Clinical Outcomes of Transcatheter Aortic Valve Implantation (TAVI)

KONRAD NILSSON
Aortic stenosis (AS) is the most common valvular heart disease and most prevalent in the elderly. In the latest decades, a new method for replacement of the aortic valve: transcatheter aortic valve implantation (TAVI) has been introduced. This has enabled treatment of patients who were earlier not candidates for surgery, and has also led to a shift towards TAVI from open surgery for many patients with symptomatic AS. The aims of this thesis were to examine clinical outcomes after TAVI since its implementation in Sweden.

In Study I we analysed the burden of disease after TAVI with focus on causes of hospitalisation, hospitalisation patterns and predictors of repeated hospitalisation. We identified that hospitalisations are common and from various indications. Heart failure was the most prevalent diagnosis and efforts should be made to reduce the burden of heart failure hospitalisations.

In Study II we performed an external validation of an existing prediction model of risk for short-term hospitalisations after TAVI. The model underperformed in a Swedish setting and it is therefore not recommended for clinical use in its current state. The findings highlight the challenges of developing reliable models that are valid after transportation into a new setting.

In Study III we investigated regional differences in availability to TAVI in Sweden with focus on regional procedure rates, short-term mortality and waiting times. The findings indicated no major regional differences. Hence, despite that Sweden is a geographically large and sparsely populated country the current system with a few specialised TAVI centres seems sufficient for providing national coverage of TAVI procedures.

In Study IV we examined the need for and indications for coronary interventions after TAVI. We concluded that most patients do not need interventions after TAVI and in case an intervention is needed, the outcome is in a majority of cases successful, even though the success rates are lower in patients without prior aortic valve replacement. The most common indication for intervention was non-ST elevation acute myocardial infarction and only a minority of patients underwent angiography at the time of a myocardial infarction post TAVI.

**Keywords:** transcatheter aortic valve implantation, aortic stenosis, clinical outcomes, risk prediction, geographical differences, coronary artery disease
Wherever the art of Medicine is loved,
there is also a love of Humanity
Hippocrates
To my family
List of papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


*Submitted*

*Manuscript*

Reprints were made with permission from the respective publishers.
Related work

Contents

Introduction ................................................................. 13

Normal anatomy and physiology of the aortic valve ................ 13
Aortic stenosis .................................................................. 15
Prevalence ........................................................................ 15
Rheumatic valve disease .................................................. 15
Risk factors for AS .......................................................... 16
Mortality and disability ..................................................... 16
Pathophysiology ............................................................. 16
Grading .......................................................................... 19
Multiple valve disease ..................................................... 20
Concomitant coronary artery disease (CAD) ....................... 20
Bicuspid aortic valve disease (BAV) .................................. 21
Surgical aortic valve replacement (SAVR) ......................... 22
Transcatheter aortic valve implantation (TAVI) ................. 23
Procedure ....................................................................... 23
Placement of Aortic Transcatheter Valves (PARTNER) .......... 23
PARTNER 2 ..................................................................... 24
PARTNER 3 ..................................................................... 24
U.S. CoreValve High Risk Study ....................................... 25
Surgical or Transcatheter Aortic-Valve Replacement in
Intermediate-Risk Patients (SURTAVI) ............................. 25
Evolut Low-Risk .............................................................. 25
The Nordic Aortic Valve Intervention (NOTION) ............... 26
TAVI in Sweden .............................................................. 26
TAVI registries ............................................................... 26
Observational studies ................................................................. 27
Ethics in register-based research ................................................. 27
Statistical methods .................................................................. 28
Geospatial analysis ................................................................... 29
Composite endpoints and recurrent events ................................. 30

Aims ......................................................................................... 32

Methods .................................................................................... 33

Study population ...................................................................... 33
    SWEDEHEART .................................................................... 34
    The Swedish National Population Registry ......................... 35

Statistical Methods .................................................................. 36

Paper I ..................................................................................... 36
Paper II .................................................................................... 37
Paper III ................................................................................... 37
Paper IV ................................................................................... 38

Ethics ....................................................................................... 39

Results ...................................................................................... 40

Paper I ..................................................................................... 40
    Study population .................................................................. 40

Hospitalisations after TAVI ...................................................... 40
    Predictors of hospitalisations after TAVI ............................ 41

Paper II .................................................................................... 44
    Study population .................................................................. 44

    Short-term readmissions .................................................... 44
    Model performance .......................................................... 44
    Sensitivity analyses ......................................................... 45
    Paper III ............................................................................... 47
    Study population .............................................................. 47

    Temporal trends and regional procedure rates ................. 47
Waiting times and short-term survival ........................................... 48
Paper IV ......................................................................................... 49
Study population ............................................................................ 49
Coronary angiogram and intervention ........................................... 49
Success rates .................................................................................. 49
Indications for PCI .......................................................................... 50
Discussion ........................................................................................ 52
Hospitalisations after TAVI .............................................................. 52
Prediction models and predicting outcomes after TAVI ............... 53
Regional TAVI implementation ...................................................... 54
Coronary interventions after TAVI .................................................. 55
Limitations ....................................................................................... 56
Conclusions ..................................................................................... 57
Future perspectives ........................................................................ 58
Sammanfattning på svenska ............................................................. 60
Acknowledgements ........................................................................ 62
References ....................................................................................... 64
Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS</td>
<td>Acute coronary syndrome</td>
</tr>
<tr>
<td>AF</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>AS</td>
<td>Aortic stenosis</td>
</tr>
<tr>
<td>AVA</td>
<td>Aortic valve area</td>
</tr>
<tr>
<td>AVR</td>
<td>Aortic valve replacement</td>
</tr>
<tr>
<td>BAV</td>
<td>Bicuspid aortic valve disease</td>
</tr>
<tr>
<td>BE</td>
<td>Balloon-expandable bioprosthesis</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CA</td>
<td>Coronary angiogram</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary artery bypass graft</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>CCI</td>
<td>Charlson comorbidity index</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>Chronic kidney disease epidemiology collaboration</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>EACTS</td>
<td>European association of cardio-thoracic surgery</td>
</tr>
<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
</tr>
<tr>
<td>ESC</td>
<td>European society of cardiology</td>
</tr>
<tr>
<td>GIS</td>
<td>Geographic information systems</td>
</tr>
<tr>
<td>HF</td>
<td>Heart failure</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International statistical classification of diseases and health related problems - 10th revision</td>
</tr>
<tr>
<td>IQR</td>
<td>Inter quartile range</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>MPG</td>
<td>Mean pressure gradient</td>
</tr>
<tr>
<td>NOTION</td>
<td>The nordic aortic valve intervention</td>
</tr>
<tr>
<td>NPR</td>
<td>National patient register</td>
</tr>
<tr>
<td>NSTE-ACS</td>
<td>Non-ST elevation acute coronary syndrome</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York heart association</td>
</tr>
<tr>
<td>PARTNER</td>
<td>Placement of aortic transcatheter valves</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
<tr>
<td>PVD</td>
<td>Peripheral vascular disease</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RIKS-HIA</td>
<td>Register of information and knowledge about Swedish heart intensive care admissions</td>
</tr>
<tr>
<td>SAVR</td>
<td>Surgical aortic valve replacement</td>
</tr>
<tr>
<td>SE</td>
<td>Self-expandable bioprosthesis</td>
</tr>
<tr>
<td>SEPHIA</td>
<td>Secondary prevention after heart intensive care admission</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST-elevation acute myocardial infarction</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>STS-PROM</td>
<td>Society of thoracic surgeons predicted risk of mortality</td>
</tr>
<tr>
<td>SURTAVI</td>
<td>Surgical or transcatheter aortic-valve replacement in intermediate-risk patients</td>
</tr>
<tr>
<td>SVi</td>
<td>Stroke volume index</td>
</tr>
<tr>
<td>SWEDEHEART</td>
<td>Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies</td>
</tr>
<tr>
<td>SWENTRY</td>
<td>Swedish transcatheter cardiac intervention registry</td>
</tr>
<tr>
<td>TAVI</td>
<td>Transcatheter aortic valve implantation</td>
</tr>
<tr>
<td>TAVI-NHR</td>
<td>TAVI Netherlands heart registration model</td>
</tr>
<tr>
<td>TAVR</td>
<td>Transcatheter aortic valve replacement</td>
</tr>
<tr>
<td>TPR</td>
<td>Total population register</td>
</tr>
<tr>
<td>TRIPOD</td>
<td>Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis</td>
</tr>
<tr>
<td>UCR</td>
<td>Uppsala clinical research center</td>
</tr>
<tr>
<td>Vmax</td>
<td>Peak transvalvular velocity</td>
</tr>
</tbody>
</table>
Introduction

Normal anatomy and physiology of the aortic valve

The aortic valve is located in the aortic root, connecting the left ventricle and the aorta ascendens. It regulates the blood flow by opening to allow blood flow from the left ventricle to the systemic circulation during systole, and by closing in diastole to stop blood from regurgitating back into the ventricle. The valve is estimated to complete this cycle about 40 million times a year or over three billion times during a normal life, and the blood flow can vary between 1 to 20 L/min depending on physical activity status.[1] It is supported by a fibrous skeleton made from dense fibrous tissue which encircles all of the heart’s four valves. The valve mainly collects oxygen and nutrients by diffusion from the circulating blood around it although some capillary beds are present in the proximal portion.[1,2] It consists of the three leaflets, the sinuses of Valsalva and three fibrous interleaflet triangles. The sinuses of Valsalva are located between the luminal surface of the aortic root and each leaflet and allows the valve to open properly during systole. At the top of the sinuses are a thickened aortic wall called the aortic junction, which marks the transition to the ascending aorta. In most cases, although anatomical variations can occur, the coronary arteries originate from two of the sinuses. Hence, the sinuses are named the right, left and non-coronary sinuses.[2]

A common anatomical variation is the bicuspid aortic valve (BAV) where the valve has only two or fused leaflets.[3]

The leaflets consist of three layers which are illustrated in Figure 1. A dense collagenous layer is located closest to the side facing the aortic surface (Fibrosa), a central loose connective tissue layer (Spongiososa) and a elastin rich layer facing the ventricle (Ventricularis). Furthermore, the valves are covered with valvular endothelial cells. The collagen layer forms the strength of the valve and ensures that coaptation of the valves is maintained during diastole. The elastin assists in keeping proper shape of the valve. The loose connective tissue layer protects the valve from stress and friction related damage. Finally, the valvular endothelial cells forms thromboresistance and protects structural integrity of the valve. In total, the cusps are less than 1 mm thick.[2,4]
Figure 1. Cellular architecture of the aortic valve. Reproduced from [4] with permission from Wolters Kluwer.

Figure 2. (a) Aortic valve leaflets, sinuses of Valsalva and coronary arteries when the valve is closed. (b) A simplified version of the Wiggers diagram showing the pressures in the aorta, the left ventricle and the left atrium during the phases of the cardiac cycle. Reproduced from [2] with permission from Taylor & Francis.
The leaflets are influenced by pressure changes. At the end of systole, vortices are created in the sinus Valsalva by the deacceleration of blood in the aorta ascendens which through a complex process involving both the macro and microstructure, helps maintain diastolic coaptation of the valve. The blood pole in the sinuses also supplies the coronary arteries with adequate blood flow.[5] Pressure gradients throughout the cardiac cycle are presented in **Figure 2**.

Aortic stenosis

Aortic stenosis (AS) is a progressive disease leading to obstructed left ventricular outflow and reduced cardiac output which, in turn, increases the risk of developing heart failure (HF) and dying from cardiovascular causes.

Prevalence

AS is the most common valvular heart disease. As of 2017, the global burden of calcific AS was estimated to 12.6 million cases.[6] AS is more prevalent in the elderly population with the majority of patients being older than 65 years of age at the time of the diagnosis. In patients over 75 years of age, the prevalence is around 12 percent, out of which 3 percent is considered severe AS.[7] It has equal distribution between men and women.[8] As the population is getting older, the prevalence of the disease is increasing.[9,10] In addition, for aortic sclerosis, defined as a thickened aortic valve without significant haemodynamically significant obstruction, prevalence increase linearly with age ranging from 20-40% in a population 65 years or older.[11]

Rheumatic valve disease

AS may be caused secondary to acute rheumatic fever. The disease starts with an Streptococcus A infection followed by an abnormal immunologic response causing rheumatic valve disease.[12] Improved health standards and access to penicillin have resulted in that the disease is very rare in developed countries. However, in less developed countries, the condition is still a major burden of disease.[13,14] In this thesis, focus will be on degenerative AS.
Risk factors for AS

Atherosclerotic risk factors including high serum cholesterol, hypertension, high body mass index (BMI) and smoking are causally correlated to the risk of developing AS. Nonetheless, traditional medical interventions, such as lipid lowering or anti-hypertensive agents have not been found to decrease the risk.[6,15,16] Low socioeconomic factor is also a known risk.[17] For younger individuals, a BAV is the main risk factor.

Mortality and disability

Although non-symptomatic AS does not increase the risk of death, mortality for symptomatic patients peaks up to 50% within two years after symptom onset. No medical cure exists today, making the timing of aortic valve replacement (AVR) the most important decision to make for these patients.[18,19] In 2017, 103 000 deaths where estimated globally attributable to calcific AS. The highest burden of AS death was registered in areas with high socio-demographic index, such as Western Europe or North America.[6] As mentioned earlier, AS is also correlated to low socioeconomic class and in that case more prevalent in the lower classes. The fact that mortality is highest in high socio-demographic countries is probably due to deaths from competing diseases in lower rated countries.

In total, calcific AS is estimated to cause 0.87 million Disability-Adjusted Life-Years [6] thus contributing to significant burden of disease.

Pathophysiology

For calcific AS, the most common mechanism in the Western part of the world, the underlying pathophysiology is not yet fully discovered. However, there are evidence indicating an inflammatory pathway here mechanical endothelial damage initiates an infiltration of lipid and inflammatory cells which leads to lipid oxidation and recruitment of fibroblasts that produces collagen leading to increasing fibrosis and calcification, Figure 3.[20,21]

Familial clustering, especially in patients with BAV, suggests a genetic component. Although some candidate genes have been identified, more research is needed.[22–24]

There are observed differences between men and women suggesting that for women, valvular fibrosis is predominant while for men, valvular calcification is more important.[25]
**Figure 3.** Summary of the pathological processes occurring within the valve during aortic stenosis. Reproduced from [32] with permission from Elsevier.

**Figure 4.** Disease mechanisms and time course of calcific aortic stenosis. Reproduced with permission from [18], Copyright Massachusetts Medical Society.
The transition rate from sclerosis to manifest stenosis differs between patients. Earlier studies have suggested a transition rate of ten to fifteen percent from sclerosis to valve obstruction during a follow up of two to five years.[26,27] In contrast, nearly all patients who are diagnosed with valve obstruction develops severe disease, Figure 4.[28,29] Traditional cardiovascular risk factors, such as smoking, diabetes and hyperlipidaemia, are associated with an increased risk of AS.[30,31] Still, as mentioned above, medical therapy including lipid-lowering agents does not alter the progression rate. Nonetheless, the inter-individual variation indicates that there are possible targets for medical therapy and further research is needed to investigate the specific pathogenetic pathway.[18,32]

AS is not only a disease limited to the aortic valve. As the valve narrows, the pressure afterload on the left ventricle increases which stimulates a hypertrophic growth of the myocardium to maintain a normal ejection fraction, Figure 5.[32] However, the hypertrophic response is not closely correlated to the grade of valve obstruction, but rather linked to other patient characteristics, such as hypertension or high age.[32,33] The degree of left ventricular remodelling and myocardial fibrosis also differ between sexes.[25]

Figure 5. Anatomical changes associated with aortic stenosis. Reproduced with permission from [18], Copyright Massachusetts Medical Society.
The grade of hypertrophy is a known prognostic marker for heart failure[34,35] which occurs when the left ventricle can no longer compensate for the narrowing valve. A process of cardiomyocyte apoptosis and fibrosis is then initiated and this marks a tipping point where usually symptoms is developed and the prognosis turns worse with high risk for adverse events.[18,32,36]

Differences in the extracellular matrix between BAV patients and tricuspid patients have been presented. This in turn could suggest differences in the aetiology of disease for tricuspid AS patients and stenosis in BAV patients which could have implications on future potential medical therapies.[37]

Grading

Echocardiography is the most important tool to evaluating and confirming a diagnosis of AS. Key parameters are mean pressure gradient (MPG), peak transvalvular velocity (Vmax) and aortic valve area (AVA). In addition, left ventricular ejection fraction (LVEF) and stroke volume index (SVi) are relevant parameters. MPG is considered the most accurate as it comes with least technical limitations.[9,38] From these measurements AS severity is classified as mild, moderate or severe. For patients with severe AS, four main categories can be identified:

1. High gradient AS (MPG is > 40 mmHg, Vmax > 4m/s and AVA < 1 cm²).
2. Low-flow, low-gradient AS with reduced LVEF (MPG < 40 mmHg, AVA < 1 cm², LVEF < 50 %, SVi < 35 mL/m²)
3. Low-flow, low-gradient AS with preserved LVEF (MPG < 40 mmHg, AVA < 1 cm², LVEF function > 50%, SVi < 35 mL/m²)
4. Normal-flow, low-gradient AS with preserved LVEF (MPG > 40 mmHg, AVA < 1 cm², LVEF > 50 %, SVi > 35 mL/m²)

In general, given the poor prognosis of untreated aortic stenosis,[18] intervention is recommended for all symptomatic patients with the exception of patients where the underlying prognosis due to comorbidities is expected to be less than one year. This assumption holds true for high gradient disease while for low-flow, low gradient AS, stress-echocardiography is recommended to verify severe AS before making an intervention decision. Hence, a more individual approach where comorbidities are taken into account is recommended.[9]

Computed coronary tomography is valuable to gain information regarding anatomy and the feasibility of vascular access.[39,40] Moreover, it can be used to quantify valve calcification, which is associated with worse
outcome and could, together with geometric assessment of the valve area, be utilised to grade low valve gradient aortic stenosis.[40,41]

For asymptomatic patients, intervention is recommended for severe AS with reduced LVEF, symptoms or a sustained fall in blood pressure during exercise or if there are indicators of adverse prognosis combined with low surgical risk. Concomitant valve intervention is also recommended if the patient undergoes cardiac surgery due to another indication.[9,42] There are recent data suggesting a favourable outcome and an early treatment strategy over the traditional watchful waiting strategy.[43,44] However, the results are disputed and there are ongoing trials hoping to clarify the results.[45–47]

Multiple valve disease

Multiple valve disease is common. An earlier study found a 10% prevalence of multiple valve disease in patients with valvular disease. For AS, coexisting aortic regurgitation or mitral stenosis are common.[48,49] However, there are limited studies in this area as guidelines and articles tend to focus on specific valves.[50]

Concomitant coronary artery disease (CAD)

Concomitant CAD is prevalent in the population with AS who are candidates for TAVI and AS is also a marker for CAD.[51] One large registry based study found that 50% of TAVI patients had prior CAD.[52] CAD is more prevalent in the elderly and in a study investigating coronary artery bypass graft (CABG) with simultaneous surgical aortic valve replacement (SAVR) the rate of combined disease was 7.2% in patients 50 years or younger while the rate was 51.2% in patients over 70 years of age.[53] Hence, due to the fact that the TAVI population is changing over time, moving towards a younger population, the prevalence of existing CAD is decreasing. However, as the patients are getting younger, the remaining life expectancy is increasing and thus, with the progressive nature of CAD, the burden of postoperative disease is expected to increase.[54]

AS itself, even without simultaneous significant CAD, affects the coronary blood flow. Coronary flow reserve (CFR) is defined as the increase of coronary blood flow above resting level for a given perfusion pressure when the coronary vasculature is maximally dilated.[55] Patients with AS have been demonstrated to have impaired CFR even if coronary artery atherosclerotic disease, measured by coronary angiogram (CA), is absent.
One mechanism could be a shift from a more dominant diastolic flow to a more dominant systolic flow due to pressure changes secondary to the constricted valve affecting the supply-demand ratio. Another possible mechanism is epicardial stenosis in the coronaries which is present in a large proportion of AS patients. Consequently, angina could also be present as a symptom for both AS and CAD which makes it hard to differ clinically which mechanism that is responsible for the symptom. Another aspect is that as the TAVI bioprosthesis is placed close to the orifices of the coronary arteries, there is also concern that postoperative coronary access might become an issue. As of today, patients who are eligible for TAVI or SAVR are screened for concomitant CAD. If present, SAVR patients usually undergoes both SAVR and CABG. Nonetheless, for TAVI patients, best practice is currently debated and procedural risk as well as potential benefit should be considered from case to case. One randomised trial, the ACTIVATION trial, on pre TAVI percutaneous coronary intervention (PCI) found more bleedings in the PCI arm and similar rates of death and hospitalisations. However, further trials on best practice are warranted.

There is no consensus whether the presence of CAD in patients with AS is associated with heterogeneity between studies. A recent review suggested that the CAD is more a marker of comorbidities rather than an independent risk factor.

**Bicuspid aortic valve disease (BAV)**

BAV is a condition which is present within 0.4-2.25% percent of the general population with the majority requiring an intervention during their lifespan. Males are over represented with reported ratios between 2:1 to 4:1. Typically, instead of the three aortic valve leaflets, two unequally sized leaflets are present where the larger has a central raphe which results from the fusion of the commissures. BAV could be classified according to Sievers where type 0 has no raphe, type 1 has 1 raphe (most commonly between the left and right coronary sinuses) and type 2 has two raphes. The location of the raphe is of clinical relevance as there are associations between BAV and extravalvular conditions. Non valvular findings occur in approximately 50% of BAV patients. The most common finding is a dilated ascending aorta, an association described already in 1928 by Abbot. As a consequence, dissection of the aorta is eight times more common in BAV patients, although the risk in absolute numbers is still low.

The BAV aortopathy has high heterogeneity and could include both the ascending aorta and the aortic root. The dilatation may be associated
with an inherent defect in the vessel wall integrity where vascular smooth muscle cells have different architecture causing progressive necrosis, dilatation and ultimately an aneurysm. Moreover, haemodynamic changes could also play an important role.[67]

Coarctation of the aorta is another associated disease which occurs in 7% of BAV patients.[63] When coarctation is present, it is more common that the BAV is a result of fusion of the left and right coronary leaflet. There have also been reported associations between BAV and Erdheim’s cystical medial necrosis, and various cardiac syndromes including hypoplastic left heart syndrome, Shone’s syndrome or Turner syndrome.[68–70]

In summary, when BAV is diagnosed, one should be aware of the prevalent extravalvular features and monitor these patients accordingly.

Surgical aortic valve replacement (SAVR)

The valves of the heart have been known of since the early Christian era, when Claudius Galenus described their existence. Leonardo da Vinci is claimed to be the first to accurate draw the aortic valve anatomy. However, centuries of scientific advances had to pass before the first operation on indication AS, which was performed 1913, when a digital dilatation was executed in Paris by Theodor Tuffier. The first valve implantation was performed in 1952 when Charles Hufnagel implanted an acrylic ball prosthesis on indication aortic regurgitation. Although promising, the earliest operations had high perioperative mortality rates, given the complexity of the intervention. However, key interventions, such as the heart-lung machine and better hemodynamically performance of the valves led to increasingly better results.[71,72] As a consequence, for many decades, SAVR was considered gold standard as treatment for AS and still is in selected patients.[9,73]

There are two major types of valves; mechanical and biological, with their respective advantages and disadvantages. Mechanical valves have excellent durability yet require the carrier to adhere to life-long anticoagulation treatment.[74,75] Biological valves on the other hand comes with no need of anticoagulation therapy while its long-time durability is disputed. Nonetheless, similar survival rates have been reported with both types of valves and the threshold for when to implant a biological valve is constantly reduced. Consequently, most patients over 60-years of age who are still recommended SAVR prefer biological valves to avoid anticoagulation.[72]
Transcatheter aortic valve implantation (TAVI)

Already in the mid 19th century, attempts to reach the heart through the blood vessels with a catheter were performed. In 1953 Sven Ingvar Seldinger presented the percutaneous technique[76] and made way for new forms of interventions. As the technique evolved, the idea of a catheter-based AVR arose.[71] One of the great pioneers, Dr Henning Rud Andersen, attended a lecture on the design of coronary stents in 1989 and found inspiration to develop a stent to be used for AVR. He then performed experiments in pigs and only a couple of months later he managed to perform a successful procedure where the pig received a valve prosthesis using a catheter-based method thus inventing the TAVI concept.[77] However, the novel method was met with scepticism and its transportation into use in human subjects was delayed until 2002 when a first in man procedure was performed by Cribier et al[78] and presented as a less invasive treatment option for patients with AS. Since then, following several studies indicated below, the procedure has progressively established its role in the management of elderly patients with AS. Latest guidelines favour TAVI over open surgery in patients at high surgical risk and in selected patients at intermediate risk. Open surgery is recommended in patients below 75 years of age at low surgical risk or where transfemoral access is not feasible. Guidelines also strongly support the Heart Team approach in the decision making between different treatment modalities.[9]

Procedure

The TAVI procedure is performed in a sterile room under either local or in some cases general anaesthesia. The procedure uses echocardiography and x-ray as guidance. The new valve, which consists of biological leaflets within a metallic frame, is most commonly inserted through the femoral arteries and the native aorta and expanded over the native aortic valve either with a balloon-expanding (BE) or with a self-expanding mechanism. After the procedure, recent studies have indicated no benefit of short term dual antiplatelet therapy and hence, latest guidelines recommends life-long monotherapy with aspirin for patients without recent PCI or indication for oral anticoagulant therapy.[9,79,80]

Placement of Aortic Transcatheter Valves (PARTNER)

The PARTNER trial was a randomised controlled trial, divided in two subgroups and published in 2010 and 2011 respectively. A total of 358
patients with severe AS, defined as either a MPG > 40 mmHg, AVA < 0.8 cm² or Vmax > 4 m/s, assessed not to be candidates for surgery, were randomised between standard therapy or TAVI with an Edwards SAPIEN system. Moreover 669 patients considered to be operable yet at high surgical risk based on an assessment of participating surgeons were randomised to either SAVR or TAVI. Patients with bicuspid valves were excluded as were patients with concomitant acute coronary syndrome (ACS), significant CAD, advanced renal failure, recent cerebral insult, LVEF less than 20 percent, diameter of the aortic annulus below 18 mm or over 25 mm or a severe mitral or aortic regurgitation. Primary endpoint was all-cause death and the study had at least 1 year follow-up with a median follow-up of 1.6 years. For non-operable patients, the results indicated a twenty percent points lower 1-year mortality rate and the authors concluded that TAVI should be considered as standard of care for patients not suitable for surgery. For the high-risk cohort, results were similar between the groups and non-inferiority was reached. Later published long term results with data up to five years from procedure, suggested no difference in mortality rates.[81–83].

PARTNER 2

In 2016, the PARTNER 2 trial was published where patients with severe AS, at intermediate surgical risk, defined as a Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score of at least 4 percent, were randomised to either SAVR or TAVI. Unlike in the PARTNER A trial, patients with noncomplex concomitant CAD were able to include in the trial. The trial used an updated version of the Edwards SAPIEN system for those receiving TAVI. A total of 2032 patients were enrolled and the main results were that TAVI were non-inferior in terms of all-cause death or disabling stroke up to 2 years from procedure.[84]

PARTNER 3

The PARTNER 3 trial, published in 2019, investigated patients with severe AS at low surgical risk, defined as a combination of a STS-PROM score below 4 percent and a clinical assessment by the Heart Team. The trial aimed both to test for non-inferiority and, if this criterium was met, also for superiority for TAVI over SAVR. The study used a third generation Edwards SAPIEN valve for the TAVI patients and the study only permitted randomisation of patients suitable for trans-femoral access. A total of 1000 patients were enrolled and the main results were a favourable
outcome in the TAVI group in terms of a composite endpoint of all-cause death, stroke or rehospitalisation at 2-years follow up.[85]

U.S. CoreValve High Risk Study

The trial, designed as a non-inferiority multi-centre randomised controlled trial performed at 45 clinical sites in the United States aimed to investigate SAVR versus TAVI in a population with severe AS at increased surgical risk. AS was defined as a New York Heart Association (NYHA)-class of II or higher with an AVA of < 0.6 cm² or an aortic valve index of 0.5 cm² and MPG > 40 mmHg of Vmax > 4 m/s were included. Increased surgical risk was present if two heart surgeons and one interventional cardiologist considered the mortality risk within 30 days to be between 15 and 50 %. In the TAVI group, a CoreValve self-expanding bioprosthesis (SE) was used. The primary end point was all-cause death at one year. A total of 795 patients were included and the primary endpoint was met as well as superiority for the TAVI arm. The trial concluded therefore TAVI to be superior to SAVR in a population at increased surgical risk.[86]

Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients (SURTAVI)

This study, conducted as a multi-centre, multinational, non-inferiority designed randomised controlled trial sought to examine the safety and efficacy of TAVI versus SAVR in a population with severe AS at intermediate surgical risk. There were 87 participating centres and randomisation was performed in a 1:1 ratio between SAVR and TAVI with a SE. Intermediate surgical risk was defined as a STS-PROM score of 3-15% and severe AS was defined as an AVA < 1cm² or a AVA index of < 0.6cm² per square meter body surface area and a MPG of > 40 mmHg or a Vmax of > 4 m/s. Stratification was performed according to clinical centre and the need for concomitant coronary artery revascularisation. Primary endpoint was a composite of all-cause death and stroke. A total of 1746 patients were randomised. The trial concluded that TAVR was a non-inferior alternative to SAVR in patients at intermediate surgical risk.[87]

Evolut Low-Risk

Published in 2019, this multi-centre, international study investigated patients with severe AS at low surgical risk with respect of SAVR versus
TAVI. A self-expanding prosthesis was used in the TAVI group. Unlike the PARTNER studies, an AVA < 1 cm² was considered as severe AS. A total of 1468 patients underwent randomisation on a 1:1 ratio. At 2 years, main results indicated that TAVI was non-inferior in terms of death or disabling stroke.[88]

The Nordic Aortic Valve Intervention (NOTION)

This investigator-initiated, multicentre, randomised, nonblinded, superiority trial randomised patients with severe AS at low surgical risk to either TAVI or SAVR between 2010 and 2013. They concluded no significant differences in their primary endpoint of all-cause death, ACS, stroke or prosthesis intervention after one year.[89] The investigators continued with long term follow up and have presented the results in several papers.[90,91] At eight years post inclusion, no significant differences were found in terms of the primary endpoint.[92] They highlight the fact that there was no difference in long term durability of the valves which is important as prior knowledge about this was scarce and an important question as TAVI is moving towards younger patients with increased life expectancy.

TAVI in Sweden

Since the first Swedish procedure in 2008, the number of interventions is constantly increasing. From year 2019 and onwards, the number of annual procedures exceeds 1000. It is currently conducted at eight centres. The latest years, mean patient age has fluctuated around 80 years. Transfemoral access is dominating and in all, most procedures are without complications. The most common complication is the need of a new pacemaker which as of 2022 occurs in 7.1 percent of the patients undergoing TAVI. For long term survival, a decrease of around 10 percent per year is observed, which gives a 25 percent survival rate after 8 years.[93]

TAVI registries

There are different national registries looking at clinical outcomes in patients treated with TAVI for symptomatic AS.[94,95] In Sweden, the Swedish Transcatheter Cardiac Intervention Registry (SWENTRY) [96] started in 2010 and consists of all consecutive entries since 2008. As part of the Swedish national quality registries, the registry has important
features such as the nationwide coverage of all TAVI procedures performed in the country and the availability of complete long-term follow-up data. Cross-linking of patients’ data between different registries (i.e., causes of hospitalisation registry) is also a unique characteristic of SWENTRY which, at variance with other national registries, allows a granular assessment of new and recurrent events after the procedure (i.e., re-hospitalisation) along a more thorough understanding of clinical outcomes after the procedure.

Observational studies

Sweden has a long history of national registries, with internationally recognised standard. Consequently, these registries are fundamental to Swedish epidemiologic research.[97,98] Within medical research, randomised, placebo-controlled trials are attributed the highest level of evidence. However, while these types of studies are ideal for investigating a specific scientific question it is seldom possible to investigate all potential questions within a study protocol. Thus, this gives observational studies an important role and the majority of studies conducted in the medical field are indeed observational.[99–101] They are especially good at answering questions such as if a certain treatment comes with late or rare adverse events or to affirm if findings from a constructed population, i.e., a trial, holds true in a real-world setting. Nonetheless, as they by definition are not randomised, one should always be aware of the risk of biases, for instance selection bias. As a result, transparency is important and there are guidelines who helps the authors structuralise the reporting of these kind of studies, for instance the STROBE-consortium.[102] The key feature of the Swedish registries is the inclusion of the personal identification number which enables long time monitoring and linking of different types of personal data. Clear infrastructure for maintaining a high data agreement is also an important factor which contributes to the internationally high quality.[103–105]

Ethics in register-based research

Throughout history, there are unfortunately examples where research have been conducted without proper ethical considerations. After the second world war, when particularly unethical experiments were revealed, several principles and guidelines have been implemented with the aim to secure the rights for individuals participating in research.[106,107] As a Swedish researcher, there are also European laws and regulations that
specifically applies.[108–110]

There are ethical aspects that are specific to register based research. For traditional intervention studies, informed consent is key while for large register-based research this is generally not applicable.[111] However, for quality monitoring registries, such as SWEDHEART, patients are informed about their participation and have the possibility to opt out.[112,113] Furthermore, to perform register-based studies using the collected data, one must apply for ethical approval from the National Ethics Committee [114] who is recognised as a representative of the population and therefore could act in their name. The rationale behind this is that register-based research rarely impose risk on the study participants and that the peoples trust in these instances are high.[115] This system have many advantages as such as procedure could possibly avoid the risk of biases associated with active inclusion of participants, where some groups could be underrepresented.[116–118] However, the main concern for register-based research is integrity of the participating subjects. By minimising the available data to include only what is necessary to perform the study and by proper data storage and methods such as pseudonymisation this risk could be kept to a minimum.[111]

In summary, registers is an important source of information and the Swedish registers provide an excellent environment for medical research. However, to maintain the public’s trust, research should only be performed when there are clear potential benefits and with transparency and adherence to good clinical practice.

Statistical methods

External validation

Types of external validation

External validation is conducted to test the performance of a model. In contrast to internal validation, where the original cohort or parts of the original cohort is used, external validation is performed in patients which are to some extent separated from the development population. Common types are:

1. Temporal validation: Most common is to test performance of the model in patient treated more recently.
2. Geographic validation: The model is tested on another location than where it was developed. This is common in collaborative studies. However, it might lead to small cohorts being tested and one should be careful when interpreting the results.
3. Fully independent validation: Conducted by independent investigaters on an independent population.[119]
**Generalisability**

The ultimate aim with medical research is to facilitate the work and improve the outcomes in a real life, clinical setting. To do so, it is crucial that the findings which are obtained in a trial or through observational studies are transferable. In other words that the findings have generalisability both if the studies are repeated and in the real world. Still, there is an ongoing debate concerning to what extent today’s medical research is reproducible,[120] where some even claim most results to be false.[121] One study examined research published in high-profile journals to see if the results were tested for reproducibility. They concluded that only a minority of the studies had done so, and out of these studies, less than half had reproducible results.[122]

Big data and artificial intelligence are becoming of increasing importance in today’s medicine. However, while these methods offer new promising possibilities such as prognostic prediction models, they also come with new challenges and sometimes, there is an overconfidence in their ability.[120,123] Moreover, as with traditional research, most developed models are not externally validated before implementation.[124] False results might lead to unbeficial or harmful practices in the clinic and as a consequence, external validation studies are important to increase the level of evidence.

**Geospatial analysis**

In the mid 19th century, John Snow published his work on a cholera outbreak in central London where he claimed contaminated water as the cause of disease, using a map featuring the location of sewers and affected residents.[125] This made him the father of epidemiology yet geographical information and mapping disease began as early as in the antique Greece. In the latest decades, Geographic Information Systems (GIS) has been increasingly used in medical research.[126] Starting in the 1970ties, when satellite information became more reliable, technical progress has continued with increasingly better software which in turn have made the method more and more available and less expensive to use.[126] Today, there are open-source software free of charge and able to use on an ordinary laptop.

Infectious diseases and immunisation are research fields where GIS plays an important role. Nonetheless, in other areas, such as emergency medicine and health systems, GIS is emerging as equally important.[126] For instance, a study used GIS to investigate which areas in Houston where knowledge about bystander cardiopulmonary resuscitation was low in case of a sudden out of hospital cardiac arrest. The results were used
to target educational efforts.[127] A fellow researcher at Uppsala University used publicly available information on driving distances to map the routes to the nearest hospital where treatment is given in the case of an acute coronary syndrome.[128] Nonetheless, the use of GIS in cardiology is sparse and there are several potential areas to investigate.

Composite endpoints and recurrent events

Through decades, information obtained from randomised clinical trials and real-life observational studies has substantially contributed to major improvements in the treatment of cardiovascular diseases with corresponding reductions in mortality and morbidity. Composite clinical endpoints, where related clinical outcomes are gathered together, have been primarily used in cardiovascular studies. In conventional survival analysis such as the Kaplan-Meier curves or Cox models, it is possible to analyse composite endpoints of different adverse events (e.g. ACS, stroke, death). However, in these methods, the individual entry is censored as soon as an adverse event occurs. Patients usually experience more than one event and including only the first event means that important supplementary information is rejected and that the treatments’ effects on subsequent events are ignored which might relevantly influence the interpretations of the study results.[129] Moreover, this can result in that the trials are driven by the less serious events.[130,131]

As a consequence, recurrent events are useful in tracking the total burden of disease for patients within a population and, from a statistical standpoint, they provide a higher number of events (that is more statistical power) for investigating differences in clinical outcomes. As an example, the Andersen-Gill model[132] is an extension of the traditional Cox model but as mentioned above it does not censor the patient after a non-fatal adverse event, thereby allowing the incorporation of several events per patient. Consequently, its all-cause hazard ratio is usually more precise than the Cox model estimator, and as a result more powerful. Nonetheless, interpreting the Andersen-Gill as an extension of the Cox model is only valid if the risk of any subsequent event is the same as the risk of the first event. In other words, the immediate risk of suffer from an adverse event is the same regardless of the number of previous events. This is seldom true in a cardiovascular setting. However, the model might still be applied as it is possible to calculate on both the so called “direct” and “indirect” effect. For instance, if a treatment has no direct effect on mortality but reduces the number of arrhythmias, the risk for that kind of events is smaller in the treatment group. The treatment group will then experience a decrease in mortality due to an indirect effect of the decrease in arrhythmias which can be included in the
modified Andersen-Gill model. However, the Anderson-Gill model does not weigh the severity of the events; all events within the composite (i.e., death and repeat revascularisation) are considered equally severe. This assumption is poorly generalisable in the real world.[129,133] Therefore, new statistical methods have been developed for weighing the severity of the individual components and provide a more meaningful interpretation of this type of analyses for clinical practice.[133,134]

Another scenario is the analysis of ordered events where subjects will experience the specified outcomes in a specific order. One example is when both readmission and death are investigated. Then death can occur anytime while readmission post mortem is impossible. Consequently, there is in this scenario a need to distinguish between the different types of events, which can be achieved by using a multistate model.[134]

In the latest years, alternatives to time-to-event analysis have also emerged in randomised controlled trials, for instance the win-ratio where outcomes are hierarchically structured and then analysed pairwise starting with the most severe event.[135–137]

In summary, knowing which statistical method that is most appropriate will improve the analysis and since there are several methods that might apply, it would be ideal to use several and compare the results.
Aims

Although several national registries exist on TAVI the Swedish registry is unique in its ability to conjoin information from several other registries. Since the TAVI procedure is quite novel there are gaps in evidence. The aim of this thesis is to use these first-class registers combined with the use of sophisticated statistical methods to gain a better understanding of the AS population and the TAVI procedure since its implementation in Sweden. Specific aims of the papers were:

I. To analyse the total burden of disease after TAVI in terms of hospitalisation causes, hospitalisation patterns and predictors of repeated hospitalisation
II. To perform a fully independent external validation of the TAVR 30 prediction model
III. To analyse the implementation of TAVI in relation to SAVR in Sweden, using geospatial data to visualise regional differences
IV. To assess the indication, the incidence, and feasibility of coronary angiography and intervention after TAVI using long-term, real-life data from Swedish national registries
Methods

Study population

All studies were performed on a cohort of merged register data including data from the SWENTRY, the National Patient Registry (NPR) and the National Cause of Death Register. The first study used data extracted in 2018 while the other studies were based on an updated data extraction available from 2022. The data application process as well as data preparation and statistical analysis were conducted by the main author of this thesis with support from statisticians at Uppsala Clinical Research Center (UCR).

![Flow chart](image)

*Figure 6. Flow chart of the study population in Paper IV.*

For Paper IV, all Swedish TAVI patients between January 2008 and April 2022 on indication AS was included in the study. Moreover, patients with at least one International Statistical Classification of Diseases and Health Related Problems - 10th revision (ICD-10) code of AS within the same time period without registered AVR were included as a reference population. A flow chart of the study population is presented in *Figure*
6. In the analysis of BE versus SE valves, all Edwards lifesciences (BE) valves and Medtronic or Boston Acurate or Acurate neo (SE) valves were included. Remaining valves were excluded from that analysis. The definition of an ACS without concomitant PCI was defined as the presence of an ICD-10 code starting with either I21 or I22 and no registered PCI within 30 days prior of post the day of the diagnosis.

SWEDHEART

The Swedish Web-system for Enhancement and Development of Evidence based care in Heart disease Evaluated according to Recommended Therapies (SWEDHEART) registry was formed 2009 through the merging of the national registry of acute cardiac care (RIKS-HIA), the Swedish coronary angiography and angioplasty registry (SCAAR), the Swedish heart surgery registry and the national registry of secondary prevention (SEPHIA). As of 2010, the Percutaneous Valve Registry, later SWENTRY is also part of SWEDHEART.

SWEDHEART is financed by the Swedish government and the Association of Local Authorities and Regions. The registry is led by a steering group, consisting of the chairmen of the working groups of the registries and representatives from the Swedish Heart Association and the Swedish Society of Cardiac Nursing. UCR has developed the web-based version of the registry and is responsible for project management, administration, monitoring, quality controls, and statistical reports.

SWEDHEART includes patients admitted to hospital because of symptoms suggestive of an ACS, and patients undergoing coronary angiography/angioplasty or heart surgery. The registry enrolls approximately 80,000 cases each year: 30,000 with ACS, 40,000 undergoing coronary angiography or angioplasty, 7,000 undergoing heart surgery, and 6,000 who are followed for 12-14 months regarding secondary prevention after an ACS. The registry is web-based with all data registered online directly by the caregiver and transferred in an encrypted format to a central server. During registration, the whole process of care is kept together in one record even if the patient is transferred between different units and hospitals. The technical platform, Qreg5, is in direct contact with the Swedish National Population Registry for immediate access to personal data and deaths. For patients admitted to hospital because of symptoms suggestive of an ACS information is collected prospectively for 106 variables and include patient demographics, admission logistics, risk factors, past medical history, medical treatment prior to admission, electrocardiographic changes, biochemical markers, other clinical features and investigations, medical treatment in hospital, interventions, hospital outcome, discharge diagnoses and discharge-medications. For patients
undergoing coronary angiography/angioplasty on any clinical indication 169 variables are registered. Every hospital in Sweden providing the relevant services participates in the SWEDHEART registry. The reliability of the information in the registry is monitored by random checks of source data, with an agreement of 96 percent.[104] As SWEDHEART includes large numbers and proportion of patients, it also operates as a platform for registry based randomised clinical trials.

All patients are informed about their participation in the registry and have the right to decline participation. Every merge of registries is approved by the National Board of Health and Welfare, the Swedish Data Inspection Board and the ethical committee at Uppsala University. After merging of the registries, researchers have access to hospital identity but not to patient identity.

All Swedish citizens have a unique personal identification number which together with name, address and hospital identity is included in the registry. This enables merging of the SWEDHEART database with the National Cause of Death Register, which includes information about vital status of all Swedish citizens, and the NPR which since 2001 includes all in-patient and outpatient visits in Sweden. Starting with in-patient visits only, the NPR has been mandatory for county councils since 1984 and from 1987 it reached national coverage including both public and private health care providers, except primary care. In 2001 all outpatient visits were added. The register receives monthly information from each county council and controls are performed on the submitted data to check its quality. The National Board of Health and Welfare, who manages the register, estimates low levels of underreporting. In 2011, a validation study was performed were the register in general had an accuracy rate of 85-95 percent.[138,139]

The Swedish National Population Registry

The Swedish National Population Registry reflects the composition, relationship and identities of the Swedish population. Sweden has established two population registers: The Population Register, maintained by the Swedish National Tax Agency [140] (“Folkbokföringsregistret”); and the Total Population Register (TPR) maintained by the government agency Statistics Sweden [141] (“Registret över totalbefolkningen”). The registers contain data on life events including birth, death, name change, marital status, family relationships and migration within Sweden as well as to and from other countries. Almost 100 percent of deaths are registered within one month in principle. Overcoverage in the observation register due to unreported deaths is assumed to be less than 0.5 percent.[103]
Statistical Methods

Paper I

All Swedish TAVI patients who underwent a procedure between 2008 and 2017 on indication AS were included in the study. Based on the ICD-10 codes hospitalisations due to cardiovascular causes were identified. For repeated hospitalisations, to avoid double registrations, a censoring of two days from latest discharge was added to the analysis. Missing data patterns were analysed. All variables except pulmonary hypertension had a missing frequency of less than one percent. Yet, to enable its inclusion, imputation based on fully conditional specification was conducted and compared with non-imputed data before analysis. Predictive mean matching was used for numerical data, logistic regression for binary data and polytomous regression for variables with more than two levels. A multistate model presented by Castañeda et al. [134] was used to investigate mortality and hospitalisations. Death and hospitalisations were treated as competing events and the model included up to three consecutive events (Figure 7).

![Hospitalisations Diagram](image)

*Figure 7. Schematic for the multistate model presented by Castañeda et al and used in Paper I*

In Table 1 an example dataset of the model is presented illustrating potential outcomes. For the patient with ID = 2, a first hospitalisation (H1) occurs after 2.3 years followed by another (H2) at 3.5 years. Finally, at 4.2 years the patient dies (D). Note that after H1, the patient has two possible transitions, either to H2 or D. Thus, when H2 occurs the patient is no longer at risk for D and this transition gets censored. The same mechanism is then applied for all consecutive events.
Table 1. Example dataset of the multistate model

<table>
<thead>
<tr>
<th>ID</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Transition</th>
<th>Status</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.0</td>
<td>1.4</td>
<td>E - H1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>0.0</td>
<td>1.4</td>
<td>E - D</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0.0</td>
<td>2.3</td>
<td>E - H1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0.0</td>
<td>2.3</td>
<td>E - D</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>2.3</td>
<td>3.5</td>
<td>H1 - H2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>2.3</td>
<td>3.5</td>
<td>H1 - D</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>3.5</td>
<td>4.2</td>
<td>H2 - H3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>3.5</td>
<td>4.2</td>
<td>H2 - D</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

The results were fitted into a multivariate-adjusted Cox proportional hazard regression model[142] creating transition rates which were presented as forest plots. Time to first event and mean and median follow up and survival times were also investigated. Patients with or without hospitalisations were stratified and compared with the $\chi^2$ test. Statistical significance level was set to $p < 0.05$. R version 4.0.2 [143] was used for all statistical analyses.

Paper II

All Swedish TAVI patients between 2008 and 2020 on indication AS were included in the study. SWENTRY data combined with ICD-codes from NPR were used to identify the variables in the prediction model. Baseline characteristics were stratified on hospitalisation status and were compared using the chi-square test for categorical variables and either two tailed t-test or the Wilcoxon rank sum test for continuous variables. Coefficients for each predictor were obtained from the supplementary appendix of the original publication. Based on the retrieved values, sums were calculated for each patient and then transformed into predicted probabilities. Predicted probabilities then were validated against hospitalisation status using the val.prob function from the “rms”[144] package followed by a decision curve using the “dcurves”[145] package. A density distribution for the external validation cohort was presented as a bar plot. All analyses were performed in R version 4.1.2.[143]

Paper III

All Swedish TAVI patients between 2008 and 2020 were included in the study. In addition, all patients with at least one ICD-10 diagnosis of AS (defined as I35.0 or I35.2) and who had undergone isolated SAVR in the
years 2008 to 2020 were included. Clinical and procedural information
was obtained from SWEDHEART. Data from Statistics Sweden [141]
were used to identify each Swedish county’s population numbers and to
find the coordinates for each county’s geographical borders. The coor-
dinates for each TAVI centre were collected from OpenStreetMap.[146]
Temporal trends were visualised with maps and area graphs. Spatial
correlation of intervention rates was analysed using Monte Carlo simu-
lation of the Moran I statistic where all regions are analysed in pairs. If
both neighbouring regions are above or below the mean they contribute
with a positive value. If the neighbours are on different sides of the
mean, they contribute with a negative value. An overall positive value
indicates similarity of neighbouring regions which could indicate a pos-
itive spatial autocorrelation and a non-random distribution of, in this
setting, regional incidences of TAVI procedures. The region of Gotland
was excluded as it consists of an island with no adjacent regional bor-
ders. A Monte Carlo simulation was then used to generate a distribution
of theoretical expected values given that, in this case, TAVI rates are
completely random spatial distribution. Next, to assess whether the re-
sult was statistically significant, the observed Moran I statistic was com-
pared with the Monte Carlo distribution of the statistic under the null
hypothesis.[147] Two standardisations were performed to address event-
tual differences in population composition between regions, one using a
regression-based method and one a direct method. Waiting times were
compared with the Wilcoxon-Mann-Whitney test. Mortality rates were
analysed with the log rank test. All analyses were performed using R
version 4.1.2.[143] The packages “SPDEP” and “tmap” were used for the
spatial analyses.[148,149]

Paper IV

The $\chi^2$-test was used to compare categorical variables and either a t-test
or the Wilcoxon Mann Whitney test for continuous variables. Cumulative
incidence graphs were calculated using the packages “survival” [150] and
“survminer”.[151] Crude graphs were presented. No significant loss of
follow up was present. Data were analysed for potential causes of bias.
As missing data was expected to be low in the investigated variables, no
imputation of missing data was performed.
Ethics

All studies conducted within this thesis are approved by the local ethics committee (Dnr 2017/455 with amendments). Data from SWEDHEART were merged with national registry data by the Swedish National Board of Health and Welfare and a pseudonymised version was made available to the author.
Results

Paper I

Study population

A total of 2821 patients with a TAVI procedure between the years 2008 to 2017 were included in the study. The follow-up time ranged from 0 to 3545 days (0–9.7 years) with a median of 626 days (1.7 years) and a mean of 805 days (2.2 years). Patients with at least one hospitalisation had a higher rate of previous cardiac surgery and a lower rate of critical procedure.

Hospitalisations after TAVI

During follow-up, 7354 hospitalisations occurred, out of which 2351 were due to cardiovascular causes. HF was the most common cause of hospitalisation, accounting for 16 percent of the total amount of readmissions and 50 percent of those classified as due to cardiovascular causes. Infection was second most common, accounting for 14 percent. Endocarditis accounted for 2 percent of hospitalisations. In total, a diverse pattern of causes of hospitalisation was identified with 1001 different main diagnoses present and 92 different for cardiovascular causes. All patients with a follow-up time exceeding six years were either hospitalised at least once or dead, see Figure 8a For cardiovascular causes, the same time period was eight years. Repeated hospitalisations after TAVI were associated with worse prognosis, Figure 8b.
Predictors of hospitalisations after TAVI

Male gender, age >90 years, high Charlson comorbidity index (CCI), atrial fibrillation (AF), present neurological disease, peripheral vascular disease (PVD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) stage V, NYHA class IV, mild mean aortic valve gradient and pulmonary hypertension were associated with increased risk for all-cause hospitalisations or death. Instead, BMI >25, female gender, previous cardiac surgery and moderate (25–50 mmHg) or severe (>50 mmHg) mean aortic valve gradient were associated with lower risk for all-cause hospitalisations or death, Figure 9.

For cardiovascular hospitalisations or death, male gender, age > 90 years, high CCI, AF, CKD-EPI stage IV, PVD, decreased LVEF, mild mean aortic valve gradient and pulmonary hypertension were associated with increased risk. Female gender, hypertension and prior cardiac surgery were associated with lower risk for cardiovascular hospitalisations or death, Figure 10.
<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Reference</th>
<th>1.00 (1.02 - 1.08)</th>
<th>0.001 *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td>65-69</td>
<td>1.17 (0.64 - 1.53)</td>
<td>0.830</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70-79</td>
<td>1.29 (0.91 - 1.80)</td>
<td>0.197</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70-79</td>
<td>1.29 (0.91 - 1.80)</td>
<td>0.197</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70-79</td>
<td>1.29 (0.91 - 1.80)</td>
<td>0.197</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70-79</td>
<td>1.29 (0.91 - 1.80)</td>
<td>0.197</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>1</td>
<td>1.08 (1.05 - 1.10)</td>
<td>0.003 **</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td></td>
<td>&lt;15</td>
<td>1.17 (0.64 - 1.53)</td>
<td>0.830</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25-29</td>
<td>1.29 (0.91 - 1.80)</td>
<td>0.197</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50-69</td>
<td>1.29 (0.91 - 1.80)</td>
<td>0.197</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60-79</td>
<td>1.29 (0.91 - 1.80)</td>
<td>0.197</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70-79</td>
<td>1.29 (0.91 - 1.80)</td>
<td>0.197</td>
</tr>
<tr>
<td>Critical</td>
<td>Yes</td>
<td>1.05 (0.94 - 1.02)</td>
<td>0.624</td>
<td>&lt;0.001 **</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes</td>
<td>1.00 (0.54 - 1.88)</td>
<td>0.910</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>1.04 (0.55 - 1.43)</td>
<td>0.861</td>
<td></td>
</tr>
<tr>
<td>Acute Ischemia</td>
<td>Yes</td>
<td>1.10 (1.04 - 1.17)</td>
<td>0.001 **</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Yes</td>
<td>1.00 (0.59 - 1.81)</td>
<td>0.996</td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>Yes</td>
<td>1.00 (0.59 - 1.81)</td>
<td>0.996</td>
<td></td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>Yes</td>
<td>1.00 (0.53 - 1.00)</td>
<td>0.996</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>Yes</td>
<td>1.00 (0.53 - 1.00)</td>
<td>0.996</td>
<td></td>
</tr>
<tr>
<td>Part. Vascular disease</td>
<td>Yes</td>
<td>1.00 (0.53 - 1.00)</td>
<td>0.996</td>
<td></td>
</tr>
<tr>
<td>Neurologic disease</td>
<td>Yes</td>
<td>1.00 (0.53 - 1.00)</td>
<td>0.996</td>
<td></td>
</tr>
<tr>
<td>CHD stage</td>
<td>1</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>47</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>51</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>53</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>56</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>61</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>62</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>63</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>64</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>66</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>67</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>68</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>69</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>71</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>73</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>74</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>76</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>77</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>78</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>79</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>81</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>82</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>83</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>84</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>86</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>87</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>88</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>89</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>91</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>92</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>93</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>94</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>95</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>97</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>98</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>99</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 9. Hazard ratio for all-cause hospitalisation or death.
Figure 10. Hazard ratio for cardiovascular hospitalisation or death.
Paper II

Study population

Out of 8459 patients who underwent TAVI in the years 2008 to 2021, 7693 had complete data for the predictors of the investigated model and were included in the study. Baseline characteristics stratified on patients with or without a readmission within thirty days were similar with only minor differences in prior cardiac surgery, chronic pulmonary disease, peripheral vascular disease, NYHA class, max and mean aortic valve gradients and aortic regurgitation.

Short-term readmissions

A total of 928 patients experienced a readmission within thirty days which corresponds to 12 percent of patients included in the study. A bar blot indicating the probability of readmission is presented in Figure 11.

![Figure 11. Distribution of probabilities in the validation cohort.](image)

Model performance

A calibration plot is presented in Figure 12. The concordance (c)-index was 0.51, implying poor discrimination. The validated model had a calibration slope of 0.07 and intercept of −0.62. In general, the model overestimates the risk of readmission although for the patients at lowest risk the
calibration is better. A decision curve, **Figure 13** indicated no net benefit in using the model as compared to a treat all or treat none strategy. An analysis which included death within 30 days (present in 21 patients) as a competing event did not change the result of the analysis.

![Calibration plot using the original estimates on the validation cohort.](image)

**Figure 12.** Calibration plot using the original estimates on the validation cohort.

### Sensitivity analyses

An analysis on imputed data did not alter the results. As one of the predictors, haemoglobin value, had a missing frequency of 26 percent in the registry, anaemia was defined as a composite of haemoglobin levels and ICD-10 codes corresponding to anaemia. A sub analysis using haemoglobin values only did not change the results. Neither did a sensitivity analysis which only included procedures performed in the years 2019-2021.
Figure 13. Decision curve comparing the model with a treat none or treat all strategy.
Paper III

Study population

A total of 7280 patients undergoing TAVI were included in the study. There were 843, 1962 and 4475 TAVI patients in the time periods of 2008-2012, 2013-2016 and 2017-2020, respectively. For SAVR, the corresponding numbers were 12026 patients, out of which there were 4743, 3871 and 3412 in the respective time periods.

Temporal trends and regional procedure rates

Temporal trends are presented in Figure 14. For TAVI, the overall rate increased substantially while the rate for SAVR remained fairly constant.

![Figure 14. Temporal trends for TAVI and isolated SAVR in patients with a diagnosis of aortic stenosis.](image)

As presented in Figure 15, regional rates for TAVI procedures per 100,000 inhabitants were not concentrated around TAVI centres. The Monte Carlo simulation of the Moran I statistic indicated no spatial correlation of the rates (p = 0.99). Standardised rates by age and sex were calculated using both direct and indirect methods with similar results. There was no statistically significant difference between counties.
with a local TAVI centre and counties without (Wilcoxon rank sum test, $p = 0.74$).

![Image of maps showing TAVI and SAVR rates](image)

**Figure 15.** Temporal trends of TAVI and SAVR per 100,000 inhabitants, grouped by county of residence.

Waiting times and short-term survival

The median waiting time from decision to intervention was 53 days. A Wilcoxon-Mann Whitney test did not indicate a statistically significant difference in waiting times between regions with a local TAVI centre and regions without. No regional differences were observed in short-term survival after procedure.
Paper IV

Study population

A total of 8818 patients who had undergone TAVI between January 2008 and April 2022 were included in the study. Furthermore, 11929 patients with a diagnosis of AS, without prior AVR were included as a reference population. Median follow-up was 893 days (IQR 411 to 1500 days).

Coronary angiogram and intervention

During follow-up, 697 CA were performed in 515 patients which corresponded to 5.8 percent of the total number of patients. The procedure was followed by PCI in 51.3 percent of the procedures (n=264). The cumulative incidence of CA with or without PCI is visualised in Figure 16. In patients with at least one PCI prior to TAVI the rate of post procedural PCI was 8 percent (n=190).

![Figure 16. Cumulative incidence of interventions.](image)

Success rates

The overall success rate for PCI was 92.5 % with no significant differences between patients implanted with BE and SE valves (93.0% vs. 91.5%; \( \chi^2 \), p=0.62). In patients with no prior AVR, the overall success rate was 95.6
% which was significantly higher than in TAVI patients ($\chi^2$, p<0.01). The target vessel was a segment of the right coronary artery in 47.6% of the unsuccessful procedures.

Fluoroscopy time and the amount of contrast agent used was increased in patients with SE, compared with BE and with patients without prior AVR, both for CA only and for CA with PCI (Kruskal-Wallis, p < 0.01), Figure 17. The number of stents used were similar between the groups.

Indications for PCI

The most common indications for PCI after TAVI were non-ST elevation acute coronary syndrome (NSTEMI) (45.8%), chronic coronary syndrome (30.3%), ST Elevation acute myocardial infarction (STEMI) (6.9%) and congestive HF (3.7%).
Figure 17. Indicators of procedure complexity.
Discussion

Hospitalisations after TAVI

In Paper I, hospitalisations and repeat hospitalisations after TAVI caused by various diagnoses were frequent. These findings are in line with previous studies on both short-term and long-term hospitalisation [152,153] and further support that hospitalisations after TAVI are prevalent and a major cause of disability. Repeat hospitalisations were also associated with worse prognosis. Cardiovascular causes accounted for 16 % of the total number of hospitalisations with HF being most prevalent.

In the general population, hospitalisations are increasing with age and elderly patients account for a significant proportion of visits to the emergency department. The visits do also more often result in an admission. For older adults, it is suggested that the hospital admission rates are 2 to 6 times greater than for a younger population.[154–158] Furthermore, medical diagnoses are the major bulk in the elderly and in an earlier study, HF had a prevalence of 6.4 % of emergency visits and had a relative risk increase of 1.86 in patients aged 85 years or older as compared to patients aged 60 to 64 years.[159] Hence, it is not surprising that HF was a prevalent cause of hospitalisation after TAVI in Paper I. Moreover, the proportion of HF readmissions in Paper I was half of cardiovascular readmissions, which suggest that these readmissions are equally high or higher as compared to the general elderly population, even after TAVI. Furthermore, it has been demonstrated that a diagnosis of HF, irrespective of LVEF, prior to TAVI is associated with an increased risk for hospitalisations and worse outcome after TAVI.[160] Consequently, it is important to reduce the burden of HF.

Frequent hospitalisations are a concern. Many patients lives with already impaired quality of life (QoL) due to chronic illnesses. Hospitalisations could possibly further influence the estimated levels. Hospitalisations could of course be associated with a temporary increase in QoL due to decongestion of disease yet are also strongly associated with worse prognosis,[161,162] which was also found in Paper I. Moreover, for the health care system readmissions are costly with expenditures increasing over time. [163,164]

In Paper I, impaired LVEF and a low-flow, low-gradient AS were predictors of elevated risk. This may support a more aggressive intervention
strategy which is also consistent with the findings in the earlier mentioned AVATAR and RECOVERY trials.[43,44] AF was also prevalent and as a known risk factor for HF and death this is a target for further investigation. Renal function was also associated with increased risk, further consolidating evidence from earlier studies.[165] In addition, hospitalisations due to ACS was more prevalent than in earlier publications and this highlights the question of timing of coronary intervention which is currently debated.[166,167]

In summary, hospitalisations after TAVI are common and efforts should be taken to try to decrease the rates. Moreover, as hospitalisations are common and increasing with age, this should be part of the consideration when selecting patients for intervention.

Prediction models and predicting outcomes after TAVI

Clinical risk prediction models are an increasingly important tool to support medical decision-making, especially in the cardiovascular field. [168] As a consequence, there are a lot of models being developed and presented, where the TAVI field is no exception. Several models are available for use, mostly to predict mortality or hospitalisations.[172]

Although prediction model can facilitate the clinical management it is important to validate the model in the intended setting.[173] In Paper II, an external validation of the TAVR-30 model was performed which indicated an inadequate performance of the model in a Swedish setting. Several explanations to the model’s poor performance were identified. In general, inadequate statistical analysis methods is a common cause of suboptimal performance. In development, stepwise backward regression was used to identify potential predictors and this method comes with the risk of an overfit model.[119] However, the authors reported the use of the Aikaike index criterion which should reduce the risk.[174,175] Nonetheless, the model was overfit and the choice of method might have contributed to this finding. In addition, in the internal validation had limitations as it appears that the internal validation was performed by assuming that the final 9-parameter model was predefined and not derived from a screening process. Moreover, in the external validation presented in the original paper the concordance (c)-index was higher and thus, the question arises whether the model was actually recalibrated rather than using the original coefficients. However, there were also reason to believe that the definitions of the included variables differed between the different data sources which could explain the model’s poor performance. This is not an uncommon issue when transporting models to a different setting.[173,176]
The above highlights two things. First, the importance of validation before implementing a novel model and second, the challenge of having both clinical and statistical expertise.[177,178]

Apart from validation, one important aspect is how novel prediction models are implemented in clinical practice.[179] There are a lot of publications presenting novel models but there is less on how they actually change medical decision-making.[180] Ideally, an implementation analysis should be performed, for instance by doing a before-after study[173] or randomise between standard of care and utilising the prediction tool.[168,181]

One must also convince the physicians of actually using the instrument. For a prediction model to be accepted it should be user friendly, comprehensible and logical.[179,182,183]

In conclusion, prediction models are potentially helpful tools in clinical practice. Unfortunately the TAVR-30 model did not perform adequate but there are other models for TAVI outcomes with fair performances in a Swedish setting, such as the TARI score [170] or the TAVI Netherlands Heart Registration model (TAVI-NHR) [184] which was externally validated with a concordance (c)-index of 0.67 during the PhD period.[185] In my opinion, more focus should be set on implementing models, best practice and effectiveness of established models rather than only developing new ones without getting them into clinical practice.

Regional TAVI implementation

In Paper III, no major regional differences in terms of availability or short-term mortality were found.

Swedish citizens have universal access to tax-funded medical care where the aim is to provide equal care with high quality irrespective of place of residence.[186] Complex or rare interventions often require a concentration to specialised centres. There is also evidence of a correlation between higher number of procedures and improved outcomes both for TAVI and other procedures.[187–189] On the other hand, centralisation may lead to unequal care, due to a higher threshold for receiving treatment for patients living far away. This is a consequence of both the distance itself in combination with patient characteristics and organisational aspects.[190] Sweden is a sparsely populated, geographically large country with a very decentralised health care, with relatively autonomous management by local politically elected regional authorities. This may contribute to potential regional differences.[141,186,191]

As a consequence, the findings in Paper III are interesting in this context. No regional differences in availability to care or short-term mortality
were found which suggest that despite a highly decentralised health care system with local economic frameworks, a few centralised centres are sufficient to maintain an equal availability to TAVI.

Still, there are areas of concern. One of them is waiting times. Being on the waiting list for TAVI is associated with significant mortality risk, in earlier publications between two and four percent, with numbers as high as 14 percent reported.[187,192,193] In Paper III, the mean and median waiting times were around two months and there were no significant differences between regions. Nonetheless, patients who did not reach intervention were not captured by the registry and thus selection bias could be present. Furthermore, TAVI are increasing and are expected to do so over time and consequently, even if the current number of centres are sufficient today, capacity might become an issue.

Coronary interventions after TAVI

Although CAD is prevalent in the AS population Paper IV concluded that most patients does not require CAs or interventions after TAVI. The rates of ACS were low which is in line with or lower than previous studies where rates between 2 and 10 percent were reported.[194,195] However, 72 % of post TAVI PCI occurred in patients with a PCI prior to TAVI which is an important finding. The majority of ACS consisted of NSTE-ACS both in our and in both studies referenced to above. The proportion of NSTE-ACS at the time of a ACS has been found to have an almost linear correlation with age [196] It has been suggested that this is due to higher prevalence of prior ACS, multivessel disease, hypertension and ventricular hypertrophy which may contribute to global subendocardial ischemia and myocardial hypoperfusion.[196–198]

Interestingly, only a minority of patients in Paper IV with ACS following TAVI proceeded to PCI. Elderly patients are not as well studied in randomised controlled trials and thus reference rates are harder to find.[199] However, a large population based study reported that the rate of patients admitted for PCI at the time of an ACS in patients over 70 years of age have steadily moved upwards from low levels and by year 2013 it was estimated to just below 30 percent, and around 25 percent for patients presenting with NSTE-ACS.[200] In this context, the rates of 39% in Paper IV are plausibly comparable to those in an age matched general population.

There has been concern that coronary access could be more difficult after implantation of a TAVI prosthesis as the prosthesis is positioned closely to the coronary ostiae. In Paper IV, the success rate for PCI after TAVI was high with over 90% successful procedures. Nonetheless, it was
lower than in the reference population without prior TAVI. The difference might be subtle but as TAVI is probably becoming the method of choice for increasingly younger patients, longer life-expectancy combined with more time to develop significant CAD may result in the difference becoming clinically significant.

Prior studies have indicated a difference in success rates between the right and left coronary arteries.[201,202] However, this was not confirmed in Paper IV. Neither were any differences in success rates found between BE and SE valves, although SE had an increased fluoroscopy time and level of contrast agent used, indicating a more complex procedure.

Limitations

All studies in this thesis were retrospective and register based and this kind of data comes with inherited limitations. The registers used report high data agreement [104,138] but nonetheless, variable definitions and interpretation are sources of confounding. Furthermore, human errors, built in factors in the registries and incorrect ICD-10 diagnoses are inherited weaknesses.

In both Paper I and Paper IV, a major drawback was the lack of a control group from the general population. Ideally, the numbers of re-hospitalisation and its characteristics would have been compared with a matched cohort in Paper I as would have coronary interventions and PCI rates in Paper IV.

In Paper III, several limitations were present. As patients were not registered in SWENTRY until after procedure this may have created a selection bias affecting the analysis of waiting times. Despite adjustment for age and sex, there could also be unaccounted differences in case mix between regions. In addition, there could also be regional differences in the timing of intervention which were not studied.
Conclusions

- Repeated readmissions following TAVI are common and not only caused by cardiovascular comorbidities but due to various indications
- HF is the most common cause of hospitalisation after TAVI
- For patients with follow up time exceeding 6 years, all were either hospitalised at least once or dead
- The TAVR-30 prediction model underperformed in a Swedish context. It is difficult to construct valid and generalisable prediction models based on a few predictors as patients undergoing TAVI are old with prevalent comorbidities
- The TAVI-NHR risk model could be a better alternative in a Swedish context
- As of today, the current system with a limited number of highly specialised centres performing TAVI seem sufficient for providing national coverage of the procedure
- Coronary events after TAVI are uncommon and coronary access is most of the time not an issue. However, patients with prior PCI are at risk. As a consequence, this raises the question which patients that have a need for screening and intervention prior to TAVI
Future perspectives

Research on TAVI is interesting as the indications for treatment are currently broadened which raises new questions regarding evidence and best practice. In addition, the procedural volumes and follow up time are now starting to be sufficient for studies on a proper cohort of patients. In the European guidelines for valvular heart disease there is a section covering gaps in evidence.[9] Interestingly, many of the questions listed are linked to the questions addressed in this thesis, such as minimum volumes of procedures required for optimal results or the role of coronary access and coronary events after TAVI. While this thesis may contribute in adding new evidence there are many unanswered questions.

As new evidence indicates that TAVI is a feasible and safe alternative to SAVR, even in a population at low surgical risk there is an ongoing shift towards TAVI becoming the method of choice for most patients.[9,42] With younger patients, the expected remaining life time increases and durability of the implanted prosthesis becomes crucial. Although there are some studies with promising results on durability they are based upon patients at higher risk or with first generation valves and therefore not necessarily valid in a younger population with latest generation valves.[91,203] Hence, further studies are wanted and the Swedish registries are a great asset for such investigations.

In younger patients one could also expect an increase in candidates with bicuspid valves and for this patient population, in addition to durability, one must also consider the fact that many patients have extravalvular features.[3,63] For instance dilatation of the thoracic aorta could pose a challenge. There are studies on isolated BAV indicating favourable short term results[204,205] yet they are mainly observational. Consequently, the use of TAVI for BAV needs to be further investigated with randomised trials and long-term follow up.[206]

As the population is changing, it would also be interesting to redo Paper I in the future with an updated population to see whether the hospitalisation patterns are changing with a changing patient population.

If TAVI becomes method of choice in low risk individuals, one must also try to further minimise clinical complications such as paravalvular leak, need for permanent pacemaker and vascular complications which remains an issue.[207,208] Here again, the Swedish registries are an important platform. For instance, from 2021 and onwards, detailed electrocardiographic information is included which enables investigation of risk
factors for the need of permanent pacemaker.

Even if long-term durability is promising so far, with an increasingly younger population, one must also expect an increase in valve-in-valve procedures due to structural valvular degeneration. This condition occurs has been estimated to occur in 1.4-6.7 % of TAVI patients.\cite{209} and there is a need for more evidence in this patient group.

CAD is another area with gaps in evidence. Although Paper IV concluded that coronary interventions post TAVI are relatively rare there is a need to identify patients at risk and to better understand the underlying pathophysiology of joint disease.\cite{54} Advances in imaging could play an important part, where for instance aortic valve calcium score have been shown to be a marker of increased risk after TAVI.\cite{210} In addition, several newer TAVI valves comes with the possibility of commissural alignment, that is aiming for the best angular relationship between the native and the bioprosthetic valve commissures which in turn could facilitate coronary access.\cite{211,212}

Moreover, one must also keep in mind that there is much of the pathophysiology of AS that is not fully understood. Ideally, a better understanding may lead to a much lower need for intervention if targeted medical therapies are developed which could then change the course of need for TAVI. Several potential targets have been identified. DPP4 inhibitors are one, where the hypothesis is that endothelial dysfunction leads to an over expression which could promote degeneration of the valve. Another is the Renin-angiotensin-aldosterone system, where inhibitors could potentially reduce the pro-fibrotic process. Furthermore, apoB-containing atherogenic lipoprotein particles including Lp(a) are known to be involved in the disease process and despite that statins do not alter the progression there may be other alternative therapies, such as PSCK9 inhibitors.\cite{213,214}

In summary, research on TAVI is a dynamic field with a lot of opportunities for further investigations and an interesting future.
Sammanfattning på svenska


Första ingreppet på människa utfördes år 2002 och sedan dess har användandet expanderat kraftigt. Bara i Sverige görs nu över 1500 ingrepp årligen. Införandet av den nya metoden har inneburit både en möjlighet att behandla patienter där det tidigare ansågs för riskfylt med kirurgi och man ser även ett långsamt skifte där TAVI används i allt högre grad även hos operabla patienter. Detta då randomiserade jämförande studier mellan metoderna har visat att TAVI är minst lika bra eller bättre för stora delar av patientgruppen med aortastenos. Det genomgripande temat för den här avhandlingen är olika aspekter på kliniska utfall hos patienter som genomgått TAVI.


I den andra studien genomförde vi en extern validering av en modell för att beräkna risken för att drabbas av en återinläggning inom 30 dagar efter genomgången TAVI. Modellen var utvecklad i USA och genom att återanvända estimaten på data hämtade från våra svenska register med samtliga TAVI patienter i Sverige kunde vi utvärdera hur bra modellen var på att förutsäga risk för inläggning hos svenska patienter. Dessvärre kunde vi visa att modellen inte var tillräckligt precis för att användas i en svensk kontext.
I den tredje studien studerades regionala skillnader i införandet av TAVI i Sverige. I dagslaget utförs TAVI på ett fåtal högspecialiserade center vilket har fördelen att det kan vara lättare att upprätthålla kvalitet då man får en vana avseende ingreppet. Å andra sidan är Sverige ett relativt glesbefolkat land med stora avstånd vilket skulle kunna bidra till en ojämlik tillgänglighet om ingreppet endast erbjuds vid ett fåtal center. Studien kunde inte påvisa några signifikanta skillnader i tillgång till TAVI eller korttidsmortalitet efter ingreppet. Slutsatsen blev därmed att nuvarande struktur av vården förefaller tillsynligst för att tillgodose det nationella behovet.

I den avslutande fjärde studien adresserades frågan om behovet av och möjligheten att genomföra interventioner krankärleri efter genomgången TAVI. Klaffprotesen placeras i nära anslutning till där hjärtats krankärli avgår vilket skulle kunna ge upphov till svårigheter att nå ut med en ledare och genomföra ingrepp i kärleri. Studien visade att behovet av ingrepp efter TAVI är relativt litet och att det i de alla flesta fall resulterar i ett lyckat utfall. Dock kunde vi också se att endast en mindre del av patienter med en genomgången TAVI behandlas med ballongvidgning och inläggning av stent i händelse av hjärtinfarkt efter TAVI.
Acknowledgements

I want to express my appreciation and sincere gratitude to everyone who helped me complete this thesis. A special thank you to:

Stefan James, my main supervisor, for you excellent guiding into the wonderful world of research, for your never ending enthusiasm and knowledge, for believing in me and for providing the most inspirational research environment.

Christina Christersson, my co-supervisor, for your support, encouragement and for always making me feel welcome and as a part of the team.

Giovanna Sarno, my co-supervisor, for your expertise and precise knowledge, for carefully reviewing the manuscripts and identifying crucial details.

Daniel Lindholm, co-author, for excellent supervision of my research project when I was a medical student, thereby motivating me to pursue a scientific career and for introducing me to the R programming language.

Sergio Buccheri, co-author, for your support, kindness and for always helping me out.

Johan Lindbäck, Henrik Renlund, co-authors, for top-of-the line statistical support and interesting discussions on methodology, statistical possibilities and pitfalls.

Bahira Shahim, co-author, for you enthusiasm and for challenging and encouraging me to reach new goals.

Jenny Backes, Henrik Bjursten, Henrik Hagström, Sasha Koul, Johan Nilsson, Pétur Pétursson, Andreas Rück, Magnus Settergren, my co-authors, for interesting discussions, ideas and feedback that substantially improved the quality of the papers in this thesis. I look forward to further collaborations.

All participants in SWEDEHEART and other national registries for making the registers first class and thereby contributing to many scientific advances.
Anita Öström, secretary at UCR, for supporting everything practical in the best possible way.

Sören Gustafsson at the UCR IT department, for helping me find solutions to be able to work remotely.

Anna Skoglund, clinical supervisor on Gotland. Thank you for your guidance on how to navigate through my residency.

My colleagues at the Department of Internal Medicine, Visby hospital, for making the vast field of internal medicine comprehensible and for making it fun to go to work. My fellow residents for being like a small family at work. Kristina Fritz, for your commitment in making the environment as a resident as rewarding as possible. Veronica Snoder, Joakim Bragd, my superiors, for allowing me to combine research and clinical work.

Gotland health care research foundation and Swedish Society of Cardiology for providing financial support for activities related to this thesis.

Friends from medical school, for all the fun and memorable moments, for making the years in Uppsala contain so much more than just a university degree.

Avec Vokalensemble, Orphei Drängar, S:t Clemens Kammarkör and other musical constellations, for the opportunity to perform music on a high level, for being a source of energy and for genuine friendship.

Jakob, David, for solid friendship throughout the years, and for a lot of fun memories.

Ludwig, for always being there and for being like a brother for as long as I can remember.

Anette, Thomas, my future parents-in-law, for your warm welcome into your family. Frida, Mikael, Tilde, Junie, Kajsa, Jonatan, for your care about my family and for always making me feel like a part of yours.

My mother, May, for your unconditional love, for always listening and for your unwavering support throughout my life.

My son, Ivar, for your curiosity and for reminding me of what really matters in life. I am proud to be your father.

My fiancée, Liza, for your love, support and for putting up with me despite late evening coding and writing sessions. Thank you for making me happy and for being by my side. I look forward to our continued journey together.
References


65. Abbott ME. Coarctation of the aorta of the adult type: II. A statistical study and historical retrospect of 200 recorded cases with autopsy, of stenosis or obliteration of the descending arch in subjects above the age of two years. American Heart Journal. 1928 Jun;3(5):574–618.


71. Kuijpers' 'PetraMJC. History in medicine: The aortic valve. 18(9).


96. SWENTRY - SWEDHEART. https://www.ucr.uu.se/swedeheart /start-swentry/1096-swentry;


114. Logga in | Logga in | Etikprövningsmyndigheten. https://www.etikprovningsansokan.se/eprm/login;


140. Skatteverket. In English. https://shorturl.at/lACW7;


Acta Universitatis Upsaliensis

Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 1990

Editor: The Dean of the Faculty of Medicine

A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)