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Transcatheter aortic valve implantation versus surgical aortic valve replacement: a propensity score analysis in patients at high surgical risk

Dissertation

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1. Introduction

1.1. Historical Context

Senile calcific Aortic stenosis (AS) is the most common valvular disease among the ageing population. Its clinical importance becomes apparent when considering the prevalence which is approximately 4.6% for severe AS in adults more than 75 years of age. (Nkomo et al. 2006)

Due to the fact that the outcome of conservative medical treatment is poor once the effective orifice area is reduced significantly and leads to hemodynamic impairment of the left ventricle, conventional surgical aortic valve replacement was introduced in 1960 and has become the gold standard for the treatment of aortic valve disease. It can be performed in a highly standardized manner with excellent results regarding perioperative mortality and morbidity even in octogenarians and in patients at high surgical risk and was for a long time the only effective form of treatment in adults with acquired AS. (Bose et al. 2007, Gummert et al. 2007, Melby et al. 2007, Rosendorff 2005, Sundt et al. 2000)

Due to the low perioperative morbidity, aortic valve replacement may be indicated even in asymptomatic patients with severe aortic stenosis (Brown et al. 2008). Operative mortality in octogenarians is 4.9% (Brown et al. 2009). It is therefore clearly superior to any conservative treatment option (Ross et al. 1968), with an observed survival of less than 50% in two years when untreated after the first onset of symptoms. However, it is a clinical reality that a substantial share of patients are denied surgery due to presumed or real contraindications or because operative risk is deemed prohibitively high due to comorbidities (Iung et al. 2005). Most of the contraindications relate to the use of extra-corporal circulation and aortic cross-clamping. Potential factors are porcelain aorta, renal dysfunction and malignant diseases. Representative comorbidities that increase the risk of open heart surgery are renal insufficiency, cardiomyopathy, extra-cardiac vascular disease, chronic lung disease and neurological dysfunction (Rosendorff 2005).

Nevertheless, the proportion of patients at high surgical risk increases among the ageing population in developed countries. Currently approximately 67 % of patients with severe aortic stenosis are being treated surgically (Iung et al. 2005). Until recently, surgical substitution of the native valve by biological or mechanical heart valve prosthesis was the only durable treatment option.

It is for this growing population of high-risk patients that less invasive, beating-heart transarterial retrograde or transapical antegrade aortic valve implantation (TAVI) procedures have been developed and introduced into clinical practise for primary valve implantation (Walther et al. 2007, Webb et al. 2007), in combination with percutaneous

coronary interventions (PCI) (Conradi et al. 2011) or even for redo valve-in-valve procedures (Seiffert et al. 2010).

1.2. Definition, symptoms and epidemiology of aortic stenosis

AS can either be congenital or acquired, whereas the acquired form can either be from calcific senile AS or rheumatic AS. (Rosendorff 2005)

Senile, aortic valve stenosis is usually of degenerative origin. The valve that normally has a trileaflet structure, becomes fused due to calcification and thus the effective orifice area (EOA) decreases. When the EOA, becomes significantly reduced to about one fourth of its physiological value of 2.5 to 3.5 cm^2, substantial hemodynamic obstruction is present. The ventricle adapts by developing left ventricular hypertrophy to maintain cardiac output. Consequently the gradient across the aortic valve as well as the left ventricular end-diastolic pressure increase. Severe AS is present when the effective orifice area is < 1.0 cm^2, the pressure gradient ≥ 40 mmHg and the peak aortic jet velocity ≥ 4m/s.

Patients are typically asymptomatic during the period of left ventricular remodelling. When symptomatic, patients clinically often present a triad of angina, syncope and dyspnea (Rosendorff 2005).

Angina is due to the increased oxygen demand of cardiomyocytes caused by hypertrophy and reduced coronary flow reserve. Coronary blood flow may also be reduced due to low post-stenotic pressure of the affected valve.

Syncope occurs when the left ventricle is hemodynamically compromised and fails to adapt on exertion, resulting in low cerebral perfusion. Exertional dizziness may appear instead and bears the same significance as syncope.

Dyspnea on exertion can be present early in the clinical course and is caused by the elevated left ventricular end-diastolic pressure. More severe but later manifestations of the disease are orthopnea, paroxysmal nocturnal dyspnea and sudden cardiac death. (Rosendorff 2005)

Prevalence of acquired degenerative aortic stenosis increases with age, thus being 1-2% in patients aged 75-76 and nearly 6% in those aged 85 to 86 years (Lindroos et al. 1993). Several studies indicate that calcific valve disease is associated with equal risk factors as for artherosclerosis, including age, gender, lipoprotein (A), low density lipoprotein (LDL), hypertension and smoking (Fendley Stewart et al. 1997). However, as only 50% of patients with aortic stenosis also have significant coronary artery disease, other factors of the pathogenesis are still subject of current investigations.

Inflammation, angiogenesis and remodelling of the extracellular matrix, leading to severe calcification in the aortic valve, present the progressive process of AS (Falcão-Pires et al. 2012).

1.3 Indications and options for treatment of severe aortic valve stenosis

1.3.1. Indications for treatment

The reference treatment for acquired aortic stenosis in adults is surgical aortic valve replacement (AVR). According to international guidelines (Iung et al. 2002), it is indicated even in asymptomatic patients with severe aortic stenosis (EOA <1.0 cm^2), when there is abnormal response to exercise (i.e. inadequate blood pressure rise or fall, impaired exercise tolerance), a peak jet velocity of ≥ 4.0 m/s with fast annual progression, moderate to severe calcification and in patients with impaired left ventricular function (<50%). With lower evidence, treatment may as well be indicated in the asymptomatic patient presenting severe left ventricular hypertrophy (wall thickness > 15mm) and severe ventricular arrhythmias, unless other causes, related to these symptoms, cannot be identified. Patients undergoing coronary artery bypass grafting (CABG) or other cardiac surgery should also receive AVR (Bonow et al. 2008). Asymptomatic patients may only be treated if the surgeon considers that comorbidities are low and do not pose an excessive risk to undergo surgery (Iung et al. 2002).

Guidelines recommend early treatment for patients with symptomatic (angina, syncope, dyspnea) and severe (EOA < 1.0 cm^2, Vmax ≥ 4 m/s, mean gradient ≥ 40 mmHg) AS (Bonow et al. 2008).

1.3.2. Surgical Aortic valve replacement

Surgical aortic valve replacement (AVR) has become a gold standard procedure since the introduction of extra-corporal circulation. Known complications are stroke, wound infections, atrial fibrillation, heart block requiring implantation of a permanent pacemaker and renal failure (Kim et al. 2009).

Access to the aortic valve is achieved via median sternotomy or minimally-invasive techniques such as partial upper sternotomy and the subsequent establishment of cardiopulmonary bypass by aortic and right atrial or femoral cannulation. Cardiac arrest is achieved by antegrade or retrograde administration of cardioplegia and moderate hypothermia of 32° centigrade (Fullerton 2007). A transverse aortotomy is made distal to the right coronary artery and the leaflets are excised. Next the calcified annulus is debrided. The appropriate valve size is chosen by using valve sizers.

The surgeon places pledgeted horizontal sutures through the native aortic annulus and brings the sutures through the valve sewing ring. Then the valve is seated and the

sutures are tied. When the valve is sewn in place, the transverse aortotomy is closed, and aortic cross-clamp is removed, leading to myocardial reperfusion (Fullerton 2007).

1.3.3. Transcatheter aortic valve implantation

It has been reported that despite all efforts the mortality of patients undergoing routine AVR can be as high as 20% if comorbidities are severe, including impaired left ventricular function and advanced age (Alexander et al. 2000). As many as 31.8 % of patients are therefore not considered suitable candidates for surgery (lung et al. 2003), therefore new treatment options have been introduced.

Transcatheter aortic valve implantation (TAVI) is a minimally invasive, off-pump technique for treatment of severe aortic stenosis in high-risk patients. The first TAVI procedure was performed by Cribier in France in 2002 (Cribier et al. 2002).

Percutaneous valve implantation was initially directed to the pulmonary valve and has been successful in many patients with former congenital anomalies, suffering from degenerated homografts (Lurz et al. 2008). When the procedure was extended to the aortic valve, the incidence of significant paravalvular leakage was initially about 25% and a high rate of need for pacemaker implantation due to atrioventricular blockage was noticed. As a consequence, larger prostheses were introduced and alternative approaches were developed (Walther et al. 2007).

TAVI can be performed in an either antegrade or retrograde manner, being transapical and transarterial, in order to implant a stented, biological valve. The transarterial approach can be performed through access to the femoral or subclavian artery, or the ascending aorta. Transapical AVI is done by an anterolateral mini-thoracotomy via the apex of the left ventricle.

The Edwards SAPIEN^{TM} valve was approved for commercial use in the European Union in 2007 for transfemoral delivery and in 2008 for transapical delivery (Wendler et al. 2010). In its current generation it is a balloon-expandable, cobalt-chrome-stented valve made of bovine pericardium (Edwards Lifesciences, Irvine, Calif;, 2011). Besides the Edwards Sapien TM valve, there are also self-expandable, nitinol-based valves such as the Medtronic CoreValve, JenaValve and Symetis Accurate.

Following actual guideline of the ESC and EACTS (Vahanian et al. 2012) transapical and transfemoral aortic valve implantation should be performed in a hybrid operating room under fluoroscopic and echocardiographic guidance, simultaneously providing adequate sterility and standby cardiopulmonary bypass.

Patient screening should be performed by standard preoperative evaluation and suitable candidates for TAVI should be assessed by an interdisciplinary heart team consisting of experienced cardiac surgeons and cardiologists. All patients with elevated

risk should be discussed in an interdisciplinary conference before being allocated to one or the other treatment option.

When a patient is considered a suitable candidate for TAVI, a choice concerning the adequate approach has to be made. Potential contraindications for TF-AVI are peripheral vascular disease, small calibre of the groin vessels and aorto-iliac disease, such as tortuosity of the abdominal aorta, aneurysm and severe calcification of the aortic arch. Potential contraindications for TA-AVI are severe pulmonary disease or ventricular aneurysms.

1.3.3.1. Transapical aortic valve implantation

For transapical Implantation of an Edwrads Sapien valve a pigtail catheter is placed in the aortic root at the level of the aortic annulus to visualize the aortic valve by angiography.

The surgeon then performs an anterolateral mini-thoracotomy in the fifth or sixth intercostal space. Wires for epicardial pacing are placed and tested. Then two apical felt-pledgeted purse string sutures are placed in the myocardium near to the apex. The procedure is continued after intravenous administration of Heparin. After positioning of fluoroscopy, perpendicular to the aortic annulus, the apex is punctured and a guide wire is inserted antegrade across the aortic valve. It is then replaced by a stiff guide wire which is positioned across the aortic arch into the descending aorta (Walther et al. 2009).

As a next step, balloon valvuloplasty is performed by expansion of a contrast media filled balloon in the aortic annulus during rapid ventricular pacing (RVP) to avoid balloon displacement by cardiac output. The rate of RVP should range between 160/min and 200/min. After valvuloplasty of the native valve, the balloon catheter is retrieved.

The valve size is selected according to the pre-operative measurements in CT or TEE. Special attention should be taken to evaluate the width of the sinuses and the distance of coronary ostia to the annulus to reduce the risk of coronary obstruction during TAVI.

The delivery sheath is inserted and is kept stable in position. Simultaneously the valve is crimped on the delivery catheter balloon.

The most critical step during TAVI is exact valve positioning. The crimped valve is introduced into the annulus under angiographic and echocardiographic guidance. The valve should be in coaxial position and perpendicular to the aortic annulus. It is positioned within the calcified annulus, along the entire circumference.

Rapid ventricular pacing (RVP) is performed with instantaneous balloon inflation to implant the valve and to make sure that there is no misplacement due to left ventricular outflow. (Walther et al. 2009)

Repeat dilation may be performed when moderate (2+) paravalvular leakage is present. Another episode of RVP is installed to perform redilation, filling the balloon with slightly more contrast media than previously used.

After implantation, both sheath and guidewire are removed and the apex is closed with previously placed purse string sutures. Protamine may be administered in the presence of diffuse bleeding.

The pericardium is closed to cover the apex. A pleural chest tube is inserted and the chest wall is closed in multiple layers. The patient is then extubated on the operating table.

1.3.3.2. Transarterial aortic valve implantation

Transarterial implantation of an Edwards Sapien valve can be performed by access of the femoral artery, the subclavian artery or via the ascending aorta, with the TF approach being the most commonly used. In some centres, TF is performed under analgosedation to avoid intubation and the risks of general anaesthesia.

Temporary transvenous pacing wires are placed in the right ventricle, a pigtail catheter is placed in the aortic root via an arterial sheath in the femoral artery to obtain the fluoroscopic annular plane (Willson et al. 2011).

Then the contralateral common femoral artery is punctured most commonly using a femoral closure device followed by the insertion of a 16-18 French sheath. Guidewires are placed under fluoroscopic guidance,advanced toward the aortic valve and placed in the left ventricle. Care must be taken to avoid the mitral apparatus and ventricular perforation.

Balloon aortic valvuloplasty is performed under rapid pacing as previously described.

After dilation of the native valve the delivery catheter is inserted and the reversely crimped valve is positioned in the aortic annulus.

After valve deployment, the balloon and delivery system are removed (Willson et al. 2011). Blood pressure and ST-Segments should be observed for early onset of complications. Valve function is assessed by transesophageal echocardiography and when the wire is withdrawn, aortography can be performed for evaluation of valve function, possible leaks and patency of coronary arteries.

The common femoral arteriotomy is closed percutaneously and the patient may be extubated on the operating table.

Numerous complications of the transapical and transfemoral procedures were seen in the past. In case of hemodynamic compromise during or after balloon valvuloplasty or valve insertion, cardiopulmonary bypass may be required, converting the procedure from off-pump to on-pump technique. Coronary artery obstruction is described to be a rare but severe complication of this procedure. Severe valve dysfunction may be caused by intrinsic prosthetic valve leaflet dysfunction or low position of the stented valve. In those cases, placement of a second valve may be required.

The occurrence of valve embolization requires conversion to surgery. Also tear or rupture of the aortic root is a reason for immediate surgery to repair or replace the aortic root.

Perioperative stroke can occur from atheroembolism and pacemaker implantation can become necessary subsequently, as the periannular tissue and the conduction system may be compressed.

1.4. Objectives

AVR has to serve as the clinical benchmark for any new treatment option of AS. It provides lasting relief of symptoms and results in improved quality of life and excellent short- and long-term survival. In this study, outcomes of a cohort of 82 consecutive TAVI procedures were analyzed and compared to a propensity adjusted control group of patients after surgical AVR.

The aim was to construct two comparable study cohorts consisting of patients similar in regard to preoperative comorbidities and risk factors in order to assess the different outcomes after the respective procedure, as well as to identify predictors of periprocedural success for each procedure. The statistical hypothesis was non-directional, since the different effects of TAVI and AVR in similar patients were still unclear. Consequently we observed differences in outcome of survival, hemodynamic and relief of symptoms. Secondly we sought to identify the benefits or potential harm for patients in the two cohorts from either of the two procedures. Furthermore, differences in outcome between subgroups of TAVI according to access (TF vs. TA) were analysed.

The data of this study was published in 2011 in the Journal of Thoracic and Cardiovascular Surgery (Conradi et al. 2011). The following dissertation demonstrates methods and results in more detail and discusses them in the context of current studies (Status: 2011). Conclusions made from these data may be similar to phrases used in the publication.

2. Methods

2.1 Study design and limitations

This is a retrospective, observational, non-randomised, single-center cohort study with two patient groups.

Patients were not randomized to receive either TAVI or AVR. Therefore unknown and potentially confounding variables may have had an impact on outcomes. However, risk adjustment yielded two patient cohorts which were similar regarding many baseline demographics and risk factors. The retrospective nature and limited patient number in this study are further potential limitations.

Nevertheless the study represents a real world experience of a newly introduced treatment alternative in comparison to the reference treatment.

2.2. Patient selection

2.2.1. Treatment group

From June 2009 through June 2010, 82 consecutive patients with severe aortic stenosis underwent TAVI via transapical (TA, n = 60) or transfemoral approach (TF, n = 22) using the Edwards Sapien^{TM} balloon expandable pericardial xenograft. Decision-making for TAVI or AVR was a formal process involving a dedicated interdisciplinary heart team of cardiac surgeons, interventional and non-interventional cardiologists, cardiac anaesthetists and intensive care physicians. All patients with elevated risk were discussed in an interdisciplinary conference and were allocated to one or the other treatment option by mutual agreement. All TAVI procedures were performed by the heart team in a hybrid operating theatre. Transesophageal echocardiography and fluoroscopy were employed to guide the implantation procedure. Patients considered eligible for TAVI were generally > 75 years of age although age alone did not qualify as a single criterion for TAVI. All patients were considered to be at high surgical risk due to comorbidities with a logistic European System of Cardiac Operative Risk Evaluation (logEuroSCORE) of 20% or greater.

Patients deemed poor surgical candidates, were primarily evaluated for a transfemoral approach and allocated to a transapical procedure in case of severe aorto-iliac disease or peripheral vessels otherwise unsuitable for transfemoral access. Special consideration was given to sclerosis of the aortic arch which when present led to a liberal indication of TA procedures in order to avoid potential mobilization and embolism of atheroma. Due to their age and cardiovascular risk profile, sclerosis of the aortic arch is common in the typical TAVI population, leading to a ratio of approximately 1:1 TA:TF in our overall experience and 3:1 TA:TF in our study cohort of 82 consecutive patients.

2.2.2. Control group

In order to derive a surgical control group, 499 patients aged 75 years or older were identified from the hospital records out of a total of 1656 patients treated by isolated AVR for aortic stenosis between 2001 and 2009 at our center. From these, 82 patients were extracted by means of propensity scoring regarding the following variables: age, gender distribution, logEuroSCORE I, STS predicted risk of mortality (STS-PROM), NYHA functional class, left ventricular ejection fraction (LVEF), moderate reduction of LVEF (30-50%), severe reduction of LVEF (< 30%), prior stroke, cerebrovascular disease, peripheral artery disease, coronary artery disease (CAD), creatinine, diabetes, arterial hypertension, pulmonary hypertension > 60 mmHg, COPD ≥ GOLD II, malignant disease, previous cardiac surgery, atrial fibrillation and prior pacemaker implantation.

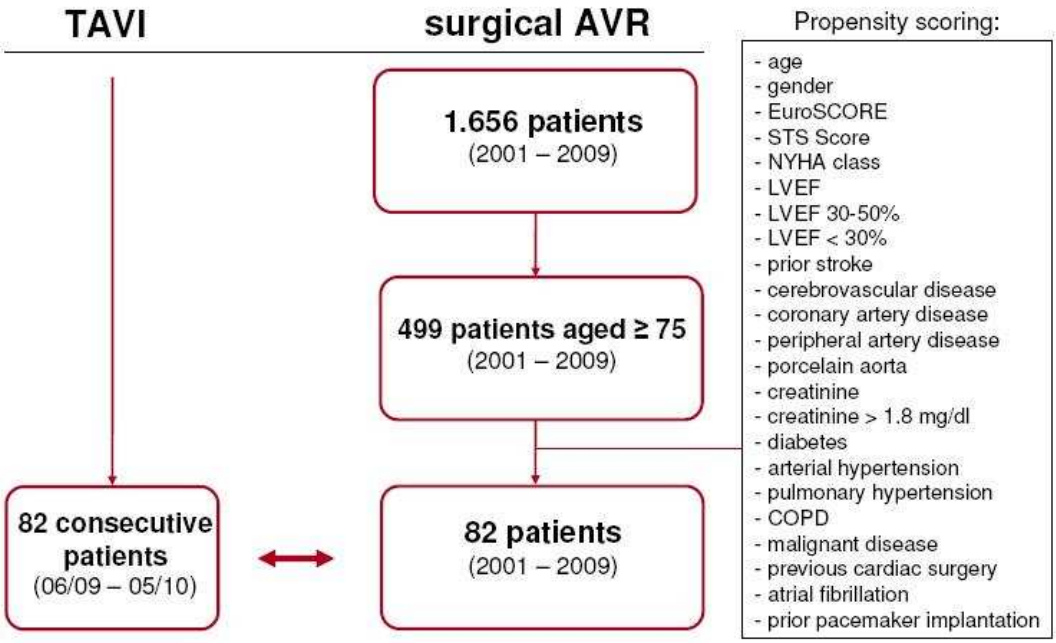

Figure 1: Mode of patient selection in order to derive a propensity score matched control group, identifying the individuals nearest to the case group subjects.

Patients were followed until 180 days after the procedure. Patient data of the two respective cohorts are detailed in table 1.

2.3. Data collection

Patient files were collected and source documents were investigated to derive as many baseline data as possible. Important source documents from the patient records used

for research were discharge letters, records of intensive care stay, echo reports, anaesthesia protocols and lab reports.

STS predicted risk of mortality (STS-PROM) and logistic EuroSCORE were calculated using online calculators. (http://riskcalc.sts.org/STSWebRiskCalc273/de.aspx ; http://www.euroscore.org/calcold.html, status: February 2012)

Detailed baseline demographics and risk factors are summarized in Table 1, page 17.

Questionnaires were sent to surgical control group patients in order to obtain informed consent for the request of patient data from outside hospitals or general practitioners, as well as to achieve knowledge about the patients' general health condition and possible adverse events that may have occurred since the operation.

Follow up for the control group was completed on behalf of the questionnaires, direct telephone contact to the patients and their relatives or during follow-up, in our outpatient clinic.

All TAVI patients had given informed consent to be followed up during the postoperative period.

All data was depersonalized and retrospectively entered into a dedicated database.

2.4. Primary endpoints of the study

The primary endpoints of the study were all-cause mortality at 30 and 180 days and incidence of Major adverse cardiac and cerebral events (MACCE) at 30 and 180 days.

MACCE were defined as the composite endpoint death, stroke, re-operation and myocardial infarction. Additionally, outcomes at 30 days are reported in accordance to the composite endpoint definitions by the valve academic research consortium (VARC), including the combined 30-day endpoints device success and the combined safety endpoint (all-cause mortality, major stroke, Life-threatening bleeding, Acute kidney injury Stage 3 according to the modified RIFLE-classification, peri-procedural MI and Repeat procedure for valve-related dysfunction) (Leon et al. 2011).

2.5. Secondary endpoints of the study

The secondary endpoints of the study were conversion to surgery using cardiopulmonary bypass (CPB), intraprocedural complication, impact of respective procedure on renal function, predictive value of EuroSCORE I and STS predicted risk of mortality for transcatheter-based procedures in comparison to AVR, predictors of 90-day mortality, the number of periprocedural packed red blood cell units (PRBC) transfused, the need for postprocedural pacemaker implantation, other periprocedural adverse events, length of ICU and hospital stay, improvement in NYHA Class during follow-up and hemodynamic improvement at follow-up. Secondary endpoints can not

be reported according to the VARC definitions because data collection was performed prior to publication of VARC criteria in 2011 and could not be analysed retrospectively.

2.6. Statistical analysis

Data are presented as absolute numbers and percentages for categorical variables and mean values and standard deviations for continuous variables. Dichotomous variables were compared using Fisher's exact test and continuous variables by unpaired or paired t-tests. In case of trend for categorical variables we used the Cochran-Armitage trend test.

Time to death and time to event are based on days past valve implant, without consideration of discharge from hospital. Kaplan-Meier analysis and log-rank test were used for time–to-event analyses. P-values are reported without correction for multiple testing. Level of significance was set to a two tailed $p<0.05$.

A logistic regression model was employed to generate a surgical control group matched for the variables detailed above. The propensity score was enabled to derive 1:1 matching on many variables out of a large database of surgical AVR patients. Each patient was selected randomly from the treatment group and was matched with a partner from the control group regarding risk factors considered by the propensity score in order to provide unbiased estimation of treatment effects. We presumed that a substantial overlap between treatment and comparison group was present and consequently aimed to identify these patients by propensity scoring.

Group differences were therefore reduced as much as possible, but hidden bias could not be excluded as in any retrospective study.

Predictors of periprocedural mortality were generated stepwise, analyzing many preoperative characteristics in a univariable analysis and subsequently performing a multivariable logistic regression analysis for suspected risk factors. Univariable risk analyses were performed by Fisher´s exact test for binary risk factors and by logistic regression for continuous risk factors; there was no imputation made for missing data in the univariate analysis. The multivariable analysis was performed by enter method and missing baseline values of the respective variables were considered to be the mean of observed values. Correlation between STS-PROM and logistic EuroSCORE I in predicting perioperative mortality was demonstrated on behalf of the Spearman´s coefficient. The discriminatory power of the logistic EuroSCORE I and the STS-PROM was evaluated using c-statistic, the area under the receiver operating characteristic curve (ROC-Curve), with 95% confidence interval (CI).

A c-statistic of 0.5 indicates no predictive ability, while a c-statistic of 1.0 would signify perfect discrimination. If a value reaches an area under the curve (AUC) of .0.7, the test is considered to be of acceptable predictive ability.

All statistical analyses were performed using SPSS 19.0 or the statistical package R version 2.12.2 [17].

3. Results

3.1. Baseline characteristics of study cohorts

The two study cohorts did not differ significantly with regard to most clinical baseline characteristics reflecting the patients´ preoperative risk profiles, such as the logistic EuroSCORE I, STS-PROM, NYHA functional status, left ventricular function and other variables, summarized in Table 1. Differences between the two cohorts were found regarding some preoperative hemodynamic parameters: effective orifice area, peak and mean transvalvular pressure gradients .

Table 1. Baseline demographics and risk factors for TAVI and AVR cohorts in the study population.

	TAVI	**AVR**	**p value**
N	82	82	
Age (years)	81.9 ± 5.2	82.5 ± 4.1	0.39
Female gender	**52 (63.4%)**	**48 (58.5%)**	0.52
logEuroSCORE (%)	23.9 ± 11.5	23.6 ± 10.4	0.85
STS PROM (%)	8.5 ± 1.3	9.0 ± 4.9	0.74
NYHA functional class	3.1 ± 0.6	3.2 ± 0.6	0.15
NYHA I	**1 (1.2%)**	**0**	1.0
NYHA II	**7 (8.5%)**	**5 (6.1%)**	0.77
NYHA III	**57 (69.5%)**	**46 (56.1%)**	0.11
NYHA IV	**13 (15.9%)**	**19 (23.2%)**	0.32
LVEF (%)	52.5 ± 8.4	50.6 ± 10.7	0.23
LVEF 30-50%	**18 (22.0%)**	**22 (26.8%)**	0.85
LVEF < 30%	**3 (3.7%)**	**8 (9.8%)**	0.21
Mean EOA (cm^2)	0.7 ± 0.2	0.6 ± 0.1	0.02
Mean / peak gradient (mmHg)	39.2 ± 16.3 / 65.0 ± 24.9	45.8 ± 16.7 / 75.3 ± 25.5	0.02 / 0.01
Prior stroke or TIA	**16 (19.5%)**	**14 (17.1%)**	0.84

Cerebrovascular disease	**19 (23.2%)**	**18 (22.0%)**	1.00
Coronary artery disease	**42 (51.2%)**	**35 (42.7%)**	0.35
Peripheral artery disease > Fontaine II (%)	**16 (19.5%)**	**12 (14.6%)**	0.53
Porcelain aorta (%)	**2 (2.4%)**	0	0.50
Creatinine (mg/dl)	1.4 ± 1.2	1.3 ± 0.5	0.44
Creatinine > 1.8 mg/dl (%)	**10 (12.2%)**	**7 (8.5%)**	0.46
Diabetes (%)	**28 (34.2%)**	**25 (30.5%)**	0.74
Arterial hypertension (%)	**68 (82.9%)**	**73 (89.0%)**	0.27
Pulmonary hypertension > 60 mmHg (%)	**14 (17.0%)**	**20 (24.4%)**	0.34
COPD ≥ GOLD II (%)	**24 (29.3%)**	**27 (32.9%)**	0.74
Malignant disease (%)	**7 (8.5%)**	**2 (2.4%)**	0.17
Previous cardiac surgery (%)	**20 (24.4%)**	**11 (13.4%)**	0.11
Atrial fibrillation (%)	**25 (30.5%)**	**35 (42.7%)**	0.14
Prior pacemaker implantation (%)	**6 (7.3%)**	**5 (6.1%)**	1.00

n (%) listed for categorical variables; logEuroSCORE I logistic European System for Cardiac Operative Risk Evaluation I, STS-PROM Society of Thoracic Surgeons Predicted Risk of Mortality, NYHA New York Heart Association functional class, LVEF left ventricular ejection fraction, EOA effective orifice area, TIA transient ischemic attack, COPD chronic obstructive pulmonary disease, GOLD Global Initiative for Chronic Obstructive Lung Disease

3.2. Periprocedural results to 30 days

3.2.1. Intraprocedural data

In the TAVI group, procedural success with deployment of a functional prosthesis was achieved in 79 patients (96.3%). In 2 patients (2.4%), conversion to surgery and cardiopulmonary bypass became necessary for dislocation of the prosthesis into the left ventricular outflow tract in one case and apical rupture in another. In the surgical group, valve implantation was successful in all cases. Operative times differed significantly between the two groups: Mean procedure time in TAVI was 128.9 ± 9.0 minutes vs. 200.9 ± 7.6 minutes in AVR (p=0.04). Median procedure times were 105.0 minutes in TAVI and 197.5 minutes in AVR. There were no intraoperative deaths in the AVR cohort. 2 patients in the TAVI cohort died during the procedure (2.4%): one

patient due to a Stanford Type A aortic dissection after transfemoral TAVI and one patient due to apical rupture after a transapical procedure. Additional intraoperative data are summarized in table 2.

In the TAVI cohort, 59 patients (72.0%) were extubated in the OR immediately following the procedure. Mean ventilation times (p<0.01) and mean duration of stay in the intensive care unit (p=0.008) were significantly shorter in the TAVI group. Perioperative bleeding (p=0.07) and transfusion requirements (p<0.01) were also lower in TAVI patients compared to the surgical control group.

Table 2. Intraoperative data.

	TAVI (n = 82)	**AVR (n = 82)**	**p value**
Procedure time (min)	128.9 ± 9.0	200.9 ± 58.1	< 0.0001
Cardiopulmonary bypass (min)	n/a	111.0 ± 36.2	-
Aortic cross clamp time (min)	n/a	70.8 ± 23.2	-
Fluoroscopy time (min)	9.8 ± 8.5	n/a	-
Contrast agent (ml)	198.3 ± 93.1	n/a	-
Valve size (mm)	24.3 ± 1.7	22.2 ± 1.8	< 0.0001
19 mm	n/a	**7 (8.5%)**	-
21 mm	n/a	**33 (40.2%)**	-
23 mm	**49 (59.8%)**	**31 (37.8%)**	-
25 mm	n/a	**7 (8.5%)**	-
26 mm	**30 (36.6%)**	-	-
27 mm	n/a	**4 (4.9%)**	-
29 mm	**3 (3.7%)**	-	-
Procedural success (%)	**79 (96.3%)**	**82 (100.0%)**	0.25
Conversion to surgery (%)	**2 (2.4%)**	-	-
Intraprocedural death (%)	**2 (2.4%)**	0	0.50

n (%) listed for categorical variables

3.2.2. Acute mortality to 30 days

All-cause mortality rates at 30 days did not differ significantly between TAVI (n=6, 7.3%) and AVR cohorts (n=7, 8.6%, p=1.0). Causes of death at 30 days were aortic dissection (n=1), rupture of the apex (n=1), cardiogenic shock (n=2) and sepsis with subsequent multiorgan failure (MOF, n=1) in TAVI. One death was not procedure related, as the patient had a rupture of a pulmonary cyst resulting in fatal bleeding during 30-day follow-up. In the AVR cohort, all deaths within 30 days after implant were procedure related. AVR patients had similar reasons for a fatal outcome at 30 days, as they presented cardiac decompensation (n=2) with respiratory failure (n=1), acute heart failure (n=3) and sepsis followed by MOF (n=1). .

For greater detail of acute clinical and hemodynamic outcomes see table 3.

Table 3. Acute postoperative results and complications.

	TAVI (n = 82)	**AVR (n = 82)**	**p value**
Ventilation time (hrs)	5.1 ± 20.6	19.9 ± 14.7	< 0.001
Patients extubated in OR	**59 (72.0%)**	0	< 0.001
Duration of ICU stay (d)	2.5 ± 2.2	3.8 ± 3.3	0.008
Duration of hospital stay (d)	13.5 ± 13.1	10.6 ± 7.7	0.11
Mean gradient at discharge (mmHg)	11.3 ± 5.6	11.8 ± 5.3	0.62
19 mm	**n/a**	**8.8 ± 5.1**	-
21 mm	**n/a**	**12.9 ± 4.7**	-
23 mm	**11.8 ± 6.2**	**12.7 ± 5.9**	-
25 mm	**n/a**	**7.6 ± 3.4**	-
26 mm	**10.5 ± 4.3**	**n/a**	-
27 mm	**n/a**	**10.8 ± 6.0**	-
29 mm	**5.3 ± 1.2**	**n/a**	-
Peak gradient at discharge (mmHg)	21.5 ± 10.0	22.9 ± 10.1	0.41
Paravalvular aortic regurgitation (grade)	0.8 ± 0.7	0	< 0.001
Total amount of drain fluid (ml)	521.1 ± 844.1	888.6 ± 1477.3	0.07
Transfusion (units PRBC)	0.1 ± 0.6	1.8 ± 1.7	< 0.001

Patients receiving transfusion	**6 (7.3%)**	**53 (64.6%)**	< 0.001
Impaired wound healing	**5 (6.1%)**	**3 (3.7%)**	0.72
Pacemaker implantation (%)	**3 (3.7%)**	**2 (2.4%)**	1.00
Stroke to 30 days	**2 (2.4%)**	**2 (2.4%)**	1.00
30-day mortality (%)	**6 (7.3%)**	**7 (8.6%)**	1.00

n (%) listed for categorical variables; OR operating room, ICU intensive care unit, PRBC packed red blood cells

3.2.3. MACCE at 30 days and combined 30-day safety endpoint

MACCE were defined as stroke, re-operation, myocardial infarction and death.

Two strokes occurred in each cohort (2.4%); in the TAVI cohort, one after a transfemoral and one after a transapical procedure after 10 and 11 days respectively. In the surgical cohort strokes occurred after 2 and 22 days. No surgical revisions or myocardial infarctions were seen up to 30 days after the procedure in either group.

Incidence of the VARC combined 30-day safety endpoint, including all cause mortality, stroke, bleeding, acute kidney injury stage 3, periprocedural MI and repeat procedure for valve-related dysfunction, was 18.3 % in the TAVI group (n = 15) vs. 24.4% in AVR patients (p= 0.4462).

3.2.4. Hemodynamic results

Aortic regurgitation and acute hemodynamic outcome

Echocardiography at discharge revealed good hemodynamic function of the implanted valves. Transvalvular pressure gradients were comparable between the two cohorts, while mean grade of paravalvular leakage was higher in the TAVI cohort (p<0.001). In the TAVI cohort, 50% (n=41) of patients had some degree of paravalvular leakage which was trivial to mild in 40 patients and moderate in one patient. Presence of PVL, however, did not correlate with mortality at 90 days in the logistic regression analysis (p=0.986). In the surgical cohort, no paravalvular leakage was observed in any patient. Postoperative transvalvular aortic regurgitation was present in 25.6% (n=21) of surgical patients and it was trivial in all of these cases.

Patient prosthesis mismatch

Severe patient-prosthesis mismatch (PPM, defined as indexed effective orifice area (iEOA) ≤ 0.65) was present in 10 (12.2%) TAVI patients. 2 of these patients died during follow-up. One patient due to cancer 260 days after the procedure, and another patient at 160 days after the procedure due to progressive heart failure.

According to VARC criteria, device success was achieved in 85.4% of TAVI patients (n=70). Unsuccessful delivery and deployment of the valve was present in two cases, leading to conversion to open surgery. Impaired performance of the prosthetic valve according to PPM criteria was present in 10 patients .

In the AVR cohort, severe PPM was present in one patient (1.2%) who died on postoperative day 291 after an acute myocardial infarction.

3.2.5. Impact on renal function

In the TAVI cohort 82.3 % and in the AVR cohort 59.1 % of patients showed an increase in creatinine (p=0.004). The mean difference compared to baseline values was 0.52 mg/dl (p<0.01) after TAVI and 0.2 mg/dl after AVR (p=0.005). No patient required haemodialysis for acute renal injury in either cohort. Creatinine increase was significantly higher in TAVI patients, compared to the surgical cohort (p=0.019). The patients that had an increase in creatinine were divided in two groups according to an increase of >25% or <25% compared to baseline value respectively. Increase >25 % of baseline creatinine value was seen in 45.6 % of patients in the TAVI group, compared to 28.8 % in the control group (p = 0.003). Acute kidney injury (AKI) was defined by the acute kidney injury network as an increase in creatinine of over >0.3 mg/dl from the baseline value in less than 48 hours (Mehta et al. 2007). According to their definition, AKI was present in 34.41% (n=28) after TAVI versus 24.4% (n=20) after AVR respectively (p=0.229).

For results of impact on renal function see Figure 2.

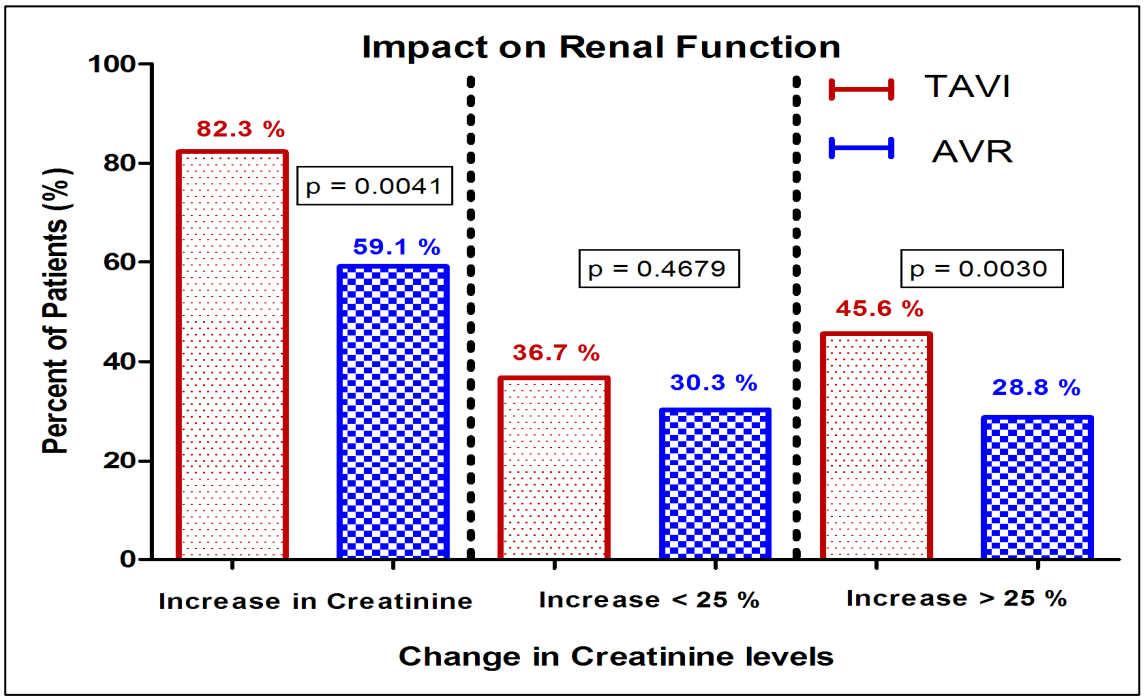

Figure 2: Periprocedural change in creatinine levels, differentiated by increase major and minor 25% of baseline values. Increase by more than 25% occurred more frequently in TAVI patients compared to surgical candidates. No patient required hemodialysis for acute kidney injury in either group.

3.2.6. Incidence of other adverse events

3.2.6.1. Incidence of postprocedural pacemaker implantation

The overall incidence of postoperative pacemaker implantation was 13.41 % (n=11) among TAVI patients and was 2.4 % (n=2) for AVR. These results demonstrate a higher odds ratio for overall PM Implantation after TAVI as compared to the AVR group (p = 0.017, OR: 6.19, 95% CI: 1.33— 28.9).

Pacemaker implantation for new onset of total atrioventricular block (TAVB) became necessary in 3 TAVI patients (3.7%) and in 2 patients from the surgical cohort (2.4%, p = 1.0). All implants were necessary within 5 days in the TAVI group (days 0, 1 and 5 after implantation), whereas the implantation for TAVB occurred on days 4 and 7 after AVR.

Pacemaker implantation for indications other than TAVB, such as left bundle branch block, sick sinus syndrome, bradycardic atrial fibrillation or asystole after implant became necessary in 8 TAVI patients (9.7 %) and in no AVR patient postoperatively (p = 0.003). 72.7% of pacemaker implantations became necessary within 5 days after TAVI. Pacemakers were implanted up to 19 days after TAVI, while mean time to implant was 5 ± 5.7 days after TAVI and 5.5±2.1 days after AVR.

3.2.6.2. Other adverse events after TAVI and AVR

Overall incidence of adverse events during hospital stay was higher in the surgical cohort compared to TAVI (44 vs. 21 adverse events, p < 0.01). This was mainly driven by the need for rethoracotomy (p= 0.017) as it was necessary for bleeding in 11 surgical patients (13.4%) compared to 2 patients in the TAVI cohort (2.4%). Obstruction of the coronary ostia by native valve leaflets occurred in the TAVI group (2.4%), leading to ST-elevation in one case and required percutaneous coronary intervention (PCI) in both patients (p= 0.496). One patient with a relevant pneumothorax was observed in the AVR group (p= 1.0).

Rates of adverse events among both study cohorts are shown in Table 4.

Table 4: Incidence of adverse events in patients undergoing TAVI and AVR. Overall incidence of adverse events was higher in AVR than in TAVI. Only the rate of

rethoracotomy was significantly higher in the surgical group. CPR = cardiopulmonary resuscitation; IABP = intraaortic balloon pump; pericardial/pleural effusions = relevant when drainage was indicated.

Event	TAVI (%)	AVR (%)	*p* value
CPR	6.1	10.9	0.402
Coronary ostium obstruction	2.4	0	0.496
Rethoracotomy	2.4	13.4	0.017
IABP	0	2.4	0.496
Pericardial/Pleural effusions	0	4.8	0.120
Cardiac decompensation	1.2	3.6	0.719
Impaired wound healing	6.1	3.6	0.719

3.3. Follow-up data

3.3.1. Predictors of periprocedural success and adverse outcome at 90 days

3.3.1.1. Univariate Analysis

Univariate analysis discriminated logEuroSCORE (p= 0.046) and STS-PROM (p= 0.003) as predictors for death at 90 days in TAVI, while this was not the case in AVR patients. In the surgical cohort, the number of periprocedural blood tranfusions was a significant predictor (p= 0.048) for death at 90 days.

Variables with presumed influence on outcome were included in a multivariable analysis. These were, with regard to p-values in the univariate analysis, the following variables: mean serum creatinine at baseline (p= 0.081), LVEF under 30% (p= 0.085) pulmonary Hypertension ≥ 60mmHg (p= 0.087) in the TAVI cohort and carotid artery disease at baseline (44.4% vs. 20.5%, p= 0.201) and a perioperative increase of creatinine > 1.8 mg/dl (p= 0.067) in surgical patients.

Table 5: Baseline and peri-procedural characteristics of patients undergoing transcatheter aortic valve implantation and surgical aortic valve replacement, according to the occurrence of observed 90 day mortality.

Death within 90 days						
	TAVI			**AVR**		
Variable	Yes (n = 11)	No (n = 71)	P-value	Yes (n = 9)	No (n = 73)	P-value
Baseline characteristics						
Age (years)	82.2± 4.8	81.8± 5.2	0.822	82.7± 4.8	82.5± 4.1	0.891
BMI	27.3± 7.7	27.8± 5.9	0.818	26.6± 6.7	25.6± 4.2	0.536
Female (%)	63.3	66.2	1.000	66.6	57.5	0.729
Diabetes (%)	36.4	33.8	1.000	11.1	32.8	0.264
Hypertension (%)	90.9	80.3	0.679	77.7	89.0	0.301
NYHA I-II (%)	18.2	8.5	0.291	0	6.8	1.000
NYHA III-IV (%)	72.7	87.3	0.199	88.8	78.1	0.676
Previous cardiac intervention (%)	36.4	45.0	0.747	33.3	26.4	0.697
Carotid artery stenosis > 50% (%)	27.2	25.5	0.692	44.4	20.5	0.201
Peripheral vascular disease (%)	63.6	41.4	0.203	33.3	27.4	0.705
COPD GOLD > II (%)	9.1	11.3	1.000	11.1	9.6	1.000
Serum creatinine mg/dl	1.9± 1.9	1.3± 1.0	0.081	1.4± 0.6	1.3± 0.5	0.516
Log EuroSCORE %	**30.9± 18.5**	**22.8± 10.1**	**0.046**	25.7± 8.3	23.1± 10.6	0.484
STS-PROM %	**13.7± 10.5**	**7.8± 4.5**	**0.003**	9.4± 4.8	8.9± 4.9	0.764
LVEF 30-50 % (%)	9.1	23.9	0.447	22.2	27.4	1.000
LVEF < 30 (%)	**18.2**	**2.8**	**0.085**	22.2	8.2	0.211
Mean gradient mmHg	35.8± 15.5	39.7± 16.5	0.465	46.4± 19.1	45.7± 16.6	0.918
Efective orifice area (cm²)	0.70± 0.2	0.65± 0.2	0.503	0.59± 0.1	0.60± 0.1	0.855
Pulmonary HPT > 60 mmHg	**36.4**	**14.1**	**0.087**	22.2	24.6	1.000
Periprocedural data						
Procedure time	146.9± 96.3	120.8± 68.0	0.279	221.1± 81.6	195.3± 54.6	0.290
Amount of Contrast media (mL)	153.4± 56.9	203.8± 96.1	0.109	-	-	-
Number of red blood cell units	0	0.23± 1.5	-	**2.9± 2.1**	**1.7± 1.6**	**0.048**
Increase in Creatinine > 1.8 mg/dl	36.4	23.9	0.460	**44.4**	**16.4**	**0.067**

NYHA = New York Heart association Classification system for chronic heart failure; Previous cardiac intervention was defined as previous percutaneuous coronary intervention or previous coronary artery bypass grafting; COPD = Chronic obstructive pulmonary disease, staged by the Global Initiative for Chronic Obstructive Lung Disease (GOLD); STS-PROM = Society of thoracic surgeons predicted risk of mortality; LVEF = Left ventricular ejection fraction; Pulmonary HPT = Pulmonary Hypertension.

3.3.1.2. Multivariable Analysis

The baseline variables, considered as possible predictors of 90-day mortality, were imputed in a multivariable logistic regression. The logistic regression analysis identified STS-PROM (p=0.005) and LVEF at baseline (p=0.05) as independent predictors of death at 90 days for TAVI patients. Furthermore, patients with a strong increase in creatinine levels during the early postoperative course were more likely to decease during follow-up (p=0.005). The logistic EuroSCORE had a trend towards prediction of negative outcome in TAVI (p=0.061) although this did not reach statistical significance.

In the control group, we identified 4 independent predictors for death at 90 days: presence of pulmonary hypertension (p=0.046), carotid artery disease (p= 0.05), the

need for intraoperative blood transfusions (p=0.048). Additionally, increase in creatinine >1.8 mg/dl postoperatively served as an independent predictor (p= 0.028), whereas any increase in creatinine after surgery was not significant (p= 0.065). According to the multivariable logistic regression, STS-PROM and logistic EuroSCORE were not helpful in estimation of positive or negative outcome after AVR.
For greater detail, see Table 6.

Table 6: Multivariable analysis of suspected predictors for mortality at 90 days. Independent risk factors were STS-PROM and any increase in creatinine (crea) in TAVI. Carotid artery disease, pulmonary hypertension, need for blood transfusions and increase in creatinine >1.8 mg/dl had negative influence on outcome after AVR. Logistic EuroSCORE was not significant in both groups but had a trend as a positive predictor in TAVI.

	TAVI	
Effect	***p* value**	**odds ratio (95% CI)**
STS-PROM	0.005	1.2 (1.1-1.4)
LVEF Baseline	0.053	3.7 (0.9-9.7)
Increase in Crea post-op	0.005	1.9 (1.2-3.2)
	AVR	
Carotid artery disease	0.050	6.1 (0.9-38.4)
Pulmonary Hypertension	0.046	4.3 (1.0-18.4)
Blood Transfusions	0.048	1.7 (1.0-3.1)
Increase in Crea post-op	0.065	2.1 (0.9-4.7)
Crea > 1.8 mg/dl post-op	0.028	8.4 (1.2-55.9)

3.3.2. Mortality rates at 90 and 180 days

During further follow-up overall mortality rates were similar for the two patient cohorts. For TAVI and AVR, mortality rates were 13.6% and 11.1% (p=0.8) at 90 days and 17.8 and 16.9% (p=1.0) at 180 days (figure 1). While the majority of deaths during 30 days follow-up were procedure related (84.6%) in both cohorts, late mortality was mostly related to the patients´ comorbidities. From 21 patients (25.6%) in the TAVI cohort with a left ventricular ejection fraction of ≤50%, 4 died during follow-up, resulting in a mortality rate of 19.0%, which is insignificantly higher compared to 17.1% in the overall TAVI cohort (p=0.76). Furthermore, from 41 TAVI patients (50%) with any degree of paravalvular leakage, aortic regurgitation was graded as mild in 8 and as moderate in 1

case. From 9 patients with mild or moderate paravalvular leakage, one death occurred (11.1%) at 5 months after the procedure.

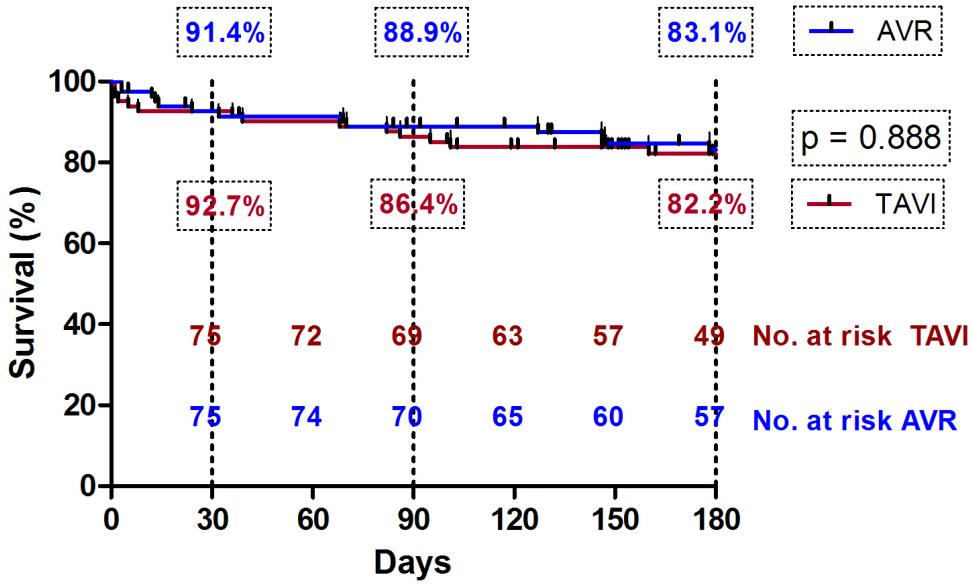

Figure 3: Kaplan Meier survival curves for patients receiving TAVI compared to a surgical control group after AVR. During a follow-up of 180 days, no statistically significant differences were noted.

An additional Kaplan-Meier analysis of causes of death (COD) in TAVI and AVR revealed, that all deaths up to 90 days were cardiac deaths in AVR (n=10,11.1%), whereas a number of TAVI patients died within 90 days after implantation due to their multiple comorbidities, such as malignant diseases or severe pulmonary fibrosis leading to fatal bleeding (n=3, 3.6%). Later, from 90 to 180 days of follow-up, mostly comorbidity related deaths occurred in both groups, with 6.1% and 4.8% in TAVI and AVR respectively (p=0.314). Deaths of unknown cause occurred in 3 TAVI, and 2 AVR patients. For greater detail of mortality causes and differences between the groups, see Figure 4.

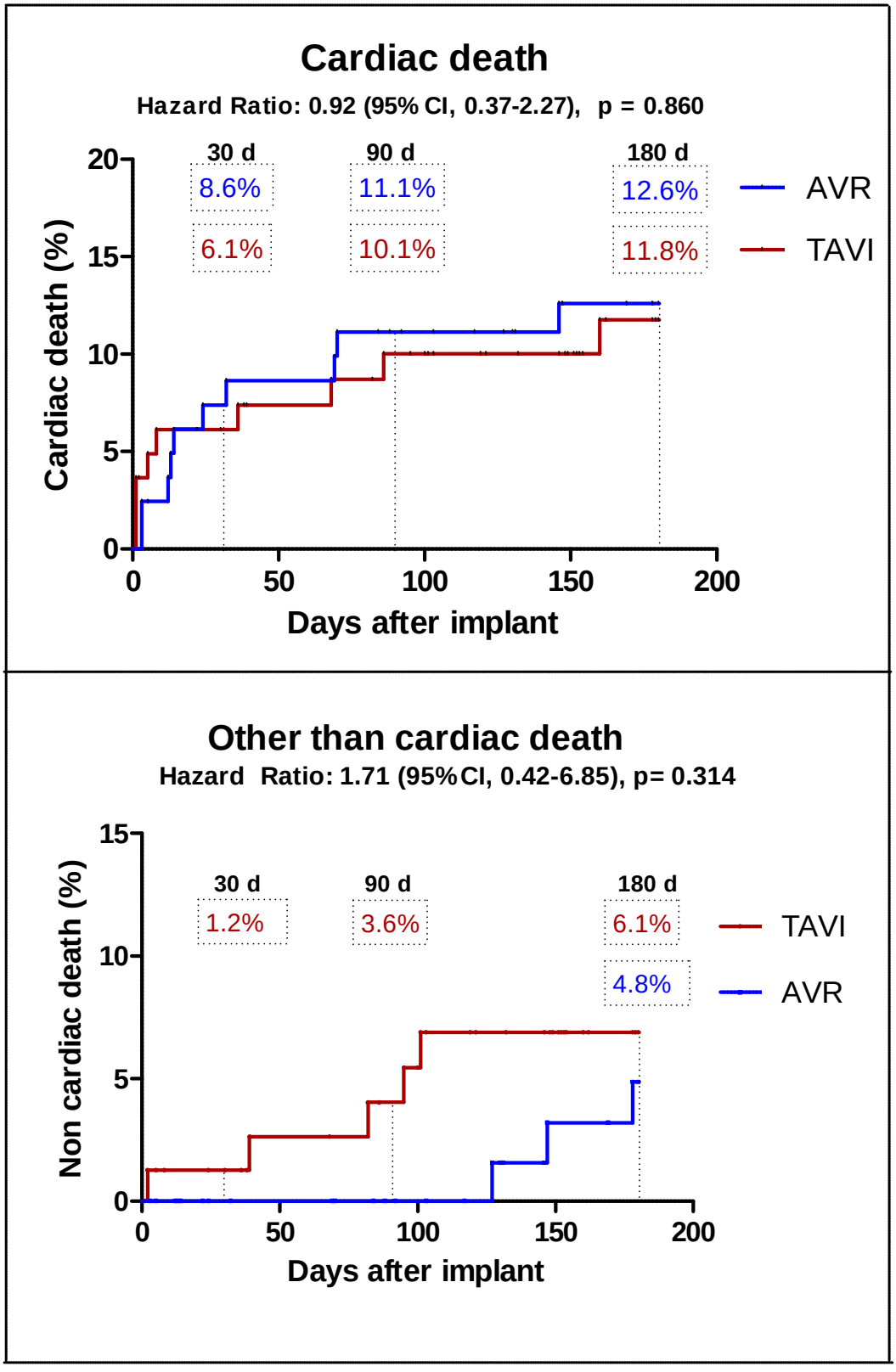

Figure 4: Cardiac and non-cardiac related mortality rates. Non-cardiac causes were stroke, malignant disease and severe pulmonary fibrosis with rupture of a pulmonary cyst. Unknown causes were allocated to the non-cardiac cohort.

3.3.3. MACCE at 90 and 180 days

Rates of MACCE were also comparable between the two groups. Incidence of MACCE for TAVI and AVR was 16.1% and 13.5% (p=0.83) at 90 days and 21.7% and 19.1% (p=0.84) at 180 days (figure 2). 3 strokes occurred in the TAVI cohort during the follow-up period (3.6%). In the AVR cohort, two patients had cerebrovascular events (2.4%). Of the latter, one patient had two strokes, the first occurred on day 2 and the second on day 127, leading to death immediately. In both groups there were no myocardial infarctions or reoperations during 180 days of follow-up.

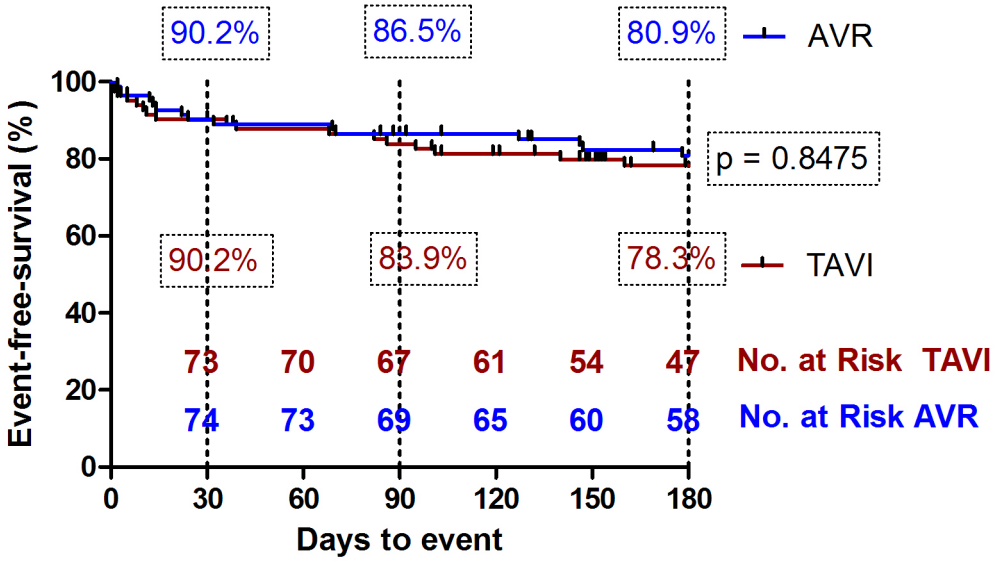

Figure 5: Kaplan Meier analysis for MACCE-free survival (MACCE: death, stroke, acute myocardial infarction, reoperation). Event rates were similar between the two cohorts.

3.3.4. Relief of symptoms

Clinically, patients improved markedly during the further postoperative course. Preoperatively, the majority of patients had been in NYHA functional class III (62.8%) or IV (19.5%) with mean NYHA of 3.1 ± 0.6 and 3.2 ± 0.6 for TAVI and AVR respectively (n = 65 in TAVI and n = 60 in AVR). Postoperatively, marked improval in patients´ NYHA class was noted in both cohorts and this effect remained stable to the latest follow-up. At 30 days, 73.2% (n=120) of patients had improved by one or more NYHA classes. At 180 days postoperatively, mean NYHA class was 2.2 ± 0.8 and 2.3 ± 1.0 for TAVI and AVR respectively (n= 38 for TAVI and n = 54 for AVR). Mean difference in NYHA class between baseline and 180 days of follow-up was 0.9 (95% CI: 0.6-1.3) in TAVI and similarly 0.9 (95% CI: 0.7 – 1.3) in AVR. This was a significant change in both cohorts ($p < 0.01$). In 11.7% (n=8) of the surviving TAVI patients, the symptoms worsened or did not improve during six-month follow up, reflected by

functional NYHA class. In comparison, in the AVR cohort, 21.7% (n=15) of the survivors did not improve or worsened during follow-up (p= 0.169).

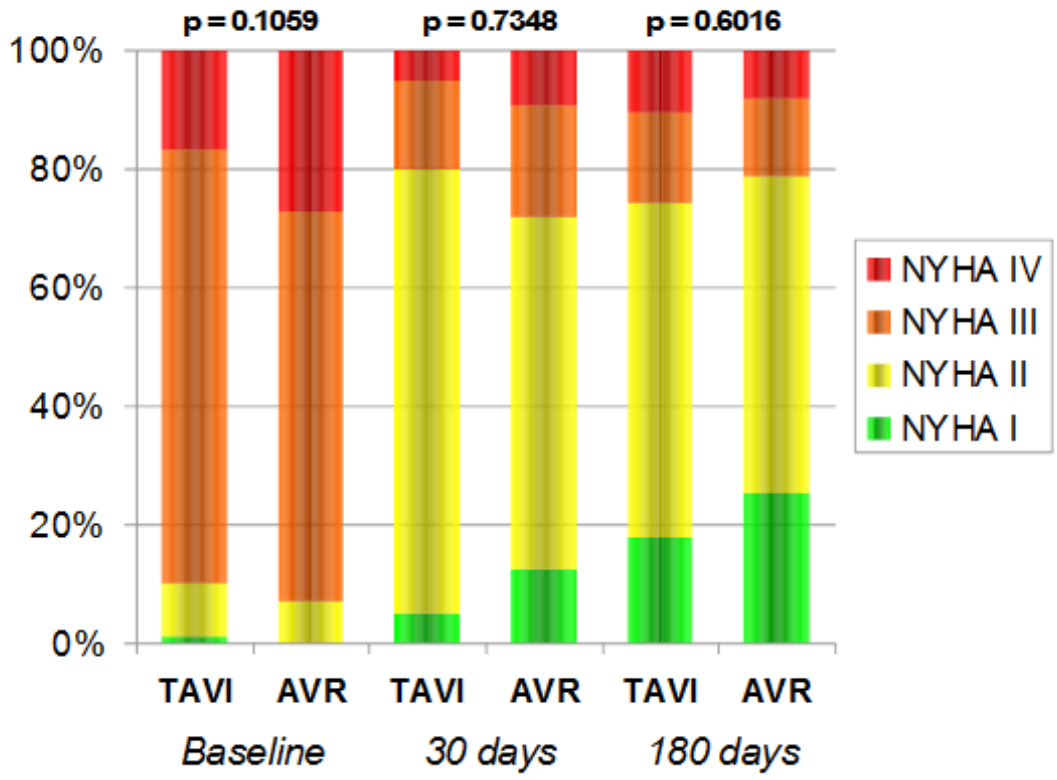

Figure 6: Improvement of NYHA Class after 30 and 180 days in TAVI and AVR Patients.

3.3.5. Prediction of adverse outcome using surgical risk stratification systems (logistic EuroSCORE I, STS-PROM)

The observed mortality rates of TAVI and AVR were 7.3% and 8.6% at 90 days. Even though the logistic EuroScore I is designed to predict 30-day mortality it still overestimated risk of mortality at 30 days with values of 23.9% and 23.6% for TAVI and AVR respectively. The STS predicted risk of mortality was 8.5% and 9.0% for TAVI and AVR respectively, being more accurate in predicting mean mortality in a cohort of high-risk patients.

After differential analysis of cohorts in three subgroups of medium risk (logistic EuroSCORE < 30%), high-risk (logistic EuroSCORE between 30 and 50%) and very-high-risk (logistic EuroSCORE > 50%), we observed a linear correlation for 30-day-mortality (p< 0.01) and 6-month-mortality (p= 0.02) in TAVI. For details see Tables 7 and 8.

Table 7: Outcome after Transcatheter aortic valve implantation in relation to the preoperative risk profile. The subgroups represent medium, high-risk and very-high risk patients. The mortality rates increase from medium to very-high risk in the 30-days- (p< 0.01) and 6-months- (p = 0.02) columns. LogES = logistic EuroSCORE.

	n	30-day mortality (%)	6-month mortality (%)
Total	82	7.3	13.6
LogES < 30	58	3.4	12.1
30 < logES < 50	19	5.3	21.0
LogES > 50	5	60.0	60.0

Subgroup analysis was also made for AVR and showed, that the mortality rates increased from medium to high-risk in the 30-days mortality column, but were not higher in the very high-risk group, as none of the 4 individuals, previously considered being at very-high-risk, died within 30 days of follow-up (p= 0.158). In the column demonstrating the mortality at 6-month a trend towards increase of mortality from medium to very high risk was seen, but this was not significant (p= 0.079).
The results are shown in Table 8.

Table 8: Subgroup analysis of patients undergoing AVR. Patients with lower risk profile had a trend towards better survival at 180 days of follow-up (p = 0.079). LogES = logistic EuroSCORE.

	n	30-day mortality (%)	6-month mortality (%)
Total	82	8.6	16.9
LogES < 30	67	5.9	14.9
30 < logES < 50	11	18.2	18.2
LogES > 50	4	0	25

The predicted risk of mortality by logEuroSCORE in TAVI patients that died during 30 and 90 day follow up was higher than in those who survived 30 and 90 days after the procedure. For 30 days the mean logEuroSCORE of the deceased patients was 35.6% versus 23.3% in the alive (p = 0.036) and 30.8% versus 22.9% for 90 days (p= 0.05).
On the contrary, the logEuroSCORE of AVR patients that died within 30 days after the procedure was not significantly different from the rest of the population, with 26.2 % in the deceased patients versus 23.5 % in the survivors (p = 0.546), and for 90 days 25.7% versus 23.3% respectively (p= 0.516).

There was a positive correlation (p = 0.01) between logEuroSCORE and STS-PROM both in TAVI and AVR patients, although the correlation of these two risk scores was probably stronger in TAVI, as Spearman´s Correlation coefficient of the two risk scoring systems was 0.431 in TAVI and 0.294 in AVR.

ROC-curve analysis was performed for each patient cohort. In the TAVI cohort (AUC) for predicting 30 day mortality was 0.642 (0.310-0.973 95% CI) for the logistic EuroSCORE and 0.774 (0.553-0.994 95% CI) for STS-PROM, although both did not reach significance levels (p = 0.341 for logEuroSCORE; p = 0.067 for STS-PROM).

In the AVR group AUC for mortality at 30 days was 0.613 (95% [CI] 0.383-0.843) for the logEuroSCORE and 0.512 for STS-PROM (95% [CI] 0.263-0.761) which was not significant either (p = 0.117 for EuroSCORE and p = 0.127 for STS-PROM).

Thus c-statistics indicated that there was no power of either logEuroSCORE or STS-PROM for predicting 30-day-mortality in either cohort Nevertheless there was a trend towards more predictive power by STS-PROM in TAVI than in the comparison group.

Results of the c-statistic are illustrated in Figures 7 and 8.

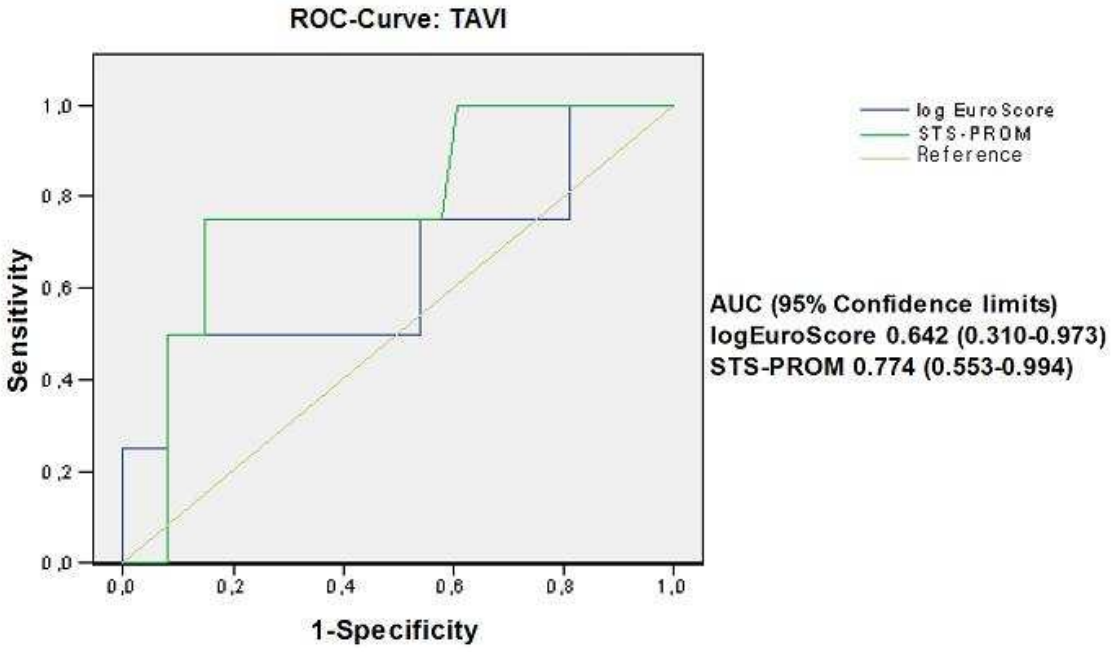

Figure 7: TAVI ROC curve. C-statistic for log EuroSCORE and STS-PROM, p-value was 0.341 for log EuroScore and 0.067 for STS-PROM.

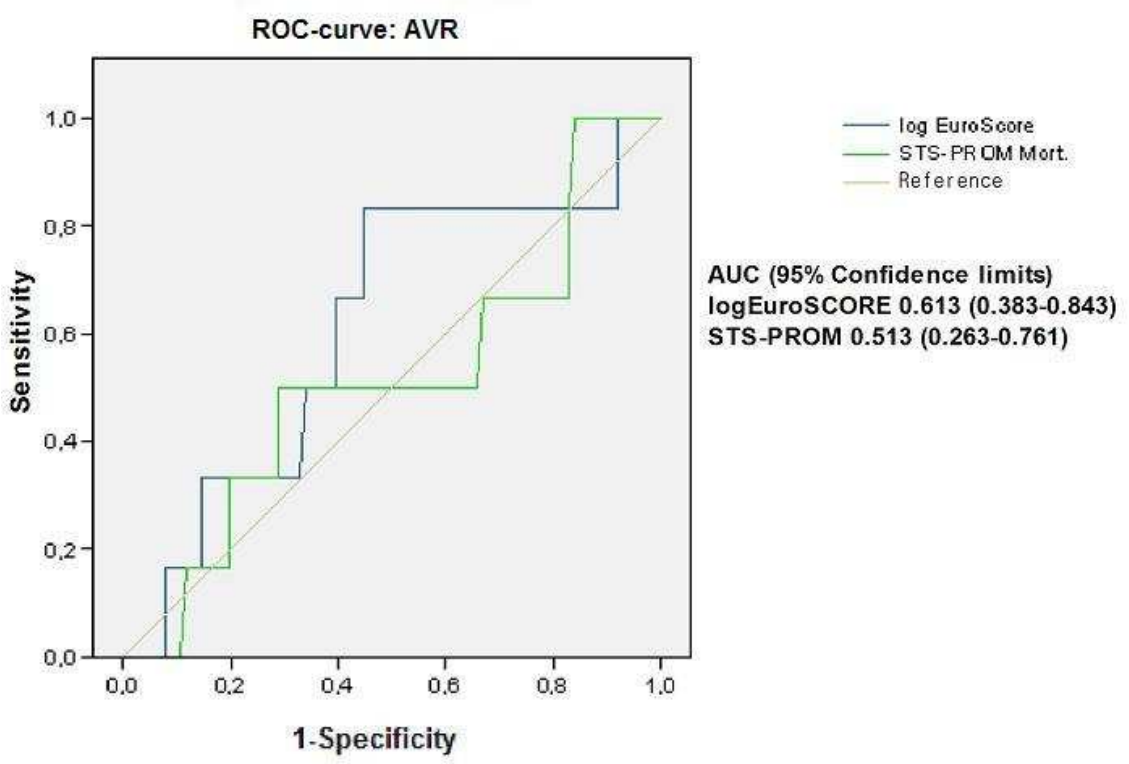

Figure 8: AVR ROC Curve. C-statistic for log EuroSCORE and STS-PROM, p-value was 0.359 for log EuroSCORE and 0.922 for STS-PROM.

4.0 Discussion

4.1. Limitations

There are some limitations in our study. In the TAVI cohort we had 82 consecutive cases, whereas we derived 82 surgical patients treated during a much longer time period (2001-2009). As in any retrospective analysis, there may be hidden bias despite careful matching of patient cohorts.

4.2. Baseline demographics of patient cohorts

In order to derive a control group comparable to the patient group undergoing TAVI, we extracted a patient cohort from our hospital database by means of propensity matching. Table 1 demonstrates, that the groups were well matched regarding most baseline variables and that they differed only concerning hemodynamic parameters (effective orifice area and baseline gradients).

We therefore conclude that a comparison of outcomes after the respective procedures is valid.

4.3. Clinical safety and possible advantages of TAVI in a high risk population compared to AVR

4.3.1. Mortality and incidence of MACCE

As recently shown in the multicenter prospective randomized Placement of Transcatheter Aortic Valves (PARTNER) Trial, TAVI is effective in reducing all-cause mortality in inoperable patients compared to best medical therapy (Leon et al. 2010) and has non-inferior survival rates compared to surgical AVR (Smith et al. 2011) in high-risk patients. Furthermore, TAVI has been advocated to decrease operative morbidity and mortality in patients at high surgical risk since it eliminates the need for median sternotomy, cardiopulmonary bypass and aortic cross-clamping with their respective inherent risks. However, to date limited evidence exists on the effectiveness of TAVI compared to surgical AVR from real-world clinical experience. In 2009, Zierer and co-workers presented a study on their initial experience in 21 patients undergoing transapical TAVI and compared outcomes to a matched group of 30 patients after minimally-invasive surgical AVR via a partial upper sternotomy (Zierer et al. 2009). They found that TAVI resulted in faster postoperative recovery, e.g. shorter postoperative ventilation times and shorter duration of intensive care unit and overall hospital stay. Regarding acute and one year mortality, no statistically significant differences were observed, although there was a trend towards more favourable outcome in the surgical group. However, since the initial TAVI experience was

compared to an established concept of minimally-invasive AVR this observation may at least in part result from the learning curve associated with any new surgical procedure. In another study 100 consecutive transapical TAVI procedures were compared to 100 propensity-score matched cases of surgical AVR. Patients undergoing TAVI had a significantly higher likelihood to be managed without any intensive care postoperatively and benefited from an insignificantly lower stroke rate compared to surgical candidates. Mortality rates were not different between the two approaches (Walther et al. 2010).

In the present study we present the results from a single-center, real world experience with outcomes after 82 consecutive transfemoral or transapical TAVI procedures using the Edwards Sapien^{TM} heart valve. Results from both the transcatheter as well as the surgical control group are acceptable, particularly when considering the high surgical risk of the study population. Regarding mortality, no significant differences were found between the two respective cohorts in our experience. Overall 30- and 180-day mortality rates correspond to those reported from other European single center experiences or national registries (Bosmans et al. 2011, Elhmidi et al. 2011, Figulla et al. 2011, Seiffert et al. 2010, Walther et al. 2010).

To date, results from only one prospective randomized trial exists comparing outcomes after TAVI and surgical AVR in high-risk patients. Data of the PARTNER Trial Cohort A were recently published (Smith et al. 2011). Patients were randomized to receive either transfemoral or transapical TAVI (n=348) or surgical AVR (n=351). Primary endpoint of the study was all-cause mortality at one year; secondary endpoints included safety and clinical effectiveness issues. Overall 30-day mortality was 3.4% in the TAVI cohort which is the lowest reported in any TAVI series to date, compared to 6.5% in the surgical cohort (p=0.07). Exclusion criteria as defined in the study protocol such as severely reduced left ventricular function (left ventricular ejection fraction < 20%) or severe renal dysfunction (serum creatinine > 3.0 mg/dl or dialysis dependent) may have contributed to this difference when compared to the European real-world experience outside the constraints of a randomized trial. In addition, the trial consisted of a highly selected group of patients, survival rates for 30days were counted for time of randomization instead of time since operation and long waiting times for TAVI resulting in patients dying on the waiting list. Thus results reported by the authors may differentiate from our clinical experience. After one year, mortality was 24.2% in the TAVI cohort versus 26.8% in the surgical cohort, meeting the non-inferiority hypothesis (p=0.001). The study investigators conclude that TAVI is an acceptable alternative to surgical AVR for selected high-risk patients.

COD in our study were comparable to the analysis by Walther and co-workers in 2010. The patients of their TAVI cohort died mostly from cardiac causes (e.g. low-cardiac

output, sudden death) but death was also due to extracardiac, non-procedure related causes (e.g. abdominal complications in three cases at 30 days) (Walther et al. 2010). Causes of death were also comparable to our findings in the report made by Zierer and co-workers. They observed an aortic dissection and two multi-organ failures in the peri-interventional phase. Similarly, during the long-term follow-up, their patients died mostly from comorbidities (Zierer et al. 2009).

The incidence of MACCE in our cohorts were relatively low, as 2.4% of the patients in both cohorts suffered from stroke during 30 day-follow-up and no further MACCE (myocardial infarction, surgical revision) occurred during the perioperative period. This seems comparable to the results of the PARTNER trial, where the observed stroke rate at 30 days was 3.8% in TAVI and 2.1% in AVR (p=0.20, Smith et al. 2011).

The combined safety endpoints at 30 days, defined by the VARC, did not differ significantly between the two groups (p=0.4462), although there was a higher rate of bleeding requiring intervention in the AVR cohort (p=0.017). Our results regarding the VARC endpoints in TAVI correspond to the outcomes reported widely in literature (Stähli et al. 2011).

The incidence of stroke after a follow-up period of 180 days was remarkably low in both of our cohorts (3.6% in TAVI vs. 2.4% in AVR, p=0.83). At 180 days, still no myocardial infarction or reoperation occurred in our study cohorts. Smith et al. reported a higher incidence of stroke in the TAVI cohort after 1 year of follow up (8.3% vs. 4.3% in TAVI and AVR, p=0.04) and they considered the higher rate of neurologic events a main concern about TAVI (Smith et al. 2011). The authors did not specify, if strokes occurred more often in the transfemoral or transapical group. On the contrary, an extremely low stroke risk for transapical TAVI was reported in a retrospective analysis (Walther et al. 2010). Their results suggest, that the transapical approach is possibly associated with a lower stroke rate compared to the transfemoral approach, especially when considering that the antegrade approach avoids manipulation of the aortic arch. Later on a meta-analysis of over 10 000 published patients, performed by Eggebrecht and co-workers, confirmed this observation (Eggebrecht et al. 2012). They reported that the mean 30-day stroke/TIA rate was 2.7% for transapical TAVI and 4.2% for transarterial TAVI using the ES valve. However, our results could not confirm whether less neurologic complications occur in the transapical group, because strokes occurred in both groups. As procedure specific outcomes are best revealed in 30-day results, we can state that TAVI is safe and equivalent to AVR in our experience when considering acute neurologic complications.

Long-term neurological outcome, on the other hand, needs to be further evaluated in the future.

In conclusion, our results and the results of other observational trials as well as the randomized PARTNER trial suggest the decision for TAVI or AVR for treatment of aortic stenosis in high-risk patients has to be based on clinical judgment and on the individual patient´s characteristics and risk factors. At present, TAVI and AVR seem to be complementary approaches for treatment of high-risk patients with severe aortic stenosis and permit a patient-orientated, tailor-made treatment strategy. It seems likely that with technical refinement of existing devices and mounting clinical experience of implanting physicians, further improvement of clinical outcome after TAVI can be anticipated.

4.3.2. Perioperative hemodynamic parameters

There was a significantly higher mean grade of postoperative aortic regurgitation in the TAVI cohort. 50% of patients had some degree of paravalvular leakage which was trivial or mild in all but one patient. The latter however had an uneventful clinical course, no signs of hemolysis were observed in any patient. Neither impaired left ventricular function nor grade of paravalvular leakage had a negative impact on patient outcome in our series after multivariate analysis ($p = 0.986$ for PVL and $p=0.454$ for impaired left ventricular function at baseline).

Even though mean valve size, as specified by the manufacturer, was significantly larger in the TAVI cohort, postprocedural peak and mean transvalvular gradients were similar compared to the AVR cohort. Possibly, this is at least in part due to incomplete expansion of TAVI prostheses, especially in cases with heavily calcified valve cusps. Correspondingly, severe PPM, defined as an iEOA<0.65, was present in 10 TAVI patients (12.2%) but only in one AVR patient (1.2%). However, in this population of elderly, comorbid patients, PPM did not seem to influence survival during a follow-up of 180 days.

4.3.3. Postoperative recovery and relief of symptoms

Similar to two previous studies (Zierer et al. 2009, Walther et al. 2010), we found significant advantages for patients undergoing TAVI regarding ventilation time and duration of stay in the intensive care unit, suggesting faster postoperative recovery when compared to patients after AVR. However, this did not translate into shorter overall duration of hospital stay in the TAVI cohort mostly owing to the fact that TAVI patients were kept under continuous ECG surveillance for an extended period after the procedure for detection of late occurrence of conduction disorders.

Regarding functional NYHA class, the patients in both cohorts improved significantly after the intervention, TAVI patients improved from a mean NYHA 3.1 ± 0.5 to a NYHA

of 2.1 ± 0.8 at 180 days ($p < 0.01$). In surgical patients, considerable improvement in NYHA class was noted, as well (NYHA Class was 2.3±1 at 180 days, mean difference to baseline was 0.9 [95% CI 0.7-1.3]).

Direct comparison of improvement regarding NYHA classes between the two cohorts was not possible, due to lack of data in AVR patients. Results from the PARTNER trial indicated, that at 30 days the benefits were greater with transcatheter implantation than with surgical replacement ($p< 0.001$; Smith et al. 2011). A systematic review reported that in the literature 50%-100% of TAVI patients improved by at least 1 functional NYHA class during 30 days of follow-up. Unfortunately, follow-up data found by the authors were not reliable enough to evaluate long-term outcomes (Yan et al. 2010).

In conclusion, we found that both procedures have a positive impact on the relief of symptoms, reflected by NYHA functional class. To date, limited evidence exists whether TAVI patients experience greater extent of symptom relief. TAVI patients seem to experience faster postoperative recovery documented by superior mean NYHA functional class compared to AVR.

4.4. Evaluation of the predictive value of surgical risk stratification systems for TAVI compared to AVR

The STS-PROM estimated mean mortality of both groups quite precisely, whereas the logistic EuroSCORE overestimated mortality in our patients. The mean STS-PROM was 8.5 ± 1.3 % and the mean logistic EuroSCORE was 23.9 ± 11.5% in TAVI, whereas actual mortality was 7.3% at 30 days. In AVR, patients had an STS-PROM of 9.0 ± 4.9% and a logistic EuroSCORE of 23.6 ± 10.4%; mortality at 30 days was 8.6%. Several studies have demonstrated the accuracy of different models for prediction of operative mortality in patients undergoing cardiac surgery. (Roques et al. 2001, Geissler et al. 2000, Nashef et al. 2002). The most important scoring systems are the logEuroSCORE and the STS-PROM. During the past years, these models were employed for non-standard or experimental procedures in patients, whose calculated risk profile was excessively high and prohibitive for conventional surgery (Wendler et al. 2010). These risk models were often applied as a part of the patient selection process and as an inclusion criterion.

In the present study, the c-statistic of the two important risk scoring systems indicated, that there was no discriminatory power in predicting 30-day mortality in patients receiving TAVI or AVR of either of the two scores. It was remarkable, that there was a trend towards better predictive ability of STS-PROM in TAVI than AVR ($p= 0.067$ for STS-PROM in TAVI vs. $p=0.922$ in AVR). The STS-PROM reached an AUC above 0.7, and may be considered as an acceptable predictor of early mortality in TAVI. However,

it did not reach significance level (p=0.067) and the lower confidence interval was near an AUC of 0.5, indicating that there is a possibility of coincidence in the results. Therefore it is difficult to say whether this predictive ability in TAVI patients was accidental or not. Nevertheless, the small number of patients in our cohorts may be unfavourable for performance of a ROC-analysis and there is a possibility that any conclusions made from the results of these analyses maybe inaccurate.
The decrease of discriminatory power of the logEuroSCORE in octogenarians and surgical high-risk patients has been reported previously (Wendt et al. 2009). The present study shows, that it should be questioned, whether these scores can be applied for selection of inoperable patients among high-risk candidates. Within a group of patients with severe comorbidities, both logEuroSCORE and STS-PROM fail to discriminate between survivors and non-survivors in the peri-interventional phase. The development of more accurate risk stratification systems remains a task for the future. The results of our study and others (Wendt et al. 2009) suggest, that there is a need for evidence-based decision making in high-risk patients. Until this happens, decision making for either TAVI or AVR has to be made individually according to the clinical judgement of a dedicated, interdisciplinary heart team.

4.5. Impact on renal function of the respective procedures

The literature has reported a strong association of AKI with morbidity and mortality after conventional cardiac surgery (Rosner et al. 2006). Lately, a number of studies suggested the same for AKI after TAVI procedures (Bagur et al. 2010, Sinning et al. 2010). Both procedures carry a recognized risk of AKI: TAVI mainly due to exposure to contrast media and periods of hypotension during rapid ventricular pacing. During surgical aortic valve replacement, with use of extracorporal circulation, malperfusion and loss of pulsatile blood flow is also known to compromise renal function.
Assessment of renal injury was performed in three different ways: observing any increase in creatinine, increases by more than 25% compared to baseline values and increases in creatinine to values greater than 1.8 mg/dl. We found that kidney function was affected by both types of procedure. The majority of all patients had at least some increase in creatinine values (82.3% in TAVI and 59.1% in AVR respectively), while increases by more than 25% was more frequent in TAVI compared to AVR (45.6% and 28.8%; p= 0.003). The mean difference of baseline to peak creatinine value postoperatively was also higher in the TAVI cohort (p=0.019). Multivariate analysis demonstrated that the stronger the increase in creatinine in TAVI patients, the more 90-day survival is affected significantly (p=0.005). On the other hand only an increase exceeding a value of 1.8 mg/dl was associated with fatal outcome in AVR patients.

Similarly to our results, Bagur et al. reported a higher in-hospital mortality of patients with acute kidney injury (AKI) after TAVI and AVR. However, the occurrence of AKI in their study cohorts was more frequent in patients undergoing AVR (9.2% in TAVI vs. 25.9% in AVR, p = 0.014). The amount of contrast media used in their TAVI cohort was 97 ± 57 cm^3 and the incidence of intraprocedural complications leading to severe hypotension, such as CPR, was 5%. The TAVI patients at our centre received an average amount of contrast media of 198 ± 93 cm^3 and 6% had complications leading to maintained hypotension. The higher incidence of renal impairment may be explained by this observation. However, Sinning and co-workers reported that the application of contrast agent was not necessarily associated with the onset of AKI. In addition, they found an association between AKI and the presence of peripheral vascular disease and the onset of systemic inflammatory response syndrome (SIRS) following TAVI. They assumed that valvuloplasty and catheter passage through the calcified aorta generate arterial emboli, resulting in a subsequent decrease in GFR. They concluded that SIRS induces inflammatory reactions leading to cardiorenal syndrome (Sinning et al. 2010). Our results indicate that patients undergoing TAVI may benefit from strategies to prevent AKI, like sufficient hydration, reduced amounts of contrast media and restrictive use of rapid ventricular pacing. However, further factors of renal damage in TAVI remain unclear and have to be assessed in the future.

4.6. Incidence of adverse events following TAVI and AVR

4.6.1. Incidence of Pacemaker implantation

Injury of the cardiac conduction system with the subsequent need for PM therapy has been reported as a major complication of TAVI and is also a known complication of AVR (Dawkins et al. 2008, Wendler et al. 2009). The need for pacemaker implantation is assumed to be related to compression of the interventricular septal conduction system in TAVI by the valve stent (Ancona et al. 2011). In AVR, the surgical trauma secondary to decalcification and suture placement in the annular circumference of the acoronary cusp is considered as a cause of atrioventricular or bundle injury. (Fukuda et al. 1976)

In our analysis, there was a more than 6-fold higher risk for TAVI patients to receive a permanent pacemaker after the procedure (13.4% vs. 2.4% for TAVI and AVR). The high rate of permanent pacemaker implantation in TAVI has been described previously by Erkapic et al. in 2011. In their meta-analytic approach they reported that approximately every 7^{th} patient undergoing TAVI will require a permanent PM after the procedure (15%). Our study suggests similar findings, as about every 8^{th} patient of the treatment group was in need for PM implantation postoperatively (13.4%). Data from

the SOURCE registry suggests a rate of 7.3% in patients receiving the Edwards SAPIEN^{TM} valve, compared to a 13.4% incidence in our cohort.

On the contrary, no difference between the need for PM implantation in TAVI (3.8%) and AVR (3.6%) was observed in the PARTNER trial. The authors did not specify the indications for pacemaker implantation, however (Smith et al. 2011). When considering only PM implantations for new-onset TAVB alone, we had similar findings to the PARTNER trial, being 3.7% for TAVI and 2.4% for AVR.

A mean incidence of of 15% has been described after TAVI, regardless of the type of the implanted prosthesis (Erkapic et al. 2011). However, incidence of PM implantation for any type of conduction disturbances was not a predictor of impaired survival in TAVI and AVR in the multivariable regression of our cohort ($p=0.223$ for TAVI and $p = 0.631$ for AVR). Accordingly, in the univariate analysis of the SOURCE registry it was not a predictor either ($p =1.0$).

In summary, new onset of conduction disturbances requiring PM implantation did not have an impact on overall survival in our experience.

4.6.2. Other observed adverse events

We compared type and frequency of in-hospital adverse events after TAVI and AVR among our cohorts. The events were considered for our analysis, if they were either life-threatening, requiring intervention or if they resulted in a prolonged hospital stay.

Overall, we observed events more frequently after AVR ($p < 0.01$) and the most frequent one was the need for rethoracotomy (13.4%). All other differences in complications seen between the two cohorts were insignificant. However, there was no need for IABP implantation after TAVI in our experience. Otherwise, coronary ostium obstruction and need for PCI was only seen in TAVI but not in the AVR cohort. Furthermore, lower transfusion requirements were noted in the TAVI cohort.

Stanford type A aortic dissection was present in one patient (5%) and was caused by the inflation of the balloon during valvuloplasty experienced by Zierer and co-workers (Zierer et al. 2009). In a systematic review, however, aortic dissection or ruptures were shown to be a quite rare complication with an incidence in the literature ranging from 0% to 4% (Yan et al. 2010). Emergency PCI became necessary in 0% - 8% of cases.

Due to the small number of patients in our study cohorts, conclusions about common events after TAVI and AVR can hardly be made. It is probable that the same complications seen after AVR can as well occur after TAVI. Severe bleeding seems less problematic after TAVI compared to AVR, as the need for rethoracotomy was lower, fewer blood transfusions were required and no hemodynamic relevant pleural or pericardial effusions were observed in our cohort.

Care must be taken to avoid major vascular injury when manipulating with catheters and patency of the coronary ostium must be assured after valvuloplasty and placement of the valve.

4.7. Independent predictors for adverse outcome after TAVI and AVR

Since the introduction of TAVI into clinical practice the selection of patients with expected benefit from the procedure remains a challenging task.

Furthermore, periprocedural events and complications associated with adverse outcome after TAVI are still under debate.

Univariate and multivariate logistic regression models were employed for patients in the SOURCE registry and significant risk factors were reported by Wendler et al. in 2010. In their multi-centre experience independent predictors of impaired outcome in TAVI after 30 days were the scaled logEuroSCORE (p= 0.002) and the presence of carotid artery stenosis (p= 0.015). Additionally, they stated that left ventricular ejection fraction was a possible predictor of survival, but this was uncertain due to missing data in baseline values (Wendler et al. 2010). They did not perform this analysis for periprocedural variables, such as AKI or conduction disorders, possibly determining early and late operative outcome.

Due to the low absolute number of fatal events after 30 days in our cohort, we performed univariate and multivariate analyses of death at 90 days, as the dependent variable. As Wendler and his colleagues used a scaled logistic EuroSCORE in groups over 20% and 30%, we used the continuous logistic EuroSCORE for our analyses and therefore comparison of this data may be biased.

In our TAVI cohort, the continuous logEuroSCORE was a predictor of 90 day survival in the univariate but not in the multivariate analysis (p= 0.046 and p = 0.429 respectively). In AVR patients it was not a predictor of survival in either, univariate or multivariate regression models. These results confirm evidence from the literature that the logEuroSCORE is not reliable for prediction of acute mortality. Values must be interpreted carefully and may at best classify a patient in risk categories of low, medium, high and very-high-risk subgroups as shown in our analysis and in the literature (Walther et al. 2010; Wendler et al. 2010). Wendler and co-workers did not include the STS-PROM in their risk analyses. We found, that the STS-PROM was a predictor of 90-day survival for TAVI patients in univariate and multivariate analysis (p=0.003 and p=0.005 respectively), whereas in AVR patients it was not significant (p= 0.764 and p=0.156 respectively). Adequateness of standard surgical risk stratification tools for the evaluation of risks inherent in TAVI procedures remains controversial (Mack et al. 2011).

Similar to the SOURCE registry, where left ventricular ejection fraction was not a certain predictor, we saw a tendency of this variable in being predictive. Poor LVEF (<30%) was insignificantly more frequent in those who died compared to the survivors in the univariate analysis (p=0.085) but only slightly missed significance level in the multivariate analysis (p=0.053). On the contrary, Pilgrim and co-workers observed a rapid recovery of LVEF among patients undergoing TAVI and no difference in survival of patients with reduced LVEF at baseline versus uncompromised LVEF was seen in their cohort (p= 1.0). They stated that TAVI can be performed safely in patients with reduced LVEF and that reduced LVEF is not associated with an increased perioperative risk (Pilgrim et al. 2011). However, only 14% (n=37) of their patients presented with poor LVEF at baseline and they did not perform multivariate logistic regression analysis, so that interpretation of data from this low number of patients may be biased. Walther et al. stated that a low ejection fraction was not associated with a worse outcome in their propensity matched cohorts (Walther et al. 2010).
Regarding the presence of carotid artery disease (Stenosis > 50% or previously treated by TEA), we found that it was not an independent predictor in TAVI but it was in AVR (p= 0.739 and p= 0.027 respectively). This is in contrast to the analysis by Wendler and colleagues, as they found carotid artery disease to be a significant predictor in TAVI. Nevertheless, the SOURCE registry consisted of a greater number of patients (n= 575), hence their results may be more representative.

Data from the PARTNER cohort A trial showed that carotid artery disease was not a predictor of mortality either but it was found that women without a history of CABG had a lower risk for perioperative mortality (Smith et al. 2011). Walther stated that patients with respiratory dysfunction were at a higher risk of mortality in their cohorts (Walther et al 2010). In our experience, COPD was not a risk factor in the multivariate analysis.
In our surgical cohort, patients with severe pulmonary hypertension had a higher risk for mortality (p= 0.046), while this was not the case in TAVI patients (p = 0.343). This is in line to the propensity matched cohorts by Walther in 2010, where pulmonary hypertension was not a risk factor in transapical TAVI.
In summary, the STS-PROM seems to be somewhat predictive for the early outcome of TAVI patients. The logEuroSCORE is not reliable for individual risk prediction but can be helpful to categorize patients in low, medium, high- and very high risk categories. The baseline LVEF is a variable with need for further investigation, as the impact on clinical outcome is still debated in the literature and remains unclear. It seems that patients with pulmonary hypertension can undergo TAVI safely (Walther et al. 2010). The presence of carotid artery disease may influence survival remarkably (Wendler et

al. 2010), although this was not the case in the PARTNER trial (Smith et al. 2011) and also not in our cohort (p=0.409).

Decision for the one or other treatment option should be made within a heart centre by an interdisciplinary dedicated heart valve team including cardiologists, cardiac surgeons, cardiac anaesthetists and intensive care physicians and should be independent from any financial or budget-related bias.

The question whether this development will justify extension of the technique to patients with a lower risk profile cannot be answered at present and warrants the conductance of further randomized trials.

5. Summary

TAVI has recently been advocated to decrease perioperative risk in high-risk patients and has become the treatment of choice at many centers for patients considered inoperable due to exceedingly high surgical risk. In this retrospective propensity-score adjusted analysis we compared outcomes after TAVI to those after surgical AVR. From June 2009 through June 2010, 82 consecutive patients underwent TAVI via a transapical (n=60) or transfemoral (n=22) approach using the Edwards SAPIEN^{TM} prosthesis. Mean patient age was 81.9±5.2 years, 64.6% were females. Logistic EuroSCORE I was 23.6±1.4% and STS score was 8.7±1.3%. A group of 82 patients after surgical AVR was retrieved from our database yielding a control group that was matched to the cases with respect to baseline demographics and typical risk factors. Overall mortality did not differ significantly between TAVI and AVR groups at 30 days (7.3% vs. 8.6%), 90 days (13.6% vs. 11.1%) or 180 days (17.8 vs. 18.9%, p=0.889). Conversion to surgery was necessary in 2 TAVI cases (2.4%). Perioperative stroke occurred in 2 cases per group (2.4%). Pacemakers were implanted for new-onset total atrioventricular block in 3.7% and 2.4% in the TAVI and AVR group respectively (p=1.0). Overall rate of postoperative pacemaker implantation was 13.4% and 2.4% in TAVI and AVR (p=0.017). TAVI resulted in shorter operative times (p<0.001), shorter ventilation times (p<0.001) and shorter length of stay in the intensive care unit (p=0.008). AKI as documented by increase in creatinine levels was significantly more pronounced in TAVI compared to AVR (p=0.003) and was a predictor of survival in TAVI and as well in AVR, when over 1.8 mg/dl. The overall incidence of adverse events was lower in TAVI compared to AVR (p<0.01). For prediction of acute mortality, STS-PROM was superior to the logistic EuroSCORE I for patients undergoing TAVI (AUC= 0.642 for logEuroSCORE I vs. AUC= 0.774 for STS-PROM). In patients undergoing AVR, neither logistic EuroSCORE I nor STS-PROM were predictive for acute mortality. Predictors for 90-day survival were STS-PROM and post-operative increase in creatinine in TAVI patients. By comparison, predictors of mortality at 90 days in AVR patients were carotid artery disease, pulmonary hypertension, the amount of perioperative blood transfusions and an increase in creatinine to values greater than 1.8 mg/dl. At 180 days of follow-up, there was substantial or even significant relief of symptoms in both groups, as reflected by functional NYHA class.

In conclusion, our experience demonstrated that mortality rates are similar after both types of procedure. Patients receiving TAVI benefit from faster postoperative recovery and less perioperative complications. The increased rates of pacemaker implantation and AKI compared to surgical AVR remain a concern. Patients with high predicted risk by STS-PROM and impaired LVEF may not benefit from TAVI. Nevertheless, until

more clinical data become available, the optimal procedure has to be determined for each patient according to individual risk factors.

6. List of abbreviations

AE	Adverse event
AKI	Acute kidney injury
AS	Aortic stenosis
AUC	Area under the curve
AVI	Aortic valve implantation
AVR	(surgical) aortic valve replacement
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CI	Confidence interval
COD	Cause of Death
COPD	Chronic obstructive pulmonary disease
CPB	Cardiopulmonary bypass
EOA	Effective orifice area
GFR	Glomerular filtration rate
GOLD	Global initiative for chronic obstructive lung disease
IABP	Intraaortic balloon pump
ICU	Intensive care unit
iEOA	indexed effective orifice area
LDL	Low density lipoprotein
LVEF	Left ventricular ejection fraction
logES/ logEuroSCORE	logistic European System for Cardiac Operative Risk Evaluation
MACCE	Major adverse cardiac and cerebral events
MOF	Multi organ failure
NYHA	New York Heart Association
OR	Operating room
PCI	Percutaneous coronary intervention
PM	Pacemaker
PPM	Patient prosthesis mismatch
PVL	Paravalvular leakage
PRBC	Packed red blood cell units
ROC	Receiver operating characteristic
RVP	Rapid ventricular pacing
SIRS	Systemic inflammatory response syndrome
STS-PROM	Society of thoracic surgeons predicted risk of mortality

TAVI	Transcatheter aortic valve implantation
TA	Transapical
TAVB	Total atrioventricular block
TF	Transfemoral
VARC	Valve Academic Research Consortium

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8. List of publications

Abstracts

Conradi L, Treede H, **Silaschi M**, Franzen O, Seiffert M, Baldus S, Schirmer J, Meinertz T, Reichenspurner H. Transcatheter aortic valve implantation versus surgical aortic valve replacement for treatment of high-risk patients: a propensity score analysis. *Thorac Cardiovasc Surg* 2011;59:Suppl.1:S37.

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Conradi L, **Silaschi M**, Schnabel R, Seiffert M, Schön G, Diemert P, Schirmer J, Blankenberg S, Reichenspurner H, Treede H, Baldus S.
Predictive reliability of logistic EuroSCORE II in patients undergoing transcatheter aortic valve implantation: assessment and comparison to classic systems of preoperative risk stratification. *J Am Coll Cardiol* 2012;60Suppl:B246.

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Manuscripts

Conradi L, Seiffert M, Treede H, **Silaschi M**, Baldus S, Schirmer J, Kersten JF, Meinertz T, Reichenspurner H. Transcatheter aortic valve implantation versus surgical aortic valve replacement: a propensity score analysis in patients at high surgical risk. *J Thorac Cardiovasc Surg* 2012;143:64-71.

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9. Curriculum Vitae

Education

1994- 1998	Primary School, Bad Oeynhausen, Germany
1998-2004	Immanuel-Kant-Gymnasium, Bad Oeynhausen, Germany
2004-2005	English Redland School, Santiago de Chile
2005-2007	Immanuel-Kant-Gymnasium, Bad Oeynhausen, Germany
2007-2013	School of Medicine, University of Hamburg , Germany

Languages

German, native
English, B2-Level
Spanish, B2-Level

Doctorial thesis

Since 2010 Department of Cardiovascular Surgery, University Heart Center Hamburg, Prof. Dr. Dr. H. Reichenspurner

Transcatheter aortic valve implantation versus surgical aortic valve replacement: a propensity score analysis in patients at high surgical risk

Clinical electives

19.07.2010-18.08.2010	Department of Cardiovascular Surgery University Heart Center Hamburg
25.07.2011-25.08.2011	Department of Internal Medicine, Hospital Wilhelmsburg Groß-Sand, Hamburg
16.04.2012-17.05.2012	Department of Hepatobiliar and Transplant Surgery, University Hospital Hamburg Eppendorf

28.05.2012-29.06.2012	Department of Gynecology and Obstetrics, Hospital Barros Luco, Santiago de Chile

Internships

20.08.2012-09.12.2012	Department of Cardiovascular Surgery, University Heart Center Hamburg
10.12.2012-31.03.2013	Department of Internal Medicine, Israelite Hospital Hamburg
01.07.2013-21.07.2013	Department of General Surgery, Catholic Marienkrankenhaus Hamburg

Scholarships

02/2010-09/2013	Scholarship for exceptional academic achievement and outstanding political or social commitment by the Konrad-Adenauer-Stiftung

Work experience

15.10.2009-15.02.2010	Student research assistant, Department of Anatomy and Experimental Morphology, University of Hamburg
31.08.2010-31.06.2013	Clinical research assistant at the clinical research office, Department of Cardiovascular Surgery, University Heart Center Hamburg

Clinical study experience

2010	Edwards Sapien Study, Clinical trial
2010-2011	Jena Valve Study, CE Mark Study
2011-2013	Engager Study, Pivotal Trial Medtronic Valve

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11. Declaration

I hereby declare that this doctoral thesis has been written only by the undersigned and without any assistance from third parties.
Furthermore, I confirm that no sources have been used in the preparation of this thesis other than those indicated in the thesis itself.

Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.
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Hamburg, den 21. März 2013

Unterschrift: .....