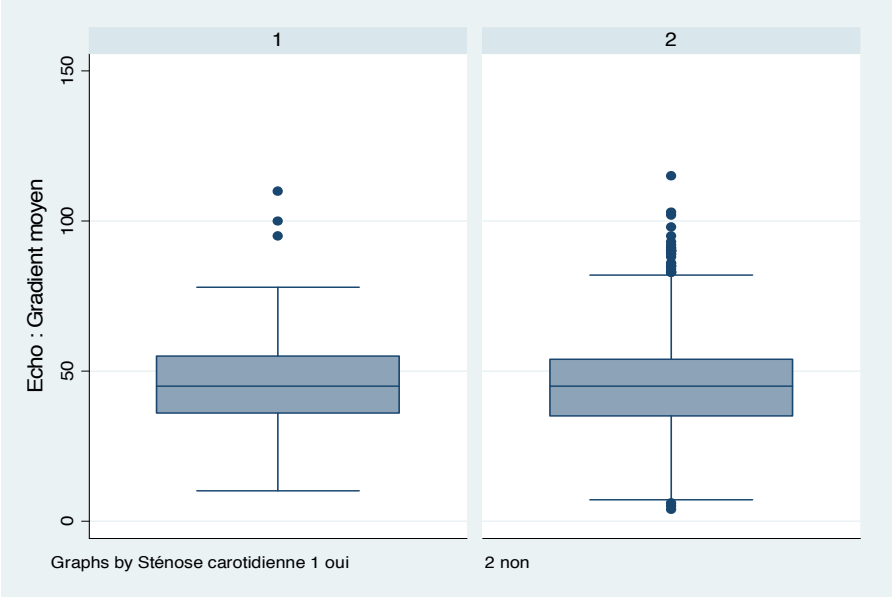
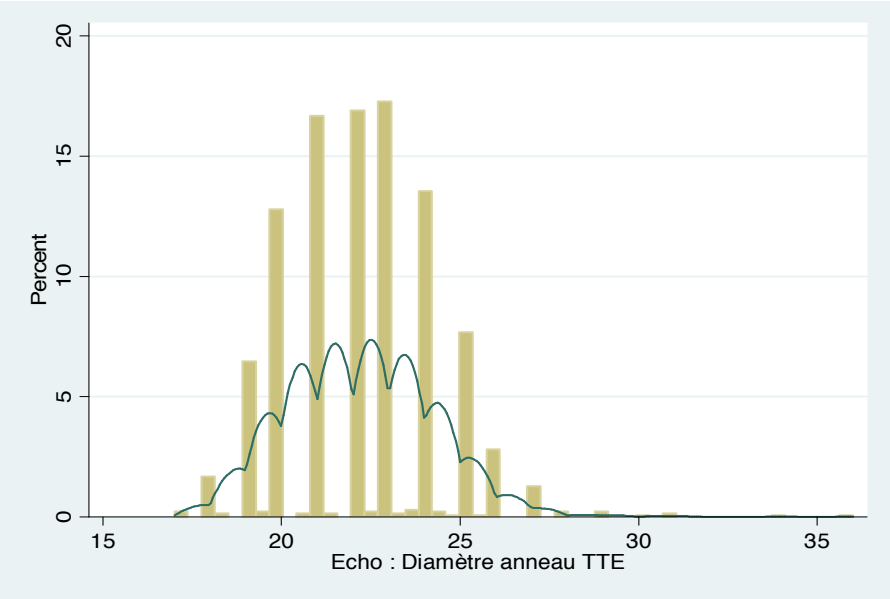
4
6
8
10
0
50
100
150
Echo : Gradient moyen


1
2
Echo : Gradient moyen
0
50
100
150
Graphs by Sténose carotidienne 1 oui
2 non


Percent
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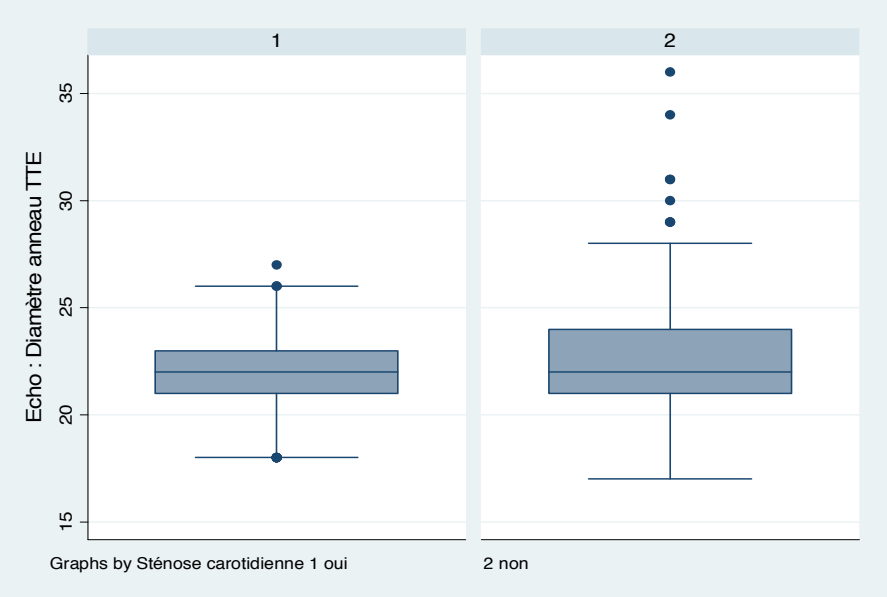
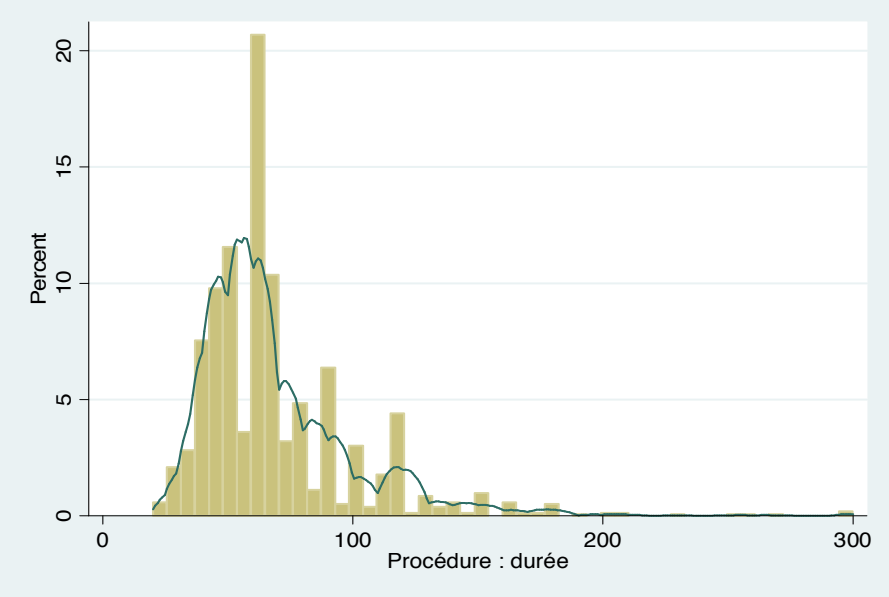
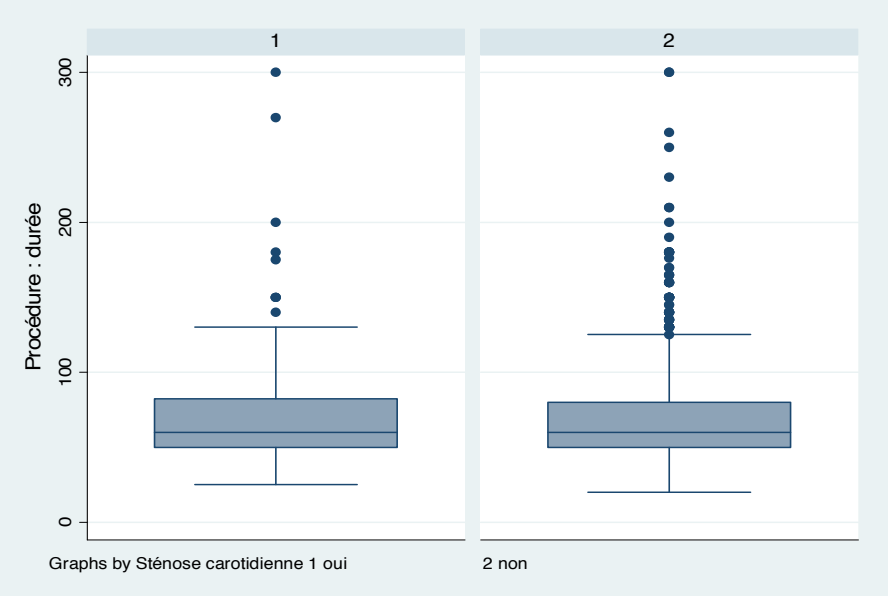
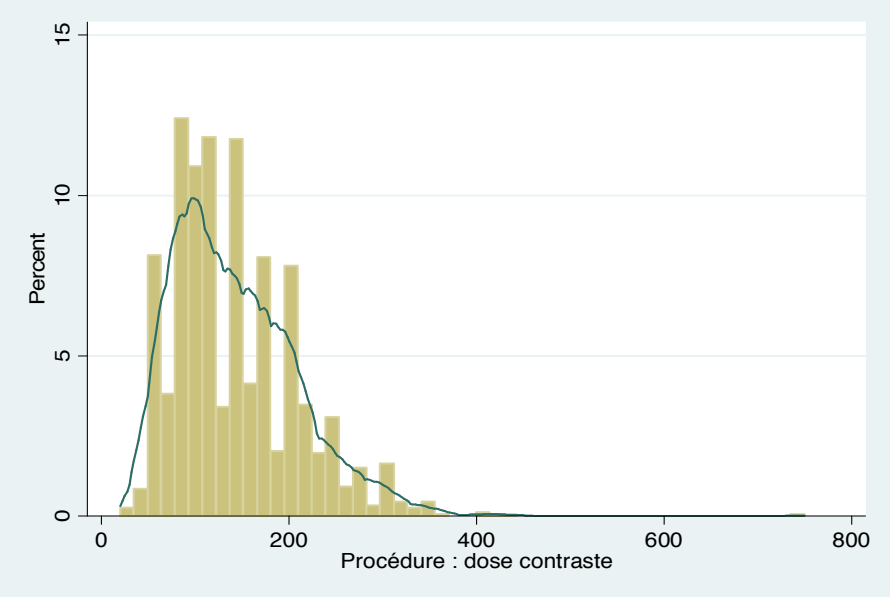
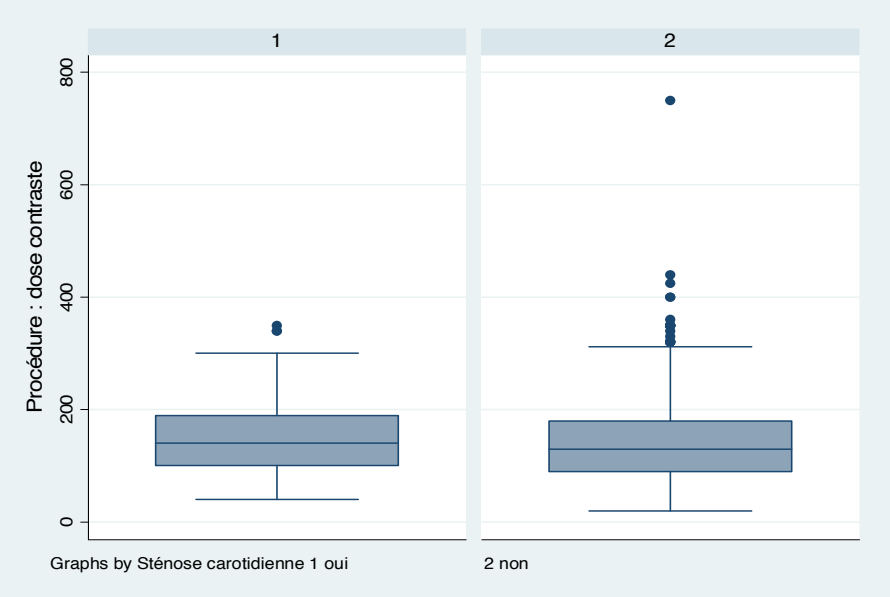
10
15
20
15
20
25
30
35
Echo : Diamètre anneau TTE


1
2
Echo : Diamètre anneau TTE
15
20
25
30
35
Graphs by Sténose carotidienne 1 oui
2 non


Percent
0
5
10
15
20
0
100
200
300
Procédure : durée


1
2
Procédure : durée
0
100
200
300
Graphs by Sténose carotidienne 1 oui
2 non


Percent
0
5
10
15
0
200
400
600
800
Procédure : dose contraste


1
2
Procédure : dose contraste
0
200
400
600
800
Graphs by Sténose carotidienne 1 oui
2 non

Follow-up

All patients underwent clinical surveillance, bio-chemical tests, electrocardiogram and echocardiogram before hospital discharge. The follow-up assessment included medical examination, electrocardiogram and echocardiogram to perform valve imaging and hemodynamic evaluation. It was performed in our center or by the treating cardiologist at 30 days and at one year.

The events considered were mortality (by all-cause and cardiovascular death), myocardial infarction, stroke and transient ischemic attack (TIA), bleeding (minor and life-threatening bleeding), acute renal failure, vascular complications, disturb of conduction and arrhythmias and the combined criteria of safety, according to VARC and VARC 2 definitions. [27,28]

Procedure

Coronary artery disease (CAD) as well as carotid artery disease and peripheral artery diseases are often found concurrently in elderly patients presenting with severe symptomatic AS undergoing TAVI. Presence of CAD was demonstrated to negatively affect prognosis in patients undergoing aortic valve replacement and TAVI and was consequently evaluated in the most commonly used surgical risk scores. [36] Moreover, the coexistence of carotid and peripheral

artery diseases not only further increases risk and long-term mortality but influences also technical approaches since all centers adopted a policy of using the transfemoral approach first, with criteria for the use of non-transfemoral approaches that were based on the size and degree of tortuosity, calcifications, and atheroma of the aorto-iliofemoral arterial tree, as assessed by the multidisciplinary team. [37]

Preventive measures have been taken to limit the risk associated to the procedure in our patients presenting carotid artery stenosis.

Pre procedural mesures

In hypertensive subjects is recommended a good pharmacological control of blood pressure (BP) to avoid the occurrence of hypertensive postprocedural crisis. It has also benn shown that in patients with controlled BP (<140/90 mmHg), the symptomatic response after TAVI was significantly better compared to patients with uncontrolled BP with cumulative all-cause and cardiovascular mortality significantly lower. [38] In our patients a statin treatment was administered as it has been observed a protective role of these drugs in improving operative and interventional outcomes. [39] A strict control of the glycemic profile has been performed in order to protect against a possible dangerous association of hyperglycemia and cerebral ischemia during and after the procedure. [40]

Anesthesia

The procedure could be performed under general anesthesia, or conscious sedation. Transapical TAVI (requiring mini-thoractomy) in usually performed under general anesthesia with endotracheal intubation. For transfemoral TAVI, there is growing controversy whether general anesthesia should be still considered the standard of care. General anesthesia enables the use of periprocedural TEE and facilitates the immediate detection/treatment of complications. On the other hand, conscious sedation avoids hemodynamic instability frequently associated with induction of general anesthesia, enables the prompt detection of adverse neurologic events in awaken patients, and should allow for shorter procedural and recovery times. TEE can occasionally also be performed under sedation. Moreover, TEE is not considered mandatory (TEE is recommended only as important adjunct to fluoroscopy) and, at least in transfemoral TAVI, can be in part substituted by transthoracic echocardiography. Until now, there are no randomized controlled trials addressing the question whether conscious sedation is superior to general anesthesia.

Valve type selection and delivery method

The devices implanted in our patients were the Edwards SAPIEN (ES) and SAPIEN XT (SXT) valve and CoreValve (CV).

The ES valve consists of a stainless steel balloon-expandable stent with 3 integrated valve leaflets composed of bovine pericardium. It is implanted through the transfemoral route using the Retroflex 3 delivery system or through the transapical route using the Ascendra delivery system. The new generation, Edwards SAPIEN XT valve has a smaller profile and consists of a new cobalt-chromium design and is delivered using the Novaflex system for transfemoral route or the Ascendra 2 system for the transapical route. Both the Edwards SAPIEN and the Edwards SAPIEN XT valves are available in 23, 26 and 29 mm sizes.

The CoreValve consists of a self-expanding nitinol frame with 3 integrated porcine pericardial leaflets. It is currently available in 23, 26, 29 and 31-mm sizes.

The method of delivery relied on a tailored approach to procedural planning by the multidisciplinary team. The assessment of optimum valve and delivery method was based on evaluation of aortic annular size and peripheral anatomy. The most commonly used pathway was the transfemoral route. However, if there were contraindications to the transfemoral route or the patient had borderline characteristics for this approach, alternative delivery methods were considered if feasible such as transapical or transaxillary/subclavian, transaortic approach. [42]

Antithrombotic and anticoagulant treatment

Usual dose of 5,000 IU bolus of unfractionated heparin was administered followed by additional boluses to maintain an activated clotting time ≥250 s. Heparin anticoagulation was usually reversed by administration of protamine sulfate at a milligram-to-milligram neutralization dose.

After TAVI single antiplatelet therapy with aspirin (70 mg to 160 mg daily) has been prescribed. Clopidogrel was associated only if there was an indication related to pre operative coronary stenting.

All procedural data are summarized in table 4.

Statistical analysis

Continuous data were expressed as mean and standard deviation. Qualitative data are presented as frequencies and/or percentages. Differences between groups were evaluated using non-parametric tests (Student's t - test) for continuous variables and the Fisher exact test or the Chi-square for categorical variables. A p value < 0.05 was considered statistically significant.

Results

Characteristic of population

Baseline demographic, clinical, echocardiographic and procedural characteristics are summarized in Table 1, 2 and 3.

Of the entire population, 216 patients (14,2%) presented an asymptomatic carotid artery stenosis (ACAS); 54,6% prevalence of carotid artery disease was found in men compared to women (45,4%, p = 0.016).

Diabetes was observed in 399 (26,2%) patients with no difference in ACAS and non-ACAS patients, hypertension in 1138 (74.7%) and dyslipidemia in 675 (44,3%) with significant in ACAS (50,9 %) and non-ACAS (43,2 %) p=0,349.

The body mass index was similar in the two subgroups (25.5 ± 4.7 kg/m² vs 25.8 ± 4.7 Kg/m², p=0,036).

Patient with ACAS showed higher burden of cardiovascular disease like coronary artery disease (68,1% vs 51,6%; p<0,001), myocardial infarction (17,4% vs 7,6%; p>0,001), porcelain aorta (7,9% vs 4,4%; p=0,031), lower extremity artery disease (41,7% vs 15,7%; p>0,001); severe of aortic valve calcifications (82,8% vs 75%; p=0,0136).

Patients with ACAS had a significantly higher logistic EuroSCORE (26,0 ± 11,1 vs 21,9 ± 11, p<0.001) whereas the STS score was similar (10,3± 5.9 vs 9,6 ± 6,7).

No significant differences about the prevalence of atrial fibrillation were observed between the two subgroups.

Regarding antithrombotic therapy, 95.9% patients assumed aspirin, 43,3% clopidogrel and 26.5% oral anticoagulation without differences between the two subgroups.

Procedural aspects Procedural characteristics are summarized in Table 4.

In 42,5% of patients was implanted a prosthesis ES, 51,4% of patients received a Corevalve and in 6,1 % of patients other devices were implanted. The subgroup with carotid artery stenosis received a significantly higher number of ES (47,2% vs 41,7%; p=0,037).

A transfemoral approach was performed in 1281 cases (84,1%), transapical in 92 cases (6,04%), subclavian in 48 (3,2%) and transaortic approach in 102 cases (6,7%), the transaortic and transapical approach were significantly higher in the ACSA (respectively 10,6% vs 6,1% and 11,6% vs 5,9% p>0,001) and lower the transfemoral approach (75% vs 85,6% p>0,001).

The procedure took place in 77 % of cases under general anesthesia and the average duration of the procedure was 69,5 ± 32,2 minutes, without no significant difference between the two subgroups.

Moreover, in the two subgroups there were not significant differences regarding the size of the prosthesis nor the size of the balloon for valvuloplasty used before the placement of the prosthesis. In 14,4 % of case a balloon postdilatation was performed no significant differences between subgroups were observed.

At the end of the procedure the rate of aortic prosthetic and paraprosthetic regurgitation did not differ between the two subgroups, as well as the rate of device success at the end of the procedure (90,3 % vs 91,8%).

	n	%
Sténose carotide	216	14,2
Pas de sténose carot.	1307	85,8
Total	1523	

Table 4

	Sténose carotide		Pas de sténose carot.		Tous		p
	n	%	n	%	n	%	
Anesthésie Générale							NS (0,13)
Oui	175	81,0	998	76,4	1 173	77,0	
Non	41	19,0	309	23,6	350	23,0	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
Accès							S (0,0001)
Fémoral ou iliaque	162	75,0	1 119	85,6	1 281	84,1	
Transapical	23	0,1	69	0,1	92	0,1	
Sous-clavier	6	2,8	42	3,2	48	3,2	
Transaortique	25	11,6	77	5,9	102	6,7	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
Guidage ETO							S (0,0001)
Oui	110	50,9	487	37,3	597	39,2	
Non	106	49,1	820	62,7	926	60,8	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
Type de prothèse							S (0,0370)
Sapien ou Sapien XT	102	47,2	545	41,7	647	42,5	
Corevalve	98	45,4	685	52,4	783	51,4	
Lotus	7	3,2	43	3,3	50	3,3	
Autres (S3, Portico, Evolut…	9	4,2	34	2,6	43	2,8	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
Taille de la prothèse							NS (0,59)
< 26	41	19,0	216	16,5	257	16,9	
26	86	39,8	513	39,3	599	39,3	
≥ 29	89	41,2	578	44,2	667	43,8	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
Durée de la procédure							
Minimum	25		20		20,0		
Moyenne	71	+/- 36	69	+/- 32	69,5	+/- 32,2	NS
Maximum	300		300		300,0		p=0,44
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
Dose de produit de contraste							
Minimum	40		20		20		
Moyenne	145	+/- 64	143	+/- 68	143	+/- 68	NS
Maximum	350		750		750		p=0,70
Non disponible	*0*	*0,0*	*1*	*0,1*	*1*	*0,1*	
Total donnée disponible	*216*		*1 306*		*1 522*		
Valvulo-ballon							NS (0,09)
Oui	167	77,3	937	71,7	1 104	72,5	
Non	49	22,7	370	28,3	419	27,5	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
Seconde Valve in Valve							NS (0,16)
Oui	2	0,9	32	2,5	34	2,2	
Non	214	99,1	1 274	97,5	1 488	97,8	
Non disponible	*0*	*0,0*	*1*	*0,1*	*1*	*0,1*	
Total donnée disponible	*216*		*1 306*		*1 522*		

	Sténose carotide		Pas de sténose carot.		Tous		p
	n	%	n	%	n	%	
Post-dilatation prothèse							NS (0,52)
Oui	28	13,0	191	14,6	219	14,4	
Non	188	87,0	1 114	85,4	1 302	85,6	
Non disponible	*0*	*0,0*	*2*	*0,2*	*2*	*0,1*	
Total donnée disponible	*216*		*1 305*		*1 521*		
Fuite para-prothétique finale							NS (0,40)
Non	72	33,6	496	38,2	568	41,7	
Grade 1	121	56,5	672	51,7	793	58,3	
> Grade 1	21	9,8	131	10,1	*152*	*10,0*	
Non disponible	*2*	*0,9*	*8*	*0,6*	*1 361*		
Total donnée disponible	*214*		*1 299*		*1 513*		
Fuite intra-prothétique finale							NS (0,30)
Non	185	86,0	1 156	88,9	1 341	88,7	
Grade 1	30	14,0	141	10,8	171	11,3	
> Grade 1	0	0,0	4	0,3	*4*	*0,3*	
Non disponible	*1*	*0,5*	*6*	*0,5*	*1 512*		
Total donnée disponible	*215*		*1 301*		*1 516*		
Succès de la procédure (donnée saisie)							NS (0,45)
Oui	195	90,3	1 200	91,8	1 395	91,6	
Non	21	9,7	107	8,2	128	8,4	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
Patient vivant à la fin de la procédure							NS (0,16)
Oui	212	98,1	1 296	99,2	1 508	99,0	
Non	4	1,9	11	0,8	15	1,0	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		

30-days outcome

Table 5 summarize the clinical outcomes at 30-days.

The mortality rate was 6.2% with a higher mortality in the ACSA patients (9,7% vs 5,7%, p=0,02).

The composite endpoint of early safety was similar for the subgroups (87,4% vs 87,4%).

The prevalence of stroke/TIA was of 1,9% and 2,5%. The prevalence of bleeding was similar in the two subgroups (13,1% vs 14,4%, p=0.13).

No differences were observed regarding the prevalence of myocardial infarction (3,7% vs 1,9%, p=0.09), of vascular complications (19,3% vs 14,8%, p=0.59) nor of acute kidney injury (16.2% vs 12,4%, p=0.12).

In 13.8% of patients an episode of new onset atrial fibrillation has been documented during the 30-days follow-up, without significative differences between the two subgroups.

1-year outcome

855 (56,14%) patients completed one-year follow-up. The composite endpoint of cardiovascular mortality and stroke/TIA was similar between the ACAS and the non ACAS subgroups (18,5 vs 15,9%; p=0,33).

Kaplan–Meier curves (Figure 2 and 3) show a similar trend towards mortality rate in patients with and without ACAS.

Concerning causes of death, no differences were found between ACAS and No CAS patients; all cause mortality after one-year follow-up was 12.48% and it was similar between the two subgroups.

We found a correlation between 1 year mortality and the transapical delivery approach (34,8%; p=0,001); no differences were shown by the femoral or the transaortic approach.

Other procedural aspects that can impact one year mortality are a paravalvular leak of more than grade 1 at the end of the procedure (p<0,001; RR=1,91) and the need to implant a second valve (p=0,005; RR=2,4).

Other predictive factors for the endpoints evaluated (combined cardiovascular mortality and stroke/TIA) were a previous history of coronary artery disease (p=0,006; RR=1,44); lower extremity artery disease (p=0,001; RR=1,58); patients undergoing hemodialysis (p=0,002; RR=2,45); severe chronic renal failure defined by a clearance < 30 lm/min (p=0,001; RR=1,42); diabetic patients (p=0,003; RR=1,34); patients in worse NYHA class as NYHA III (p=0,006; RR=1,80), and NYHA IV (p=0,001; RR=2,35).

Complete data are shown in table 6.

CRITERES VARC POUR LES 30 PREMIERS JOURS

	n	%
Sténose carotide	216	14,2
Pas de sténose carot.	1307	85,8
Total	1523	

Table 5

	Sténose carotide		Pas de sténose carot.		Tous		p
	n	%	n	%	n	%	
Device success VARC (patient vivant, pas de V in V, pas de fuite paraproth finale de grade 2 à 4)							NS (0,89)
Oui	188	87,4	1 142	87,8	1 330	87,7	
Non	27	12,6	159	12,2	186	12,3	
*Non disponible **	*1*	*0,5*	*6*	*0,5*	*7*	*0,5*	
Total donnée disponible	*215*		*1 301*		*1 516*		
Décès au cours du premier mois							S (0,0223)
Oui	21	9,7	74	5,7	95	6,2	
Non	195	90,3	1 233	94,3	1 428	93,8	
Non disponible	*0*	*0,0*	*0*	*0,0*	*0*	*0,0*	
Total donnée disponible	*216*		*1 307*		*1 523*		
IDM péri-procédural							NS (0,18)
Oui	7	3,2	24	1,8	31	2,0	
Non	209	96,8	1 282	98,2	1 491	98,0	
Non disponible	*0*	*0,0*	*1*	*0,1*	*1*	*0,1*	
Total donnée disponible	*216*		*1 306*		*1 522*		
IDM au cours du premier mois (dont péri-procéduraux)							NS (0,09)
Oui	8	3,7	25	1,9	33	2,2	
Non	208	96,3	1 281	98,1	1 489	97,8	
Non disponible	*0*	*0,0*	*1*	*0,1*	*1*	*0,1*	
Total donnée disponible	*216*		*1 306*		*1 522*		
AVC/AIT au cours du premier mois							NS (0,55)
Oui	4	1,9	33	2,5	37	2,4	
Non	212	98,1	1 273	97,5	1 485	97,6	
Non disponible	*0*	*0,0*	*1*	*0,1*	*1*	*0,1*	
Total donnée disponible	*216*		*1 306*		*1 522*		
Hémorragie "life-threatening" au cours du premier mois							NS (0,13)
Oui	9	4,2	31	2,4	40	2,7	
Non	205	95,8	1 262	97,6	1 467	97,3	
Non disponible	*2*	*0,9*	*14*	*1,1*	*16*	*1,1*	
Total donnée disponible	*214*		*1 293*		*1 507*		
Hémorragie (life-threatening, majeure ou mineure) au cours du premier mois							NS (0,60)
Oui	28	13,1	187	14,4	215	14,2	
Non	186	86,9	1 108	85,6	1 294	85,8	
Non disponible	*2*	*0,9*	*12*	*0,9*	*14*	*0,9*	
Total donnée disponible	*214*		*1 295*		*1 509*		
Complication vasculaire majeure au cours du premier mois							NS (0,07)
Oui	14	6,6	50	3,9	64	4,2	
Non	199	93,4	1 245	96,1	1 444	95,8	
Non disponible	*3*	*1,4*	*12*	*0,9*	*15*	*1,0*	
Total donnée disponible	*213*		*1 295*		*1 508*		
Complication vasculaire majeure ou mineure au cours du premier mois							NS (0,59)
Oui	16	19,3	65	14,8	81	15,5	
Non	67	80,7	373	85,2	440	84,5	
Non disponible	*133*	*61,6*	*869*	*66,5*	*1 002*	*65,8*	
Total donnée disponible	*83*		*438*		*521*		
Acute Kidney Injury							NS (0,12)
Oui	35	16,2	162	12,4	197	12,9	
Non	181	83,8	1 145	87,6	1 326	87,1	
Non disponible	***0***	***0,0***	***0***	***0,0***	***0***	***0,0***	
Total donnée disponible	*216*		*1 307*		*1 523*		
Combined safety endpoint au terme du premier mois							NS (0,38)
Echec	65	30,1	356	27,2	421	27,6	
Succès	151	69,9	951	72,8	1 102	72,4	
Non disponible	***0***	***0,0***	***0***	***0,0***	***0***	***0,0***	
Total donnée disponible	*216*		*1 307*		*1 523*		

** donnée manquante ou recul insuffisant (< 1 mois).*

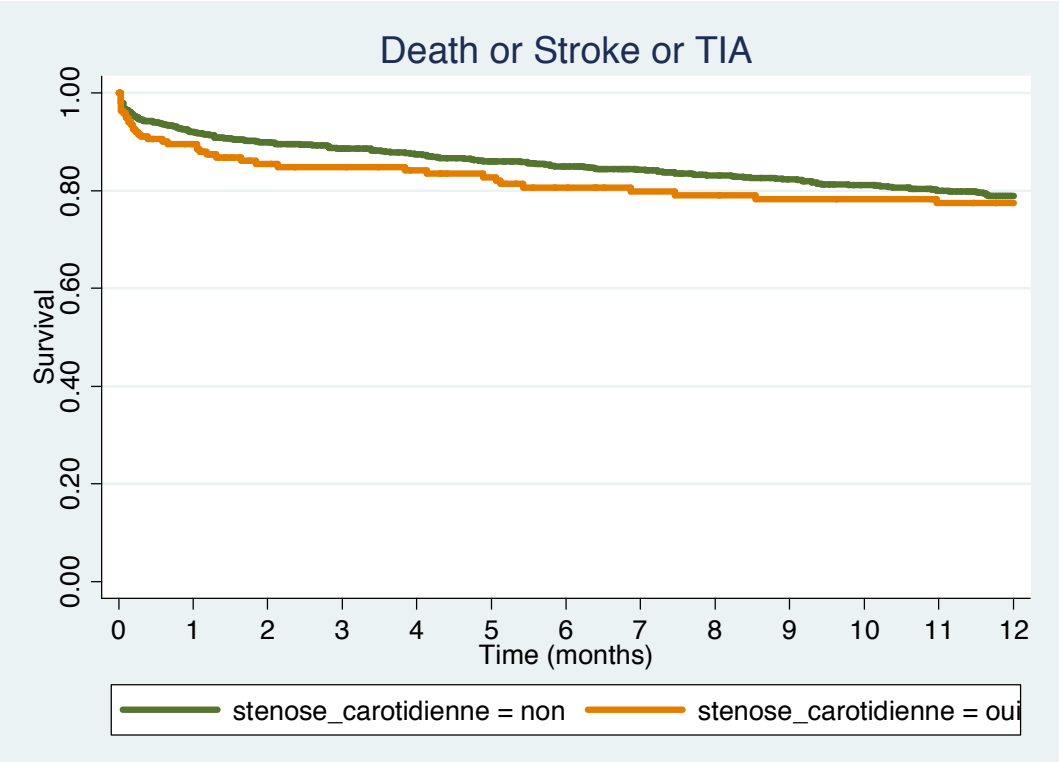
STENOSES CAROTIDIENNES

TAVI PASTEUR / RANGUEIL

n= 1523

II - CARACTERISTIQUES DES SUJETS ET SURVENUE DU DECES, D'UN AVC OU D'UN AIT AU COURS DES 12 PREMIERS MOIS

ANALYSES NON AJUSTEES - RISQUES RELATIFS "BRUTS"



SURVIE (ENDPOINT DC OU AVC OU AIT A 1 AN)
ANALYSES NON AJUSTEES

	n	%
Décès, AVC ou AIT à 1 an	248	16,3
Vivant indemne AVC/AIT à 1 an	607	39,9
Suivi < 1 an	668	43,9
Total	1523	100,0

Table 6

Parmi ces 248 personnes pour lesquelles la survenue de cet endpoint composite a été observée, 213 sont des décès avant 1 an.

	Endpoint Décès ou AVC ou AIT à 1 an					
	n	**%**	**p Logrank**	**RR brut**	**IC 95%**	**p**
Centre			0,66			
Pasteur	153	15,3		1,00		
Rangueil	95	18,2		0,94	0,73 - 1,22	0,66
Sténose carotidienne			0,33			
Oui	40	18,5		**1,18**	**0,84 - 1,66**	**0,33**
Non	208	15,9		1,00		
Sexe			0,90			
Hommes	121	15,9		0,98	0,77 - 1,26	0,90
Femmes	127	16,6		1,00		
Age *(pour une augmentation d'un an)*				1,00	0,98 - 1,01	0,61
ATCD de maladie coronarienne			0,0052			
Oui	156	19,0		1,44	1,11 - 1,86	0,006
Non	92	13,1		1,00		
ATCD de pontage coronarien			0,03			
Oui	27	12,6		0,65	0,43 - 0,97	0,03
Non	221	16,9		1,00		
ATCD d'ATC			0,73			
Oui	90	16,2		0,96	0,74 - 1,24	0,73
Non	158	16,4		1,00		
ATCD AVC/AIT			0,0160			
Oui	37	24,7		1,53	1,08 - 2,17	0,017
Non	211	15,4		1,00		
ATCD AOMI			0,0012			
Oui	68	23,1		1,58	1,19 - 2,08	0,001
Non	180	14,7		1,00		
ATCD anévrisme aortique (thoracique ou abdominal)			0,77			
Oui	7	20,6		1,12	0,53 - 2,37	0,77
Non	241	16,2		1,00		
ATCD aorte porcelaine			0,49			
Oui	14	18,7		1,21	0,71 - 2,07	0,49
Non	234	16,2		1,00		
ATCD hémodialyse			0,0011			
Oui	13	35,1		2,45	1,40 - 4,27	0,002
Non	235	15,8		1,00		
ATCD valvuloplastie au ballon			0,08			
Oui	72	20,9		1,28	0,97 - 1,69	0,08
Non	176	14,9		1,00		
ATCD chirurgie valvulaire			0,95			
Oui	11	15,9		1,02	0,56 - 1,87	0,95
Non	237	16,3		1,00		

		Endpoint Décès ou AVC ou AIT à 1 an				
	n	%	p Logrank	RR brut	IC 95%	p
ATCD dégénérescence bioprothèse aortique			0,91			
Oui	7	15,9		1,05	0,49 - 2,22	0,91
Non	241	16,3		1,00		
ATCD diabète			0,0324			
Oui	80	20,1		1,34	1,02 - 1,74	0,0330
Non	168	14,9		1,00		
ATCD HTA			0,0047			
Oui	168	14,8		0,68	0,52 - 0,89	0,0050
Non	80	20,8		1,00		
ATCD dyslipidémie			0,94			
Oui	113	16,7		1,01	0,79 - 1,30	0,94
Non	135	15,9		1,00		
Tabagisme actif ou sevré < 1 an			0,24			
Oui	37	14,3		0,81	0,57 - 1,15	0,24
Non	211	16,7		1,00		
Maladie cognitive			0,43			
Oui	10	13,7		0,78	0,41 - 1,46	0,44
Non	238	16,4		1,00		
Maladie respiratoire			0,76			
Oui	81	17,2		1,04	0,80 - 1,36	0,76
Non	167	15,9		1,00		
TRAITEMENTS EN COURS AVANT						
Aspirine			0,18			
Oui	195	16,0		0,81	0,60 - 1,10	0,18
Non	53	17,5		1,00		
Clopidogrel			0,71			
Oui	107	16,2		1,05	0,82 - 1,35	0,71
Non	141	16,3		1,00		
Anti-coagulant oral			0,29			
Oui	73	18,1		1,16	0,88 - 1,42	0,29
Non	175	15,6		1,00		
Statine			0,68			
Oui	128	16,5		0,95	0,74 - 1,22	0,68
Non	120	16,1		1,00		
Amiodarone			0,57			
Oui	45	17,8		1,10	0,79 - 1,51	0,58
Non	203	16,0		1,00		
Digoxine			0,99			
Oui	11	16,2		1,00	0,55 - 1,84	0,99
Non	237	16,3		1,00		
SYMPTOMES						
Classe NYHA initiale			0,0016			
I ou II	25	8,6		1,00		
III	170	16,9		1,80	1,18 - 2,74	0,006
IV	53	23,5		2,35	1,46 - 3,79	0,001
Hospitalisation <1 an pour AS			0,26			
Oui	174	17,9		1,17	0,89 - 1,54	0,26
Non	74	13,4		1,00		
Logistic Euroscore moyen				1,01	0,99 - 1,02	0,12
STS moyen *				1,02	1,002 - 1,04	0,025
BMI moyen *				0,97	0,94 - 0,99	0,038

		Endpoint Décès ou AVC ou AIT à 1 an					
		n	%	p Logrank	RR brut	IC 95%	p
	Clairance MDRD			0,0005			
	< 30	67	22,5		1,00		
	30 et +	180	14,9		0,61	0,46 - 0,81	0,001
ECG INITIAL	**Rythme sinusal**			0,13			
	Oui	182	15,6		0,81	0,61 - 1,07	0,14
	Non	66	18,7		1,00		
	FA			0,14			
	Perm ou Parox	63	18,9		1,24	0,93 - 1,65	0,14
	Non	185	15,5		1,00		
	BAV			0,68			
	I, II ou III	42	16,2		0,93	0,67 - 1,30	0,68
	Non	206	16,3		1,00		
	BBD			0,08			
	Oui	46	19,7		1,32	0,96 - 1,82	0,09
	Non	202	15,7		1,00		
	BBG			0,76			
	Oui	49	16,4		0,95	0,70 - 1,30	0,76
	Non	199	16,3		1,00		
	Présence d'un Pace-Maker			0,74			
	Oui	35	16,3		0,94	0,66 - 1,35	0,75
	Non	213	16,3		1,00		
	FEVG moyenne				1,00	0,99 - 1,01	0,89
	Aire Valve Aortique moyenne *				0,75	0,39 - 1,47	0,41
	Gradient moyen moyenne *				1,00	0,99 - 1,01	0,82
	Diamètre TTE moyenne *				0,97	0,91 - 1,03	0,31
	Fuite aortique			0,57			
	Non	86	15,4		1,00		
	Grade 1	129	17,0		1,10	0,84 - 1,45	0,48
	Grades 2 à 4	24	13,2		0,90	0,57 - 1,41	0,64
AORTO-CORO	**Aorto-coro (attention bcp de données manquantes)**			0,36			
	Lésion>50%	80	15,7		0,88	0,68 - 1,15	0,37
	Pas de lésion>50%	168	16,6		1,00		
	Calcification valve aortique			0,32			
	Sévère	190	16,4		1,16	0,86 - 1,57	0,32
	Aucune ou modérée	56	15,4		1,00		
	Anesthésie Générale			0,22			
	Oui	205	17,5		1,23	0,88 - 1,71	0,22
	Non	43	12,3		1,00		
	Accès			0,0005			
	Fémoral ou iliaque	186	14,5		1,00		
	Transapical	32	34,8		2,19	1,50 - 3,18	0,0010
	Sous-clavier	11	22,9		1,28	0,70 - 2,36	0,42
	Transaortique	19	18,6		1,22	0,76 - 1,96	0,41
	Guidage ETO			0,014			
	Oui	128	21,4		1,37	1,06 - 1,75	0,015
	Non	120	13,0		1,00		
	Type de prothèse			0,32			
	Sapien ou Sapien XT	117	18,1		1,00		
	Corevalve	120	15,3		0,91	0,71 - 1,18	0,4900
	Lotus	7	14,0		0,67	0,31 - 1,45	0,31
	Autres (S3, Portico, Evolu	4	9,3		0,46	0,17 - 1,24	0,12

	Endpoint Décès ou AVC ou AIT à 1 an					
	n	%	p Logrank	RR brut	IC 95%	p
Taille de la prothèse			0,12			
< 26	49	19,1		1,00		
26	111	18,5		0,97	0,69 - 1,36	0,87
≥ 29	88	13,2		0,75	0,53 - 1,06	0,10
Durée de la procédure				1,00	1,01 - 1,08	0,002
Valvulo-ballon			0,52			
Oui	193	17,5		1,10	0,82 - 1,49	0,520
Non	55	13,1		1,00		
Seconde Valve in Valve			0,0033			
Oui	11	32,4		2,40	1,31 - 4,40	0,005
Non	236	15,9		1,00		
Post-dilatation prothèse			0,17			
Oui	41	18,7		1,26	0,90 - 1,77	0,170
Non	207	15,9		1,00		
Fuite para-prothétique finale			< 0,001			
Non	128	16,1		1,00		
Grade 1	72	12,7		0,81	0,61 - 1,08	0,15
> Grade 1	42	27,6		1,91	1,35 - 2,71	< 0,001
Fuite intra-prothétique finale			0,40			
Non	25	14,6		1,00		
Grade 1	217	16,2		1,29	0,85 - 1,96	0,22
> Grade 1	1	25,0		2,27	0,31 - 16,8	0,42
Succès de la procédure (donnée saisie)			< 0,001			
Oui	210	15,1		0,40	0,28 - 0,56	0,001
Non	38	29,7		1,00		

Discussion

The main findings of the current study are the following:

- no correlation has been observed about the presence of an asymptomatic carotid artery stenosis discovered before the TAVI procedure and rate of cerebrovascular events (stroke or TIA) and myocardial infarction during the first postoperative month;

- In the ACSA patients the 30 days mortality was higher probably because they were more complex, thay had a more severe vascular disease with a higher prevalence of dyslipidemia, myocardial infarction, CAD, CABG, porcelain aorta as documented by a higher Logiistic Euroscore.

- no differences concerning all-causes and cardiovascular mortality and onset of cerebrovascular events (stroke/TIA) at long-term have been shown between patients with and without CAS.

A number of studies, in settings other than TAVI, examined the prevalence of asymptomatic CAS in patients with aortic valve stenosis of varying severity [43,44,45]. In the study of Novo et al., conducted on AS of any degree of severity, CAS (defined as any carotid plaque) was evident in 70% of 135 patients with AS (vs. 42%

in controls with a normal aortic valve, P<0.0001), although the severity of the carotid stenosis and their distribution (unilateral vs. bilateral) were not reported. [45] Studies conducted in the surgical setting have provided inconsistent results. Anselmi et al. performed a Doppler study in 1,012 patients referred for isolated valve surgery, without coronary bypass grafting. Among the 1012 patients, 26.4% had carotid stenosis graded >50%and 6% had carotid stenosis >70% and underwent combined valvular surgery and carotid endarterectomy (CEA); 86% had carotid stenosis >50% to ≤ 69% and received valvular cardiac surgery under hypothermic cardiopulmonary bypass. Operative mortality and the rate of perioperative adverse neurological events were comparable among the groups. [43] Zayed et al. analyzed Doppler data from 177 patients undergoing isolated valve surgery, of whom 98 patients had severe AS. The prevalence of clinically significant CAS could not have exceeded 5%. [44]

Data from systematic studies examining the prevalence of CAS in TAVI patients are few. In a recent study of Steinvil, by multivariate analysis, smoking and a higher Euroscore independently predicted the presence of CAS. Patients in the TAVI cohort had a significantly higher prevalence of both unilateral and bilateral significative CAS and it was not independently associated with 30-day mortality or stroke rates. [46]

The mechanistic role of asymptomatic CAS, even when of high-grade severity, in the pathogenesis of periprocedural stroke following open cardiac surgery is questionable, based on detailed clinical and imaging data revealing that 95% of these events occur without anatomic relation to evident CAS. [47] The clinical importance of CAS in TAVI-related stroke is also unclear. Cerebral injury during TAVI can result from liberation of embolic debris during valve positioning and implantation [32], or through traversing a diseased aortic arch with wires and devices. [48]

Because CAS is well-correlated with the presence of aortic arch atheroma visualized by transesophageal echocardiography [49,50], carotid lesions may, therefore, be a marker of a higher stroke risk in TAVI.

Moreover, neurological injury caused by prolonged hypotension might be associated with or potentiated by hemodynamically significant CAS. [51]

A recent meta-analysis on more than 10,000 patients showed a prevalence of acute (<24h) TIA/Stroke of 1.5 ± 1.4% and the overall 30-day prevalence of 3.3 ± 1.8%, with the majority being major strokes (2.9 ± 1.8%). During the first year after TAVI, stroke/TIA increased up to 5.2 ± 3.4%. Differences in stroke rates were associated with different approaches and valve prostheses used with lowest stroke rates after transapical TAVI (2.7 ± 1.4%). [52] In the

Canadian multicenter registry of TAVI an incidence of 0.6 % of procedural stroke was reported, but the VARC classification was not applied. [53]

After heart surgery, less than 65% of neurological events occur early after the procedure. [56,57] More than 50% of stroke having occurred in the first 24 hours, is probably related to technical reasons inherent in proceedings, for which the use of endovascular embolic protection or cerebral deflection devices are encouraged to be used especially in patients with carotid stenosis, to minimize this risk of debris embolisation. [58,59]

A recent study showed that macroscopic debris were captured by a distal protection system during TAVI in 75% patients. This material was mainly composed of thrombus and debris from the native valve leaflets and aortic wall. These findings favor the procedural embolic etiology of stroke rather than the low cerebral flow and that could explain the lack of impact of the carotid stenosis on acute stroke / TIA.

In patients with carotid stenosis, the balloon predilatation and the choice of a balloon expandable prosthesis could have been thought to be avoided to minimize the low-flow cerebral episodes, but in our study, the two sub groups did not differ in terms of the pre-dilation balloon.

The procedural parameters did not differ between the subgroups. The overall mortality at 30 days in our study was 6,2%. This is comparable to the results reported in literature. The overall 30-day stroke/TIA was 2,4%, with the majority being major strokes (1.9%). During the first year after TAVI, stroke/TIA increased up to 5.2 ± 3.4%. Differences in stroke rates were associated with different approaches and valve prostheses used with lowest stroke rates after transapical TAVI (2.7 ± 1.4%). The registry FRANCE2 reported a mortality rate at 30-days of 9.7% [25] and the United Kingdom registry UK TAVI mortality reported a 7.9% 30-days mortality. [60] The PARTNER trial showed 5% of all-cause mortality and 4.5% mortality for cardiovascular cause. [14,18] In our study the rate stroke/TIA at 30 days was 2.6%. This finding is consistent with previous datas reported in literature with a rate of about 3.5%, ranging from 1.7% in SOURCE registry to 4.1% in UK TAVI. [60,61]

The composite endpoint of cardiovascular death and stroke/TIA in our study was 14.8% without differences between the presence and the absence of CAS. There were no significant differences between transfemoral and transapical approach or between the MCV and ES valve. The overall mortality rate at one year in our population was 12.5%. Mortality reported in FRANCE2 register was 24% and in the UK TAVI registry 11.4%. In our population, presence of carotid stenosis did not influence the mortality at one year.

A period of stroke vulnerability can be identified extending to the first month after TAVI. Nombela-Franco et al. [55] and Nuis et al. [54], identified acute stroke (within 24 h) in, respectively, 54% and 42% of their patients. These acute events could be associated to the procedure and do not correlate with the presence of carotid artery disease. In fact they can occur at various steps of the procedures, for example, crossing the aortic valve, balloon valvuloplasty, placement of the valve, deployment of the valve, and withdrawal of the delivery system. The embolic nature of periprocedural stroke has already been demonstrated. [32,48,62]

Nombela-Franco et al. identified post-dilation balloon and valve dislodgment/embolization as predictors of acute CVEs (<24 h), whereas new-onset atrial fibrillation determined a higher risk for subacute CVEs (1 to 30 days), and the number of late events (>30 days) were higher in patients with a history of chronic atrial fibrillation, cerebrovascular disease, and peripheral vascular disease. [55]

Atrial fibrillation has not been identified as a predictor of stroke and this is consistent with the data reported in registries. [25] This event was mainly captured during in-hospital monitoring, and its real frequency may be underestimated because of the difficulty in recording it during a longer follow-up with electrocardiograms obtained only at 1 month, 6 months, and then yearly.

Anticoagulant treatment may be a factor associated with the occurrence of cerebrovascular events. One explanation could be a more thorough and prolonged treatment in patients presenting atrial fibrillation, most of the time in combination with aspirin alone. Conversely, patients with new-onset atrial fibrillation may not receive adequate anticoagulant treatment at the time of the event. However we have observed that these factors are independent and do not appear to be related to the presence or absence of carotid artery disease.

Study limitations

Despite the care taken in the collection of data and the use of VARC criteria, a certain degree of observational bias is expected.

The absence of independent and systematic neurological evaluation before and after TAVI can not exclude that the incidence of cerebrovascular events could be underestimated.

Since the study is ongoing and the 1 year follow-up has been reached in 56% of patients it is important to analyze the 1 year follow up of the entire study population.

Conclusions

The presence of asymptomatic carotid stenosis is a risk factor for higher mortality at 30 days due to a more complex patient but not at 1 year.

There were no differences in cerebrovascular events after percutaneous aortic valve implantation at 30 days and one-year follow-up. Cerebrovascular events after TAVI occur in a vulnerability period extending to 1 month post-procedure. No difference exists in the CVE rate with regard to the type of valve or the access route.

Coronary, carotid, aortic, iliac and femoral artery disease are often found in elderly patients presenting with severe symptomatic AS undergoing TAVI. These patients are also affected by several clinical factors and frailty that correlate with the presence and severity of arterial pathologies and can impact on incidence of CVEs and long-term survival.

Predictive factors for the endpoints evaluated (combined 1 year cardiovascular mortality and stroke/TIA) were previous history of coronary artery disease, lower extremity artery disease, severe chronic renal failure, diabetes, NYHA class III and IV; as procedural aspects the transapical approach, the need to implant a second valve in the same procedure and a paravalvular leak of more than

grade 1 at the end of the procedure were related to a worse 1 year outcome.

References

1. Aortic valve disease. In: Topol EJ, Califf RM, et al, eds. Textbook of Cardiovascular Medicine. Section Two. 3rd ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2007:Chap 23.
2. Ross J Jr, Braunwald E. Aortic stenosis.Circulation 1968;38:61-7.
3. Davies SW, Gershlick AH, Balcon R.Progression of valvular aortic stenosis: a long-term retrospective study. Eur Heart J 1991;12:10-4.
4. Turina J, Hess O, Sepulcri F, Krayenbuehl HP. Spontaneous course of aortic valve disease. Eur Heart J 1987;8:471-83.
5. Schwarz F, Baumann P, Manthey J, et al. The effect of aortic valve replacement on survival. Circulation 1982;66:1105-10.
6. Lund O. Preoperative risk evaluation and stratification of long-term survival after valve replacement for aortic stenosis: reasons for earlier operative intervention. Circulation 1990;82:124-39.
7. Charlson E. Decision-making and outcomes in severe symptomatic AS. Journal of heart valve dis 15(3):312-21, 2006.
8. Bach DS, Siao D, Girard SE, Duvernoy C, McCallister BD Jr, Gualano SK. Evaluation of patients with severe symptomatic aortic stenosis who do not undergo aortic valve replacement. Circ Cardiovasc Qual Outcomes 2009;2:533-9.
9. Dewey TM, Brown D, Ryan WH, Herbert MA, Prince SL, Mack MJ. Reliability of risk algorithms in predicting early and late operative outcomes in high-risk patients undergoing aortic valve replacement. J Thorac Cardiovasc Surg 2008;135:180-7.
10. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, et al. Guidelines on the management of valvular heart disease (version 2012): The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. Oct 2012;33(19):2451-96.
11. Townsend CM, et al. *Sabiston Textbook of Surgery*. 18th ed. Saunders; 2008:1841-1844.
12. Tissot CM, Attias D, Himbert D, Ducrocq G, Iung B, Dilly MP, Juliard JM, Lepage L, De´taint D, Messika-Zeitoun D, Nataf P,

Vahanian A. Reappraisal of percutaneous aortic balloon valvuloplasty as a preliminary treatment strategyin the transcatheter aortic valve implantation era. EuroIntervention 2011;7:49–56.

13. Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation 2002;106:3006-8.
14. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. Oct 21 2010;363(17):1597-607
15. Clavel, MA, et al. Comparison Between Transcatheter and Surgical Prosthetic Valve Implantation in Patients With Severe Aortic Stenosis and Reduced Left Ventricular Ejection Fraction. Circulation. Nov 9 2010Vol;. 122 No.19.
16. Nowicki ER, Birkmeyer NJ et al. Northern New England Cardiovascular Disease Study Group and the Center for Evaluative Clinical Sciences, Dartmouth Medical School. Multivariable prediction of in-hospital mortality associated with aortic and mitral valve surgery in Northern New England. Ann Thorac Surg. 2004 Jun;77(6):1966-77
17. Herrmann HC, Pibarot P, Hueter I, Gertz ZM, Stewart WJ, Kapadia S, et al. Predictors of Mortality and Outcomes of Therapy in Low-Flow Severe Aortic Stenosis: A Placement of Aortic Transcatheter Valves (PARTNER) Trial Analysis. *Circulation*. Jun 11 2013;127(23):2316-26.
18. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. Jun 9 2011;364(23):2187-98.
19. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Prosthesis. *N Engl J Med*. Mar 29 2014
20. Dewey TM, Brown D, Ryan WH, Herbert MA, Prince SL, Mack MJ. Reliability ofrisk algorithms in predicting early and late operative outcomes in high-risk patients undergoing aortic valve replacement. J Thorac Cardiovasc Surg 2008; 135:180–187.

21. Stortecky S, Buellesfeld L, Wenaweser P, Windecker S. Transcatheter aortic valve implantation: the procedure. Heart. 2012 Nov;98 Suppl 4:iv44-51. doi: 10.1136/heartjnl-2012-302401.

22. Himbert D, Descoutures F, Al-Attar N, Iung B, Ducrocq G, Detaint D, Brochet E, Messika-Zeitoun D, Francis F, Ibrahim H, Nataf P, Vahanian A. Results of transfemoral or transapical aortic valve implantation following a uniform assessment in high-risk patients with aortic stenosis. J Am Coll Cardiol. 2009; 54: 303– 311

23. Fraccaro C, Napodano M, Tarantini G, Gasparetto V, Gerosa G, Bianco R, Bonato R, Pittarello D, Isabella G, Iliceto S, Ramondo A. Expanding the eligibility for transcatheter aortic valve implantation the trans-subclavian retrograde approach using the III generation CoreValve revalving system. J Am Coll Cardiol Cardiovasc Interv. 2009; 2: 828– 833

24. Abdel-Wahab M, Mehilli J et al. Comparison of balloon-expandable vs self-expandable valves in patients undergoing transcatheter aortic valve replacement: the CHOICE randomized clinical trial. JAMA. 2014 Apr 16;311(15):1503-14. doi: 10.1001/jama.2014.3316.

25. Gilard M, Eltchaninoff H et Al.; FRANCE 2 Investigators. Registry of transcatheter aortic-valve implantation in high-risk patients. N Engl J Med. 2012;366:1705-15

26. M. B. Leon, N. Piazza, E. Nikolsky et al., "Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium," European Heart Journal, vol. 32, no. 2, pp. 205–217, 2011.

27. Kappetein AP, Head SJ, Généreux P, Piazza N et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol. 2012 Oct 9;60(15):1438-54.

28. Genereux P, Head S, Mieghem N, et al. Clinical outcomes after transcatheter aortic valve replacement (TAVR) using valve academic research consortium (VARC) definitions: a weighted meta-analysis of 3,519 patients from 17 studies. *J Am Coll Cardiol.* 2012;59(13s1):E228

29. Erkapic D, De Rosa S et al. Risk for permanent pacemaker after transcatheter aortic valve implantation: a comprehensive analysis of the literature. J Cardiovasc Electrophysiol. 2012Apr;23(4):391-7. doi: 10.1111/j.1540-8167.2011.02211.x. Epub 2011 Nov 3.
30. Tchetche D, Farah B et al. Cerebrovascular events post-transcatheter aortic valve replacement in a large cohort of patients: a FRANCE-2 registry substudy. JACC Cardiovasc Interv. 2014 Oct;7(10):1138-45.
31. Kahlert P, Knipp SC, Schlamann M et al. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion weighted magnetic resonance imaging study. Circulation 2010;121:870–878
32. Rodés-Cabau J, Dumont E, Boone RH et al. Cerebral embolism following transcatheter aortic valve implantation: comparison of transfemoral and transapical. J Am Coll Cardiol 2011;57:18–28.
33. W.R. Jamieson, F.H. Edwards, M. Schwartz et al. Risk stratification for cardiac valve replacement. National Cardiac Surgery Database. Database Committee of the Society of Thoracic Surgeons. AnnThorac Surg 1999;67:943–951
34. F. Roques, S.A. Nashef, P. Michel et al. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. Eur J Cardiothorac Surg 1999;15: 816–822 [discussion 822–3].
35. European Stroke Organisation, Tendera M, Aboyans V, Bartelink ML et al. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2011 Nov;32(22):2851-906.
36. Dewey TM, Brown DL, Herbert MA et al (2010) Effect of concomitant coronary artery disease on procedural and late outcomes of transcatheter aortic valve implantation. Ann Thorac Surg 89:758–767
37. Fusini L, Mirea O, Tamborini G et al. Incidence and severity of atherosclerotic cardiovascular artery disease in patients

undergoing TAVI. Int J Cardiovasc Imaging. 2015 Mar 25. [Epub ahead of print] PubMed PMID: 25805046

38. Reinthaler M, Stähli BE et al. Post-procedural arterial hypertension: implications for clinical outcome after transcatheter aortic valve implantation. J Heart Valve Dis. 2014 Nov;23(6):675-82.
39. Antoniou GA, Hajibandeh S, et al. Meta-analysis of the effects of statins on perioperative outcomes in vascular and endovascular surgery. J Vasc Surg. 2015 Feb;61(2):519-532.e1
40. Lopez GA, Afshinnik A, Samuels O. Care of the stroke patient: routine management to lifesaving treatment options. Neurotherapeutics. 2011 Jul;8(3):414-24.
41. Rex S. Anesthesia for transcatheter aortic valve implantation: an update. Curr Opin Anaesthesiol. 2013 Aug;26(4):456-66
42. Schymik G, Würth A, Bramlage P et al. Long-term results of transapical versus transfemoral TAVI in a real world population of 1000 patients with severe symptomatic aortic stenosis. Circ Cardiovasc Interv. 2014 Dec 31;8(1).
43. Anselmi A, Gaudino M, Risalvato N, et al. Asymptomatic carotid artery disease in valvular heart surgery: Impact of systematic screening on surgical strategy and neurological outcome. Angiology 2012;63:171–177
44. Zayed H, Ali A, Wendler O, Rashid H. Selective screening for asymptomatic carotid artery disease prior to isolated heart valve surgery. Angiology 2009;60:633–636
45. Novo G, Guarneri FP, Ferro G et al. Association between asymptomatic carotid atherosclerosis and degenerative aortic stenosis. Atherosclerosis 2012;223:519–522
46. Steinvil A, Leshem-Rubinow E et al. Prevalence and predictors of carotid artery stenosis in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation. Catheter Cardiovasc Interv. 2014 Nov 15;84(6):1007-12.
47. Li Y, Walicki D, Mathiesen C, et al. Strokes after cardiac surgery and relationship to carotid stenosis. Arch Neurol 2009;66: 1091–1096.
48. Stortecky S, Wenaweser P, Windecker S. Transcatheter aortic valve implantation and cerebrovascular accidents. EuroIntervention 2012;8 Suppl Q:Q60–Q69

49. Demopoulos LA, Tunick PA et al. Protruding atheromas of the aortic arch in symptomatic patients with carotid artery disease. Am Heart J 1995;129:40–44.
50. Arko FR, Fritcher S et al. Manning LG. Mobile atheroma of the aortic arch and the risk of carotid artery disease. Am J Surg 1999;178:206–208
51. Billings FTT, Kodali SK, Shanewise JS. Transcatheter aortic valve implantation: Anesthetic considerations. Anesth Analg 2009;108:1453–1462.
52. Eggebrecht H, Schmermund A, Voigtlander T, et al. Risk of stroke after transcatheter aortic valve implantation (TAVI): a meta-analysis of 10,037 published patients. EuroIntervention 2012;8:129-38
53. Rodés-Cabau J, Webb JG, Cheung A, et al. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. J Am Coll Cardiol 2010;55:1080–1090.
54. Nuis RJ, Van Mieghem NM, Schuktz CJ. Frequency and Causes of Stroke During or After Transcatheter Aortic Valve Implantation. AM J Cardiol 2012;109:1637-43
55. Nombela-Franco L, Webb JG, de Jaegere PP et al. Timing, Predictive Factors, and Prognostic Value of Cerebrovascular Events in a Large Cohort of Patients Undergoing Transcatheter Aortic Valve Implantation. Circulation 2012;126:341-53.
56. Hogue CW Jr, Murphy SF, Schechtman KBet et al. Risk factors for early or delayed stroke after cardiac surgery. Circulation 1999;100:642–647.
57. Filsoufi F, Rahmanian PB, Castillo JGet et al. Incidence, imaging analysis, and early and late outcomes of stroke after cardiac valve operation. Am J Cardiol 2008;101:1472–1478.
58. Nietlispach F, Wijesinghe N, Gurvitch R, et al. An embolic deflection device for aortic valve interventions. JACC Cardiovasc Intv 2010;3:1133–1138
59. Naber CK, Ghanem A, Abizais AA et al. First in men use of a novel embolic protection device for patients undergoing transcatheter aortic valve implantation. Eurointervention 2012;8:43-50.

60. Moat NE, Ludman P, de Belder MA et al. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. J Am Coll Cardiol 2011;58:2130–2138.

61. Thomas M, Schymik G, Walther T, et al. Thirty-day results of the SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) Registry: a European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. Circulation 2010;122:62–69.

62. Van Mieghem NM, Schipper ME, Ladich E, et al. Histopathology of embolic debris captured during transcatheter aortic valve replacement. Circulation 2013;127:2194–201

63. Tchetche D, Van der Boon RM, Dumonteil N et al. Adverse impact of bleeding and transfusion on the outcome post–transcatheter aortic valve implantation: insights from the Pooled-RotterdAm-Milano-Toulouse In Collaboration Plus (PRAGMATIC Plus) initiative. Am Heart J 2012;164:402–9

64. Tchetche D, Van Mieghem NM. New-generation TAVI devices: description and specifications. EuroIntervention. 2014 Sep;10 Suppl U:U90-U100. doi: 10.4244/EIJV10SUA13.