Transcatheter Aortic Valve Implantation

Risk assessment and Clinical Outcome

Malin Johansson

LundUniv_ENG_C2line_Black

DOCTORAL DISSERTATION

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| **Abstract**  **Background:** Transcatheter aortic valve implantation (TAVI) has emerged as a treatment for patients with aortic stenosis (AS) and high surgical risk. To date, reports of short- and mid-term survival have been favourable. The aim of this thesis was to evaluate early safety, risk assessment and late survival following TAVI.  **Methods:** In this work we studied clinical outcome, prediction of 30-day mortality and acute kidney injury and late renal dysfunction following TAVI. In paper I and IV, a comparisons to propensity score matched patients undergoing AVR were made.  **Results:** The 30-day mortality following TAVI and AVR was 4.2% and 4.8% respectively (*p*=0.81); however, significant differences were seen in corresponding rates of survival (51.7±5.8% vs 72.3±4.3%; *p*<0.001) and in cumulative re-hospitalizations for congestive heart failure (CHF) (41.3±7.2% vs 23±4.3%; *p*=0.006) over a 4-year period. Postoperative AKI was diagnosed in 33% following TAVI and renal function remained impaired at 1 year of follow-up. The observed/expected mortality ratio was 0.16 for logistic EuroSCORE, 0.56 for STS score, and 0.52 for EuroSCORE II. The AUC was 0.69 (95% CI 0.54–0.84) for the logistic EuroSCORE, 0.60 (95% CI 0.38–0.82) for the STS score, and 0.66 (95% CI 0.46–0.86) for the EuroSCORE II.  **Conclusions:** The results of this thesis confirm the merit of TAVI in high risk patients with AS, although late outcome with TAVI proved inferior to that of AVR in propensity score matched patients. In our view, the relationship between TAVI and AVR appears to be complementary rather than substitutive. Furthermore, more accurate risk assessment tools are needed. | | |
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*To Patrik, Klara, Bob and Alice*

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1. *Transapical Versus Transfemoral Aortic Valve Implantation: A Comparison of Survival and Safety*

Malin Johansson, Shahab Nozohoor, Per Ola Kimblad, Jan Harnek, Göran K. Olivecrona and Johan Sjögren. *The Annals of Thoracic Surgery. 2011 Jan;91(1):57-63*.

1. *Acute kidney Injury Assessed by Cystatin C After Transcatheter Aortic Valve Implantation and Late Renal Dysfunction*

Malin Johansson, Shahab Nozohoor, Henrik Bjursten, Per Ola Kimblad and Johan Sjögren *Journal of Cardiothoracic and Vascular Anesthesia, 2014 Vol 28,No4(August),:pp972–977*

1. *Prediction of 30-day mortality after Transcatheter Aortic Valve Implantation: a comparison of logistic EuroSCORE, STS score, and EuroSCORE II*

Malin Johansson, Shahab Nozohoor, Igor Zindovic, Johan Nilsson, Per Ola Kimblad, and Johan, Sjögren. *The journal of Heart Valve Disease, 2014;24:567-574*

1. *Transcatheter Aortic Valve Implantation: Late Survival and Re-hospitalization for heart failure*

Malin Johansson, Shahab Nozohoor, Henrik Bjursten, Matthias Götberg, Per Ola Kimblad, Igor Zindovic and Johan Sjögren. *Submitted*

# Populärvetenskaplig sammanfattning (Summary in Swedish)

Aortastenos (AS) är en hjärtsjukdom, där backventilen ([hjärtklaffen](http://sv.wikipedia.org/wiki/Hj%C3%A4rtklaff)) mellan [hjärtat](http://sv.wikipedia.org/wiki/Hj%C3%A4rta) och stora kroppspulsådern, [aorta](http://sv.wikipedia.org/wiki/Aorta), är förträngd och förkalkad. AS är den vanligaste klaffsjukdomen i den industrialiserade delen av världen och ökar med stigande ålder. Förträngningen i aortaklaffen gör att hjärtat har svårt att pumpa ut blod i kroppen, och patienten får symptom som yrsel, andfåddhet, svimning, kärlkramp och hjärtsvikt. Sjukdomen minskar personens livskvalitet och risken är stor för att plötslig dö. Det finns ingen medicin mot AS utan den enda effektiva behandlingen är en hjärtoperation. Operationen kallas aortic valve replacement (AVR) och innebär att bröstbenet sågas upp, hjärtat stannas och blodet pumpas runt i kroppen med hjälp av en hjärt-lungmaskin. Sedan klipps den förkalkade och sjuka klaffen ut och ersätts med en konstgjord. Operationen är vanligt förekommande på alla universitetsjukhus och resultaten är mycket goda. Men det finns en stor grupp av patienter, som på grund av hög ålder och annan samtidig sjukdom (t.ex. tidigare hjärtopererade, tidigare strålbehandlade på grund av cancer) anses vara för sjuka för att klara av att genomgå en hjärtoperation. De är så kallade högriskpatienter och har tidigare nekats effektiv behandling.

Senaste åren har en ny mindre invasiv metod utvecklats för att behandla högriskpatienter med AS. Metoden kallas Transcatheter Aortic Valve Implantation (TAVI). Operationen innebär att en konstgjord hjärtklaff förs in i kroppen, antingen genom ljumsken (kallas transfemoralt och förkortas TF) eller genom ett litet snitt mellan revbenen på vänster sida av bröstkorgen (transapikalt, TA). Den sjuka aortaklaffen tas inte bort utan trycks istället ut mot aortaväggen. Inget bröstben behöver sågas upp, inget hjärta stannas och ingen hjärt-lungmaskin behövs. TAVI är en revolutionerande behandling som gett ett flertal patienter möjlighet att få förlängt liv med förbättrad livskvalitet. Tekniken sprider sig över hela världen och vi har i Lund som första center i Sverige, sedan 2008 erbjudit TAVI till dessa högriskpatienter. Både lokala resultat och från större internationella studier visar att TAVI fungerar utmärkt som behandling mot AS och en internationell debatt pågår huruvida TAVI även ska erbjudas till patienter som inte är fullt så sjuka att de inte kan klara av vanlig hjärtkirurgi. I dagsläget är TAVI endast rekommenderat till högriskpatienter med AS och det är viktigt att ett hjärtteam som består av både thoraxkirurger och kardiologer beslutar om vilken behandling som lämpar sig bäst för den enskilde patienten. Nackdelar med TAVI är bland annat att ett njurskadligt kontrastedel behövs, att endast biologiska klaffar med begränsad livslängd kan användas och att det helt saknas långtidsresultat.

Eftersom patienter som genomgår TAVI oftast är nekade vanlig hjärtkirurgi på grund av annan samtidig sjukdom så skiljer sig denna patientgrupp från patienter som genomgår traditionell hjärtkirurgi, vilket gör det näst intill omöjligt att jämföra resultaten med varandra. Några enstaka studier finns där man slumpmässigt har jämfört de två operationsmetoderna (randomiserade studier) och ytterligare sådana studier pågår. Vi har i denna avhandling använt en statistisk modell som kallas propensity score matchning i ett försöka att jämföra patientgrupperna med varandra.

Syftet med den här avhandlingen var att studera resultatet av TAVI; dvs överlevnad, komplikationer, hur njuren påverkas, hur väl olika riskmodeller stämmer överens med resultatet samt att studera återinläggningar på sjukhus på grund av hjärtsvikt och hjärtinfarkt samt att kartlägga riskfaktorer för detta. Avhandlingen syftar även till att jämföra resultatet av TAVI med standardbehandlingen av aortastenos, AVR.

### Slutsatser av avhandlingens delarbeten

**Delarbete I**. Transapikal TAVI kan utföras säkert för högriskpatienter med AS och efter ett år var överlevnaden efter TAVI och AVR lika bra.

**Delarbete II**. Det är stor risk att utveckla akut njursvikt (AKI) efter TAVI. För patienter med AKI återhämtar sig inte njurarna fullt på längre sikt. Ett vanligt sätt att mäta njurfunktionen är genom ett blodprov, kreatinin. Ett annat blodprov, Cystatin C kan vara ett värdefullt tillägg.

**Delarbete III**. Dagens modeller för att beräkna patientens operationsrisk stämmer inte överens med det verkliga resultatet efter TAVI. Vi tror att den nyare modellen EuroSCORE II kan vara värdefullt i den kliniska bedömningen av patienter, men bättre riskmodeller för TAVI behövs.

**Delarbete IV**. På kort sikt har TAVI och AVR lika bra resultat med tanke på säkerhet och överlevnad. Men på längre sikt, upp till fyra år efter operationen så är patienter som opererats med TAVI oftare inlagda på sjukhus för hjärtsvikt och hjärtinfarkt. Patienter som redan innan operationen har allvarlig hjärtsvikt med andfåddhet och trötthet redan i vila, löper större risk för att bli återinlagd på sjukhus för just hjärtsviktsproblem. Vi tror att dessa patienter behöver noggrann uppföljning, information och medicinering för att undvika att försämras i sin hjärtsvikt.

# Abbreviations

AKI Acute kidney injury

AS Aortic stenosis

AVR Aortic valve replacement

BAV Balloon aortic valvuloplasty

CABG Coronary artery bypass grafting

CAD Coronary artery disease

CHF Congestive heart failure

CPB Cardiopulmonary bypass

eGFR Estimated Glomerular filtration rate

LV Left ventricle

LVEF Left ventricular ejection fraction

MI myocardial infarction

PVR Paravalvular regurgitation

RIFLE Risk Injury Failure Loss End-stage

TAVI Transcatheter Aortic valve implantation

TA Transapical

TF Transfemoral

VARC Valve academic research consortium

# Introduction

With the introduction of transcatheter aortic valve implantation (TAVI), high-risk patients with severe aortic stenosis (AS) can now be offered a therapeutic option using a less invasive technique without the need for cardiopulmonary bypass (CPB) [[1](#_ENREF_1)]. TAVI has led to improved outcomes in elderly patients with severe AS and significant comorbidity [[2-4](#_ENREF_2)]. To date, TAVI has been performed in about 150,000 patients worldwide and requests for the procedure continue to rise [[5](#_ENREF_5)]. The early and mid-term results are promising, however, some questions remain unsolved, including the knowledge about accurate patient selection and long-term results.

## Aortic valve stenosis

Aortic valve stenosis (AS) is a chronic and progressively debilitating heart valve disease, with no effective medical treatment [[6-8](#_ENREF_6)] . The prevalence increases with age, varying from 0.2 percent of patients aged between 50 to 60 years, up to 9.8 percent for patients aged between 80 to 90 years [[9](#_ENREF_9)]. Age-related degenerative calcifications are the most common cause of AS in adults, while congenital causes dominate in the younger age group and rheumatic AS has now become rare [[7](#_ENREF_7)]. Patients with AS may be unaware of their condition for decades, since the disease generally doesn't initially produce symptoms or warning signs except for a systolic murmur. However, when narrowing of the valve is severe, then symptoms such as chest pain (angina), syncope and heart failure generally develop. Echocardiography is the gold standard for the diagnosis of AS, which assesses the degree of valve calcification, left ventricular function, and provides prognostic information [[6](#_ENREF_6)]. Asymptomatic patients have a similar survival to the healthy population, but these patients need to be carefully educated about the importance both of follow-up visits including echocardiography, and of reporting symptoms as soon as they develop [[10](#_ENREF_10)]. For symptomatic patients with severe AS, the prognosis worsens significantly, and approximately 50% of these patients are reported dead within 3–5 years [[11](#_ENREF_11), [12](#_ENREF_12)].

Since medical treatment provides only temporary symptomatic relief but is not effective in the long term, the only effective definitive long term treatment for AS is aortic valve replacement (AVR) [[6-8](#_ENREF_6)]. Although conventional AVR remains the standard treatment for AS, many patients are not suitable as surgical candidates due to the higher-than-acceptable perioperative risk of mortality. According to the European Heart Survey on Valvular Heart Disease, 31.8% of patients with severe symptomatic aortic stenosis did not undergo intervention, mainly because of comorbidities [[13](#_ENREF_13)].

### Pathophysiology

The most common cause of AS in adults is an age-related degenerative calcification of the aortic valve [[7](#_ENREF_7)]. As the disease progresses, the heart valve leaflets become thicker since calcium nodules form within the layers of the leaflets [[14](#_ENREF_14)]. The calcium nodules bulge out into the aorta, causing restricted leaflet motion and obstruction during ventricular systole [[14](#_ENREF_14), [15](#_ENREF_15)]. The normal aortic valve orifice area is 3–4 cm² and narrowing this area to half its size usually causes little obstruction of cardiac output and a small pressure gradient across the valve. When the stenosis progresses however, the left ventricle starts to adapt through hypertrophy to the systolic pressure overload, resulting in a concentric increased wall thickness and preserved left ventricular ejection fraction (LVEF) [[7](#_ENREF_7), [16](#_ENREF_16)]. This compensatory mechanism, together with the patient’s physical ability, may keep the patient asymptomatic for decades. Although cardiac muscle hypertrophy initially helps to preserve the left ventricular systolic performance, this compensational mechanism may however have detrimental consequences, since it decreases the myocardial elasticity and increases the diastolic pressure leading to impaired coronary blood flow. Therefore, any extra hemodynamic stress such as exercise or tachycardia can produce ischemia, even in the absence of coronary artery disease. Furthermore, late manifestations of the left ventricular hypertrophy include a smaller left ventricular chamber size, with decreased preload and worsened systolic dysfunction, with an insufficient stroke volume and cardiac output, and decreased LVEF. Finally, increased left ventricular pressure is transmitted backwards to the lungs, causing pulmonary congestion with pulmonary venous hypertension and reactive vasoconstriction [[15](#_ENREF_15), [17](#_ENREF_17)].

### Aortic valve replacement

Since its introduction in the 1960s, AVR has dramatically improved the outcome for patients with AS, and is considered the definitive therapy for severe and symptomatic AS, producing survival rates in AS patients similar to those of a healthy age- and gender-matched population [[6-8](#_ENREF_6)]. When aortic valve replacement is considered, the choice is between mechanical and bioprosthetic valves. Bioprosthetic options include stented valves, stentless valves, aortic homografts, and the Ross procedure (i.e. pulmonary autograft in the aortic position). For most patients, the choice is between a mechanical valve and a stented bioprosthesis. Mechanical valves require the patient to take lifelong oral anticoagulation (warfarin); this is not required with a bioprosthesis. However, mechanical valves have longer durability and therefore tend to benefit younger patients (i.e. <60 years). Bioprosthesis have reduced valve durability due to the risk of structural valve degeneration, and are therefore generally recommended for older patients (<65 years). According to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, the choice of prosthesis type should depend on factors including anticoagulation contraindications, the risk of thrombosis, current tricuspid or mitral mechanical valves, and patient preferences [[6](#_ENREF_6)]. Moreover, rather than setting arbitrary age limits, the European Society of Cardiology/European Association for Cardiothoracic Surgery (ESC/EACTS) guidelines recommend that prosthesis should be individualized and discussed between the patient, cardiologists and surgeons, since patients aged of 60–65 years may have the choice of both options [[10](#_ENREF_10)].

The 30-day mortality following isolated AVR is approximately 1–4% [[13](#_ENREF_13), [18](#_ENREF_18), [19](#_ENREF_19)]. The operative mortality associated with AVR is dependent both on patient risk factors and the skill and experience of the surgical team. Risk factors for both perioperative mortality and impaired long-term survival include age, LV dysfunction, concomitant coronary artery disease (CAD), previous coronary artery bypass grafting (CABG), renal insufficiency, and chronic pulmonary disease. In addition, poor postoperative outcomes may result from prosthesis-related complications and suboptimal prosthetic valve hemodynamic performance [[20](#_ENREF_20)]. Postoperative complications such as stroke have an incidence of 1.5%, [[21](#_ENREF_21)] and mainly occur intraoperative or within the first 2 days of surgery [[22-24](#_ENREF_22)].

## Transcatheter Aortic Valve Implantation

Catheter-based treatment for patients with severe inoperable AS began in 1985 with the development of balloon aortic valvuloplasty (BAV). However, patients experienced only short term improvement, which led to the idea of a permanent catheter-based valve implantation therapy. Andersen and colleagues successfully implanted the first transcatheter aortic valve implantations in a pig model in 1992 [[25](#_ENREF_25)]. Eight years later, Bonhoeffer and colleagues performed the first human implantation of a catheter-based stented valve in a pediatric patient who had a degenerated right ventricle to pulmonary artery conduit [[26](#_ENREF_26)]. In April 2002, Cribier and colleagues performed the first in-human transcatheter aortic valve implantation [[27](#_ENREF_27)]. In 2007, two separate transcatheter aortic valve prostheses were granted the Conformité Européene (CE) mark approval for use, and thereafter, TAVI as a treatment for inoperable or high-risk patients with aortic stenosis gained acceptance and has since expanded. Lund University Hospital implemented TAVI, as the first center in Sweden, in January 2008 [[2](#_ENREF_2)].

To date, over 150,000 patients worldwide have been treated with TAVI and requests for the treatment continue to grow at the rate of about 40% annually[[5](#_ENREF_5)]. TAVI has revolutionized the treatment of inoperable patients with severe symptomatic AS and is a class I B recommendation for those patients with severe AS not suitable for AVR under the current ESC/EACTS guidelines, [[10](#_ENREF_10)], and a Class IIa, B recommendation in high-risk patients with severe and symptomatic AS who may still be suitable for AVR, but in whom TAVI is favored by a cardiac team. The early- and mid-term results have been promising; however, due to the recent introduction of TAVI, and the aged and comorbid nature of the patient population, the long-term outcome following TAVI remains limited [[3](#_ENREF_3), [4](#_ENREF_4), [28](#_ENREF_28), [29](#_ENREF_29)].

### Patient selection and risk assessment

The criteria for the selection of suitable candidates for TAVI are under debate and various risk stratification models, initially developed for cardiac surgery, have been used to obtain an objective risk assessment. The two most established surgical risk scores for identifying patients at high risk for conventional cardiac surgery are the European System for Cardiac Operative Risk Evaluation (EuroSCORE), and the Society of Thoracic Surgeons (STS) predicted risk of mortality score [[21](#_ENREF_21), [30](#_ENREF_30)]. A logistic EuroSCORE of >20% and/or a STS score >10% have been utilized as inclusion criteria in previous clinical TAVI trials such as the PARTNER trial, [[31](#_ENREF_31)] and the SOURCE Registry, [[32](#_ENREF_32)] and have therefore been used in clinical practice in order to screen patients for TAVI, along with the clinical judgment of a multidisciplinary heart team. However, due to the poor predictive performance of these scoring systems, the cut-off values have been excluded in recently published guidelines; [[10](#_ENREF_10)] and TAVI is suggested to patients denied surgery or at high surgical risk due to comorbidities evaluated at a multi-disciplinary meeting, i.e. the Heart Team, including a cardiologist, interventional cardiologist, and cardiothoracic surgeon. This approach allows risk factors such as patent grafts, malignancy, porcelain aorta, previous radiation therapy, liver cirrhosis, general frailty and the ability of postoperative mobilization to be taken into account.

Recently, EuroSCORE II, the up-dated version of the logistic EuroSCORE, was developed in order to improve the predictive accuracy for mortality in modern cardiac surgery [[33](#_ENREF_33)]. The EuroSCORE II has been evaluated as a prediction model for TAVI, but with inconclusive results [[34-39](#_ENREF_34)]. An accurate risk stratification system implemented clinically would help choose the correct therapy for each individual patient.

Preoperative screening before TAVI includes transthoracic echocardiography (TTE), computed tomography (CT), coronary angiography, and if necessary, percutaneous coronary artery intervention (PCI), all performed at least 1 week before the TAVI procedure, to reduce the risk of nephrotoxicity. The size of the aortic annulus is measured by CT angiography. Accurate measurement of the aortic annulus and calcification assessment is crucial to determine the correct transcatheter valve size. CT studies have clearly shown the oval shape of the aortic annulus in most patients, further highlighting the complexity of aortic annulus measurement. In addition, CT angiography with 3D-imaging reconstruction also provides spatial and other important information for the evaluation of the aortic annulus [[40](#_ENREF_40)].

### Prosthetic heart valves

Transcatheter prosthetic heart valves (THV) are only available as a bioprosthesis, and consist of a 3 leaflets of bovine or porcine pericardial tissue mounted in a stent. The insertion is via an antegrade (transapical) or retrograde (transfemoral TF, subclavian or direct aortic) access. The two valves with the most clinical experience and published data to date are the balloon expandable Edwards SAPIEN™ (Edwards Lifesciences Inc., Irvine, CA) (initially Cribier-Edwards) and self-expandable Medtronic CoreValve® (Medtronic Inc., Minneapolis, USA), the latter only accessible via the retrograde approach.

Developments in existing valves increasing the safety with TAVI, and minimizing of complications such as paravalvular regurgitation (PVR) and vascular complications due to wide introducer sheaths, have led to improvements and to the development of a second and third generation of valves such as the Edwards Sapien XT, Edwards Sapien 3, Medtronic CoreValve Evolut and Medtronic CoreValve Evolut-R. The repositionable Boston Scientific Lotus® valve (Boston Scientific Corp, Marlborough, MA, USA), has also been introduced, and is current the third largest transcatheter valve on the market due to the safety and minimal PVR attributes of the valve, demonstrated in the recently published Reprise II study [[41](#_ENREF_41)]. Other valves are: the JenaValve™ (JenaValve Technology GmbH, Munich, Germany), the Symetis Acurate™ (Symetis, Lausanne, Switzerland) and the repositionable St. Jude Medical Portico (St. Jude Medical, Minneapolis, USA).

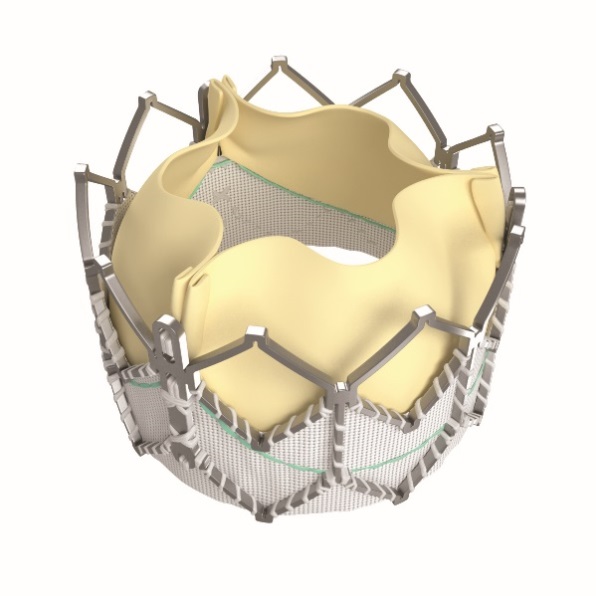


Figure 1a

Balloon expandable transcatheter heart valve. Reprinted with the permission of Edwards Lifesciences Inc.

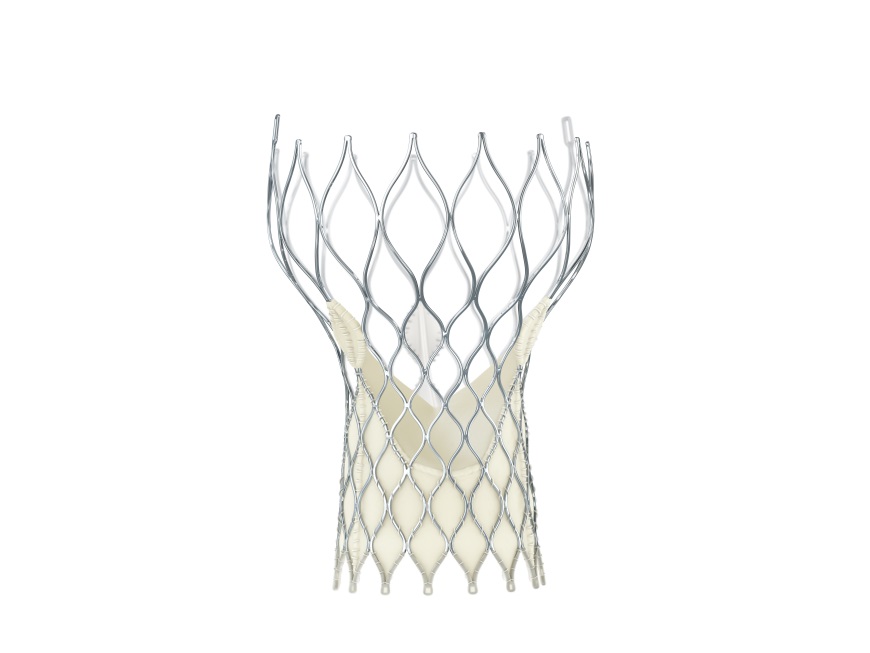


Figure 1b

Self–expandable transcatheter heart valve. Reprinted with the permission of Medtronic Inc.

### Operative Management

All TAVI procedures are performed in a catheterization laboratory or hybrid operating room under surveillance using fluoroscopy and using the standard Seldinger technique [[42-46](#_ENREF_42)]. A temporary pacemaker wire is inserted transvenously before the implantation.

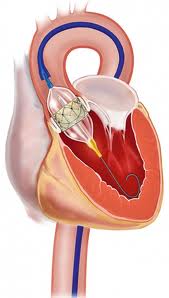


Figure 2a

Transfemoral TAVI. Reprinted with the permission from Edwards Lifesciences Inc.

#### Transfemoral approach

The transfemoral (TF) approach is the first choice in the vast majority of centers performing TAVI procedures. An accurate evaluation with computed tomography of the iliofemoral anatomy is of major importance in determining the suitability for each individual patient. Although surgical cut-down was the technique used at the beginning of the TAVI experience, most centers are now using a fully percutaneous technique for this approach. The TF approach often makes it possible to avoid the use of general anesthesia.

The TF procedure starts by inserting a pigtail catheter in the contralateral femoral artery, placed retrograde in the right coronary cusp, for the purposes of visualizing the aortic root [[47](#_ENREF_47)]. Then a segment of the femoral vessel without calcification on the anterior wall is selected as the puncture site. After puncture and wire insertion, sutures for closure technique are put in place. Heparin is then administered. A sheath is then placed over an extra stiff wire. The native aortic valve is crossed, and the catheter is exchanged for a straight pigtail catheter. Thereafter a stiff wire is placed through the pigtail catheter and into the LV apex. This wire placement into the LV should be done carefully and under fluoroscopy, and care taken to avoid positioning it in the mitral apparatus.

In a case of severe calcification, BAV can then be performed, although this is not always necessary. BAV is performed during a brief episode of rapid ventricular pacing.

Thereafter, the valve is delivered through the introducer sheath, and positioned according to the particular recommendations relevant to the valve type. Aortic root injections are used to confirm the position of the valve and its three-dimensional orientation. Preferably, the valve should be perpendicular to the aortic annulus and longitudinal to the ascending aorta. The valve is deployed during direct fluoroscopic visualization within another brief period of rapid ventricular pacing. Clear communication is critical during this brief period of the procedure; and one person should dictate the timing of each step of the procedure in a standard clear format. Rapid ventricular pacing is not required with the repositionable Boston Scientific Lotus® (Boston Scientific Corp, Marlborough, MA, USA) prosthesis.

After deployment, another angiographic root injection is performed to confirm the position of the valve, to rule out a paravalvular or central leak and to confirm the patency of the coronary arteries. Occasionally, the valve may require postdilatation with additional saline in the balloon in order to ensure full expansion of the valve. In case of severe regurgitation or suboptimal positioning, a second valve can be deployed into the first one.

Once the result is deemed to be satisfactory, protamine is administered, the introducer sheath is removed and the puncture site is closed by using the previously placed sutures, and the contralateral arterial sheath is removed and closed after angiographic verification of vessel patency.

For postoperative anticoagulation, 75 mg clopidogrel daily is administered for 1 month, together with a lifetime dose of 75 mg daily aspirin. Patients with atrial fibrillation or other indications for warfarin receive warfarin in monotherapy.

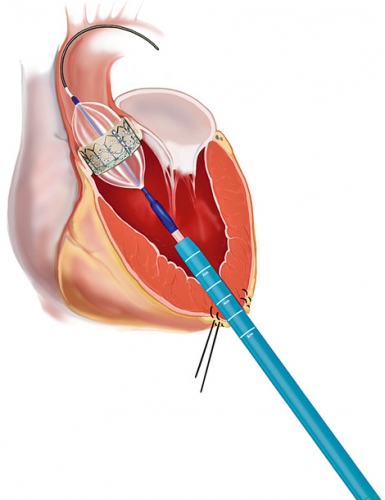


Figure 2b

Transapical TAVI. Reprinted with the permission from Edwards Lifesciences Inc.

#### Transapical approach

The transapical (TA) approach, first reported with the Cribier-Edwards valve system in 2006 [[45](#_ENREF_45)] is an alternative to the TF approach, and is mainly selected in patients in whom the TF approach has been rejected due to small, heavily calcified and tortuous femoral arteries.

This approach requires general anesthesia. The apex is identified by transthoracic ultrasound. A small left lateral thoracotomy is made and a pericardiotomy is performed over the LV apex. Heparin is administrated. Double layers of pledged reinforced purse string sutures are placed at the LV apex. The apex is punctured with a standard access needle, and a soft access wire is inserted through the needle and followed by a 6F sheath delivered into the LV apex to maintain intraventricular access. Then, a stiff wire is inserted through the catheter and a 20–26F introducer sheath is delivered over the wire into the LV apex.

The BAV and valve deployment is similar to the TF approach (see TF approach).

Once the result is satisfactory, the introducer sheath is removed during a brief episode of rapid ventricular pacing and the purse string sutures are tied to secure hemostasis. Protamine is administered and a left pleural chest tube is inserted. Routine closure of the access site incision is performed. The postoperative routine is similar to that of the TF approach.

## Complications

The TAVI procedure has inherent risks for peri- and postoperative complications. The perioperative complications include: increased risk of vascular injury, apical laceration, hemorrhage, cardiac rupture of the aortic root or annulus, heart block requiring permanent pacemaker implantation, arrhythmia, myocardial ischemia or infarction, mitral valve apparatus injury and worsening of mitral regurgitation, embolization, coronary ostial obstruction and paravalvular or central regurgitation and death. Complications such as complete heart block and the occurrence of PVR are more frequent following TAVI than AVR [[48-51](#_ENREF_48)]. Following TAVI, the risk of stroke is considerable with a reported incidence of 2–6% [[52](#_ENREF_52), [53](#_ENREF_53)] and is probably the result of vascular injury during implantation or from aortic debris from the native calcified valve. Both stroke and vascular injury negatively affect the likelihood of survival following TAVI [[48-50](#_ENREF_48)].

### Postoperative pacemaker

Postoperative atrioventricular (AV) block requiring permanent pacemaker implantation is a well-described complication after both AVR and TAVI. However, postoperative permanent pacemaker implantation is more common after TAVI (0–44%) than after AVR (3–8%) [[41](#_ENREF_41), [54-61](#_ENREF_54)], with the incidence varying within TAVI with the use of different valves, from that of 9–44% with the CoreValve®, approximately 28% with the Boston scientific Lotus [[41](#_ENREF_41)] and 0–12% after implantation of the Edwards SAPIEN® valve (Edwards Lifesciences Inc., Irvine, CA, USA). Important structures of the conduction system are hard to visualize at a macroscopic level and the close location of the implantation site with the conduction system (membranous septum with atrioventricular bundle, left- and right-bundle branch), can cause a valve prosthesis to exert pressure on surrounding tissues and cause AV-block. The actual stent material is probably also of importance, since a nitinol (nickel/titanium) frame (i.e. the CoreValve) might apply greater pressure on the ventricular septum over time than the stainless steel or cobalt chromium frame (i.e. Edwards SAPIEN valve) [[62](#_ENREF_62)]. Furthermore, a higher placement of the THV may decrease the need for a pacemaker but instead may increase the risk of another common and feared complication, paravalvular regurgitation [[63](#_ENREF_63)]. According to Erkapic et al [[64](#_ENREF_64)], 63% of AV blocks requiring pacemaker implantation occurred immediately or within 24 hours after TAVI, 32% within 1 week, and 5% >7 days after TAVI [[64](#_ENREF_64)].

### Paravalvular regurgitation

Paravalvular regurgitation (PVR) is a well-described complication following TAVI, initially seen in up to 70% of patients following the procedure, and in approximately 15% of those have moderate or severe PVR [[65](#_ENREF_65)]. PVR has a significant impact on prognosis, with a two- to four-fold increase in mortality risk at 1 year for patients with severe or moderate PVR compared with patients without PVR [[49](#_ENREF_49), [65-70](#_ENREF_65)]. However, the results of the PARTNER cohort A Trial have suggested that even a minor degree of PVR following TAVI is associated with impaired survival [[4](#_ENREF_4), [49](#_ENREF_49)].

PVR is characterized by a considerable diastolic runoff of blood back into the left LV, leading to volume overload. Patients with severe and symptomatic AS commonly have noncompliant and hypertrophic LV due to chronic pressure adaption, and are therefore unable to increase the end-diastolic volume. This results in rapidly increased left ventricular end-diastolic pressure with consecutive decrease in cardiac output leading to hemodynamic deterioration [[71](#_ENREF_71)].

To minimize the likelihood of postoperative PVR, an accurate preoperative measurement of the aortic annulus and a calcification assessment is of importance in determining the correct choice of valve and its size. Managing perioperative PVR includes perioperative angiographic root injection to confirm the position of the valve, and if needed, a postdilatation with additional saline in the balloon in order to ensure full expansion of the valve. In case of severe regurgitation or placement in a suboptimal position, a second valve can be deployed into the first with an additional postdilatation. An interventional closure of paravalvular leaks after TAVI has been described [[72](#_ENREF_72), [73](#_ENREF_73)], although not clinical routinely used.

### Acute Kidney Injury

Acute kidney injury (AKI) is considered a serious complication after cardiac surgery with cardiopulmonary bypass (CPB), and is associated with prolonged hospital stay and increased mortality [[74-77](#_ENREF_74)]. AKI can occur from a variety of causes, including intraoperative hypotension, hemolysis, atheroemboli, contrast agent exposure, and postoperative cardiac complications that impair renal perfusion such as anemia and transfusions [[77](#_ENREF_77), [78](#_ENREF_78)]. Patient-related risk factors for developing AKI are: female gender, heart failure, diabetes mellitus, peripheral vascular disease, chronic obstructive pulmonary disease and elevated preoperative s-creatinine. Additionally, pharmacological therapy, neuro-hormonal activation, inflammation and oxidative stress related to the intra- and postoperative management can be added to the known patient risk factors for AKI [[79](#_ENREF_79), [80](#_ENREF_80)].

TAVI has the benefit of avoiding the need for CPB; however, embolization of aortic debris, sequences of rapid pacing with hypoperfusion, the use of a nephrotoxic contrast agent, and a patient population with a greater incidence of preoperative chronic kidney disease are all potential risk factors for postoperative AKI. Previous studies have demonstrated that AKI following TAVI is common, with a reported incidence up to 57% [[81-85](#_ENREF_81)], and that AKI is associated with increased postoperative mortality following TAVI [[48](#_ENREF_48), [82](#_ENREF_82), [86](#_ENREF_86)]. However, the incidence of AKI following TAVI is variable, mainly due to the different definitions and classifications of AKI used over the years [[87](#_ENREF_87)].

#### Acute kidney injury classification

The term AKI has replaced the earlier terms acute renal failure and acute renal dysfunction [[88](#_ENREF_88)]. AKI is defined as a sudden decrease in kidney function, resulting in disturbance in electrolyte and acid-base balance, derangement of extracellular fluid volume, retention of nitrogenous waste products, and often decreased urine output [[89](#_ENREF_89)]. Classifications used to diagnose AKI include the established Risk/Injury/Failure/Loss/Endstage renal disease (RIFLE) [[90](#_ENREF_90)] and the Acute Kidney Injury Network (AKIN) [[88](#_ENREF_88)] classifications, as well as the more recent Kidney Disease Improving Global Outcomes (KDIGO) classification [[91](#_ENREF_91)] (a combination of RIFLE and AKIN); which needs to be explored.

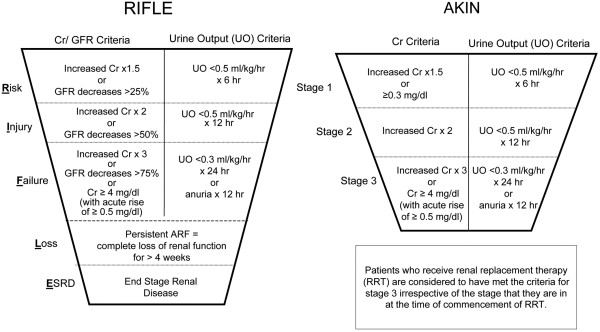


Figure 3

RIFLE by Bellomo *et al.* [[90](#_ENREF_90)]. AKIN by Mehta *et al.*[[88](#_ENREF_88)*]*. Reprinted with the permission of the editorial of Journal of Critical care.

#### RIFLE

First published in 2002 by the Acute Dialysis Quality Initiative (ADQI) group, the RIFLE classification was developed by nephrologists and intensivists in order to define AKI [[90](#_ENREF_90)]. The classifications of Risk, Injury and Failure reflect acute changes (i.e. within 7 days) in GFR, creatinine or urine output; while Loss and End stage kidney disease reflect more chronic conditions. The RIFLE classification has been largely validated in determining AKI and its prognostic ability in hospitalized patients [[92-96](#_ENREF_92)]

#### AKIN

A modified version of RIFLE criteria, the Acute Kidney Injury Network (AKIN) classification of AKI was published in 2007 [[88](#_ENREF_88)]. The AKIN classification is based on changes in creatinine and urine output, and not on GFR changes. AKI is defined as an acute (i.e. within 48 hours) decrease in kidney function, containing classification stages 1, 2 and 3. A limitation of the AKIN classification of AKI is the short time-frame of the definition, not allowing for diagnosis of AKI in patients with renal deterioration after postoperative day 2.

#### Cystatin C

Cystatin C is a biomarker for kidney function initially identified in Lund by Dr Grubb and colleagues in an attempt to overcome known limitations with s-creatinine [[97](#_ENREF_97), [98](#_ENREF_98)]. Cystatin C is an endogenous cysteine proteinase inhibitor with a low molecular weight (13kDa). Like creatinine, cystatin C is freely filtered at the glomerulus. However, cystatin C is constantly produced and nearly completely metabolized in proximal tubular cells without additional secretion or reabsorption, and without the influence of muscle mass or dietary protein intake. Thus, a reduction in GFR correlates well with a rise in cystatin C levels, and vice versa.

Cystatin C levels may however be altered with older age, the use of corticosteroids, abnormal thyroid function, and elevated C-reactive protein [[99](#_ENREF_99)]. The diagnostic value of cystatin C as an estimate of GFR has been shown to be superior to that of creatinine in discriminating between normal and impaired kidney function, and compared with creatinine, cystatin C may be a better estimator of GFR than creatinine in patients with lower creatinine levels, such as elderly patients, those with cirrhosis and those suffering from malnutrition [[100-102](#_ENREF_100)].

## VARC criteria

In order to create consistency and facilitate comparisons with present and future TAVI studies, the Valve Academic Research Consortium (VARC) consensus manuscript was published in January 2011 [[103](#_ENREF_103)]. An up-dated version, the VARC-2 consensus document [[104](#_ENREF_104)], has been available since January 2013, which includes the composite endpoints, device success, early safety (at 30 days), clinical efficacy (after 30 days) and time-related valve safety, Table 1.

## Randomized trials

Randomized studies are the gold standard for clinical research, forming the basis for clinical guidelines and recommendations. However, patients with porcelain aorta, post-radiation therapy, malignancies and cirrhosis are often denied surgery and thus may be disqualified from inclusion in randomized studies comparing TAVI and AVR. To date, three randomized TAVI trials comparing TAVI and AVR have been published [[50](#_ENREF_50), [105](#_ENREF_105), [106](#_ENREF_106)]. They were preceded by a randomized trial comparing TAVI with medical treatment for inoperable patients with AS, the Cohort B of the Placement of Aortic Transcatheter Valves (PARTNER) trial [[107](#_ENREF_107)]. This study involved 21 sites (17 in the United States), and compared TAVI (n=179) with medical treatment including BAV (n=179). By demonstrating superior survival for inoperable patients undergoing TAVI compared to medical treatment, it has led to the emerging acceptance and expansion of TAVI as a treatment for inoperable patients with aortic stenosis. Thereafter, the Cohort A of the Placement of Aortic Transcatheter Valves (PARTNER) trial was published, involving 25 centers, and 699 high risk patients with severe aortic stenosis were randomized to either TAVI (n=348) or AVR (n=351). Results up to five years of follow up did not identify any significant differences in all-cause mortality between patients undergoing TAVI and AVR [[4](#_ENREF_4), [49](#_ENREF_49), [50](#_ENREF_50)].

The STACCATO trial was conducted in 2 Danish centers [[106](#_ENREF_106)]. Patients included in this study presented with a lower surgical risk than those in the PARTNER trial, and all TAVI patients underwent the TA approach. Although 200 patients were planned for inclusion in the study, the STACCATO trial was prematurely terminated upon advice of the Data Safety Monitoring Board due to unexpectedly poor outcomes in the TAVI cohort (n=34), compared to the SAVR cohort (n=36). Authors of this trial concluded that current indications for TAVI should remain restricted to surgically inoperable patients only.

In May 2014, the Core Valve trial by Adams was published [[105](#_ENREF_105)], a randomized study comparing high risk patients with AS undergoing TAVI (n=390) and AVR (n=357) at 45 centers in the United States. This study demonstrated that survival at 1 year following TAVI was superior compared to that after AVR.

# Aims

## Paper I

The aim of this study was to evaluate the complications occurring when using the TF and the TA techniques and to compare clinical outcome of TAVI to a propensity score matched group undergoing conventional AVR.

## Paper II

The aim of this study was to evaluate AKI with cystatin C following TAVI and to assess the impact of postoperative AKI on outcome and late renal function.

## Paper III

The aim of this study was to evaluate whether the performance of the EuroSCORE II for predicting 30-day mortality following TAVI is superior to that of the currently used logistic EuroSCORE and STS score risk stratification models.

## Paper IV

The aim of this study was to evaluate late survival and composite clinical endpoints specified by the Valve Academic Research Consortium (VARC)-2, including re-hospitalization for congestive heart failure (CHF) following TAVI.

# Material and Methods

## Patients and study design

The patients included in all four studies underwent TAVI at the Department of Cardiothoracic Surgery, Cardiothoracic Anesthesia and Intensive Care, Skane University Hospital, Lund University, Sweden. TAVI has been an alternative therapeutic option for inoperable or high risk patients at our Department since January 2008.

The baseline risk of the patient population was estimated using the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) [[30](#_ENREF_30)] and/or the Society of Thoracic surgeons (STS) score [[21](#_ENREF_21)] providing quantitative risk assessment, which was used together with clinical judgment in order to establish whether conventional AVR was associated with too high risks for these patients. The patients were allocated to TAVI if logistic EuroSCORE was ≥20% or deemed to be of excessive risk due to comorbidities at a multi-disciplinary meeting (cardiologist, interventional cardiologist, and cardiothoracic surgeon). This approach allowed risk factors such as malignancy, porcelain aorta, previous radiation therapy, liver cirrhosis, general frailty and the ability of postoperative mobilization to be taken into account. Preprocedural screening included transthoracic echocardiography, computed tomography (CT), and coronary angiography. Pre-, peri-, and postoperative variables were prospectively collected and entered into the department’s computerized cardiac surgical database for retrospective analysis. Survival data was obtained from the Swedish National Board of Health and Welfare, and the incidence and cause of hospitalization and the cause of death were obtained from patient records.

**Paper I** was a retrospective study, in which 40 consecutive patients with severe symptomatic aortic stenosis underwent TAVI (41 procedures) with the 23-mm or 26-mm Edwards SAPIEN transcatheter heart valve (Edwards Lifesciences Irvine, CA) between January 2008 and November 2009. Follow-up was performed in January 2010 and was 100% complete. The mean follow-up time was 10±8 months (median 7.5; interquartile range, 16). A comparison to propensity score matched patients undergoing AVR was made.

**Paper II** was a prospective study, in which 68 consecutive patients with severe, symptomatic aortic stenosis underwent both transfemoral and transapical TAVI with the 23-mm or 26-mm Edwards SAPIEN transcatheter heart valve (Edwards Lifesciences Inc., Irvine, CA) between September 2009 and September 2012. As two intraoperative deaths occurred, and two patients were converted to conventional AVR due to dislocation of the prosthesis in the left ventricle, the final study population consisted of 64 patients. Blood samples were collected on 4 occasions during the early part of the study to determine levels of s-creatinine and cystatin C: preoperatively (on admission to the ward, usually the day before the procedure), on arrival at the ICU, and on the first (D1) and third (D3) days postoperatively. Additionally, s-creatinine was collected at follow up 12 months postoperatively. The eGFR was calculated in two ways: The s-creatinine- based simplified Modification of Diet in Renal Disease formula [[108](#_ENREF_108)], eGFR (s-creatinine); and the cystatin C estimation of renal function [[109](#_ENREF_109)], eGFR (cystatinC).

Renal function was assessed at a mean of 11.5±4 months postoperatively (median 12 months; interquartile range (IQR) 10 to 13 months) and was 87% complete. The collection of survival data was completed in October 2012, giving a mean follow-up of 17±12 months (median 17 months; IQR 6 to 29 months), and was 100% complete. AKI was defined according to the RIFLE classification.

**Paper III** was a retrospective study, in which 123 patients with severe symptomatic aortic stenosis underwent TAVI with the 23 mm, 26 mm, or 29 mm Edwards SAPIEN™ or SAPIEN XT™ Transcatheter Heart Valve (Edwards Lifesciences Inc., Irvine, CA) between January 2008 and April 2013. The logistic EuroSCORE was calculated prospectively using an on-line calculator (http://www.euroscore.org), while the STS score (in case of no preoperative calculation) and the EuroSCORE II were calculated retrospectively using web-based systems ([http://209.220.160.181/STS WebRisk Calc261/de.aspx](http://209.220.160.181/STS%20WebRisk%20Calc261/de.aspx) and http://www.euroscore.org, respectively). The follow up examination was performed in May 2013 and was 100% complete for the primary endpoint (30-day mortality). Intraprocedural device success was defined according to the Valve Academic Research Consortium (VARC-2) (24). The mean follow up was 1.7±1.5 years (median: 1.2 years; interquartile range: 0.4-2.9 years).

**Paper IV** was a retrospective study, in which 166 consecutive patients with severe symptomatic aortic stenosis underwent TAVI with 168 procedures, between January 2008 and April 2014, using the Edwards SAPIEN™/Edward SAPIEN XT Transcatheter Heart Valve (Edwards Lifesciences Inc., Irvine, CA) or the Boston Scientific Lotus® (Boston Scientific Corp., Marlborough, MA). A total of 45% (n=76) underwent the TF access and 55% (n=92) underwent the TA access. Composite endpoints were defined according to the VARC-2 criteria [[104](#_ENREF_104)]. Rehospitalization for CHF, MI and the VARC-2 criteria were obtained from patient record. AKI was defined according to the AKIN classification. Follow-up analysis, conducted in May 2014, was 100% complete for survival and re-hospitalization, with means of 1.8±1.6 years (median, 1.3 years; interquartile range, 2.6 years) for TAVI and 4.6±3.0 years (median, 4.3 years; interquartile range, 4.9 years) for propensity score matched patients undergoing AVR.

Table 1.

Composite endpoints according to the VARC-2 criteria

|  |
| --- |
| *Device success*  Absence of procedural mortality AND  Correct positioning of a single prosthetic heart valve into the proper anatomical location AND  Intended performance of the prosthetic heart valve (no prosthesis–patient mismatcha and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, AND no moderate or severe prosthetic valve regurgitationa) |
| *Early safety (at 30 days)*  All-cause mortality  All stroke (disabling and non-disabling)  Life-threatening bleeding  Acute kidney injury—Stage 2 or 3 (including renal replacement therapy)  Coronary artery obstruction requiring intervention  Major vascular complication  Valve-related dysfunction requiring repeat procedure (BAV, TAVI, or AVR) |
| *Clinical efficacy (after 30 days)*  All-cause mortality  All stroke (disabling and non-disabling)  Requiring hospitalizations for valve-related symptoms or worsening congestive heart failureb  NYHA class III or IV  Valve-related dysfunction (mean aortic valve gradient ≥20 mmHg, EOA ≤0.9–1.1 cm2c and/or DVI <0. 35 m/s, AND/OR moderate or severe prosthetic valve regurgitationa) |
| *Time-related valve safety*  Structural valve deterioration  Valve-related dysfunction AND/OR moderate or severe prosthetic valve regurgitation  Requiring repeated procedure (TAVI or SAVR)  Prosthetic valve endocarditis  Prosthetic valve thrombosis  Thrombo-embolic events (e.g. stroke)  VARC bleeding, unless clearly unrelated to valve therapy (e.g. trauma) |

BAV, balloon aortic valvuloplasty; TAVI, transcatheter aortic valve implantation; AVR, aortic valve replacement. aRefers to VARC definitions. bIncludes heart failure, angina, or syncope due to aortic valve disease requiring intervention or intensified medical management. cDepending on the body surface area.

### 

### Patients undergoing conventional Aortic Valve Replacement

The patients included in Paper I and Paper IV underwent conventional AVR with or without coronary artery bypass surgery at Department of Cardiothoracic Surgery, Cardiothoracic Anesthesia and Intensive Care, Skane University Hospital, Lund University, Sweden. Aortic valve replacement was performed through median sternotomy, using standard surgical techniques, with extracorporeal circulation. Pre-, peri-, and postoperative variables were prospectively collected and entered into the department’s computerized cardiac surgical database for retrospective analysis. Survival data was obtained from the Swedish National Board of Health and Welfare, and the incidence and cause of hospitalization and the cause of death were obtained from patient records.

Between January 1999 and April 2009, 2,262 patients underwent conventional AVR with or without coronary artery bypass surgery at our department. Using this population, matching (relation 1:1) based on the propensity score was used to compare patients undergoing the different procedures in Paper I.

Between September 1999 and September 2013, 2883 consecutive patients underwent conventional AVR with or without coronary artery bypass surgery (CABG) at our department. This population was used for matching based on the propensity score in Paper IV.

### Ethical aspects

The studies were performed according to the principles of the Helsinki Declaration of Human Rights and were approved by The Ethics Committee for Clinical Research at Lund University, Sweden.

## Statistical analysis

All statistical analyses were performed and graphs plotted using the SPSS statistical software (SPSS Inc, Chicago, IL); version 17 in Paper I, version 20 in Paper II, version 21 in Paper III, and version 22 in Paper IV. Statistical significance was defined as p≤0.05. Data for continuous variables are presented as mean ± standard deviation. Categorical variables are presented as proportions with number of patients and percentage. Proportions were compared using the chi-squared or Fisher’s exact test (when frequencies were less than five), and continuous variables using Student’s t-test.

Survival function was illustrated by Kaplan–Meier curves and log-rank test was used to compare statistical differences between groups.

Calibration analysis (the degree to which the actual outcome is similar to the expected probability produced by the model) was examined by comparing average observed and predicted mortality. The Hosmer-Lemeshow test for goodness-of-fit was performed, where a p-value >0.05 indicates a well-calibrated model for the study population. Model calibration was also evaluated using the risk-adjusted mortality ratio. An observed/expected ratio >1.0 indicates that the model underestimates mortality, while an observed/expected ratio <1.0 indicates that the model overestimates mortality.

Discrimination analysis was made to assess the prognostic value of a risk score model, using a receiver-operating characteristic curve (ROC) analysis and the C-index (area under the receiver-operating characteristic curve [AUC]) and its 95% confidence intervals. A C-index of 0.5 indicates no predictive ability, whereas a C-index of 1.0 represents perfect discrimination. U-statistics were used to investigate differences in C-index across different risk scores. The population was analyzed for specificity and sensitivity using established cut-off values: logistic EuroSCORE (>20%) and STS score (>10%). Furthermore, four different cut-off values for EuroSCORE II: >2.5%, >5%, >7.5%, and >10% were used for analysis of specificity and sensitivity.

Linearized ratio (percentage per patient/year) for re-hospitalization for congestive heart failure and myocardial infarction were calculated in Paper IV.

Multivariate Cox’s proportional hazard regression analysis was performed to determine independent predictors of late survival and re-hospitalization for congestive heart failure in Paper IV. The inclusion criterion for each outcome in the multivariate model was p<0.25 in the univariate analysis, and the limit for backward was p<0.05 for the exponential of the beta coefficient.

### Propensity-score matching

Because treatment assignment in the thesis was not based on random allocation, propensity score adjustment [[110](#_ENREF_110), [111](#_ENREF_111)] was used to reduce imbalances in covariates at baseline in Paper I and Paper IV. A logistic regression model was fitted (Hosmer-Lemeshow goodness-of-fit) where treatment (TAVI vs AVR) was the outcome, and baseline characteristics from the EuroSCORE model in addition to presence of coronary artery disease (defined as previous coronary artery bypass graft or PCI before the TAVI procedure) were the covariates in a bivariate analysis in Paper I. Propensity scores were generated for the AVR and TAVI patients using an SPSS macro (SPSS, Chicago, IL), and used to match patients from the two groups in a nearest neighbor fashion. In Paper I, the propensity score adjusted sample included 40 patients who underwent AVR and 40 who underwent TAVI (TA, n=30; TF, n=10). The covariate balance achieved by matching was assessed by checking that the variables included in the propensity score were no longer significant in the matched sample as well as calculating the absolute standardized differences in covariates between patients undergoing AVR and TAVI. An absolute standardized difference of less than 10 % for the measured covariate suggests appropriate balance between the patients undergoing the different treatment modalities.

In Paper IV, the EuroSCORE model, the presence of coronary artery disease (defined as previous coronary artery bypass graft or PCI before the TAVI procedure), body mass index, aortic peak- and mean gradient, hemoglobin, eGFR were added to the covariates in a bivariate analysis. Further, a non-parsimonious propensity score matching was built. TAVI and AVR patients with the same probability score (caliper 0.2 match with 3-digit approximation) were matched. When matching pairs of TAVI and AVR with a caliper higher than 0.2, the propensity score analysis resulted in a 1:1 match but with less balanced groups and with greater differences in baseline characteristics. The propensity matching finally selected 125 propensity-matched patients.

# Results

## Paper I

The preoperative characteristics of patients undergoing TAVI and AVR are presented in Table I.1. The propensity score adjustment between TAVI and AVR with and without concomitant CABG is presented in Table I.2.

### Operative Data

The overall procedural success of TAVI was 92.5% (37 of 40). In the TA group, it was 93% (28 of 30), and in the TF group, it was 91% (10 of 11; 1 TF patient was converted to TA-TAVI). The TF procedure was converted owing to a rupture of the femoral artery after insertion of the introducer sheath. A Fluency Plus self-expanding covered graft (Bard Peripheral Vascular, Tempe, AZ) was inserted into the left femoral artery, covering the rupture. The patient was uneventfully discharged after 5 days and underwent TA-TAVI successfully 5 months later. Procedural failure occurred in 2 patients in the TA group: open surgery had to be performed in 1 patient owing to dislocation of the valve in the left ventricle; and one procedure was discontinued because of transient obstruction of the left main coronary artery during the initial balloon valvuloplasty. One patient (TA-TAVI) required valve-in-valve treatment (SAPIEN-in-SAPIEN) due to severe transprosthetic regurgitation.

### Postoperative Complications

Postoperative outcome is summarized in Table I.3. Major postoperative vascular complications occurred in 3 of 10 patients (30%) in the TF group. One patient underwent reoperation because of severe bleeding from the femoral access point caused by a dislocated wound closure device (Prostar XL, Abbott Vascular, Abbott Park, IL). The patient was taken to the operating room, an explorative laparotomy was performed, and the insertion point in the femoral artery was surgically closed. The second patient had a severe hemorrhage from the right femoral artery shortly after arrival in the intensive care unit and underwent emergent surgery with a repair of a ruptured branch of the femoral artery. Thereafter, an arterial embolectomy was successfully performed because of clinical signs of limb ischemia. The third patient had critical ischemia and was embolectomized at the same side as the femoral access in the lower limb on the 10th postoperative day. As the ischemia progressed slowly, the patient underwent a transtibial amputation, but died of multiple organ failure on the 35th postoperative day. Cerebrovascular events occurred in 3 patients (2 TF and 1 TA). The 2 TF patients were diagnosed with cerebrovascular ischemia due to embolism, and the TA patient had a traumatically incurred subarachnoid hemorrhage after falling in the ward. Four patients (3 TA and 1 TF) had renal failure (in this study defined as increased creatinine to >200 mmol/L or anuria). Two of the 3 TA patients with renal failure required hemodialysis. New-onset postoperative atrial fibrillation occurred in 3 patients, all in the TA group. No patient required pacemaker implantation for postoperative atrioventricular block.

### Early and Late Outcome

There was no intraoperative mortality. The overall 30-day mortality was 5.0% (2 of 40). The in-hospital mortality was 10.0% (4 of 40): TA group 6.7% (2 of 30) versus TF group 20% (2 of 10). In the TA group, 1 patient died of traumatic subarachnoid hemorrhage 8 days postoperatively due to accidentally falling in the ward while on warfarin treatment. The second patient died of multiorgan failure 17 days postoperatively. In the TF group, 1 patient died of intestinal carcinoma with liver metastases 31 days postoperatively. One patient died of multiorgan failure related to critical ischemia in the lower limb 35 days postoperatively. Autopsies demonstrated functional valve prosthesis in all 4 patients. Late survival after TAVI was 77% both at 6 months and 1 year. One patient in the TF group died of heart failure with pulmonary edema 96 days postoperatively. Four patients in the TA group died during follow-up, 3 of myocardial infarction at 133, 153, and 481 days, and 1 died of heart failure 123 days postoperatively. The results after propensity score adjustment are given in Table I.2. Propensity score adjusted Kaplan-Meier survival estimates for the TF and TA treatment groups are compared with those for conventional AVR in Figure I.1, demonstrating that conventional AVR was not associated with a higher survival rate than the TAVI procedure (TA, p= 0.73; TF, p= 0.59).

Table I.1.

Preoperative characteristics of the patients undergoing transcatheter aortic valve implantation (TAVI) and aortic valve replacement (AVR)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | TF | |  | TA | |  | AVR | |  |
| Variable | n = 10 | % |  | n = 30 | % |  | n=40 | % | p-value |
| Female | 5 | 50 |  | 15 | 50 |  | 22 | 55 | 0.91 |
| Hypertension | 3 | 30 |  | 16 | 53 |  | 14 | 35 | 0.23 |
| Redo surgery  previous CABG  previous AVR | 4  0 | 40  0 |  | 5  1 | 17  3 |  | 10 | 25 | 0.45 |
| Diabetes mellitus | 1 | 10 |  | 9 | 30 |  | 4 | 10 | 0.074 |
| Chronic obstructive pulmonary disease | 1 | 10 |  | 12 | 40 |  | 12 | 30 | 0.20 |
| Neurological dysfunction | 1 | 10 |  | 4 | 13 |  | 4 | 10 | 0.90 |
| Renal failure | 1 | 10 |  | 1 | 3 |  | 3 | 33 | 0.53 |
| Preoperative dialysis | 1 | 10 |  | 1 | 3 |  | 0 | 0 | 0.18 |
| Recent myocardial infarction | 1 | 10 |  | 4 | 13 |  | 4 | 10 | 0.90 |
| Pulmonary hypertension | 0 | 0 |  | 4 | 13 |  | 1 | 3 | 0.12 |
| Peripheral vascular disease | 5 | 50 |  | 14 | 47 |  | 17 | 43 | 0.89 |
| Atrial fibrillation | 2 | 20 |  | 12 | 40 |  | 9 | 23 | 0.29 |
| NYHA IV | 1 | 10 |  | 11 | 37 |  | 2 | 5 | 0.002 |
| LVEF 30-50 | 1 | 10 |  | 8 | 27 |  | 10 | 25 | 0.54 |
| LVEF <30 | 2 | 20 |  | 3 | 10 |  | 5 | 13 | 0.71 |
| PCI prior to TAVI | 5 | 50 |  | 11 | 37 |  | NA |  | 0.48 |
| Cancer | 1 | 10 |  | 3 | 10 |  | NA |  | 1.00 |
| Porcelain aorta | 0 | 0 |  | 8 | 27 |  | NA |  | 0.17 |
| Other severe comorbidity | 6 | 60 |  | 21 | 70 |  | NA |  | 0.70 |
|  | Mean | SD |  | Mean | SD |  | Mean | SD |  |
| Age (years) | 83 | 6 |  | 80 | 6 |  | 81 | 5 | 0.36 |
| Standard EuroSCORE (points) | 11 | 2 |  | 10 | 3 |  | 11 | 3 | 0.88 |
| Logistic EuroSCORE (%) | 25.6 | 15 |  | 23.5 | 17 |  | 22.7 | 16 | 0.73 |
| Creatinine | 117 | 61 |  | 104 | 50 |  | 99 | 29 | 0.50 |
| BMI (kg/m²) | 28 | 5 |  | 27 | 4 |  | 26 | 5 | 0.50 |
| Aortic gradient (mmHg)  peak  mean | 89  54 | 38  24 |  | 80  45 | 24  15 |  | 87  NA | 23 | 0.49  0.17 |
| LVOT (mm) | 22 | 2 |  | 22 | 2 |  | NA |  | 0.54 |

Values given are number and percentage of patients, or mean ± SD. NA = data not available or applicable; NYHA = New York Heart Association Classification; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; BMI = body mass index; LVOT = Left ventricle outflow tractTable I.2.

Propensity-score adjustment between transcatheter aortic valve implantation (TAVI) with coronary artery disease and aortic valve replacement (AVR) with or without concomitant coronary artery bypass graft surgery at baseline

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | TAVI | |  | AVR | |  |  |
| Variable | n = 40 | % |  | n = 40 | % | *p-*value | AbSD (%) |
| Female gender | 20 | 50 |  | 22 | 55 | 0.65 | -10 |
| Redo surgery | 10 | 25 |  | 10 | 25 | 1.0 | ±0 |
| COPD | 13 | 32.5 |  | 12 | 30 | 0.81 | 5.4 |
| Neurological dysfunction | 5 | 12.5 |  | 4 | 10 | 1.0 | 7.9 |
| Renal failure | 2 | 5 |  | 1 | 2.5 | 1.0 | 13.1 |
| Recent myocardial infarction | 5 | 12.5 |  | 4 | 10 | 1.0 | 7.9 |
| Pulmonary hypertension | 4 | 10 |  | 1 | 2.5 | 0.36 | 31 |
| Peripheral vascular disease | 19 | 47.5 |  | 17 | 43 | 0.65 | 9.1 |
| LVEF 30-50 | 9 | 22.5 |  | 10 | 25 | 0.79 | -5.9 |
| LVEF <30 | 5 | 12.5 |  | 5 | 12.5 | 1.0 | ±0 |
| Coronary artery disease | 25 | 62.5 |  | 23 | 57.5 | 0.65 | -10.2 |
|  | Mean | SD |  | Mean | SD |  |  |
| Age (years) | 81 | 6 |  | 81 | 5 | 0.73 | -5.6 |
| Standard EuroSCORE | 11 | 3 |  | 11 | 3 | 0.8 | -4.8 |
| Logistic EuroSCORE (%) | 24 | 17 |  | 23 | 16 | 0.71 | 6.8 |
| Propensity Score | 0.19 | 0.21 |  | 0.16 | 0.17 | 0.50 |  |

Values given are number and percentage of patients, or mean ± SD. AbSD = Absolute standardized difference; COPD = Chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction

Table I.3.

Intra- and postoperative data for transcatheter aortic valve implantation patients

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | TF Approach | |  | TA Approach | |  |
| Variable | n = 10 | % |  | n = 30 | % | *p-*value |
| Prosthesis size  23 mm  26 mm | 4  6 | 40  60 |  | 13  16 | 45  55 |  |
| Hemodialysis | 0 | 0 |  | 2 | 6.7 | 1.00 |
| Prolonged ventilator time | 1 | 10 |  | 1 | 3.3 | 0.44 |
| New onset postop. AF | 0 | 0 |  | 3 | 10 | 0.56 |
| Levosimendan infusion | 0 | 0 |  | 1 | 3.3 |  |
| Norepinephrine >48 h | 2 | 20 |  | 1 | 3.3 | 0.15 |
| Dobutamine >48 h | 2 | 20 |  | 1 | 3.3 | 0.15 |
|  | Mean | SD |  | Mean | SD |  |
| Contrast medium, mL | 288 | 47 |  | 209 | 100 | 0.03 |
| Creatinine peak, μmol/L | 179 | 143 |  | 152 | 107 | 0.52 |
| Urine output 12 hours, mL | 1300 | 450 |  | 1200 | 550 | 0.63 |
| Ventilator time, hours | 16 | 20 |  | 8 | 10 | 0.25 |
| Perioperative bank blood (units)  ICU bank blood (units) | 1.6  0.8 | 2.1  1.1 |  | 0.9  0.6 | 1.4  1.1 | 0.25  0.23 |
| Length of Stay  ICU, hours, median (IQR)  Total, days, median (IQR) | 34  13 | 26 (19-23)  11 (7-23) |  | 40  7 | 61 (5-23)  3 (3-6) | 0.75  0.11 |
| TnT peak, μg/L | 0.2 | 0.2 |  | 0.5 | 0.3 | 0.01 |
| CK-MB peak, μg/L | 7.7 | 3.2 |  | 20.1 | 7.8 | <0.001 |
| Hemoglobin, g/L  Preoperatively  At ICU discharge | 118  112 | 16  13 |  | 129  110 | 14  12 | 0.038  0.65 |

Values given are number and percentage of patients, mean ± SD, or median and interquartile range (IQR). Prolonged ventilator time = ventilator >48 h postoperatively; AF = atrial fibrillation; CK-MB = Creatine kinase-myocardial band; ICU = intensive care unit; TA = transapical; TF = transfemoral; TnT = Troponin T.



Patients at risk

**AVR 40 32 30 27 26 26 26 25**

**TA 30 22 15 12 9 6 4 0**

**TF 10 6 6 6 6 3 3 1**

Figure I.1.

Comparison between 2-years survival estimates for patients who underwent aortic valve replacement. AVR (straight line), transapical transcatheter aortic valve implantation (TA, broken thin line), and transfemoral transcatheter aortic valve implantation (TF, broken thick line) in propensity-matched groups. TAVI = transcatheter aortic valve implantation.

## Paper II

### Incidence and risk factors of acute kidney injury

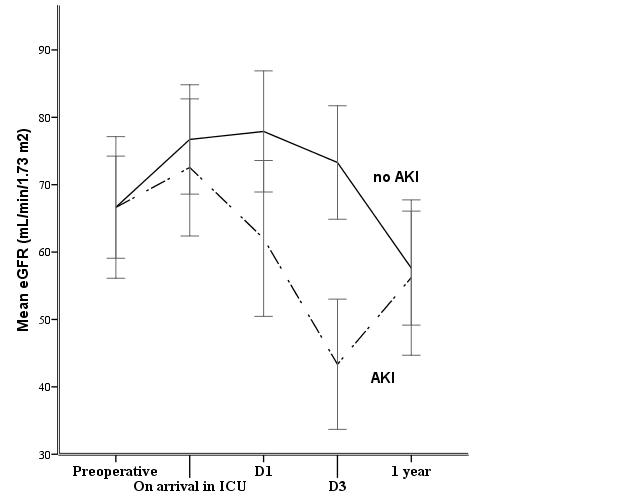
The procedural success rate was 94% (64/68). Acute kidney injury was diagnosed in 25 patients (39%) with eGFR (cystatinC) and in 21 patients (33%) with eGFR (s-creatinine). One patient in the AKI+ group required postoperative hemodialysis. By univariate analysis, the AKI+ patients underwent TAVI with the TA approach significantly more often (p=0.001), received more peri-and postoperative red bloodcell (RBC) transfusions (p=0.009), and had a longer ICU stay (p=0.05). Other patient characteristics and laboratory parameters did not differ significantly between the AKI+ and AKI– groups (Table II.1). The mean preoperative eGFR (s-creatinine) was 67±24 mL/min/1.73m² compared to 45±21 mL/min/1.73 m² with eGFR (cystatinC) (p<0.001). In univariate analysis, preoperative renal impairment (CKD stage 3 or 4, eGFR < 60 mL/min/1.73 m²), did not significantly increase the risk of postoperative AKI (s-creatinine p=0.7 and cystatin C p=0.9).

### Late renal function.

The mean eGFR based on s-creatinine and cystatinC for the AKI+ and AKI- groups at the different points are given in Table II.2. The mean differences in eGFR(s-creatinine) between preoperative values and the values at arrival in the ICU, on postoperative D1, postoperative D3, and 12 months following TAVI are presented in Figure II.1. In the AKI+ group, the mean eGFR was 57± 21 mL/min/1.73m² after 12 months compared to 67±23 mL/min/1.73m² preoperatively, p=0.071. The mean eGFR in the AKI+ group at 12 months follow up was improved significantly in comparison to the mean eGFR at D3 (57±21 vs 43±21 mL/min/1.73m², p=0.023). In the AKI- group, the mean eGFR was 60±21 mL/min/1.73m² at 12-month follow up compared to 67±24 mL/min/1.73m² preoperatively, p=0.057. The mean eGFR in the AKI- group at 12 months follow up was reduced compared to D3 (60±21 vs 73±27 mL/min/1.73m², p=0.001). There was no significant difference in mean eGFR between the AKI+ group and the AKI- group at12-month follow up (57±21 mL/min/ 1.73 m² vs 60±21 mL/min/1.73m², p=0.49).

### Survival

The eGFR for patients with postoperative AKI and those without AKI surviving to 1 year, and patients with and without AKI who did not survive within the first year are presented in Figure II.2. Overall survival, including 2 intraoperative deaths (n=66), was 95.4± 2.6% at 30 days, 90.7±3.6% at 90 days, and 77.1±5.7% at 12 months. Causes of death are presented in Table II.2. The 30-day mortality was 4.8% for the AKI+ group and 0% for the AKI- group (p=0.33). The 90-day mortality was 14.3% for the AKI+ group and 2.3% for the AKI- group (p=0.099). For the AKI+ group, survival was 90.2±6.6% at 30 days, 85.2± 7.9% at 90 days, and 73.7± 10.2% at 12 months. For the AKI- group, survival was 97.6± 2.4% at 30 days, 97.6± 2.4% at 90 days, and 82.6±6.6% at 12 months, (logrank p=0.16), Figure II.3.



p=0.04

p=0.54

p<0.001

p=0.49

Figure II.1

Time course of mean estimated glomerular filtration rate creatinine (eGFR, mL/min/1.73m²) over 12 months for patients with acute kidney injury (AKI) and without AKI (no AKI) following TAVI. eGFR <60-30 mL/min/1.73m² indicates chronic kidney disease stage 3 and eGFR<29 mL/min/1.73m² indicates chronic kidney disease stage 4. Bars show mean, 95% CI.

**Table II.1.** Pre- peri- and postoperative characteristics, according to the occurrence of postoperative acute kidney injury (AKI) following transcatheter aortic valve implantation (TAVI)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Clinical characteristics | All (n=64) | AKI+ (n=21) | AKI− (n=43) | p |
| Age (years) | 80 ± 8 | 79 ± 7 | 80 ± 9 | 0.7 |
| Female | 36 (56) | 10 (48) | 26 (61) | 0.3 |
| Previous surgery  CABG  AVR | 20 (31)  19 (30)  2 (3) | 6 (29)  6 (29)  0 | 14 (33)  13 (30)  2 (5) | 0.8  0.9  1.0 |
| Previous PCI | 26 (41) | 7 (33) | 19 (44) | 0.4 |
| Diabetes mellitus | 15 (23) | 5 (24) | 10 (23) | 1.0 |
| chronic obstructive pulmonary disease | 10 (16) | 4 (19) | 6 (14) | 0.7 |
| Hypertension | 31 (48) | 12 (57) | 19 (44) | 0.3 |
| Preoperative dialysis | 0 | 0 | 0 |  |
| Chronic kidney disease  Creatinine (eGFR<60mL/min per 1.73m²)  Cystatin C (eGFR<60mL/min per 1.73m²) | 25 (39)  49 (77) | 9 (43)  19/25 (76) | 16 (37)  30/39 (77) | 0.7  0.9 |
| Pulmonary hypertension | 7 (11) | 2 (10) | 5 (12) | 1.0 |
| Peripheral vascular disease | 36 (56) | 14 (67) | 22 (51) | 0.2 |
| Atrial fibrillation | 18 (28) | 5 (24) | 13 (30) | 0.7 |
| NYHA IV | 15 (23) | 5 (24) | 10 (23) | 1.0 |
| Malignancy | 3 (4.7) | 0 | 3 (7) | 0.5 |
| Porcelain aorta | 6 (9) | 2 (10) | 4 (9) | 1.0 |
| Other severe comorbidities | 61 (95) | 21 (100) | 40 (93) | 0.2 |
| BMI (kg/m²) | 27 ± 6 | 26 ± 8 | 27 ± 5 | 0.31 |
| Standard EuroSCORE (points) | 9.2 ± 3.5 | 8.7 ± 3.5 | 9.4 ± 3.5 | 0.42 |
| Logistic EuroSCORE (%) | 22 ± 12 | 19 ± 10 | 23 ± 13 | 0.20 |
| LVEF 30–50%  LVEF <30% | 14 (22)  6 (9) | 5 (24)  2 (10) | 9 (21)  4 (9) | 0.8  1.0 |
| AV peak gradient (mmHg)  AV mean gradient (mmHg) | 79 ± 19  48 ± 12 | 84 ± 22  49 ± 15 | 77 ± 16  48 ± 11 | 0.16  0.80 |
| Transapical TAVI  Transfemoral TAVI | 47 (73)  17 (27) | 21(100)  0 | 26 (61)  17 (40) | 0.001  0.001 |
| Amount of contrast agent (mL) | 130 ± 38 | 139 ± 42 | 126 ± 36 | 0.2 |
| Need of inotropic support† > 48 h | 1 (2) | 1 (5) | 0 | 0.3 |
| RBC transfusion | 14 (22) | 9 (43) | 5 (12) | 0.009 |
| Number of RBC transfusions | 0.6 ± 1.3 | 1.1 ± 1.7 | 0.3 ± 0.9 | 0.06 |
| CVI | 2 (3) | 2 (10) | 0 | 0.10 |
| Major bleeding | 2(3) | 1 (5) | 1 (2) | 1.0 |
| Time in ICU (h) | 39 ± 49 | 63 ± 79 | 28 ± 13 | 0.051 |

Values given are numbers and percentages of patients, or mean ± SD. Abbreviations: AV, aortic valve; AVR, AVR, aortic valve replacement; BMI, body mass index; CABG, coronary artery bypass grafting; CVI, cerebrovascular insult; ; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association classification; PCI, percutaneous coronary intervention; RBC, red blood cells. †: including levosimendan (Simdax® Orion Pharma, Finland), dobutamine (Dobutrex® Hameln, Germany)

Table II.2. Pre- and postoperative renal function, according to the RIFLE criteria; eGFR(creatinine) and eGFR(cystatin-C) following TAVI and cause of death in relation to acute kidney injury.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | eGFR(creatinine) | | | eGFR(cystatin C) | | |
|  | AKI+  (n=21) | AKI−  (n=43) | p-value | AKI+  (n=25) | AKI−  (n=39) | p-value |
| Preoperative  On arrival in the ICU  D1  D3  At 12 months  Cause of death  Malignant disease  Cardiac failure/AMI  Traumatic CVI with MOF  Thromboembolic CVI  Renal and cardiac failure  Pneumonia/meningitis with MOF | 67±23  73±22  62±25  43±21  57±21  AKI+  1  2  1  1  1  1 | 67±24  77±26  78±29  73±27  60±21  AKI−  1  3  1  0  0  2 | 1.0  0.54  0.04  <0.001  0.49 | 48±23  56±25  45±28  27±17  NA | 43±19  54±18  52±20  42±18  NA | 0.41  0.68  0.22  <0.001 |

Values given are mean ± SD. Abbreviations: AKI, acute kidney injury; CVI, cerebrovascular insult; D1, day 1 postoperatively; D3, day 3 postoperatively; eGFR, estimated glomerular filtration rate (mL/min/1.73 m²); ICU, intensive care unit; MOF, multiorgan failure; NA, not available.

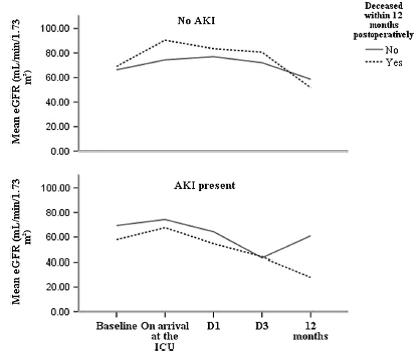


Figure II.2

eGFR for patients with acute kidney injury (AKI) and without (no AKI) surviving to 1 year and patients with and without AKI who did not survive.

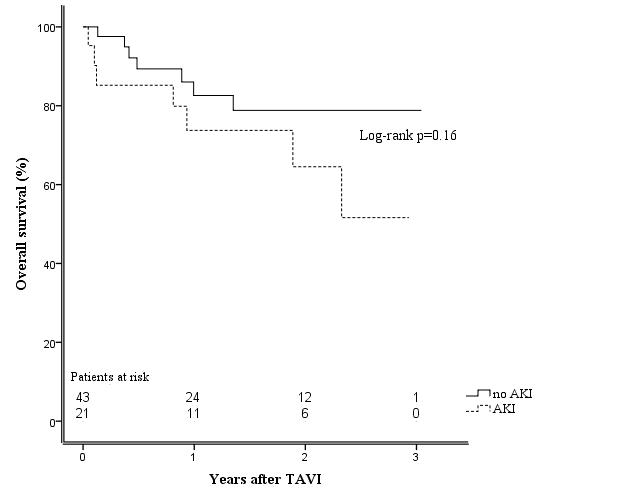


Figure II.3

Kaplan-Meier survival curves for patients with acute kidney injury (AKI) and without (no AKI) following TAVI**.**

## Paper III

### Operative data

The baseline preoperative characteristics of the study population are listed in Table III.1. During the relevant study period, 123 patients underwent TAVI, with a transapical access for valve implantation being used in 85 patients (69%) and a transfemoral access in 38 (31%). Transapical patients had significantly more peripheral vascular disease (64.7% versus 44.9%; p = 0.04) and a higher EuroSCORE II (8.8 ± 9.9 versus 5.6 ± 4.3; p = 0.01) compared to transfemoral patients.

Percutaneous coronary intervention for significant coronary stenosis was performed preoperatively in 43 patients (35%). The distribution of valve sizes implanted for the Edwards SAPIEN Transcatheter Heart Valve or SAPIEN XT in the study population was 23 mm (n = 46), 26 mm (n = 63), and 29 mm (n = 14). Intraprocedural device success according to the VARC-2 criteria was 95.9% (118/123).

### 30-day mortality and causes of death

All-cause mortality within 30 days was 4.1% (5/123). There was one death (2.6%) in the transfemoral group, and four deaths (4.7%) in the transapical group. The cause of death for the patient in the transfemoral group was intraprocedural dissection of the left anterior descending artery leading to conversion to a salvage procedure with coronary artery bypass grafting (CABG) while on extracorporeal circulation. The patient succumbed to low cardiac output syndrome in the intensive care unit later the same day. Causes of death in the transapical group were intraprocedural heart failure and circulatory collapse (n = 1), traumatic subarachnoid hemorrhage eight days postoperatively due to an accidental fall in the ward while receiving warfarin treatment (n = 1), and multiorgan failure on the 17th (n = 1) and 24th (n = 1) postoperative days. The individual risk scores for each risk stratification system in the diseased patients are listed in Table III.2.

### Calibration analysis and observed versus expected 30-day mortality

The predicted 30-day mortality was 25.0 ± 15.7% by logistic EuroSCORE, 7.3 ± 6.9% by the STS score, and 7.8 ± 8.7% by EuroSCORE II. A majority of the patients (58.5%; 72/123) had a logistic EuroSCORE >20%, and 17.1% (21/123) had a STS score >10%. The H-L test demonstrated a poor calibration for logistic EuroSCORE, both for the overall study population (p <0.0001) as well as for the transapical group (p = 0.0003), but an acceptable calibration for the transfemoral group (p = 0.23). The H-L test for the STS score and EuroSCORE II showed an acceptable calibration for the overall study population as well as for the transapical and transfemoral groups. The riskadjusted mortality ratio indicated that all three evaluated risk score models were inadequately calibrated (Table III.3). All three risk score models overestimated 30-day mortality, both in the study population, as well as for the transapical and transfemoral groups. The logistic EuroSCORE overestimated mortality to a high extent in both the transapical group and the transfemoral group. In the transapical group, the STS score demonstrated the best calibration of the three risk models (observed/expected ratio 0.65). In the transfemoral group, the EuroSCORE II presented the best observed/expected ratio (0.62) of the three risk models.

### Discrimination analysis of 30-day mortality

The discrimination analysis for the overall population, as well as for the transapical and transfemoral groups, is presented in Table III.4. The logistic EuroSCORE demonstrated the largest area under curve (AUC) for the overall study population (AUC 0.69; 95% CI 0.54-0.84) as well as for the transfemoral group (AUC 0.84; 95% CI 0.72-0.96), while the EuroSCORE II demonstrated the largest AUC (0.70) in the transapical group. The receiver operating curves of the logistic EuroSCORE, the STS score, and the EuroSCORE II are illustrated in Figure III.1. There was no significant difference in AUC between the three risk scores models: logistic EuroSCORE versus STS score (p=0.54); logistic EuroSCORE versus EuroSCORE II (p=0.79); STS score versus EuroSCORE II (p=0.67). The sensitivity and specificity for different cut-off values in each risk score model are listed in Table III.5.

Table III.1.

Preoperative patient characteristics

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | Overall (n=123) | TA (n=85) | TF (n=38) | *p*-value |
| Age (years) ̽ | 80.5 ± 7.5 | 80.2 ± 7.6 | 81.4 ± 7.3 | 0.400 |
| Female gender | 58 (47.2) | 36 (42.4) | 22 (57.9) | 0.11 |
| BMI (kg/m²)̽ | 27.2 ± 6.3 | 27.0 ± 6.9 | 27.8 ±4.8 | 0.487 |
| Hypertension | 59 (48.0) | 39 (45.9) | 20 (52.6) | 0.49 |
| Diabetes mellitus | 32 (26.0) | 25 (29.4) | 7 (18.4) | 0.20 |
| PCI prior to TAVI | 43 (35.0) | 32 (37.6) | 11 (28.9) | 0.35 |
| Previous cardiac surgery | 40 (32.5) | 32 (37.7) | 8 (21.1) | 0.07 |
| COPD | 26 (21.1) | 21 (24.7) | 5 (13.2) | 0.15 |
| Cerebrovascular disease | 9 (7.3) | 5 (5.9) | 4 (10.5) | 0.46 |
| Renal failure† | 22 (17.9) | 15 (12.2) | 7 (18.4) | 0.92 |
| Creatinine (µmol/L) | 104.0 ± 51.4 | 100.7 ± 39.3 | 111.5 ± 71.6 | 0.284 |
| Preoperative dialysis | 8 (6.5) | 4 (4.7) | 4 (10.5) | 0.25 |
| Recent MI (<90 days) | 13 (10.6) | 9 (10.6) | 4 (10.5) | 1.0 |
| Pulmonary hypertension (>55mmHg) | 16 (13.0) | 11 (12.9) | 5 (13.2) | 1.0 |
| Peripheral vascular disease | 72 (58.5) | 55 (64.7) | 17 (44.7) | 0.04 |
| Atrial fibrillation | 40 (32.5) | 30 (35.3) | 10 (26.3) | 0.33 |
| NYHA Class IV | 24 (19.5) | 20 (23.5) | 4 (10.5) | 0.09 |
| LVEF 30-50% | 33 (26.8) | 25 (29.4) | 8 (21.1) | 0.33 |
| LVEF 20-30% | 13 (10.6) | 8 (9.4) | 5 (13.2) | 0.54 |
| LVEF <20% | 1 (0.8) | 1 (1.2) | 0 (0) | 1.0 |
| Logistic EuroSCORE (%) ̽ | 25.0 ± 15.7 | 25.9 ± 17.2 | 23.1 ± 11.7 | 0.294 |
| EuroSCORE II ̽ | 7.8 ± 8.7 | 8.8 ± 9.9 | 5.6 ± 4.3 | 0.013 |
| STS score ̽ | 7.3 ± 6.9 | 7.3 ± 6.2 | 7.3 ± 8.3 | 0.977 |
| Aortic gradient, peak (mmHg) ̽ | 79.0 ± 22.3 | 78.3 ± 20.8 | 80.7 ± 25.5 | 0.604 |

̽ Values are mean ± SD. Values in parenthesis are percentages. † Creatinine clearance estimate <50mL/min/1.73m². BMI: body mass index; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NYHA = New York Heart Association Classification; PCI: percutaneous coronary intervention; TA: transapical; TF: transfemoral

Table III.2.

Risk scores for deceased patients (within 30 days post-procedure)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Patient no. | Mortality (days post-procedure) | Valve implantation access | Logistic EuroSCORE (%) | STS score (%) | Euro-SCORE II (%) |
| #1 | 0 | TA | 26.2 | 3.6 | 10.8 |
| #2 | 0 | TF | 33.3 | 4.9 | 3.8 |
| #3 | 8 | TA | 40.0 | 6.3 | 5.4 |
| #4 | 17 | TA | 38.2 | 12.4 | 26.3 |
| #5 | 24 | TA | 19.6 | 10.1 | 6.3 |

TA= Transapical; TF = Transfemoral

Table III.3.

|  |  |  |  |
| --- | --- | --- | --- |
| Risk Score | Observed/  Expected Ratio | H-L  statistics | H-L  p-value |
| Logistic EuroSCORE |  |  |  |
| Overall | 0.16 | 37.1 | <0.0001 |
| Transapical | 0.18 | 29.4 | 0.0003 |
| Transfemoral | 0.22 | 10.6 | 0.23 |
| STS score |  |  |  |
| Overall | 0.56 | 8.5 | 0.39 |
| Transapical | 0.65 | 7.4 | 0.50 |
| Transfemoral | 0.32 | 8.5 | 0.39 |
| EuroSCORE II |  |  |  |
| Overall | 0.52 | 5.9 | 0.66 |
| Transapical | 0.53 | 6.2 | 0.63 |
| Transfemoral | 0.62 | 7.2 | 0.52 |

Calibration analysis

H-L = Hosmer-Lemeshow test

Table III.4.

Discrimination analysis

|  |  |  |
| --- | --- | --- |
| Risk Score | AUC | 95% CI |
| Logistic EuroSCORE |  |  |
| Overall | 0.69 | (0.54-0.84) |
| Transapical | 0.66 | (0.49-0.82) |
| Transfemoral | 0.84 | (0.72-0.96) |
| STS score |  |  |
| Overall | 0.60 | (0.38-0.82) |
| Transapical | 0.63 | (0.37-0.88) |
| Transfemoral | 0.46 | (0.30-0.62) |
| EuroSCORE II |  |  |
| Overall | 0.66 | (0.46-0.86) |
| Transapical | 0.70 | (0.52-0.88) |
| Transfemoral | 0.38 | (0.22-0.54) |

AUC: area under the curve; CI=confidence interval

Table III.5.

Cut-off values for logistic EuroSCORE, STS score, and EuroSCORE II

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Cut-off value | n  (%) | Observed mortality (%)  (95% CI) | Predicted mortality (%)  (95% CI) | Sensitivity  (%) | Specificity  (%) | PPV  (%) | NPV  (%) |
| Log EuroSCORE >20% | 72 (59) | 5.6 (0.2-10.9) | 34.8 (31.7-37.8) | 80.0 | 42.4 | 5.6 | 98.0 |
| STS score >10% | 21 (17) | 9.5 (0.0-22.4) | 18.6 (14.4-22.9) | 40.0 | 83.9 | 9.5 | 97.1 |
| EuroSCORE II >2.5% | 100 (81) | 5.0 (0.7-9.3) | 9.2 (7.4-11.0) | 100 | 19.5 | 5.0 | 100 |
| EuroSCORE II >5% | 67 (54) | 6.0 (0.3-11.7) | 11.9 (9.5-14.3) | 80.0 | 46.6 | 6.0 | 98.2 |
| EuroSCORE II >7.5% | 38 (31) | 5.3 (0.0-12.5) | 16.5 (12.9-20.2) | 40.0 | 69.5 | 5.3 | 96.5 |
| EuroSCORE II >10% | 27 (22) | 7.4 (0.0-17.5) | 19.7 (15.1-24.3) | 40.0 | 78.8 | 7.4 | 96.9 |

PPV: positive predictive value; NPV: negative predictive value

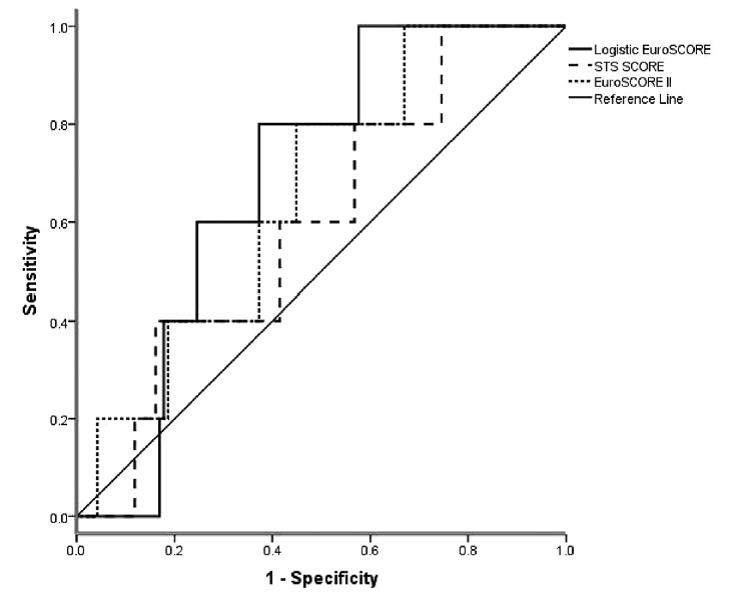


Figure III.1

Risk-score discrimination and 30-day mortality. Reciever operating characteristic (ROC) curves for the logistic EuroSCORE, the STS score, and the EuroSCORE II

## Paper IV

Baseline preoperative characteristics for unmatched and propensity score-matched TAVI and AVR groups are presented in Table IV.1. Despite attempted matching, baseline characteristics of the two treatment groups differed significantly. Patients in the TAVI group more often were older patients (*p*=0.007) of female gender (*p*=0.032) with pulmonary hypertension (*p*=0.033) and peripheral vascular disease (*p*=0.035) who had undergone CABG (*p*=0.005) and percutaneous coronary intervention (PCI) (*p*=0.025) procedures prior to TAVI. Concomitant CABG was performed in 59% (n=74) of the propensity score-matched AVR population.

### Device success

Composite endpoints following TAVI and AVR are presented in Table IV.2. Device success was 94.0% (158/168) in the TAVI group. Intraprocedural mortality with TAVI was 1.8% (n=3). These patients succumbed due to; intraoperative dissection of the left anterior descending coronary artery leading to left ventricle rupture despite a salvage CABG procedure with ECC (n=1); intraoperative heart failure with circulatory collapse (n=1); intraoperative aortic root rupture during valve deployment leading to an unsuccessful salvage AVR procedure with ECC (n=1). There was no perioperative death in the AVR-group.

Correct positioning of a single prosthetic valve in the TAVI group was achieved in 95.8% (161/168). Prosthetic valve migration occurred in two patients. Four patients in the TAVI group did not receive a prosthetic valve at the first attempt due to transient obstruction of the left main coronary artery during the initial balloon valvuloplasty (n=1), heavy calcification in the common femoral artery (n=1) (the patient successfully received a TA-TAVI five months later), and heavy calcification in the ascending aorta preventing transfemoral passage (n=1). One transfemoral Boston Scientific Lotus valve was placed in incorrect position and the respositioning mechanism failed, whereas the implantation was aborted (the patient underwent a successful TF Sapien 5 weeks later). In a single instance where severe perioperative transprosthetic regurgitation was evident by transesophageal echocardiography, valve-in-valve placement (SAPIEN-in-SAPIEN) was required. Perioperative transesophageal echocardiography demonstrated no moderate or severe trans- or paravalvular regurgitation, or mean gradient higher than 20 mmHg in the TAVI group.

### 

### Early safety (at 30 days)

In TAVI and AVR treatment groups, 30-day mortality rates were 4.2% and 4.8% (p=0.81) and all-cause stroke rates were 3.0% and 0.8% (p=0.24), respectively. Early safety at 30 days was 87% (146/168) in the TAVI group and 86% (108/125) in the AVR group (*p*=1.0) (Table IV.2). Postoperative permanent pacemaker implantation was required in 9.0% (n=15) and 5.6% (n=7) of TAVI- and AVR-treated patients, respectively (p=0.24).

### Clinical efficacy and time-related valve safety

Survival rates were 80.5±3.4% vs 89.6±2.7% at 1 year and 51.8±5.8% vs 72.3±4.3% at 4 years for TAVI and AVR groups, respectively (p=0.001) (Figure IV.1). Clinical efficacy rates were 78.2±3.5% vs 89.6±2.7% at 1 year and 34.9±5.2% vs 66.8±4.4% at 4 years for TAVI and AVR groups, respectively (p<0.001). Rates of freedom from all-cause stroke were 92.3±2.2% vs 99.2±0.8% at 1 year and 81.2±5.2% vs 95.6±2.2% at 4 years for TAVI and AVR groups, respectively (p=0.001). Prosthetic valve endocarditis was diagnosed in four patients (two per group): TAVI, 1.3%; AVR, 1.7% (p=1.0). Deaths in the TAVI group are listed by cause in Table IV.3.

### Re-hospitalization due to congestive heart failure and myocardial infarction

Cumulative incidences of re-hospitalization for CHF were16.3±3.2% vs 6.8±2.3% at 1 year and 41.3±7.2% vs 23±4.3% at 4 years after TAVI and AVR, respectively (p=0.006) (Figure IV.2a). Corresponding linearized rates of re-hospitalization due to CHF were 24.5% (n=72) vs 15.0% (n=86) per patient/year. Cumulative incidences of re-hospitalization for MI were 3.5±1.8% vs 0.8±0.8% at 1 year and 17.1±5.5% vs 4.8±2.4% at 4 years after TAVI and AVR, respectively (p=0.003) (Figure IV.2b). Corresponding linearized rates of re-hospitalization for MI were 5.1% (n=15) vs 1.6% (n=9) per patient/year.

### Independent risk factors for mortality and for re-hospitalization due to congestive heart failure

Uni- and multivariate analyses of risk factors for mortality and re-hospitalization due to CHF are delineated in Table IV.4. Independent risk factors for mortality were diabetes mellitus (hazard ratio [HR]=2.0; 95% confidence interval [CI], 1.15-3.47; p=0.015) and estimated glomerular filtration rate (HR=0.98; 95% CI, 0.97-0.99; p=0.011). NYHA Functional Class IV preoperative status was identified as an independent risk factor for re-hospitalization due to CHF (HR=2.43; 95% CI, 1.19-4.95; p=0.015).

Table IV.1

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Unmatched | |  | | Matched | |  |
| Variable | AVR  n=2883  n (%) | TAVI  n=166  n (%) | p-value | | AVR  n=125  n (%) | TAVI  n=166  n (%) | p-value |
| Female  NYHA Class IV  Diabetes mellitus  COPD  Pulmonary hypertension  Peripheral vascular disease  Neurological dysfunction  Recent MI  Previous cardiac surgery  CABG  AVR  PCI prior to TAVI/AVR  Preoperative dialysis  **Critical preoperative state**  LVEF  <50%  <30% | 791 (27)  157 (5)  315 (11)  246 (9)  86 (3)  244 (8)  37 (1)  300 (10)  84 (3)  98 (3)  31 (1)  44 (2)  488 (17)  153 (5) | 81 (49)  35 (21)  40 (24)  29 (18)  27 (16)  86 (52)  13 (7.8)  17 (10)  81 (49)  4 (2.4)  52 (32)  11 (6.7)  0  64 (39)  5 (3.0) | 0.123  <0.001  0.021  0.129  <0.001  <0.001  <0.001  0.044  <0.001  <0.001  <0.001  0.174  0.001  0.016 | | 46 (37)  17 (14)  20 (16)  19 (15)  10 (8)  49 (39)  10 (8)  16 (13)  40 (32)  2 (1.6)  24 (19)  4 (3.2)  3 (2.4)  51 (41)  9 (7.2) | 81 (49)  35 (21)  40 (24)  29 (18)  27 (16)  86 (52)  13 (7.8)  17 (10)  81 (49)  4 (2.4)  52 (32)  11 (6.7)  0  64 (39)  5 (3.0) | 0.032  0.093  0.080  0.570  0.033  0.035  0.986  0.523  0.005  0.025  0.182  0.170  0.668  0.104 |
|  | Mean ± SD | | *p-*value | Mean ± SD | | | *p-*value |
| Age  Body Mass Index  Aortic gradient, mmHg  Peak  Mean  Hemoglobin, g/L  eGFR  Logistic EuroSCORE | 76±7  27±4  78±25  45±14  129±13  73±24  12±11 | 80±9  27±5  78±22  44±12  125±15  56±25  23±15 | <0.001  0.703  0.745  0.745  0.002  <0.001  <0.001 | | 78±6  27±4  78±25  44±14  129±18  61±22  20±14 | 80±9  27±5  78±22  44±12  125±15  56±25  23±15 | 0.007  0.883  0.976  0.974  0.092  0.091  0.083 |

Propensity score adjustment (TAVI and AVR) with or without concomitant CABG at baseline.

Values expressed as number and percentage of patients, mean ± SD. AVR = aortic valve replacement, TAVI = transcatheter aortic valve implantation, NYHA = New York Heart Association Functional Classification, COPD = chronic obstructive pulmonary disease, Pulmonary hypertension = >60mmHg, CABG = coronary artery bypass grafting, PCI = percutaneous coronary intervention, LVEF = left ventricular ejection fraction, eGFR = estimated glomerular filtration rate (calculated by abbreviated MDRD equation)

Table IV.2.

Composite endpoints following transcatheter aortic valve implantation (TAVI) and propensity score-matched aortic valve replacement (AVR)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable |  | TAVI  n=168 (%) | AVR  n=125 (%) | *p*-value |
| *Device success*  *Early Safety (at 30 days)*  All-cause mortality  All-cause stroke  Life-threatening bleeding  Acute kidney injury\* – Stage 2 or 3  Coronary obstruction requiring intervention  Major vascular complications  Repeated procedure (valve-related dysfunction) | | 158 (94.0%)  146 (86.9%)  7 (4.2%)  5 (3.0%)  10 (5.9%)  7 (4.2%)  1 (0.6%)  8 (4.8%)  0 | -  108 (86.4%)  6 (4.8%)  1 (0.8%)  8 (6.4%)  7 (5.6%)  0  0  0 | -  1.000  0.812  0.242  0.725  0.575  1.000  0.021  - |

Composite endpoints expressed as number and (%)

\*Defined by AKIN

Table IV.3.

Cause of death in patients undergoing transcatheter aortic valve implantation (TAVI)

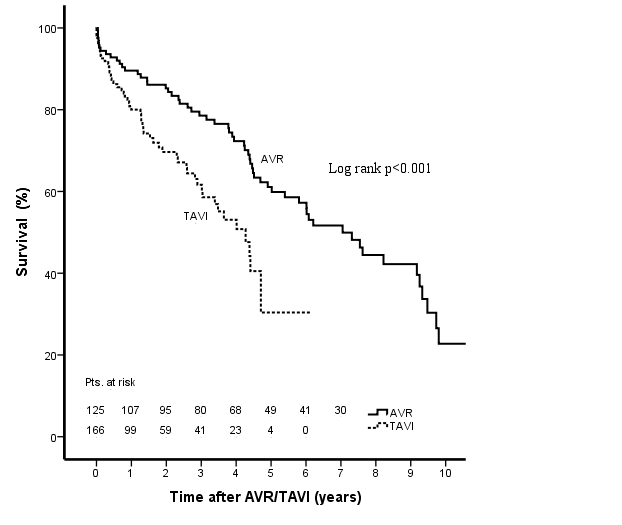
|  |  |  |
| --- | --- | --- |
| Deaths (n=56) by cause | TAVI  (n=166) | Postoperative day |
| Procedure related  *Cardiovascular mortality*  Congestive heart failure  Acute myocardial infarction  Sudden death  Stroke, ischemic  Ruptured aortic  Unknown  *Noncardiovascular mortality*  Malignancy  Traumatic hemorrhage  Pneumonia  Sepsis  Hepatic failure  Gastrointestinal hemorrhage  Renal failure  Multi-organ failure | 3  10  7  1  2  1  10  5  3  4  3  1  1  2  3 | 0, 0, 0  23, 86, 123, 130, 136, 263, 296, 493, 653, 1055  37, 133, 363, 481, 946, 1292, 1559  152  466, 689  467  218, 344, 460, 593, 849, 1108, 1332, 1465, 1599, 1718  151, 157, 341, 560, 1680  8, 44, 48  177, 324, 941, 1102  285, 1030, 1718  1283  839  15, 1270  25, 37, 489 |

Table IV.4.

Cox regression analysis: predictors of mortality and re-hospitalization for congestive heart failure following TAVI.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Univariate analysis | | | Multivariate analysis | | |
| Predictors of mortality | HR | (95% CI) | *p-*value | HR | (95% CI) | *p-*value |
| Age, per 1-year increment | 1.03 | 0.99-1.07 | 0.166 |  |  |  |
| Female gender | 0.76 | 0.45-1.30 | 0.319 |  |  |  |
| Hypertension | 1.7 | 1.02-2.96 | 0.041 | 1.59 | 0.93-2.72 | 0.088 |
| Diabetes mellitus | 2.1 | 1.19-3.61 | 0.010 | 2.0 | 1.15-3.47 | 0.015 |
| LVEF<50 | 1.53 | 0.90-2.61 | 0.118 |  |  |  |
| NYHA Class IV | 1.45 | 0.81-2.60 | 0.212 |  |  |  |
| eGFR | 0.98 | 0.97-0.99 | 0.007 | 0.98 | 0.97-0.99 | 0.011 |
| Renal replacement therapy | 0.87 | 0.27-2.80 | 0.873 |  |  |  |
| COPD | 1.04 | 0.56-1.94 | 0.898 |  |  |  |
| Aortic gradient, mean | 0.99 | 0.97-1.02 | 0.591 |  |  |  |
| Pulmonary hypertension | 1.95 | 1.04-3.63 | 0.036 |  |  |  |
| Previous CABG | 1.74 | 1.02-2.96 | 0.041 |  |  |  |
| Previous PCI | 0.83 | 0.48-1.45 | 0.510 |  |  |  |
|  |  |  |  |  |  |  |
| Predictors of re-hospitalization for congestive heart failure | HR | (95% CI) | *p-*value | HR | (95% CI) | *p-*value |
| Age, per 1-year increment | 1.04 | 0.99-1.01 | 0.111 | 1.05 | 0.99-1.12 | 0.079 |
| Female gender | 1.23 | 0.62-2.42 | 0.558 |  |  |  |
| Hypertension | 0.95 | 0.48-1.89 | 0.892 |  |  |  |
| Diabetes mellitus | 1.41 | 0.65-3.07 | 0.391 |  |  |  |
| LVEF<50 | 1.91 | 0.95-3.83 | 0.069 | 2.01 | 0.98-4.12 | 0.055 |
| NYHA Class IV | 2.67 | 1.31-5.45 | 0.007 | 2.43 | 1.19-4.95 | 0.015 |
| eGFR | 0.99 | 0.98-1.01 | 0.288 |  |  |  |
| Renal replacement therapy | 0.78 | 0.18-3.32 | 0.734 |  |  |  |
| COPD | 0.85 | 0.35-2.06 | 0.714 |  |  |  |
| Aortic gradient, mean | 1.01 | 0.98-1.04 | 0.628 |  |  |  |
| Pulmonary hypertension | 2.02 | 0.91-4.50 | 0.084 |  |  |  |
| Previous CABG | 0.95 | 0.48-1.88 | 0.892 |  |  |  |
| Previous PCI | 1.07 | 0.53-2.14 | 0.854 |  |  |  |

HR = Hazard ratio, CI = Confidence interval, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association Functional Classification, eGFR = estimated glomerular filtration rate (calculated by abbreviated MDRD equation), COPD = chronic obstructive pulmonary disease, Pulmonary hypertension = >60mmHg, CABG = coronary artery bypass grafting, PCI = percutaneous coronary intervention.



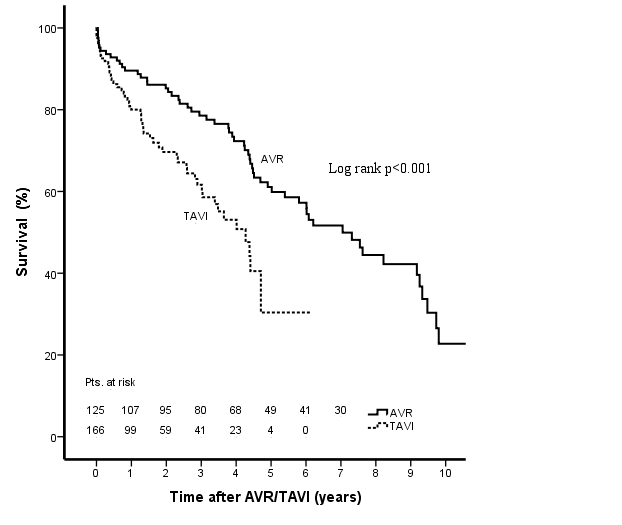


Figure IV.1

Comparison between survival for high risk patients undergoing transcatheter aortic valve implantation (TAVI) and propensity score matched patients undergoing aortic valve replacement (AVR).

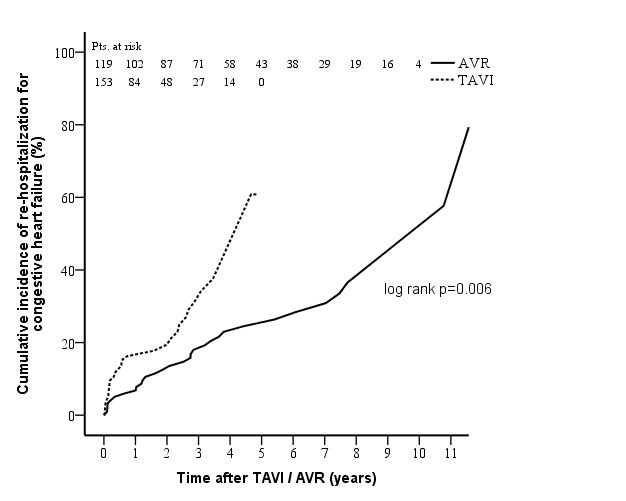


Figure IV.2a

Cumulative incidences of re-hospitalization for congestive heart failure in high-risk- patients undergoing transcatheter aortic valve implantation (TAVI) and propensity score matched patients undergoing aortic valve replacement (AVR).

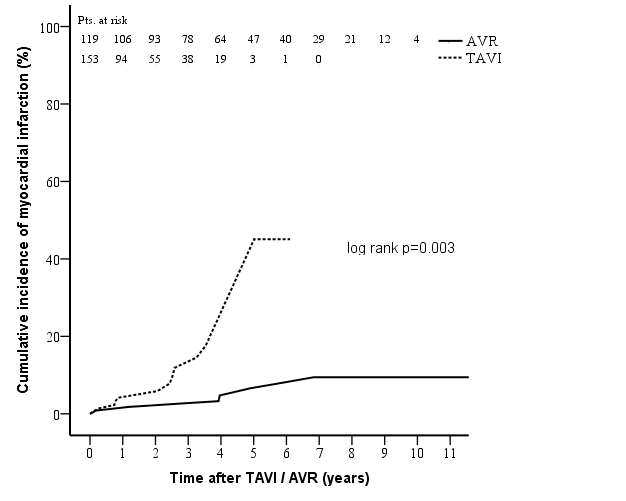


Figure IV.2b

Cumulative incidences of re-hospitalization for myocardial infarction in high-risk- patients undergoing transcatheter aortic valve implantation (TAVI) and propensity score matched patients undergoing aortic valve replacement (AVR).

# Discussion

The results of the present thesis confirm the merits of TAVI as a therapeutic option in high-risk patients with AS [[2](#_ENREF_2)]. Early safety was excellent, although the risk of postoperative AKI was considerable [[83](#_ENREF_83)]. The clinical efficacy and late survival following TAVI was inferior compared to that of AVR in propensity-matched subjects, and we observed a higher incidence of re-hospitalization for CHF and MI following TAVI. Furthermore, when evaluating performance in predicting the 30-day mortality, the three evaluated risk scores models demonstrated rather poor performance in general, and more accurate TAVI-specific risk score models are needed [[112](#_ENREF_112)].

## Comparison to AVR

In the present thesis an attempt to compare TAVI and AVR was made in Paper I and Paper IV. It is difficult to compare outcomes between TAVI and AVR owing to obvious differences in baseline characteristics, as patients determined for TAVI are considered high-risk and commonly denied conventional AVR. To minimize the wide discrepancy between the two different patient populations, we performed propensity score matching to try to balance baseline covariates. However, our matching was not perfect, either in Paper I or in Paper IV. In some previous studies using propensity score matching, the TAVI population was reduced as well in order to find a better 1:1 match, leaving the sickest TAVI patents outside the study [[55](#_ENREF_55), [113](#_ENREF_113)]. In Paper IV, we selected an AVR group smaller than the TAVI group for better matching. Despite this, there are significant differences in the two populations, and once again the TAVI patients carry more comorbidity and have a higher risk profile.

In Paper I, a comparison between one year survival for patients undergoing TAVI and AVR was made, showing that survival with both the TF and TA approaches was similar to that after AVR (Figure I.1). When increasing the study population (Paper IV) the TAVI group showed inferior survival rates (Figure IV.1). This finding contrasts with two previously randomized studies and the meta-analysis by Takagi et al, in which TAVI was similar or superior to AVR in survival [[49](#_ENREF_49), [105](#_ENREF_105), [114](#_ENREF_114)]. Our TAVI group consisted of mixed high risk patients and patients denied AVR. For patients denied AVR, there remained no other available treatment but TAVI [[3](#_ENREF_3), [115](#_ENREF_115)] and therefore poorer late outcomes may be expected compared to AVR [[116](#_ENREF_116), [117](#_ENREF_117)]. However, early safety (including all-cause mortality, all-cause stroke, life-threatening bleeding, AKI, coronary obstruction requiring intervention, major vascular complications and repeated procedure, all within 30 days) was surprisingly excellent for both TAVI and AVR groups, reflecting careful patient selection, good clinical performance and optimal postoperative care in this vulnerable patient cohort.

The TAVI procedure has an integrated risk of procedural failure without parallel in AVR. In Paper IV, the device success was 94%, leaving 10 patients with an unsatisfying result, related to the 0% perioperative mortality in the AVR group. Our device success was comparable with that of previous studies [[118-120](#_ENREF_118)]. However, how to manage this result is of great importance, since exclusions from further analysis may have a significant impact on the overall outcomes and skew the results in favor of TAVI.

In Paper IV, in the present thesis, we found that re-hospitalizations for CHF and MI were more frequent following TAVI than with AVR. Even if our comparison was not ideal, the purpose of intervention for elderly patients with AS and significant comorbidities should be symptom relief, and not only prolonged life-expectancy. One can assume that more frequent hospitalizations due to CHF and MI may affect the patients’ quality of life, although this was not evaluated in this thesis. However, some previous published studies have linked untreated significant coronary artery disease with poorer survival following TAVI [[121](#_ENREF_121), [122](#_ENREF_122)]. Likewise, a recent study by Thalji et al [[123](#_ENREF_123)] has shown that concomitant CABG during AVR improved survival. Our increased rates of re-hospitalization for CHF and MI observed after TAVI raise the question of whether a subgroup of candidates for TAVI would benefit from prior revascularization to a greater extent.

## Renal function

Acute kidney injury (AKI) is a serious complication following cardiac surgery with CPB, associated with impaired outcome [[74-76](#_ENREF_74)]. TAVI has the benefit of avoiding CPB, however, embolization of aortic debris, sequences of rapid pacing with hypoperfusion, the use of a nephrotoxic contrast agent and patient population with preoperative chronic kidney disease to a higher extent are all potential risk factors for postoperative AKI.

Data from Paper II in the present thesis indicates that AKI following TAVI is common, with approximately 30% to 40% developing AKI after TAVI. However, data from study IV in the present thesis demonstrates only 4.2% of AKI following TAVI. This obvious discrepancy in incidence of postoperative AKI can be explained by the different classifications of AKI (i.e. RIFLE and AKIN) [[88](#_ENREF_88), [90](#_ENREF_90)], Figure 3.

All patients with postoperative AKI in Paper II had undergone TAVI using the TA approach, similar to that of previously published data [[84](#_ENREF_84)]. The most likely explanation is more prominent generalized arteriosclerosis and more advanced disease and comorbidity in TA patients [[81](#_ENREF_81)], and similar with a Hartrumpf et al [[124](#_ENREF_124)], we did not observe a higher amount of contrast agent used in the TA approach in Paper I. However, another explanation may be the additional hypoperfusion for patients undergoing TA approach since an extra sequence of rapid pacing is needed during the introducer retraction. Furthermore, a recent study by Petronio et al, showed that general anesthesia generated a higher incidence of AKI stage 3 compared to local anesthesia [[125](#_ENREF_125)].

Interestingly, at 12 months follow up, the mean eGFR in the AKI+ group had recovered compared to the lowest postoperative eGFR. However, there was a trend towards impaired renal function compared to preoperative eGFR levels, for both AKI+ (p=0.071) and AKI-patients (p=0.057). Even if these differences were not statistically significant, it seems plausible that the result could have attained statistical significance had the number of patients been larger. The current findings may suggest that patients with or without AKI following TAVI demonstrate a deteriorating renal function over time. Causes of renal impairment are multifactorial with a plethora of etiologies of which several are chronic and progressive with the potential of affecting renal function during the postoperative period. Diabetes mellitus, hypertensive cardiovascular and peripheral vascular disease are common co-morbidities in this patient population, with established long-term negative effects on renal function.

In Paper II in the present thesis, there was a significant difference in preoperative eGFR between creatinine and cystatin C. This may reflect a diminished muscle mass in aged patients with severe aortic stenosis and reduced functional capacity. One of the hemodynamic consequences of valve replacement due to AS is an afterload reduction leading to improved systodiastolic function, cardiac reverse remodeling and symptom relief. Postoperatively, patients often demonstrate a substantial improvement in their physical ability and exercise tolerance and may therefore rebuild muscle mass with an increase in creatinine that cannot be translated into a renal functional impairment over time.

## 

## Prediction of 30-day mortality

The ability to predict postoperative mortality in patients undergoing cardiac surgery and TAVI is necessary in order to individualize current treatment for AS. Since logistic EuroSCORE have lost its advantage in calibration over the years [[126](#_ENREF_126)], and the STS score has been shown to underestimate mortality after conventional AVR [[127](#_ENREF_127)], a more accurate risk assessment tool is needed. The EuroSCORE II has recently been introduced and has demonstrated improved discrimination compared to the logistic EuroSCORE in cardiac surgery [[33](#_ENREF_33), [128](#_ENREF_128)].

However, in parity with the EuroSCORE and the STS score, the EuroSCORE II was never intended to be applied to the TAVI cohort, and few reports have evaluated the accuracy of the EuroSCORE II in predicting early mortality following TAVI [[34-39](#_ENREF_34)].

In Paper III in the present thesis, we found a good calibration for the EuroSCORE II and the STS score, but despite this the risk score models overestimated 30-day mortality by factors of 1.8 and 1.9, respectively. The logistic EuroSCORE was poorly calibrated in the overall population (H-L test, *p*<0.0001) and in the TA group (H-L test, *p*=0.0003), but had acceptable calibration in the TF group (H-L test, *p*= 0.23). The logistic EuroSCORE also overestimated 30-day mortality with a factor of 6.3, which was similar to the data reported previously by Goetzenich et al [[35](#_ENREF_35)]. The present data were similar to those in a previous report from Sedaghat and colleagues [[37](#_ENREF_37)], who demonstrated a tendency to overestimate mortality for all three risk models.

In contrast to recent studies [[34](#_ENREF_34), [37](#_ENREF_37), [39](#_ENREF_39)], the present study was unable to identify an improved discriminatory power for the EuroSCORE II compared to the logistic EuroSCORE. The EuroSCORE II presented good discriminative power in the TA group (AUC 0.70), and even though the logistic EuroSCORE demonstrated a very good discriminative power in the TF group (AUC 0.84) this may be questionable since we only had one event in the TF group.

The present data indicated that a large number of patients undergoing TAVI were selected based on other criteria than those presented in the evaluated risk score models. As increasing numbers of patients with intermediate EuroSCORE/STS scores are being referred for TAVI, and all of the established risk score models are limited by an inadequate estimation of 30-day mortality, a well-calibrated and accurate risk stratification model is necessary.

### 

### Limitations

The limitations of the present thesis were the limited number of patients and the mainly retrospective and observational single-center design, such that the data acquired may not be generalized to other clinical settings or may influence the strength of the statistical inferences drawn. Even though propensity-score matching can be used to balance measured baseline covariates, patients selected for TAVI are more likely to have comorbidities such as porcelain aorta, malignancies and cirrhosis that may remain unadjusted for, compared to the AVR group. The causes of AKI (nephrotoxic, ischemic, or atheroembolic) could not be determined due to the absence of renal biopsies. Unfortunately, we have not studied the incidence and consequences of PVR following TAVI. Finally, the TAVI population included our early experience, which may have included learning curve effects.

# Conclusions

Based on the findings of the studies presented in this thesis, the following conclusions can be drawn:

**Paper I**. TAVI can be safely performed in selected high-risk patients. After propensity score matching, survival with both the TA and TF approaches was similar to that after conventional AVR. However, owing to the lack of long-term data, the relationship between TAVI and AVR appears to be complementary rather than substitutive.

**Paper II**. The risk of postoperative AKI is considerable following TAVI, and the acute postoperative renal impairment in these patients does not fully recover in the long term. There is a progressive renal impairment in both groups postoperatively. Cystatin C may be a valuable adjunct to the established biomarker creatinine for preoperative risk assessment and postoperative diagnosis of AKI.

**Paper III**. EuroSCORE II predict 30-day mortality more accurately for the TAVI cohort compared to the more established logistic EuroSCORE and compares on par with the STS-score. In general, all three evaluated risk scores models demonstrated rather poor performance in predicting 30-day mortality after TAVI. In lack of a more TAVI-oriented risk stratification system, the EuroSCORE II may be a valuable adjunct in the clinical setting.

**Paper IV**. Results of this study confirm the merit of TAVI as a therapeutic option in high risk patients with aortic stenosis, even though late survival with TAVI proved inferior to that of AVR in propensity-matched subjects. Early safety was excellent for both treatment groups, however, patients undergoing TAVI had a higher incidence of re-hospitalization for CHF an MI during follow up. In our, view, patients with severe CHF should be carefully monitored and aggressively treated to improve above outcome measures.

# Future perspectives

TAVI has revolutionized the treatment of inoperable patients with severe symptomatic AS [[3](#_ENREF_3), [4](#_ENREF_4)]. The early and mid-term results are promising, and the request for minimally invasive surgery is growing. Today’s patients are often well-informed about their condition and therapeutic options. Therefore, a minimally-invasive treatment such as TAVI may appear attractive even for lower risk patients with AS. Despite a lack of support in the current guidelines, an expansion of indications for TAVI into the category of intermediate-risk patients has already started in some centers in Europe [[55](#_ENREF_55), [60](#_ENREF_60), [129](#_ENREF_129)]. However, AVR and re-do AVR have very good results, even in the elderly [[130](#_ENREF_130), [131](#_ENREF_131)], thus beneficial long-term data and more TAVI specific risk models for optimizing patient selection will be needed before expanding the indications for TAVI.

There are ongoing randomized studies comparing TAVI and AVR in intermediate risk patients, i.e. the PARTNER II Trial (Placement of AoRTic TraNscathetER Valves), with completed inclusion calculated for December 2015 (n=6650) and the Medtronic CoreValve SURTAVI Trial (SURgical replacement and Transcatheter Aortic Valve Implantation) with complete inclusion (n=2500) calculated for August 2016, and with 5 years of follow-up thereafter. It will be interesting to see the clinical outcome from these two large randomized studies, since they may almost certainly be influential in the future management of AS.

One of the main issues with TAVI is the occurrence and unfavorable consequences of PVR. Whether or not ongoing prosthesis development and more accurate preoperative calcification imaging will lead to a decreasing problem with PVR remains to be elucidated [[40](#_ENREF_40), [41](#_ENREF_41)].

Finally, the TF TAVI-procedure performed on conscious patients without the need of general anesthesia may be a tremendous improvement for this elderly, vulnerable patient population, eliminating the risks for postoperative complications [[125](#_ENREF_125)].

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