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THE INFLUENCE OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE UPON
CLINICAL OUTCOMES AND QUALITY OF LIFE
IN PATIENTS UNDERGOING TRANSCATHETER AORTIC VALVE IMPLANTATION.
THE EFFECTS OF DIFFERENT ACCESS ROUTE APPROACHES

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INTRODUCTION AND PURPOSE OF THIS STUDY

Nonrheumatic, senile, calcific aortic stenosis (AS) is the most common valvular degenerative abnormality in Europe and the most frequently acquired valve disease in elderly patients. (1,2) At 75 years of age 4.6% of the population have severe AS (3) and by 85 years old this has risen to 8%. (1)

Prolonged life expectancy has resulted in an aging population and, consequently, in an increased number of patients with degenerative calcific AS. (4)

Once symptoms develop, the two-year and five-year survival rates of unoperated patients are dramatically curtailed at 50% and 20%, respectively. (5-9) Even in apparently asymptomatic patients, when the valve area is 0.8 cm² or less, the mortality rate is high without aortic valve surgery. (8,10)

Symptomatic, severe AS is therefore a class I indication for a surgical aortic valve replacement (sAVR) (7), whose efficacy for symptomatic AS is well established. (11,12) Surgical aortic valve replacement is the treatment of choice for a vast majority of patients, offering symptomatic relief and improving long-term survival. (4) It has been estimated that 300,000 patients have severe aortic stenosis in the United States, and approximately 60,000 undergo sAVR every year. Despite several series indicate excellent results with sAVR in elderly patients, physicians remain reluctant to recommend surgical intervention for those patients considered at high risk. (13-16) An estimated 30% to 45% of patients may be denied sAVR because of physician fear of poor outcome. The most common comorbidities of concern are age older than 80 and poor left ventricular ejection fraction (LVEF). (2,17,18)

Whilst the increased risk associated with these variables is well documented, there are few studies that evaluate surgical outcome attributable to other common comorbidities.

It is in these patients that transcatheter aortic valve implantation (TAVI) has seen its most marked growth since it was first clinically demonstrated by Dr. Cribier using a transvenous, transseptal approach. (19)

Over the past decade, TAVI has emerged as an effective treatment for patients with AS who are considered at excessive peri-operative risk for sAVR. (20-23) Two-year results from inoperable (24) and three-year results from high-risk operable randomized Placement of AoRTic TraNscathetER Valve (PARTNER) trial cohorts (25) confirmed that TAVI is

better than medical therapy and is noninferior to sAVR in these patients. The follow-up results from randomized PARTNER trials establish a significant reduction in symptoms, similar in both TAVI and sAVR groups, and maintained for at least 2 years.

At this stage, according to the Food and Drug Administration-approved product labeling, TAVI is not indicated for individuals who can be treated by open-heart surgery. It is also contraindicated in patients who can not tolerate anti-coagulation/anti-platelet therapy, or who have active bacterial endocarditis, or other active infections. Actually, the use of a transcatheter heart valve (THV) is approved by the Food and Drug Administration (FDA) for patients who are not eligible for open-heart surgery for replacement of their aortic valve and have a calcified aortic annulus (calcium build-up in the fibrous ring of the aortic heart valve). (26)

Given that the decision to intervene on severe AS is driven by the appearance of significant symptoms, assessment of the impact of TAVI upon patients' quality of life (QoL) – in addition to traditional end-points such as mortality and morbidity – is paramount. (27,28) The introduction of any new technology requires the assessment of cost-effectiveness including both length and quality of life.

As most of the TAVI teams are now getting patients who come to them with very little options and with end-stage disease processes like renal failure and severe chronic obstructive pulmonary disease (COPD), it would be useful to reappropriate such resources to patients who have a fighting chance for survival.

Patients affected by pulmonary dysfunction in particular represent a paradigmatic common example, being very frequently the patients operated on. Their main symptom is shortness of breath as aortic stenosis' is. Alas, after the operation not only it would appear they don't live very long, but they don't feel any better. Actually, there are very few data about symptomatic improvement, particularly in patients with pulmonary dysfunction where nothing is often really accomplished, perhaps.

The first aim of this study was to evaluate the specific contribution made by pulmonary disease to the clinical outcomes and QoL, in patients undergoing TAVI. The results of this could demonstrate the importance of recognizing this preexisting comorbid condition before making operative decisions for TAVI and influence such decision in terms of appropriateness.

New frontiers in TAVI are improving the deliverability of the device and minimizing patient morbidity and mortality through device development and patient selection. Patient screening, scoring ('general assessment') and eventual selection for a specific procedure ('specific/local assessment') has to be carefully evaluated. (Table 1)

After the pioneering works, transfemoral TAVI [TF-TAVI] has rapidly evolved into smaller profile devices. Therefore, it has gone from 22- and 24-F to 18- and 16-F balloon-expandable introducer sheaths. Despite this rapid progress, the devices in use still remain relatively bulky coupled with the high incidence of peripheral vascular disease in cardiac and elderly patients, has driven TAVI to evolve alternative options of delivery (transapical [TA-TAVI], transaxillary/subclavian [TAx-TAVI], transiliac [TI-TAVI] and direct transaortic [TAo-TAVI]) in order to offer the most adequate treatment for the individual patient.

Table 1. Indications to surgical aortic valve replacement (sAVR)/transcatheter aortic valve implantation (TAVI).

The patient	Heart team conference
	Consider guidelines
	Regular risk: conventional sAVR. High/prohibitive risk: TAVI
The timing	Severe symptomatic AS
	Compensated patient
	Age and risk profile
The team	Interdisciplinary cooperation
	Hybrid operating theatre/Catheterization laboratory
The procedure	Conventional sAVR (sternotomy/minimally invasive)
	TAVI
	<ul style="list-style-type: none"> • Transarterial (TF/TI)
	<ul style="list-style-type: none"> • Transsubclavian/axillary (TAx)
	<ul style="list-style-type: none"> • Transapical (TA)
	<ul style="list-style-type: none"> • Transaortic (TAo)
	<ul style="list-style-type: none"> • Transcarotid

One of the unique variables for successful TAVI involves the ability to secure an access route for deployment of the aortic prosthesis. A thorough knowledge of various alternative access techniques and expertise in rescue repair are therefore important and required by the implanting cardiologists and cardiac surgeons involved in transcatheter aortic valve therapy.

In this study we described the various surgical and percutaneous access techniques available for the implantation of transcatheter aortic bioprostheses.

Patients undergoing TAVI in the PARTNER trial demonstrated improvements in generic and specific health-related QoL measures at both 1 month and 12 months. (29) However, the impact of the access route upon QoL is less clear.

Reynolds et al. (30) compared QoL between TAVI and sAVR at 1, 6 and 12 months and found transapical TAVI (TA-TAVI) patients did not show any QoL benefit compared to sAVR. A direct health status comparison among the several possible access routes for TAVI has yet to be performed.

The last aim of this study is to evaluate the effects of access route on the clinical results and QoL in patients undergoing TAVI through different access routes (transfemoral, transapical and transaortic) using the Edwards SAPIEN or SAPIEN XT bioprostheses (Edwards Lifesciences Inc., CA, USA). Even more specifically, the present study would evaluate the impact of COPD on the outcomes of patients treated for severe AS across all access modalities.

Chapter 1. BACKGROUND

1.1. Quality of Life after Transcatheter Aortic Valve Implantation

QoL is a critical measure of effectiveness of TAVI in patients with severe AS. There are studies that showed a marked improvement in health status and QoL compared with baseline for patients with severe AS. (27-31) Most of these studies compared scores on the Medical Outcome Study 12-Item Short-Form Health Survey (SF-12), the Medical Outcome Study 36-Item Short-Form Health Survey (SF-36), or the Minnesota Living With Heart Failure Questionnaire from baseline to 1 or 2 follow-up time points and included patients treated predominantly via transarterial TAVI approaches.

PARTNER B trial demonstrated a large survival benefit with TAVI compared with standard therapy in patients with severe AS who were not suitable candidates for sAVR, despite the major incidence of neurologic events (including all strokes and major strokes), major vascular complications, and major bleeding events in the TAVI group. (24) In this preplanned substudy, TAVI was also found to provide substantial benefits over standard therapy in terms of symptoms and health-related QoL. These differences were seen as early as 1 month and continued to increase over the 12-month follow-up of the study.

That was confirmed in the PARTNER B-QoL trial in which measures of both disease-specific and generic QoL improved to a greater extent with TAVI than with standard therapy, with effect sizes that were both large and clinically meaningful. (29)

In the PARTNER A trial, it was found that both methods of valve replacement led to substantial improvement in both disease-specific and general health status in high-risk surgical candidates. (25) In particular, outcomes at 12 months were similar when comparing TAVI and sAVR regardless of the TAVI access site. In addition, among patients who were eligible for a TF-TAVI approach, there were both statistically significant and clinically relevant differences in health status and QoL at 1-month follow-up in favour of TAVI. On the other hand, among patients treated via the TA approach, health status was not better at any time point after TAVI than after sAVR with trends and, in some cases, borderline statistically significant differences in favour of sAVR both at 1 and 6 months. (30)

Ussia et al. (28) evaluated 1 year changes in QoL in patients who underwent TAVI. A total of 143 patients undergone successful TAVI using the 18 F CoreValve (Medtronic Inc, Minneapolis, MN) or the Edwards Sapien XT heart valve

(Edwards Lifescience, Irvine, CA) comprised the study population. Mean pre-procedural shorter SF-12 version 2 (SF-12v2) scores showed an important upgrading after TAVI: physical component summary (PCS) improved from 28.3 to 44.0 at 5 months and 42.4 at 12 months ($p < 0.001$); mental component summary (MCS) increased from 38.0 to 47.3 at 5 months and 48.2 at 12 months ($p < 0.001$). Both the physical and mental score summaries at follow-up of these post-TAVI patients were not significantly different from the anticipated thresholds of the general Italian population over the age of 75 years. New York Heart Association (NYHA) functional class improvement was reported in all patients. The authors concluded that these findings showed a marked mid-term improvement in functional status as well as physical and mental health in patients who underwent TAVI.

Georgiadou et al. (31) assessed changes in QoL along with functional status and late survival after TAVI. A total of 36 consecutive patients with a logistic Euroscore of 29.7 ± 13.7 underwent TAVI using the 18-F CoreValve prosthesis via a femoral or a subclavian arterial approach. QoL was evaluated by administering the SF-36 tool and SF-12v2 questionnaires before and 1 year after TAVI. Transcatheter aortic valve implantation was successfully performed in all patients. One-year follow-up showed a significant change in NYHA functional class (3 ± 0.7 versus 1.2 ± 0.4 , $p < 0.001$). Both pre-procedural summary SF-36 and SF-12v2 physical and mental scores showed a significant improvement 1 year after TAVI. The authors concluded that these findings showed a marked 1-year clinical benefit in functional status as well as physical and mental health in patients who underwent TAVI.

The QoL instrument used in this study, the European Quality of Life-5 dimensions (EQ-5D) has been criticized as non specific instrument - but no aortic stenosis specific QoL tool currently exists. The EQ-5D questionnaire is widely employed in the cardiology field, involving populations affected by coronaropathies, by heart failure, associated with heart transplant, and in the rehabilitation programs, as well (32). It is a generic instrument, whose required characteristics are supplied completely: 1) an easy 'add-on' to studies using existing instruments; 2) capable of being disseminated as a postal questionnaire for selfcompletion; 3) relatively undemanding - taking only a few minutes to complete; 4) relevant to all respondents: healthy or severely ill; at home or in hospital; of all ages; 5) capable of producing a single index value; 6) consistent with health states 'worse than dead' (33).

In recent years use of the EQ-5D to measure patient QoL in published studies within the cardiovascular field has increased. This largely reflects the growing requirement, over time, of clinical trials to consider cost-effectiveness

alongside the clinical effectiveness of new interventions. As the 'gold standard' form of economic evaluation in many health care systems, cost-utility analyses rely on generic measures such as the EQ-5D for the calculation of QoL. Increased use of the EQ-5D may also support the view that patient reported outcomes and QoL are becoming more widely accepted as routine measures in clinical studies, with the EQ-5D being an internationally recognized generic measure of QoL.

Stratification of EQ-5D index scores by disease severity (measured by Canadian Cardiovascular Society [CCS] Angina Grading Scale or NYHA heart failure scales) revealed that scores decreased from a mean of 0.78 (standard deviation [SD] 0.18) to 0.51 (SD 0.21) for mild to severe disease in heart failure patients and from 0.80 (SD 0.05) to 0.45 (SD 0.22) for mild to severe disease in angina patients. (32) However, calculation of pooled means across studies using meta-analytic techniques is not appropriate, given the high level of heterogeneity in terms of study design and patient characteristics.

In general, evaluations of the validity and reliability of the EQ-5D suggested fairly strong convergent validity when assessed by correlations with other QoL measures. Despite the evidence of strong ceiling effects across each domain for the index values, EQ-5D has been shown to have good discriminative abilities in detecting patients whose health status changed by a given clinical magnitude. (32)

1.2. Dyspnea

Shortness of breath (dyspnea) from heart failure is the most frequent symptom of AS and ominous sign, too. It reflects the heart muscle's failure to compensate for the extreme pressure load of aortic stenosis. Shortness of breath (SOB) is caused by increased pressure in the blood vessels of the lung due to the increased pressure required to fill the left ventricle. Initially, SOB occurs only during activity. As the disease progresses, dyspnea occurs at rest. Patients can find it difficult to lie flat without becoming short of breath (orthopnea). Without treatment, the average life expectancy after the onset of heart failure due to AS is between 6 to 24 months.

Dyspnea is a common symptom and can be caused by many different conditions. It often has multiple etiologies.

Although other causes may contribute, the cardiac and pulmonary organ systems are most frequently involved in the etiology of dyspnea. (34)

According to the American Thoracic Society- Consensus Statement on Dyspnea (35), even after dealing with the underlying problem such as heart disease, the patient often continues to experience significant breathlessness. That is because sometimes the problem involves a combination of symptoms associated with two major illnesses such as COPD and congestive heart failure (HF).

Chronic obstructive pulmonary disease is an important public health issue in many countries which is estimated to become the fifth cause of disability and the third cause of mortality in the world within 2020. (36)

In clinical practice it is commonly associated with HF since they share the same pathogenic mechanism (**Figure 1**). Both conditions incur significant morbidity and mortality. Therefore, the prognosis of COPD and HF combined is poorer than for either disease alone. Nevertheless, usually only one of them is diagnosed.

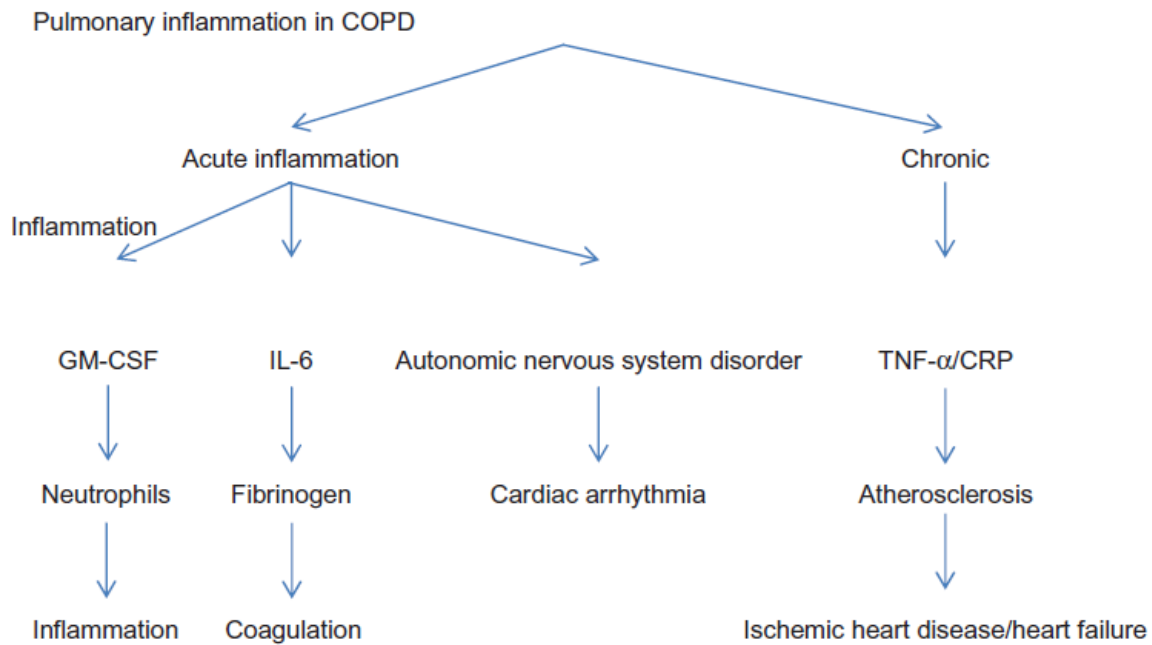


Figure 1. Common inflammatory pathogenesis of chronic pulmonary disease and chronic heart failure.

Lung inflammation in chronic obstructive pulmonary disease may contribute to the appearance of cardiovascular events. COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-6, interleukin-6; TNF- α , tumor necrosis factor- α . Reproduced from: de Miguel Díez J, Chancafe Morgan J, Jiménez García R. The association between COPD and heart failure risk: a review. *Int J Chron Obstruct Pulmon Dis.* 2013;8:305-12. (37)

In a recent study, the prevalence and prognostic implications of the coexistence of COPD and HF were assessed using objective measurements. The prevalence of airways obstruction among chronic HF patients was 37.3% and the prevalence of ventricular dysfunction among COPD patients was 17%. (37)

The combination of COPD and HF presents many therapeutic challenges. Patients with AS and COPD have been considered at high risk for sAVR, which results in some patients being denied this life-saving operation. (36,37)

Specifically, Thourani and colleagues showed that those patients with both preoperative renal and pulmonary organ dysfunction have a significantly high mortality. (38) Pulmonary organ dysfunction (a forced expiratory volume in 1 second less than 50% predicted) was one of the largest contributors to poor postoperative outcomes. In-hospital mortality for

these patients was 9.4% at 30 days (odds ratio [OR] 1.86) with a major adverse cardiac events OR of 1.66 ($p < 0.05$). The mortality hazard ratio (HR) was 2.4 ($p < 0.001$), second only to renal organ dysfunction.

Adabag and colleagues (39) found an adjusted OR of 2.4 for 30-day mortality in patients with moderate to severe COPD after cardiac surgery. In their series, these patients also had longer lengths of intensive care unit and hospital stays and a higher incidence of ventilation beyond 48 hours. Similarly, in their matched cohort analysis of 242 patients undergoing cardiac surgery, Ried and colleagues (40) found a 6.1% for 30-day mortality among patients with COPD compared with 0.8% in non-COPD patients. The authors' suggestion was that, in this high-risk patient population, less invasive alternatives (i.e. TAVI) should be considered.

Accordingly, Baine and colleagues (41), in the attempt of characterizing the referral pattern and treatment allocation among patients referred for TAVI at a large tertiary cardiac care center, found that, although age should not be a deterrent for SAVR, significant lung disease associated with excessive frailty may preclude an operation. Multivariate-adjustment identified the absence of COPD (HR 0.30, $p < 0.05$) and the absence of frailty (HR 0.19, $p < 0.01$) as independent predictors of conventional AVR.

The outcomes of AS patients with COPD undergoing TAVI have not been systematically studied.

In 2010, the multicenter Canadian experience (42) published that a TAVI program including both TF and TA approaches was associated with comparable mortality as predicted by surgical risk calculators for the treatment of patients at very high or prohibitive surgical risk. Baseline (pulmonary hypertension, COPD, chronic kidney disease) and peri-procedural (haemodynamic support, sepsis) factors - but not the approach - determined worse outcomes.

In another series, Kempfert and colleagues (43) showed that of all preoperative and intraoperative factors analyzed, only a reduced vital capacity of less than 70% could be identified as independent risk factors for 30-day mortality by stepwise multivariate regression.

The combination of older age, frailty, and poor respiratory reserve may result in an excessive risk of respiratory failure and reintubation in these patients. The exact quantification of preoperative respiratory dysfunction and the differentiation from effects of AS represent a challenging area in need of further clinical evaluation.

In the study of Toggweiler and colleagues (44), comorbidities, notably chronic lung disease and at least moderate paravalvular regurgitation, were associated with reduced long-term survival (adjusted HR: 2.17; 95% confidence interval

[CI]: 1.28 to 3.70 and adjusted HR: 2.98; 95% CI: 1.44 to 6.17, respectively). Median survival in patients without COPD was 3.9 years but only 2.3 years in those with COPD.

Even in the multicenter Canadian experience (45), the first predictor of late mortality was COPD (HR: 2.18), followed by chronic kidney disease (HR: 1.08), chronic atrial fibrillation (HR: 1.44), and frailty (HR: 1.52).

In the UK TAVI Registry (46) there was a marked attrition in survival between 30 days and 1 year. Survival at 30 days was 92.9%, and it was 78.6% and 73.7% at 1 year and 2 years, respectively. In a univariate model, survival was significantly adversely affected by renal dysfunction, the presence of coronary artery disease, and a nontransfemoral approach; whereas left ventricular function (ejection fraction <30%), the presence of moderate/severe aortic regurgitation, and COPD remained the only independent predictors of mortality in the multivariate model.

Regarding the QoL in patients with COPD undergoing TAVI, in the cohort B of the PARTNER study, the extent of benefit with TAVI was less for patients with oxygen-dependent COPD at the 6-month follow-up (5.6 versus 23.7 points; $p=0.02$ for interaction). By the 1-year follow-up, there were no significant differences in the effect of TAVI on the primary QoL end point across each of the subgroups, including the presence or absence of oxygen-dependent COPD (24.5 versus 25.8; $p=0.74$ for interaction). (29)

De Oliveira and colleagues (36) outlined the profile of patients with COPD showing characteristics of an elderly population, with multiple comorbidities, suggesting a health related QoL lower than expected. They emphasized that almost 20% of COPD patients took regularly antidepressants, a possible direct reflex of patients' compromised health status and quality of life. In this context, they quoted a recent case-control study with more than 35,000 patients with COPD (47) which identified that the existence of COPD itself doubles the risk of depression (OR 2.01, 95% CI: 1.45-2.78).

Additional studies providing new data on the pathogenesis and management of patients with COPD and HF are needed, with the purpose of trying to improve quality of life as well as survival of these patients.

1.3. Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease is a highly prevalent chronic disease, characterized by expiratory airflow limitation, which is not fully reversible and usually progressive. The Global initiative for chronic Obstructive Lung Disease (GOLD) classified the severity of COPD in mild (stage I), moderate (stage II), severe (stage III), or very severe (stage IV) according to the severity of airway obstruction and the presence of respiratory failure. Despite optimal medical treatment, patients experience symptoms such as dyspnea, fatigue, and/or chronic cough. Consequently, patients have a poor exercise capacity and limited performance in daily life activities. (48)

Health status can be defined as 'the impact of health on a person's ability to perform and derive fulfillment from the activities of daily life'. A patient's self-reported health status thus includes health-related quality of life and functional status. Patients suffering from COPD in all GOLD stages report an impaired health status, with worst scores reported by GOLD stage IV patients. Therefore, improvement of health status is an important component in COPD management, including pulmonary rehabilitation. (49)

A careful assessment of patient's health status is necessary to identify targets for (non-) pharmacological interventions, as well as to evaluate the effects of these interventions.

Disease-specific health status questionnaires (i.e., related to a specific condition or group) or generic health status questionnaires (i.e., intended for general use, irrespective of the underlying disease) can be used as instruments to assess health status. For instance, the Saint George's Respiratory Questionnaire (SGRQ) is a commonly used instrument measuring disease-specific health status among patients with COPD, while the EQ-5D, Assessment of Quality of Life Instrument (AQoL), and the SF-36 are used to assess generic health status.

Previous cross-sectional studies found that disease-specific and generic health status questionnaires are moderately to strongly correlated in patients with COPD. (50) Increasing severity of COPD was associated with a significant decline in EQ-5D visual analogue scale (EQ-5D VAS) scores and utility scores. Rutten-van Mölken et al. have demonstrated that the GOLD staging of COPD severity corresponds to significant differences in generic health-related QoL, as assessed by the EQ-5D VAS and utility scores. Importantly, these differences were maintained after correction for other variables that were known to or were expected to affect QoL, especially comorbidity. These results demonstrate that a generic instrument can assess COPD impact on QoL and that the scores discriminate between patient groups of known severity. These utility scores will be useful in cost-effectiveness assessments. (51,52)

A longitudinal study by Wilke et al. (50) extends these findings and shows that SGRQ total scores were moderately to strongly correlated with the EQ-5D index score, AQL total score, and SF-36 PCS score at four consecutive time points during one year follow-up. SGRQ total scores were weakly correlated with SF-36 MCS scores at four, eight, and 12 months.

The EQ-5D is generally suitable to measure QoL in exacerbations of severe COPD, although the high proportion of patients reporting full health at discharge poses a problem (ceiling effect). (53,54)

In COPD patients receiving rehabilitation, responsiveness of EQ-5D utility was poor. There was no 'floor effect' but a significant 'ceiling effect' for EQ-5D, which might explain the poor responsiveness of this instrument. (55)

Disease-specific questionnaires include relevant questions related to the patient's disease and may generally be more sensitive to the disease and small changes in health status. Generic health status questionnaires are intended for general use and are universally applicable: they tend to cover a broad variety of aspects (e.g. functional states, perceptions, social opportunities). Indeed, disease-specific instruments may be more responsive to change in clinical status or more sensitive in distinguishing patients with different disease severities while generic measures may be more likely to detect unexpected events which are probably not related to the disease and detect effects of diverse aspects on a disease. As a matter of fact, health economists prefer the use of generic instruments, because they enable the comparison of health states as well as the benefits of medical interventions across diseases. (52)

Chapter 2. CURRENT STATUS OF AORTIC TRANSCATHETER HEART VALVES

At the present time, the most data available for TAVI are based upon 2 specific devices: the Edwards SAPIEN valve (Edwards Lifesciences Inc., Irvine, CA, USA) (Figure 2.1.1.) and the CoreValve ReValving system (Medtronic, Inc., Minneapolis, MN, USA) (Figure. 2.2.1.).

2.1. Edwards SAPIEN transcatheter heart valve

The balloon-expandable THV consists of 3 pericardial leaflets - initially equine (Cribier-Edwards), and currently bovine (Edwards SAPIEN) - mounted within a balloon-expandable stent. (Figure 2.1.1., Figure 2.1.2.)

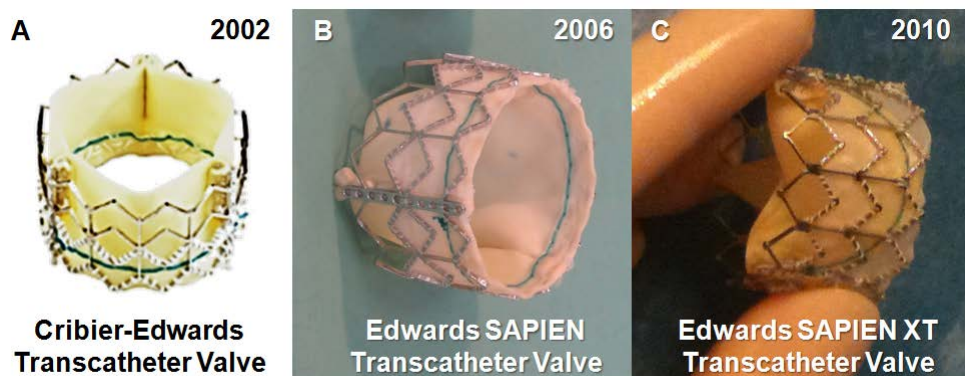


Figure 2.1.1. Edwards SAPIEN transcatheter heart valve evolution.

A. The Cribier-Edwards equine prosthesis mounted within a balloon-expandable stainless steel stent. B. The Edwards SAPIEN prosthesis with bovine pericardial leaflets. C. The Edwards SAPIEN XT, bovine pericardium for the leaflets and cobalt-chromium alloy for the balloon-expandable stent.

The most recent iteration of the former is a trileaflet bovine pericardial valve mounted with a tubular slotted balloon-expandable stent composed of a cobalt-chromium alloy (Edwards SAPIEN XT THV). (Figure 2.1.1.C, Figure 2.1.2.)

The pericardial leaflet material is treated with a similar process to the one used for the surgical Carpentier-Edwards Perimount Magna pericardial valves (Thermafix anticalcification treatment, leaflet deflection testing for matched elasticity, and proprietary tissue processing).

The valve is crimped on a balloon just before implantation with a specially designed mechanical crimper to achieve a symmetrical low profile and ensure retention onto the delivery system. (Figure 2.1.2., Figure 2.1.3.)

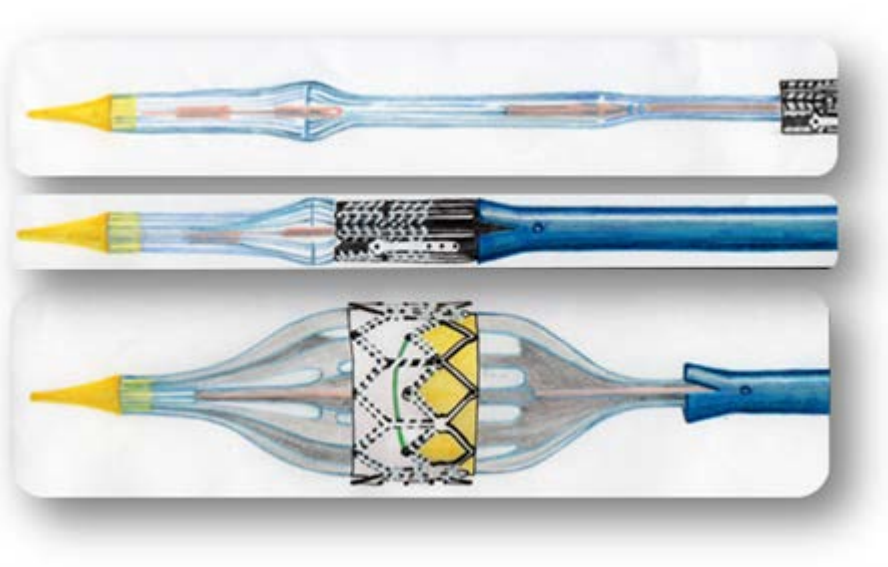


Figure 2.1.2. The balloon-expandable Edwards SAPIEN XT prosthesis.

The pre-dilated valve is retained onto the delivery system after symmetrical reduction to low profile. The valve is then charged onto the balloon and deployed by balloon inflation.

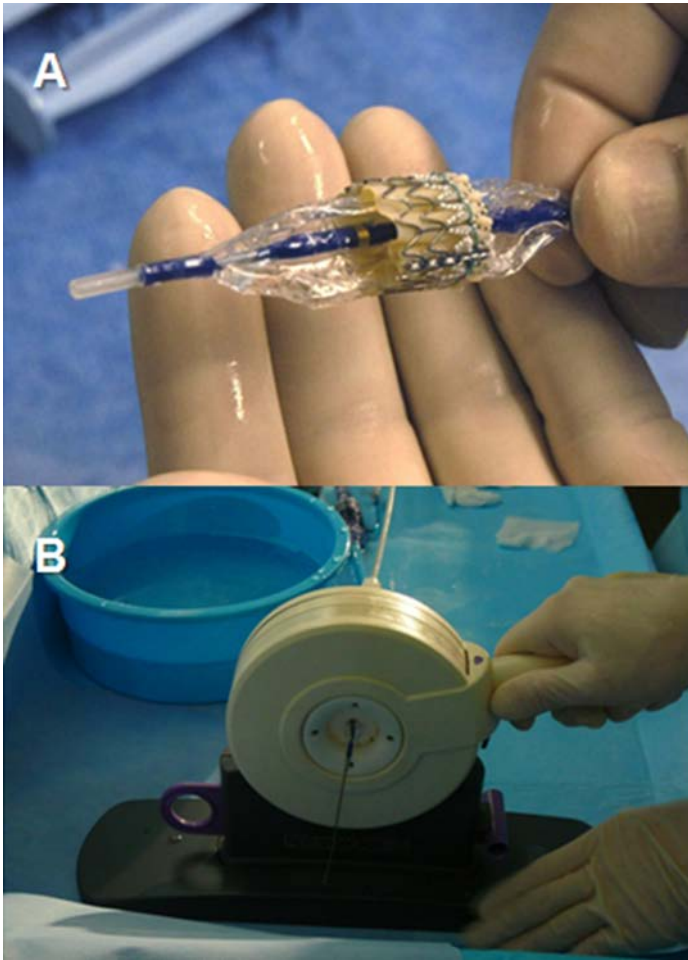


Figure 2.1.3. Edwards SAPIEN transcatheter valve preparation.

The prosthesis is prepared separately just before implantation: it is crimped onto the balloon (A) with a specially designed mechanical crimper (B).

The Edwards SAPIEN valve is commercially available in 23-mm and 26-mm sizes in the United States. The Edwards SAPIEN XT THV is currently available in 23-mm, 26-mm, and 29-mm sizes in Europe and can be implanted in native annuli with diameters of 16 to 27 mm. (Figure 2.1.4.)

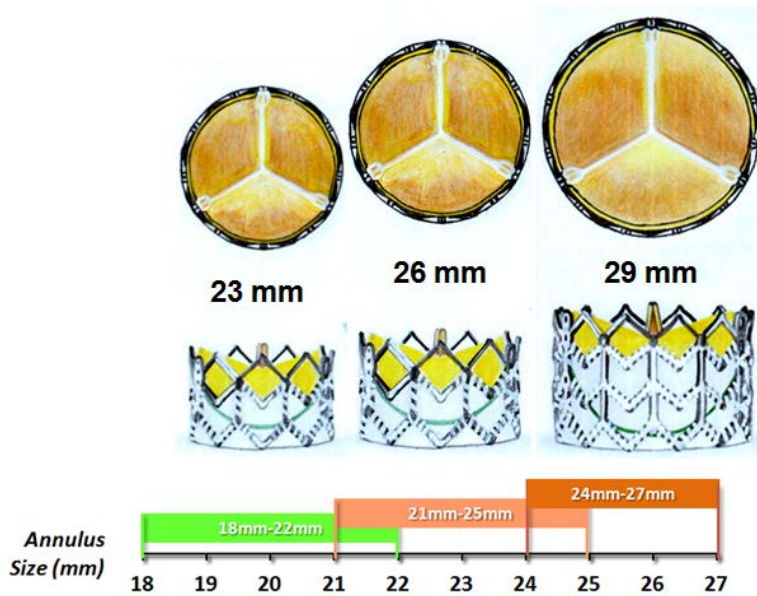


Figure 2.1.4. Edwards SAPIEN transcatheter valve sizes.

The Edwards SAPIEN XT transcatheter valve is currently available in three sizes (23, 26 and 29 mm) and can treat aortic annuli diameters ranging from 16 to 27 mm.

The initial devices required a 22-F or 24-F sheath for delivery of the prosthesis.

The RetroFlex catheter delivery system has an 18-F shaft that increases in the distal end to 22 F or 24 F for the 23-mm and 26-mm valve, respectively. Because of the large delivery system utilized, surgical repair of the vascular access site was required. (56-58) Recent iterations (NovaFlex device-delivery system, Edwards Lifesciences Inc, CA, USA, **Figure 2.1.5.**) have decreased the sheath to 16-, 18-, and 20-F devices (low profile with dynamic expansion eSheath, Edwards Lifesciences Inc, CA, USA, **Figure 2.1.6.**), through which the 23-mm, 26-mm, and 29-mm Sapien XT valves can, respectively, be delivered transfemorally.

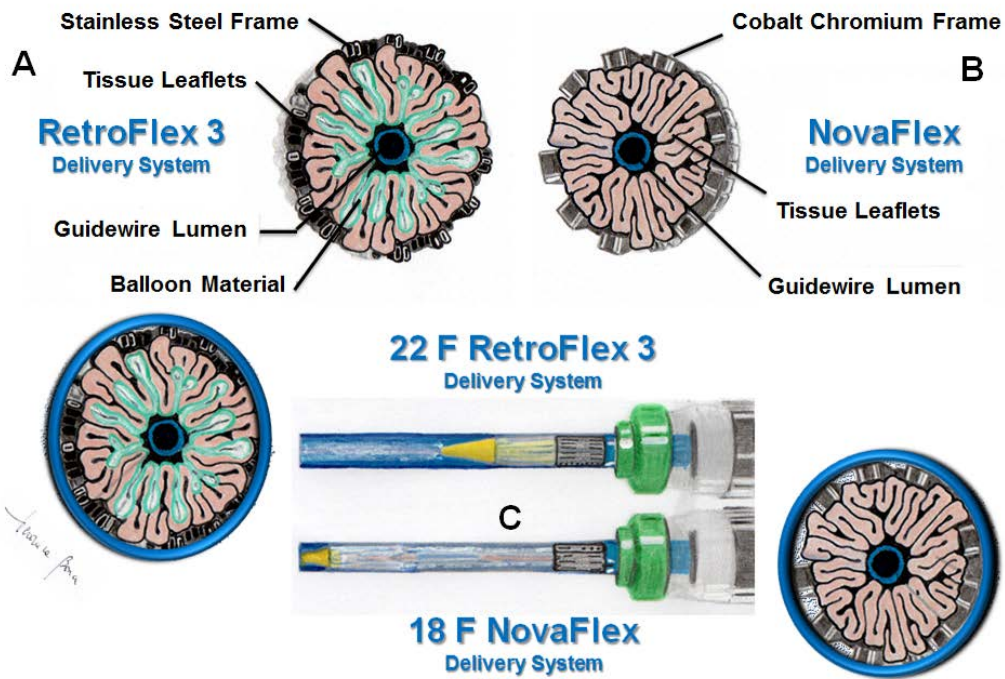


Figure 2.1.5. The Novaflex delivery system.

The new design solution optimizes delivery profile for the bovine pericardial Edwards SAPIEN XT valve since it removes the bulk of the unexpanded balloon (A) from the crimped profile of the delivery system (B). The Edwards SAPIEN XT valve is crimped proximal to the balloon to begin the procedure (C).

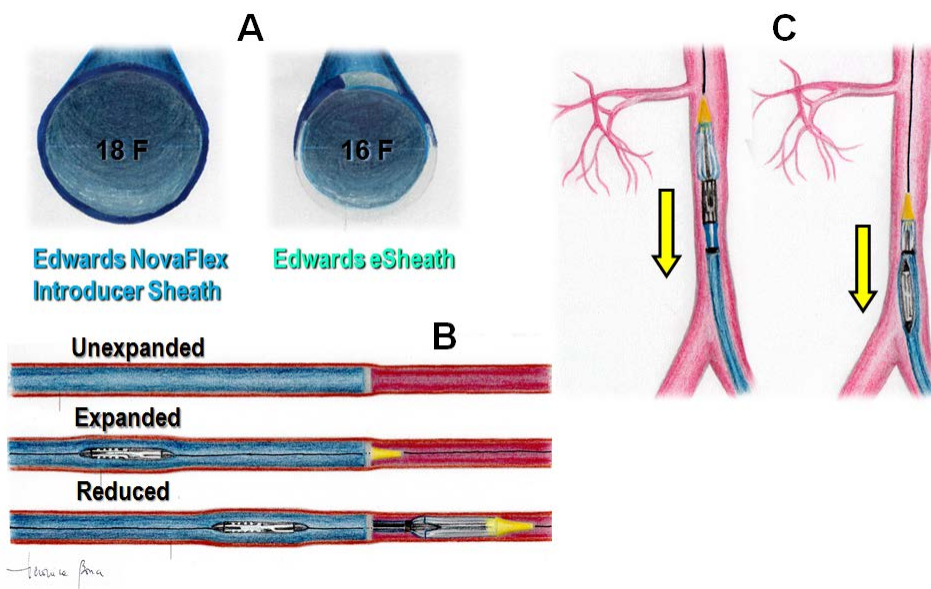


Figure 2.1.6. The expandable Edwards eSheath.

This introducer sheath combines a low profile (A) with Dynamic Expansion Mechanism (DEM), which allows for transient sheath expansion during delivery system passage (B) and for valve retrieval after valve alignment procedure and prior to deployment (C).

Similar to a 'snake swallowing its prey' concept, the mechanism of the eSheath allows the valve delivery system to stretch within the sheath as it is advanced along the femoral and iliac artery, until it reaches the abdominal aorta, where size of the vessel is no longer an issue. (Figure 2.1.6.) This newer technology has already been used in Europe and has recently begun clinical use in the United States as part of the PARTNER 2A study. Presumably, the smaller sheaths allow for a lower threshold of TF access, can improve safety, and reduce vascular complications.

Transapical aortic valve implantation (TA-TAVI) has been performed using the Edwards SAPIEN prosthesis and the Ascendra delivery system (Edwards Lifesciences, Inc., Irvine, CA, USA). Meanwhile, refinements of the systems led to the Edwards SAPIEN XT transcatheter heart valve and the Ascendra-II delivery system for the TA-TAVI approach. The system's benefits are achieved through a smaller introducer catheter and a more intuitive handle. Improvements in comparison with the first-generation SAPIEN valve and Ascendra delivery system are as follows: semi-closed leaflet position of the valve to allow for safer closure during diastole, pusher integration into the handle of the Ascendra-II system to allow for easier pusher retrieval during valve implantation, easier deairing mechanism of the system and some diameter reduction to 24-F sheaths for patients who are receiving 23-mm and 26-mm valves, respectively.

The first and second generations of the Edwards device have been successfully tested in randomized controlled trials for both TF and TA implantation. (59,60) The PARTNER study was the first multicenter randomized trial comparing TAVI versus medical therapy and TAVI versus sAVR on the Edwards SAPIEN valve, in patients deemed inoperable or high risk for sAVR.

The 2- and 3-year results have been published recently. (24,25) In summary, the PARTNER trial demonstrates that TAVI maintains a sustained superiority over medical treatment in inoperable patients with symptomatic severe AS, and equivalent outcomes between TAVI and sAVR in high-risk patients.

The SAPIEN valve was approved for commercial implantation in the United States by the FDA for inoperable patients in November 2011 and more recently for high-risk patients (STS mortality risk score >8%) in October 2012. (26)

2.2. Corevalve transcatheter heart valve

The second device (CoreValve ReValving system) is comprised of 3 porcine pericardial tissue leaflets mounted in a self-expanding nitinol frame. (Figure. 2.2.1.) The prosthetic frame is manufactured by a laser-cutting tool and has an overall length of 50 mm. The lower portion of the prosthesis has high radial force to expand against the calcified leaflets and to avoid recoil. The middle portion carries the valve—the coaptation point of the leaflets is actually supra-annular—and is constrained and narrower to avoid the coronary arteries, while the upper portion is flared to center and fix the stent firmly in the ascending aorta and to provide longitudinal stability. The device is deployed via a delivery system into which the valve is loaded shortly before implantation.

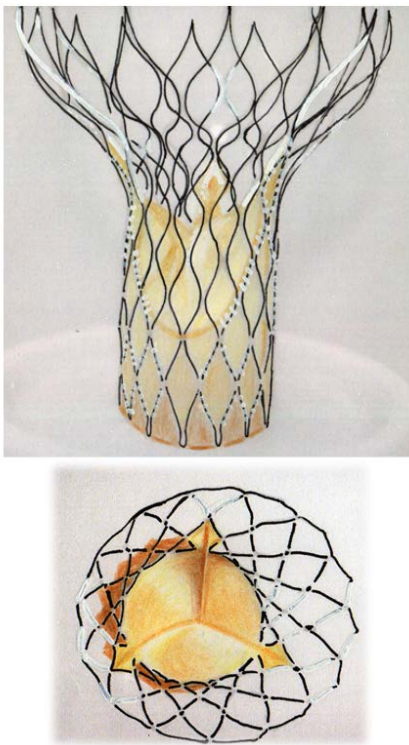


Figure 2.2.1. The Medtronic CoreValve® ReValving System.

The Medtronic CoreValve® ReValving System consists of 3 porcine pericardial tissue leaflets and a self-expanding multi-level frame with supra-annular function.

The CoreValve is currently available in three sizes (26 mm, 29 mm and 31 mm) and can be implanted in native annuli with diameters ranging from 20 to 29 mm (Figure 2.2.2.).

This valve has also continued to iterate, with the initial devices being 25-F, but now 18-F delivery sheaths are used. This valve has only been used by a retrograde approach — either via transfemoral, subclavian, or direct aortic access.

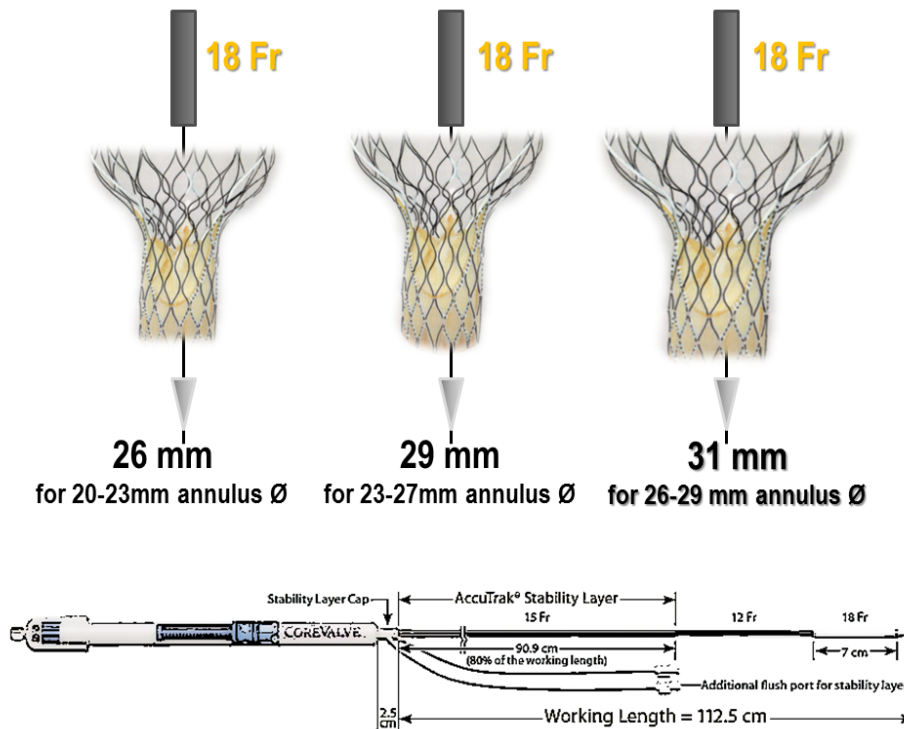


Figure 2.2.2. The Medtronic CoreValve Family.

The full range of valve sizes comes in diameters of 26, 29, and 31 mm and treats annulus diameters from 20 to 29 mm. The CoreValve delivery system features the AccuTrak® Stability Layer (Medtronic Inc., Minneapolis, MN, USA), provides full valve functionality and partial repositionability during deployment, and a 18-F delivery profile across all valve sizes and access routes.

The CoreValve is not for distribution in markets where it has not been approved yet (USA, Canada or Japan). In the USA the Medtronic CoreValve® U.S. Pivotal Trial (NCT01240902), randomising AS patients at high operative risk to TAVI with the Medtronic CoreValve® (Medtronic Inc., Minneapolis, MN, USA) or SAVR and also exploring TAVI with the Medtronic CoreValve in inoperable patients (not randomised), has recently completed enrolment and the results are anticipated in due course.

2.3. Competitor aortic transcatheter heart valves

Suboptimal valve positioning is a common problem seen in TAVI. The first-generation valves, i.e. the Edwards SAPIEN THV, the Edwards SAPIEN XT and the CoreValve®, could not be retrieved after positioning and thus, in case of an erroneous placement, the operator had to deploy a second device or refers the patient for urgent sAVR. To overcome this limitation several new valve systems have been developed that can be repositioned or even be retrieved if needed. Some of them have been tested in a clinical setting and a few have already acquired Conformité Européenne (CE) mark approval such as: the Direct Flow Medical valve (Direct Flow Medical Inc., Santa Rosa, CA, USA) that is both retrievable and repositionable, the JenaValve (JenaValve, Munich, Germany) and the Portico (St. Jude Medical, St Paul, MN, USA) that are both retrievable until being fully deployed, the Engager (Medtronic, Minneapolis, MN, USA) that is only repositionable, and the Symetis® Acurate™ (Symetis SA, Ecublens, Switzerland) that has a self-seating and self-sealing design that conforms with the native anatomy potentially leading to a lower incidence of paravalvular leak. (Figure 2.3.1.)

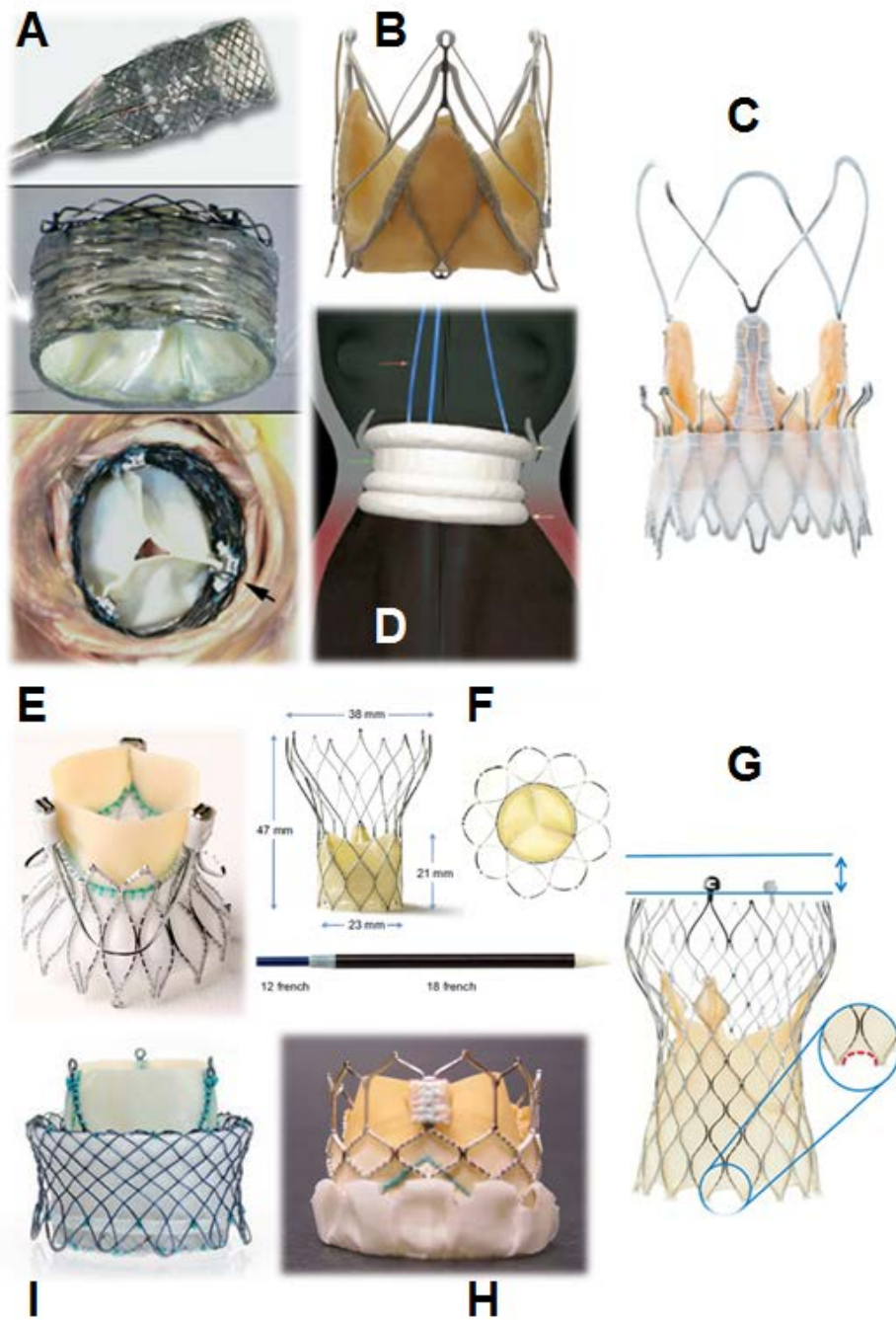


Figure 2.3.1. Competitor THVs.

(A) Lotus (Boston Scientific Inc., Natick, MA, USA), (B) JenaClip (JenaValve Inc., Munich, Germany), (C) Acurate valve (Symetis Inc., Ecublens, Switzerland), (D) Direct Flow (Direct Flow Medical Inc., Santa Rosa, CA, USA), (E) Engager (Medtronic Inc., Minneapolis, MN, USA), (F) Portico (St. Jude Medical Inc., St. Paul, MN, USA), (G) CoreValve Evolut R (Medtronic, Minneapolis, MN, USA), (H) Sapien III (Edwards Lifesciences, Irvine, CA, USA) and (I) HLT (HLT Inc., Maple Grove, MN, USA).

Apart from the devices mentioned above that have already acquired CE mark approval, several other valves have been designed that are currently undergoing clinical evaluation such as the Sapien III (Edwards Lifesciences, Irvine, CA, USA), which incorporates an additional cuff that covers the frame of the valve and is anticipated to reduce the incidence of paravalvular leak; the Lotus valve that is both retrievable and repositionable (Boston Scientific, Natick, MA, USA), the CoreValve Evolut R (Medtronic, Minneapolis, MN, USA) that has a low delivery profile; the self-expanding Centera (Edwards Lifesciences, Irvine, CA, USA) valve, which has a low frame height to reduce the risk of conduction disturbances, as well as the HLT™ (HLT Inc., Maple Grove, MN, USA) valve that was initially implanted in humans in 2009 where it was found to be associated with an increased risk of complications. This last device has recently been redesigned and currently there is a plan for clinical evaluation. (61,62) (Figure 2.3.1.)

Chapter 3. TRANSCATHETER AORTIC VALVE IMPLANTATION ROUTES

There are several approaches to the aortic valve, which can be broadly categorized as retrograde or antegrade.

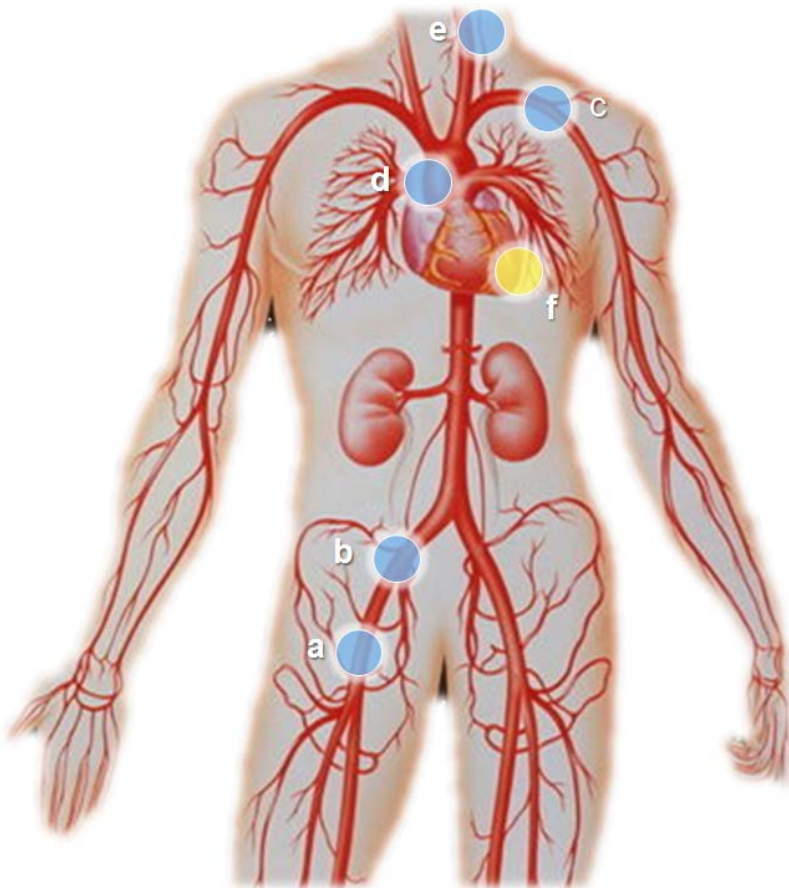


Figure 3.1. Access routes for Transcatheter Aortic Valve Implantation.

Retrograde (blue circles): a. Transfemoral, b. Transiliac (with or without conduit), c. Transsubclavian/axillary (with or without conduit), d. Direct transaortic, e. Transcarotid. Antegrade (yellow circle): f. Transapical.

The Cribier Edwards THV (Edwards Lifesciences Inc., Irvine, CA) was initially implanted via the antegrade transseptal approach. Nevertheless, further experience with the antegrade approach proved its limitations due to technical complexities and risks. (56) The retrograde approach has since been shown to be safer with the use of a proprietary steerable delivery catheter. Retrograde passage is generally performed via the femoral artery, by either a standard

percutaneous femoral arterial access or a surgical exposure of the artery. There are obvious limitations in patients with peripheral arterial disease or small vessels.

Thanks to recent advances in stent and valve technologies, retrograde transarterial aortic valve implantation is feasible in humans and provides haemodynamic and clinical improvements for up to 2 years in patients with severe symptomatic AS at high risk or with contraindications for surgery. (63)

In parallel, a minimally invasive antegrade TA-TAVI (via a left minithoracotomy in 5th or 6th intercostal space) has been developed to overcome the limitations inherent to the retrograde approach. (64)

Among the growing number of centres that are introducing the TAVI procedure, associated surgical and cardiology teams developed additional retrograde options transvascular accesses for TAVI (transsubclavian/axillary, direct ascending aortic puncture or even transcarotid) to offer the most adequate treatment for the individual patient. (65)

Currently, whilst the SAPIEN valve is FDA-mark approved for antegrade TA-TAVI and retrograde TF-TAVI and Conformité Européenne (CE) mark approved for antegrade TA-TAVI and retrograde TF-TAVI, TI-TAVI and TAo-TAVI approaches, the CoreValve ReValving system is CE mark approved for transfemoral, transaxillary, and transaortic approaches. (66)

In rare cases, the carotid access or access through a conduit can be attempted.

JenaValve and Symetis® Acurate™ system are CE mark approved only for TA approach.

In the United States, the SAPIEN valve is the only FDA-approved and commercially available device to treat surgically inoperable or high-risk patients. Recently, there has been a rapid expansion in the number of studies investigating TAVI by various approaches in the last 5 years, and these have demonstrated promising results in terms of feasibility, safety, and efficacy. (65)

Chapter 4. PATIENTS' GENERAL ASSESSMENT

Patient selection plays a crucial role in the success of TAVI. It requires meticulous attention to the smallest of details and needs to be performed in a systematic manner for every patient. Basically, the patient must be assessed from access to implantation site.

In Europe, TAVI is indicated for high or prohibitive surgical risk patients with severe aortic stenosis. Some patients, however, are too high risk even for TAVI (*futility*). (56,67)

In addition to patient risk evaluation, anatomical selection criteria need to be considered. Multimodality imaging, using a combination of angiography, echocardiography and multidetector computed tomography (MDCT) is necessary to determine the anatomical suitability for the procedure. In particular, assessment of the peripheral vasculature and aortic valvular complex will allow selection of the best access route and prosthesis type and size, respectively.

Patients with severe symptomatic AS are usually referred for TAVI by other hospitals or by independent cardiologists.

Those who are confirmed to be at high surgical risk or to have contraindications to sAVR, are evaluated for TAVI.

Overall, a valve clinic should offer patients a personalized approach for the evaluation and treatment of complex valve diseases with the availability of a cardiologist and a cardiac surgeon specialized in valve disorders.

Screening should include: clinical evaluation, revision of the prior diagnostic studies and additional diagnostic imaging, such as, transthoracic echocardiography (TTE) and, if necessary, transesophageal echocardiography (TOE), coronary angiography and/or ECG-gated MDCT, non-contrast or contrast enhanced computed tomography (CT) and/or aortic and femoroiliac angiography, and, if possible, cardiac magnetic resonance (CMR), all performed as clinically indicated. (63)

On the basis of a holistic clinical assessment incorporating patient's age, comorbidities, imaging and operative risks measured by the European System for Cardiac Operative Risk Evaluation (EuroSCORE) (63,68-70), and/or the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) (71), a medical/surgical multidisciplinary team (the aortic team) should formally review patients and agree that conventional surgery implies an excessively high risk in terms of anticipated mortality and morbidity. (63,72,73) Ideally, such a team would be comprised of the patient's primary

cardiologist, cardiac surgeon, interventional cardiologist, echocardiographer, imaging specialists, heart failure and valve disease specialist, cardiac anesthesiologist, nurse practitioner, and cardiac rehabilitation specialists.

Factors such as sex, race, availability, experience, and institutional commitment to managing very high-risk patients, technical skills, local results, referral patterns, and patient preference all may have an impact on the decision-making process and should be taken into account by this multidisciplinary team.

4.1. Patient selection

TAVI is indicated in patients with calcified pure or predominant AS. It is unlikely that it will be used in patients with pure aortic regurgitation (AR).

Transcatheter replacement of a degenerated previous aortic bioprosthesis (valve-in-valve implantation) is an attractive potential indication because of the high risk of re-operation in elderly patients. Failing bioprostheses (including THVs) due to stenosis or regurgitation (transvalvular, *not* paravalvular) in the aortic, mitral, pulmonary, or tricuspid position can successfully be treated with a valve-in-valve procedure using either the CoreValve or the Edwards SAPIEN valve. (74)

The main steps of patient selection are:

- confirmation the severity of AS;
- evaluation of symptoms;
- analysis of the risk of surgery;
- evaluation of life expectancy and quality of life;
- assessment of feasibility and exclusion criteria for TAVI.

4.1.1. Confirmation of the severity of aortic stenosis

TAVI should be performed only in severe AS. Transthoracic echocardiography is the preferred tool to assess the severity of AS according to a combination of measurements of valve area and flow-dependent indices.

Low-dose dobutamine echocardiography is useful to differentiate between severe and the rare 'pseudosevere' AS in patients with low left ventricular ejection fraction (LVEF) and low gradient. (7,63)

4.1.2. Evaluation of symptoms

At the present stage, TAVI should only be proposed in patients with severe symptoms that can definitely be attributed to valve disease. That is because of pending questions on safety and valve durability.

4.1.3. Inclusion/exclusion criteria

TAVI is appropriate currently only for a highly selected population and the aortic team should systematically identify the features that define that population with most benefit and acceptable risk.

Decision-making is particularly complex in these elderly patients who represent a heterogeneous population and require balanced and tailored analysis.

The criteria presented are based on current technology and experience. (Table 4.1.3.1.) (63) It is likely that many of these criteria will evolve over time as this technology improves, experience is gained and new data become available.

Table 4.1.3.1. Patient selection: inclusion and exclusion criteria in clinical trials.

Inclusion criteria
1. Patient has calcific AS with echocardiographically derived criteria: mean gradient >40 mm Hg or jet velocity >4.0 m/s and an initial AVA of <0.8 cm ² or indexed EOA <0.5 cm ² /m ² . Qualifying AVA baseline measurement must be within 45 days of the date of the procedure.
2. Patient is deemed to be symptomatic from his/her AS, as differentiated from symptoms related to comorbid conditions, and as demonstrated by NYHA functional class II or greater.
3. A cardiac interventionalist and 2 experienced cardiothoracic surgeons agree that medical factors either preclude operation or are high risk for surgical AVR, based on a conclusion that the probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement. The surgeons' consult notes shall specify the medical or anatomic factors leading to that conclusion and include a printout of the calculation of the STS score to additionally identify the risks in the patient. At least 1 of the cardiac surgeon assessors must have physically evaluated the patient.
Exclusion criteria (absolute)

1. Evidence of an acute MI \leq 1 month (30 days) before the intended treatment (defined as: Q-wave MI, or non-Q-wave MI with total CK elevation of CK-MB \geq twice normal in the presence of MB elevation and/or troponin level elevation [WHO definition]).
2. Severe left ventricular dysfunction with LVEF <20%.
3. Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
4. A known contraindication or hypersensitivity to all anticoagulation regimens, or inability to be anticoagulated for the study procedure.
5. Native aortic annulus size <18 mm or >29 mm as measured by echocardiogram*.
6. MRI confirmed CVA or TIA within 6 months (180 days) of the procedure.
7. Estimated life expectancy <12 months (365 days) due to noncardiac comorbid conditions.
8. Severe incapacitating dementia.
9. Severe mitral regurgitation.
Exclusion criteria (relative)
1. Aortic valve is a congenital unicuspid or congenital bicuspid valve, or is noncalcified.
2. Mixed aortic valve disease (AS and AR with predominant AR >3+).
3. Haemodynamic or respiratory instability requiring inotropic support, mechanical ventilation, or mechanical heart assistance within 30 days of screening evaluation.
4. Need for emergency surgery for any reason.
5. Hypertrophic cardiomyopathy with or without obstruction.
6. Severe pulmonary hypertension and RV dysfunction.
7. Renal failure (creatinine >3.0 mg/dL) and/or end-stage renal disease requiring chronic dialysis at the time of screening.

AS indicates aortic valve stenosis; AVA, aortic valve area; EOA, effective orifice area; NYHA, New York Heart Association; AVR, aortic valve replacement; STS, Society of Thoracic Surgeons; MI, myocardial infarction; CK, creatine kinase; MB, MB isoenzyme; WHO, World Health Organization; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; TIA, transient ischemic attack; CVA, cerebrovascular accident; AR, aortic valve regurgitation and RV, right ventricular.

*The boundaries of annulus size will continue to change in concert with changing device size.

The evaluation of the risk of surgery is based on the assessment of cardiac and extra cardiac factors. (75) Risk scores, such as the EuroSCORE (68-70), the STS Predicted Risk of Mortality score (71) or the Ambler score (76) have guided enrolment of 'high surgical risk' patients into TAVI trials. However, they all share similar limitations: predictive ability is reduced in these high-risk patients who represent only a small proportion of the population the scores were elaborated on. Moreover, high-risk patients form a particularly heterogeneous group in which it is difficult to capture important comorbidities (e.g. porcelain aorta, chest wall radiation, liver cirrhosis, pulmonary hypertension) and frailty variables that may impact clinical outcomes. (77) The newly updated logistic EuroSCORE II and STS score, however, are expected to incorporate frailty variables. (63) The predictive value of these scores for morbidity and long-term results is unknown, though.

Risk scores should guide but not dictate clinical decision-making. As reported by the 2012 American College of Cardiology Foundation/American Association for Thoracic Surgery/Society for Cardiac Angiography and Interventions/STS expert consensus document on TAVI (63), the key element to establish whether patients are at high risk for surgery is clinical judgement. This approach allows the team to take into account risk factors that are not covered in scores but often seen in clinical practice, such as chest radiation, previous aorto-coronary bypass with patent grafts, porcelain aorta, liver cirrhosis, frailty and fertility, etc. Surgical risk estimation should also bear in mind results in the given institution. (78)

At this stage, TAVI is not recommended for patients who simply refuse surgery on the basis of personal preference. Besides, the selection is subjected to local law Resolutions, that pass and refund TAVI only for clinical use in elderly patients or in patients with serious comorbidities, or both, and in those deemed to be at high risk for routine surgery.

Life expectancy is most significantly influenced by comorbidities, which should be carefully looked for. In addition to clinical evaluation, semi-quantitative scoring systems, such as those used in geriatrics, may be helpful. (73) Although TAVI is currently seldom considered in patients younger than 70 years old, age alone is not sufficient to make the

decision for its use instead of surgery. Indeed, TAVI should not be performed in patients whose life expectancy is <1 year, who should be managed conservatively.

Finally, risk and benefit, including prognosis of existing conditions, should be thoroughly discussed with the patient and family as part of the initial meeting with the TAVI team and should include a review of post-procedural complications that may extend hospitalization. Although successful procedures mostly result in improvement in dyspnea, in a heightened energy level, and in an overall improved QoL, during that meeting the very elderly patients should be made aware that symptomatic improvement may be delayed or minimal in some cases.

4.1.4. Frailty and futility

As previously discussed, the concepts of frailty and futility will assume central importance in patient selection for TAVI by virtue of the extensive comorbidities present in this population.

Frailty is an important and frequent condition in elderly patients and should be considered when dealing with invasive care in older adults. (Figure 4.1.4.1.) It is a true syndrome and is characterized by a vicious cycle of decreasing muscle mass, energy expenditure, and malnutrition culminating in vulnerability to adverse events. (79) Besides comorbidities and frequently in combination with them, frailty is likely to play a role in the assessment of the individual's candidacy for invasive care and therefore in refusing almost one half of high-risk patients with AS to any operation. (63)

The impact of frailty on the clinical course and outcome of patients presenting with severe AS is beginning to be investigated but is difficult to establish because of its multidimensional phenotype and the lack of a clear and agreed-upon assessment. The definition of frailty used in recent studies ranges from the qualitative 'eyeball test' to more quantitative scores such as the Fried Frailty Index (79), the modified Fried frailty index (80) or the 'timed gait speed over 5 m'. (81) As such, it has recently been added to the STS database upgrade (Version 2.73, July 1, 2011) and will be uniformly collected in patients undergoing cardiac surgery (82).

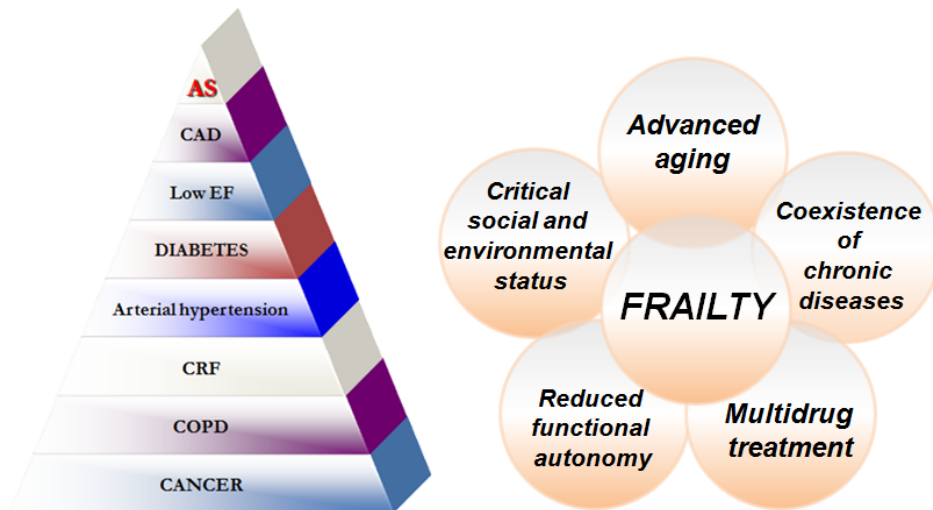


Figure 4.1.4.1.

In elderly people, frailty overlaps with disability and comorbidity, but it is a distinct syndrome characterized by a vicious cycle of decreasing muscle mass, energy expenditure, and malnutrition. AS indicates aortic stenosis; CAD, coronary artery disease; EF, ejection fraction; CRF, chronic renal failure; COPD, chronic obstructive pulmonary disease.

Futility. There may be some patients in whom TAVI procedure should not be performed because the clinical condition is too far advanced and high risk also for this less invasive procedure. In these patients, even a successful technical procedure does not improve clinical outcomes. Therapeutic futility may be determined based upon: 1) lack of medical efficacy, as judged by the patient's physician; or 2) lack of a meaningful survival, as judged by the personal values of the patient. (83,84)

The key to treatment in the group of 'inoperable' patients is to define where is the borden between utility and futility. This dilemma (PARTNER trial cohort C patients) has yet to be solved clearly. The 2012 Medicare TAVI National Coverage Decision calls for all TAVI patients to be entered into a national database so that outcomes and patient selection criteria can be analyzed and refined. Because hospital and physician reimbursement by Medicare is at stake, this will put the responsibility squarely on the physicians' shoulders to select patients extraordinarily carefully for TAVI. (67)

4.2. Imaging assessment

Imaging plays an essential role in patient selection and procedural planning, performance, and follow-up. In each of these steps, optimal imaging can help to enhance a successful outcome.

Preoperative imaging assessment is crucial to determine aortic root anatomy, prosthesis size, optimal fluoroscopic projection planes and access routes.

There is variability in the specific imaging protocols preferred in individual institutions. This variability is the result of institutional and individual experience and equipment in addition to patient's specific features to be considered. (85)

The most important preoperative investigation to determine feasibility of TAVI and to ensure procedural success is assessment of the aortic root. In most centers, multimodality imaging using echocardiography, angiography, and ECG-gated MDCT is used to evaluate the anatomy of the aortic root.

The essential information that needs to be obtained is the diameter and calcification of the aortic annulus; the projection plane of the aortic annulus; the cuspidity, length, and calcification of the aortic leaflets; location of the coronary ostia; and the dimensions and extent of calcification of sinuses of Valsalva, sinutubular junction, and ascending aorta. (56)

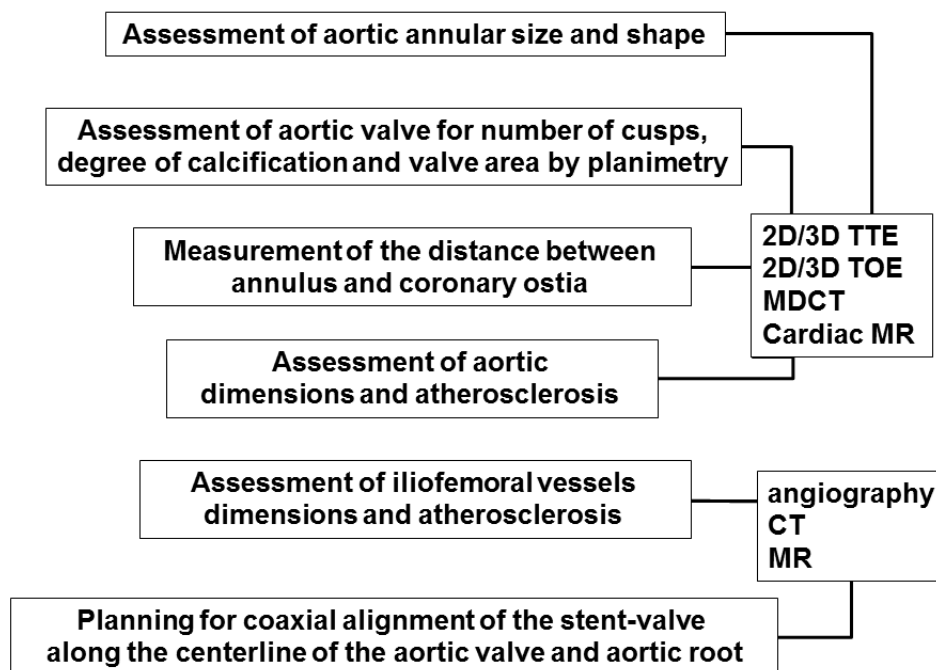


Figure 4.2.1. Preoperative imaging assessment.

The specific protocol of preoperative imaging assessment for TAVI may vary depending on the institutional and individual experience and equipment and on patient's specific features.

4.2.1. Measurement of the aortic annulus

The size of the annulus is necessary to determine the optimal size of the prosthesis, which is usually chosen slightly larger (by 5 to 30%) than the measured annular diameter to ensure stable positioning of the valve. The SAPIEN valve is produced in diameters of 23, 26, and 29 mm and is recommended for annular diameters of 18–27 mm, while the CoreValve Revalving System is somewhat larger and is produced in diameters of 26, 29, and 31 mm for annular diameters of 20–29 mm. If the prosthesis chosen is too small, paravalvular regurgitation is more likely and the valve can dislodge from its designated position. If the valve is too large, annular rupture can occur, or incomplete expansion of the valve might cause aortic regurgitation. (56,86)

Surgeons commonly define the aortic valve annulus as the semilunar crown-like ring demarcated by the 'draping' leaflet attachment line that runs across the aortic root. For the purposes of TAVI, the enigmatic 'aortic valve annulus'

corresponds to a virtual ring formed by joining the basal attachment points of the leaflets within the left ventricle. This plane represents the inlet from the left ventricle outflow tract (LVOT) into the aortic root. (56)

It can be measured by TTE or TOE, angiography, or MDCT, which often result in different measurements due to the elliptical shape of the annulus. Echocardiography usually underestimates the annular diameter in comparison to MDCT. Since there is no evidence yet which imaging modality should be preferred, many surgeons or interventionists use both MDCT and echocardiography to obtain an optimal appreciation of the aortic root anatomy. (87,88)

With either modality, the annular antero-posterior diameter is measured from a long-axis view. Ideally, measurements should be taken in systole, at the hinge point of the leaflets into the LVOT with a trailing edge to leading edge convention. Care must be taken to identify the true annulus, not overlying calcium.

Since the annulus is often elliptical, optimal assessment should include measurement of the transverse (coronal) diameter, using the short-axis view, ideally with biplane TOE approach or MDCT, which allows simultaneous long- and short-axis interrogation of the annular plane.

Depending on the orientation of the chord cut across the annulus, two-dimensional (2D) echocardiography provides a 'one-dimensional view' of the aortic annular dimensions; typically underestimating the annulus diameter with respect to MDCT. This fact explains the potential shortcomings of relying on 2D measurements of the aortic annulus for transcatheter aortic valve sizing.

MDCT multiplanar reconstructions (MPRs) can provide coronal, sagittal and axial images of the aortic root. (**Figure 4.2.1.1.**) In the axial view, the aortic valve annulus lies at a level just below the basal attachment points of the three leaflets. From this view, the maximum and minimum diameter, perimeter and area of the annulus can be measured (**Figure 4.2.1.1.C**). The maximum and minimum diameters typically correspond to coronal and sagittal planes cut across the annulus, respectively. (89)

Nevertheless, 2D echocardiography (TTE or TOE) remains the most commonly used and practical method to assess the aortic valve annulus diameter. (90)

Cardiac magnetic resonance (CMR) allows for an anatomic and functional assessment of the aortic valve and aortic root. However, similar to standard echocardiography, most CMR sequences are 2D with the plane of imaging chosen at the time of the examination.

Whole heart, echo-gated 3D CMR with contrast and a slice thickness of 1.5 mm, a spatial resolution of 1 mm in-plane and 1 mm through plane (compared with 0.5 x 0.5 x 0.5 mm by MDCT) provides isotropic images for multiplanar reconstruction and shows the oval shape of the annulus with maximal and minimal diameters. (88)

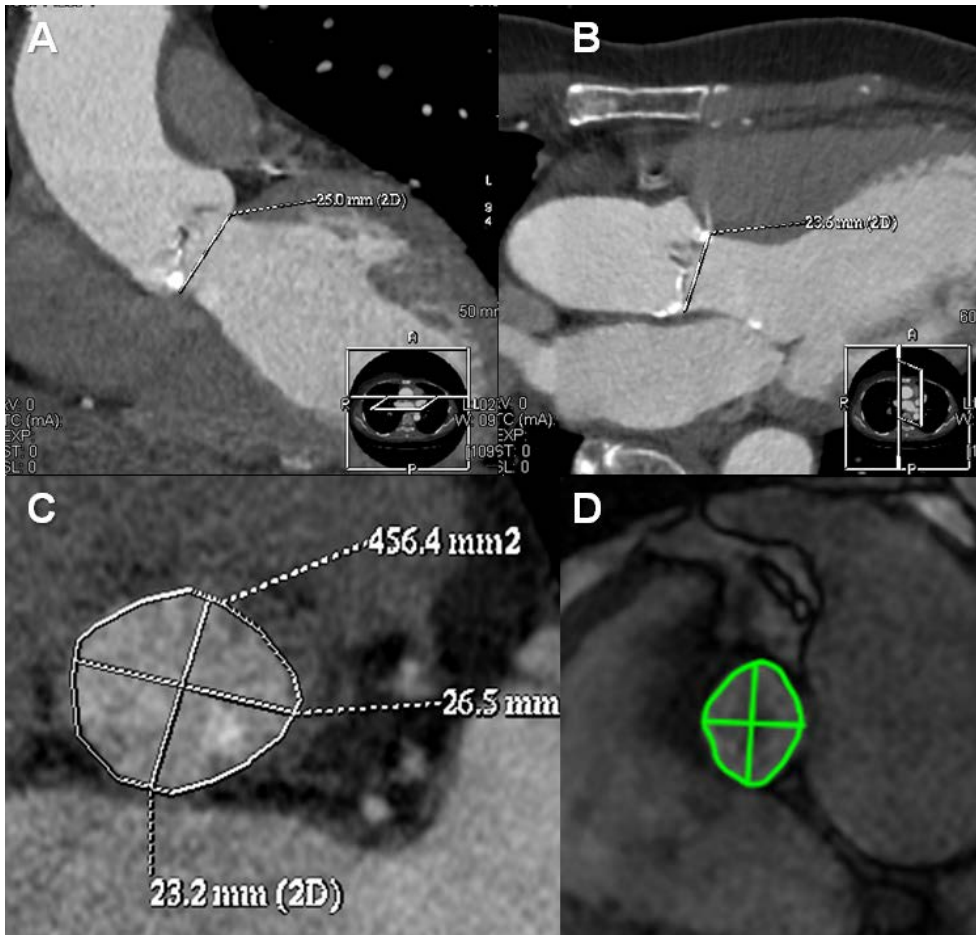


Figure 4.2.1.1. Aortic annulus imaging assessment.

MDCT multiplanar reconstructions (A, B and C) can provide coronal, sagittal and axial images of the aortic root. From the axial view (C), the maximum and minimum diameter, perimeter and area of the annulus can be measured. The maximum and minimum diameters typically correspond to coronal and sagittal planes cut across the annulus, respectively. D, Contrast-enhanced echo-gated 3D CMR technology allows to calculate the oval shape of the annulus with maximal and minimal diameters.

Besides being expensive and not applicable to pacemaker carriers and claustrophobic people (90), there are no studies to date comparing CMR measurements of the annulus with those by echocardiography or MDCT.

Due to the signal void caused by calcium, CMR is not a suitable choice to evaluate the extent, location, and distribution of aortic annulus and leaflet calcifications. (88)

Finally, aortography during preimplantation balloon aortic valvuloplasty (i.e. balloon sizing) is also a simple way to confirm the optimal valve size depending on the presence or absence of aortic regurgitation.

Besides the aortic annulus diameter, other measurements of the aortic valvar complex, such as the height and width of the sinuses of Valsalva, take-off heights of the coronary arteries, LVOT diameter, ascending aorta diameter and calcification burden, may influence the feasibility, safety and effectiveness of the procedure.

In addition, left ventricular hypertrophy is a common finding in these patients and a sigmoid septum is frequently observed. In patients with a pronounced sigmoid septum, the transapical approach could be preferred instead of the transfemoral, because the positioning and anchorage of the prosthesis with the transapical approach may be more stable. (63)

Bearing in mind the three-dimensional nature of the aortic valve, measurement of the aortic valve annulus and LVOT size may be subjected to geometrical assumptions and consequent errors in the estimation of disease severity. Indeed, like the aortic valve annulus, the LVOT may appear more elliptic-shaped, mostly when sigmoid septal hypertrophy exists. Therefore, 3D imaging techniques may constitute more accurate methods to evaluate potential candidates for TAVI. In this regard, initial experimental and clinical studies have demonstrated the higher accuracy of real-time 3D echocardiography to assess AS severity as compared to 2D echocardiographic methods. (88)

Finally, other contraindications to perform TAVI are the presence of bulky calcifications of the leaflets and of the aortic root - occasionally leading to coronary obstruction, aortic root rupture, significant paravalvular regurgitation, guidewire bending and balloon breakage (barotrauma) - and bicuspidy.

Also these evaluations can be noninvasively and easily performed with contrast-enhanced MDCT.

4.2.2. Assessment of coronary anatomy

Coronary angiography should be performed to this end. If associated coronary artery disease requires revascularization, whether to proceed surgically, percutaneously, or in a hybrid manner, as well as the chronology of interventions, should be the subject of individualized discussion based on patient's clinical condition and anatomy.

Percutaneous coronary intervention (PCI) in association with TAVI has been reported in 0 to 44% of patients.

Discrepancies exist amongst studies as to whether coronary artery disease negatively impacts survival post-TAVI.

Although concomitant and staged strategies have been reported successfully, the latter approach appears to be more commonly used. It appears that a staged approach (PCI followed by TAVI) is prudent in patients with lesions in a dominant proximal right coronary artery, left main, proximal left anterior descending and dominant proximal circumflex artery. (56,63)

In this setting, ECG-gated MDCT may represent a less invasive, alternative assessment of the underlying anatomy.

4.2.3. Aortic root disease and ascending aorta dimensions

Echocardiography, aortography, and ECG-gated MDCT, all of them can assess height and width of the Valsalva sinuses, diameter and calcification burden of the ascending aorta, angulation of the ascending aorta and the aortic arch, take-off heights of the coronary arteries, lengths of the aortic leaflets. (63,91)

To minimize the risk of coronary artery obstruction either from the device itself or from cusp calcification being shifted and displaced into the coronary during balloon or valve expansion, the distance of the coronary ostia to the annulus should be assessed preoperatively. Though no definite minimum distance has been established, a minimal distance of 10–14 mm has been suggested for the SAPIEN valve. Short and shallow sinuses of Valsalva as well as heavily calcified and elongated cusps probably further increase the risk of coronary obstruction. The CoreValve Revalving System is designed with a supra-annular location of the porcine pericardial valve, located in the sinus of Valsalva. As a result, the manufacturer suggests a minimum height of the sinuses of Valsalva of 15 mm, a diameter of the sinuses of more than 27–29 mm, and an ascending aortic diameter of less than 40–43 mm depending on the size of the valve. (86)

In general, MDCT provides a more comprehensive assessment of the relationship of the coronary arteries to the annulus and valve leaflets. Nevertheless, echocardiography, particularly TOE, can measure the distance from the aortic valve

annulus to the right coronary ostium. Since the left coronary does not lie in a standard TOE or TTE imaging plane that intersects the annulus, measurement from 3D datasets may be the right method to deal with this. (63,88)

4.2.4. Multidetector Computed Tomography

MDCT in the context of TAVI eligibility assessment has become routine in many large-volume centres, providing whole assessment of the aortic root, atherosclerotic burden, and course of the thoraco-abdominal aorta and its iliofemoral branches. (63) (Figure 4.2.4.1.)

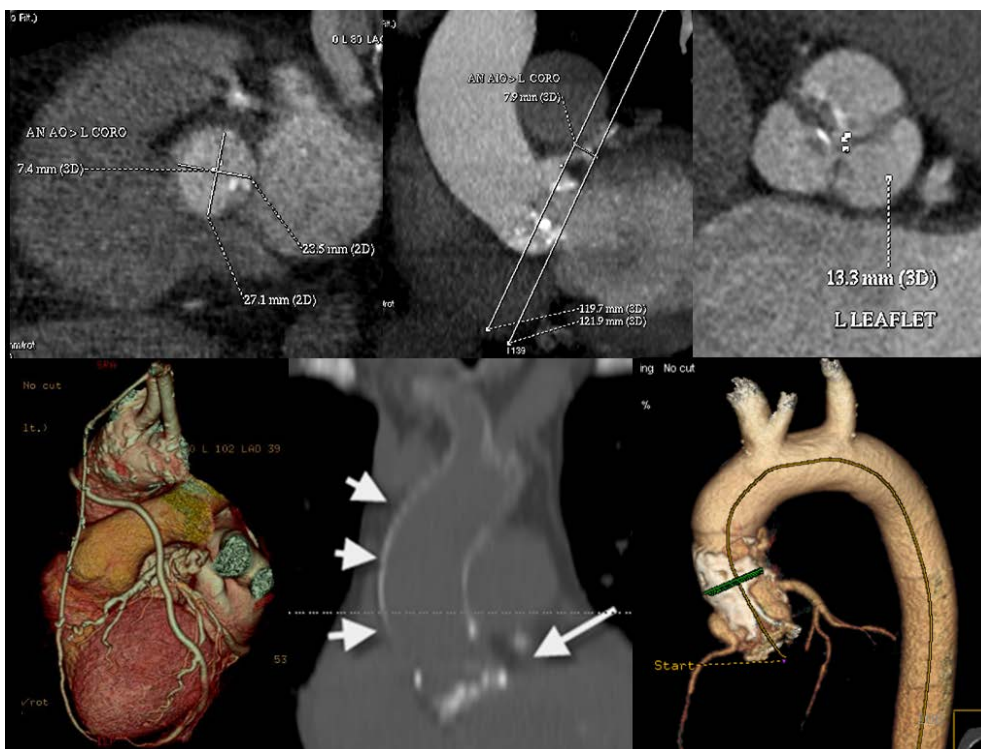


Figure 4.2.4.1. ECG-gated Multidetector Computed Tomography.

ECG-gated MDCT multiplanar and 3D reconstructions provide comprehensive assessment of the aortic root including annulus size and shape, coronary anatomy, atherosclerotic burden, course of the thoracic aorta and right cusps projection for valve deployment.

ECG-synchronized imaging of the aortic root is important to avoid image quality degradation due to motion artifacts, and image reconstruction is performed at the desired phase of the cardiac cycle (e.g., a systolic 30% to 40% phase for valve area and annular assessment). Using the retrospectively ECG-gated helical acquisition, CT data can be acquired

throughout the entire cardiac cycle, enabling 4D image reconstructions for evaluation of valvular function, albeit at the expense of a higher radiation dose. (92) However, protocols with newer generation scanners allow prospective acquisition at a lower radiation dose with subsequent display of cine loops. (93) Although radiation exposure is important to consider with any CT acquisition, it is less a concern in the elderly patients currently considered for TAVI. Because a standard bolus of 80 mL to 120 mL of low-osmolar iodinated contrast is necessary, the benefits versus risks of iodinated contrast need to be carefully weighed. (94) If contrast administration is not feasible, a noncontrast scan, although not optimal, still allows the assessment of overall vessel size, calcification, and tortuosity.

As previously mentioned, analysis and measurement of the annulus size and shape are crucial for procedural success. Typical annulus measurements, obtained using 2D TTE or TOE provide a single diameter measurement, assuming a circular annular orifice (95). In contrast, 3D MDCT systolic reconstruction of the annulus orthogonal to the center-axis of the LVOT allows for the assessment of minimal and maximal diameter, circumference, and area measurements (63,90,96,97). (Figure 4.2.4.1.) Indeed, these studies have demonstrated that the LVOT is often oval, rather than circular. Hence, multimodality imaging might improve the accuracy of measurements and reduce the chance for prosthesis-sizing errors in patients considered for TAVI.

Complete coronary assessment with MDCT is obviously limited in the current population evaluated for TAVI because of the very high prevalence of advanced calcified disease, precluding precise assessment of luminal stenosis. However, MDCT allows measurement of the distance between annulus and coronary ostia, which identifies patients at risk for coronary occlusion during TAVI. (98)

Optimal coaxial alignment of the stent valve along the centerline of the aortic valve and aortic root is important during positioning. Ascertainment of the right projection for deployment (three cusps alignment) is important to avoid too high or too low placement, aortic regurgitation and optimize valve function. (63) Although traditional assessment of root orientation is performed using multiple invasive aortograms in 1 or 2 orthogonal planes, double-oblique multiplanar MDCT reconstruction allows preprocedural prediction of the aortic root angle. This potentially decreases the number of

aortograms required during the procedure, therefore shortening both procedure time and contrast usage, and improves precision of deployment. (99,100)

4.2.5. Evaluation of size, tortuosity and calcification of peripheral arteries

As vascular injury is one of the most frequent complications of TAVI, occurring in 2% to 30% of patients - the conflicting reports being due to heterogeneous end-point definitions -, a thorough imaging of the arterial vasculature is essential before choosing the most suitable access route. (101-104)

A basic assessment can be done by conventional peripheral angiography at the time of coronary angiography with relatively lower costs, lower contrast dye injection and lower radiation exposure compared with MDCT. However, more detailed information on luminal diameter, atherosclerosis, and vessel tortuosity can be gained by this latter imaging. MDCT allows measuring luminal diameter at an exactly orthogonal plane to the vessel by using multiplanar reconstructions. (56,86,88)

Finally, magnetic resonance imaging is helpful to accomplish such information in patients with renal insufficiency. (63)

The femoral artery is typically used as the default vascular access. The high risk of vascular injury in TAVI via a peripheral access is due to the large introducer sheaths, though a substantial reduction in sheath diameter has been achieved over the last few years. The CoreValve Revalving system is inserted via an 18 F sheath, while the SAPIEN XT Valve delivery system ranges from 16 to 20 F, depending on the size of the valve. The acceptable minimal iliofemoral diameter for implantation of the 26, 29 and 31 mm Medtronic CoreValve prostheses is 6.0 mm, whilst the acceptable minimal iliofemoral diameters for implantation of the 23, 26 and 29 mm Edwards SAPIEN XT prostheses range between 6.0 and 7.0 mm, depending on the prosthesis and delivery system used.

Expectedly, the higher the atherosclerotic burden and the degree of tortuosity, the higher the risk of vascular injury. (87) Hayashida et al. (101) reported that the ratio of outer sheath diameter to artery luminal diameter (SFAR) should be lower than 1.05 to minimize the risk of arterial damage. In heavily calcified arteries, the maximum ratio should be 1.00, whereas noncalcified, flexible vessels allow a ratio of 1.10.

Additional predictors of vascular complications are concentric calcifications and calcifications surrounding more than 180° of the vessel circumference. (87,88,101,105)

Similarly, the lower the atherosclerotic burden, the higher the accepted vessel tortuosity. Significant tortuosity alone of the iliofemoral vessels is not necessarily a contraindication to TAVI as long as the vessels are otherwise healthy and compliant. The gentle advancement of the stiff guidewire or vascular access sheath will tend to straighten the vessel.

(100)

Features such as calcifications of the aortic arch, aortic thrombi, dissections, stents or vascular bypass grafts are further useful findings on MDCT.

If a transapical access is planned, the orientation of the left-ventricular apex and outflow tract as well as the presence of left-ventricular thrombi can be shown on MDCT. (87)

4.3. Procedural location and anesthetic considerations

The 2012 American College of Cardiology Foundation/American Association for Thoracic Surgery/Society for Cardiac Angiography and Interventions/STS expert consensus document on TAVI provides general recommendations on the performance of TAVI. (63)

A functional and cooperative heart team comprising members of the cardiac/cardiovascular surgery, interventional cardiology, anesthesiology, echocardiography and postprocedural care departments is essential to the success of the TAVI program. Further important members of the team are a cardiac anesthesiologist and a perfusionist in case cardiopulmonary bypass (CPB) is necessary.

Procedural location will vary from institution to institution related to several factors including current available resources. A spacious (approximately ≥ 800 square feet) and well-ventilated - appropriate air handling and air exchange modifications in order to meet sterility prerequisites - cardiac catheterization laboratory is acceptable for performing the TAVI procedure, even if the preference is for a fully hybrid operating room. In the future, hybrid rooms will become the standard of care for these team-based therapies. (63)

The location should provide adequate fluoroscopic imaging and full interventional cardiology equipment as well as surgical equipment including that for temporary assist devices. (106)

Optimal equipment requirements include a state-of-the-art, large-field-of-view fluoroscopic imaging system — preferably a fixed overhead or floormounted system that has positioning capability rather than a portable C-arm system. This system needs to have the ability to store and review images and accommodate varying patient sizes. (Figure 4.3.1.) A potentially important adjunct to this is the availability of either biplane imaging or imaging programs that can automatically help in the selection of orthogonal views during valve positioning.

Integration with TOE imaging, particularly 3D capabilities, is helpful; the availability of CT or CMR imaging is a significant advantage, particularly when image overlay is possible, which will become more widely used in the future. (106)

On site back-up cardiovascular surgery facilities, like on-site heart-lung machines, are mandatory as well as related ancillary interventional cardiology supplies like equipment for balloon aortic valvuloplasty, coronary balloons, stents, and

.014-inch wires if coronary occlusion occurs as a complication of device deployment. As the vascular access is critical, the availability of a variety of vascular closure devices as well as rescue peripheral arterial balloons and covered stents for treatment of peripheral vascular complications is paramount.



Figure 4.3.1. Multifunctional hybrid room.

State-of-the-art, large-field-of-view fluoroscopic imaging system - preferably a fixed overhead or floormounted system –, 3D-TOE capabilities and very high-resolution monitors represents the standard of care for TAVI transapical and transfemoral procedures. Anesthesia services, including advanced airway management, general anesthesia, full haemodynamic monitoring, and on site back-up cardiovascular surgery facilities are mandatory.

TAVI is a minimally invasive off-pump procedure that usually proceeds in a straightforward fashion. However, unpredictable events with serious haemodynamic consequences can occur at any time. Haemodynamic compromise may occur after balloon dilatation or after valve insertion, which may require immediate conversion from the off-pump to an on-pump technique. Cannulation for blood pumps for circulatory support can usually be safely accomplished using

the existing femoral access. CPB is rarely necessary for TAVI, but it is a prerequisite for the procedure to have the heart–lung machine ready to use in the operating room as an important part of the safety net. (4)

The procedural location should also be fully capable of providing anesthesia services, including advanced airway management, general anesthesia, full haemodynamic monitoring, and administration of vasoactive agents into the central circulation. Although general anesthesia is generally used for the TAVI procedures, at some experienced institutions transfemoral TAVI is performed with conscious sedation or under local anesthetics (19,106). With the latter, the patient is awake and breaths spontaneously with no oro-tracheal intubation. In such a situation, intraoperative TOE for procedural guidance may be difficult or impossible. Adequacy of ventilation and oxygenation should be continuously assessed during conscious sedation or local anesthetics and qualified personnel and equipment to perform emergent oro-tracheal intubation and mechanical ventilatory support should be available immediately in case of complications.

Treating structural heart disease percutaneously represents a totally new challenge in the catheterization laboratory, and the learning curve on TAVI procedures is steep for the whole hospital team. Ongoing TAVI developments require operating theatre and catheterization laboratory personnel to get more knowledge about transcatheter and endovascular techniques and to become familiar with the numerous devices employed such as sheaths, guide wires, catheters, stents and stent-grafts. Personnel training is essential in order to build a team, that knows what to do, and deliver optimal workflow even in case of complicated procedures. Some of the elements of the structured training and certification program are controlled by the THV manufacturing companies.

Radiation exposure can be particularly high for both the patient and personnel in the operating theatre/cardiac catheterization laboratory. Appropriate protection, including thyroid shields and dosimeters are mandatory. The TAVI care team should follow a preventive and safety program for X-ray protection.

5.1. Decision tree for transcatheter valve implantations

There is no simplified algorithm for access route decision. Optimal decision making comes from the interdisciplinary team, respectful of their knowledge and expertise regarding the different approaches and techniques of TAVI.

A group that implants both prostheses currently available and masters all potential access sites may use the following decision tree for the primary planning of the procedure. (Figure 5.1.1.)

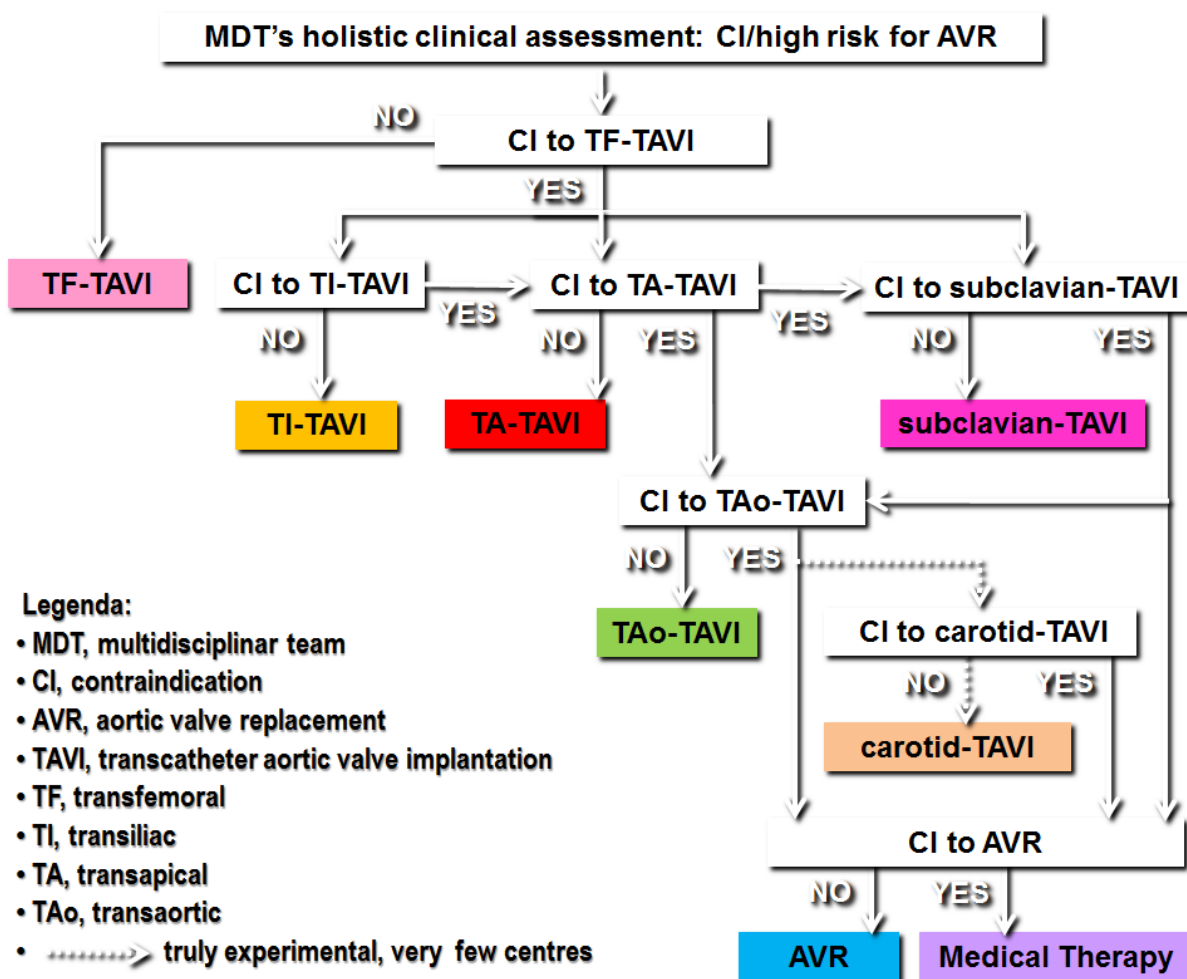


Figure 5.1.1. Possible decision tree for vascular access during transcatheter implantation of the aortic valve. Please, see the text below for comments.

This algorithm may be applied for all patients considered for TAVI in the following manner.

As a first step the *transfemoral* approach is considered and investigated. If this access is feasible according to the criteria described in this chapter, the choice of the valve type is based on clinical preference, the size of the aortic annulus and the vessel diameters.

For small annulus sizes between 18 and 20 mm, to date, only the Edwards-SAPIEN prosthesis is acceptable, for very large sizes, between 27 and 29 mm, only the Medtronic CoreValve. Furthermore, if the peripheral vessel diameter does not exceed 6 mm at the narrowest site, only the 18-F Medtronic CoreValve delivery systems may be considered for a transfemoral implant, as 26-mm and 29-mm Edwards-SAPIEN require a minimum vessel diameter ranging between 6 and 7 mm, depending on the size of the prosthesis and the Edwards delivery system used.

On the other hand, an increased diameter of the sinotubular junction beyond 42 mm precludes a Medtronic CoreValve while an exceptionally short distance between the coronary arteries and the aortic valve ring (<1 cm) precludes the Edwards SAPIEN prosthesis.

A large number of the high-risk patients with critical AS referred for TAVI approach may not be candidates for the femoral approach due to peripheral vascular disease with morbidity and mortality increased several fold in patients who develop access related complications. (107)

Although less preferred by several operators, a *retroperitoneal transiliac* approach (without or with conduit) can be used as an effective resort, granted at least iliac vessels suitable for retrograde TAVI approach.

If the transfemoral-transiliac access has to be disregarded, due to atherosclerosis or unfavorable anatomy of the aorta or iliofemoral artery or both, the successive step is to evaluate the left *transsubclavian/axillary* access.

In regard to the subclavian/axillary vessel diameter and morphology, the same selection criteria exist as for the femoral approach. For the choice of the valve prosthesis, the same parameters have to be considered as for the transfemoral approach. The right subclavian artery should be used only in highly selected cases where no other access is possible, because the delivery system enters the ascending aorta from the innominate artery perpendicularly, which puts the prosthesis in an improper angle to the plane of the native valve ring.

If the subclavian access route is not suitable (as still off-label for the Edwards-SAPIEN valve or uncomfortable approach for some operators), the next step will be to evaluate the *transapical* approach.

Since the transapical access is very safe, it should also be considered in cases where the transarterial access might be possible but where it seems unreasonably dangerous. The only contraindications for the transapical approach might be severe previous skin injury following radiation therapy for breast cancer or severe COPD. Moreover, since only the Edwards SAPIEN prosthesis is available for this approach to date, the exclusion criteria given by the valve ring diameter have to be respected.

If for different reasons no other access route seems feasible, the *transaortic* approach should be considered.

In rare instances, when a patient is not a candidate for a conventional ventricular apical approach, peripheral arteries and the aorta are not suitable for access due to vascular occlusive disease and the axillary artery is not available, due to presence of a pacemaker or other device, a *transcarotid artery* approach has been reported as a last resort, using the Medtronic CoreValve device. (108,109)

For the ultimate decision process, advanced knowledge in peripheral vascular disease is mandatory to better evaluate the potential risk of complications when manipulating with large introducers and stiff wires in elderly patients with frequently calcified and tortuous vessels. Therefore, careful screening and analysis of the entire vascular anatomy from the access site to the aortic valve anatomy should be a systematic part of the preoperative assessment and its importance is not to be underestimated.

5.2. Transfemoral approach

5.2.1. Patient Selection

The transfemoral access (TF) is the predominant route for implantation of both the CoreValve and the Edwards SAPIEN prosthesis. (110)

Assessment of the peripheral arterial system begins with a detailed history and physical exam. The history should evaluate associated risk factors (e.g., diabetes, smoking, hypertension, and hypercholesterolemia), prior history of peripheral arterial bypass surgery and symptoms of peripheral arterial disease.

Then, imaging techniques such as fluoroscopic angiography, contrast MDCT, and MR angiography can provide objective information of the peripheral arterial system — salient features include vessel diameter, degree of calcification and atherosclerosis, obstruction, tortuosity and ulceration. (111)

Although it is the least invasive, the TF route may not be feasible in every patient and carries a potential risk of stroke. General (absolute and relative) contraindications to the TF approach include severely calcified or tortuous iliac arteries; an iliofemoral artery diameter of <6 mm to <9 mm, depending on the device used; a previous aortofemoral bypass graft; severely angulated aorta or atherosclerotic aortic arch; transverse ascending arch (for balloon-expandable devices); aortic aneurysm with extensive mural thrombus and coarctation of the aorta.

It is beyond the purpose of this chapter to determine which imaging modality (peripheral angiography, MDCT or MRI) provides the most accurate analysis of the diameter, degree of atherosclerosis, tortuosity and calcification of the arterial vessels. Indeed, a combination of two imaging modalities is recommended. (110)

Assessing the feasibility and more importantly the safety of the TF route is in general the first step in chronologic order when a patient is accepted for TAVI. To which extent the TF approach should still be considered an acceptable option in difficult anatomies in regard to the potential risk of iliac rupture is again a difficult question but some rules, tips and tricks, and technical aspects can be provided. Basically, we re-emphasize the need to respect some basic rules that should lead to the exclusion of the femoral approach:

- iliofemoral artery diameter <6.0 mm,

- circumferential arterial calcifications,
- external iliac artery loops,
- severe kinking or tortuosity of the abdominal or intrathoracic aorta,
- considering the different levels of expertise of the interventional cardiologist and the cardiac surgeon in peripheral vascular disease, a highly individualized and thoughtful approach is required.

As stated before, the minimum vessel diameter required to accommodate a 16-F or 18-F sheath is 6 mm.

The second step is to assess the feasibility and safety of advancing the introducer sheath through the iliac arteries. This step is more difficult and requires a comprehensive analysis of diameter, tortuosity, lesions, and degree of calcification, the latter playing a major role in the decision making. Ideally, the preoperative setting should include at least an angiogram of the aortoiliac arteries with the use of a graduated pigtail catheter. For more detailed information, a MDCT or MRI can be useful to assess circumferential calcifications, or a mural thrombus in relation to an unsuspected arterial aneurysm.

Subjective quantification of vessel calcification and atherosclerosis by using any of the aforementioned imaging modalities can help to anticipate potential areas of dissection, rupture, or problems with advancing the delivery catheter system. Furthermore, some physicians consider circumferential calcification observed on MDCT or severe atherosclerotic narrowing (>50%–70%) of the iliofemoral vessels to be contraindications to TAVI. (111)

Actually, both mural thrombus and aneurysms provide a relative contraindication to TF-TAVI, since the Edwards e-Sheath's Dynamic Expansion Mechanism as well as other available transfemoral sheath systems combine innovative design and advanced manufacturing technology (optimal strength, flexibility and maneuverability) to create a high performance catheterization but minimizing access vessel trauma. (Figure 2.1.6.)

Peripheral vascular disease is not an absolute contraindication to TAVI. However, significantly it increases the risk of complications. Physicians must be skilled or have the necessary resources to treat vascular injuries (percutaneously or surgically). Some physicians attempt to cautiously advance the vascular access sheath and catheter delivery system across the diseased vasculature, implant the valve and repair any complications such as dissections 'on the way out' by percutaneous transluminal angioplasty/stent implantation. Alternatively, peripheral vascular interventions (percutaneous

transluminal angioplasty or stent implantation) can be performed prior to valve implantation. Even if this latter approach has been performed successfully in experienced centres, the risk of dislodging the implanted stent during advancement of the vascular access sheath or delivery catheter needs to be considered. (56,111)

5.2.2. Surgical and percutaneous femoral artery access

The femoral artery can be accessed by surgical cut down or percutaneously.

Surgical exposure of the common femoral is preferred by many and provides an extra level of security especially when the preassessment showed vessels with challenging characteristics.

Percutaneous access is an excellent choice in patients with large vessels and mild or no calcification, and by teams who have acquired significant experience with the percutaneous valve procedure.

OPEN RETROGRADE FEMORAL ACCESS TECHNIQUE

In an open vertical approach, a curved 6 to 8 cm vertical skin incision is made slightly lateral to the pulsation of the femoral artery. (Figure 5.2.2.1.)

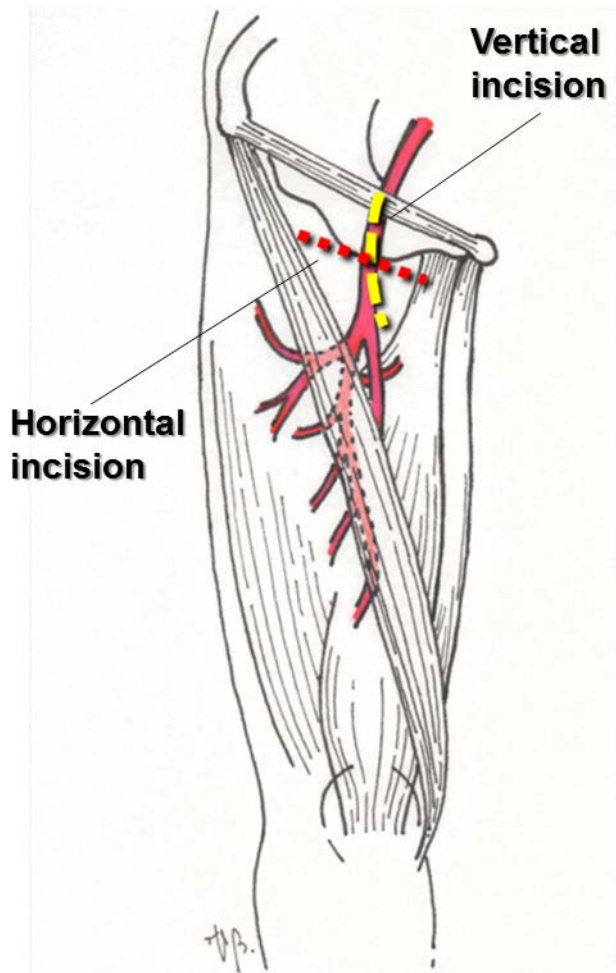


Figure 5.2.2.1. Surgical approach to the common femoral artery.

A curved 6 to 8 cm vertical skin incision is made slightly lateral to the pulsation of the femoral artery (yellow dashed line). Alternatively, a transverse incision is made two-finger breadths above the groin crease and over the palpable femoral pulse (red dotted line).

A minimal mobilization of the common femoral artery is obtained to achieve adequate proximal and distal control of the vessel. A silastic vessel loop and a Rummel tourniquet are applied to the common femoral artery to serve as proximal and distal control, respectively. (Figure 5.2.2.2.A-B)

Retrograde cannulation of the common femoral artery is then performed with a beveled needle (18 gauge) until pulsatile blood flow is visualized. A soft angled tip guidewire is advanced in the vessels under fluoroscopy and an introducer sheath is then advanced over the guidewire with the dilator preceding the introducer sheath by a few inches again under fluoroscopic visualization.

Retrograde percutaneous access is usually performed in the contralateral common femoral artery for pigtail catheter insertion and in the common femoral vein for temporary pacing wire positioning.

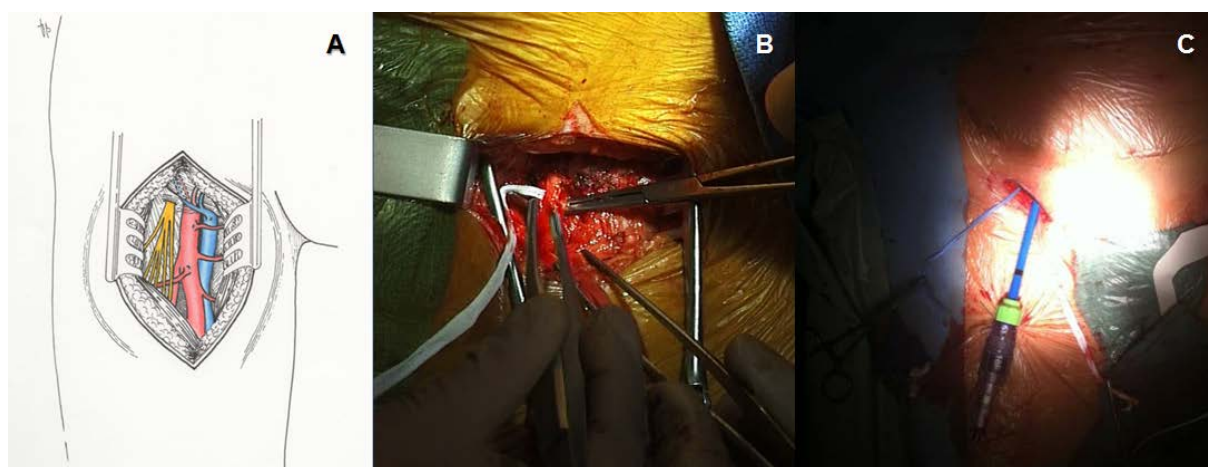


Figure 5.2.2.2. Femoral artery mobilization.

After obtaining a minimal mobilization of the common femoral artery by either the vertical (A,B) or the horizontal incision, a silastic vessel loop and a Rummel tourniquet are applied to control proximally and distally, respectively (B,C); the THV introducer sheath is then retrogradely advanced over the guidewire (C).

Alternatively, a transverse incision is made two-finger breadths above the groin crease and over the palpable femoral pulse. (Figure 5.2.2.1. and Figure 5.2.2.2.C) The inguinal ligament is mobilized and freed along its length to allow retraction superiorly.

Once the procedure is completed all wires and sheaths are removed under fluoroscopic guidance to ensure that no injury is caused to the vessel wall. The arteriotomy is then closed with a 5/0 prolene suture after achieving proximal and distal control.

PERCUTANEOUS RETROGRADE FEMORAL ACCESS TECHNIQUE

The main advantages of the less invasive percutaneous technique are an increased patient comfort immediately after the procedure and a diminished requirement for anesthetic drugs during and after the procedure. Indeed, in most

patients, the percutaneous technique of placement and removal of large diameter femoral arterial sheaths can be performed under only local anesthesia.

After the pulse is identified, the inguinal ligament is found by tracing a line between the anterior iliac spine and the pubic tubercle. Often, especially in obese patients or in abdominal distension, the inguinal crease is inferior to this landmark. Access should be gained below the inguinal ligament corresponding to the common femoral artery. (112)

A properly equipped endovascular suite will allow fluoroscopic imaging of the groin to identify all anatomic landmarks. In addition to surface landmarks, most physicians use the medial half of the femoral head to guide femoral artery access; this ensures common femoral artery entry and avoids the complications of a higher puncture. It is also useful in the pulseless femoral artery. The relationship of ideal puncture site (common femoral artery) to bony femoral head usually corresponds to middle or upper third of femoral head. Femoral bifurcation is avoided by puncturing in upper quadrant of femoral head.

A careful palpation of the femoral pulse is performed and the needle is introduced through the arterial wall at a 45° angle.

Percutaneous arterial femoral access is usually obtained by the Seldinger technique. A soft tip-angled .035-inch guidewire is introduced through the central lumen of the needle under fluoroscopic guidance. Once access is achieved, a small nick is made in the skin with a #11 blade and an introducer sheath is then advanced over the guidewire with the dilator preceding the introducer sheath by a few inches again under fluoroscopic visualization.

Preclosure using a single Prostar XL device (Abbott Vascular Devices, CA, USA) is commonly used with percutaneous access. Some operators use two Prostar devices or two 6-F Proglide suture-mediated closure devices (Abbott Vascular Devices, CA, USA). Three aspects are essential for the selection: (i) the femoral artery wall must be free of calcified plaque at the area of puncture, (ii) the diameter of the femoral and iliac arteries must be large enough to accommodate the necessary sheath and (iii) the distance between the front wall of the artery and the skin should be less than 9 cm.

The use of MDCT angiography to reliably and noninvasively judge the femoral artery as suitable to percutaneous closure device is advised. (113)

Some operators use ultrasound guidance to improve safety of the femoral puncture. Typically with a sterile packed 5 to 10 MHz linear array transducer.

In case of failure, after positioning a rescue PTA balloon to temporarily stop the bleeding, percutaneous (a covered stent or a stent-graft) or surgical repair technique are then mandatory.

COMPLICATIONS OF OPEN AND PERCUTANEOUS RETROGRADE FEMORAL ARTERY ACCESS

Although it is beyond the purpose of this paper to assess all the possible complications of surgical and percutaneous retrograde femoral artery access, over all in TAVI - where vascular complications remain the main problem despite downsizing of delivery catheters diameter and judicious patient selection - we will only make mention. For a more detailed discussion, please refer to dedicated publications. (98,103,114,115)

According to Valve Academic Research Consortium (VARC) classification (116), major vascular complications are: vascular perforation (any location) or dissection resulting in 'clinical' hypoperfusion requiring repair with either a stent or surgical intervention or with untreated 'clinical' hypoperfusion to major side branches, or vascular, access-related complications (i.e. haematoma, bleeding, pseudoaneurysm or severe vessel stenosis) requiring repair, distal embolization requiring surgery or resulting in amputation or other major endorgan compromise (e.g., brain, kidney), access site infection requiring surgical debridement.

Minor vascular complications are: vessel perforation treated with observation or balloon tamponade, vascular dissection not requiring treatment and without adverse clinical sequelae, access site pseudoaneurysm or arteriovenous fistula not requiring treatment at all, distal embolisation treated with embolectomy and/or thrombectomy and not resulting in clinical sequelae, access site infection treated with antibiotics, unplanned CPB use for repair of entry site.

Percutaneous closure devices failure is considered a major complication according to VARC-1 (116) and VARC-2 (117) definitions.

In the PARTNER trial, dissection, perforation, and groin haematoma were the most frequent vascular complications and were associated with a significantly higher mortality at 30 days and 1 year post-procedure. (118) Risk factors include

peripheral artery disease, severely calcified and tortuous vessels, circumferential calcifications, and an external sheath diameter larger than the minimal luminal diameter of the access vessel. (87,101,105, see chapters 4.2.5. and 5.2.1.)

Study data supports and expounds on the theory that transverse incision to vertical groin incision offers lower short and long term wound complications such as infections and lymphatic leaks. (119) Moreover, among the aims of switching to percutaneous approach to femoral artery there is the intention to reduce some open surgical femoral artery access complications – even more frequent in elderly and obese patients - like skin site wound infections, seromas, haematomas and ugly scars, as well as vascular problems related to arterial suture. (120)

5.2.3. Procedure

The THV is prepared separately, and, in case of Edwards SAPIEN THV, crimped onto the delivery system using the specially designed Edwards crimper. (Figure 2.1.2., Figure 2.1.3.)

Procedures may be performed under general anesthesia or conscious sedation as determined by physician's preference and as per hospital protocol, with fluoroscopic and TOE guidance, the latter providing useful information about aortic valve morphology, LV function, positioning of the prosthesis across the aortic root and can readily identify certain procedural complications. (121). In the case of a conscious patient, TOE control is replaced by TTE and angiography.

Transvenous intraventricular pacing wires should be placed for rapid ventricular pacing if required and to permit ventricular pacing in case of post-procedural heart block. During the procedure, heparin should be administered to maintain an activated clotting time of 250–300 seconds, which can be reversed by protamine at the end of the procedure.

A pigtail catheter is positioned in the aortic root for aortography.

Depending on the approach, the access site is then punctured or surgically exposed and the sheaths inserted. The aortic valve is crossed with a guide wire and usually balloon valvuloplasty (BAV) is performed during rapid pacing to prepare the native annulus for implantation before valve deployment. (Figure 5.2.3.1.)

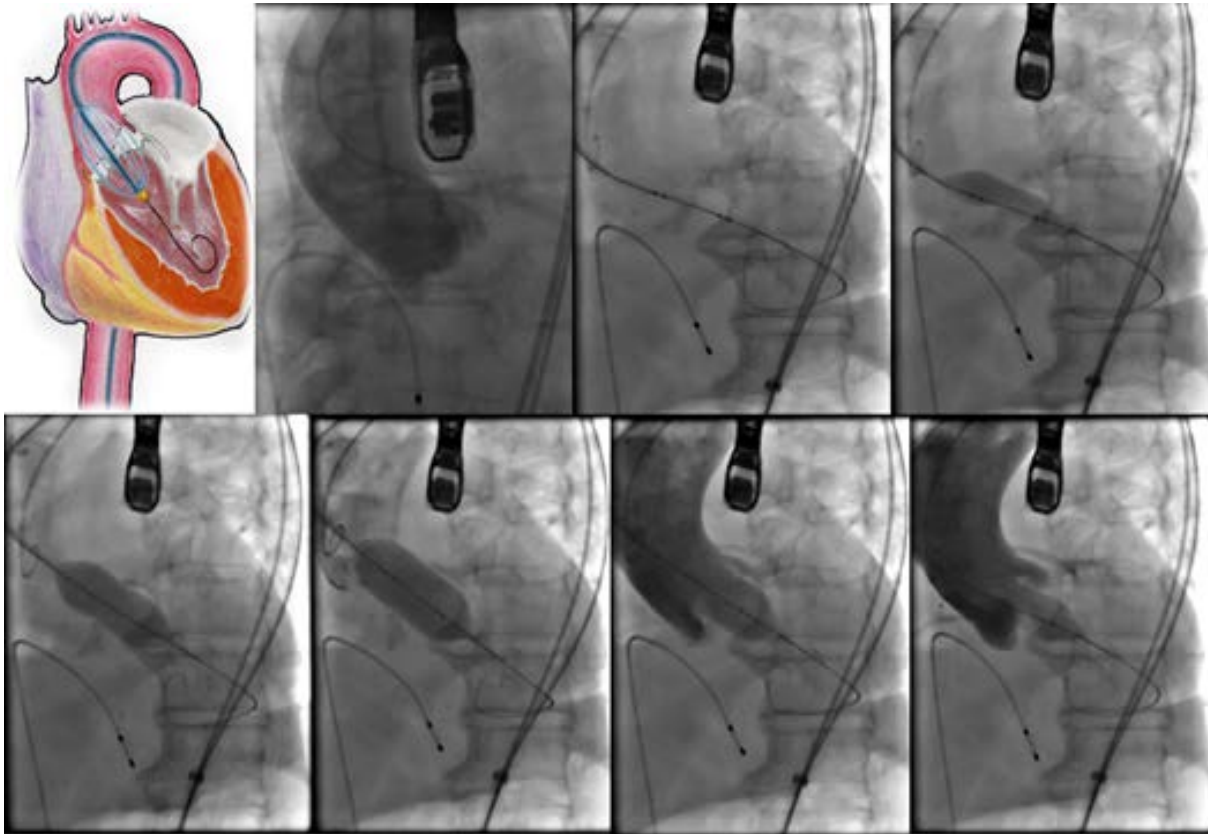


Figure 5.2.3.1. Balloon aortic valvuloplasty.

A properly tip-curved Amplatz extra-stiff guidewire is advanced and placed across the aortic arch and through the stenosed aortic valve into the left ventricle using the AL1 or AL2 catheter. Balloon aortic valvuloplasty (BAV) is performed. During BAV, a selective supra-aortic angiogram can be performed in order to size the annulus and to evaluate the effect of the leaflets pushed against the aortic wall and the coronary ostia.

The two available different stented valves are deployed in two different ways: the Sapien XT THV is expanded inflating the inner catheter-balloon under rapid cardiac pacing (heart beat rate ≥ 180 bpm) (Figure 5.2.3.2., Figure 5.2.3.3.) whereas the CoreValve® self-expands after the withdrawal of the delivery system. (86) (Figure 5.2.3.4.)

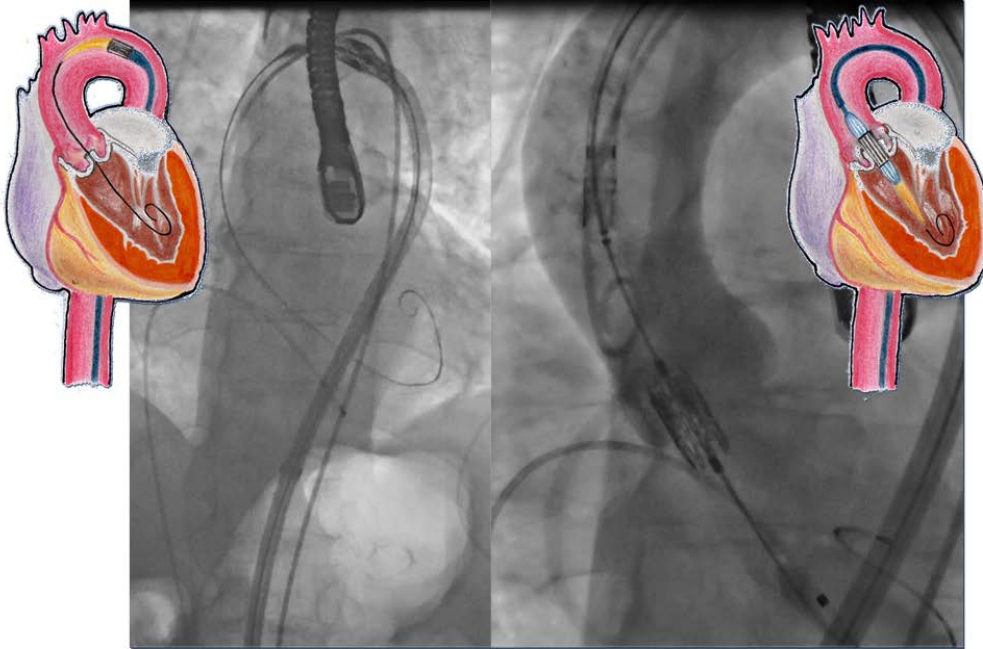


Figure 5.2.3.2. Retrograde introduction of the Novaflex delivery system and positioning of the Edwards SAPIEN XT prosthesis across the native valve.

Left: the Novaflex delivery system is navigated through the aortic arch. Right: the prosthesis positioning may require angiographies to verify the right placement of the crimped stented valve in the ideal landing zone (the Edwards SAPIEN XT THV may lie 50% on the aortic side and 50% on the ventricular side).

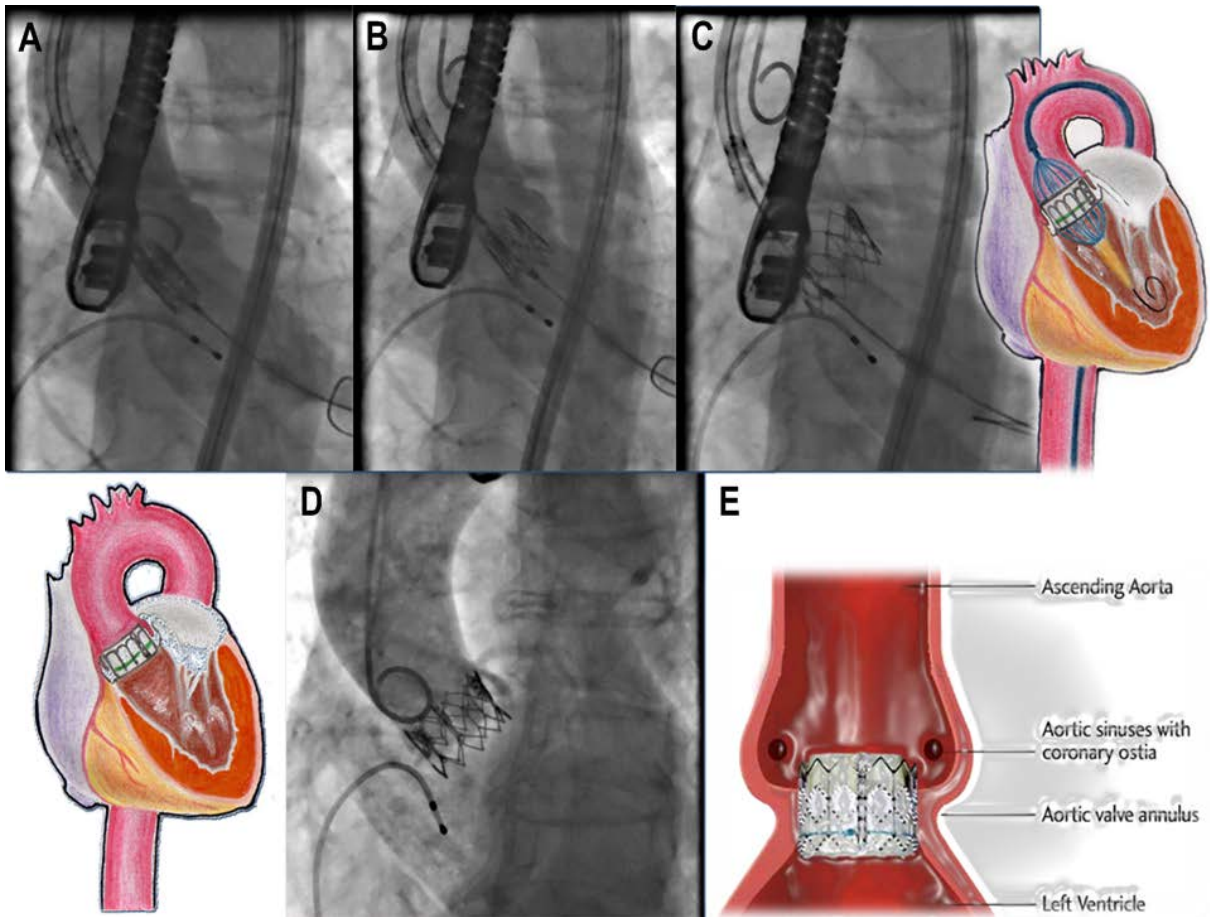


Figure 5.2.3.3. Edwards SAPIEN XT valve implantation.

When accurate positioning is verified (A), rapid pacing is started and the transcatheter prosthesis is deployed through complete balloon inflation (B,C). Following deployment, the Novaflex delivery system is dearticulated and removed from the sheath. D. A postoperative angiographic control is routinely performed to verify the coronary patency and the absence of major paravalvular leaks. E. Anatomical annular placement of the Edwards SAPIEN XT valve.

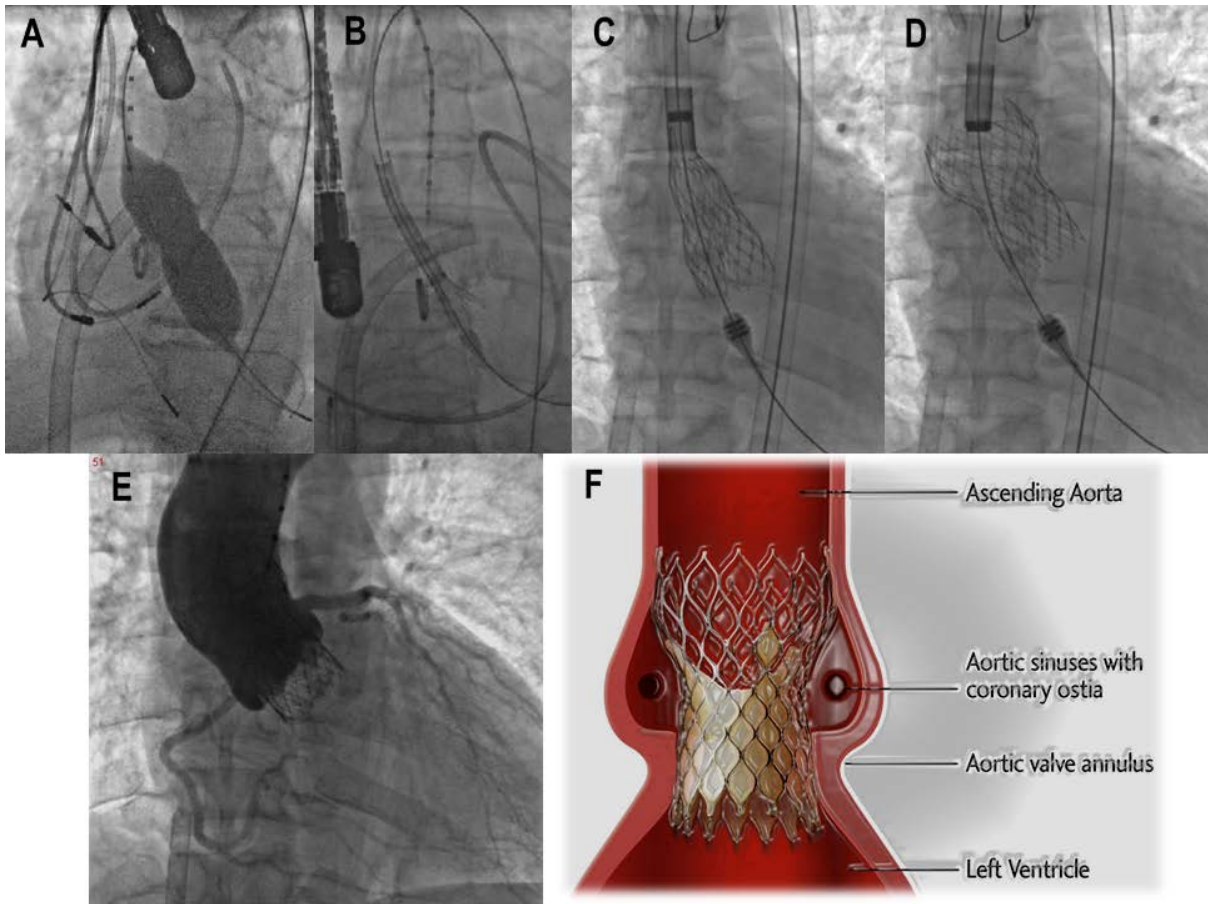


Figure 5.2.3.4. CoreValve® implantation.

A. Routine balloon valvuloplasty is performed before valve deployment. B. The CoreValve bioprosthesis is positioned with the inflow portion within the aortic annulus (<6 mm below the annulus, the pigtail catheter in the sinuses serves as a guidance marker). The bioprosthesis is slowly deployed withdrawing the delivery system (C,D). E. Final aortogram to assess proper expansion and positioning of the bioprosthesis. F. Supra-annular placement of the CoreValve.

Since it allows a fully percutaneous procedure, the femoral access route is very attractive. Nonetheless, sometimes a femoral cut down may be required. Smaller introducer sheaths and percutaneous vascular closure devices have significantly facilitated the percutaneous approach over the past few years, and several new closure devices are currently under clinical evaluation. However, one of the most important disadvantages of the transfemoral access route is the risk of vascular injury, especially if a large valve is needed or if the patient's vasculature is unfavorable. Therefore, preoperative imaging is crucial to determine the feasibility of a transfemoral approach. Further, a transfemoral transcatheter valve is more difficult to position than a valve inserted via a more direct approach. (87,101,105,122,123)

Some studies have reported a higher incidence of neurologic events with the transfemoral route, which is probably because the sheath has to pass through the curved aortic arch, but others could not support these findings. (124-126)

5.3. Transiliac approach

5.3.1. Procedure

Thorough preoperative planning, understanding the pathology of aortoiliac occlusive disease, advanced endovascular skills and ability to use alternate access sites including able to perform an iliac conduit via a retroperitoneal approach are advised to achieve excellent results.

Patients with small, calcified, tortuous - or a combination of any of these factors - femoral arteries may make femoral delivery of a transcatheter aortic valve device hazardous. Nevertheless, in case of iliac vessels suitable for retrograde TAVI approach, direct or by means of a conduit iliac artery access can be gained through a retroperitoneal approach.

(107) (Figure 5.3.1.1., Figure 5.3.1.2.)

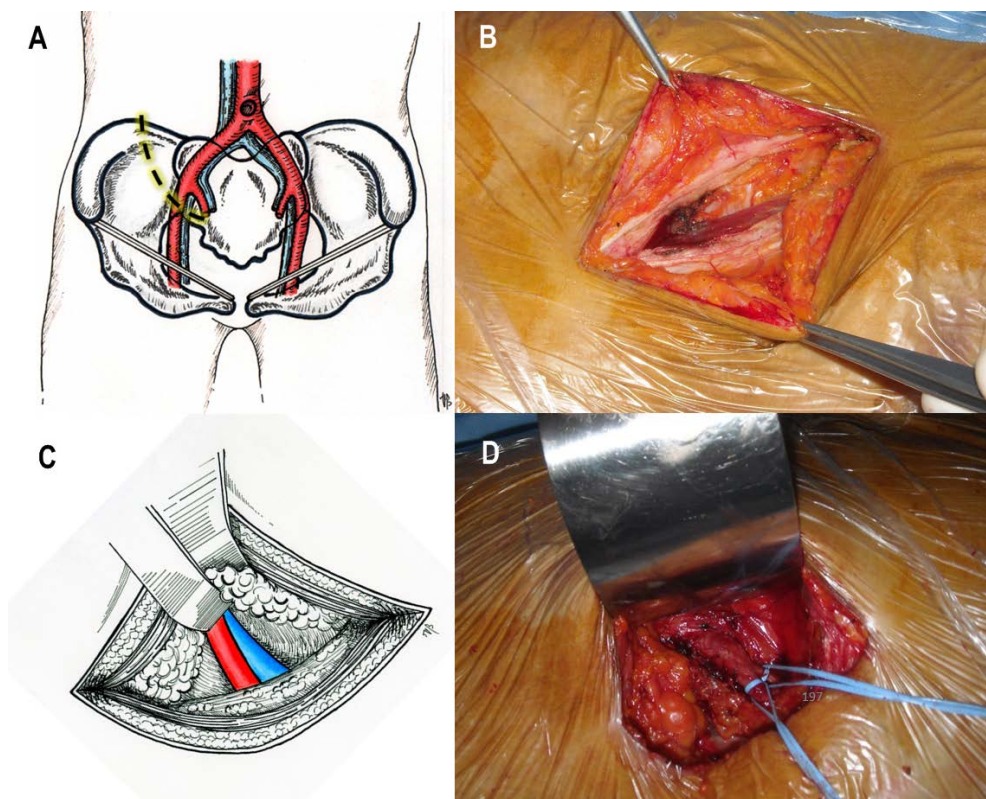


Figure 5.3.1.1. Retroperitoneal transiliac access.

A. A 15-cm semilunar right flank incision is made four-finger breadths above the groin crease. B. Division of the external oblique, internal oblique, and transversus abdominus muscle is performed in the direction of their fibers. C. Extraperitoneal fascia and peritoneum are retracted medially with the help of a retractor providing excellent exposure of

the lower infrarenal aorta, common iliac artery, and iliac bifurcation. D. Rummel tourniquets or vascular clamps are applied to control the common iliac artery, the external iliac artery, and origin of the hypogastric artery.

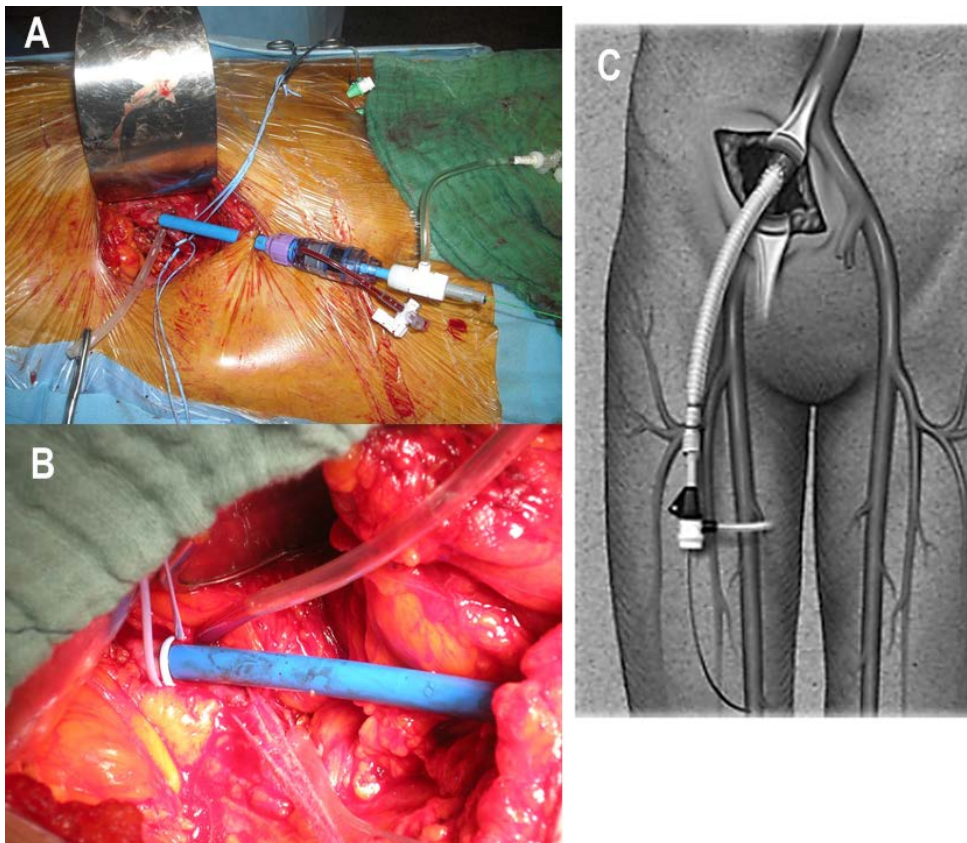


Figure 5.3.1.2. Retroperitoneal Access Techniques.

A. An 18-gauge needle is used to access the iliac artery followed by percutaneous introduction of a guidewire and the introducer sheath (B, magnified). The transcatheter valve can then be introduced into the delivery sheath and deployed to the target area. C. Deliverability of large sheath devices through tortuous anatomy or old graft material may be facilitated by more proximal access provided by construction of an iliac conduit.

The conduit can either be trimmed to the appropriate length and the conduit tied off as a stump (Figure 5.3.1.2.C) or the distal end of the conduit can be sewn to the more distal iliac system in an end-to-end fashion, as an interposition graft. More commonly the conduit can be tunneled to the groin under the inguinal ligament in order to perform either an end-to-end anastomosis or an iliofemoral conduit. (Figure 5.3.1.3.) Since the conduit may be reused through a simple

infrainguinal incision in the future, the iliofemoral conduit is the best for patients who may require further intervention for diffuse thoracic aneurismal disease.

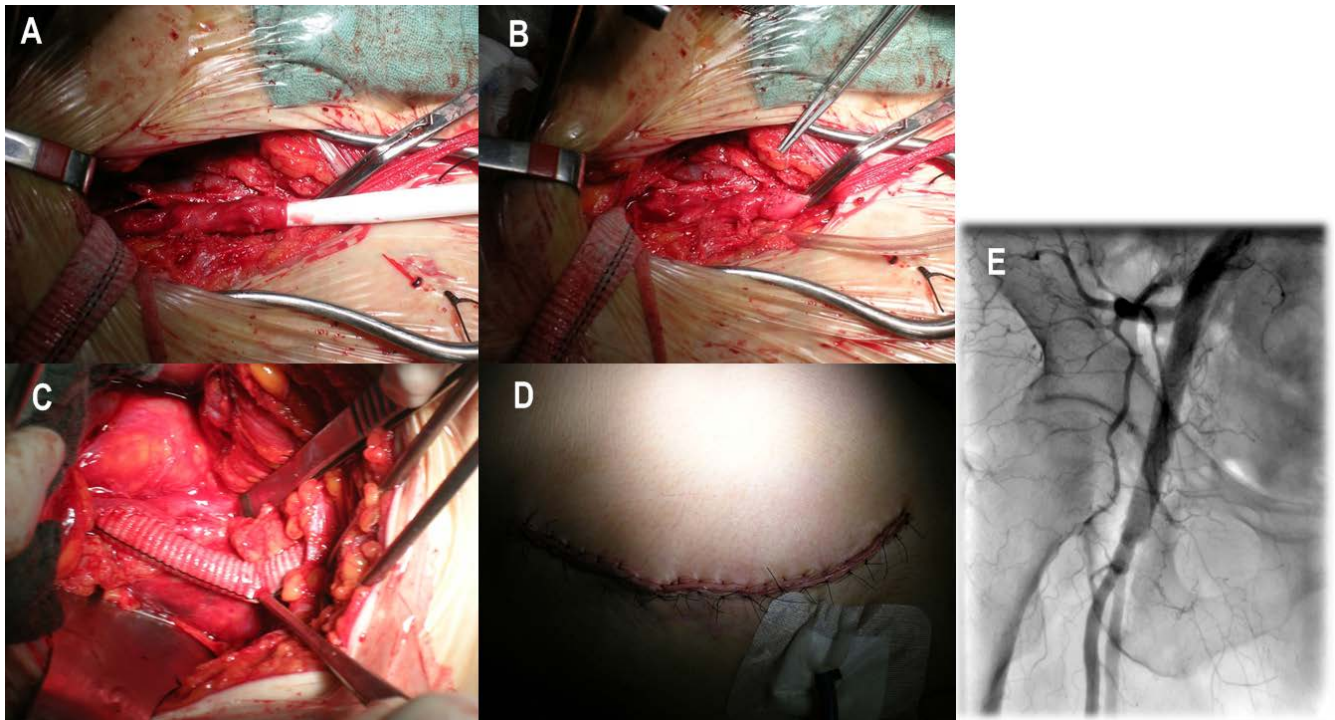


Figure 5.3.1.3. Retroperitoneal access via iliac conduit.

A. An arteriotomy is made on the common iliac artery close to the bifurcation of the hypogastric artery and the external iliac artery. B. A 10-mm conduit is sewn in an end-to-side fashion with a 5/0 prolene suture, then tunneled through the retroperitoneal space beneath the inguinal ligament (C), and brought out through the groin incision. The conduit is subsequently looped with a Rummel tourniquet and ready to be punctured. After TAVI, the distal end of the conduit is sewn to the more distal iliofemoral system. D. The incision closure in layers. E. Angiographic control showing neither leak nor stenosis.

The same technique can be applied to the infrarenal aorta and thoracic aorta. Similarly, end-to-side grafting of a conduit to the axillary artery to facilitate deep hypothermic circulatory arrest also provides excellent access to the thoracic aorta via the innominate. (127)

An endoconduit is an alternative percutaneous technique that can be used to deliver a THV in a patient with a small, calcified, or tortuous vessel instead of the conventional iliofemoral conduit. This technique can be applied in high-risk patients who have a relative contraindication to conventional open surgical techniques under general anesthesia.

The endoluminal conduit technique allows aggressive balloon dilation of long segments of iliofemoral stenosis without the risk of vessel rupture. It can be custom-assembled using grafts diameters of at least 8 mm and preferably 10 mm deployed into the external/common iliac artery. Via a 9-F sheath, balloon angioplasty can be performed to gently pre-dilate the vessel; subsequently an endoluminal graft or a stent graft can be deployed across the common iliac and external iliac artery. Post-deployment balloon angioplasty is eventually performed with a balloon to expand the endoluminal graft. This technique has been referred to as *cracking and paving*. (128)

The 9-F sheath is then exchanged to a 16-F to 20-F delivery sheath, which is required to deliver the THV.

5.4. Transsubclavian/transaxillary approach

5.4.1. Patient Selection

In contrast to the iliofemoral vessels, the subclavian and proximal axillary arteries are usually good-sized vessels and are often free of atherosclerotic disease, thus fulfilling the anatomic and morphologic requirements. In cases where the anatomy of the iliofemoral vessels is unacceptable, the second option for vascular access with the CoreValve system should be the subclavian artery, which is simple and familiar to cardiac surgeons and provided good stability of the sheath and valve delivery system. (129,130)

Nevertheless, to date little is known about the safety of this approach for the TAVI procedure compared with the femoral access that has been the usual route since the pioneering experience. (110)

As a result, some anatomical criteria should lead to the exclusion of axillary/subclavian route:

- arterial vessel diameter <6.0 mm
- severe tortuosity
- circumferential calcifications
- the left subclavian artery is preferred over the right.

Preoperatively, it must be determined that the size of the arteries (≥ 6 mm) is suitable for cannulation and that they are free of stenosis that are not amenable to angioplasty.

The transsubclavian approach is performed preferably via the left subclavian artery. Hence, a patent left internal mammary artery (LIMA) graft is a relative contraindication for TAVI from the left side. Successful cases have been performed in its presence with a minimum vessel diameter requirement of 6.5 to 7.0 mm. In order to reduce the risk of retrograde dissection of the, LIMA graft, the segment of the subclavian artery proximal to the internal mammary should be free of atherosclerotic disease. (131)

Despite the risk of pacemaker-led damage and infection, the presence of a permanent pacemaker in the left pectoral region is not an absolute contraindication.

In these patients, the right subclavian artery can be used; however, it is difficult to achieve the correct angulation of the device during positioning. (130)

As for the femoral route, angiogram, MDCT, or MRI provide accurate analysis of the diameter, tortuosity, and degree of calcifications of the subclavian/axillary artery vessels in relation to the aortic arch, mammary, and carotid arteries.

Particular attention should be devoted to the debranching site of the subclavian artery from the aortic arch, where most frequently stenosing calcification is to be expected. (132)

5.4.2. Procedure

The patient is placed in the standard supine position. For better exposure of the axillary artery, the arm is positioned near the body with the hand down to the side and the elbow slightly flexed, almost as if the hand was placed in an imaginary pants pocket. Arterial pressure is monitored via arterial lines placed routinely in both radial.

The axillary artery is easily surgically exposed under the vein and gently mobilized for 2 cm, without touching the medial and lateral cords of the brachial plexus. (132) **(Figure 5.4.2.1.)**

Two concentric purse-string sutures armed with Teflon after each insertion into the artery wall are applied. The subclavian artery is cannulated either directly or indirectly - through a longitudinal arteriotomy via a 10-mm woven Dacron graft anastomosed with 5/0 polypropylene suture - after a side-bite clamp has been applied across the artery. Such a graft can then be used as the access site for transcatheter valve deployment. (107)

Recently, a percutaneous TAx approach has been reported. (133) To avoid major bleeding, and as a target for the puncture, a wire is advanced via the ipsilateral brachial artery followed by a balloon that is placed into the subclavian artery via the femoral artery for temporary vessel blockade before percutaneous vessel closure with vascular closure devices.

Puncture of the axillary artery is performed at a distance of 1 to 1.5 cm lateral to the outer border of the first rib.

This has been reported to be a feasible and relatively safe option.(132)

Valve position and implantation proceeds as usual for Medtronic CoreValve TF-TAVI.

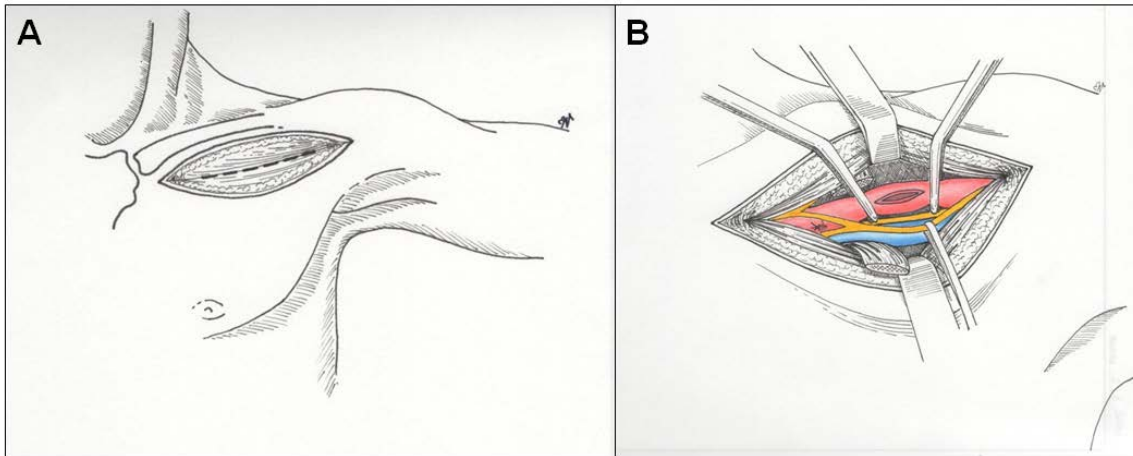


Figure 5.4.2.1. Transsubclavian approach.

A. A 5-cm long skin incision is made below the left clavicle, starting lateral to the sternal margin. B. The underlying muscle is retracted or divided. The left subclavian artery is isolated, and slings are placed around it.

Feared complications of this approach are the same as the peripheral femoroiliac approach: artery rupture, kinking of the THV with inability to advance, subclavian stenosis due to surgical suture, haemorrhage due to percutaneous closure device failure.

The TAx approach was first used as an alternative access to deploy CoreValve in patients with unfavorable femoral anatomy, with the first implant reported in June 2006. As of May 2011, over 800 CoreValve implants in more than 150 centers have been performed worldwide using the subclavian artery, with 5.4-9% major vascular complication rate and 4.4-12% 30-day mortality among European registries. (134)

Petronio and colleagues (135) recently reported the 2-year propensity-matched outcomes of 141 TAx-TAVI v. 141 TF-TAVI patients and found similar rates of procedural success, vascular complications, and survival (74.0% TAx-TAVI v. 73.7% TF-TAVI, $p=0.78$).

The Edwards SAPIEN valve has also been implanted via TAx approach with favorable outcomes. (67)

5.5. Transapical approach

5.5.1. Patient Selection

To date, the only available antegrade approach is the transapical approach, which is feasible solely with the Edwards SAPIEN balloon-expandable valve. (63)

The transapical route is an option for patients with iliofemoral occlusive peripheral vascular disease in which a conduit is not indicated and may have some advantages with respect to ease of device positioning and implantation. (107)

Antegrade passage of wires, catheters, and sheaths through the stenotic aortic valve simplifies the procedure.

Additionally, the insertion point is close and in a straight line to the aortic valve, rendering valve positioning easier and more accurate. The possibility of a reduced stroke rate is under discussion. (90,122,124)

Contraindications for the TA approach are: left ventricular thrombus, previous surgical patch of the left ventricle (e.g., Dor procedure), calcified pericardium, and the inability to access the left ventricular apex due to anatomical constraints (e.g., chest deformity). Furthermore, the reported mortality and morbidity rates for TA are higher, reflecting the patient characteristics and invasive nature of the procedure. This is especially true in patients with severely impaired respiratory function, impaired left ventricular function, and frail, elderly patients. The TA approach is also concerning if, in addition to a forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ratio <70%, either the absolute value of FEV1 was < 1 L or FEV1 <60%. (66)

5.5.2. Procedure

Typically, the procedure is performed under general anesthesia with fluoroscopic and TOE guidance.

The THV is prepared separately, and, in case of Edwards SAPIEN THV, the valve is crimped onto the delivery system by using the specially designed Edwards crimper.

It is recommended to identify the apex of the left ventricle by using TTE and mark the apex on the skin. (Figure

5.5.2.1.A-B) The apex of the left ventricle may occasionally be palpated prior to skin incision. Evaluation of a preoperative MDCT addressing the relationship of the apex to the chest wall can help with the positioning of the incision.

Introducing the valve through the left-ventricular apex is performed via a 3 to 4 cm left anterior thoracotomy through the fifth or sixth intercostal space. (Figure 5.5.2.1.C) The mid-clavicular line should be in the center of the incision.

Using a soft tissue retractor can optimize exposure and minimize rib spreading. (Figure 5.5.2.1.D)

After opening the pericardium, purse-string sutures are placed with sufficiently deep bites in the myocardium - close to the apex and lateral to the left anterior descending coronary artery - and the valve sheath is inserted. (107)

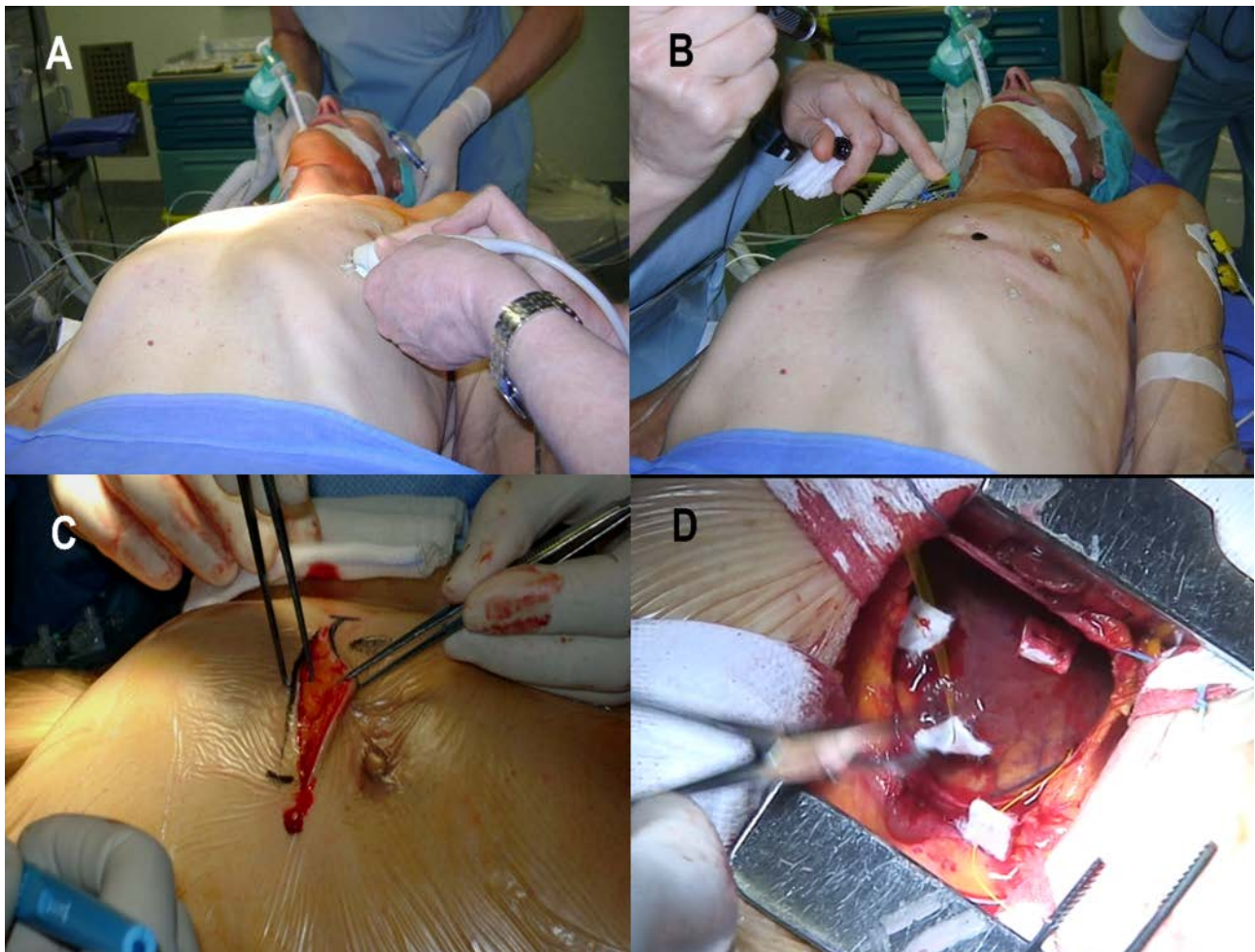


Figure 5.5.2.1. Transapical access.

A. The apex of the left ventricle is identified by using TTE. B. Its projection is marked on the skin. C. A 3 to 4 cm skin incision is performed below the left nipple and the chest is entered through the fifth or sixth intercostal space. D. A soft tissue retractor (Edwards, Cardiovation) can help with exposure and minimize rib spreading. After opening the pericardium, purse-string sutures are placed with sufficiently deep bites in a relatively fat-free myocardium around the apex.

There are two different techniques for placing the sutures: either two perpendicular sutures armed with big Teflon felts or two concentric purse-string sutures armed with Teflon after each insertion into the myocardium (Figure 5.5.2.1.D).

Care should be taken to ensure that adequate bites are taken of the muscle and not just the epicardial fat. These sutures should be placed by an experienced surgeon, because any technical failure may lead to severe bleeding problems or even death of the patient after an otherwise uneventful valve implantation. (136)

Rapid pacing at 160 to 200 bpm is needed for valve positioning and for closure of the apex, and it has to be kept in mind that cardiac output might be compromised during sheath introduction. (116) Bipolar pacemaker wires may be sewn to the epicardial surface - since the right ventricular myocardium may be extremely soft and fragile, especially in very old, female patients a placement on the left ventricular pericardium is recommended - or may be introduced from a percutaneous femoral access and positioned into the right ventricle for rapid pacing.

After heparin administration, the apex is punctured through the purse-string under fluoroscopic control. A .035-inch guidewire is advanced antegradely across the stenotic aortic valve in the ascending aorta followed by the introducer sheath. The tip of the sheath must be placed in the left ventricle outflow tract, at the right distance from the aortic valve.

(Figure 5.5.2.2.)

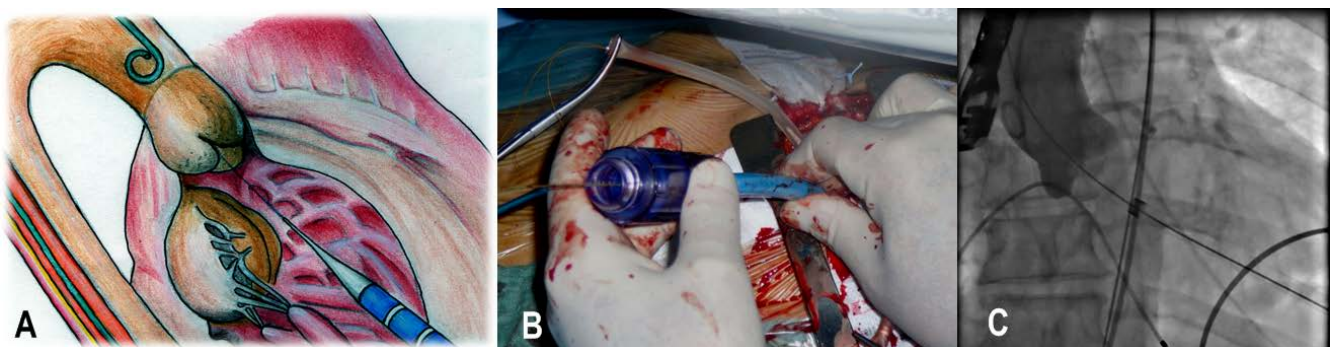


Figure 5.5.2.2. Transapical sheath insertion.

A. The tip of the Ascendra introducer sheath is positioned in the left ventricle outflow tract below the aortic valve. B. The sheath must be hold tightly and firmly. C. Angiographic control.

The valvuloplasty of the aortic valve is performed under rapid pacing by using a 20-mm Edwards SAPIEN balloon supplied with the prosthesis. (Figure 5.5.2.3.)

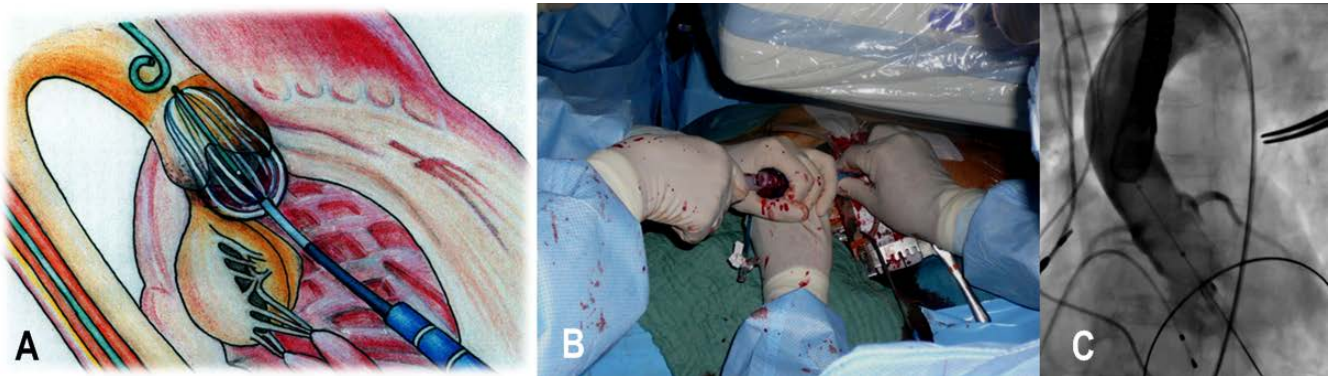


Figure 5.5.2.3. Transapical balloon aortic valvuloplasty.

A. Aortic valvuloplasty using a 20-mm Edwards SAPIEN balloon. B. The balloon catheter is introduced through the sheath. C. During BAV, a selective supra-aortic angiogram may be performed in order to size the annulus and to evaluate the effect of the leaflets pushed against the aortic wall and the coronary ostia.

After advancing the transapical delivery system through the sheath and toward the ascending aorta, correct intra-annular THV position is confirmed by aortography. After that, the valve is deployed by controlled insufflation of the balloon, again under rapid pacing. (Figure 5.5.2.4.)

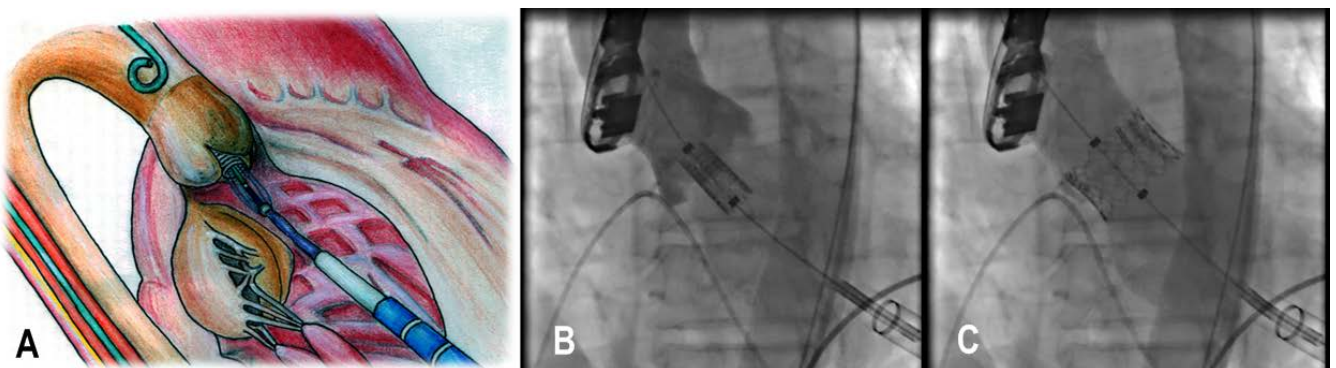


Figure 5.5.2.4. Transapical aortic valve implantation.

A. Correct intra-annular position of the deflated THV. B. Just before inflating, contrast medium is injected into the aortic root in order to check and correct the position, if necessary. C. Angiographic control of the deployed THV.

Once all bleeding has been controlled and a long-acting local anesthetic has been injected in the intercostals spaces, the chest wall and incision are closed in a routine fashion.

Depending on local practice, the patient can be immediately extubated in the operating room or shortly thereafter upon transfer to the intensive care or coronary care unit in the majority of cases.

Some of the notable disadvantages of the transapical approach include pain from the thoracotomy site: since a thoracotomy is required, the transapical approach results in increased post-operative pain contributing to post-operative respiratory compromise. (110)

Bleeding and tamponade, myocardial injury, ventricular aneurysm formation, and damage to the mitral valve are rare but possible risks that must be considered. (122) Barbash et al. (137) assessed the degree of apical ventricular dysfunction after transapical TAVI and concluded that 30% of patients showed apical dysfunction that was associated with a nonsignificant trend toward a reduced ejection fraction. The dysfunction was transient in 50% of cases and did not affect mortality. To ease the procedure, a number of apical access and closure devices have been developed, some of which are currently undergoing clinical evaluation. (67)

It appears consistently among all published series that there is a learning curve period to achieve good outcomes in TA-TAVI. (67,122,138,139) Survival among TA patients is consistent across reported series and similar to those in PARTNER 1A, ranging 65–68% at 2 years. (25,138)

A progressive decline in survival of 58% at 3 years and 41% at 4 years among these high-risk patients should prompt us to carefully select candidates for TA-TAVI, given these survival figures are not dissimilar to those with end-staged renal failure on dialysis. (25,67,74)

When reviewing data on the comparison of TA-TAVI and TF-TAVI routes, it must be noted that most centres have a 'femoral-first' approach. Subsequently, the patient subgroups undergoing TA-TAVI and TF-TAVI usually show significant differences with regard to their baseline characteristics. As an example, in PARTNER A, patients having TA-TAVI had significantly more coronary artery disease, cerebrovascular disease, peripheral artery disease, and porcelain aortas. (138)

Most studies comparing the transfemoral and transapical approach did not show a significant difference regarding mortality. (67,125,139,140) Bleiziffer et al. (125) reported their experience with 203 patients undergoing TAVI and did not show a significant influence of the choice of access route on survival. The procedure was faster using the femoral access route, but longer fluoroscopy and larger volume of contrast agent were required. There was no significant difference concerning intra-procedural hemodynamic status, post-operative renal insufficiency, or improvement of functional status. Although the type of access site complications were different (eg, vessel rupture or haematoma for femoral access, bleeding or tamponade for transapical access), they occurred with a similar frequency, and were fatal in a similar percentage of patients. A significant difference was shown concerning the incidence of periprocedural stroke, which occurred in 5% of transfemoral cases and none of the transapical patients.

A propensity-matched or randomized study will make comparisons between the 2 approaches more clinically relevant, but expert consensus agrees that the patient's anatomy and associated comorbidities should be considered when determining access, and that the approach most comfortable to the heart team, with the goal of minimizing complications, should be performed.

5.6. Transaortic approach

5.6.1. Patient Selection

A more recent approach that has gained interest and acceptance is the direct aortic (or transaortic) approach. Despite transsubclavian approach is promising, yet itself has inherent problems. The subclavian artery can be less compliant and more friable, especially in the elderly. (129,141) It is also prey to the same concerns regarding calibre and calcification as the TF approach, whereas TAO is feasible in all but the true porcelain aorta. Vascular complications, including dissection and problematic haemostasis with associated increase in blood transfusion, can be difficult to deal with due subclavian vessel's topographic anatomy. (141,142)

Besides TA, also TAO approach offers the most direct access to the aortic valve and enhanced surgeon comfort level with a technique they are already using routinely for CPB cannulation as compared to the left ventricular apex approach and to subclavian access. In addition, the TAO approach (i) allows a less painful incision than with a left anterior thoracotomy at a lower interspace: indeed, the new approach may be most beneficial with regards to post-operative recovery in those patients with reduced respiratory reserve secondary to underlying lung pathology; (ii) avoids injury to the myocardium and apex, preserving function in patients with low LVEF; (iii) has much less movement on the aorta than TA on the apex, and makes sheath placement easier and safer; (iv) is compatible with both Edwards SAPIEN and CoreValve prostheses; (v) direct visualization of the aorta permits rapid cannulation and initiation of CPB for support. However, the difficulty of crossing the valve in a retrograde direction persists and significant ascending aortic calcification may be a contraindication. (65,67,134,143-152)

After the development of the TAO-TAVI technique, the criteria for consideration were expanded from unsuitability for a lateral thoracotomy (chest wall deformity/abnormality) to poor respiratory function (FEV1/FVC ratio of <70% and FEV1<60% of predicted or FEV1 < 1 L), poor LV function, i.e. <20% (to avoid left ventricle puncture and repair) and multiple redo surgery. (65)

A noncontrast MDCT allows us to evaluate suitability of the ascending aorta for cannulation. It is operators' experience that even in a porcelain aorta the portion of the ascending aorta intended to be cannulated is usually free from calcification. (65) Then, the site of the purse-string is chosen with the help of an on-table aortogram (**Figure 5.6.1.1**).

Choosing the correct aortic puncture site is paramount for success. To achieve this, preoperative MDCT, on-table aortography and digital palpation are often combined.

Depending on the type of valve, a specific distance between the aortic valve and the insertion point in the ascending aorta is required. Usually this spot is on the greater curvature of the ascending aorta, 1–2 cm below the origin of the innominate artery (TAo zone). (65)

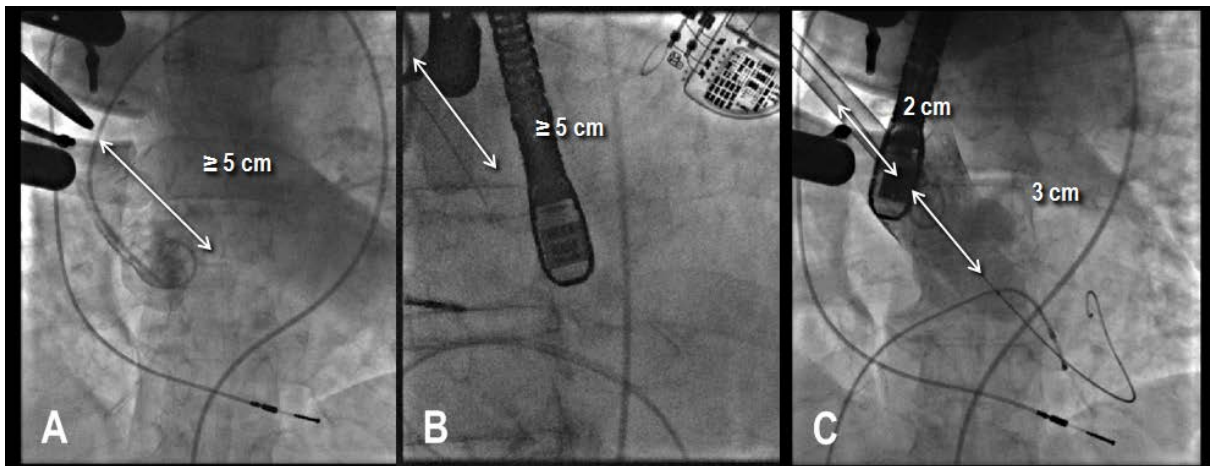


Figure 5.6.1.1. The transaortic zone.

On-table supra-aortic angiogram with a metal marker (A) identifies the spot for cannulation, which should be free of calcification, allow the sheath to be directed in a straight line to the aortic valve, and at least 5 cm from the aortic annulus (A and B), to provide enough space between the tip of the sheath and the prosthesis during deployment (C).

Lying of a LIMA graft in relation to the midline and position of the proximal anastomoses of the other grafts on to the ascending aorta should be checked by a preoperative angiography and MDCT. As the proximal anastomoses are usually performed on to the proximal 2/3rd of the ascending aorta, they are away from the cannulation site, which is in the distal 1/3rd. Moreover, LIMA is usually on the left side of the midline, hence it is protected during a right J-sternotomy.

5.6.2. Procedure

All cases are performed with the patient under general anesthesia in the hybrid operating room or cardiac catheterization laboratory under direct fluoroscopy and/or 3D TOE.

The access is through either an upper partial median sternotomy or a second or third intercostal space right minithoracotomy. (66)

A ministernotomy is preferred in obese patients, patients with an ascending aorta in the mid-line/to the left or a short ascending aorta, and in patients with poor respiratory reserve because the pleura remains intact, and it has less effect on the respiratory dynamics. This approach can also be used in patients with previous coronary artery by-pass grafting (CABG) and a patent LIMA graft provided that the LIMA graft is not in the mid-line and the innominate vein and aorta are not in close proximity to the sternum.

If the ascending aorta is horizontal and/or shifted to the right side in relation to the sternum, a mini-right thoracotomy approach through the second right intercostal space is preferred. It should also be considered in cases of previous CABG in which the LIMA graft is in the mid-line and/or the innominate vein or aorta is stuck to the sternum.

The skin incision is usually 5 cm, starting lateral to the sternal margin. The intercostal muscles are divided. The pleura is opened, and the pericardium is incised over the lateral portion of the ascending aorta. The site of the purse-string suture is chosen as through the ministernotomy approach, and the procedure is carried out in a similar manner.

Two, concentric purse-string sutures are placed at the selected spot in the ascending aorta with 2/0 or 3/0 prolene; one or both could be pledgeted.

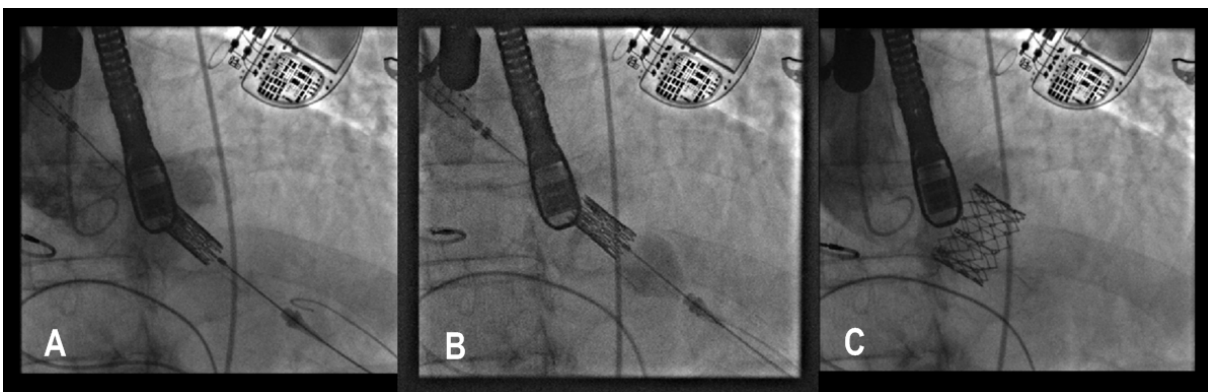


Figure 5.6.2.1. Transaortic transcatheter valve implantation.

A. Deflated Edwards SAPIEN XT prosthesis placed retrogradely in the correct position across the aortic valve. B. Slow inflation. C. Final aortogram showing the prosthesis successfully deployed in the anatomical site.

Balloon aortic valvuloplasty and valve deployment are then performed as for the other access techniques (**Figure 5.6.2.1.**) but with the valve crimped in the opposite orientation upon the delivery system.

Rapid ventricular pacing is required for balloon-expandable devices implantation but not for self-expandable systems.

The direct approach has been successfully employed and described by several groups using both the CoreValve and the SAPIEN valve. (65,134,147) Since cardiac surgeons are used to handling the ascending aorta for cannulation and access, they usually feel very comfortable with this approach.

As of June 2012, over 250 TAO cases have been performed in Europe, with 60-day follow-up available among 158 patients across 10 centers. Twenty-one patients (13.3%) had prior CABG and 19 (12.0%) had LVEF <30%. Hemi-sternotomy was performed in 138 and 14 had right mini-thoracotomy, but it is unclear if both SAPIEN valve and CoreValves are included. All-cause mortality was 7%, with no strokes and access site complications. (67) Laborde (134) reported over 100 TAO cases have been performed with the CoreValve across >10 centers. Based on the above studies, the TAO approach offers distinct advantages in patients with specific high-risk comorbidities, such as COPD and low LVEF, with noninferior outcomes compared to TA-TAVI. Compared with the transfemoral access route, valve positioning is easier due to the shorter distance, and myocardial injury is avoided. (122). Nevertheless, TAO-TAVI requires an invasive surgical procedure and, given the higher risk profile of TAO patients, it remains to be seen whether the this approach can maintain similar favorable outcomes as TF-TAVI. (86)

An increased risk of stroke has been discussed but has not been confirmed yet. (147)

5.7. Transcarotid approach

5.7.1. Patient Selection

The transcarotid approach should be considered when all other routes have been excluded and sometimes as a means of avoiding conventional transapical or transaortic access in patients with previous cardiac surgery or suffering from respiratory dysfunction. (107)

In addition, the presence of a pacemaker in the left subclavian area or CABG with a patent LIMA graft (2 situations at higher risk for left subclavian access because of potential infective endocarditis or myocardial infarction), could be valid indications for a transcarotid artery valve implantation.

In operators' experience, THV transcarotid positioning and release has been reported to be easier than transfemoral and as easy as subclavian approach, offering greater movement precision. The short distance between the carotid artery and the aortic annulus as well as the direct trajectory might explain a sense of increased control of the delivery catheter and guide wire. (109)

The proximal segment of the common carotid artery is of good size and usually only moderately diseased, even in the older population groups.

The vessels could be approached through a small incision on the base of the neck, especially in patients with pacemakers implanted in the infraclavicular area, in order to avoid the risk of infective endocarditis. (108)

Transcarotid access technique should not be performed when the circle of Willis is not complete, in order to prevent potential strokes. (108)

A MDCT angiographic scan is used to assess diameter and patency of subclavian, carotid, and vertebral arteries. Short segments of calcified or focal stenosis are not considered an exclusion criterion.

A carotid arterial diameter of 7.5 mm or greater is carefully considered and suggested to be adequate for implantation.

The left carotid artery is preferred because it offers a more direct approach in the axis of the aortic valve and also due to the catheterization room configuration.

All patients should undergo a cerebral magnetic resonance imaging to assess the patency of the Willis circle and therefore a good collateral flow in the cerebral circulation. Transcranial echo Doppler is obtained for an optimal study of cerebral perfusion. (109)

5.7.2. Procedure

A femoral access is used to insert a pigtail catheter for control angiograms during valve implantation as well as a vein access to insert a temporary pacemaker lead for rapid pacing during valvuloplasty.

A high systemic blood pressure is maintained and cerebral oxymetry monitoring is used throughout the procedure to monitor cerebral perfusion. (109)

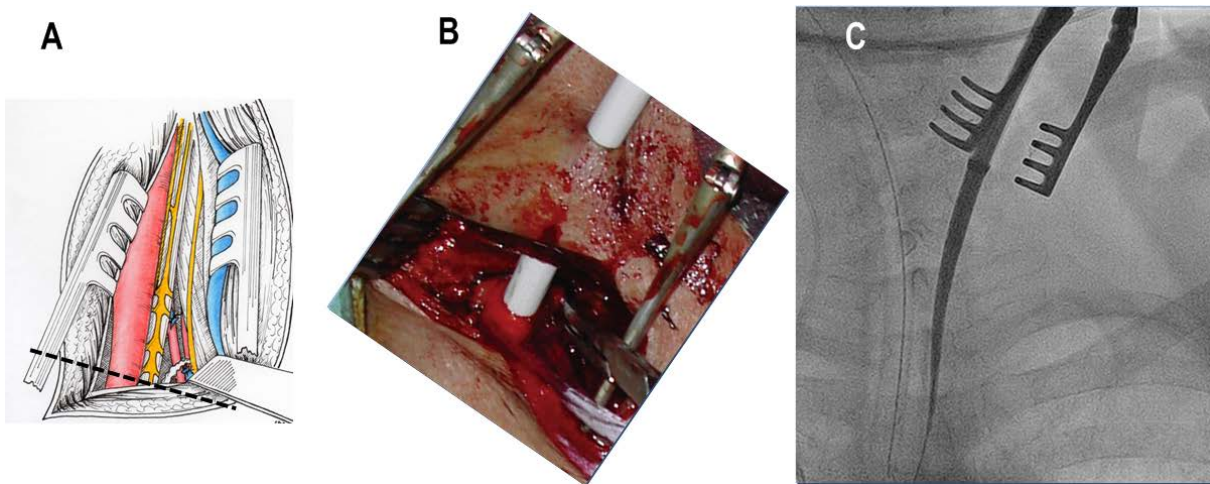


Figure 5.7.2.1. Transcarotid approach for transcatheter aortic valve implantation.

A. The proximal common carotid artery is exposed in a routine fashion through a small incision 2 cm above the left clavicle. B. Progressive artery dilatation using dilators with increasing diameters (14, 16, and 18 F) is performed. C. Under fluoroscopic guidance, the 18-F sheath is then carefully inserted, whose tip is positioned in the upper part of the ascending aorta.

After exposing the proximal common carotid artery through a small incision 2 cm above the left clavicle (**Figure 5.7.2.1.A**), it is accessed with an 18-gauge needle and a soft-angled guidewire is advanced into the ascending aorta and a short 6-F sheath introduced using a percutaneous technique.

The native valve is crossed using a conventional technique that includes an Amplatz catheter and straight wire exchanged to a manually preshaped .035-inch stiff Amplatz wire in the ventricular cavity. To reduce theoretical cerebral hypoperfusion duration, a 12-F sheath is inserted initially to achieve the balloon aortic valvuloplasty. BAV is performed under rapid pacing.

Progressive artery dilatation using dilators with increasing diameters (14, 16, and 18 F) is performed. (Figure 5.7.2.1.B) Under fluoroscopic guidance, the 18-F sheath is then carefully inserted (Figure 5.7.2.1.C), whose tip is positioned in the upper part of the ascending aorta. (109)

Balloon aortic valvuloplasty and valve deployment are then performed as for the other access techniques but with the valve crimped in the opposite orientation upon the delivery system.

There are few case reports showing the feasibility of this approach, but a concomitant carotid-subclavian bypass, either temporary (shunt) or permanent (Dacron graft), needs to be performed to lower the risk of cerebrovascular ischemia.

(153) The decision to use this method requires a truly dedicated TAVI team approach, establishing a unique access for TAVI patients without regular access options.

In centers where a heart team approach of TAVI is effective, using surgical access of the left carotid artery under certain conditions (mainly the lack of available alternative arterial and transapical routes), could be life-saving. (109)

Confirmation of the efficacy and safety of this technique will, of course, require a larger population.

Reported complications arisen with this technique include retrograde type A dissection from using a long sheath instead of a short sheath. The retrograde dissection required no surgical intervention, as the metallic struts of the outflow tract of the THV apposed the false and true lumen together so excluding any flow to the false lumen, resulting in complete healing and resolution of the dissection at follow-up. (107)

Chapter 6. MATERIAL AND METHODS

6.1. Aims of the study

The introduction of a new technology, like TAVI, requires cost-effective data. This requires assessments of both length of life and QoL, when the new technology is used in the real world.

As most of the TAVI teams are now getting patients who come to them with very little options and with end-stage disease processes like renal failure and severe COPD, it would be useful to allocate such resources to patients who have a fighting chance for survival.

Main objectives of this study are: *(i)* to evaluate the specific contribution made by the pulmonary disease to the clinical outcomes and QoL, in patients undergoing TAVI; *(ii)* to evaluate the effects of access route on clinical results and QoL in patients with COPD undergoing TAVI via different access routes (transfemoral, transapical and transaortic) using the Edwards SAPIEN or SAPIEN XT bioprostheses (Edwards Lifesciences Inc., CA, USA).

6.2. Methods

A prospective analysis was performed upon data from 285 consecutive patients receiving TF-TAVI, TA-TAVI or TAO-TAVI for severe symptomatic AS at two European Centres (St. Thomas' Hospital, London, and Cardiologico Monzino Centre, Milan) between January 2008 and October 2011. Data was taken from patients enrolled in the Edwards SAPIEN Aortic Bioprosthesis European Outcome Registry (SOURCE) (Milan) and Edwards SAPIEN XT Aortic Bioprosthesis European Outcome Registry (SOURCE XT) (Milan and London).

Across the two Centers there were no transsubclavian implants, being such approach 'off label' for Edwards SAPIEN prosthesis at the time of data collection and therefore not included in the registries. Severe AS was defined as an aortic valve area of $<1 \text{ cm}^2$ or a mean transvalvular gradient of at least 40mmHg or a peak velocity of $>4.0 \text{ m/s}$, on transthoracic echocardiography, stress or transesophageal echocardiography. (7)

All patients underwent assessment as previously described (65). Each case was considered by a multidisciplinary team comprising interventional cardiologists, imaging-specialist cardiologists and cardiovascular surgeons. Patients were accepted for TAVI when it was agreed that conventional surgery was of excessive risk according to the EuroSCORE (68) or patients suffered from specific conditions likely to contribute to excessive perioperative risk that were not reflected in EuroSCORE: surgical technical concerns, morbid obesity, porcelain aorta and other co-morbidities (79).

A patient was indicated as affected by chronic pulmonary disease if on chronic inhaled or oral bronchodilator therapy *and/or* chronic steroid therapy aimed at lung disease according to the EuroSCORE definition.

Patients unsuitable for TF-TAVI due to peripheral vascular disease and without thoracic anatomical or technical considerations were accepted for TA-TAVI. After the development of the TAO-TAVI technique, the criteria for consideration were expanded from unsuitability for a lateral thoracotomy to poor respiratory function (FEV1/FVC ratio of $<70\%$ and FEV1 $<60\%$ of predicted or FEV1 $< 1 \text{ L}$) and poor LV function i.e. $<20\%$ (to avoid LV puncture and repair). (65)

All patients received Edwards-SAPIEN or SAPIEN XT balloon-expandable prostheses as previously described (4,22,154).

QoL was assessed using the self-reported European Quality of Life-5 Dimensions (EQ-5D) questionnaire, a health-related quality of life measure, consisting of five three-level items, representing various aspects of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression (155). Respondents can score each domain from 1 (no problems) to 3 (extreme problems). A visual analogue scale (EQ-5DVAS) is also included in the EQ-5D and for subjects to rate their health status between the worst imaginable health state (score 0) to the best imaginable health state (score 100) (Figure 6.2.1.). An utility index (EQ-5Dindex) score was calculated for each by applying the time trade-off-based valuations from a general UK population sample to the observed EQ-5D profile, as data from an Italian norm are not available at the present time (155,156).

Patients were confirmed and stratified with regard to lung disease severity on the basis of pulmonary function test results and data on oxygen-dependency. The severity of airway obstruction was categorized according to GOLD guidelines (48,157). Thus, among patients with an FEV1/FVC ratio <0.7 , those with an FEV1 $\geq 80\%$ predicted were categorized as stage I (mild) obstruction, ones with FEV1 between 50% and 79% of predicted were categorized as stage II (moderate) obstruction, those with FEV1 between 30% and 49% of predicted were categorized as stage III (severe) obstruction, and patients with FEV1 $<30\%$ of predicted were categorized as stage IV (very severe) obstruction. (158)

In order to assess the effect of COPD on outcomes following TAVI, patients without COPD were compared to those with COPD.

All COPD patients were further stratified by disease clinical severity. Of the 71 patients affected by obstructive lung disease, a total of 58 patients with moderate-severe COPD were identified and analyzed. Comparison with the nonCOPD control group was repeated in these patients to call for consistency and credibility of our results among other studies.

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Best imaginable health state
100
90
80
70
60
50
40
30
20
10
0
Worst imaginable health state

Mobility
I have no problems in walking about 1
I have some problems in walking about 2
I am confined to bed 3

Self-Care
I have no problems with self-care 1
I have some problems washing or dressing myself 2
I am unable to wash or dress myself 3

Usual activities (e.g. work, study, housework, family or leisure activities)
I have no problems with performing my usual activities 1
I have some problems with performing my usual activities 2
I am unable to perform my usual activities 3

Pain/discomfort
I have no pain or discomfort 1
I have moderate pain or discomfort 2
I have extreme pain or discomfort 3

Anxiety/depression
I am not anxious or depressed 1
I am moderately anxious or depressed 2
I am extremely anxious or depressed 3

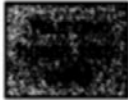


Figure 6.2.1. EQ-5D self-classifier and visual analogue scale.

Respondents can score each domain from 1 (no problems) to 3 (extreme problems). A visual analogue scale is included in the EQ-5D to enable the respondent to provide a self-rating of their own health status between the worst imaginable (score 0) to the best imaginable health state (score 100). Reproduced from: Rabin R, Oemar M, Oppe M. On behalf of the EuroQol Group. EQ-5D-5L User Guide. Basic information on how to use the EQ-5D-5L instrument. Version 4.0. www.euroqol.org, by permission of EuroQol Group Foundation.

An appropriately trained researcher administered the EQ-5D questionnaire according to the EuroQol Group guidelines (155) the day before operation. Follow-up questionnaires were administered during scheduled follow-up visits, by mail or by telephone interview. Validated translations of the original questionnaires – obtained exclusively from the EuroQol Executive Office - were provided to non-English speakers.

The study complied with the Declaration of Helsinki and was approved by the relevant local Research Ethics Committees.

Study End Points

The primary end points were health-related QoL data at baseline, 30 days and 1 year using the EQ-5D descriptive system, further dichotomised into 'no problems' (i.e. level 1) and 'problems' (i.e. levels 2 and 3), as well the 'global' EQ-5Dindex and analogue EQ-5DVAS score. Secondary end points were defined on the basis of Valve Academic Research Consortium (VARC) criteria (116). Death dates were collected May 31st, 2013; patients alive on that date were considered censored for survival analysis purposes. Time to death was calculated for each patient.

Statistical analysis

Patients were organized into mutually exclusive groups according to pulmonary dysfunction (nonCOPD and COPD) and according to airflow limitation severity in COPD patients (mild and moderate to severe COPD).

Categorical variables are summarized as frequencies and percentages. Continuous variables were assessed for normality using the Shapiro–Wilks test and are presented as median and interquartile range (IQR). Comparison of categorical variables (such the incidence of 'problems' in each EQ-5D dimension) was performed by χ^2 test or Fisher's exact test. Continuous variables were analyzed by the student's independent T-test or two-tailed Mann-Whitney U test (e.g., the magnitude of improvement, 'delta', for the EQ-5Dindex and analogue EQ-5DVAS score). Continuous variables among more than two groups were analyzed by the Kruskal-Wallis test.

Intra-individual comparisons of continuous variables before and after transcatheter procedures were performed by the Wilcoxon signed-matched pair test.

Time-related categorical variables were analyzed by the Kaplan–Meier method and compared using the log-rank method. The time course of continuous variables (e.g. 30-day and 1-year EQ-5Dindex and EQ-5DVAS) was compared by repeated-measures analysis of covariance (ANCOVA), adjusting for baseline values of the same variables. Missing data from dead people and unattended follow-up interviews were treated as missing data test-by-test.

To determine the effect of COPD and route of access on postoperative outcomes and long-term survival, several regression models were constructed under various confounding adjustments. Univariate and stepwise multiple analyses

of predictors of QoL restoration were performed with logistic regression. All variables demonstrating a significant relationship with outcome in univariate regression were entered into the model. Then, using a backward selection with an inclusion criteria of $p \leq 0.05$, the weakest predictor variables were removed and the regression re-calculated. The procedure was repeated until only useful predictor variables remained in the model.

All tests were two-sided with a significance level of 0.05 and performed using IBM® SPSS® Statistics version 20.0 (IBM Corporation, Armonk, NY, U.S.A).

6.3. Results

6.3.1. NONCOPD VERSUS COPD PATIENTS

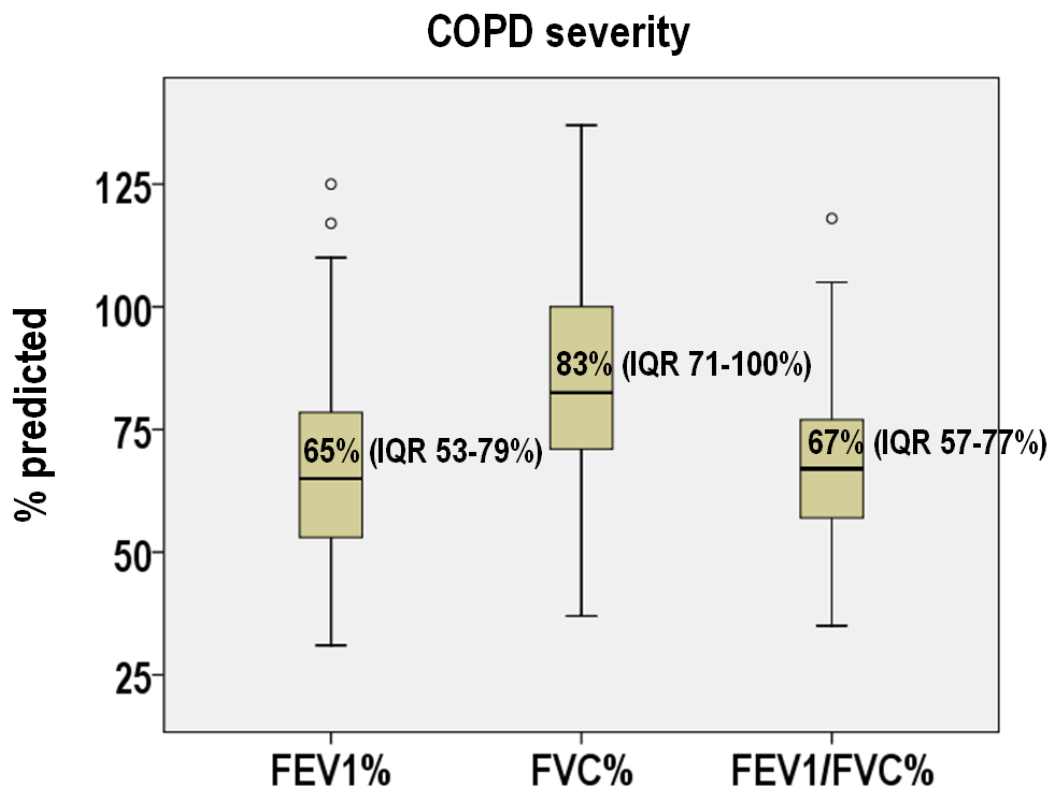
Baseline Demographics

Baseline characteristics of this study population, stratified by pulmonary disfunction, are shown in Table 6.3.1.1. All patients had severe symptomatic AS (median aortic valve area [AVA] 0.65 [IQR 0.51-0.76] cm²).

Of the 285 patients who underwent TAVI, 71 (25%) had a diagnosis of COPD (median FEV1/FVC 0.67 [IQR 0.57-0.77]), with a median FEV1 of 65% (IQR 53-79%) and requiring a median of 2 (IQR 1-3) respiratory inhaler medications.

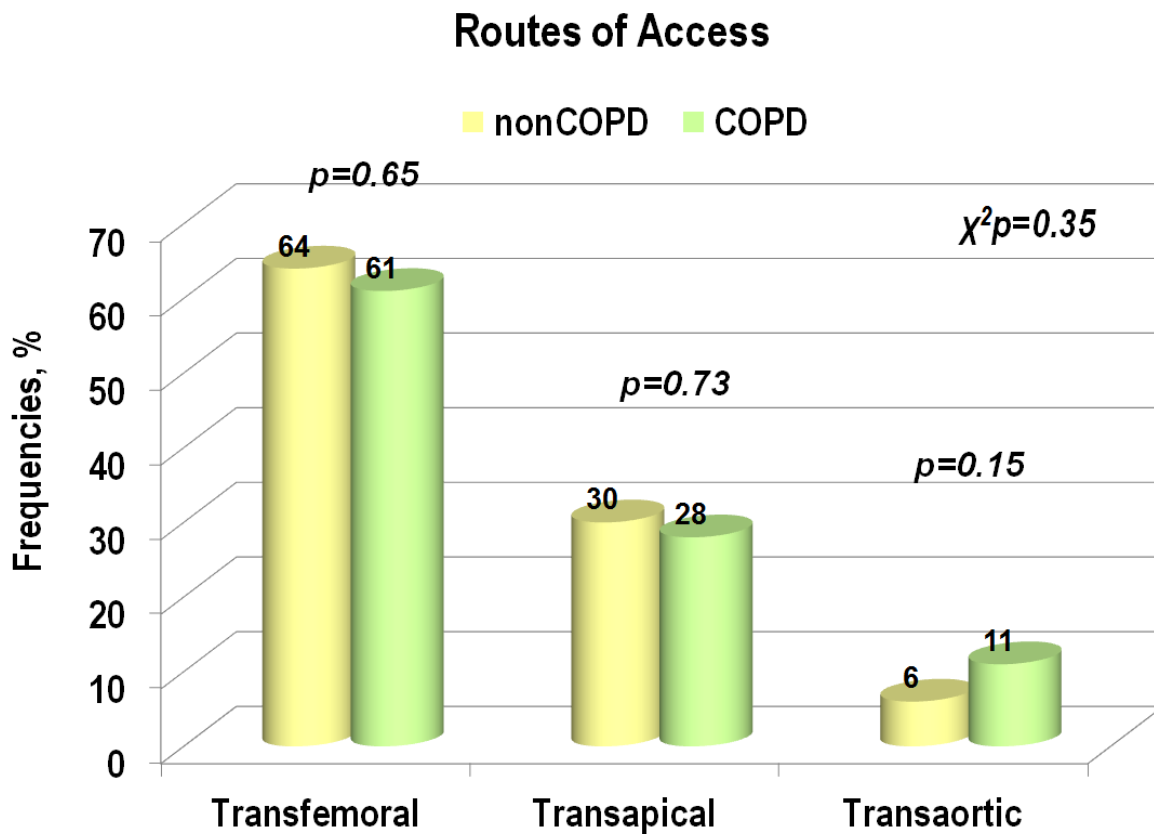
(Figure 6.3.1.1.)

Figure 6.3.1.1. Non v. COPD. Lung disease severity.



179 (68%) patients underwent TF-TAVI (136 [64%] nonCOPD v. 43 [61%] COPD patients, $p=0.65$), 85 (32%) patients underwent TA-TAVI (65 [30%] nonCOPD v. 20 [28%] COPD patients, $p=0.73$) and 21 (7%) underwent TAO-TAVI (13 [6%] nonCOPD v. 8 [11%] COPD patients, $p=0.15$). (Figure 6.3.1.2.)

Figure 6.3.1.2. Non vs. COPD. Access distribution.



Patient characteristics in the two cohorts were significantly different according to higher STS risk of mortality score in the COPD patients (6.4%[IQR 4.1-10%] v. 10.6%[IQR 6-16.5%], $p=0.01$) – even though no statistical significant difference was noted in logistic Euroscore - , greater incidence of patients in NYHA failure class \geq III (161 [75%] v. 64 [90%], $p=0.01$) and on atrial fibrillation heart rhythm (33 patients [15%] v. 23 patients [37%], $p<0.01$). (Table 6.3.1.1.)

There was no significant difference in severity of AS: mean transaortic valve gradient was 50mmHg (IQR 41-59mmHg) v. 49mmHg (IQR 37-58mmHg) ($p=0.40$) and AVA was 0.65 cm²(IQR 0.51-0.76 cm²) v. 0.66 cm²(IQR 0.51-0.75 cm²) ($p=0.67$). COPD patients had lower baseline left ventricular ejection fraction (LVEF) (58% [IQR 49-65%] v. 55% [IQR 42-62%], $p=0.04$).

Table 6.3.1.1. Demographics.

	All (n=285)	nonCOPD (n=214)	COPD (n=71)	<i>p value</i>
Age, years (IQR)	82 (77,86)	82 (77,86)	83 (77,86)	0.57
Female sex, n (%)	181 (64)	139 (65)	42 (59)	0.38
Body Mass Index (IQR)	24.7 (22.5,27.9)	25 (22.4,28.4)	24.3 (22.6,27.5)	0.61
Logistic EuroSCORE,% (IQR)	18 (13,27)	17 (12,25)	20 (13,28)	0.21
STS risk of mortality,% (IQR)	7.2 (4.3,11.5)	6.4 (4.1,10)	10.6 (6,16.5)	0.01
NYHA failure class≥III, n (%)	225 (79)	161 (75)	64 (90)	0.01
<i>Baseline NYHA</i>				0.02
NYHA I n (%)	0 (0)	0 (0)	0 (0)	1.00
NYHA II n (%)	60 (21)	53 (25)	7 (10)	0.01
NYHA III n (%)	159 (56)	116 (54)	43 (61)	0.35
NYHA IV n (%)	66 (23)	45 (21)	21 (30)	0.15
Frailty (79), n (%)	67 (24)	48 (22)	19 (27)	0.46
Recent cardiogenic shock, n (%)	17 (6)	12 (6)	5 (7)	0.77
Hypertension, n (%)	232 (81)	174 (81)	58 (82)	0.94
Dyslipidemia, n (%)	139 (49)	102 (48)	37 (53)	0.47
Diabetes mellitus, n (%)	62 (22)	48 (22)	14 (20)	0.67
Prior/current Smoking, n (%)	94 (33)	65 (30)	29 (41)	0.10
Coronary Artery Disease, n (%)	147 (52)	110 (51)	37 (52)	0.92
Chronic Obstructive Pulmonary Disease, n (%)	71 (25)			
Chronic renal dysfunction*, n (%)	35 (12)	28 (13)	7 (10)	0.47
Pulmonary Hypertension, n (%)	32 (11)	22 (10)	10 (15)	0.36

Peripheral artery obstructive disease, n (%)	104 (37)	84 (39)	20 (28)	0.93
Porcelain aorta, n (%)	12 (4)	8 (4)	4 (6)	0.5
Prior cardiac surgery, n (%)	64 (23)	50 (23)	14 (20)	0.52
Prior sAVR, n (%)	13 (5)	10 (5)	3 (4)	1.00
Prior CABG, n (%)	43 (15)	33 (15)	10 (14)	0.79
Prior PCI, n (%)	60 (21)	47 (22)	13 (18)	0.51
Other severe comorbidities, n (%)	107 (38)	79 (37)	28 (39)	0.7
Prior stroke, n (%)	20 (7)	13 (6)	7 (10)	0.28
Synus rhythm, n (%)	209 (73)	166 (78)	43 (61)	0.01
Atrial fibrillation, n (%)	59 (21)	33 (15)	23 (37)	<0.01
Pacemaker, n (%)	35 (12)	26 (12)	9 (13)	0.91
Mean transaortic valve gradient, mmHg (IQR)	49 (40,58)	50 (41,59)	49 (37,58)	0.40
AVA, cm ² (IQR)	0.65 (0.51,0.76)	0.65 (0.51,0.76)	0.66 (0.51,0.75)	0.67
LVEF, % (IQR)	57 (47,64)	58 (49,65)	55 (42,62)	0.04
LVEF%<30, n (%)	17 (6)	13 (6)	4 (6)	1.00
<i>Route of Access</i>				0.35
Transfemoral access, n (%)	179 (63)	136 (64)	43 (61)	0.65
Transapical access, n (%)	85 (30)	65 (30)	20 (28)	0.73
Transaortic access, n (%)	21 (7)	13 (6)	8 (11)	0.15

Categorical variables are defined on the basis of EuroSCORE definitions unless noted otherwise.

*Renal dysfunction was defined as serum creatinine exceeding 130 µmol/L.

STS, Society of Thoracic Surgeon. CABG, coronary artery by-pass graft. PCI, percutaneous coronary intervention. AVA, aortic valve area. LVEF, left ventricular ejection fraction.

Peri-procedural Outcomes

Early procedural results are summarized in **Table 6.3.1.2**. Procedural success was comparable between the two cohorts (99% [213 procedures] for the nonCOPD group v. 97% [69 procedures] for the COPD group, $p=0.15$).

There was a greater incidence of major vascular complications in the COPD patients (7 [10%] v. 8 [4%], $p=0.05$). No statistical difference was noted between the two groups in terms of complications like infection, re-oro-tracheal intubation or tracheostomy and pleural effusion or pneumothorax drainage. Post-procedural Intensive/Coronary Care Unit stay (1 day [IQR 1-2] for both nonCOPD and COPD cohorts) and overall in-patient stay (8 days [IQR 7-11] v. 8 days [IQR 6-12]) were comparable between the two cohorts ($p=0.88$ and $p=0.78$, respectively), as well.

Table 6.3.1.2. Peri-procedural Outcomes.

	All (n=285)	nonCOPD (n=214)	COPD (n=71)	<i>p value</i>
Procedural success, n (%)	282 (99)	213 (99)	69 (97)	0.15
Coronary obstruction, n (%)	6 (2)	5 (2)	1 (1)	1.00
Life-threatening or disabling bleeding, n (%)	19 (7)	16 (8)	3 (4)	0.42
Stroke, n (%)	6 (2)	6 (3)	0 (0)	0.34
Vascular complication (major), n (%)	15 (5)	8 (4)	7 (10)	0.05
Heart conduction block requiring PPM, n (%)	15 (5)	12 (6)	3 (4)	0.77
Acute kidney injury (stage 2 and 3), n (%)	40 (14)	31 (15)	9 (13)	0.69
Pleural effusion or PNx drainage, n (%)	34 (12)	26 (12)	8 (11)	0.84
re-OTI or tracheostomy, n (%)	4 (1)	2 (1)	2 (3)	0.26
Infection, n (%)	10 (4)	8 (4)	2 (3)	1.00
Intensive Care Unit stay, days (IQR)	1 (1,2)	1 (1,2)	1 (1,2)	0.88
Hospital stay*, days (IQR)	8 (7,11)	8 (7,11)	8 (6,12)	0.78
30-day AVA, cm ² (IQR)	2.08 (1.75,2.46)	2.10 (1.76,2.48)	2.03 (1.63,2.41)	0.30
30-day mean transvalvular gradient, mmHg (IQR)	10 (8,13)	10 (8,13)	10 (8,13)	0.41
30-day LVEF, % (IQR)	57 (51,64)	59 (52,65)	54 (47,60)	0.02
Δ 30-day LVEF, % (IQR)	1 (-4,7)	1 (-4,8)	0 (-4,5)	0.38
30-day mortality, n (%)	10 (4)	7 (3)	3 (4)	0.71§
1-year AVA, cm ² (IQR)	1.95 (1.60,2.30)	1.93 (1.54,2.25)	2.04 (1.73,2.49)	0.19
1-year mean transvalvular gradient, mmHg (IQR)	11 (9,14)	11 (9,14)	11 (8,14)	0.58
1-year LVEF, % (IQR)	60 (54,67)	61 (55,68)	57 (47,65)	0.07
Δ 1-year LVEF, % (IQR)	3 (-4,10)	3 (-4,11)	2 (-5,10)	0.85
1-year mortality, n (%)	46 (16)	30 (14)	16 (23)	0.09†

Noncardiovascular death, n (%)	46 (16)	32 (15)	46 (16)	0.34
	All	nonCOPD	COPD	p value
	(n=275)	(n=207)	(n=68)	
<i>NYHA failure class at 30 days</i>				0.40
NYHA I, n (%)	172 (63)	134 (65)	38 (56)	0.19
NYHA II, n (%)	88 (32)	64 (31)	24 (35)	0.50
NYHA III, n (%)	13 (5)	8 (4)	5 (7)	0.32
NYHA IV, n (%)	2 (1)	1 (1)	1 (2)	0.43
30-day NYHA improvement, n (%)	262 (95)	200 (97)	62 (91)	0.07
	All	nonCOPD	COPD	p value
	(n=237)	(n=183)	(n=54)	
<i>NYHA failure class at 1 year</i>				0.78
NYHA I, n (%)	145 (61)	113 (62)	32 (59)	0.74
NYHA II, n (%)	79 (33)	60 (33)	19 (35)	0.74
NYHA III, n (%)	11 (5)	9 (5)	2 (4)	1.00
NYHA IV, n (%)	2 (1)	1 (1)	1 (2)	0.41
1-year NYHA improvement, n (%)	220 (93)	169 (92)	51 (94)	0.60

*Days from procedure to discharge home.

§ Fisher's exact test

† Pearson χ^2 test

PPM = pacemaker; PNX = pneumothorax; OTI = oro-tracheal intubation.

Haemodynamic effects

Echocardiographic assessment revealed excellent haemodynamic function of the prostheses with significantly improved mean aortic gradient and effective orifice area at 30 days ($p < 0.01$ for both the cohorts), which remained stable at 1-year follow-up ($p < 0.01$ for both the cohorts). (Figure 6.3.1.3. Non v. COPD. Haemodynamics improvement. Wilcoxon.)

LVEF improved significantly after TAVI in the nonCOPD group ($p < 0.01$ at 1-month and at 1-year follow-up), but it did not in the COPD group ($p = 0.6$ at 1 month and $p = 0.06$ at 1 year). (Figure 6.3.1.3.) Despite that, the absolute LVEF improvement (Δ LVEF%) was comparable between the two cohorts at both 30-day and 1-year time points ($p = 0.38$ at 1-month and $p = 0.85$ at 1-year follow-up). (Table 6.3.1.2.)

Repeated measures ANCOVA showed comparable mean transvalvular gradient ($p = 0.41$ at 30 days and $p = 0.58$ at 1 year) and effective orifice area ($p = 0.30$ at 30 days and $p = 0.19$ at 1 year) between the two groups at 1-month and at 1-year follow-up; it showed a higher LVEF in the nonCOPD cohort at 1 month ($p = 0.02$), but the values were comparable at 1 year follow-up ($p = 0.07$). (Figure 6.3.1.4. Non v. COPD. Haemodynamics improvement. ANCOVA.)

Figure 6.3.1.3. Non v. COPD. Haemodynamics improvement. Wilcoxon.

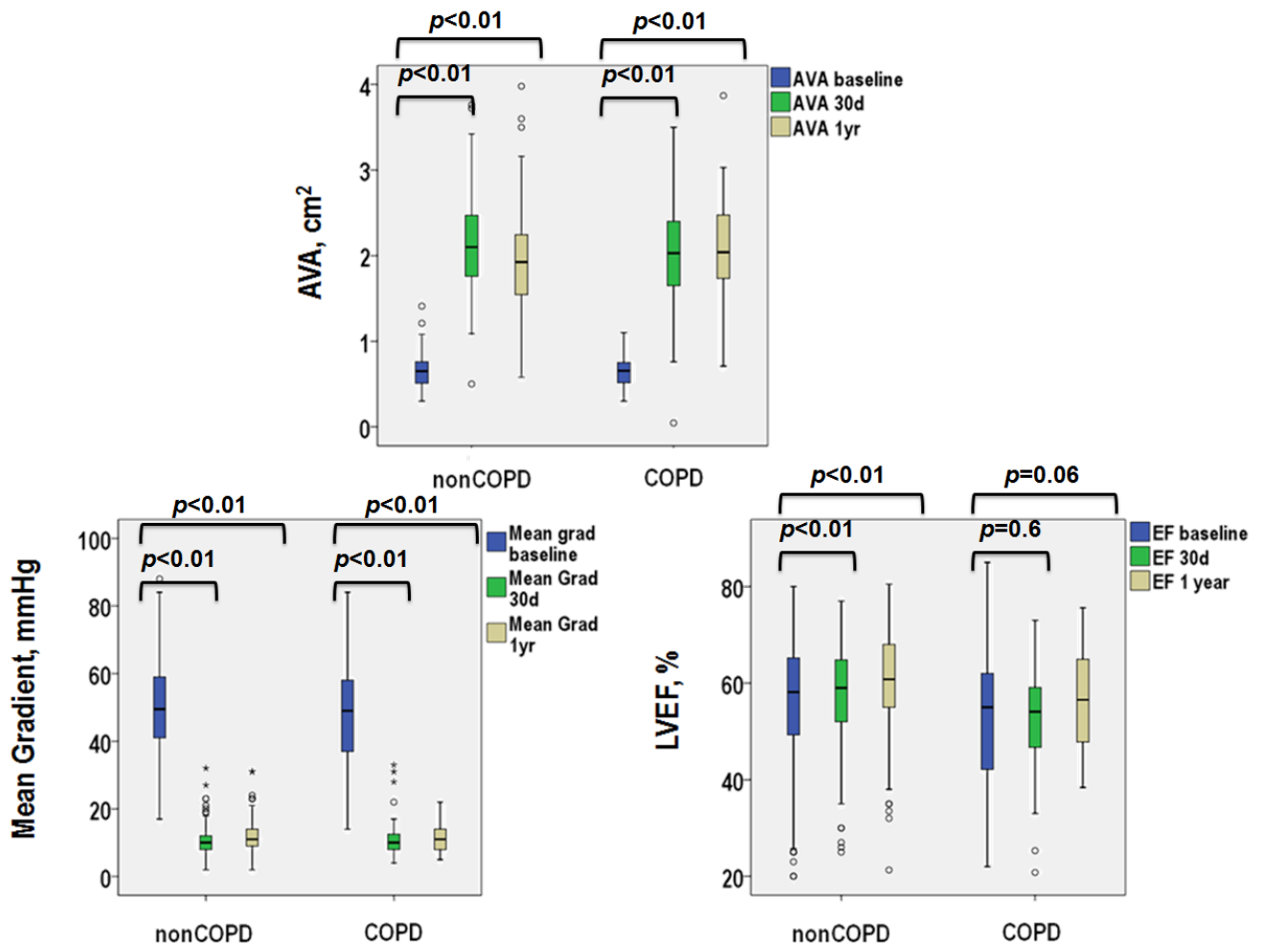
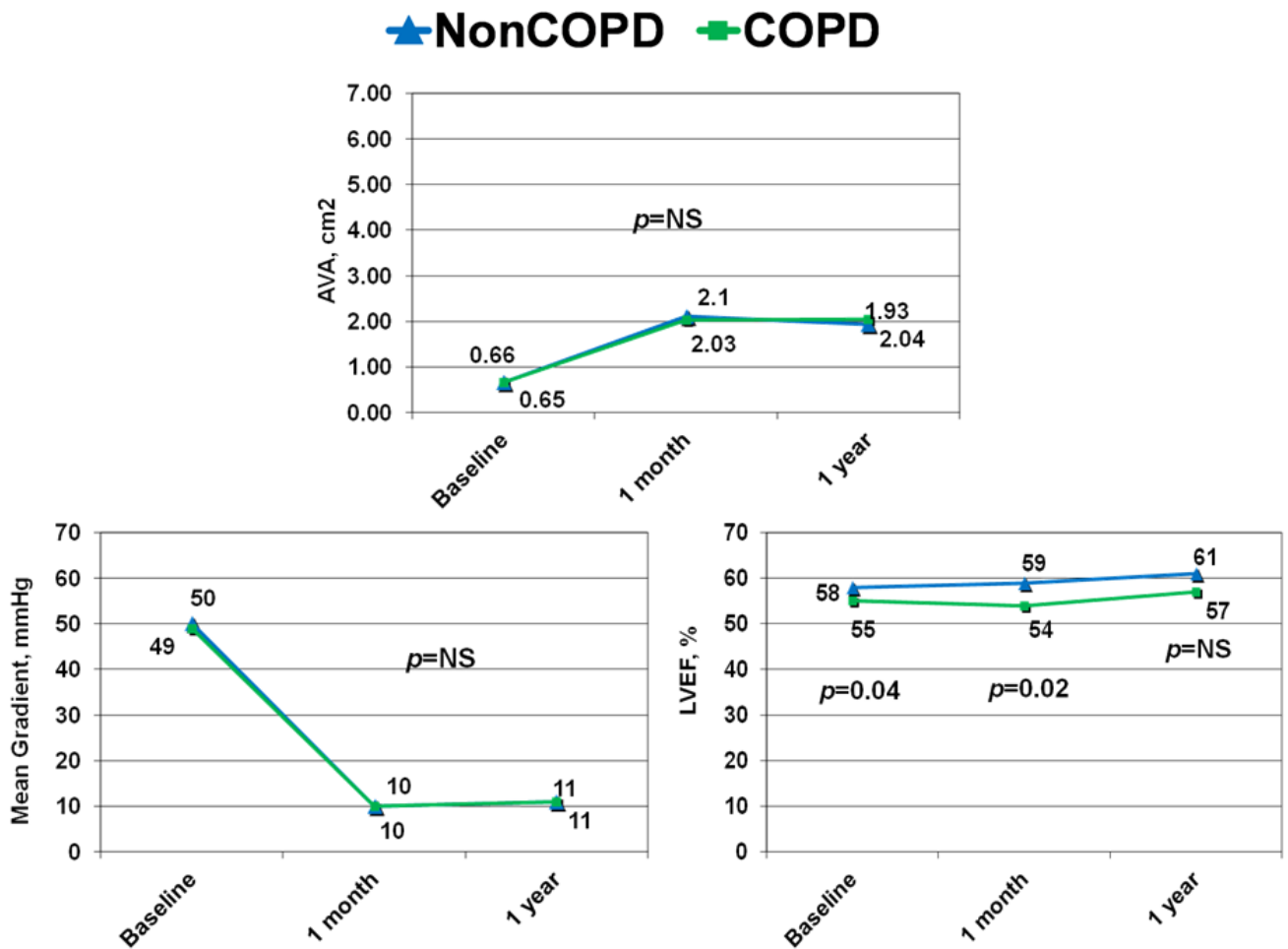


Figure 6.3.1.4. Non v. COPD. Haemodynamics improvement. ANCOVA.

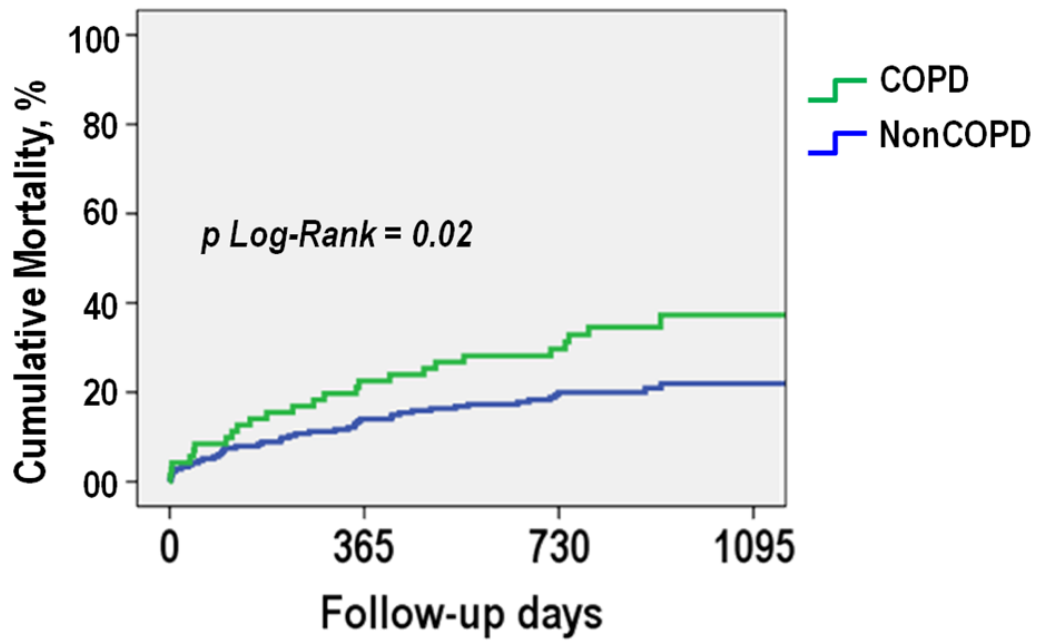


Mortality

The 30-day mortality rates were similar between groups (3% for the nonCOPD group v. 4% for the COPD group, $p=0.71$) (Table 6.3.1.2.). At 1 year, all-cause mortality was still not significantly different between the two cohorts (14% for the nonCOPD group v. 23% for the COPD group, $p=0.09$), but deeply divergent.

Median follow-up was 27 months (IQR 22-45 months) with no differences between groups (nonCOPD: 28 months [IQR 22-44 months] v. COPD: 27 months [IQR 16-45 months], $p=0.34$). Overall mortality at the median follow-up was higher in the COPD cohort (p Log-Rank 0.02, Kaplan-Meier curves for mortality from any cause are shown in Figure 6.3.1.5.).

Figure 6.3.1.5. Time-to-event curves for mortality from any cause.



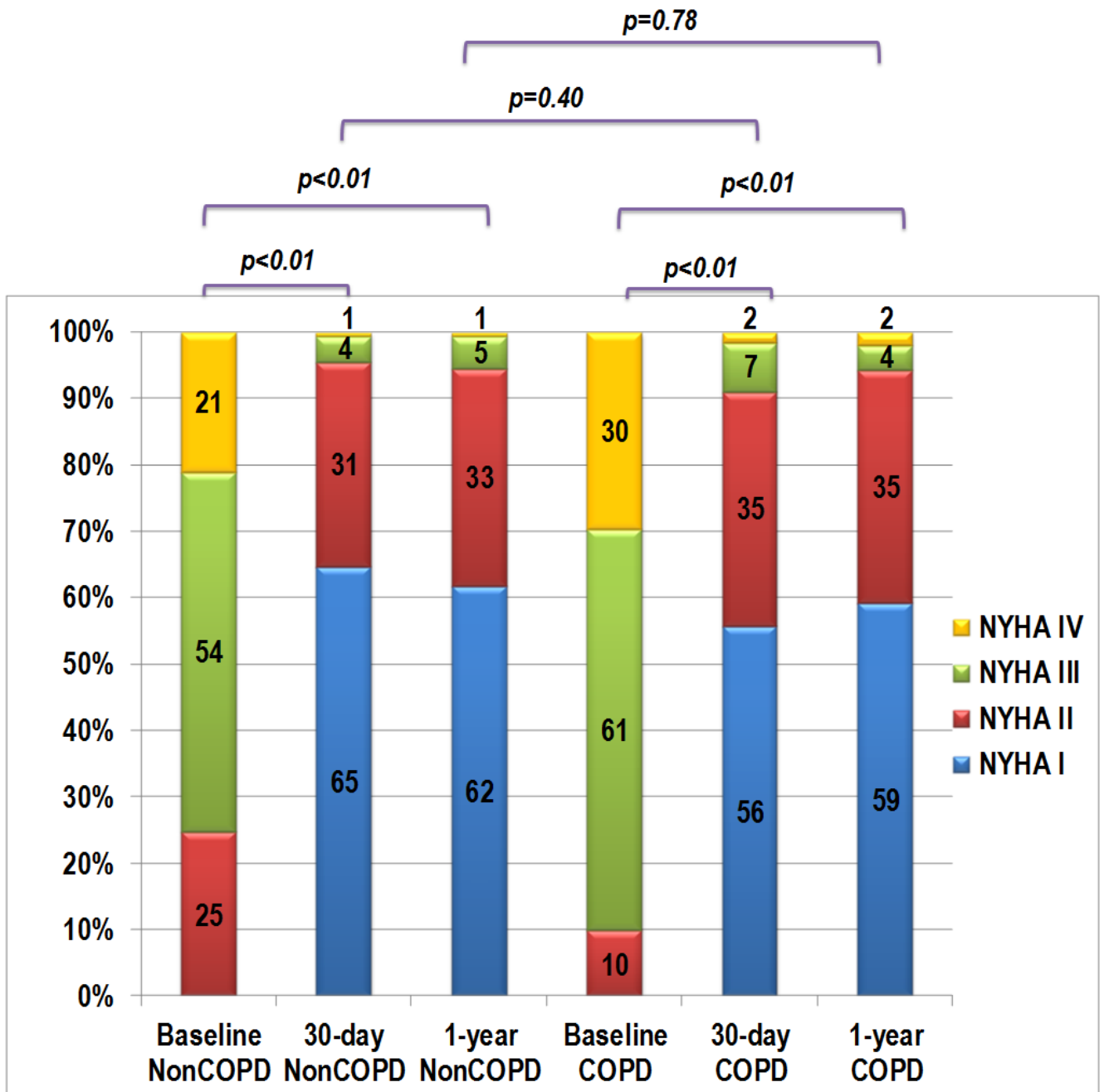
Patients at Risk

COPD	71	55	45	20
NonCOPD	214	184	143	61

NYHA functional class

Before receiving TAVI, 161 (75%) of nonCOPD patients and 64 (90%) of COPD patients were in New York Heart Association (NYHA) class III-IV. At 30 days, 198 (96%) of nonCOPD patients and 62 (92%) of COPD patients were in NYHA functional class I-II ($p=0.40$). At 1 year, NYHA class had improved by ≥ 1 class in both groups ($p<0.01$, for both) (Figure 6.3.1.6. Non vs. COPD. NYHA.). After adjustments for baseline values, NYHA absolute improvement during follow-up was comparable between nonCOPD and COPD patients at 30 days ($p=0.07$) and at 1 year ($p=0.60$) (Table 6.3.1.2, Figure 6.3.1.6. Non vs. COPD. NYHA.).

Figure 6.3.1.6. Non vs. COPD. NYHA.



Quality of Life

At baseline, COPD patients reported as many problems in mobility, self-care, usual activities, pain/discomfort and anxiety/depression as nonCOPD patients. Baseline EQ-5Dindex and EQ-5DVAS were comparable ($p= 0.99$ and $p=0.39$, respectively), too. (Table 6.3.1.3., Figure 6.3.1.7.)

Table 6.3.1.3. Baseline Quality of Life.

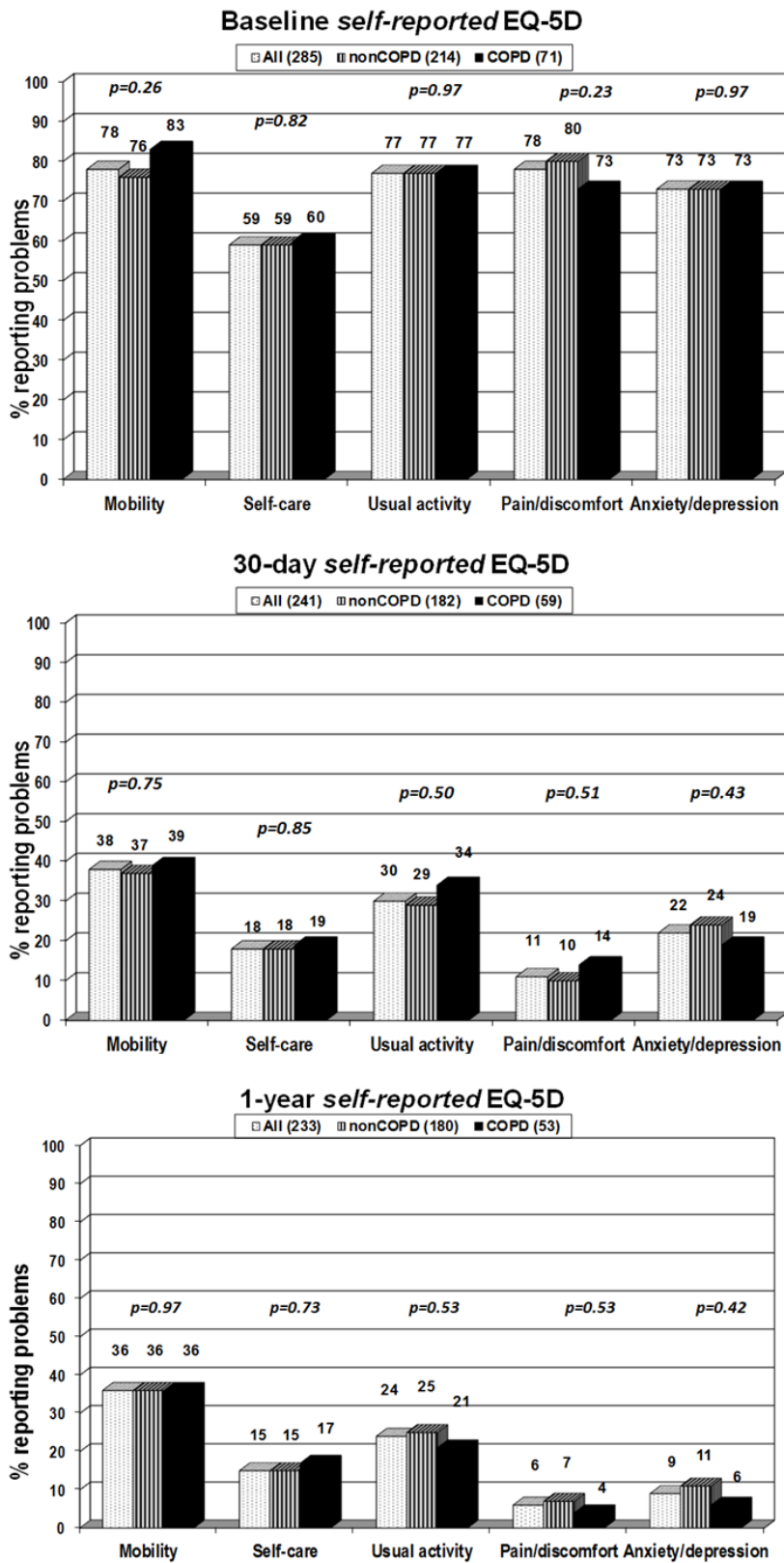
Baseline		All	nonCOPD	COPD	<i>p value</i>
EQ-5D dimensions		(n=285)	(n=214)	(n=71)	
Mobility	Problems*, n (%)	220 (78%)	162 (76%)	58 (83%)	0.26
Self-care	Problems, n (%)	166 (59%)	124 (59%)	42 (60%)	0.82
Usual activities	Problems, n (%)	218 (77%)	164 (77%)	54 (77%)	0.97
Pain/Discomfort	Problems, n (%)	220 (78%)	169 (80%)	51 (73%)	0.23
Anxiety/Depression	Problems, n (%)	206 (73%)	155 (73%)	51 (73%)	0.97
EQ-5Dindex (IQR)		0.52 (-0.02,0.71)	0.52 (-0.02,0.71)	0.52 (-0.03,0.72)	0.99
EQ-5DVAS (IQR)		35 (15,50)	30 (11,50)	43 (15,60)	0.39

*Sum of the proportion of reported level 2 and level 3 problems for each of the 5 EQ-5D dimensions.

EQ-5Dindex = EQ-5D utility index

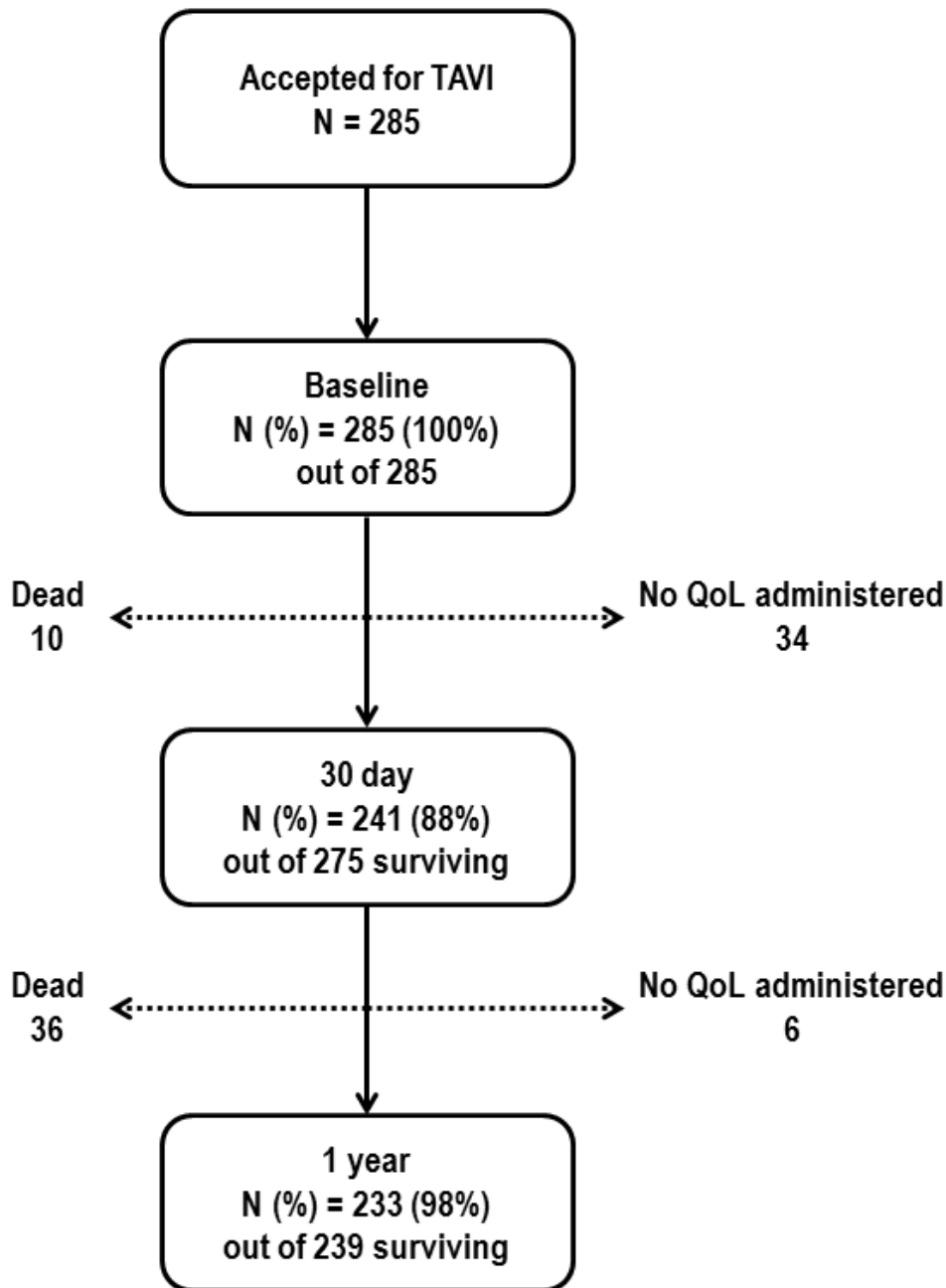
EQ-5DVAS = EQ-5D visual analogue scale

Figure 6.3.1.7: Quality of Life profile of the populations. % reporting problems (EQ-5D score \geq 2) in each domain at baseline, 30-day and 1 year.



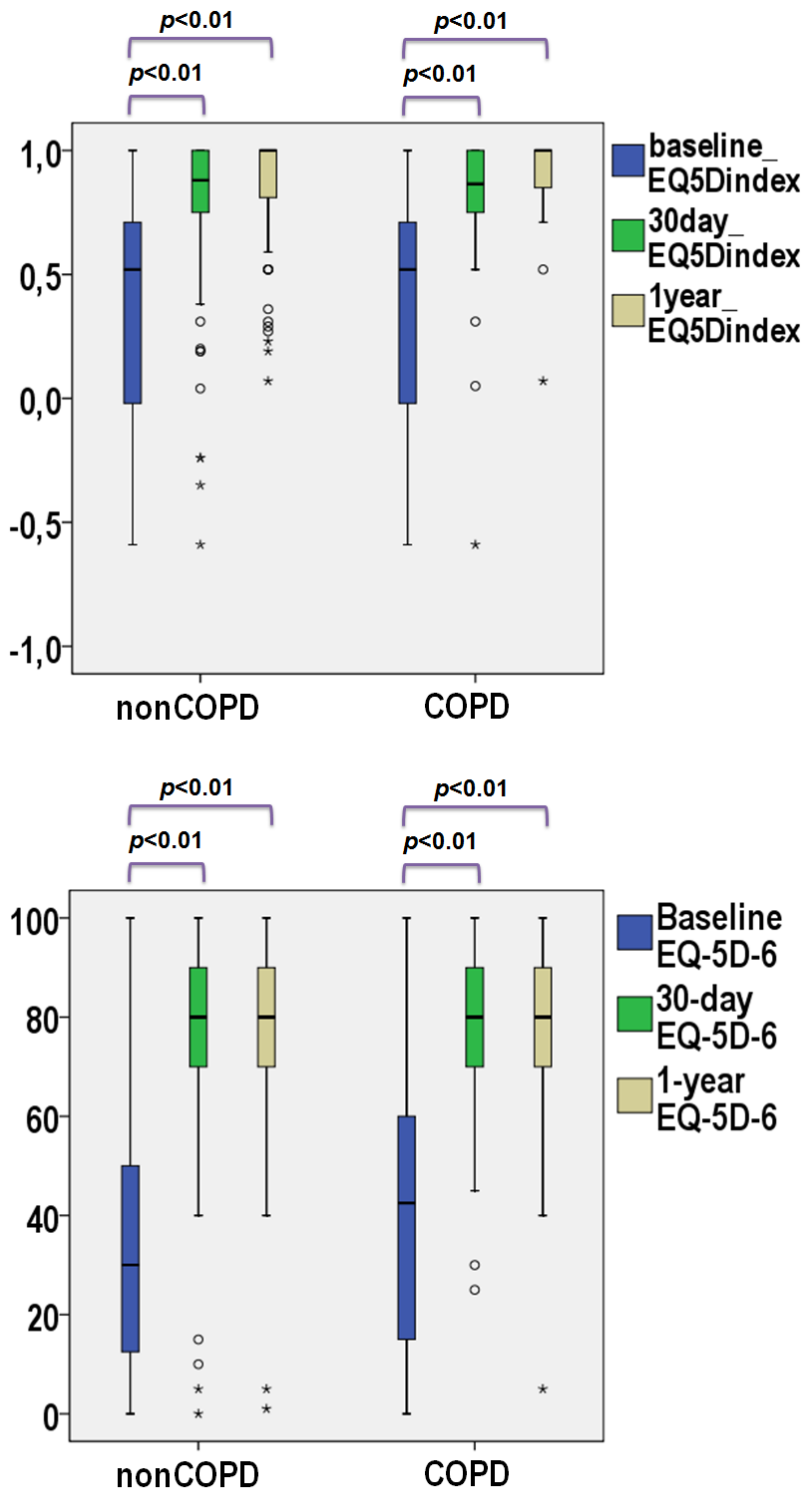
Follow-up questionnaires were obtained from 88% of surviving subjects at 30 days. At 1 year, follow-up questionnaires were obtained from 98% of nonCOPD and COPD surviving subjects (Figure 6.3.1.8.).

Figure 6.3.1.8. Flow chart of patients who filled in the EQ-5D Quality of Life questionnaire.



EQ-5D questionnaire assessment revealed significantly improved health related QoL at 30 days ($p < 0.01$ for both EQ-5D index and EQ-5D VAS in either nonCOPD and COPD groups) and at 1-year follow-up ($p < 0.01$ for both EQ-5D index and EQ-5D VAS in either nonCOPD and COPD groups) (Figure 6.3.1.9.).

Figure 6.3.1.9. EQ5Dindex and VAS improvement.



At 30 days the COPD patients reported as few problems in mobility, self-care, usual activities, pain/discomfort and anxiety/depression as nonCOPD patients (Table 6.3.1.4, Figure 6.3.1.7.). 30-day EQ-5Dindex and EQ-5DVAS were comparable ($p=0.94$ and $p=0.57$, respectively) between the two cohorts as well as the absolute improvement compared to baseline: Δ EQ-5Dindex was 0.34 (IQR 0.15-0.91) v. 0.30 (IQR 0.16-0.79) ($p=0.55$) and Δ EQ-VAS calculated as 45 points (IQR 20-60) v. 40 points (IQR 25-60) ($p=0.63$) (Figure 6.3.1.10.).

Table 6.3.1.4. 30-day Quality of Life.

30-day		All	nonCOPD	COPD	<i>p value</i>
EQ-5D dimensions		(n=241)	(n=182)	(n=59)	
Mobility	Problems*, n (%)	91 (38%)	68 (37%)	23 (39%)	0.75
Self-care	Problems, n (%)	43 (18%)	32 (18%)	11 (19%)	0.85
Usual activities	Problems, n (%)	73 (30%)	53 (29%)	20 (34%)	0.50
Pain/Discomfort	Problems, n (%)	27 (11%)	19 (10%)	8 (14%)	0.51
Anxiety/Depression	Problems, n (%)	54 (22%)	43 (24%)	11 (19%)	0.43
30-day EQ-5Dindex (IQR)		0.88 (0.75,1)	0.88 (0.75,1)	0.87 (0.75,1)	0.94
30-day EQ-5DVAS (IQR)		80 (70,90)	80 (70,90)	80 (70,90)	0.57
30-day Δ EQ-5Dindex (IQR)		0.31 (0.16,0.80)	0.30 (0.16,0.79)	0.34 (0.15,0.91)	0.55
30-day Δ EQ-5DVAS (IQR)		40 (20,60)	40 (25,60)	45 (20,60)	0.63

*Sum of the proportion of reported level 2 and level 3 problems for each of the 5 EQ-5D dimensions.

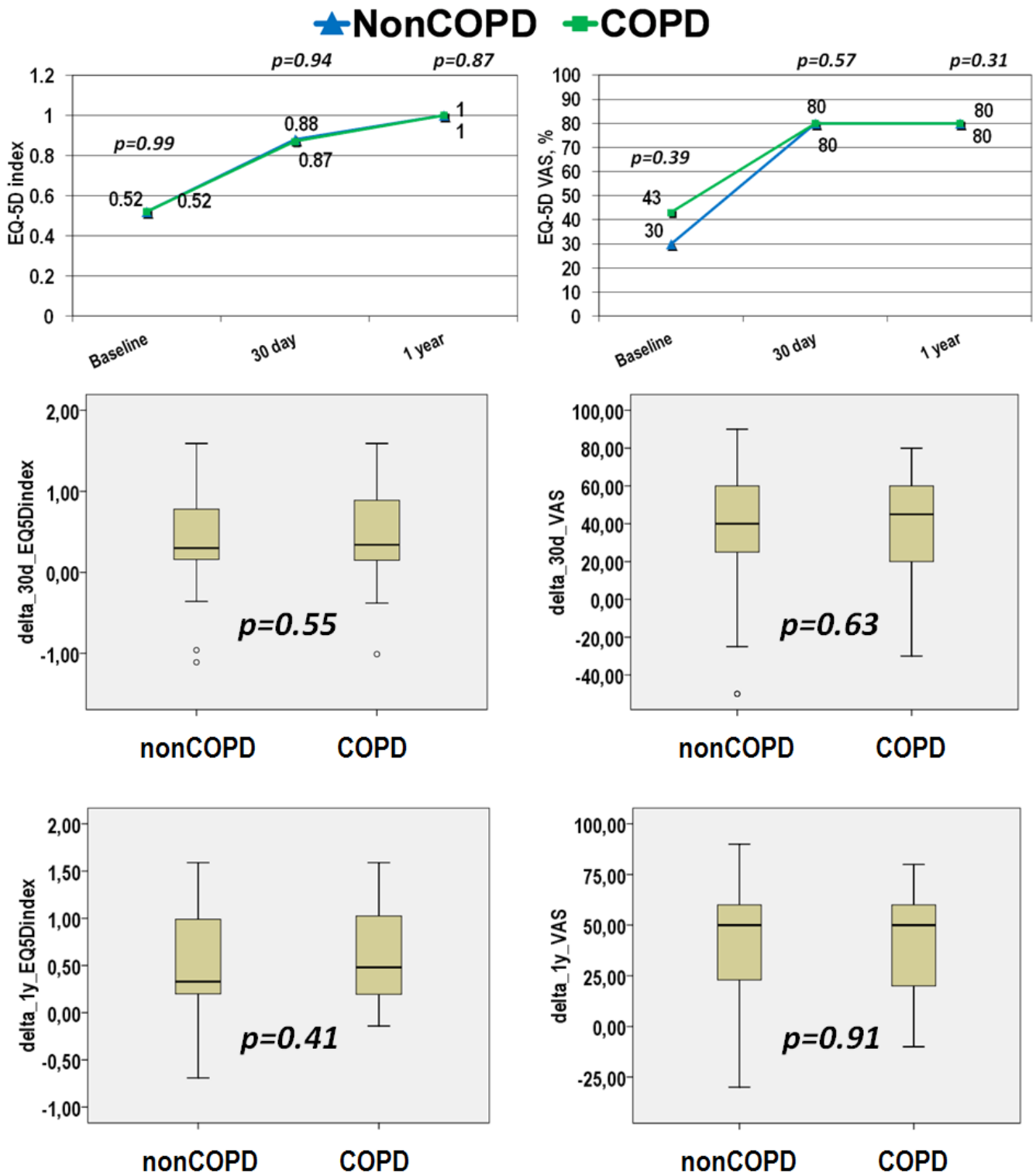
By 1 year there were still no differences between nonCOPD and COPD patients in any EQ-5D domain (Table 6.3.1.5., Figure 6.3.1.7.), in EQ-5Dindex nor in EQ-5DVAS (Figure 6.3.1.10.). Similarly, the absolute improvement in health related QoL remained comparable between nonCOPD and COPD groups (Δ EQ-5Dindex 0.33 points [IQR 0.20-1] v. 0.48 points [IQR 0.20-1.03], $p=0.41$ and Δ EQ-5DVAS 50 points [IQR 22-60] v. 50 points [IQR 20-60], $p=0.91$) (Figure 6.3.1.10.).

Table 6.3.1.5. 1-year Quality of Life.

1-year self-reported EQ-5D dimensions		All (n=233)	nonCOPD (n=180)	COPD (n=53)	<i>p value</i>
Mobility	Problems*, n (%)	83 (36%)	64 (36%)	19 (36%)	0.97
Self-care	Problems, n (%)	36 (15%)	27 (15%)	9 (17%)	0.73
Usual activities	Problems, n (%)	56 (24%)	45 (25%)	11 (21%)	0.53
Pain/Discomfort	Problems, n (%)	15 (6%)	13 (7%)	2 (4%)	0.53
Anxiety/Depression	Problems, n (%)	22 (9%)	19 (11%)	3 (6%)	0.42
1-year EQ-5Dindex (IQR)		1 (0.81,1)	1 (0.81,1)	1 (0.85,1)	0.87
1-year EQ-5DVAS (IQR)		80 (70,90)	80 (70,90)	80 (70,90)	0.31
1-year Δ EQ-5Dindex (IQR)		0.38 (0.20,1.02)	0.33 (0.20,1)	0.48 (0.20,1.03)	0.41
1-year Δ EQ-5DVAS (IQR)		50 (20,60)	50 (22,60)	50 (20,60)	0.91

*Sum of the proportion of reported level 2 and level 3 problems for each of the 5 EQ-5D dimensions.

Figure 6.3.1.10. Improvements in Quality of Life. Top, time-course of 'global' EQ-5Dindex and EQ-5DVAS score. Middle and bottom, 30-day and 1-year absolute improvement in EQ-5Dindex and EQ-5DVAS.



6.3.2. NONCOPD VERSUS MODERATE TO SEVERE COPD PATIENTS

Baseline Demographics

Based on spirometry, among the 71 COPD patients who underwent TAVI, 58 (82%) patients were affected by moderate to severe COPD (median FEV1/FVC 0.65 [IQR 0.57-0.72]), with a median FEV1 of 58% (IQR 51-70%) whilst 13 (18%) patients were affected by mild disease. (Figure 6.3.2.1. and Figure 6.3.2.2.) The spectrum of COPD frequency and severity among this population resembles that of published series evaluating outcomes in COPD patients undergoing sAVR or TAVI (36,38-40,46,154,155).

Baseline characteristics of these patients, compared to nonCOPD patients, are shown in Table 6.3.2.1.

Figure 6.3.2.1. Non v. modsevCOPD. GOLD grade.

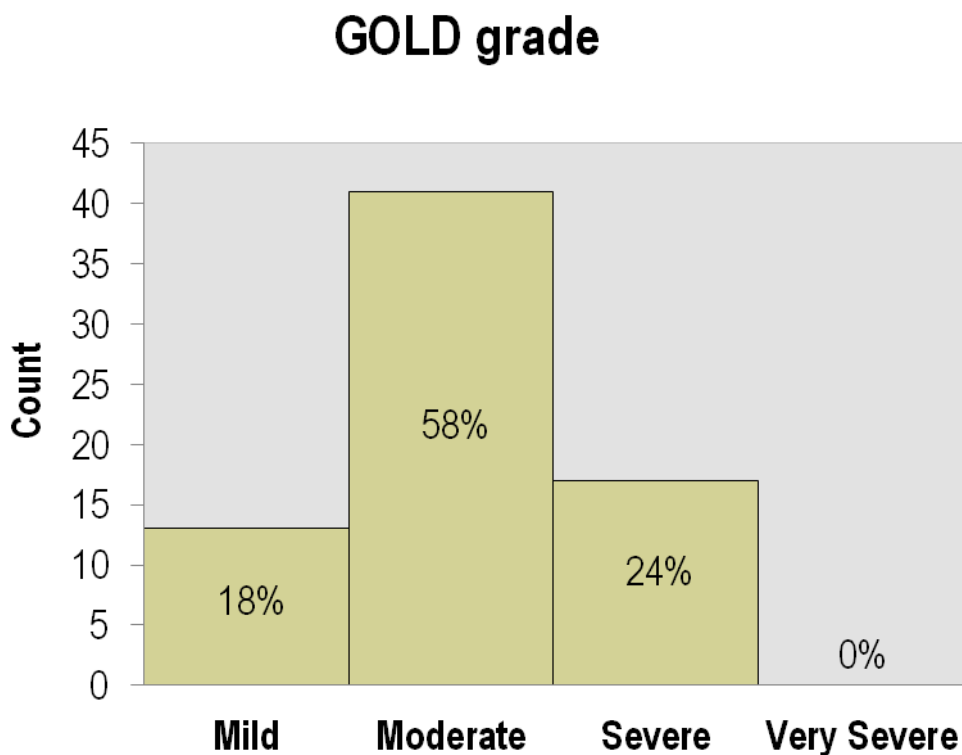
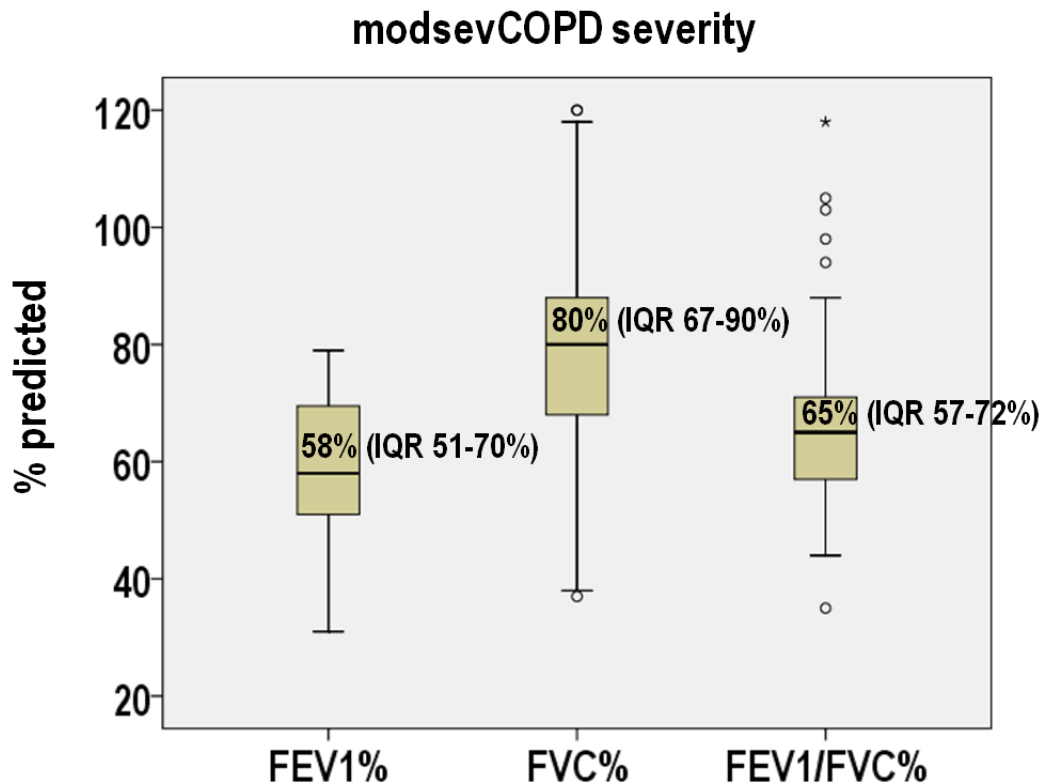


Figure 6.3.2.2. Non v. modsevCOPD. Lung disease severity.



Similarly to what was seen for the entire COPD cohort, COPD patients affected by moderate to severe COPD (modsev COPD) had higher STS score (11.2% [IQR 6.5-17.2%] v. 6.4% [IQR 4.1-10%], $p < 0.01$), incidence of patients in NYHA failure class \geq III (53 [91%] v. 161 [75%], $p < 0.01$) and incidence of patients on atrial fibrillation heart rhythm (23 patients [40%] v. 33 patients [15%], $p < 0.01$) than patients without COPD (Table 6.3.2.1. Non v. modsevCOPD.

Demographics.). Differently, there was no significant difference in baseline LVEF between nonCOPD and modsevCOPD patients (58% [IQR 49-65%] v. 54% [IQR 42-62%], $p = 0.05$).

All kinds of access routes were used in modsevCOPD patients (Figure 6.3.3.1.). Rates of access routes were still not different between the two groups (TF-TAVI: 34 [59%] modsevCOPD v. 136 [64%] nonCOPD patients, $p = 0.49$; TA-TAVI: 17 [29%] modsevCOPD v. 65 [30%] nonCOPD patients, $p = 0.88$; TAO: 7 [12%] modsevCOPD v. 13 [6%] nonCOPD patients, $p = 0.12$).

Table 6.3.2.1. Non v. modsevCOPD. Demographics.

	nonCOPD (n=214)	modsevCOPD (n=58)	<i>p value</i>
Age, years (IQR)	82 (77,86)	83 (77,86)	0.72
Female sex, n (%)	139 (65)	35 (60)	0.52
Body Mass Index (IQR)	25 (22.4,28.4)	24.3 (22.5,27.2)	0.37
Logistic EuroSCORE,% (IQR)	17 (12,25)	21 (15,29)	0.11
STS risk of mortality,% (IQR)	6.4 (4.1,10)	11.2 (6.5,17.2)	<0.01
NYHA failure class≥III, n (%)	161 (75)	53 (91)	<0.01
<i>Baseline NYHA</i>			0.01
NYHA I n (%)	0 (0)	0 (0)	1.00
NYHA II n (%)	53 (25)	5 (9)	0.01
NYHA III n (%)	116 (54)	33 (57)	0.72
NYHA IV n (%)	45 (21)	20 (35)	0.03
Frailty (79), n (%)	48 (22)	16 (28)	0.41
Recent cardiogenic shock, n (%)	12 (6)	4 (7)	0.75
Hypertension, n (%)	174 (81)	49 (85)	0.58
Dyslipidemia, n (%)	102 (48)	28 (49)	0.87
Diabetes mellitus, n (%)	48 (22)	12 (21)	0.82
Prior/current Smoking, n (%)	65 (30)	23 (40)	0.18
Coronary Artery Disease, n (%)	110 (51)	30 (52)	1.00
Chronic renal dysfunction*, n (%)	28 (13)	5 (9)	0.36
Pulmonary Hypertension, n (%)	22 (10)	9 (16)	0.26
Peripheral artery obstructive disease, n (%)	84 (39)	16 (28)	0.10

Porcelain aorta, n (%)	8 (4)	3 (5)	0.62
Prior cardiac surgery, n (%)	50 (23)	12 (21)	0.67
Prior sAVR, n (%)	10 (5)	3 (5)	1.00
Prior CABG, n (%)	33 (15)	8 (14)	0.76
Prior PCI, n (%)	47 (22)	9 (16)	0.28
Other severe comorbidities, n (%)	79 (37)	25 (43)	0.39
Prior stroke, n (%)	13 (6)	6 (10)	0.26
Synus rhythm, n (%)	166 (78)	33 (57)	<0.01
Atrial fibrillation, n (%)	33 (15)	23 (40)	<0.01
Pacemaker, n (%)	26 (12)	7 (12)	1.00
Mean transaortic valve gradient, mmHg (IQR)	50 (41,59)	49 (37,57)	0.37
AVA, cm ² (IQR)	0.65 (0.51,0.76)	0.65 (0.51,0.76)	0.83
LVEF, % (IQR)	58 (49,65)	54 (42,62)	0.05
LVEF%<30, n (%)	13 (6)	4 (7)	0.77
<i>Route of Access</i>			0.30
Transfemoral access, n (%)	136 (64)	34 (59)	0.49
Transapical access, n (%)	65 (30)	17 (29)	0.88
Transaortic access, n (%)	13 (6)	7 (12)	0.12

Categorical variables are defined on the basis of EuroSCORE definitions unless noted otherwise.

*Renal dysfunction was defined as serum creatinine exceeding 130 µmol/L.

STS, Society of Thoracic Surgeon. CABG, coronary artery by-pass graft. PCI, percutaneous coronary intervention. AVA, aortic valve area. LVEF, left ventricular ejection fraction.

Post-procedural Outcomes

Clinical outcomes after TAVI, grouped according to the presence of moderate to severe COPD, are shown in **Table 6.3.2.2. Non v. modsevCOPD. Post-procedural Outcomes**. Procedural success was still comparable between the two cohorts (99% [213 procedures] for the nonCOPD group v. 98% [57 procedures] for the modsevCOPD group, $p=0.32$).

There were no significant differences in peri-procedural VARC-related complications between nonCOPD and modsevCOPD patients. Even in this subgroup, post-procedural Intensive/Coronary Care Unit stay (1 day [IQR 1-2] for both nonCOPD and modsevCOPD cohorts) and overall in-patient stay (8 days [IQR 7-11] v. 8 days [IQR 6-12]) were comparable between the two cohorts ($p=0.72$ and $p=0.98$, respectively).

Table 6.3.2.2. Non v. modsevCOPD. Post-procedural Outcomes.

	All (n=272)	nonCOPD (n=214)	modsevCOPD (n=58)	<i>p value</i>
Procedural success, n (%)		213 (99)	57 (98)	0.32
Coronary obstruction, n (%)		5 (2)	1 (2)	1.00
Life-threatening or disabling bleeding, n (%)		16 (8)	3 (5)	0.54
Stroke, n (%)		6 (3)	0 (0)	0.20
Vascular complication (major), n (%)		8 (4)	5 (9)	0.16
Heart conduction block requiring PPM, n (%)		12 (6)	3 (5)	0.90
Acute kidney injury (stage 2 and 3), n (%)		31 (15)	8 (14)	0.88
Pleural effusion or PNX drainage, n (%)		26 (12)	5 (9)	0.45
re-OTI or tracheostomy n (%)		2 (1)	1 (2)	0.61
Infection n (%)		8 (4)	2 (3)	0.92
Intensive Care Unit stay, days (IQR)		1 (1,2)	1 (1,2)	0.72
Hospital stay*, days (IQR)		8 (7,11)	8 (6,12)	0.98
30-day AVA, cm2 (IQR)		2.10 (1.76,2.48)	2.05 (1.60,2.44)	0.37
30-day mean transvalvular gradient, mmHg (IQR)		10 (8,13)	10 (8,13)	0.64
30-day LVEF, % (IQR)		59 (52,65)	52 (46,60)	0.02
Δ 30-day LVEF, % (IQR)		1 (-4,8)	0 (-4,6)	0.38
30-day mortality, n (%)	10 (4)	7 (3)	3 (5)	0.45§
1-year AVA, cm2 (IQR)		1.93 (1.54,2.25)	2.12 (1.73,2.54)	0.17
1-year mean transvalvular gradient, mmHg (IQR)		11 (9,14)	11 (8,14)	0.53
1-year LVEF, % (IQR)		61 (55,68)	57 (45,64)	0.07
Δ 1-year LVEF, % (IQR)		3 (-4,11)	3 (-5,10)	0.97
1-year mortality, n (%)	44 (16)	30 (14)	14 (24)	0.06†
Noncardiovascular death n (%)		32 (15)	14 (20)	0.10

	All (n=262)	nonCOPD (n=207)	modsevCOPD (n=55)	<i>p value</i>
<i>NYHA failure class at 30 days</i>				<i>0.43</i>
NYHA I, n (%)		134 (65)	31 (56)	<i>0.25</i>
NYHA II, n (%)		64 (31)	19 (35)	<i>0.61</i>
NYHA III, n (%)		8 (4)	4 (7)	<i>0.28</i>
NYHA IV, n (%)		1 (1)	1 (2)	<i>0.31</i>
30-day NYHA improvement, n (%)	251 (96)	200 (97)	51 (93)	<i>0.25</i>

	All (n=226)	nonCOPD (n=184)	modsevCOPD (n=43)	<i>p value</i>
<i>NYHA failure class at 1 year</i>				<i>0.71</i>
NYHA I, n (%)		113 (62)	25 (58)	<i>0.66</i>
NYHA II, n (%)		60 (33)	15 (35)	<i>0.79</i>
NYHA III, n (%)		9 (5)	2 (5)	<i>1.00</i>
NYHA IV, n (%)		1 (1)	1 (2)	<i>0.32</i>
1-year NYHA improvement, n (%)	209 (93)	169 (92)	40 (93)	<i>1.00</i>

*Days from procedure to discharge home.

§ Fisher's exact test

† Pearson χ^2 test

PPM = pacemaker; PNX = pneumothorax; OTI = oro-tracheal intubation.

Haemodynamic effects

In each group, good haemodynamic function of the prostheses and improvement in mean aortic gradient and effective orifice area at 30 days ($p < 0.01$ for both the cohorts) and at 1-year follow-up ($p < 0.01$ for both the cohorts) were confirmed. Alike for LVEF improvement at 30 days ($p = 0.02$) and at 1-year follow-up ($p < 0.01$) in nonCOPD patients.

(**Figure 6.3.2.3. Non v. modsevCOPD. Haemodynamic improvement. Wilcoxon.**) Despite *in-group* LVEF improvement at 30 days and 1 year resulted nonsignificant in modsevCOPD patients ($p = 0.68$ and $p = 0.08$), comparable *in-group* LVEF absolute improvement after TAVI (Δ LVEF%) was confirmed at 30 days and 1-year ($p = 0.38$ and $p = 0.97$, respectively). (**Table 6.3.2.2. Non v. modsevCOPD. Post-procedural Outcomes.**)

At 1-month and at 1-year follow-up repeated measures ANCOVA showed *between-group* comparable mean transvalvular gradient ($p = 0.64$ at 30 days and $p = 0.53$ at 1 year) and effective orifice area ($p = 0.37$ at 30 days and $p = 0.17$ at 1 year). The same as analyzing the entire COPD cohort, a lower LVEF was showed in the modsevCOPD cohort at 1 month ($p = 0.02$), but by 1 year the values were comparable *between groups* ($p = 0.07$). (**Figure 6.3.2.4. Non vs. modsevCOPD. Haemodynamics improvement. ANCOVA.**)

Figure 6.3.2.3. Non v. modsevCOPD. Haemodynamics improvement. Wilcoxon.

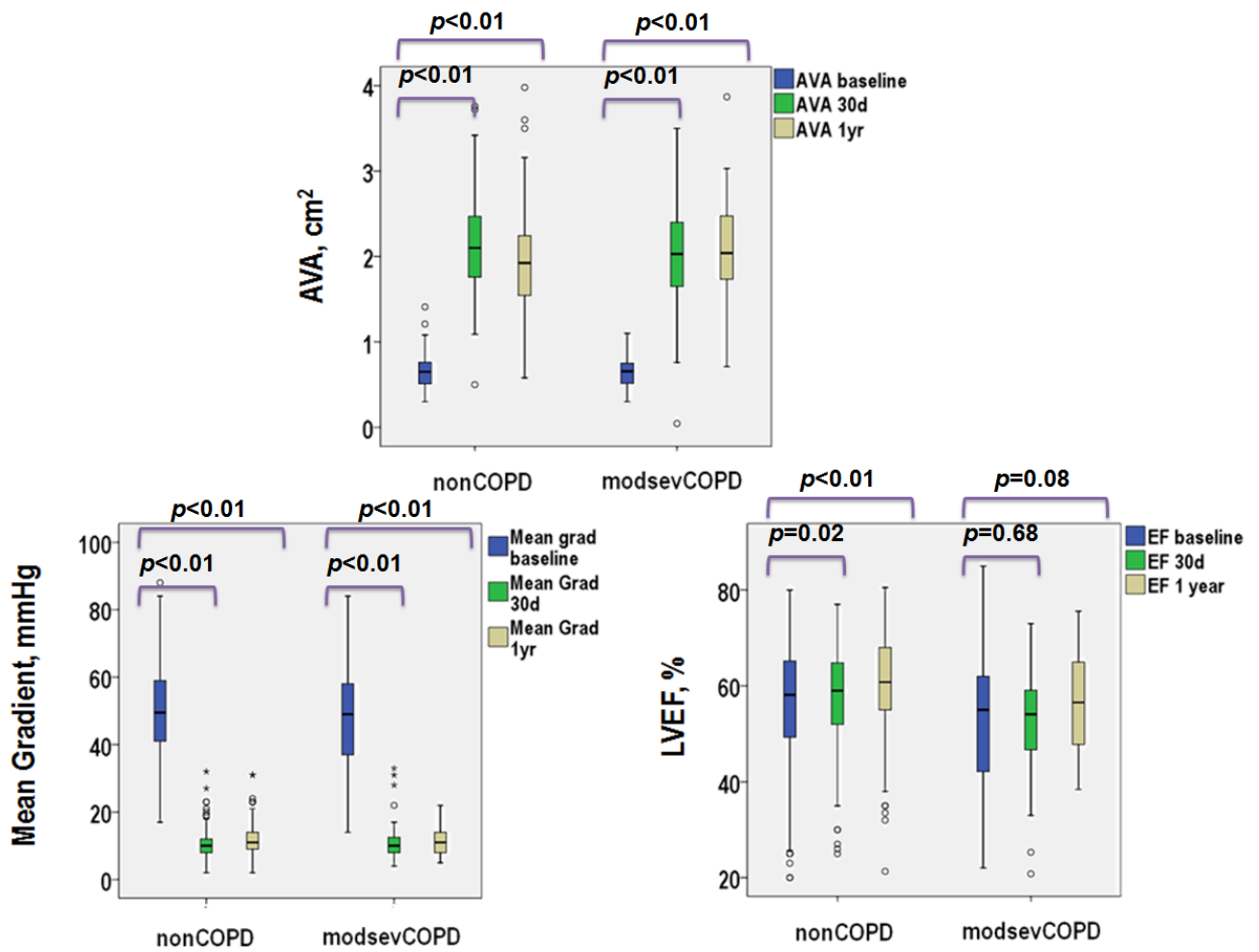
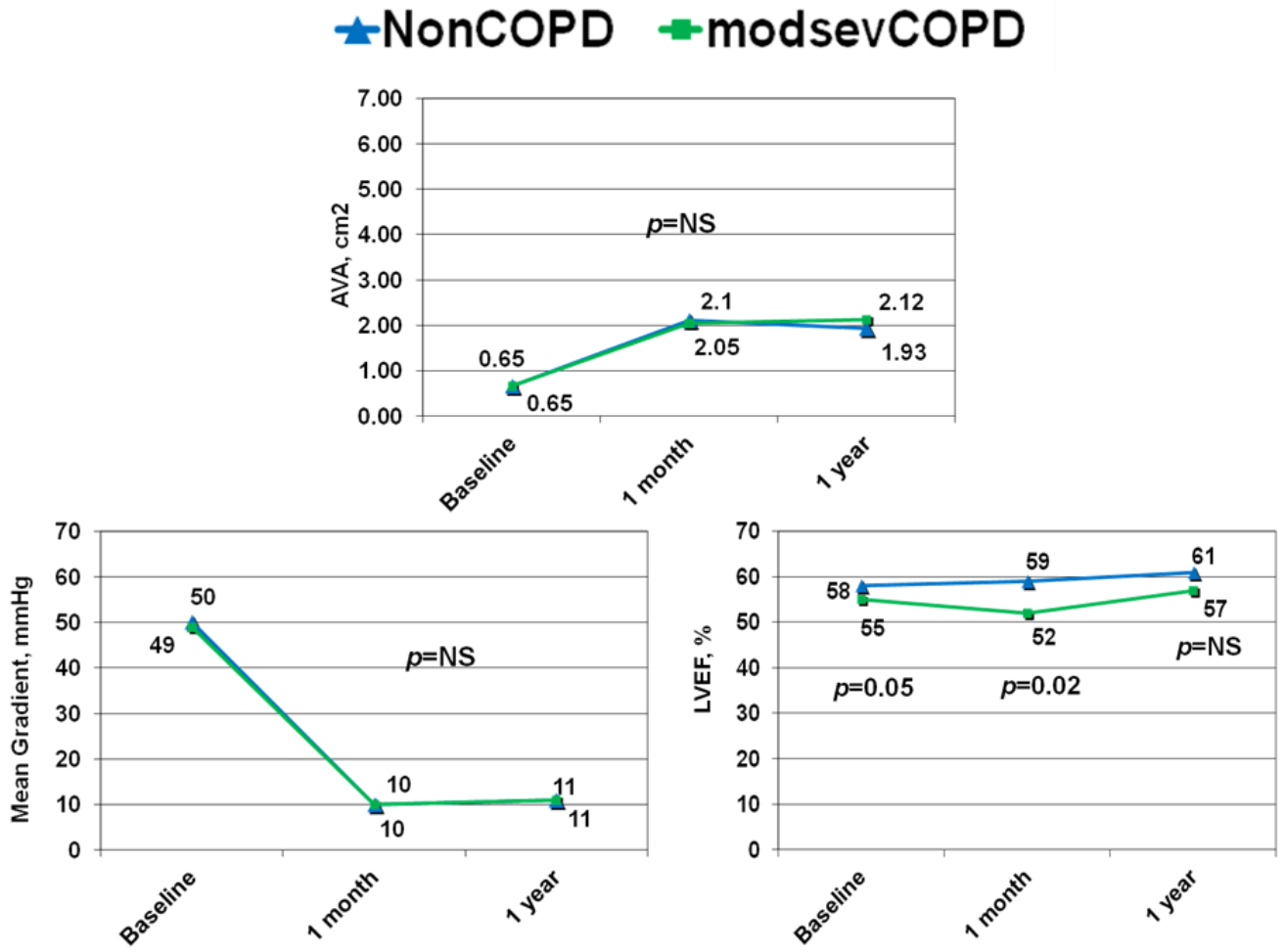


Figure 6.3.2.4. Non v. modsevCOPD. Haemodynamics improvement. ANCOVA.



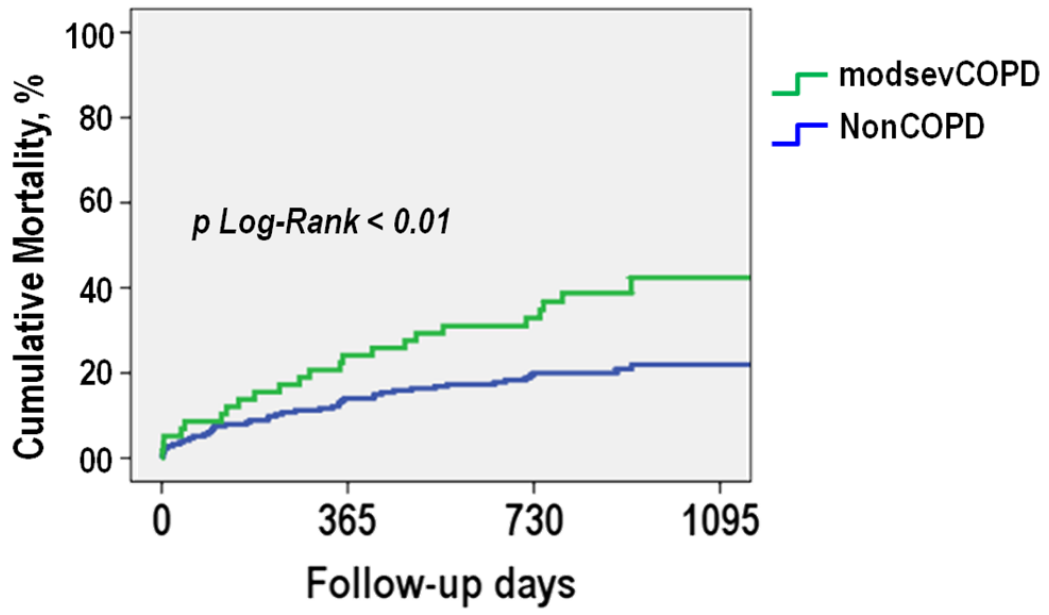
Mortality

Similarly to what was seen with the entire COPD cohort, 30-day mortality resulted similar between groups (3% for the nonCOPD group vs. 5% for the modsevCOPD group, $p=0.45$), but 1-year all-cause mortality, although not statistically different between the two cohorts, resulted more and more divergent (14% for the nonCOPD group vs. 24% for the modsevCOPD group, $p=0.06$) (Table 6.3.2.2. Non v. modsevCOPD. Post-procedural Outcomes.).

At a median follow-up of 27 months (IQR 22-44 months), not different between groups (nonCOPD: 28 months [IQR 22-44 months] v. modsevCOPD: 27 months [IQR 13-31 months], $p=0.14$), cumulative mortality was significantly higher in the modsevCOPD patients compared to nonCOPD patients (p Log-Rank <0.01 , Kaplan-Meier curves for mortality from any cause are shown in Figure 6.3.2.5.).

The variables associated with a higher cumulative mortality are shown in Table 6.3.2.3. COPD was associated with a higher cumulative mortality rate on univariate analysis (HR: 2.09; 95% CI: 1.26 to 3.46; $p<0.01$) and was identified as an independent predictor of cumulative late mortality in the multivariate analysis (HR: 1.80; 95% CI: 1.07 to 3.03; $p=0.03$). (Table 6.3.2.3.)

Figure 6.3.2.5. Non vs. modsevCOPD. Time-to-event curves for mortality from any cause.



Patients at Risk

modsevCOPD	58	44	36	13
NonCOPD	214	184	143	61

Table 6.3.2.3. Univariate and Multivariate Predictors of Cumulative Overall Mortality in Non and modsevCOPD (n=272).

	<i>Univariate Analysis</i>		<i>Multivariate Analysis</i>	
	HR (95% CI)	<i>p value</i>	HR (95% CI)	<i>p value</i>
<i>Baseline variables</i>				
Age, years	1.03 (0.99-1.07)	0.18		
Female sex	0.56 (0.35-0.91)	0.02	0.41 (0.24-0.70)	<0.01
Body Mass Index	0.97 (0.91-1.02)	0.20		
Logistic EuroSCORE	1.04 (1.02-1.05)	<0.01	1.00 (0.98-1.02)	0.97
STS risk of mortality	1.04 (1.01-1.06)	<0.01	1.04 (1.01-1.07)	0.01
NYHA failure class≥III	2.17 (1.19-3.98)	0.01	1.13 (0.55-2.33)	0.74
Frailty (79)	2.47 (1.51-4.02)	<0.01	1.32 (0.75-2.32)	0.34
Recent cardiogenic shock	1.89 (0.86-4.13)	0.11		
Hypertension	0.67 (0.38-1.20)	0.18		
Dyslipidemia	1.00 (0.62-1.62)	0.99		
Diabetes mellitus	1.12 (0.64-1.97)	0.68		
Prior/current Smoking	1.36 (0.83-2.22)	0.22		
Coronary Artery Disease	1.35 (0.83-2.19)	0.23		
Chronic renal dysfunction *	2.65 (1.51-4.65)	<0.01	1.22 (0.57-2.59)	0.61
Pulmonary Hypertension	2.11 (1.15-3.86)	0.02	2.50 (1.33-4.71)	<0.01
Peripheral artery obstructive disease	1.79 (1.11-2.90)	0.02	2.29 (1.39-3.79)	<0.01
Porcelain aorta	1.64 (0.60-4.51)	0.34		
Prior cardiac surgery	1.23 (0.71-2.13)	0.46		

Prior sAVR	1.43 (0.52-3.93)	0.49		
Prior CABG	1.21 (0.64-2.32)	0.56		
Prior PCI	1.19 (0.68-2.09)	0.54		
Prior stroke	0.82 (0.30-2.26)	0.70		
Chronic pulmonary disease	2.09 (1.26-3.46)	<0.01	1.80 (1.07-3.03)	0.03
FEV1, % §	0.98 (0.95-1.01)	0.16		
<i>Synus rhythm</i>				
Atrial fibrillation	1.62 (0.95-2.75)	0.08		
Pacemaker	2.37 (1.33-4.22)	<0.01	1.99 (1.09-3.63)	0.02
Mean transaortic valve gradient, mmHg	0.98 (0.97-1.00)	0.02	0.99 (0.97-1.01)	0.37
AVA, cm2	3.25 (0.80-13.15)	0.10		
LVEF, %	0.97 (0.96-0.99)	<0.01	1.00 (0.98-1.02)	0.88
<i>Route of Access</i>				
Transfemoral access	0.55 (0.34-0.89)	0.01	1.02 (0.40-2.58)	0.97
Transapical access	1.68 (1.03-2.74)	0.04	1.21 (0.48-3.09)	0.68
Transaortic access	1.49 (0.64-3.45)	0.36		
Baseline EQ-5Dindex	0.63 (0.38-1.05)	0.08		
Baseline EQ-5DVAS	1.00 (0.99-1.01)	0.35		
<i>Peri-procedural variables</i>				
Vascular complication (major)	2.96 (1.28-6.86)	0.01	3.9 (1.61-9.87)	<0.01
Acute kidney injury (stage 2 and 3)	4.30 (2.60-7.14)	<0.01	3.99 (2.35-6.78)	<0.01
re-OTI or tracheostomy	4.07 (0.99-16.66)	0.05		

Infection	3.04 (1.22-7.57)	0.02	2.05 (0.76-5.51)	0.15
Life-threatening or disabling bleeding	2.00 (0.91-4.39)	0.08		

Categorical variables are defined on the basis of EuroSCORE definitions unless noted otherwise.

*Renal dysfunction was defined as serum creatinine exceeding 130 $\mu\text{mol/L}$.

§ For each decrease of FEV1 by 5%.

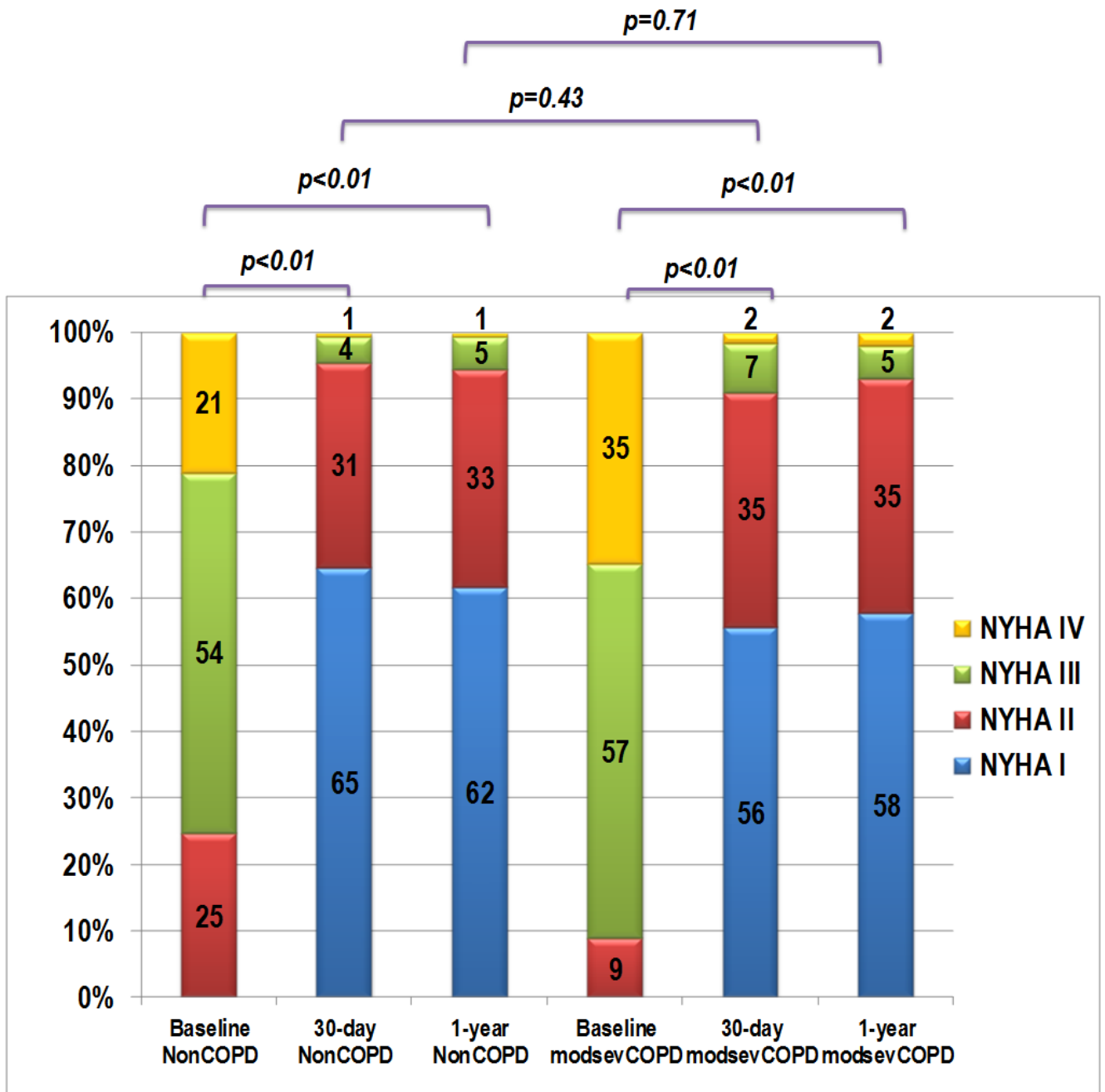
STS, Society of Thoracic Surgeon. CABG, coronary artery by-pass graft. PCI, percutaneous coronary intervention. AVA, aortic valve area. LVEF, left ventricular ejection fraction. PNx = pneumothorax; OTI = oro-tracheal intubation.

NYHA functional class

The changes in functional status according to the presence of moderate to severe COPD are shown in **Figure 6.3.2.6**.

At the follow up time points of 30 days and 1 year NYHA class had improved by 1 class at least in both groups ($p < 0.01$ at 30 days and 1 year for both groups). NYHA absolute improvement during follow-up was comparable between nonCOPD and modsevCOPD patients at 30 days (97% v. 93%, $p = 0.25$) and at 1 year (92% v. 93%, $p = 1.00$). (**Table 6.3.2.2. Non v. modsevCOPD. Post-procedural Outcomes., Figure 6.3.2.6.**)

Figure 6.3.2.6. Non v. modsevCOPD. NYHA.



Quality of Life

At baseline, modsevCOPD patients reported less problems (EQ-5D score \geq 2) in pain/discomfort than nonCOPD patients (38[67%] v. 169[80%], $p=0.04$). EQ-5Dindex and EQ-5DVAS were comparable ($p=0.46$ and $p=0.30$, respectively) (Table 6.3.2.4., Figure 6.3.2.7.).

Table 6.3.2.4. Non v. modsevCOPD. Baseline Quality of Life.

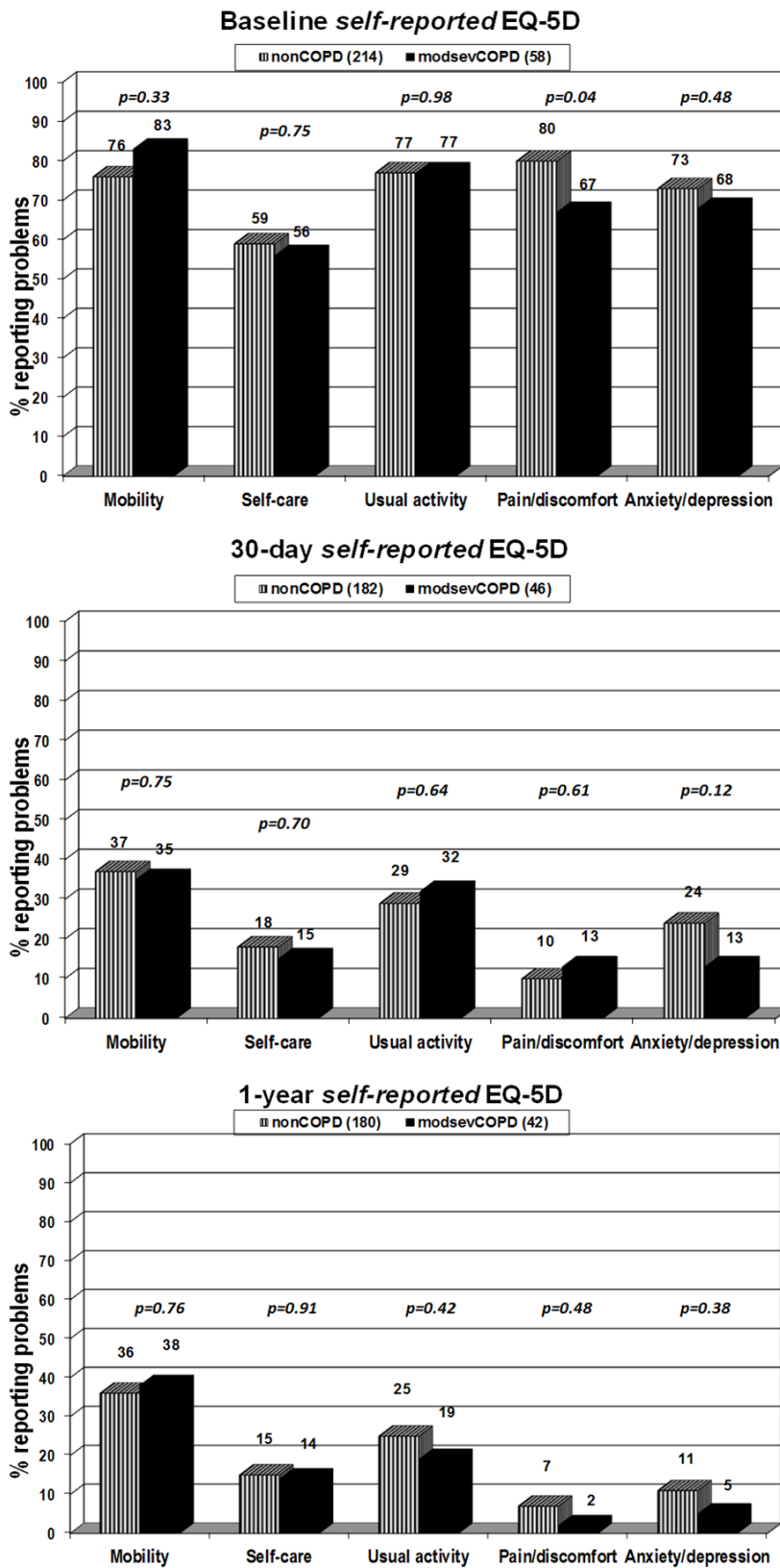
Baseline		All	nonCOPD	COPD	<i>p value</i>
EQ-5D dimensions		(n=272)	(n=214)	(n=58)	
Mobility	Problems*, n (%)		162 (76%)	47 (83%)	0.33
Self-care	Problems, n (%)		124 (59%)	32 (56%)	0.75
Usual activities	Problems, n (%)		164 (77%)	44 (77%)	0.98
Pain/Discomfort	Problems, n (%)		169 (80%)	38 (67%)	0.04
Anxiety/Depression	Problems, n (%)		155 (73%)	39 (68%)	0.48
EQ-5Dindex (IQR)			0.52 (-0.02,0.71)	0.52 (0.06,0.74)	0.46
EQ-5DVAS (IQR)			30 (11,50)	45 (15,60)	0.30

*Sum of the proportion of reported level 2 and level 3 problems for each of the 5 EQ-5D dimensions.

EQ-5Dindex = EQ-5D utility index

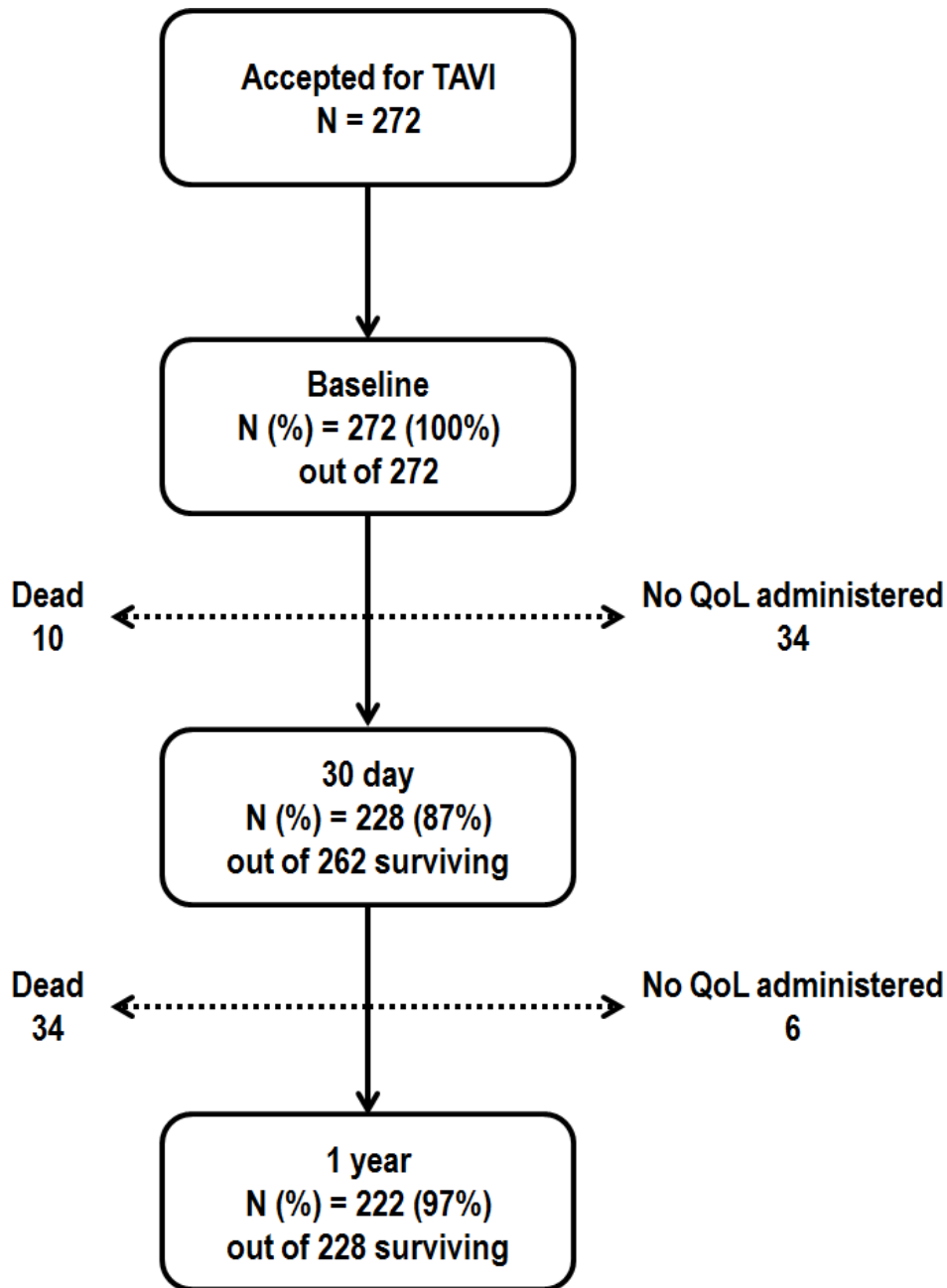
EQ-5DVAS = EQ-5D visual analogue scale

Figure 6.3.2.7. Non v. modsevCOPD. Quality of Life profile of the populations. % reporting problems (EQ-5D score \geq 2) in each domain at baseline, 30-day and 1 year.



Follow-up questionnaires were available in 87% of surviving subjects at 30 days (182 nonCOPD and 46 modsevCOPD patients). At 1 year, follow-up questionnaires were obtained from 97% of nonCOPD and modsevCOPD surviving subjects (Figure 6.3.2.8.).

Figure 6.3.2.8. Non v. modsevCOPD. Flow chart of patients who filled in the EQ-5D Quality of Life questionnaire.



EQ-5D questionnaire assessment revealed *in-group* significantly improved health related QoL at 30 days and at 1-year follow-up ($p < 0.01$ for both EQ-5D index and EQ-5D VAS in either nonCOPD and modsevCOPD groups) (**Figure 6.3.2.9**).

The same as considering all the COPD patients, at 30 days modsevCOPD patients reported as few problems in mobility, self-care, usual activities, pain/discomfort and anxiety/depression as nonCOPD patients (**Table 6.3.2.5, Figure 6.3.2.7**). Likewise, 30-day EQ-5Dindex and EQ-5DVAS were comparable ($p = 0.75$ and $p = 0.81$, respectively) between the two cohorts as well as the absolute improvement compared to baseline: Δ EQ-5Dindex was 0.31 (IQR 0.15-0.79) for the modsevCOPD group v. 0.30 (IQR 0.16-0.79) for the nonCOPD group, $p = 0.95$ and Δ EQ-VAS calculated as 45 points (IQR 20-60) for the modsevCOPD group v. 40 points (IQR 25-60) for the nonCOPD group, $p = 0.84$ (**Figure 6.3.1.10**). By 1 year there were still no differences between nonCOPD and modsevCOPD patients in any EQ-5D domain (**Table 6.3.2.6, Figure 6.3.1.7**), in EQ-5Dindex nor in EQ-5DVAS (**Figure 6.3.1.10**). Similarly and again, the absolute improvement in health related QoL remained comparable between modsevCOPD and nonCOPD groups (Δ EQ-5Dindex 0.41 points [IQR 0.19-0.93] v 0.33 points [IQR 0.20-1], $p = 0.96$ and Δ EQ-5DVAS 50 points [IQR 20-65] v. 50 points [IQR 22-60], $p = 0.97$) (**Figure 6.3.1.10**).

Figure 6.3.2.9. Non v. modsevCOPD. EQ5Dindex and VAS improvement.

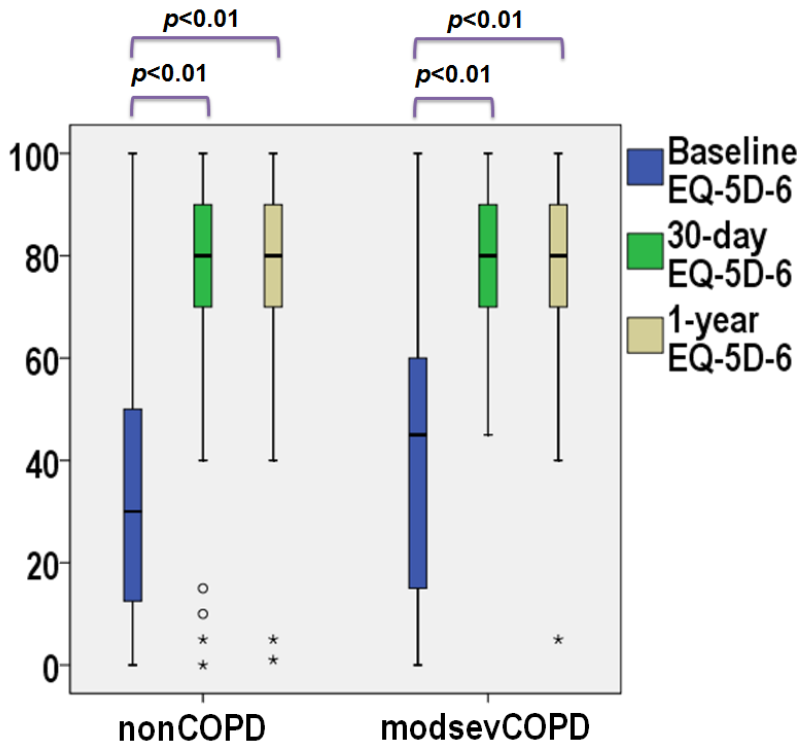
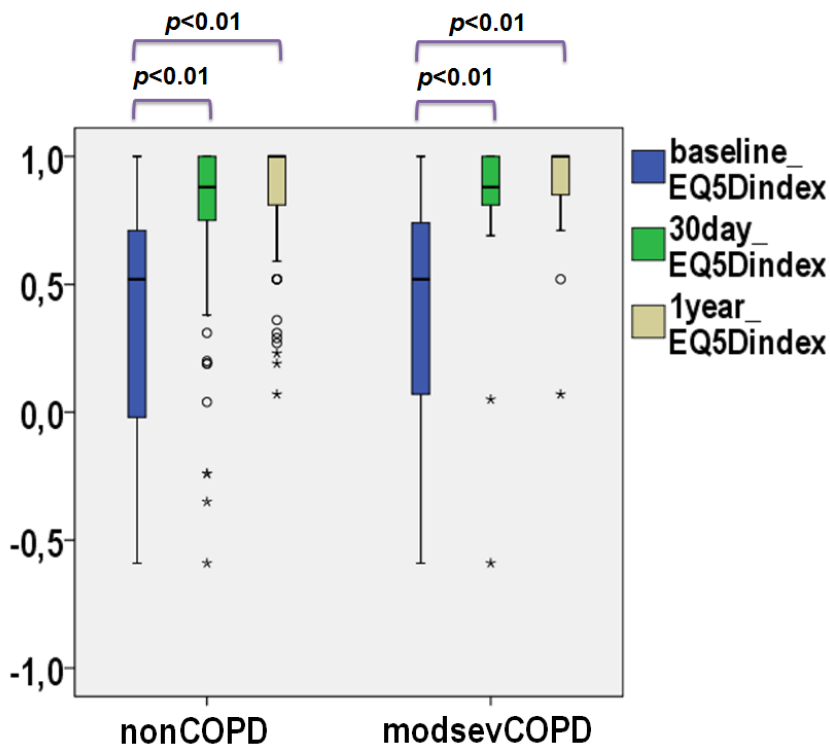


Table 6.3.2.5. Non vs. modsevCOPD. 30-day Quality of Life.

30-day		All	nonCOPD	COPD	<i>p value</i>
EQ-5D dimensions		(n=228)	(n=182)	(n=46)	
Mobility	Problems*, n (%)		68 (37%)	16 (35%)	0.75
Self-care	Problems, n (%)		32 (18%)	7 (15%)	0.70
Usual activities	Problems, n (%)		53 (29%)	15 (32%)	0.64
Pain/Discomfort	Problems, n (%)		19 (10%)	6 (13%)	0.61
Anxiety/Depression	Problems, n (%)		43 (24%)	6 (13%)	0.12
30-day EQ-5Dindex (IQR)			0.88 (0.75,1)	0.88 (0.80,1)	0.75
30-day EQ-5DVAS (IQR)			80 (70,90)	80 (70,90)	0.81
30-day Δ EQ-5Dindex (IQR)			0.30 (0.16,0.79)	0.31 (0.15,0.79)	0.95
30-day Δ EQ-5DVAS (IQR)			40 (25,60)	45 (20,60)	0.84

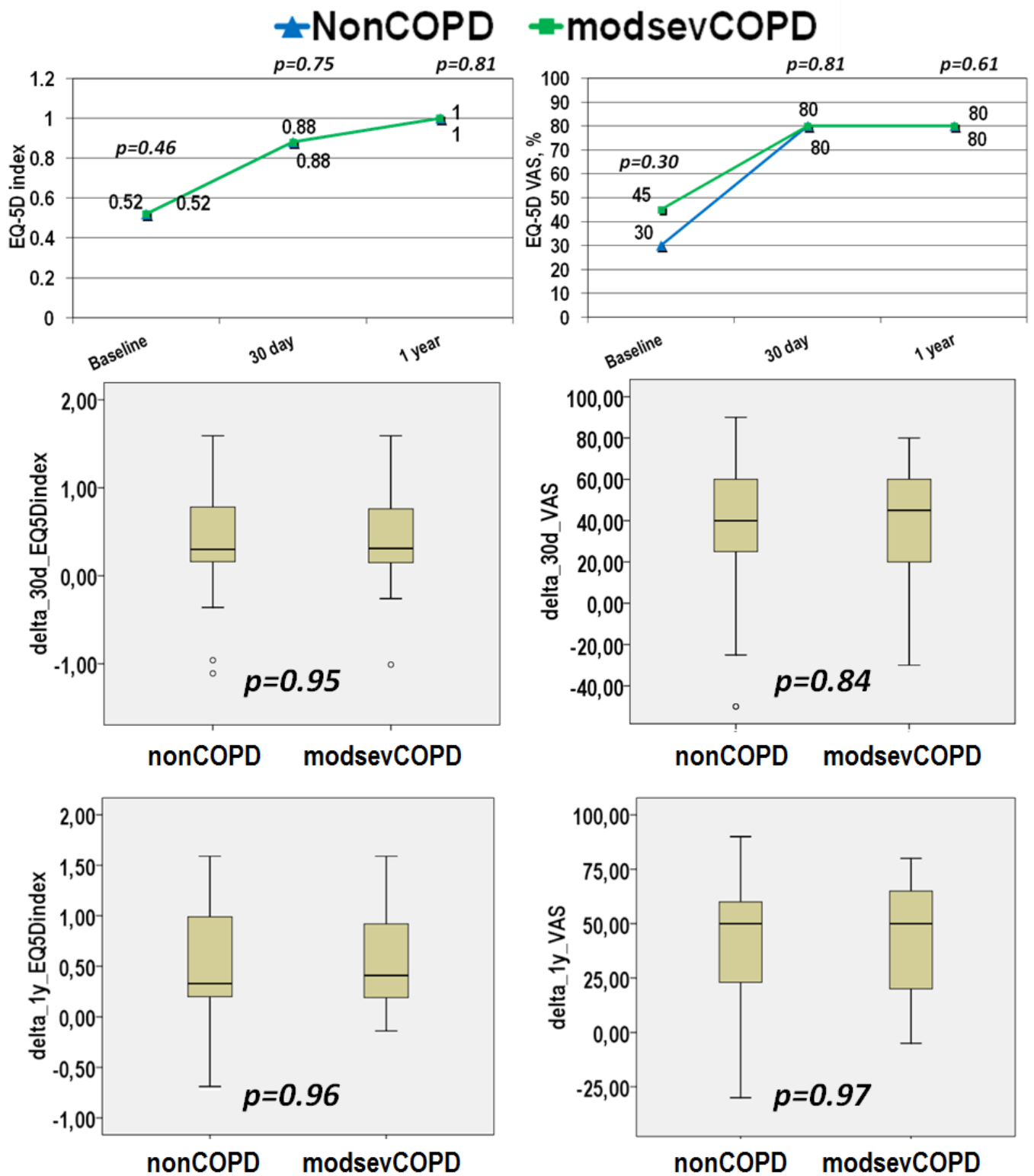
*Sum of the proportion of reported level 2 and level 3 problems for each of the 5 EQ-5D dimensions.

Table 6.3.2.6. Non v. modsevCOPD.1-year Quality of Life.

1-year self-reported EQ-5D dimensions		All (n=222)	nonCOPD (n=180)	COPD (n=42)	<i>p value</i>
Mobility	Problems*, n (%)		64 (36%)	16 (38%)	0.76
Self-care	Problems, n (%)		27 (15%)	6 (14%)	0.91
Usual activities	Problems, n (%)		45 (25%)	8 (19%)	0.42
Pain/Discomfort	Problems, n (%)		13 (7%)	1 (2%)	0.48
Anxiety/Depression	Problems, n (%)		19 (11%)	2 (5%)	0.38
1-year EQ-5Dindex (IQR)			1 (0.81,1)	1 (0.85,1)	0.81
1-year EQ-5DVAS (IQR)			80 (70,90)	80 (70,90)	0.61
1-year Δ EQ-5Dindex (IQR)			0.33 (0.20,1)	0.41 (0.19,0.93)	0.96
1-year Δ EQ-5DVAS (IQR)			50 (22,60)	50 (20,65)	0.97

*Sum of the proportion of reported level 2 and level 3 problems for each of the 5 EQ-5D dimensions.

Figure 6.3.2.10. Non v. modsevCOPD. Improvements in Quality of Life. Top, time-course of 'global' EQ-5Dindex and EQ-5DVAS score. Middle and bottom, 30-day and 1-year absolute improvement in EQ-5Dindex and EQ-5DVAS.

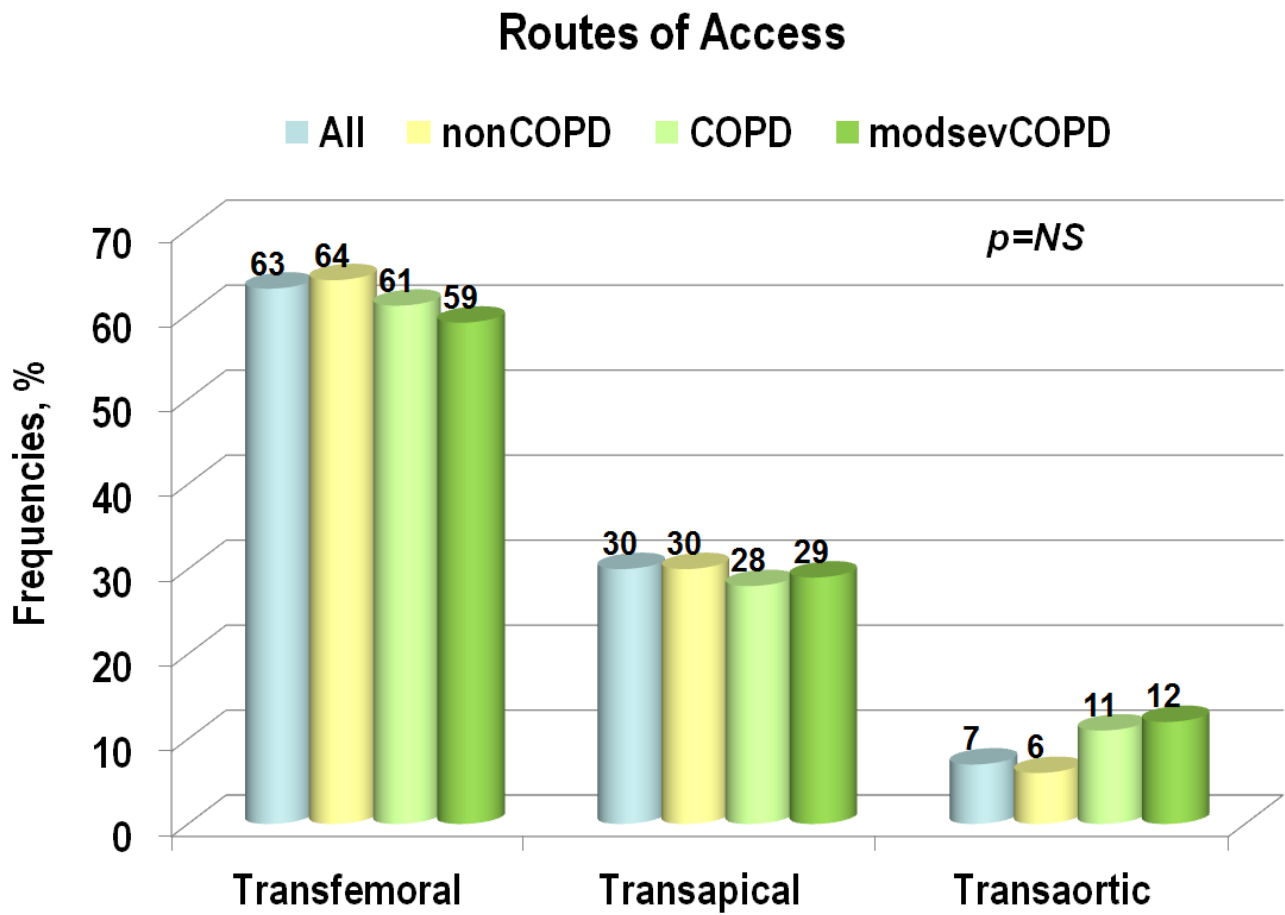


6.3.3. COPD PATIENTS ACROSS ACCESS

Kind of access in COPD patients

Rates of access routes were not different among the groups. A slight prevalence for nonTA access was noted in the COPD cohort.

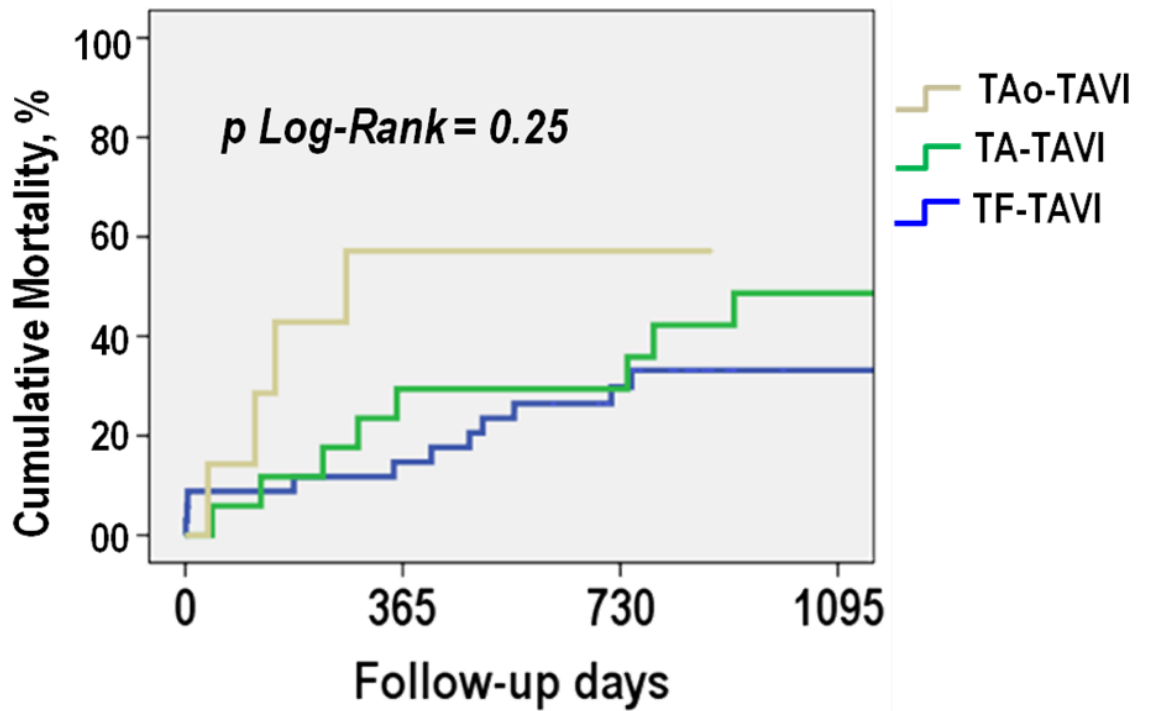
Figure 6.3.3.1.



Effect of transfemoral access route upon mortality

TF access route has been shown to have a slight protective effect upon 1-year survival (TF all-cause mortality v. nonTF all-cause mortality, $p=0.05$). Nevertheless, Kaplan Meier curves of survival showed no significant difference in terms of access-related cumulative mortality at mid-term follow-up in moderate to severe COPD patients (p Log-Rank = 0.25 when comparing TF-, TA- and TAO-TAVI patients and p Log-Rank = 0.21 when comparing nontransfemoral and transfemoral approaches; Kaplan-Meier curves for mortality from any cause are shown in **Figure 6.3.3.2.** and **Figure 6.3.3.3.**).

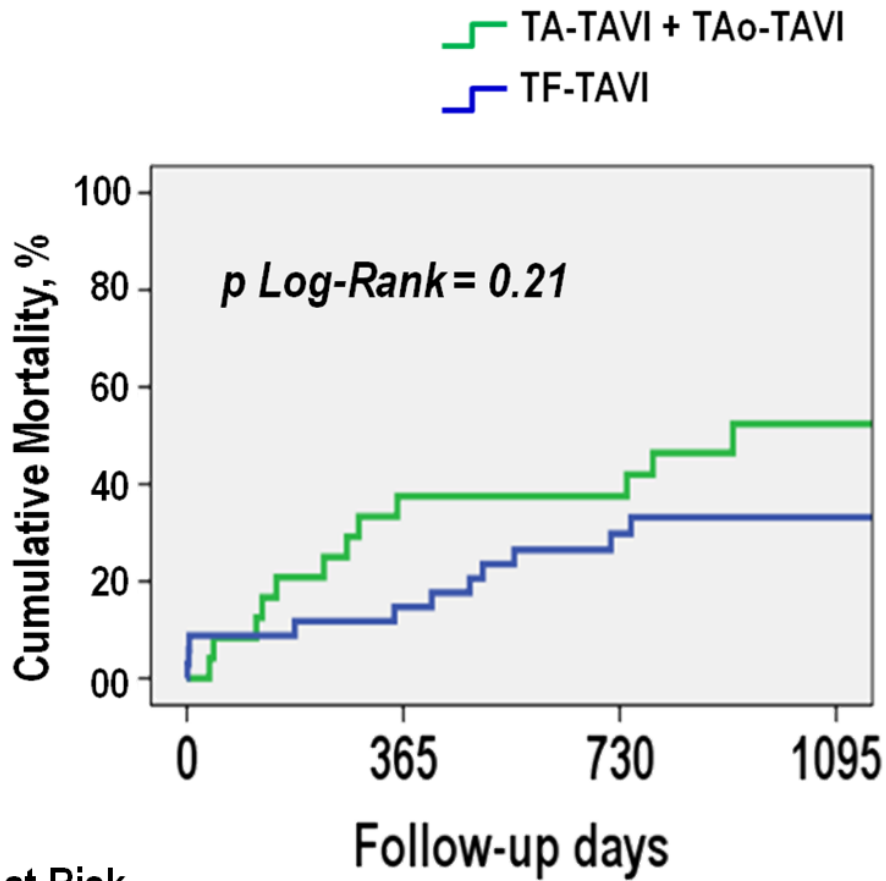
Figure 6.3.3.2. ModsevCOPD. Time-to-event curves for mortality from any cause across different access routes.



Patients at Risk

TF-TAVI	34	29	21	5
TA-TAVI	17	12	12	8
TAO-TAVI	7	3	3	

Figure 6.3.3.3. ModsevCOPD. Time-to-event curves for mortality from any cause after nontransfemoral and transfemoral TAVI approach.



Patients at Risk

TA-TAVI + TAO-TAVI	24	15	15	8
TF-TAVI	34	29	21	5

QoL in moderate to severe COPD patients across access route approach

Looking at the 58 COPD patients affected by moderate to severe lung disease stratified for access route (**Figure 6.3.3.4.**):

- the number of patients submitted to TAO-TAVI in this series was too small to give statistical significance to their specific analysis;
- the probability of QoL improvement (Δ EQ-5D index) at 30 days was significantly different among moderate to severe COPD patients undergone TAVI via different access routes ($p=0.04$) (**Figure 6.3.3.4.**);
- the probability of EQ-5D VAS absolute improvement at 30 days and the improvement at 1 year (Δ EQ-5D index and Δ EQ-5D VAS) resulted independent of the access route (**Figure 6.3.3.4.**).

Diabetes Mellitus (OR 0.10, 95% CI: 0.01 to 0.74, $p=0.02$), a prior sAVR (OR 0.05, 95% CI: 0.00 to 0.72, $p=0.03$), a prior CABG (OR 0.11, 95% CI: 0.02 to 0.77, $p=0.03$), baseline mean transvalvular gradient (OR 1.17, 95% CI: 1.01 to 1.36, $p=0.04$) and transfemoral access (OR 10.00, 95% CI: 1.06 to 94.68, $p=0.04$) resulted independently associated factors of QoL improvement, i.e. Δ EQ-5D index at 30 days, at the univariate logistic regression. (**Table 6.3.3.1.**)

On multivariate analysis, only higher mean transvalvular gradient at baseline (OR 1.14, 95% CI: 1.03 to 1.27, $p=0.02$) and transfemoral access (OR 17.81, 95% CI: 1.08 to 293.12, $p=0.04$) were independently associated with improvement in QoL, i.e. Δ EQ-5D index at 30 days (Hosmer-Lemeshow goodness-of-fit test: 4.74 with 7 df, $p=0.69$). (**Table 6.3.3.1.**)

Figure 6.3.3.4. QoL improvement in moderate to severe COPD patients across access route approach.

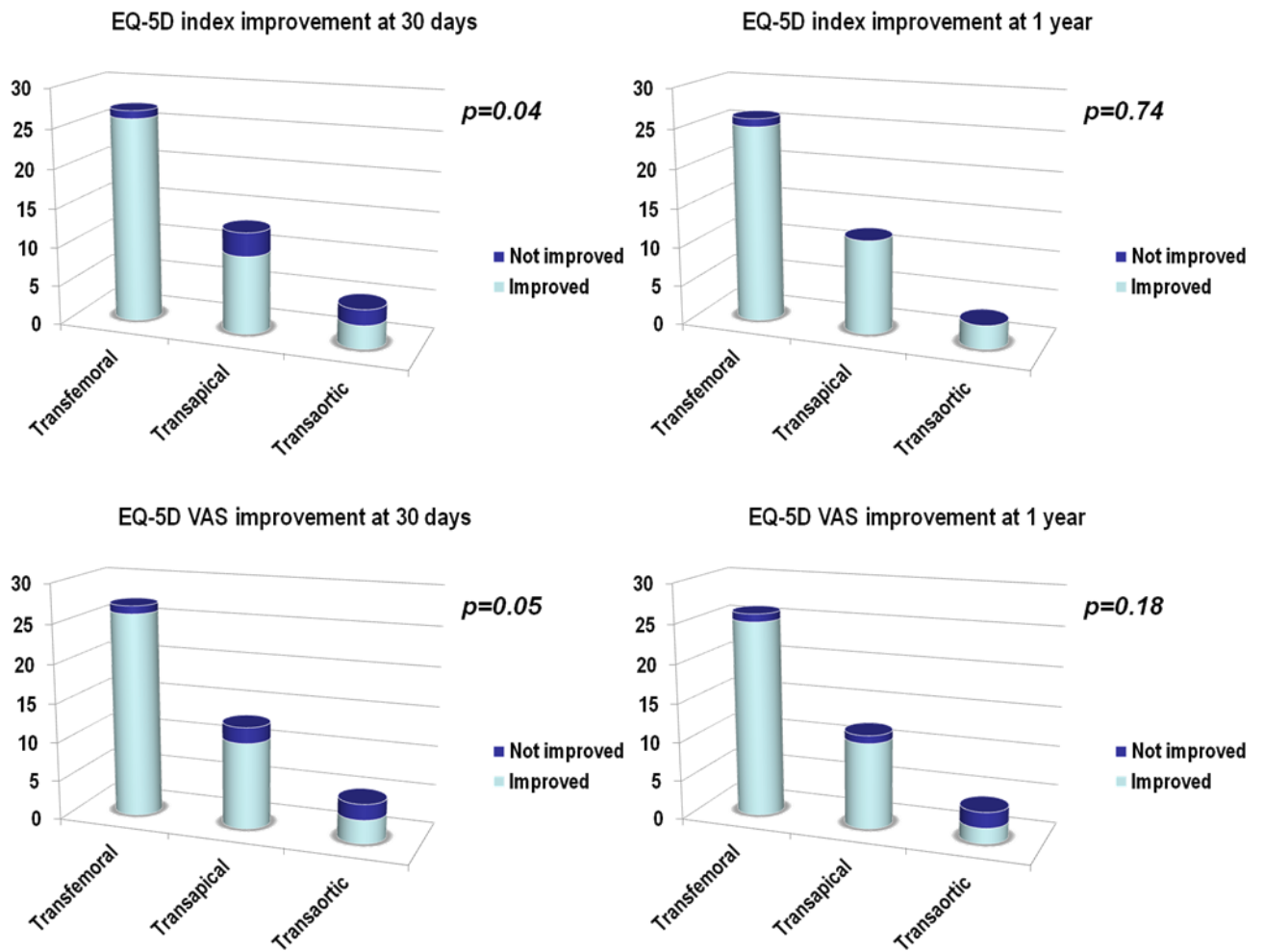


Table 6.3.3.1. Predictors of QoL improvement (30-day delta EQ-5Dindex>0) in modsevCOPD patients (n=58).

LOGISTIC regression. Univariate and multivariate analysis.

30-day delta EQ-5Dindex plus	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
<i>Baseline variables</i>				
Age, years	1.02 (0.89-1.18)	0.78		
Female sex	1.79 (0.32-10.06)	0.51		
Body Mass Index	1.02 (0.84-1.24)	0.81		
Logistic EuroSCORE	0.98 (0.92-1.05)	0.60		
STS risk of mortality	1.01 (0.91-1.13)	0.81		
NYHA failure class≥III	3.40 (0.49-23.65)	0.22		
Frailty (79)	0.69 (0.11-4.36)	0.69		
Recent cardiogenic shock	*			
Hypertension	1.10 (0.11-11.15)	0.94		
Dyslipidemia	0.25 (0.03-2.32)	0.22		
Diabetes mellitus	0.10 (0.01-0.74)	0.02	0.23 (0.01-3.68)	0.30
Prior/current Smoking	0.17 (0.03-1.09)	0.06		
Coronary Artery Disease	0.95 (0.17-5.30)	0.95		
Chronic renal dysfunction §	0.57 (0.05-6.19)	0.65		
Pulmonary Hypertension	*			
Peripheral artery obstructive disease	2.22 (0.23-21.13)	0.49		
Porcelain aorta	*			
Prior cardiac surgery	0.22 (0.04-1.32)	0.10		

Prior sAVR	0.05 (0.00-0.72)	0.03	0.45 (0.01-34.01)	0.71
Prior CABG	0.11 (0.02-0.77)	0.03	0.98 (0.03-27.47)	0.99
Prior PCI	0.91 (0.09-9.22)	0.94		
Prior stroke	0.42 (0.04-4.82)	0.48		
FEV1 % †	0.98 (0.90-1.06)	0.59		
Atrial fibrillation	4.29 (0.46-40.15)	0.20		
Pacemaker	0.91 (0.09-9.22)	0.94		
Mean transaortic valve gradient, mmHg	1.17 (1.01-1.36)	0.04	1.14 (1.03-1.27)	0.02
AVA, cm2	0.15 (0.00-1520.34)	0.69		
LVEF%<30	6.49 (0.09-482.17)	0.39		
<i>Route of Access</i>				
Transfemoral access	10.00 (1.06-94.68)	0.04	17.81 (1.08-293.12)	0.04
Transapical access	0.34 (0.06-1.99)	0.23		
Transaortic access	0.17 (0.02-1.32)	0.09		
<i>Peri-procedural variables</i>				
Vascular complication (major)	7.60 (0.41-141.54)	0.17		
Acute kidney injury (stage 2 and 3)	*			
re-OTI or tracheostomy	*			
Infection	*			
Life-threatening or disabling bleeding	*			

*Uncomputable due to constant N. ‡Renal dysfunction was defined as serum creatinine exceeding 130 µmol/L.

† For each decrease of FEV1 by 5%. Abbreviations and definitions as in previous Tables in the text.

Chapter 7. DISCUSSION

Catheter-based therapies represent potentially transformational technologies for valvular heart disease. With evidence of feasibility, safety and mortality benefit established (24,25), a clearer definition of comorbid conditions that adversely affect survival despite successful valve implementation is becoming mandatory. Similarly, quality of life and health economic assessment is crucial, so that this therapy is appropriately used in patients likely to benefit compared with those unlikely to improve despite technical success. This is particularly true when, in the course of a progressive illness, continued use of resources other than measures for comfort, is no longer reasonable, practical, or appropriate.

Ultimately, these decisions will be guided by what our society considers to be the inherent value of human life and the resultant financial burden society is willing to bear for the provision of modern public health care.

Our study confirms that TAVI in high-risk pulmonary dysfunction patients is associated with excellent short and medium-term results in terms of morbidity and mortality and that TAVI results in significant improvements in health-related QoL, maintained to one year. This is in keeping with the PARTNER trial and other reports (29,159-161). Indeed, in our study, such a significant enhancement in QoL has been shown to be comparable between the non-pulmonary affected and the pulmonary affected patients at any time-point.

COPD is traditionally considered a risk factor for mortality and significant morbidity after cardiac surgery and it is suggested that many COPD patients do not improve clinically after sAVR (37-40). This results in many elderly patients with severe aortic stenosis being denied surgical operation (37,41) and presented for TAVI as a lower risk alternative treatment for this group of patients. (38,41) This would explain the high rate (up to 40%) of COPD patients in TAVI studies. (45,46,59,60,162-165) Nevertheless, whether COPD patients improve after TAVI is still a matter of concern. (42,43)

Several trials have suggested that baseline COPD is a predictor for mortality after TAVI (44-46) and that pulmonary complications secondary to COPD have emerged as a common etiology for non-cardiac cause of death in patients undergoing TAVI. (45,159,166)

In our study COPD was confirmed to be a predictor of mortality at mid-term follow-up, with a 1.8-fold higher risk of death among patients. (Table 6.3.2.3.) Nonetheless, in this series COPD patients did not die mainly due to pulmonary complications during the periprocedural period or due to respiratory failure secondary to COPD during mid-term follow-up (Table 6.3.1.2.). This does not occur even analysing only the moderate to severe COPD subgroup (Table 6.3.2.2.).

Other than mortality, pulmonary complications after surgical interventions increase the risk of morbidity, prolonged hospital length of stay and health care costs (167,168). COPD has been reported as an important predictor of post-operative pulmonary complications, acute kidney injury and stroke after TAVI in previous analyses (94,159,169). In our series, no statistical difference was observed between the two groups in terms of respiratory complications like infection, re-oro-tracheal intubation or tracheostomy and pleural effusion or pneumothorax requiring drainage. Post-procedural Intensive/Coronary Care Unit stay (1 day [IQR 1-2] for both nonCOPD and COPD cohorts) and in overall in-patient stay (8 days [IQR 7-11] v. 8 days [IQR 6-12]) were comparable between the two cohorts (p=0.72 and p=0.98, respectively) as well. There was a low incidence of stroke rate in both groups.

The results of our study showed a significant improvement in functional status as evaluated by NYHA functional class and QoL as evaluated by EQ-5D questionnaire after TAVI.

Although COPD patients had a lower NYHA functional class at baseline (Table 6.3.1.1., Table 6.3.2.1.), they achieved and maintained comparable improvement in their NYHA functional class at follow-up and exhibited similar improvements in QoL as the rest of the study population.

Before receiving TAVI, 75% of nonCOPD patients and 90% of COPD patients were in NYHA class III-IV (p=0.02), becoming such difference even more significant when considering the moderate to severe COPD patients (75% of nonCOPD patients and 92% of COPD patients, p=0.01). At 30 days, 96% of nonCOPD patients and 92% of all COPD (91% modsevCOPD) patients were in NYHA functional class I-II (p=0.40 and p=0.43, respectively) (Table 6.3.1.2., Figure 6.3.1.6., Table 6.3.2.2., Figure 6.3.2.6.).

At the follow up time points of 30 days and 1 year, NYHA class had improved by 1 class at least in both groups (p<0.01 at 30 days and 1 year for all groups) (Figure 6.3.1.6. and Figure 6.3.2.6.).

NYHA absolute improvement during follow-up was comparable between nonCOPD and all COPD as well as between nonCOPD and modsevCOPD patients at 30 days (97% v. 91%, $p=0.07$ and 97% v. 93%, $p=0.25$) and at 1 year (92% v. 94%, $p=0.60$ and 92% v. 93%, $p=1.00$) (Table 6.3.1.2., Figure 6.3.1.6., Table 6.3.2.2., Figure 6.3.2.6.). These results are different than those seen in other recent studies regarding clinical outcomes in COPD patients undergoing TAVI (159). The current paper contains information of two groups with a large experience with TAVI procedures and a combination of improvements in patient selection, procedural techniques, and device technologies.

De Blois et al. (170) showed that heart failure patients with COPD were overrated in terms of NYHA functional class compared with patients with a similar LVEF, a reflection of poorer exercise tolerance as a result of impaired lung function in COPD patients. As a matter of fact, our results confirmed that nonCOPD and COPD cohorts did have significant baseline differences, with the latter group representing a higher peri-operative risk (higher STS score). (171,172) This according to PARTNER and recent studies results (59,60,160).

Besides being significantly more symptomatic for dyspnea, these patients did show a significantly lower baseline LVEF, which renders diagnosis and therapy even more challenging.

According to De Oliveira and colleagues (36), COPD patients' profile identified features of an elderly population, with multiple comorbidities, suggesting a health related QoL lower than expected.

In the current analysis, at baseline, COPD patients reported as many problems in mobility, self-care, usual activities, pain/discomfort and anxiety/depression as nonCOPD patients. Baseline EQ-5Dindex and EQ-5DVAS were comparable, too. This could be explained by several factors, including some-degree of 'floor effect', typical of the EQ-5D tool, a known weak correlation in COPD patients between FEV1, symptoms and QoL impairment independent of the generic or specific instrument used (157), and a real poor health status of all the TAVI patients.

EQ-5D questionnaire assessment revealed *in-group* significantly improved health related QoL at 30 days and at 1-year follow-up ($p<0.01$ for both EQ-5 index and EQ-5 VAS in either nonCOPD and COPD groups) (Figure 6.3.1.9. and Figure 6.3.2.9). *Between-groups* analysis showed that at 30 days COPD patients reported as few problems in mobility, self-care, usual activities, pain/discomfort and anxiety/depression as nonCOPD patients (Table 6.3.1.4., Figure 6.3.1.7.,

Table 6.3.2.5. and Figure 6.3.2.7.). Likewise, 30-day EQ-5Dindex and EQ-5DVAS were comparable between the cohorts as well as the absolute improvement (Δ EQ-5Dindex and Δ EQ-VAS) (Figure 6.3.1.10. and Figure 6.3.2.10.). By 1 year there were still no differences between nonCOPD and COPD patients in any EQ-5D domain (Table 6.3.1.5, Figure 6.3.1.7, Table 6.3.2.6. and Figure 6.3.2.7.), index, VAS, and absolute improvement from baseline (Figure 6.3.1.10. and Figure 6.3.2.10.).

For many patients in this high-risk cohort, improvements in QoL are arguably more important than improvement in longevity and perhaps more realistic.

At late follow up, mortality was significantly higher in the COPD group, likely reflecting the difference in comorbidities. Nonetheless, surviving COPD patients now had similarly high QoL scores and marked improvement from baseline as the nonCOPD group (Figure 6.3.1.7. and Figure 6.3.2.7., Figure 6.3.1.10. and Figure 6.3.2.10.).

As with all health-related QoL measures, the perceived effects of an intervention upon physical, social and emotional status can be more marked in those who are initially more symptomatic and therefore more 'functionally' impaired (33). The equitability of the absolute values at 30 days and 1 year and the similar percentage of patients reporting no problems in all domains at the latter time point certainly illustrate the positive impact of TAVI treatment upon COPD patients.

In these study, the effects of access route on QoL in patients with COPD undergoing different access routes TAVI (transfemoral, transapical, transaortic), have been focused. As a matter of fact, whilst COPD has been shown to increase the risk of mortality by a factor of 1.8, TF access route has not been shown to have a protective effect on survival (Figure 6.3.3.2. and Figure 6.3.3.3.) as seen in the general population of patients undergoing TAVI (59,60,163) or demonstrated by our group in a previous analysis (161). Such a result is probably subsequent to the relatively small number of COPD patients in the series.

When looking at the 58 COPD patients affected by moderate to severe lung disease (Figure 6.3.3.4.), it has been shown that the probability of QoL improvement after TAVI resulted dependent on the access route only at 30 days (in terms of Δ EQ-5D index improvement).

Similar to the PARTNER A (30) and to our previous study findings (161), we identified differences in the QoL and recovery among cohorts at 30 days. It looks like that nonTF-TAVI patients reported more problems (i.e. a lower Δ EQ-5D index improvement, $p=0.04$) (Figure 6.3.3.4.), which could be attributed to access-specific factors such as the post-operative pain caused by rib retraction, dissection of the pleura and intercostal nerve damage (65).

Transfemoral access was shown to be a strong predictor of QoL improvement on both univariate logistic regression (OR 10.00, 95% CI: 1.06 to 94.68, $p=0.04$) and on multivariate analysis (OR 17.81, 95% CI: 1.08 to 293.12, $p=0.04$).

Unfortunately, the number of patients submitted to TAO-TAVI in this series was too small to give statistical significance to their analysis inter alia. This is explained by the fact that, at the time of data collection in the SOURCE and SOURCE XT registries, TAO technique was still in its infancy and not performed at the Italian centre yet.

Although as in previous reports, QoL short term improvement was higher in TF-TAVI patients, by 1 year the improvements were comparable among different-access route groups. When appreciated in the context of a similarly low 30-day mortality despite demonstrably higher risk patients in the nonTF cohorts, such evidence deserves attention.

The importance of a careful preoperative evaluation of COPD patients undergoing preoperative assessment for TAVI must be taken into account. (171,172) A heart-team discussion, which with these patients avails a pulmonologist, should balance the potential risks and benefits for the individual patient as well as the plan for perioperative management. As described before, the clinical manifestations of COPD and AS are often similar. (37,173) Up-to-date lung function evaluation and laboratory B-type natriuretic peptide (BNP) levels could assist in identifying symptom etiology. (174) For individual COPD patients with markers for poor outcome after TAVI, such as oxygen-dependency or immobility (159,160), TAVI should be offered only after discussing the propensity for clinical benefit. Eventually, in case of lack of consensus, very high-risk lung disease patients for whom symptom etiology is unclear, could be considered for balloon aortic valvuloplasty, for both temporary support and in order to test for symptom etiology. (175,176) COPD patients who have clinically improved after valvuloplasty can be expected to have a sustained improvement after TAVI.

When TAVI is considered in COPD patients, optimal respiratory status should be reached before the procedure. Short-term pulmonary rehabilitation and inspiratory muscle training could be offered to selected severe COPD patients before TAVI as well. (171,177-179) Additionally, although data are lacking, performing TAVI with light sedation only, rather than general anesthesia, could be a superior therapeutic approach in lung disease patients. (180-182)

As suggested by the main worldwide consensus statements and executive summaries, therapeutic interventions for COPD relieve dyspnea even by addressing different pathophysiologic mechanisms in the body, such as improving respiratory muscle function and altering central perceptions of the problem. (183)

Chapter 8. LIMITATIONS

Italian cohort patients started with lower baseline QoL indices [Italian baseline EQ-5Dindex 0.69 [IQR 0.52-0.80] vs. UK 0.73 [IQR 0.36-0.80), Italian baseline EQ-5DVAS 50 [IQR 30-70] vs. UK 60 [IQR 50-75], $p < 0.01$ for both). The 1-year EQ-5Dindex and EQ-5DVAS were greater in the Italian cohort (Italian 1-year EQ-5Dindex 1 [IQR 1-1] vs. UK 0.81 [IQR 0.70-1), Italian 1-year EQ-5D VAS 90 [IQR 80-100] vs. UK 75 [IQR 60-85], $p < 0.01$ for both). Of note, a limitation of the EQ-5D questionnaire is that there are no particular 3-level values sets for an Italian population. The consensus and the opinion of the EuroQoL Group is to apply the UK TTO scoring algorithm. This may partly explain the per country differences.

Almost all TAVI procedures in this series were performed under general anesthesia and transesophageal echocardiography guidance, and only a minimal part of the patients underwent the procedure by TAO approach. These results might therefore not apply to TAVI procedures performed with local anesthesia and by minithoracotomy, and future studies will have to evaluate the impact of COPD on patients undergoing this type of TAVI procedures.

Finally, our COPD cohort included a relatively small number of patients with no very severe COPD patients, and the results regarding the prognostic factors in COPD patients will have to be confirmed in larger studies. Also, larger studies will be needed to evaluate the predictive factors of periprocedural complications not obvious in our study and the prognostic value of oxygen dependency or respiratory medications among COPD patients.

The EQ-5D questionnaire has been criticized as nonspecific instrument - but no aortic stenosis specific QoL tool currently exists. Several previous studies have shown that both SAVR and, more recently, TAVI improve health status and QOL compared with baseline for patients with severe AS using other measures (SF-12, SF-36 etc.). The QoL instrument used in this study, the EQ-5D is widely employed in the cardiology field, involving populations affected by coronaropathies, by heart failure, associated with heart transplant, and in the rehabilitation programs, as well.

(33,156,184) Given the relatively high 1-year mortality associated with TAVI, a proportion of patients with available data diminished over time. COPD mortality was higher at late follow up. Therefore, the QoL improvements are based on the (fitter) surviving patients and the results are favourable as expected. Rather than a bias it is representative of the clinical picture in survivors.

Chapter 9. CONCLUSIONS

For every Heart Team performing TAVI, QoL should be a key outcome, given the limited life expectancy of this population. Although death is the lowest possible functional status, patients can feel survival marked by reduced physical function or independence as a worse outcome.

TAVI is effective in improving QoL in patients not suitable for sAVR without or with severe chronic obstructive pulmonary dysfunction. Overall health-related QoL is equitable at 30 days and at 1 year. Indeed, the magnitude of improvement in QoL is comparable between non and COPD affected patients at both 30 days and 1 year.

Considering clinical and QoL results, this study demonstrated that TAVI represents an appropriate, effective and safe therapy in high-risk patients with both severe AS and COPD.

It confirmed the importance of recognizing preexisting severe COPD before making operative decisions in such patients, in order to allocate medical resources to patients who have a bare possibility to regain fulfillment from activities of daily living.

In the COPD patients with moderate to severe disease, the probability of QoL improvement at 30 days and at 1 year was independent on the access route other than at 30 days, when the transfemoral access was shown to be a strong predictor of QoL improvement.

If the percutaneous femoral approach continues to represent the access of choice for the vast majority of patients proposed for TAVI, other accesses will undoubtedly continue to expand with increased experience and knowledge.

There are specific advantages and disadvantages to each TAVI technique. For the ultimate decision process for TAVI, selection of the optimal route requires consideration of specific patient anatomy, comorbidities and the device to be used.

It is important to realize that clinical judgment should not be reduced to simple algorithms or flow charts; final judgment remains with the heart team consensus, in the light of what is the best for the patient.

Chapter 10. REFERENCES

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