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PROSTHETIC AORTIC HEART VALVES

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Prosthetic Aortic Heart Valves

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Prosthetic Aortic Heart Valves

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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POPULÄRVETENSKAPLIG SAMMANFATTNING

Det finns fyra klaffar i hjärtat som öppnas och stängs varje gång hjärtat slår. Klaffarna möjliggör att blod pumpas runt till lungorna där blodet syresätts och sedan pumpas vidare ut i kroppen för syresättning av våra organ. En kropp utan hjärtklaffarnas rörelseförmåga, och därmed utan syre, är inte kompatibelt med liv. Aortaklaffen, som är lokaliserad mellan hjärtats vänstra kammare och stora kroppspulsådern, är den hjärtklaff som oftast behöver bytas genom kirurgiskt aortaklaffbyte. Vid ett kirurgiskt aortaklaffbyte klipper man ut den sjuka klaffen och ersätter den med en så kallad hjärtklaffprotes. Ungefär 1500 patienter i Sverige och nästan 300 000 patienter i världen genomgår kirurgiskt aortaklaffbyte varje år.[1] Den vanligaste indikationen för aortaklaffbyte är en förträngning i aortaklaffen, så kallad aortastenos, vilket är en sjukdom som ökar i förekomst med stigande ålder. Eftersom livslängden hela tiden ökar kan man förvänta sig att ännu fler patienter kommer vara i behov av aortaklaffbyte i framtiden.

En hjärtklaffprotes är gjord av mekaniskt material eller biologisk vävnad från gris eller ko. En mekanisk klaffprotes har fördelen att den har en mycket lång hållbarhet, men nackdelen att man efter operation måste ta medicinen Waran så länge man lever. Waran är ett mycket potent blodförtunnande läkemedel som förhindrar att blodet koagulerar runt klaffen men som samtidigt för med sig en risk för blödning. Den biologiska klaffprotesen kräver ingen behandling med Waran, men har istället en begränsad hållbarhet. Det finns därför en risk, framför allt hos yngre personer, att man senare i livet behöver genomgå ytterligare en operation för att byta ut klaffprotesen igen. Så vilken klaff väljer man – den mekaniska med en livslång risk för blödningar eller den biologiska med en risk för att behöva genomgå ytterligare en hjärtoperation? Vanligtvis rekommenderar man en mekanisk klaffprotes till yngre och i övrigt friska patienter och en biologisk klaffprotes till äldre patienter med en begränsad kvarvarande livslängd. Men var går gränsen mellan ung och gammal? Det är en av frågorna vi försökt besvara i den här avhandlingen. Vi har även studerat hållbarheten samt sjuklighet och överlevnad efter aortaklaffbyte med olika typer av klaffproteser.

I första studien jämförde vi överlevnad efter aortaklaffbyte med två olika typer av biologiska aortaklaffproteser. En av dessa klaffar är gjord av material från hjärtsäcken från kalv (Perimount) och en är gjord av klaffvävnad från gris (Mosaic). Resultatet visade ingen skillnad i långtidsöverlevnad mellan klaffarna. Mosaic-klaffen hade en högre andel av patienter där den implanterade klaffprotesen var för liten i förhållande till patientens kroppsstorlek men detta hade ingen påverkan på överlevnaden i vår studiepopulation.

I andra studien studerade vi funktionen av Mosaic-klaffen både tidigt och sent efter operation. Resultatet visade en acceptabel funktion, men det var en betydande andel av

patienterna som hade ett ökat tryck över klaffprotesen vilket kan tyda på en sämre funktion. Detta hade emellertid ingen påverkan på överlevnaden i vår studiepopulation.

I tredje studien undersökte vi långtidsöverlevnaden efter aortaklaffbyte med en mekanisk jämfört med en biologisk klaffprotes hos patienter mellan 50 och 69 år. Resultatet visade att patienter som fick en mekanisk klaffprotes hade bättre överlevnad än de som fick en biologisk klaffprotes.

I fjärde studien jämförde vi långtidsöverlevnaden efter aortaklaffbyte mellan patienter med måttlig njurfunktionsnedsättning och patienter med normal njurfunktion. Resultatet visade att patienter med måttlig njurfunktionsnedsättning hade 34% högre risk för död under uppföljningstiden.

I femte studien jämförde vi förekomsten av infektion i klaffen efter aortaklaffbyte med en mekanisk eller biologisk klaffprotes. Resultatet visade att infektion i klaffen är relativt ovanligt men att patienter med biologiska klaffproteser oftare drabbades än patienter med mekaniska klaffproteser.

I den sjätte studien gjorde vi en litteraturöversikt över studier som jämfört överlevnad efter aortaklaffbyte med en biologisk klaffprotes gjord av kalvvävnad med en klaffprotes gjord av grisvävnad. En sammanslagning av resultat från de granskade studierna, en så kallad meta-analys, visade ingen skillnad i överlevnad efter aortaklaffbyte med en klaffprotes gjord av kalvvävnad jämfört med en klaffprotes gjord av grisvävnad.

Kunskap om överlevnad efter operation med olika aortaklaffproteser och hållbarheten av olika aortaklaffproteser är viktig för att välja rätt klaffprotes till rätt patient. Genom att undersöka detta leder avhandlingens studier till ökad kunskap om aortaklaffoperationer, om funktionen av olika typer av klaffproteser och om faktorer som kan leda till ökad sjuklighet och dödlighet efter operation. Denna kunskap är till nytta för patienter som har genomgått, eller som ska genomgå operation med aortaklaffbyte, både i Sverige och i andra delar av världen.

ABSTRACT

Background Aortic valve replacement (AVR) can be performed with different types of valve prostheses. There is no perfect aortic valve prosthesis, and the prosthetic choice for each patient requires careful consideration. This thesis evaluates mortality, morbidity, and prosthetic valve function after AVR with different aortic valve prostheses.

Methods and Results

Study I We studied all-cause mortality and postoperative outcomes in all 1219 patients who underwent AVR at Karolinska University Hospital between 2002 and 2010 and received either Perimount (n=864; Edwards Lifesciences, Irvine, CA) or Mosaic (n=355; Medtronic, Inc., Minneapolis, MN) bioprostheses. There was no difference in all-cause mortality (adjusted hazard ratio (HR) 0.85, 95% confidence interval (CI) 0.65–1.11) or rate of aortic valve reoperation between the two groups. Severe prosthesis–patient mismatch (PPM) was more common in the Mosaic group than in the Perimount group (15% vs. 6%, p<0.001).

Study II We studied hemodynamic function and postoperative outcomes in all 355 patients who underwent AVR at Karolinska University Hospital between 2002 and 2008 and received a Mosaic bioprosthesis. The mean pressure gradient was 21.2 mmHg and 22.5 mmHg during early and late echocardiography, respectively. Moderate or severe PPM was found in 299 (84%) patients, and 46 patients had moderate or severe aortic stenosis at late echocardiography, but neither was associated with increased mortality.

Study III We studied all-cause mortality and postoperative outcomes in all 4545 patients aged 50–69 years who underwent primary, isolated AVR with biological (n=1832) or mechanical (n=2713) prostheses in Sweden between 1997 and 2013. The study population was obtained from the SWEDEHEART register. In a propensity score-matched analysis, patients with mechanical valve prostheses had better survival than patients with bioprostheses (HR 1.34, 95% CI 1.09–1.66, p=0.006). There was no difference in the rate of stroke, but patients with mechanical valves had a higher risk of major bleeding events and a lower risk of aortic valve reoperation than patients with bioprostheses.

Study IV We studied all-cause mortality and postoperative outcomes in all 13 102 patients with moderately reduced (n=3266), or normal (n=9836) kidney function who underwent primary AVR in Sweden between 1997 and 2013. The study population was obtained from the SWEDEHEART register. Patients with normal kidney function had better survival than patients with moderately reduced kidney function (adjusted HR 1.28, 95% CI 1.18–1.38). Patients with moderately reduced kidney function had a slightly higher risk of major bleeding events and a lower risk of aortic valve reoperation than patients with normal kidney function.

Study V We studied the incidence of prosthetic valve endocarditis (PVE) in all 26 580 patients who underwent AVR with biological (n=16 426) or mechanical (n=10 154) prostheses in Sweden between 1995 and 2012. The study population was obtained from the SWEDEHEART register. The incidence rate of PVE was 0.57% (95% CI 0.54–0.61) per person-year. The incidence of PVE was highest during the first year after surgery and remained stable thereafter for up to 18 years of follow-up. The risk of PVE was higher in patients with bioprostheses than in patients with mechanical valve prostheses (adjusted HR 1.54, 95% CI 1.29–1.83, p<0.001).

Study VI We performed a systematic review and meta-analysis evaluating all-cause mortality after AVR in 49 190 patients who received bovine (n=32 235) versus porcine (n=16 955) bioprostheses. In total, seven articles met the inclusion criteria. The random-effects model was used to obtain pooled HR and 95% CI. The meta-analysis revealed no difference in survival between the groups (pooled HR 1.00, 95% CI 0.92–1.09).

Conclusions [1] Both the Perimount and Mosaic bioprostheses are acceptable valve alternatives for AVR. [2] In patients aged 50–69 years, survival after AVR was better for those who received mechanical valve prostheses rather than bioprostheses. [3] After AVR, patients with moderately reduced kidney function have higher mortality than patients with normal kidney function. [4] After AVR, the yearly rate of PVE was 0.57%. Patients with bioprostheses had a higher risk of PVE than that of patients with mechanical valves. [5] Both bovine and porcine bioprostheses are acceptable valve choices for AVR.

LIST OF SCIENTIFIC PAPERS

I. **Glaser N**, Franco-Cereceda A, Sartipy U. Late survival after aortic valve replacement with the Perimount versus the Mosaic bioprosthesis.
Annals of Thoracic Surgery 2014;97:1314-1320.

II. **Glaser N**, Franco-Cereceda A, Sartipy U. Late haemodynamic performance and survival after aortic valve replacement with the Mosaic bioprosthesis.
Interactive Cardiovascular and Thoracic Surgery 2014;19:756-762.

III. **Glaser N**, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Aortic valve replacement with mechanical vs. biological prostheses in patients aged 50–69 years.
European Heart Journal 2016;37:2658-2667.

IV. **Glaser N**, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Late survival after aortic valve replacement in patients with moderately reduced kidney function.
Journal of the American Heart Association 2016;5:e004287.

V. **Glaser N**, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Prosthetic valve endocarditis after surgical aortic valve replacement.
Circulation 2017;136:329-331.

VI. **Glaser N**, Jackson V, Franco-Cereceda A, Sartipy U. Survival after aortic valve replacement with bovine or porcine valve prostheses: a systematic review and meta-analysis.
The Thoracic and Cardiovascular Surgeon. (In press)

CONTENTS

LIST OF ABBREVIATIONS

AVR	Aortic valve replacement
BMI	Body mass index
BSA	Body surface area
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
eGFR	estimated Glomerular filtration rate
ESRD	End-stage renal disease
HR	Hazard ratio
ICD	International Classification of Diseases
INR	International normalized ratio
LISA	Longitudinal integration database for health insurance and labor market studies
LVEF	Left ventricular ejection fraction
MPG	Mean pressure gradient
PPG	Peak pressure gradient
PPM	Prosthesis-patient mismatch
PVE	Prosthetic valve endocarditis
RCT	Randomized controlled trial
SD	Standard deviation
sHR	subdistribution Hazard ratio
SVD	Structural valve deterioration
SWEDEHEART	The Swedish Web system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies
TAVI	Transcatheter aortic valve implantation

INTRODUCTION

Aortic valve replacement (AVR) is the standard treatment for patients with severe aortic valve disease. Surgical AVR is one of the most commonly performed cardiac procedures worldwide, and it is performed in approximately 280 000 patients worldwide each year.[1] AVR is a procedure during which a diseased aortic valve is replaced with an aortic valve prosthesis. Operative mortality after isolated AVR is approximately 2%–3%.[2,3] However, life expectancy after AVR is similar to that of the general population.

Aortic valve prostheses are made of either biological tissue or mechanical material. Mechanical valves have excellent durability but necessitate lifelong anticoagulation treatment with warfarin, which requires a lifelong commitment to regular health care visits and increases the patient's susceptibility to excessive bleeding. However, biological valves, or bioprostheses, do not require treatment with warfarin but have limited durability, which may necessitate reoperation. Bioprostheses are usually made from porcine heart valve tissue or bovine pericardial tissue. Several studies reported better hemodynamic function after AVR with bovine than porcine bioprostheses.[4-6] However, whether this translates to better survival for patients who receive a bovine than a porcine valve prosthesis is unknown.

There are advantages and disadvantages to all types of aortic valve prostheses, and the prosthesis type has to be carefully selected for each patient.

In this thesis, we studied the morbidity, mortality, and function of different types of valve prostheses after AVR. The overall aim was to increase the community's level of knowledge about AVR and aortic valve prostheses.

BACKGROUND

Aortic Stenosis

Aortic stenosis is most commonly caused by calcification that narrows the opening of the aortic valve and subsequently obstructs blood flow. Aortic stenosis is responsible for a high number of hospitalizations and deaths every year. It is a common disorder, especially in the aging population, and it affects around 2% of the population aged above 65 years[7] and up to 12% of the population aged above 75 years.[8]

The aortic valve is composed of three cusps (therefore, it is also called the "tricuspid" valve), which are fused to the aortic root by three commissures. In younger patients with aortic stenosis, degenerative changes are often imposed on a congenital bicuspid valve (two cusps instead of the usual three). In contrast, older patients more commonly have acquired calcific changes in a tricuspid valve.[9] Aortic valve disease can also be caused by a few less common conditions, such as endocarditis, rheumatic fever, aortic aneurysms, vasculitis, and Marfan's syndrome.

Patients with aortic stenosis have a wide array of clinical presentations, ranging from no symptoms to syncope and sudden death. The standard diagnostic tool for aortic valve disease is Doppler echocardiography. Valve structure, blood flow across the aortic valve, and the dimensions and function of the left ventricle are measured. Severe aortic stenosis is defined as a peak transvalvular velocity greater than 4 m/s, an aortic valve area less than 1 cm^2, or a mean pressure gradient (MPG) across the valve greater than 40 mmHg.[10,11]

The prognosis of untreated aortic stenosis is poor, and the natural course of the disease is a progressive narrowing of the valve causing an increased cardiac workload, cardiac hypertrophy, cardiac failure, and eventually death. After the onset of symptoms, the annual mortality is 25%, and the average survival is 2–3 years.[12] At present, no medical treatment cures or halts the progression of severe aortic valve stenosis, and the only curative treatment is AVR.

Aortic Valve Surgery

The first aortic valvuloplasty was performed in the 1920s with rather disappointing results.[13] Not until after the first cardiac procedure with cardiopulmonary bypass in 1953 did the first AVR take place in the early 1960s.[13] In the beginning, caged ball prostheses were used, soon followed by homograft implantation. In the mid-1960s, a heterograft using porcine valve tissue was developed and implanted in a patient for the first time.[13] The first stented bovine pericardial prosthesis was implanted in 1971. In 1977, the first bileaflet mechanical valve was implanted, and that remains the most

commonly used type of mechanical valve prosthesis. The first transcatheter aortic valve implantation (TAVI) was performed in 2002 in France.[14]

Surgical Aortic Valve Replacement

Surgical AVR is one of the most commonly performed cardiac surgeries in the world, and approximately 280 000 AVRs are performed worldwide every year.[1] The operation is recommended in symptomatic patients with severe aortic stenosis or regurgitation, and in asymptomatic patients with reduced left ventricular systolic function. It should be considered in case of severe aortic regurgitation with dilatation of the left ventricle.[10,11] AVR is also performed in case of bacterial endocarditis or aortic dissection that affects the aortic valve.

AVR is usually performed via full median sternotomy; however, in the last 2–3 decades, minimally invasive methods using a small chest wall incision have emerged as surgical options.[15] Commonly used methods for minimally invasive AVR are upper hemisternotomy and right anterior thoracotomy. Studies have shown that a minimally invasive approach decreases postoperative pain, length of hospital stay, amount of blood transfusion, and incidence of postoperative atrial fibrillation, but at the expense of prolonged aortic cross-clamp time.[16-18] Furthermore, less-invasive methods can only be used in selected patients.

AVR is performed with cardiopulmonary bypass established with central venous and arterial cannulation before the proximal aorta is occluded with a cross-clamp. To prevent myocardial damage, cold blood or crystalloid cardioplegia is delivered through the coronary arteries or the sinus coronarius. The aortic valve is visualized through a partial aortotomy proximal to the aortic cross-clamp. The diseased valve is excised, and the aortic annulus is thoroughly decalcified before the aortic valve prosthesis is implanted.

Operative mortality after isolated AVR is 2%–3%.[2,3] In case of concomitant coronary artery bypass grafting or multiple valve intervention, operative mortality approximately doubles.[2] The life expectancy of patients above 65 years of age after undergoing AVR is excellent and similar to that of the general population, and in patients below 65 years of age, it is approximately five years less than that of the general population.[19]

The aortic valve can sometimes be repaired instead of replaced. Aortic valve repair is most commonly performed in patients with isolated aortic regurgitation, with the valve being modified by sutures and patches. This procedure allows the patient to keep his or her own valve, and excellent long-term results have been reported.[20,21] However, aortic valve repair is usually more technically challenging than AVR, and it is reserved for selected patients.[22] Aortic valve-sparing surgery with reimplantation of the aortic valve and the coronary arteries[23] (i.e., David or Yacoub technique) into an aortic graft is another surgical technique that can be performed in selected patients.

Transcatheter Aortic Valve Implantation

An alternative to open heart surgery for patients with symptomatic aortic valve disease is TAVI, a procedure in which an aortic valve prosthesis is implanted through a catheter, preferably via the femoral artery, but the possibility of using this access depends on the patient's anatomy. The aortic prosthesis can also be delivered via the subclavian artery or transaortic or transapical approaches. The aortic valve prosthesis is implanted without removing the old, damaged valve. The entire procedure typically takes 1–2 hours and can usually be performed with conscious sedation and local anesthesia rather than general anesthesia.

Since the first TAVI procedure was performed in 2002, the method has rapidly gained ground. In 2016, it was estimated that TAVI had been performed in more than 200 000 patients worldwide.[24] The latest guidelines recommend TAVI in patients who have a life expectancy of more than one year and who are considered inoperable.[10,25] In patients with high and intermediate surgical risk, TAVI is considered a reasonable alternative to surgical AVR.[10,25] Randomized controlled trials (RCTs) investigating the use of TAVI in low-risk patients are ongoing. The choice of intervention (surgical AVR or TAVI) should be discussed by a multidisciplinary heart team after careful individual evaluation. TAVI carries a higher risk of postoperative need for pacemaker implantation, paravalvular leakage, and vascular complications than surgical AVR.[26,27] However, TAVI has the advantage of a percutaneous approach allowing for a less invasive method with fewer postoperative bleeding complications and faster recovery. TAVI has also been associated with a lower risk of acute kidney injury and new-onset atrial fibrillation than surgical AVR.[26,27] The 5-year durability after TAVI is similar to that of surgical AVR.[28] Further studies evaluating the long-term prognosis after TAVI are needed and ongoing.

Complications after Aortic Valve Replacement

Possible complications after AVR include bleeding, stroke, structural valve deterioration (SVD), infections including endocarditis and mediastinitis, thromboembolism, atrioventricular blocks requiring pacemaker implantation, and other arrhythmias such as atrial fibrillation.[29]

Prosthesis-Patient Mismatch

Prosthesis–patient mismatch (PPM) is present when the inserted prosthetic valve is too small in relation to the patient's body surface area (BSA). The indexed effective orifice area is used to define PPM and is equal to the aortic valve area divided by the patient's BSA. PPM and severe PPM are considered to be present when the indexed effective orifice area is less than 0.85 cm^2/m^2 and less than 0.65 cm^2/m^2, respectively.[30]

PPM has been widely discussed over the last decades, and the evidence for its clinical impact is controversial. Several studies have shown a correlation between PPM and

reduced left ventricular mass regression, higher incidence of cardiac complications, and increased all-cause mortality.[31,32] Other studies did not find that PPM is correlated with increased mortality.[33,34]

Structural Valve Deterioration

SVD is the deterioration of bioprostheses that typically takes place gradually over years. SVD is defined as leaflet calcification, tearing, thickening, or disruption of the prosthetic valve materials that manifest as aortic stenosis or regurgitation.[35] Risk factors for SVD include young patient age, kidney failure, metabolic syndrome, hypertension, abnormal calcium metabolism, and PPM. The predicted 15-year risk of SVD is approximately 20% for patients 50 years of age, 30% for patients 40 years of age, and 50% for patients 20 years of age.[25] Surgical AVR or TAVI should be considered in symptomatic patients with SVD and severe aortic stenosis or regurgitation, or moderate stenosis and moderate regurgitation.[35]

Prosthetic Valve Endocarditis

Infective endocarditis is a rare but severe infection that can affect any surface with endocardial lining.[36,37] It often affects heart valves,[38] especially prosthetic ones. Prosthetic valve endocarditis (PVE) is the most severe form of infective endocarditis,[39,40] and it accounts for 12% to 22% of all cases of infective endocarditis.[40,41] The number of infections caused by staphylococci has increased over the last few decades to surpass streptococci as the most common pathogen in infective endocarditis in the Western world.[41-43] This is believed to be caused partly by an increased number of nosocomial infections. Additionally, infective endocarditis now exhibits a more acute progression than in the past. It also more frequently affects older patients with prosthetic heart valves or cardiac devices, in contrast to earlier mainly affecting younger patients with rheumatic valve disease. PVE can result in valve dysfunction, embolic stroke, and sepsis. Without treatment, PVE is almost always fatal. Antibiotics should be started as soon as PVE is diagnosed, and surgery should be considered in all patients with PVE.[44] Even with treatment, the reported in-hospital mortality rate of PVE is 15%–23%.[40,45] The incidence of infective endocarditis in the general population ranges from 0.002% to 0.012% per person-year.[46] However, the incidence of PVE after AVR has not been extensively studied, and whether PVE affects biological and mechanical aortic valve prostheses to the same extent remains unknown.

Aortic Valve Prostheses

The aortic valve can be replaced by either a biological or mechanical valve prosthesis. Mechanical prostheses have high long-term durability but necessitate lifelong anticoagulant therapy with warfarin, whereas biological prostheses do not require the use of anticoagulants but have limited durability. Bioprostheses typically last 10–20 years but usually degenerate faster in younger patients.[47,48] However, treatment with

warfarin requires a lifelong commitment to regular tests and an increased risk of bleeding-related complications. Additionally, in case of major bleeding or subsequent cardiac or non-cardiac surgery, anticoagulation therapy may have to be discontinued, with a subsequent risk of mechanical valve thrombosis and death.

Thus, there is no perfect aortic valve prosthesis, and the type of prosthesis has to be carefully selected for each patient. In general, bioprostheses are recommended for older patients with more comorbidities, and mechanical valves are recommended for younger patients with a longer life expectancy. There are several different types and brands of aortic valve prostheses, which mainly differ in terms of structure and material.

Mechanical Valve Prostheses

Mechanical valves are either unileaflet, bileaflet, or caged ball valves, with the latter no longer in clinical use. The most commonly used mechanical valve is a bileaflet prosthesis made from pyrolytic carbon (Figure 1a). In case of aortic root replacement or concomitant aorta ascendens surgery, a Dacron graft with a mechanical valve sutured into one side can be used.

Mechanical valves have excellent durability but require lifelong treatment with warfarin. The RE-ALIGN study was conducted to find an alternative to warfarin for these patients.[49] The authors compared warfarin with dabigatran in patients with mechanical valves, but the study was terminated prematurely because the patients treated with dabigatran had a higher risk of major bleeding events and stroke than patients treated with warfarin had.[49] The standard international normalized ratio (INR) target for patients with mechanical aortic heart valves is 2.0–3.0. The On-X valve (On-X Life Technologies Inc., Austin, Texas) was FDA-approved in 2002 and is designed to be safe with less anticoagulation. The PROACT study[50] consist of two arms: the low-risk arm was performed to compare dual antiplatelet therapy (clopidogrel and aspirin) with the standard regimen of warfarin and aspirin, and the high-risk arm compared aspirin and warfarin in patients with INR targets of 1.5–2.0 versus 2.0–3.0. The low-risk arm was terminated because of a higher rate of ischemic stroke in the dual antiplatelet therapy group. In the high-risk arm, patients with INR targets of 1.5–2.0 did not show an increased risk of thromboembolic events and had a lower rate of bleeding events. The guidelines from the American Heart Association state that “a lower target INR of 1.5 to 2.0 may be reasonable in patients with mechanical On-X AVR and no thromboembolic risk factors.”[25] However, the guidelines from the European Society of Cardiology still recommend a median INR of 2.5 for these patients.[10]

Apart from the disadvantage of lifelong anticoagulant treatment, the opening and closing of the mechanical valve can sometimes be audible outside the body, which some patients find disturbing.

Biological Valve Prostheses

Biological prostheses are usually made from porcine aortic valve tissue or bovine pericardial tissue. The biological tissue is attached to a stent (for support) that is covered with a fine fabric to facilitate suturing of the prosthesis to the patient's aortic root (Figures 1b and 1c).

If the entire aortic root has to be replaced, for example in patients with endocarditis and extensive vegetations, stentless aortic root prostheses (e.g., the Freestyle prosthesis (Medtronic, Inc., Minneapolis, MN, USA) made from porcine heart valve tissue, Figure 1d) or homografts can be used. Another option is the Ross procedure, in which the aortic root is replaced with the patient's own pulmonary valve, and the pulmonary valve is replaced with a homograft. In these operations, the coronary arteries are usually reimplanted to the prosthetic aortic root.[22]

During the last 15 years, sutureless, self-expanding aortic valve bioprostheses (also called rapid deployment valves) have been introduced, allowing for shorter cardiopulmonary bypass times and easier implantation (Figure 1e). Some studies reported promising initial results.[51,52] However, other studies reported an increased risk of pacemaker implantation and disabling stroke in patients who received rapid deployment valves compared with conventional valves.[53] The long-term function of these valves and their role in the treatment of aortic valve disease need to be evaluated further.

The valve prostheses used for TAVI are usually made from either porcine or bovine tissue (Figure 1f). TAVI can be performed as a primary surgery or as a valve-in-valve procedure as an alternative to reoperation in failing biological valve prostheses.[54]

Figure 1a-f. *The St Jude Medical Regent mechanical[55] (Abbott, St Paul, Minnesota, USA; upper left), the Perimount bovine (Edwards Lifesciences, Irvine, CA, USA; upper middle), the Mosaic porcine (Medtronic, Inc, Minneapolis, MN, USA; upper right), the Freestyle porcine (Medtronic, Inc, Minneapolis, MN, USA; lower left), the Perceval sutureless (LivaNova, Milan, Italy; lower middle), and the SAPIEN 3 transcatheter (Edwards Lifesciences, Irvine, CA, USA; lower right), aortic valve prostheses. Images reprinted with permission.*

Bovine and Porcine Bioprostheses

Several previous investigations reported advantages of pericardial bioprostheses compared with porcine aortic bioprostheses regarding hemodynamics, left ventricular mass regression, and PPM, factors considered to correlate with survival.[4-6] However, no difference in long-term survival has been shown between these two types of bioprostheses.[56,57]

The Aortic Perimount and Mosaic Bioprostheses

The Carpentier-Edwards Perimount pericardial aortic bioprosthesis (Edwards Lifesciences, Irvine, CA, USA) and the Medtronic Mosaic porcine aortic bioprosthesis (Medtronic, Inc, Minneapolis, MN, USA) are two of the world's most commonly used bioprostheses.

The Perimount bioprosthesis (Figure 1b) has been in clinical use since 1981 and is made from bovine pericardial tissue mounted on a cobalt-chromium stent. It was designed to improve durability and decrease the incidence of SVD compared with previous bioprostheses. Repeated studies have shown that it has excellent long-term function.[47,58] Patients who received the Perimount bioprosthesis have been reported to have a larger valve area, greater regression of left ventricular mass, and better valvular hemodynamics than patients with other bioprostheses have.[4,6,59] However, no differences in survival or rate of reoperation between this type of prosthesis and other bioprostheses have been reported.[6]

The Mosaic bioprosthesis (Figure 1c) is a stented porcine bioprosthesis that is treated with a combination of alpha-amino oleic acid and glutaraldehyde fixation at zero pressure to improve tissue durability and hemodynamic performance. It has been in clinical use since 1994, and follow-up studies have shown excellent results regarding both clinical outcomes and hemodynamic performance.[60-62] However, a few studies have shown higher transvalvular gradients, a higher prevalence of PPM, and earlier reoperation caused by SVD with the Mosaic bioprosthesis than with other contemporary bioprostheses.[4,63,64] Additionally, six cases of early bioprosthetic failure of the Mosaic bioprosthesis have been reported,[65,66] which warrants further evaluation.

Aortic Valve Replacement in Middle-Aged Patients

There is no perfect aortic valve prosthesis, and many factors have to be considered before choosing the type of valve prosthesis for each particular patient. Patient age is one factor that should be taken into consideration. Other factors in this decision include the patient's preference, bleeding susceptibility, expected lifespan, probability of compliance to warfarin therapy, comorbidities, size of the aortic annulus, and the wish to become pregnant in women of childbearing age.

Under the current guidelines, bioprostheses should be considered in patients older than 65–70 years (65 and 70 years according to the European and American guidelines, respectively).[10,25] Mechanical prostheses are considered to be reasonable alternatives in patients aged below 50–60 years (60 and 50 years according to the European and American guidelines, respectively).[10,25] At ages 60–65 years (European guidelines) and 50–70 years (American guidelines), both valve types are considered reasonable options.[10,25]

Presumably because of the development of longer-lasting aortic bioprostheses, patient reluctance to warfarin treatment, and the development of TAVI as a possible alternative to reoperation, bioprostheses are increasingly used even in younger-aged patients.[67,68] However, there is no convincing scientific evidence to support this trend.

Prior studies investigating survival and clinical outcomes following AVR with a mechanical or bioprosthetic valve in middle-aged patients have reported contradictory results. Some studies have shown better long-term clinical outcomes in patients who received a mechanical valve.[69,70] Others reported no significant difference in long-term survival between patients who underwent AVR with a bioprosthesis compared with a mechanical valve.[71,72]

In summary, the optimal prosthesis type in middle-aged patients remains unknown, and a large RCT would be needed for better guidance. Until then, several different factors need to be assessed, and every patient has to be assessed thoroughly and individually.

Aortic Valve Replacement in Patients with Reduced Renal Function

There is a well-known association between chronic kidney disease (CKD) and valvular heart disease, especially aortic stenosis.[73,74] The imbalance in phosphate and calcium levels seen in patients with chronic renal failure is believed to cause a higher degree of calcification in the valvular annulus and leaflets, leading to aortic stenosis.[73] Additionally, patients with chronic renal failure are believed to be in a chronic inflammatory state, leading to accumulation of macrophages and T lymphocytes, eventually leading to increased calcium deposits[73] and aortic stenosis.

Patients with end-stage renal disease (ESRD) have a worse prognosis after cardiac surgery than patients with normal renal function have.[75,76] They also have a higher risk of postoperative bleeding and a prolonged hospital stay following AVR.[77,78] Aortic stenosis progresses more rapidly in patients with ESRD,[74,79] and consequently, it is believed that calcification leading to SVD after AVR is more common in these patients. It has been debated whether or not these patients benefit more from a biological or mechanical valve prosthesis. It is hypothesized that these patients generally die from other causes before SVD becomes their main problem. In line with this hypothesis, most studies have not found a difference in mortality between patients with ESRD who

received a biological or mechanical aortic valve prosthesis.[80,81] Even though moderately reduced kidney function is much more common than ESRD, studies investigating these patients' prognosis after AVR are scarce.

In many studies, creatinine values are used as an estimation of kidney function. However, the estimated glomerular filtration rate (eGFR) is a preferable indicator[82,83] because creatinine levels are influenced by age, muscle mass, and gender. eGFR has been shown to be a powerful predictor of outcome after valvular surgery.[84] Two common methods to calculate eGFR are the Modification of Diet in Renal Disease formula and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. These two methods are equally accurate in patients with CKD, but the CKD-EPI formula is believed to yield more accurate results in patients with eGFR values of >60 mL/min/1.73m^2.[85]

AIMS

This thesis aimed to investigate mortality, morbidity, and prosthetic valve function after AVR with different aortic valve prostheses.

The specific aims of the individual studies were:

Study I To analyze long-term, all-cause mortality in patients who underwent AVR and received Perimount versus Mosaic bioprostheses.

Study II To analyze the hemodynamic function of patients who underwent AVR and received Mosaic bioprostheses.

Study III To analyze the long-term, all-cause mortality in patients aged 50–69 years who underwent AVR with bioprostheses versus mechanical valve prostheses.

Study IV To analyze the long-term, all-cause mortality after AVR in patients with moderately reduced versus normal kidney function.

Study V To analyze the incidence and risk of PVE in patients who underwent AVR with bioprostheses versus mechanical valve prostheses.

Study VI To systematically review the literature and perform a meta-analysis of long-term, all-cause mortality after AVR in patients who received bovine versus porcine bioprostheses.

PATIENTS AND METHODS

Swedish National Registers

SWEDEHEART

The Swedish Web system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) contains information about all patients in Sweden who: [1] received care at a coronary care unit, [2] were followed for secondary prevention after acute coronary syndrome, [3] underwent coronary angiography, [4] underwent percutaneous valve intervention, or [5] underwent open heart surgery. SWEDEHEART was started in 2009 by a merger of four already existing national quality registers: the Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA; since 1991), the Swedish Coronary Angiography and Angioplasty (SCAAR; since 1991/1992), the National Registry of Secondary Prevention (SEPHIA; since 2005), and the Swedish Heart Surgery Registry. The Swedish Heart Surgery Registry covers all patients who underwent cardiac surgery for any reason since 1992. The register has complete coverage from all eight hospitals that perform cardiac surgery in Sweden. The agreement between SWEDEHEART and medical records has been reported to be 93%–97%.[86-88]

National Patient Register

The Swedish National Patient Register was founded in 1964 and has complete coverage since 1987. It is maintained by the Swedish National Board of Health and Welfare and covers more than 99% of all somatic and psychiatric hospital discharges, including patient data, geographic data, administrative data about the hospital stay, and medical data. A senior physician establishes the diagnosis at hospital discharge, and the diagnosis is then forwarded to the National Patient Register by computer. These routines are standardized in Sweden. The diagnoses used in the National Patient Register are based on the World Health Organization's International Classification of Diseases (ICD). The validity of the register has been repeatedly shown to be high, with 95% validity for primary diagnosis of heart failure and positive predictive values of 98.6% for stroke and 98%–100% for myocardial infarction.[89,90]

Longitudinal Integration Database for Health Insurance and Labor Market Studies

The longitudinal integration database for health insurance and labor market studies (LISA) register is a national register maintained by Statistics Sweden that covers all individuals aged above 16 years in Sweden since 1990.[91] It is updated annually and provides information about employment, education, income, country of birth, place of residence, parental countries of birth, and educational status.

Cause of Death Register

The Swedish Cause of Death Register[92] contains data since 1961 and includes the cause and date of death. Since 2012, the data have been obtained from the death certificates of all individuals who died in Sweden, regardless of whether the person died in Sweden or abroad and whether or not the person was registered in Sweden. Before 2012, only deaths of individuals registered in Sweden were included in the register. The Cause of Death Register is updated annually, and the diagnoses in the register are coded according to the ICD.

Total Population Register

The Total Population Register is a national register maintained by Statistics Sweden that covers all people registered in Sweden since 1968. The register is updated continuously and provides information about places of birth and residency, civil status, migration status, and dates of birth and death.[93]

Swedish Personal Identity Number

The personal identity number is a unique 10-digit number assigned to every Swedish citizen since 1947. The number consists of the year, month, and date of birth followed by a gender-specific four-digit number. The personal identity number allows crosslinking of a large number of Swedish quality registers and is therefore an invaluable tool in medical research.[94]

Ethical Considerations

Study I–V were approved by the regional Human Research Ethics Committee in Stockholm, Sweden. Informed consent for Study II was obtained from all patients who underwent additional echocardiography. Informed consent for Study I, III, IV and V was not obtained because these were large database studies. Study VI is a systematic review and meta-analysis for which ethical approval is not necessary.

Study Design and Patient Population

The study designs and patient populations of the included studies are summarized in Table 1.

Table 1. Methodological overview of Study I to VI.

	Study I	Study II	Study III	Study IV	Study V	Study VI
Design	Observational, population-based cohort study		Observational, population-based, nationwide cohort study			Systematic review and meta-analysis
Exposure	Perimount vs. Mosaic aortic bioprosthesis	Mosaic aortic bioprosthesis	Biological vs. mechanical aortic prosthesis	Moderately reduced vs. normal renal function	Biological vs. mechanical aortic prosthesis	Bovine vs. porcine aortic valve prosthesis
Primary outcome	All-cause mortality	Long-term aortic valve hemodynamics	All-cause mortality		Incidence of PVE	All-cause mortality
Secondary outcomes	Early mortality, aortic valve reoperation, and effect of PPM on late survival	All-cause mortality; aortic valve reoperation, and rate of PPM and effect of PPM on late survival	Stroke, aortic valve reoperation, major bleeding	Early mortality, major bleeding, aortic valve reoperation, and all-cause mortality bioprosthesis vs. mechanical	Early PVE, late PVE, and all-cause mortality after PVE	-
Setting	Karolinska University Hospital			Nationwide		Austria, Canada, USA, Sweden, England and Wales
Period	2002-2010	2002-2008	1997-2013		1995-2012	1976-2013
End of follow-up	15 March 2013	1 October 2013	24 March 2014		31 December 2012	-
Statistical method	Cox regression		Cox regression, propensity-score matching	Cox regression		Meta-analysis

PVE = prosthetic valve endocarditis, PPM = prosthesis-patient mismatch.

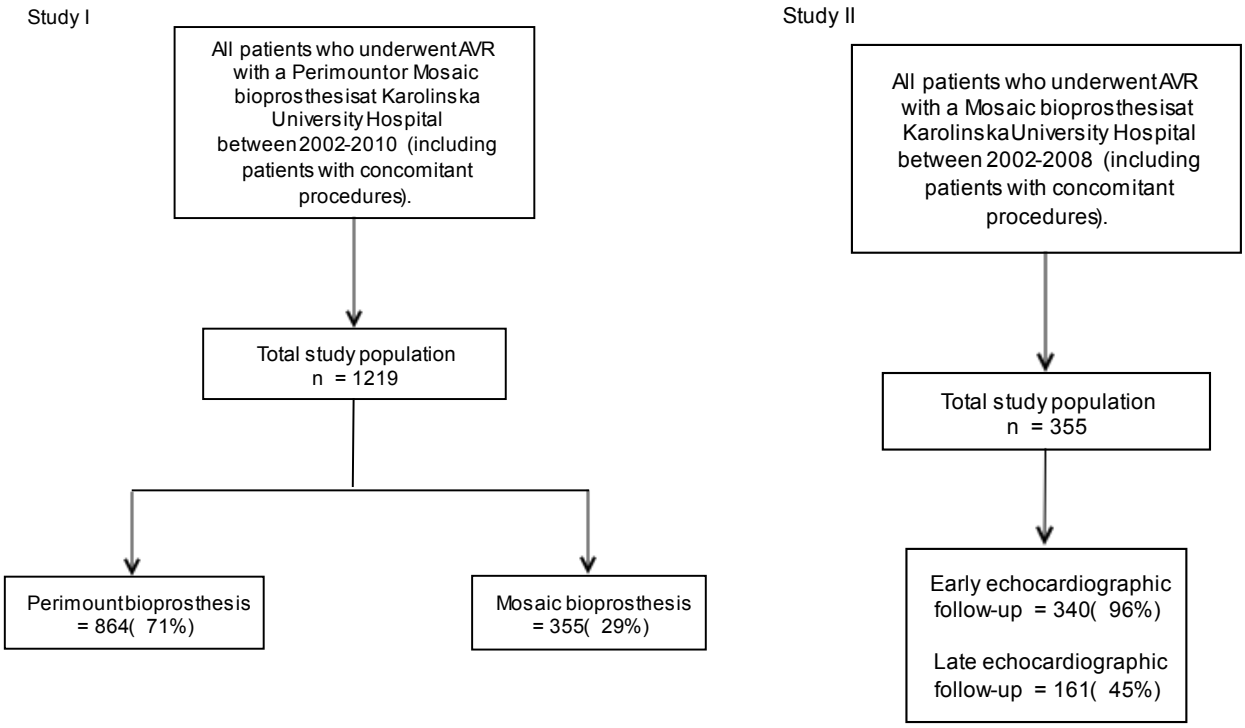

Figure 2 and 3. *Flowcharts of Study I and II.*

Study I

Study I was a population-based cohort study. We included all patients who underwent AVR and received either Perimount or Mosaic bioprostheses at Karolinska University Hospital between 2002 and 2010. As a result of institutional directives, the Mosaic valve was mainly used between 2002 and 2004, and the Perimount valve was mainly used between 2005 and 2010. The primary outcome was all-cause mortality. The secondary outcomes were early mortality, aortic valve reoperation, and the effects of PPM on late survival. A flowchart containing the inclusion and exclusion criteria is shown in Figure 2.

Study II

Study II was a descriptive, population-based cohort study. We included all patients who underwent AVR and received Mosaic bioprostheses at Karolinska University Hospital between 2002 and 2008. The primary outcome was hemodynamic function. The secondary outcomes were all-cause mortality, aortic valve reoperation, and the rate of PPM and its effects on survival. Valve hemodynamics were assessed as mean and peak pressure gradients (PPG) obtained from echocardiography. If the PPG was missing, it was calculated from the maximum transvalvular velocity according to the simplified Bernoulli equation. Early postoperative echocardiography was most commonly performed on the third day after surgery. All patients alive in August 2012 were offered

an additional transthoracic echocardiographic examination. In patients who were unwilling or unable to undergo the additional examination, information about hemodynamic function was obtained from the most recent echocardiography available in their medical records. A flowchart containing the inclusion and exclusion criteria is shown in Figure 3.

Study III

Study III was an observational, population-based, nationwide cohort study. We included all patients aged 50–69 years who underwent primary, isolated AVR with biological or mechanical prostheses in Sweden between 1997 and 2013. The primary outcome was all-cause mortality in patients who received biological versus mechanical valve prostheses. The secondary outcomes were the rates of aortic valve reoperation, stroke, major bleeding, and cardiovascular mortality. A flowchart containing the inclusion and exclusion criteria is shown in Figure 4.

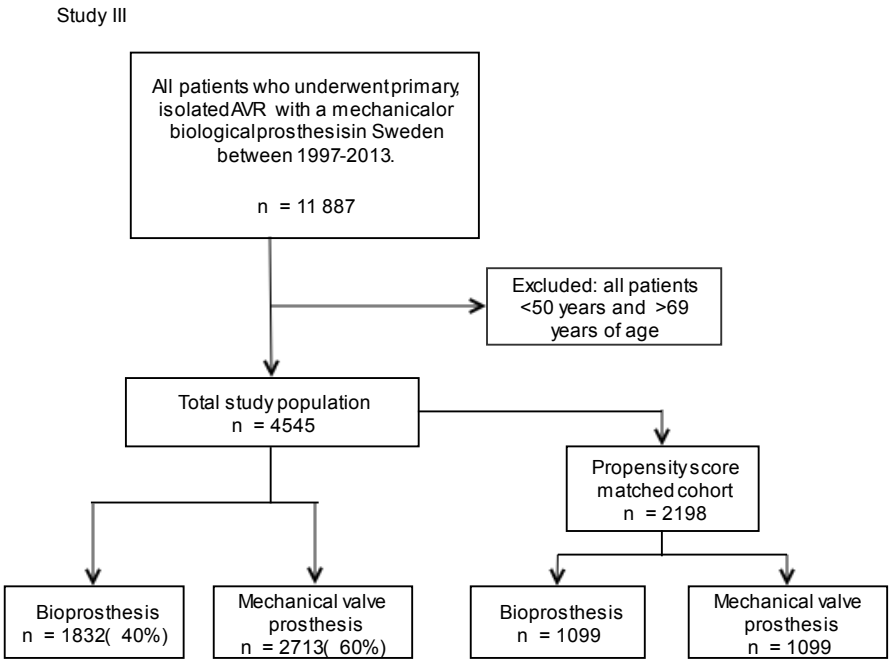

Figure 4. *Flowchart of Study III.*

Study IV

Study IV was an observational, population-based, nationwide cohort study. We included all patients who underwent primary AVR with biological or mechanical prostheses in Sweden between 1997 and 2013. Patients were divided into two groups: the normal and moderately reduced kidney function groups. The primary outcome was all-cause mortality. The secondary outcomes were early mortality, aortic valve reoperation, and major bleeding events. We also compared all-cause mortality in patients with moderately reduced kidney function who received biological versus mechanical valve prostheses. A flowchart containing the inclusion and exclusion criteria is shown in Figure 5.

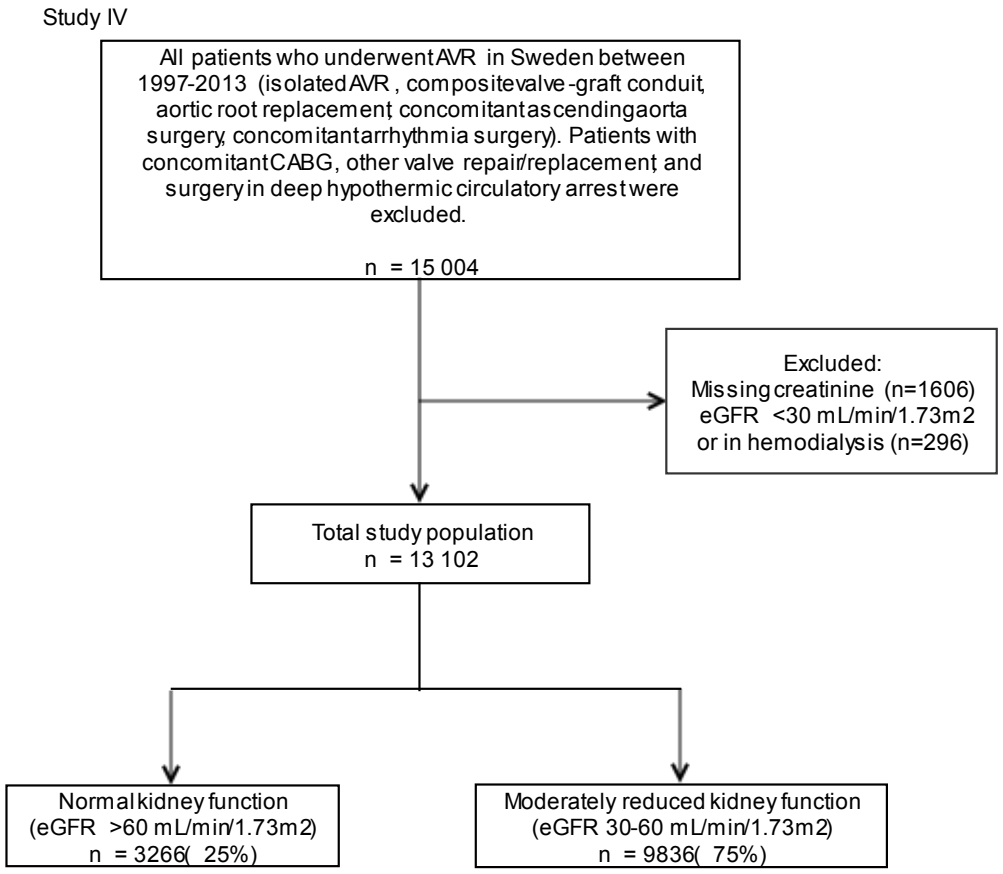

Figure 5. *Flowchart of Study IV.*

Study V

Study V was an observational, population-based, nationwide, cohort study. We included all patients who underwent AVR with biological or mechanical prostheses in Sweden between 1995 and 2012. The primary outcome was the incidence and risk of PVE in patients who received biological versus mechanical valve prostheses. The secondary outcomes were early endocarditis, late endocarditis, and all-cause mortality after PVE. A flowchart containing the inclusion and exclusion criteria is shown in Figure 6.

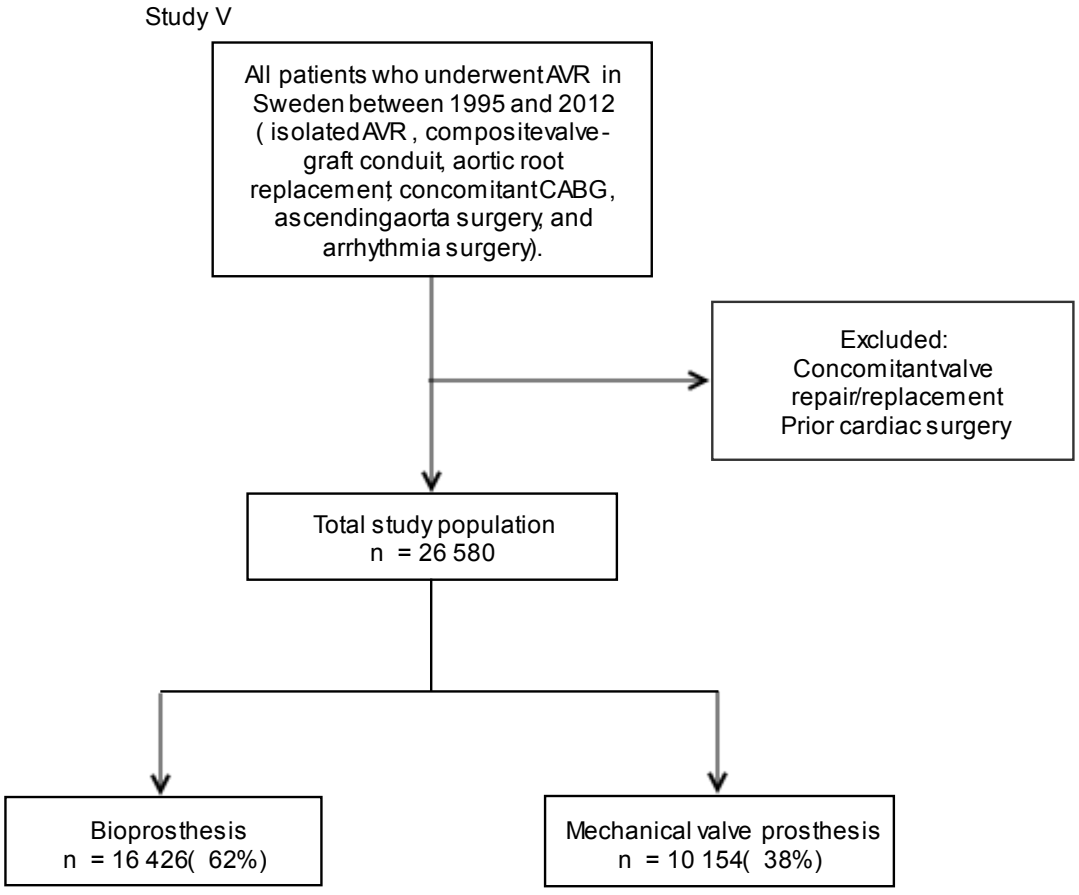

Figure 6. *Flowchart of Study V.*

Study VI

Study VI was a systematic review and meta-analysis comparing mortality after AVR with bovine versus porcine aortic valve prostheses. Quality assessment of the included studies was performed using a quality assessment tool based on relevance to our study that we created when writing the study protocol (before starting the literature search). The creation of the quality assessment tool was based on a systematic review of 86 quality assessment tools for observational studies performed by Sanderson et al.[95] A flowchart containing the inclusion and exclusion criteria is shown in Figure 7.

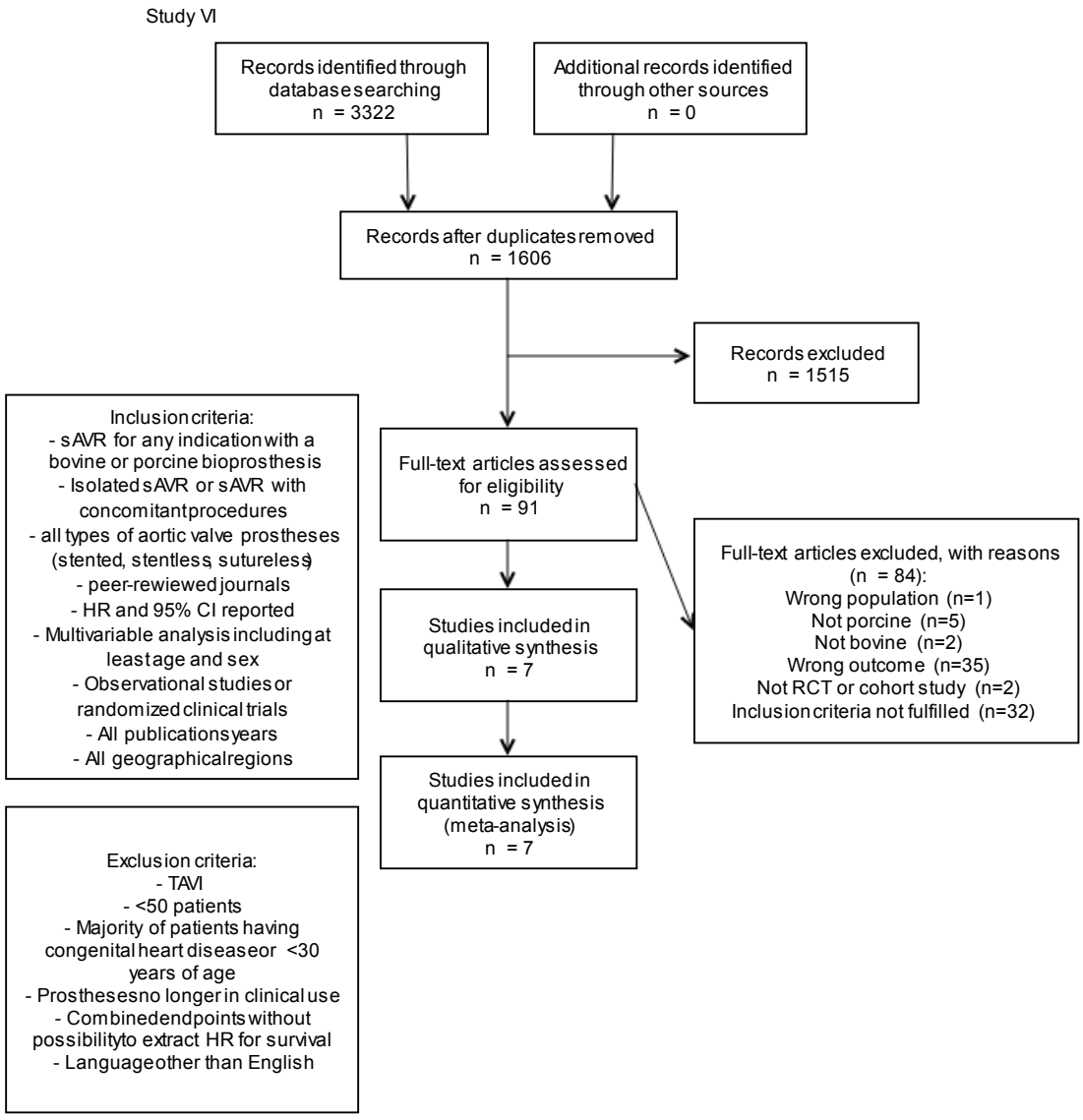

Figure 7. *Flowchart of Study VI.*

Data Collection

Study I–II

Personal identity numbers and the Total Population Register were used to obtain information about survival status. Baseline and operative characteristics were obtained from medical records. For Study II, data on early and late (for those who did not undergo additional echocardiography) hemodynamic function were obtained from medical records.

Study III–V

The study population for Study III–V was obtained from the SWEDEHEART register, which was cross-linked with other national registers to obtain further patient data. Cross-linking of the national registers was possible thanks to individual Swedish personal identity numbers. The ICD codes and national health registers used for these studies are shown in Table 2.

Study VI

A systematic literature search was performed by two professional librarians at the Karolinska Institutet University Library. Abstracts and full texts were screened by two authors (Natalie Glaser and Ulrik Sartipy), and both authors included the same articles. Data extraction from the included studies was performed by the same two authors independently. We extracted the following information from each article: first author's name, country, study design, time frame of recruitment, total number of patients, number of patients who received bovine and porcine valves, types of bovine and porcine valves, mean age of study population, statistical methods, unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CI), confounders adjusted for, and years of follow-up.

Definition and Calculation of Variables

For the data sources and ICD codes used in Study III–V, see Table 2.

All Studies

Early mortality was defined as death within 30 days after surgery. Emergent surgery was defined as surgery within 24 hours of the decision to perform surgery. The formula used to calculate body mass index (BMI) was: (weight in kg)/(length in meters^2).

Study I–II

The presence of PPM was evaluated by calculating the effective orifice area index using published in vivo measurements[1] indexed to the patient's BSA. BSA was calculated according to the Mosteller formula (BSA = $\sqrt{(((\text{height})\times\text{weight})/3600)}$).[96] Severe and

Table 2. Origin of variables and ICD codes for Study III-V.

SWEDEHEART					
Variable	**ICD-9**	**ICD-10**	**Study***		
			III	**IV**	**V**
Age			■	■	■
Gender			■	■	■
Biological valve prosthesis		FMD10	■	■	■
	3117	FMD33, FCA70		■	■
		FMD20, FMD30		■	
Mechanical valve prosthesis		FMD00	■	■	■
	3116	FCA60		■	■
Aortic valve reoperation			■	■	■
Height			■	■	■
Weight			■	■	■
Preoperative serum creatinine			■	■	■
Left ventricular ejection fraction			■	■	■
Year of surgery			■	■	■
Emergent surgery			■	■	■
Previous cardiac surgery			■	■	■
EuroSCORE				■	

LISA			
Variable	**Study***		
	III	**IV**	**V**
Civil status	■	■	■
Education	■	■	■
Region of birth	■	■	■

Cause of death Register					
Variable	**ICD-9**	**ICD-10**	**Study***		
			III	**IV**	**V**
Date of death			■	■	■
Cardiovascular death		I10 to I15.9, I20 to I25.9, I44 to I45.9 (except for I45.6 and I45.8), I46, I47.0 to I47.9, I48, I49, I50.0 to I50.9, I51.0 to I51.9 (except for I51.4), M219, R001, R008, R012, I61.0 to I61.9, I62.0, I62.9, I63.0 to I63.5, I63.8, I63.9, I64, I65.0 to I65.9, I66.0 to I66.9, I67.0, I67.2 to I67.4, I67.6, I67.8, I67.9, I70.0 to I70.9, I71.0 to I71.9, I72.0 to I72.9, I73.1, I73.8, I73.9, R960, R961	■		

Table 2. Continued.

National Patient Register					
Variable	**ICD-9**	**ICD-10**	**Study***		
			III	**IV**	**V**
Myocardial infarction	410	I21 to I21.9	■	■	■
Prior stroke at baseline	430 to 438	I60 to I69.9	■	■	■
Postoperative stroke (primary diagnosis)		I60 to I64	■		
Heart failure	428	I50 to I50.9	■	■	■
	425	I42-I43.9, I25.5, K76.1, I11.0, I13.0, I13.2	■	■	■
Atrial fibrillation	427D	I48 to I48.9	■	■	■
Chronic obstructive pulmonary disease	490 to 496	J44 to J44.9	■	■	■
Hypertension	401 to 405	I10 to I15.9	■	■	■
Hyperlipidemia	272	E78 to E78.9	■	■	■
Peripheral vascular disease	440 to 446	I65 to I65.9, I71 to I71.9, I73.8, I73.9	■	■	■
Alcohol abuse	291, 303, 571	F10 to F10.9, K70 to K70.9	■	■	■
Liver disease	570 to 573	K70 to K77.9	■	■	■
Cancer	140 to 208	C00 to C97.9	■	■	■
Endocarditis	421	I33, I33.9, I38.9	■	■	
	421, 391B	I33, I38, I39	■		■
Diabetes mellitus	250	E10 to E14.9	■	■	■
Major bleeding event	285B, 430, 431, 432, 456A, 530H, 531A, 531C, 531E, 531G, 532A, 532C, 532E, 532G, 533A, 533C, 533E, 533G, 534A, 534C, 534E, 534G, 569D, 578	D629, I60, I61, I62, I850, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K625, K920, K921, K922, I312, I230, J942, K661, M250, N421, N501A, N938, N939, N950, R041, R042, R048, R049, R31	■	■	■
Prior percutaneous coronary intervention	3080	FNG00-FNG06	■	■	■
Drug abuse	304	F11-F16, F18-F19			■
Cardiac implantable electronic device	3093-3097, 3157, 3170, V45A, V53D	FPE00, FPE10, FPE20, FPE26, FPF00, FPF10, FPF20, FPG10, FPG20, FPD30, FPG33, Z45.0			■

*Variables used in Study III-V marked with dark grey color.

moderate PPM were defined as effective orifice area index ≤0.65 cm^2/m^2 and ≤0.85 cm^2/m^2, respectively. eGFR was calculated according to the Modification of Diet in Renal Disease formula (eGFR=(preoperative creatinine value/88.4)−1.154×age−0.203×0.742 if female).[97] Acute kidney injury was defined as a serum creatinine value after surgery of 26 mmol/L or more than that before surgery. Urgent surgery was defined as surgery within the same hospitalization period as the decision to perform surgery.

In Study II, severe and moderate aortic stenosis were defined as MPG >40 mmHg and 25–40 mmHg, respectively.

Study III–V

eGFR was calculated according to the CKD-EPI formula and the most recent preoperative creatinine value:[85]

Women with creatinine ≤62 μmol/L: $(144+22 \text{ if black})\times(\text{creatinine}/0.7)^{-0.329}\times0.993^{\text{age}}$

Women with creatinine >62 μmol/L: $(144+22 \text{ if black})\times(\text{creatinine}/0.7)^{-1.209}\times0.993^{\text{age}}$

Men with creatinine ≤80 μmol/L: $(141+22 \text{ if black})\times(\text{creatinine}/0.9)^{-0.411}\times0.993^{\text{age}}$

Men with creatinine >80 μmol/L: $(141+22 \text{ if black})\times(\text{creatinine}/0.9)^{-1.209}\times0.993^{\text{age}}$

In Study IV, normal kidney function was defined as eGFR above 60 mL/min/1.73m^2, and moderately reduced kidney function (corresponding to CKD stage III) was defined as eGFR 30–60 mL/min/1.73m^2.

In Study V, PVE was defined as first-time hospitalization for infective endocarditis. Early endocarditis was defined as first-time hospitalization for endocarditis more than 90 days after surgery (to avoid including patients who underwent AVR because of endocarditis) and less than one year after surgery. Late endocarditis was defined as first-time hospitalization for infective endocarditis more than one year after surgery.

Statistical Analysis

Baseline characteristics were presented as proportions for categorical variables and as means and standard deviations (SD) for continuous variables in all studies.

Data management and statistical analysis were performed using Stata (StataCorp LP College Station, TX, USA) version 12.1 (Study I), version 13.1 (Study II and III), version 14.1 (Study IV), and version 14.2 (Study V and VI) and R (R Foundation for Statistical Computing, Vienna, Austria) version 3.0.2 (Study II), version 3.1.2 (Study III), version 3.3.0 (Study IV), and version 3.3.2 (Study V).

Cox Proportional Hazard Regression

Cox regression was used in Study I–V to assess the association between exposure and outcome. The Cox proportional hazard model is a regression technique that allows for

univariate and multivariable adjustment while accounting for time-to-event. This method also includes information from censored patients (i.e., patients who were lost to follow-up) and patients who had not experienced the event of interest by the end of follow-up.[98] Cox regression gives us the HR, which can be interpreted as the risk of having an event at each given time point. A Kaplan-Meier curve is commonly used to illustrate the proportion of patients in each group who have not yet experienced the event of interest at each time point.

Competing Risks

A competing risk is an event that eliminates an individual's risk associated with the event of interest. For example, if the event of interest is aortic valve reoperation, and the patient dies, he or she can no longer go through a reoperation (i.e., death is a competing risk of aortic valve reoperation). The proportional hazards model of subdistribution proposed by Fine and Gray[99] can account for competing risks and gives us the subdistribution HR (sHR), which is the risk of the event of interest at each given time point while accounting for competing risks.

Propensity Scores

Propensity methods can be used in nonrandomized, observational studies where patients who receive one treatment are different from those who receive another treatment (a bias called "confounding by indication").[100] For example, in our studies, older patients with more comorbidities are more likely to receive bioprostheses, whereas younger, healthier patients are more likely to receive mechanical valve prostheses. A propensity score of 0–1 is calculated based on patient characteristics to estimate the probability of receiving the treatment of interest. The propensity score can be used in different ways to obtain more comparable groups and hence reduce the risk of confounding by indication.

Multiple Imputation

Multiple imputation is a method to handle missing data. With this method, a missing variable for one patient is replaced with a value that is generated many times and then combined into one specific value. This specific value is estimated based on the assumption that data are missing at random (i.e., that the missing data are related to the observed data) and therefore can be estimated based on the observed data. Multiple imputation is advantageous because it allows for the analysis to retain statistical power and reduces selection bias resulting from not analyzing the results from patients with missing data. In Study III–V, we used multiple imputation by chained equations[101] to handle missing data. We imputed and combined 25 datasets according to Rubin's rules, and the event indicator and Nelson-Aalen estimator of the cumulative baseline hazard were included in the imputation model.[102]

Study I

Person-time was calculated as time from the date of surgery until the date of death. Patients were censored at the date of death, end of follow-up (March 15th, 2013), date of aortic valve reoperation, or date of emigration. Cox proportional hazard regression was used to assess the association between baseline characteristics, including prosthetic type, and late survival. All variables with clinical or statistical significance ($p<0.05$) were included in the multivariable analysis. The Kaplan-Meier method was used to construct survival curves. The log-rank test was used to statistically assess differences in survival between patients who received Perimount and Mosaic prostheses. Information was missing for the following variables that were included in the multivariable analysis: left ventricular ejection fraction (LVEF; 2.5%), BMI and BSA (4%), and acute kidney injury (3%). The missing data were handled by assuming that patients with missing LVEF had normal LVEF and replacing missing BMI and BSA values with the mean BMI and BSA values, respectively, for male and female patients in our cohort.

Study II

The follow-up period for late hemodynamic function was counted from the date of surgery until the date of the most recent available echocardiography. The Kaplan-Meier method was used to construct survival curves, and the log-rank test was used to statistically assess differences in survival between patients with no, moderate, and severe PPM and between patients with no and moderate or severe aortic stenosis. Cox proportional hazard regression was used to analyze the association between baseline characteristics, PPM and MPG, and late survival. Patients contributed patient-time from the date of surgery until the date of death, date of aortic valve reoperation, or end of follow-up (October 1st, 2013). Information was missing for the following variables that were included in the multivariable analysis: eGFR (5%), LVEF (4%), acute kidney injury (5%), and MPG (15%). The cumulative incidence of aortic valve reoperation was estimated using a model proposed by Fine and Gray[99] to account for the competing risk of death.

Study III

Follow-up for all-cause mortality ended on March 24th, 2014. For the secondary outcome measures of stroke, major bleeding event, and cardiovascular death, follow-up ended on December 31st, 2012, because information about these variables was only available until that date. Therefore, patients who underwent surgery during 2012 and 2013 were excluded from the secondary outcome analyses. The Kaplan-Meier method was used to calculate cumulative survival and construct survival curves. Crude incidence rates and 95% CIs were calculated. To reduce the effects of confounding by indication, a propensity score-matched cohort was constructed in addition to the overall cohort. To construct the propensity scores, we used logistic regression including all variables in Table 6 (including hospital; see Results) as independent variables and

prosthesis type as the dependent variable. Separate models that did not include variables with missing data were constructed to maximize the number of included variables for each patient. We matched patients 1:1 with the nearest neighbor and applied a caliper width of 0.2×SD of the logit of the propensity score, which reduces the measured confounding by about 99%.[100] Standardized differences were used to assess the balance between the groups post-matching, with a standard difference of less than 10% considered negligible. In both the propensity score-matched and overall cohorts, Cox proportional hazards regression was used to estimate the association between valve type and mortality. For the propensity score-matched cohort, robust standard errors that allowed for intragroup correlation were used, and the model was stratified by year of surgery and hospital. BMI was modeled according to a restricted cubic spline model, and age was represented as a continuous variable, whereas all other variables were included as categorical variables. We also performed separate analyses in patients aged 50–59 years and 60–69 years, as well as in patients who underwent AVR before 2006. For the overall cohort, unadjusted and multivariable-adjusted models were analyzed. In the multivariable analysis, we included all variables in Table 6 (see Results) and stratified by year of surgery and hospital. We also performed analyzes on the overall cohort including the propensity score using both the multivariable model and a separate model stratified into propensity score quintiles. To account for the competing risk of death, the model proposed by Fine and Gray[99] was used to calculate the sHR and 95% CI and graphically assess the cumulative incidence of the secondary outcomes. Multiple imputation by chained equations[101] was used to handle the following missing data: eGFR (12%), LVEF (31%), and BMI (14%). We included 27 variables in the imputation model.

Study IV

Follow-up for all-cause mortality ended on March 24th, 2014. Follow-up for major bleeding events and aortic valve reoperation ended on December 31st, 2012, and December 31st, 2013, respectively, because information about these variables was only available until those dates. Cox proportional hazards regression was used to analyze the association between all-cause mortality and kidney function, and the association was expressed as HR and 95% CI. Crude incidence rates and 95% CI were also calculated. The Kaplan-Meier method was used to calculate cumulative survival and construct survival curves. All variables in Table 9 (see Results) were included in the multivariable analysis, and the model was stratified by hospital and year of surgery. To account for the competing risk of death, the sHR and 95% CI were calculated using the proportional hazards model of Fine and Gray[99] to estimate the association between kidney function and secondary outcomes. In the analysis that compared patients with moderately reduced kidney function who received bioprostheses versus mechanical valve prostheses, a propensity score-matched cohort was constructed by the same method as in Study III. The logistic regression used to calculate each patient's propensity score

included all variables in Table 9 (including hospital; see Results). BMI and age were included according to a restricted cubic spline model, and all other variables were represented as categorical variables. Multiple imputation by chained equations[101] was used to handle the following missing data: LVEF (24%) and BMI (7%). The imputation model included all variables in Table 9 (See Results).

Study V

Person-time was calculated from the date of surgery until the date of diagnosis of PVE, death, or end of follow-up (December 31st, 2012, for PVE and March 24th, 2014, for death). Crude incidence rates and 95% CIs were calculated. To account for the competing risk of death, the cumulative incidence function was used to graph the absolute risk of PVE using the proportional hazards model of Fine and Gray.[99] Cox proportional hazard regression was used to estimate the relative risk of PVE and mortality after PVE and was reported as HR and 95% CI. The Cox models were stratified by calendar year of surgery and hospital. Univariable analyses, age- and gender-adjusted analyses, and multivariable models including all variables in Table 11 (including year of surgery; see Results) were performed. Age and BMI were included according to a restricted cubic spline model, and all other variables were included as categorical variables. We also performed separate analyses restricted to patients in the following categories: age >60 years, surgery performed after 2003, excluding patients with a cardiac implantable electronic device, and excluding patients with a history of drug abuse. Multiple imputation by chained equations[101] was used to handle the following missing data: eGFR (15.9%), LVEF (39.9%), and BMI (17.5%). The imputation model included 34 variables.

Study VI

The random-effects model was used to obtain the pooled HR and 95% CI values. HRs were converted so that porcine prostheses were the reference category in all studies. The most completely adjusted analysis was used. Cochrane's Q test and the I^2 test were used to explore signs of heterogeneity. The results of the I^2 test were used to categorize heterogeneity as low (<50%), moderate (50%–75%), and high (>75%).[103] Cochrane's Q-test was considered significant if $p<0.10$. To evaluate the influence of each article on the overall effect size, one article at a time was omitted in a sensitivity analysis. A funnel plot was created to assess the influence of publication bias by both visual and statistical tests (Begg and Mazumdar's[104] and Egger's[105] tests).

RESULTS

The characteristics of the studies included in this thesis are summarized in Table 3.

Table 3. Characteristics of Study I–VI.

	Study I	Study II	Study III
Number of patients	1219	355	4545
Exposure group	Mosaic bioprosthesis n = 355 (29%)	Mosaic bioprosthesis n = 355	Bioprosthesis n = 1832 (40%)
Comparison group	Perimount bioprosthesis n = 864 (71%)	-	Mechanical valve prosthesis n = 2713 (60%)
Follow-up in years, mean (maximum)	4.9 (11.1)	6.2 (11.5)	7.3 (17.2)
	Study IV	**Study V**	**Study VI**
Number of patients	13 102	26 580	49 190
Exposure group	Moderately reduced kidney function n = 3266 (25%)	Bioprosthesis n = 16 426 (62%)	Bovine prosthesis n = 32 235 (66%)
Comparison group	Normal kidney function n = 9836 (75%)	Mechanical valve prosthesis n = 10 154 (38%)	Porcine prosthesis n = 16 955 (34%)
Follow-up in years, mean (maximum)	6.2 (17.2)	6.2 (18.0)	3.6–7.4 (10.3-24.0)

Study I

Study Population

We included all 1219 patients who underwent AVR at Karolinska University Hospital between 2002 and 2010. Of these, 864 (71%) and 355 (29%) patients received Perimount and Mosaic bioprostheses, respectively. The yearly numbers of implanted prostheses are shown in Figure 8. The baseline characteristics (Table 4) and implanted prosthetic sizes were similar between the groups.

Survival

The 1-, 5-, and 8-year survival rates were 93%, 78%, and 63% in the Perimount group and 92%, 80%, and 57% in the Mosaic group, respectively. There was no difference in all-cause mortality between the groups in the unadjusted (HR 1.00, 95% CI 0.80–1.26) or multivariable-adjusted (HR 0.85, 95% CI 0.65–1.11) analyses. The unadjusted

survival curve is shown in Figure 9. Early mortality was similar between the groups (3.7% vs. 4.8%, p=0.381).

Secondary Objectives

In total, 11 and 10 patients in the Perimount and Mosaic groups, respectively, required aortic valve reoperation (either surgical AVR or valve-in-valve TAVI) during follow-up. There was no statistically significant association between valve type and reoperation (p=0.745). Severe PPM was found in 48 (15%) and 47 (6%) patients in the Mosaic and Perimount groups, respectively (p<0.001). There was no significant association between severe PPM and long-term survival, either overall or in patients with depressed LVEF.

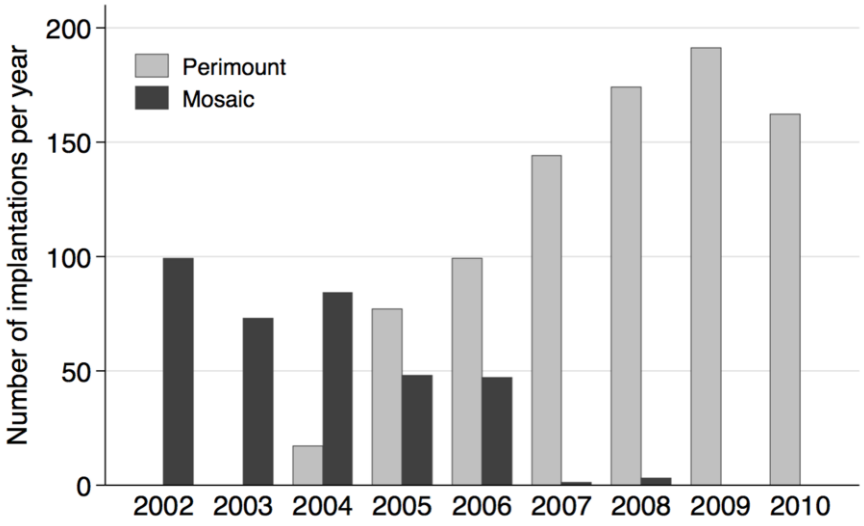

Figure 8. *Number of patients who underwent aortic valve replacement with a Perimount and a Mosaic valve per year.*

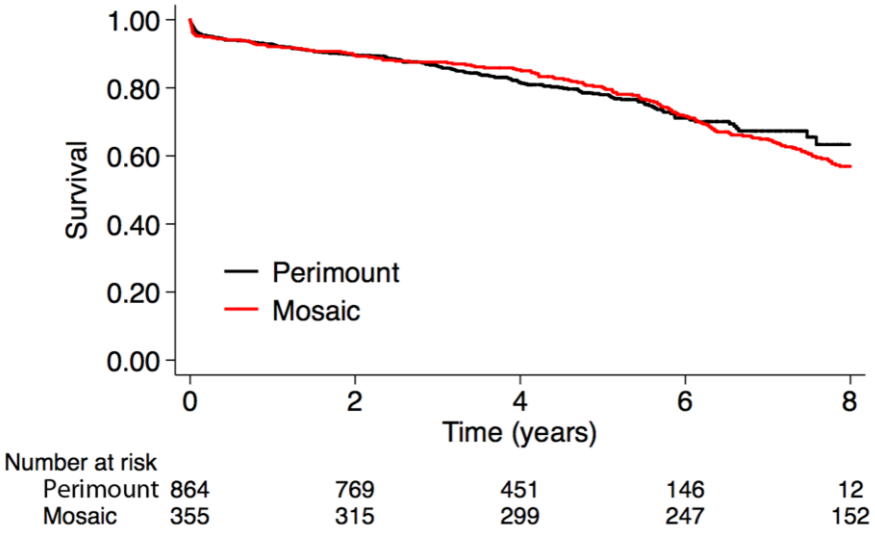

Figure 9. *Kaplan-Meier estimated unadjusted survival curve for 1219 patients who underwent aortic valve replacement with a Perimount or a Mosaic prosthesis at Karolinska University Hospital between 2002 and 2010.*

Table 4. Baseline and operative characteristics in 1219 patients who underwent aortic valve replacement with Perimount or Mosaic bioprostheses between 2002 and 2010.

	All patients	Perimount	Mosaic
Number of patients (%)	1219 (100)	864 (71)	355 (29)
Age, years (SD)	73.6 (9.6)	72.7 (9.6)	75.7 (9.4)
Female (%)	40	38	46
Body mass index (kg/cm^2)	26.2 (4.5)	26.6 (4.5)	25.1 (4.1)
eGFR (mL/min/1.73 m^2)	71 (25)	73 (24)	66 (27)
Diabetes mellitus	15	17	12
Atrial fibrillation	14	14	16
Hypertension	35	39	27
Cerebrovascular disease	13	12	15
Peripheral vascular disease	6	6	6
Chronic obstructive pulmonary disease	7	7	7
Prior percutaneous coronary intervention	6	6	4
Prior cardiac surgery	5	6	3
Left ventricular ejection fraction (%)			
>50	73	74	70
30-49	23	21	25
<30	5	4	5
Etiology of aortic valve disease			
Stenosis	84	84	84
Regurgitation	12	12	11
Stenosis and regurgitation	4	4	4
Endocarditis	4	4	3
Concomitant cardiac procedure	47	44	53
Urgency			
Elective	86	85	89
Urgent	13	14	10
Emergent	1	2	1
Aortic root enlargement	4	2	7
Acute kidney injury	33	33	31
Indexed effective orifice area			
> 0.85 (cm^2/m^2)	24	27	16
0.65 - 0.85 (cm^2/m^2)	68	67	68
<0.65 (cm^2/m^2)	8	6	15

Number of patients (%) or mean (standard deviation). eGFR = estimated glomerular filtration rate.

Study II

Study Population

We included all 355 patients who underwent AVR with a Mosaic bioprosthesis at Karolinska University Hospital between 2002 and 2008. Baseline and operative characteristics are shown in Table 5. Concomitant procedures (most often coronary artery bypass grafting) were performed in approximately half of the patients.

Hemodynamic Performance

At early echocardiography, the mean PPG of the entire cohort was 39.9 mmHg (SD 14.4), and the mean MPG was 21.1 mmHg (SD 7.7). During late echocardiography, the mean PPG was 38.6 mmHg (SD 15.6), and the mean MPG was 22.5 mmHg (SD 10.1). Early and late echocardiographic data were available for 340 (96%) and 161 (45%) patients, respectively. The mean PPG and MPG during early and late echocardiography is shown according to valve size in Figure 10. Of the patients alive in August 2012, 89 agreed to undergo additional transthoracic echocardiography, and 57 actually underwent the examination. An external cardiologist performed the additional echocardiography according to a predefined study protocol. During late echocardiography, six and 40 patients had an MPG >40 mmHg and ≥25 mmHg, corresponding to severe and moderate aortic stenosis, respectively. An MPG ≥25 mmHg was not associated with increased mortality (p = 0.702; Figure 11).

Secondary Objectives

Mortality within 30 days after surgery was 4.8%, and the unadjusted 1-, 5-, and 10-year survival rates were 92%, 79%, and 42%, respectively. In total, 10 patients (2.8%) underwent aortic valve reoperation (surgical AVR or TAVI) during follow-up. The unadjusted cumulative incidence of aortic valve reoperation at 1, 5, and 10 years was 0.3%, 1.7%, and 3.1%, respectively. Moderate and severe PPM were found in 250 (70%) and 49 (14%) patients, respectively. Moderate or severe PPM was not associated with increased mortality (p=0.194; Figure 11).

Table 5. Baseline and operative characteristics in 355 patients who underwent aortic valve replacement with Medtronic Mosaic bioprostheses between 2002 and 2008.

Number of patients (%)	355 (100)
Age, years (SD)	75.7 (9.4)
Female	46
Body mass index (kg/cm^2), mean (SD)	25.1 (4.1)
eGFR (mL/min/1.73 m^2), mean (SD)	69 (23)
Diabetes mellitus	12
Atrial fibrillation	16
Hypertension	27
Cerebrovascular disease	15
Peripheral vascular disease	6
Chronic obstructive pulmonary disease	7
Prior percutaneous coronary intervention	4
Prior cardiac surgery	3
Left ventricular ejection fraction	
>50	70
30-49	25
<30	5
Endocarditis	3
Concomitant cardiac procedure	53
Urgency	
Elective	89
Urgent	10
Emergent	1
Aortic root enlargement	7
Aortic cross clamp time, mean (SD)	78 (28)
Extracorporeal circulation, mean (SD)	109 (39)
Days in the ICU, mean	2.4
Days in the hospital, mean	8.9
Acute kidney injury	31
Acute kidney injury requiring dialysis	2.6
Indexed effective orifice area	
> 0.85 (cm^2/m^2)	16
0.65 - 0.85 (cm^2/m^2)	70
<0.65 (cm^2/m^2)	14
Early postoperative echocardiography	
Peak pressure gradient, mean mmHg (SD)	39.2 (16.3)
Mean pressure gradient, mean mmHg (SD)	22.8 (10.6)

Numbers are percentages unless otherwise stated.

SD = standard deviation, eGFR = estimated glomerular filtration rate.

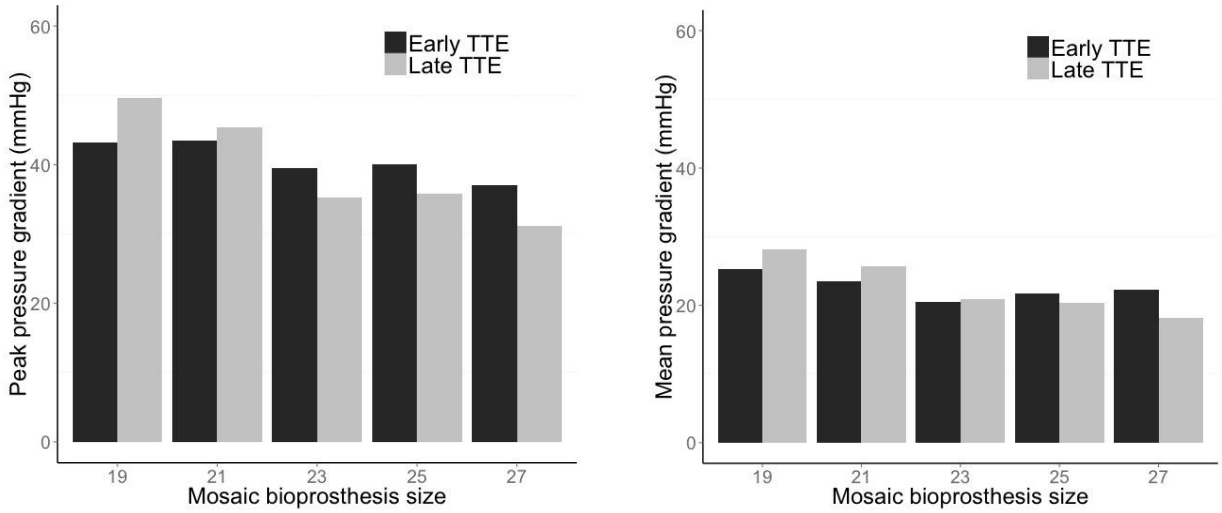

Figure 10. *The mean peak and mean pressure gradient at early and late echocardiography according to valve size.*

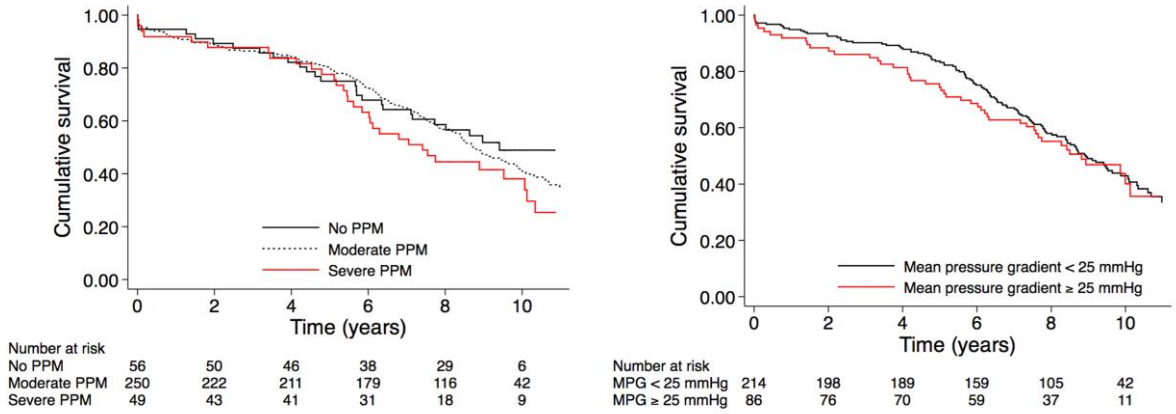

Figure 11. *Kaplan-Meier estimated unadjusted survival curve in patients who underwent aortic valve replacement with a Mosaic bioprosthesis at Karolinska University Hospital between 2002 and 2008. Patients divided by prosthesis-patient mismatch in the left-hand graph, and by mean pressure gradient at early echocardiographic follow-up in the right-hand graph.*

Study III

Study Population

We included all 4545 patients who underwent primary, isolated AVR in Sweden between 1997 and 2013. Of these, 2713 (60%) received a mechanical valve prosthesis, and 1832 (40%) received a bioprosthesis. The use of bioprostheses increased from 17% in 1997–2002 to 58% in 2006–2013, even though patient age remained similar throughout the entire study period (Figure 12). In the overall cohort, patients who received bioprostheses were generally older and had more comorbidities (Table 6). In the propensity score-matched cohort, baseline characteristics were well balanced (Table 7).

Survival

In the overall cohort, patients with mechanical valve prostheses had better survival than patients with bioprostheses had (adjusted HR 1.30, 95% CI 1.09–1.56). Analyses of the propensity score-matched cohort showed similar results (HR 1.34, 95% CI 1.09–1.66, p=0.006), as illustrated in Figure 13. The event rates and relative risks are shown in Table 8. In the propensity score-matched cohort, the 5-, 10-, and 15-year survival were 92%, 79%, and 59% in the mechanical valve group and 89%, 75%, and 50% in the bioprosthetic valve group, respectively. A subgroup analysis of 574 propensity score-matched patients aged 50–59 years showed significantly higher survival rates in patients with mechanical valve prostheses (HR 1.67, 95% CI 1.06–2.61, p=0.026). In 1502 propensity score-matched patients aged 60–69 years, no difference in survival was found between the groups who received mechanical versus biological prostheses (HR 1.08, 95% CI 0.85–1.36, p=0.539).

Secondary Objectives in the Propensity Score-Matched Cohort

There was no difference in the rate of stroke or cardiovascular mortality between patients who received mechanical and biological prostheses (sHR 1.04, 95% CI 0.72–1.50; and sHR 1.00, 95% CI 0.67–1.50, respectively). The risk of aortic valve reoperation was higher (sHR 2.36, 95% CI 1.42–3.94), but the risk of major bleeding events was lower (sHR 0.49, 95% CI 0.34–0.70), in patients who received bioprostheses compared with those who received mechanical valve prostheses. The cumulative incidence rates of the secondary outcomes are illustrated in Figure 14.

Table 6. Baseline characteristics in 4545 patients aged 50-69 who underwent aortic valve replacement with mechanical or biological aortic valve prostheses between 1997 and 2013.

	All patients (N = 4545)	Mechanical prosthesis (N = 2713)	Biological prosthesis (N = 1832)	Standardized difference (%)	p-value
Age, years, mean (SD)	61.4 (5.3)	59.9 (5.1)	63.7 (4.7)	77	<0.001
Female sex	1487 (32.7%)	848 (31.3%)	639 (34.9%)	7.7	0.011
Civil status					
Not married or cohabiting	1723 (37.9%)	993 (36.6%)	730 (39.8%)	6.7	0.028
Education					0.12
>12 years	971 (21.7%)	551 (20.7%)	420 (23.3%)	6.2	
Region of birth					
Non-Nordic countries	290 (6.4%)	167 (6.2%)	123 (6.7%)	2.3	0.45
Body mass index (kg/cm^2), mean (SD)	27.2 (4.7)	27.2 (4.6)	27.1 (4.7)	1.6	0.63
Diabetes mellitus	557 (12.3%)	265 (9.8%)	292 (15.9%)	18.5	<0.001
Atrial fibrillation	389 (8.6%)	237 (8.7%)	152 (8.3%)	1.6	0.60
Hypertension	925 (20.4%)	450 (16.6%)	475 (25.9%)	23.0	<0.001
Hyperlipidemia	376 (8.3%)	202 (7.4%)	174 (9.5%)	7.4	0.014
Stroke	269 (5.9%)	135 (5.0%)	134 (7.3%)	9.7	0.001
Peripheral vascular disease	168 (3.7%)	83 (3.1%)	85 (4.6%)	8.2	0.006
Chronic pulmonary disease	306 (6.7%)	137 (5.0%)	169 (9.2%)	16.3	<0.001
Prior myocardial infarction	275 (6.1%)	151 (5.6%)	124 (6.8%)	5.0	0.095
Prior PCI	110 (2.4%)	43 (1.6%)	67 (3.7%)	13.0	<0.001
Prior major bleeding event	175 (3.9%)	66 (2.4%)	109 (5.9%)	17.6	<0.001
Alcohol dependency	154 (3.4%)	54 (2.0%)	100 (5.5%)	18.4	<0.001
Liver disease	68 (1.5%)	26 (1.0%)	42 (2.3%)	10.6	<0.001
Cancer	256 (5.6%)	110 (4.1%)	146 (8.0%)	16.5	<0.001
eGFR (mL/min/1.73 m^2)					0.006
>60	3392 (84.3%)	1990 (85.8%)	1402 (82.3%)	9.8	
<15*	60 (1.5%)	24 (1.0%)	36 (2.1%)	8.7	
Heart failure	633 (13.9%)	376 (13.9%)	257 (14.0%)	0.5	0.87
Left ventricular ejection fraction					0.59
>50 %	2441 (77.5%)	1204 (76.9%)	1237 (78.0%)	2.7	
Endocarditis	357 (7.9%)	199 (7.3%)	158 (8.6%)	4.8	0.11
Emergent surgery	81 (1.8%)	35 (1.3%)	46 (2.5%)	8.9	0.002
Year of surgery					<0.001

Data are n (%) unless otherwise noted. *This category includes patients on preoperative dialysis
eGFR = estimated glomerular filtration rate, PCI = percutaneous coronary intervention, SD = standard deviation.

Table 7. Baseline characteristics after propensity score matching in 2198 patients aged 50-69 who underwent AVR with mechanical or biological aortic valve prostheses between 1997 and 2013.

	Mechanical prosthesis (N = 1099)	Biological prosthesis (N = 1099)	Standardized difference (%)	P Value
Age, years, mean (SD)	62.3 (4.5)	62.1 (5.1)	3.3	0.44
Female sex	380 (34.6%)	352 (32.0%)	5.4	0.21
Civil status				
Not married or cohabiting	421 (38.3%)	426 (38.8%)	0.9	0.83
Education				0.89
>12 years	233 (21.2%)	233 (21.2%)	0.0	
Region of birth				
Non-Nordic countries	69 (6.3%)	75 (6.8%)	2.2	0.60
Body mass index (kg/cm^2), mean (SD)	27.2 (4.8)	27.1 (4.9)	2.1	0.64
Diabetes mellitus	146 (13.3%)	147 (13.4%)	0.3	0.95
Atrial fibrillation	89 (8.1%)	108 (9.8%)	6.1	0.16
Hypertension	242 (22.0%)	236 (21.5%)	1.3	0.76
Hyperlipidemia	101 (9.2%)	95 (8.6%)	1.9	0.65
Stroke	60 (5.5%)	70 (6.4%)	3.9	0.37
Peripheral vascular disease	42 (3.8%)	37 (3.4%)	2.4	0.57
Chronic pulmonary disease	69 (6.3%)	74 (6.7%)	1.8	0.67
Prior myocardial infarction	60 (5.5%)	68 (6.2%)	3.1	0.47
Prior PCI	29 (2.6%)	18 (1.6%)	6.9	0.10
Prior major bleeding event	33 (3.0%)	44 (4.0%)	5.4	0.20
Alcohol dependency	39 (3.5%)	51 (4.6%)	5.5	0.20
Liver disease	13 (1.2%)	19 (1.7%)	4.6	0.29
Cancer	61 (5.6%)	57 (5.2%)	1.6	0.71
eGFR (mL/min/1.73 m^2)				0.81
>60	842 (83.9%)	848 (83.2%)	1.7	
<15*	11 (1.1%)	13 (1.3%)	1.7	
Heart failure	141 (12.8%)	165 (15.0%)	6.3	0.14
Left ventricular ejection fraction				0.91
>50 %	656 (78.5%)	674 (77.6%)	2.0	
Endocarditis	92 (8.4%)	98 (8.9%)	1.9	0.65
Emergent surgery	21 (1.9%)	21 (1.9%)	0.0	1.00
Year of surgery				0.88

Data are n (%) unless otherwise noted. *This category includes patients on preoperative dialysis eGFR = estimated glomerular filtration rate; PCI = percutaneous coronary intervention, SD = standard deviation.

Table 8. Event rates and relative risks for all-cause mortality in patients aged 50-69 who underwent aortic valve replacement with a mechanical or a biological aortic valve prosthesis.

	Mechanical			Biological		
	Events/ PY	Crude rate (95% CI) per 1000 PY	HR (95% CI)	Events/PY	Crude rate (95% CI) per 1000 PY	HR (95% CI)
Propensity score matched cohort n = 2198	180/ 7324	25 (21-28)	1.00	217/7099	31 (27-35)	1.34 (1.09-1.66)
Overall cohort n = 4545	527/ 23826	22 (20-24)		289/9163	32 (28-35)	
Unadjusted			1.00			1.67 (1.44-1.94)
Multivariable adjusted model*			1.00			1.30 (1.09-1.56)
Multivariable adjusted + PS			1.00			1.32 (1.10-1.58)
Multivariable adjusted + stratified based on PS quintiles			1.00			1.32 (1.07-1.62)

PS = propensity score, PY = person-years, CI = confidence interval, HR = hazard ratio.
*Multivariable adjustment was made for all variables in Table 6.

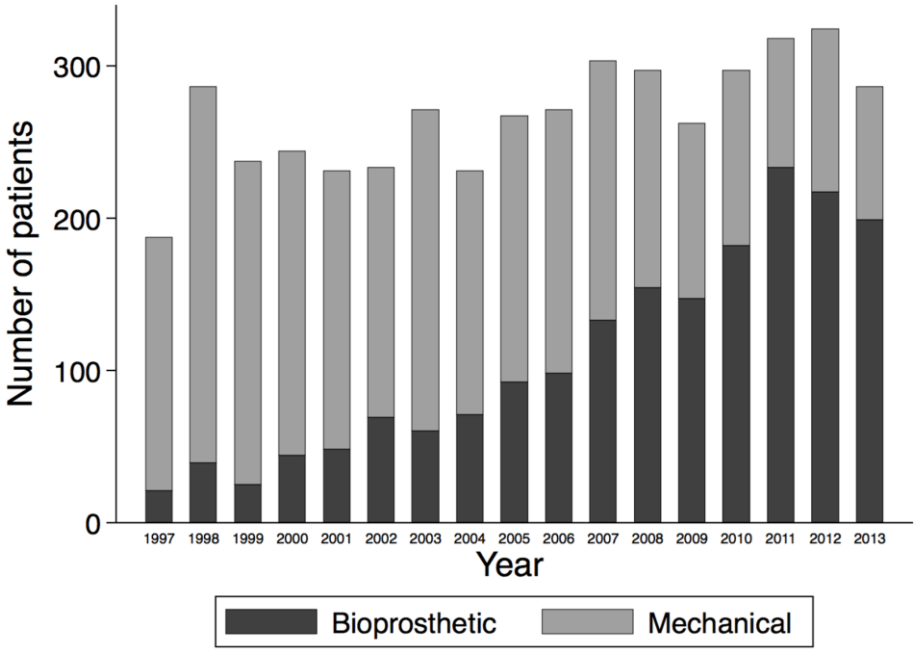

Figure 12. *Number of patients aged 50–69 years who underwent aortic valve replacement with bioprosthetic or mechanical valves in Sweden per year.*

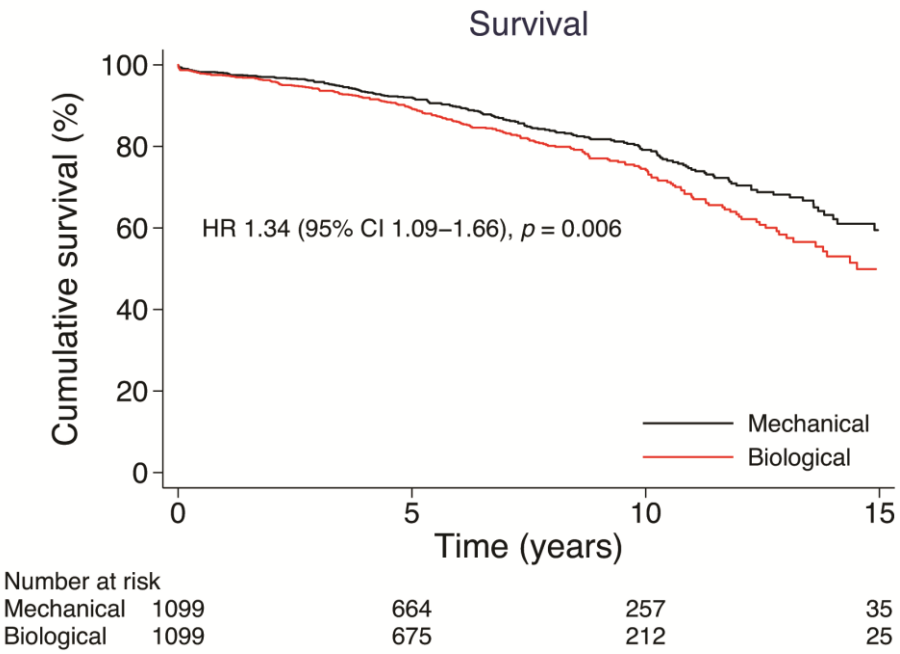

Figure 13. *Kaplan-Meier estimated survival curve in propensity score-matched patients aged 50–69 years who underwent aortic valve replacement in Sweden between 1997 and 2013.*

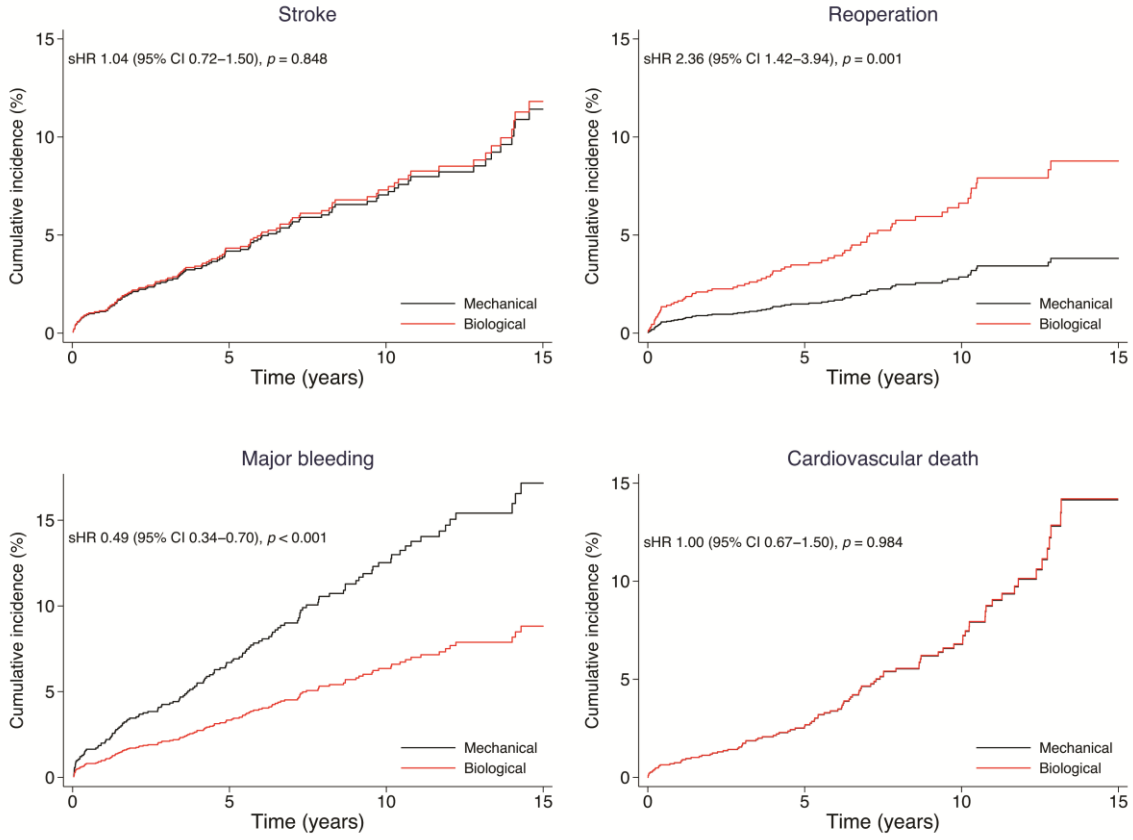

Figure 14. *Cumulative incidence of stroke, aortic valve reoperation, major bleeding events, and cardiovascular death in propensity score–matched patients aged 50–69 years who underwent aortic valve replacement with mechanical versus biological valve prostheses.*

Study IV

Study Population

We included all 13 102 patients with available preoperative creatinine values and eGFR >30 mL/min/1.73m^2 who underwent primary AVR in Sweden between 1997 and 2013. Of these, 9836 (75%) had normal kidney function, and 3266 (25%) had moderately reduced kidney function. Of the patients with moderately reduced kidney function, 2582 (79%) received bioprostheses and 684 (21%) received mechanical valve prostheses. Patients with moderately reduced kidney function were generally older and had more comorbidities (Table 9). In the propensity score-matched analysis of patients with moderately reduced kidney function who received bioprostheses versus mechanical valve prostheses, the baseline characteristics were well balanced.

Survival

The 5-, 10-, and 15-year survival rates were 89%, 73%, and 55% in patients with normal kidney function and 76%, 48%, and 25% in patients with moderately reduced kidney function, respectively. Patients with normal kidney function had significantly better survival than patients with moderately reduced kidney function had (adjusted HR 1.28, 95% CI 1.18–1.38, p<0.001). The event rates and relative risks are shown in Table 10. The unadjusted Kaplan-Meier estimated survival curves for both groups are shown in Figure 15. Early mortality was 1.23% and 3.52% in patients with normal and moderately reduced kidney function, respectively (HR 1.87, 95% CI 1.39–2.51).

Secondary Objectives

The multivariable analysis showed a nonsignificantly higher risk of major bleeding events (sHR 1.18, 95% CI 1.00–1.39, p = 0.051) and a lower risk of aortic valve reoperation (sHR 0.54, 95% CI 0.38–0.79, p=0.001) in patients with moderately reduced kidney function. The cumulative incidence of major bleeding events and aortic valve reoperation are shown in Figure 16. In 3266 patients with moderately reduced kidney function, the multivariable analysis showed no difference in all-cause mortality between those who received biological versus mechanical valve prostheses (HR 0.86, 95% CI 0.73–1.01). Analysis of a propensity score-matched cohort of 480 patient-pairs also showed no such difference (HR 0.85, 95% CI 0.70–1.03). The Kaplan-Meier estimated survival curve for the propensity score-matched cohort is shown in Figure 17.

Table 9. Baseline characteristics in 13 102 patients with moderately reduced or normal kidney function who underwent aortic valve replacement in Sweden between 1997 and 2013.

	All patients n = 13 102	**Normal kidney function n = 9836 (75%)**	**Moderately reduced kidney function n = 3266 (25%)**
Age, years, mean (SD)	66.8 (12.9)	64.3 (13.1)	74.4 (8.5)
Female sex	5222 (39.9%)	3441 (35.0%)	1781 (54.5%)
Civil status: Not married or cohabiting	5251 (40.1%)	3956 (40.2%)	1295 (39.7%)
Education >12 years	2413 (18.4%)	1979 (20.1%)	434 (13.3%)
Region of birth: Non-Nordic countries	769 (5.9%)	610 (6.2%)	159 (4.9%)
Body mass index (kg/cm^2), mean (SD)	26.7 (4.5)	26.7 (4.5)	26.8 (4.7)
Biological valve prosthesis	8258 (63.0%)	5676 (57.7%)	2582 (79.1%)
Diabetes mellitus	1713 (13.1%)	1164 (11.8%)	549 (16.8%)
Atrial fibrillation	1850 (14.1%)	1151 (11.7%)	699 (21.4%)
Hypertension	3210 (24.5%)	2142 (21.8%)	1068 (32.7%)
Hyperlipidemia	1061 (8.1%)	782 (8.0%)	279 (8.5%)
Stroke	1131 (8.6%)	769 (7.8%)	362 (11.1%)
Peripheral vascular disease	1076 (8.2%)	805 (8.2%)	271 (8.3%)
Chronic pulmonary disease	992 (7.6%)	705 (7.2%)	287 (8.8%)
Prior myocardial infarction	906 (6.9%)	569 (5.8%)	337 (10.3%)
Prior PCI	515 (3.9%)	350 (3.6%)	165 (5.1%)
Prior major bleeding event	620 (4.7%)	406 (4.1%)	214 (6.6%)
Alcohol dependency	272 (2.1%)	223 (2.3%)	49 (1.5%)
Liver disease	115 (0.9%)	83 (0.8%)	32 (1.0%)
Cancer	930 (7.1%)	622 (6.3%)	308 (9.4%)
eGFR (mL/min/1.73 m^2)			
45 to 60	2377 (18.1%)	-	2377 (72.8%)
30 to 45	889 (6.8%)	-	889 (27.2%)
Heart failure	2176 (16.6%)	1284 (13.1%)	892 (27.3%)
Left ventricular ejection fraction >50	7564 (76.3%)	5979 (77.7%)	1585 (71.3%)
Endocarditis	720 (5.5%)	565 (5.7%)	155 (4.7%)
Emergent surgery	215 (1.6%)	162 (1.6%)	53 (1.6%)
Isolated AVR	10869 (83.0%)	7934 (80.7%)	2935 (89.9%)
Year of surgery: 2007 to 2013	6748 (51.5%)	5413 (55.0%)	1335 (40.9%)

Data are n (%) unless otherwise noted.
SD = standard deviation, PCI = percutaneous coronary intervention, eGFR = estimated glomerular filtration rate.

Table 10. Event rates and relative risks for all-cause mortality in patients with normal and moderately reduced kidney function who underwent AVR in Sweden between 1997 and 2013.

	Normal kidney function			Moderately reduced kidney function		
	Events/ PY	Crude rate (95% CI) per 1000 PY	HR (95% CI)	Events /PY	Crude rate (95% CI) per 1000 PY	HR (95% CI)
All-cause mortality	1890/ 61814	31 (29-32)		1422/ 20057	71 (67-75)	
Unadjusted			1.00			2.51 (2.34-2.70)
Adjusted for age			1.00			1.38 (1.28-1.49)
Multivariable adjusted model*			1.00			1.28 (1.18-1.38)

PY = person-years, CI = confidence interval, HR = hazard ratio, eGFR = estimated glomerular filtration rate. *The multivariable model included all variables in Table 9.

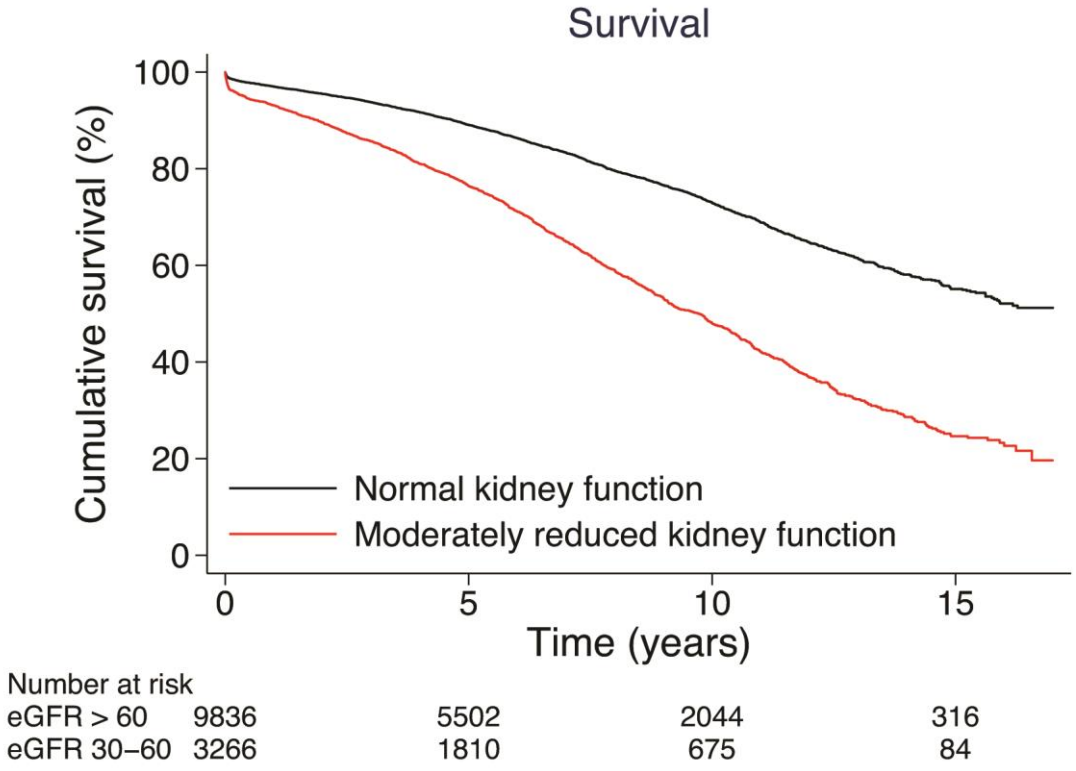

Figure 15. *Kaplan-Meier estimated unadjusted survival in 13 102 patients with moderately reduced or normal kidney function who underwent aortic valve replacement in Sweden between 1997 and 2013.*

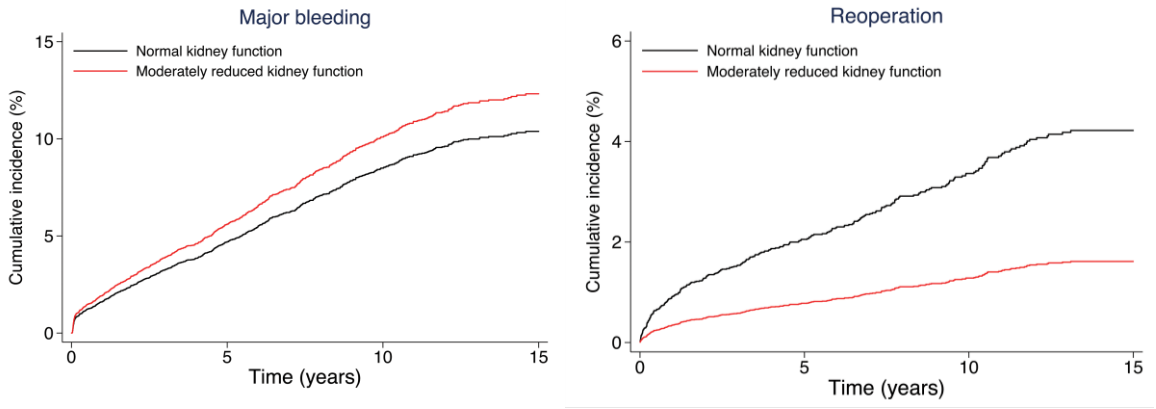

Figure 16. *Cumulative incidence of major bleeding (left) and aortic valve reoperation (right) in 13 102 patients with moderately reduced or normal kidney function who underwent aortic valve replacement in Sweden between 1997 and 2013.*

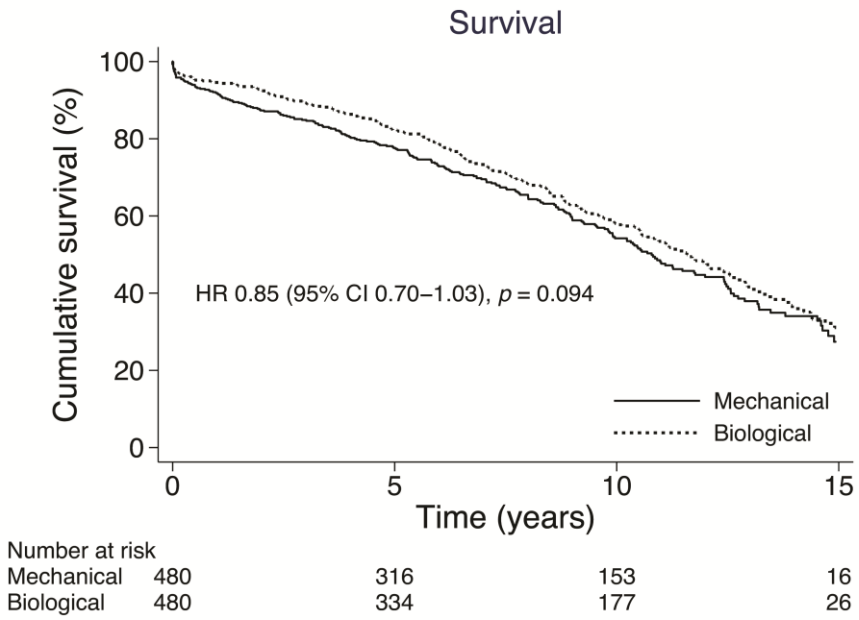

Figure 17. *Kaplan-Meier estimated survival in 960 propensity score-matched patients with moderately reduced kidney function who underwent aortic valve replacement and received biological or mechanical prostheses in Sweden between 1997 and 2013.*

Study V

Study Population

We included all 26 580 patients who underwent primary AVR in Sweden between 1995 and 2012. Of these, 16 426 (62%) received biological valve prostheses, and 10 154 (38%) received mechanical valve prostheses. The yearly numbers of implanted valve prostheses is shown in Figure 18. The use of biological valve prostheses increased during the study period. Baseline characteristics according to prosthesis type are shown in Table 11.

Prosthetic Valve Endocarditis

In total, 940 (3.5%) patients were hospitalized for infective endocarditis during follow-up. During the total follow-up time, the incidence rate of PVE was 0.57% (95% CI 0.54–0.61) per person-year. Among patients with biological and mechanical valve prostheses, 574 (3.5%) and 366 (3.6%) were hospitalized for PVE, respectively. The risks of both early and late PVE were higher in patients with bioprostheses (adjusted HR 1.54, 95% CI 1.31–1.74). Separate analyses in patients aged >60 years, patients who had surgery after 2003, all patients excluding those with cardiac implantable electronic devices, and all patients excluding those with a history of drug abuse showed similar results. The event rates, incidence rates, and relative risks of PVE are shown in Table 12. The cumulative incidence of PVE according to the type of valve prosthesis is shown in Figure 19. Other factors associated with an increased risk of PVE were male sex, concomitant surgical procedures, diabetes mellitus, a cardiac implantable electronic device, drug abuse, peripheral vascular disease, CKD stage 5, surgery for infective endocarditis and emergent surgery.

Mortality after Prosthetic Valve Endocarditis

Of the 940 patients hospitalized for PVE, 377 of 574 (66%) and 186 of 366 (51%) patients in the biological and mechanical valve groups died during follow-up, respectively. Cumulative survival rates after PVE are shown in Figure 20. In the unadjusted analysis, the risk of death after PVE was higher in patients with bioprostheses (HR 1.64, 95% CI 1.37–1.96, p<0.001). In the multivariable-adjusted analysis, there was no difference in the risk of death after PVE between the two types of prostheses (HR 1.01, 95% CI 0.76–1.34, p=0.952). Of 940 patients hospitalized for PVE, 108 (12%) underwent an aortic valve reoperation. Of these 108 patients, 13 (12%) died within 30 days. Among the 832 patients who were treated conservatively, 140 (17%) died within 30 days after the initial diagnosis of PVE. There was no statistically significant difference in 30-day mortality between those who underwent surgery and those who were treated conservatively.

Table 11. Baseline characteristics in 26 580 patients who underwent AVR with mechanical or biological aortic valve prostheses in Sweden between 1995 and 2012.

	All patients N = 26 580	**Mechanical valve prosthesis N = 10 154 (38%)**	**Biological valve prosthesis N = 16 426 (62%)**
Age, years, mean (SD)	69.1 (11.8)	61.0 (11.7)	74.1 (8.6)
Female sex	9975 (37.5%)	3058 (30.1%)	6917 (42.1%)
Civil status: Not married or cohabiting	10958 (41.2%)	4381 (43.1%)	6577 (40.0%)
Education >12 years	3895 (14.7%)	1786 (17.6%)	2109 (12.8%)
Region of birth: Non-Nordic countries	1391 (5.2%)	643 (6.3%)	748 (4.6%)
Body mass index, mean (SD)	26.6 (4.4)	26.9 (4.5)	26.5 (4.4)
Cardiac implantable electronic device	667 (2.5%)	202 (2.0%)	465 (2.8%)
Drug abuse	98 (0.4%)	38 (0.4%)	60 (0.4%)
Diabetes mellitus	4117 (15.5%)	1172 (11.5%)	2945 (17.9%)
Atrial fibrillation	3967 (14.9%)	1348 (13.3%)	2619 (15.9%)
Hypertension	6308 (23.7%)	1548 (15.2%)	4760 (29.0%)
Hyperlipidemia	2377 (8.9%)	689 (6.8%)	1688 (10.3%)
Stroke	2435 (9.2%)	674 (6.6%)	1761 (10.7%)
Peripheral vascular disease	2522 (9.5%)	1044 (10.3%)	1478 (9.0%)
Chronic pulmonary disease	1909 (7.2%)	495 (4.9%)	1414 (8.6%)
Prior myocardial infarction	3752 (14.1%)	1004 (9.9%)	2748 (16.7%)
Prior PCI	1993 (7.5%)	843 (8.3%)	1150 (7.0%)
Prior major bleeding event	1340 (5.0%)	284 (2.8%)	1056 (6.4%)
Alcohol dependency	457 (1.7%)	165 (1.6%)	292 (1.8%)
Liver disease	226 (0.9%)	64 (0.6%)	162 (1.0%)
Cancer	1901 (7.2%)	408 (4.0%)	1493 (9.1%)
eGFR (mL/min/1.73 m^2)			
>60	15287 (68.4%)	6209 (79.7%)	9078 (62.3%)
<15 or dialysis	228 (1.0%)	69 (0.9%)	159 (1.1%)
Heart failure	5065 (19.1%)	1639 (16.1%)	3426 (20.9%)
Left ventricular ejection fraction >50	11600 (72.6%)	3317 (74.2%)	8283 (72.0%)
Preoperative endocarditis	462 (1.7%)	244 (2.4%)	218 (1.3%)
Surgery for endocarditis	964 (3.6%)	456 (4.5%)	508 (3.1%)
Emergent surgery	541 (2.0%)	300 (3.0%)	241 (1.5%)
Isolated AVR	13383 (50.3%)	5200 (51.2%)	8183 (49.8%)

Data are n (%) unless otherwise stated. AVR = aortic valve replacement, SD = standard deviation, PCI = percutaneous coronary intervention, eGFR = estimated glomerular filtration rate.

Table 12. Event rates and risks for prosthetic valve endocarditis in 26 580 patients who underwent aortic valve replacement with a mechanical or a biological valve prosthesis in Sweden from 1995 to 2012.

	Overall cohort n = 26 580		Mechanical n = 10 154 (38%)			Biological n = 16 426 (62%)		
	Events/PY	Crude rate (95% CI) per 100 PY	Events /PY	Crude rate (95% CI) per 100 PY	HR (95% CI)	Events /PY	Crude rate (95% CI) per 100 PY	HR (95% CI)
Total follow-up time	940/ 164168	0.57 (0.54-0.61)	366/ 81345	0.45 (0.41-0.50)		574/ 82823	0.69 (0.64-0.75)	
Follow-up time (years)								
0-1	240/ 24309	0.99 (0.87-1.12)	67/ 9970	0.70 (0.55-0.89)		173/ 15659	1.17 (1.01-1.36)	
1-5	391/ 74068	0.53 (0.48-0.58)	140/ 36036	0.43 (0.37-0.51)		251/ 48497	0.60 (0.53-0.68)	
5-10	229/ 48286	0.47 (0.42-0.54)	101/ 34622	0.38 (0.31-0.46)		128/ 35178	0.59 (0.50-0.70)	
10-15	75/ 15898	0.47 (0.38-0.59)	53/ 20369	0.47 (0.36-0.61)		22/ 1938	0.49 (0.32-0.74)	
Unadjusted					1.00			1.51 (1.31-1.74)
Adjusted for age and sex					1.00			1.63 (1.37-1.94)
Multivariable adjusted model*					1.00			1.54 (1.29-1.83)

PY = person-years, CI = confidence interval, HR = hazard ratio.
*The multivariable model included all variables in Table 11.

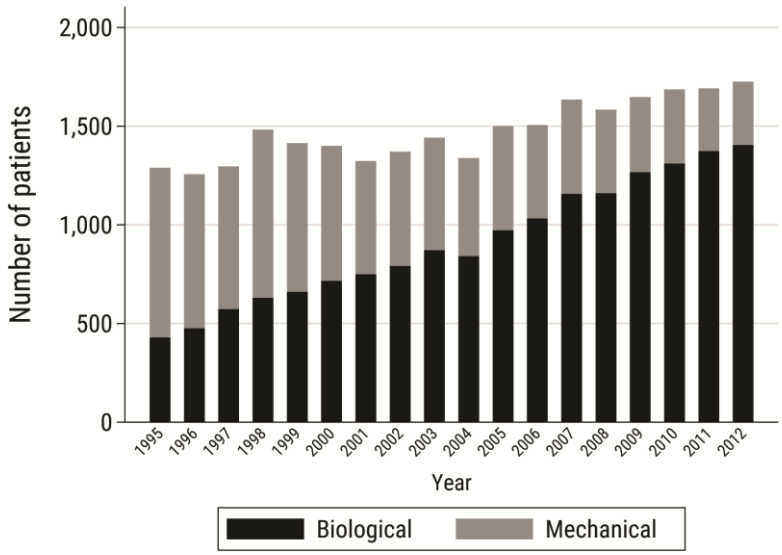

Figure 18. *Number of patients who underwent aortic valve replacement with biological or mechanical valve prostheses in Sweden between 1995 and 2012.*

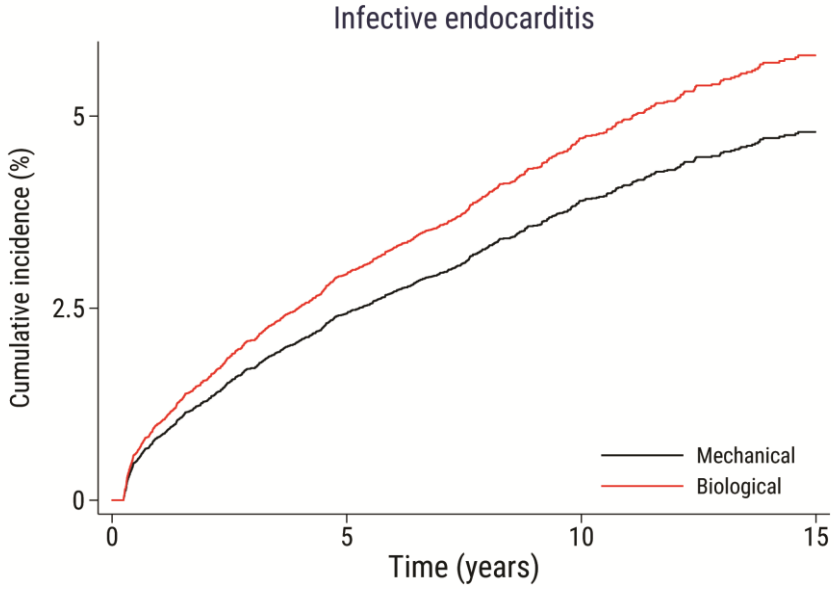

Figure 19. *Cumulative incidence of prosthetic valve endocarditis in 26 580 patients who underwent aortic valve replacement with biological or mechanical valve prostheses in Sweden between 1995 and 2012.*

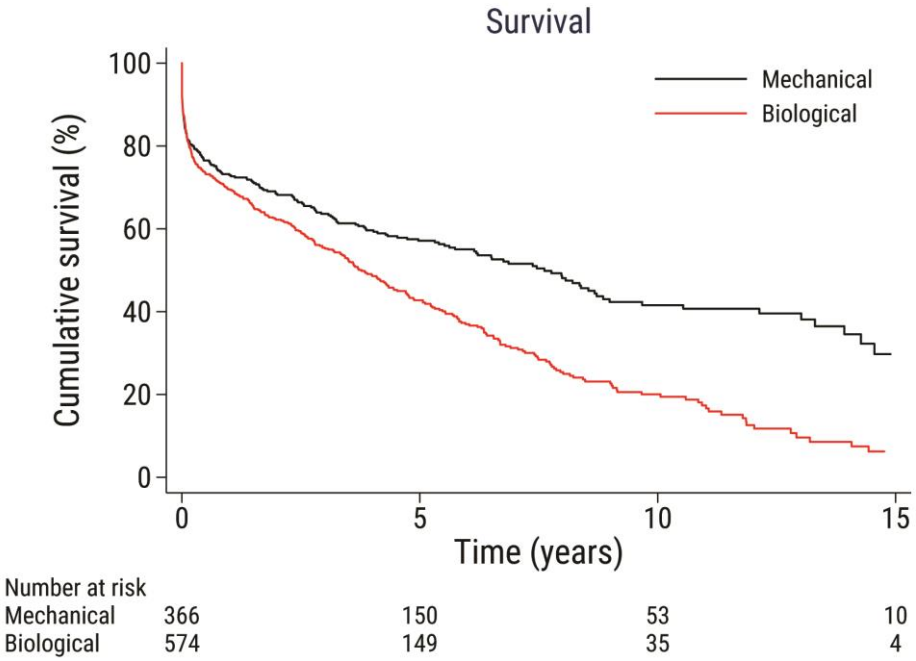

Figure 20. *Cumulative survival in 940 patients with prosthetic valve endocarditis after aortic valve replacement with biological versus mechanical valve prostheses.*

Study VI

After exclusion of 1599 articles that did not meet the inclusion criteria, seven articles were included. The flow diagram is shown in Figure 7 (see Methods), and selected characteristics of the included studies are shown in Table 13. In total, the included articles comprised 49 190 patients, of which 32 235 (66%) and 16 955 (34%) received bovine and porcine prostheses, respectively. In the meta–analysis, there was no significant difference in survival between the groups (pooled HR 1.00, 95% CI 0.92–1.09), as illustrated in Figure 21.

Table 13. Characteristics of included studies.

Source	Country and Publication year	Study period	Total number of patients (pericardial/porcine)	Mean follow-up time in years (pericardial/porcine)
Andreas	Austria 2015	2002-2008	458 (295/163)	6.0 (NA/NA)
Chan	Canada 2010	1990-2007	1659 (638/1021)	5.0 (3.9/5.6)
Ganapathi	USA 2015	1980-2013	2010 (1411/599)	5.4 (5.3/5.7)
Glaser	Sweden 2014	2002-2010	1219 (864/355)	NA (4.2/6.9)
Grunkemeier	USA 2012	1976-2010	2825 (2356/469)	NA (4.9/7.4)
Hickey	England and Wales 2015	2003-2013	38040 (24695/13345)	3.6 (median)
Said	USA 2012	1993-2007	2979 (1976/1003)	5.2 (5.2/5.1)

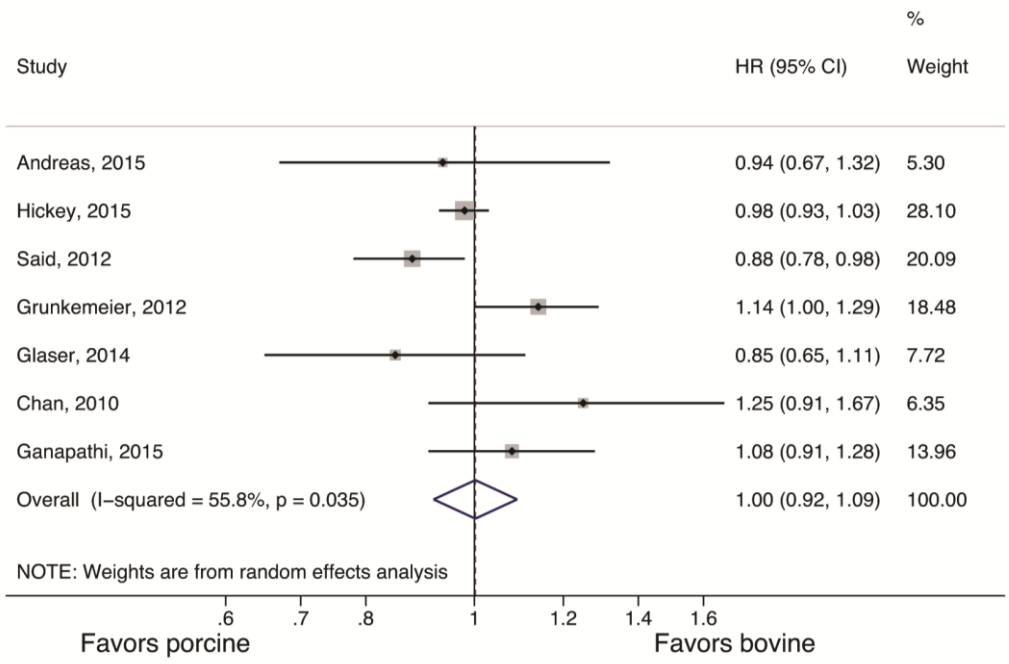

Figure 21. *Forest plot showing mortality after aortic valve replacement with bovine compared to porcine valve prostheses.*

DISCUSSION

Study I–II

Survival and Aortic Valve Reoperation

In Study I, we found no differences in mortality or rate of aortic valve reoperation after AVR between Perimount and Mosaic bioprostheses. Studies primarily analyzing mortality and the rate of reoperation after AVR using these two prostheses are scarce. However, our results are consistent with other studies which investigated long-term mortality and rate of reoperation after AVR with bovine versus porcine aortic valve prostheses.[56,57]

Because of institutional directives, the two types of bioprostheses analyzed in our study were implanted mainly during different time periods, which might have influenced the results. However, pre-, peri-, and postoperative care were all similar throughout the entire study period, and therefore, it is unlikely that this would have affected the results. There is a current trend towards operating on older patients with more comorbidities than previously, and therefore, it could be hypothesized that the groups were not comparable. In that case, the patients in the Perimount group, who received the prostheses later, should have been older and sicker than the patients in the Mosaic group. However, this was not the case as the mean ages were 75.7 and 72.7 years in the Mosaic and Perimount groups, respectively. We adjusted for age and some other smaller between-group differences using multivariable regression methods. Because prosthetic valve selection was influenced by institutional directives rather than surgeon's preference, the risk for confounding by indication (i.e., that patients in one group were different from patients in the other group), is less likely.

In general, bioprostheses have satisfactory durability for at least 10 years, especially when implanted in older patients.[58,61] It is therefore possible that the mean follow-up of 4.9 years (maximum 11.1) was not long enough to detect between-group differences. However, six cases of early valvular dysfunction requiring reoperation have been reported with the Mosaic bioprosthesis,[65,66] and therefore, even studies with shorter follow-up times are of interest.

Hemodynamic Function

In Study II, we found that patients who underwent AVR with Mosaic bioprostheses had acceptable long-term hemodynamic function. Some previous studies found that patients who underwent AVR with Mosaic bioprostheses had higher transvalvular gradients compared with patients who received other aortic bioprostheses.[4,106] In our study, during late echocardiography, 34% of the study population had MPG ≥25 mmHg, corresponding to moderate or severe aortic stenosis. Increased transvalvular gradients

did not lead to higher mortality in our study population. It is possible that higher postoperative transvalvular gradients could have had other effects, such as lower functional status or even lower quality of life. Because we did not study these outcomes, this is only speculation that remains to be analyzed in future studies.

Prosthesis–Patient Mismatch

We found a higher prevalence of PPM in patients who received Mosaic than Perimount prostheses. Even if PPM is considered to be correlated with survival,[31,32] this was not the case in our study population. However, it is possible that our study was underpowered to show such an association.

Clinical Implications

Study I was an observational study, and therefore, the aim was to analyze a possible association, not to prove causation. Study II may be used for hypothesis generation, as its primary outcome was entirely descriptive. Nevertheless, our results are consistent with those of several previous studies, which increase the likelihood of a causal effect, especially concerning patients' similar survival with Perimount and Mosaic bioprostheses. Our results support both valve types as acceptable options for AVR. However, the increased postoperative transvalvular gradients and rate of PPM in the Mosaic group warrant further investigation, preferably with larger study cohorts and longer follow-up.

Study III

In Study III, we found that patients aged 50–69 years had better long-term survival after AVR with mechanical compared with biological valve prostheses. The optimal prosthesis type for middle-aged patients has been widely debated. The risk of aortic valve reoperation caused by bioprosthetic degeneration needs to be balanced against the increased risk of bleeding associated with mechanical valves and the necessary warfarin treatment. The few RCTs that have investigated whether biological or mechanical valves are better for middle-aged patients have been limited by non-contemporaneous and small patient cohorts.[107-109] Patient preference is of the utmost importance in the choice of valve type for each patient. Therefore, it will be difficult to perform an RCT in this patient group without substantial risk for selection bias. Therefore, large, real-world observational studies of this patient group are important. Previous observational studies have however reported contradictory results.[70-72,110]

Chiang et al. performed an observational study of 4253 patients aged 50–69 years living in New York State who underwent isolated AVR with biological or mechanical valves.[72] They found no between-group differences in all-cause, long-term mortality or rate of stroke. The rate of aortic valve reoperation was higher in patients with biological valves, and the rate of major bleeding events was higher in patients with mechanical valves.

They concluded that bioprostheses might be a reasonable choice for patients as young as 50 years. In our study, which was performed in a similar way as the study by Chiang et al.[72] but in the Swedish population, we found that patients with mechanical valves had better long-term survival than that of patients with biological valves. However, the two studies should be compared with caution because of their different study cohorts. The time within the therapeutic INR-range for patients treated with warfarin in Sweden has been shown to be high,[111] which might improve the outcome of patients with mechanical valves. This is one possible explanation for the differences between our study and the study by Chiang et al. Goldstone et al.[110] found that the survival benefit for patients with mechanical aortic valves compared with bioprostheses persisted until 55 years of age. They also found a higher risk of major bleeding events and a lower risk of aortic valve reoperation with mechanical valves, which was consistent with our study and the one by Chiang et al.[72] Interestingly, in the 45–54 years age group, they found a higher risk of stroke in patients with mechanical valves. Unfortunately, they did not analyze all-cause survival in patients aged 50–69 years.

The increased use of bioprostheses has been justified partly by valve-in-valve TAVI as an alternative to surgical AVR in patients with degenerated bioprostheses, which may improve outcomes in patients with bioprostheses. However, the long-term durability of TAVI bioprostheses remains uncertain. Furthermore, in patients with certain anatomic variations (e.g., limited vascular access, bicuspid aortic valves, low take-off of the coronary arteries), and in patients having undergone surgical AVR with a small-sized prosthesis or valve-in-valve TAVI, it is not certain whether TAVI can be safely performed. Moreover, the newer generation On-X aortic mechanical valve allows for lower INR targets[50] than conventional mechanical valves do. Further, self-monitoring and self-management of oral anticoagulation and telemedicine-guided dosing of oral anticoagulation have been shown to decrease thromboembolic events and allow for lower INR targets.[112,113] This might decrease the risk of major bleeding events associated with higher INR targets and therefore improve outcomes in patients with mechanical valves.

Clinical Implications

The exact age cutoff for recommending biological or mechanical aortic valves remains controversial. No studies have found a survival benefit for middle-aged patients who received biological aortic valves, whereas several studies, including ours, found that patients with mechanical valves have better survival. These results are important because, during the last decade, bioprostheses have been increasingly used in all age groups,[68,110] despite a lack of convincing scientific evidence to support this trend. Our study contributes to the existing knowledge about outcomes after AVR in patients aged 50–69 years. This information can be used to guide prosthesis selection in middle-aged patients.

Study IV

Survival

In Study IV, we found a 28% higher long-term risk of death after AVR in patients with moderately reduced compared with normal kidney function. Several previous studies have found substantially worse survival after AVR in patients with ESRD.[75,76] Even if moderately reduced kidney function affected as many as one-quarter of the patients who underwent AVR in our study, only a few studies have evaluated survival after AVR in these patients.[84,114] Furthermore, most of these previous studies included patients with concomitant coronary artery bypass grafting, which might yield different results. Patients with coronary artery disease often have generalized atherosclerosis, which might affect the renal vasculature. Therefore, it is possible that these patients' CKD has a different etiology than that of patients without coronary artery disease. Moreover, some of these studies used creatinine as an indicator of kidney function.[75,115] Several factors influence the creatinine value, and therefore, eGFR is considered a better indicator of kidney function.[82,83]

Aortic Valve Reoperation

The risk of SVD in patients with moderately reduced kidney function is not known, but patients with ESRD are believed to have a higher risk of SVD than patients with normal kidney function have.[80] Interestingly, we found a 62% lower risk of aortic valve reoperation in patients with moderately reduced compared with normal kidney function. It is possible that patients with moderately reduced kidney function were considered to have excessive operative risk and therefore did not undergo reoperation even if SVD had occurred.

Major Bleeding Events

Patients with renal failure have susceptibility to coagulation disorders that is believed to be caused by a complex interaction between platelet defects, the coagulation cascade, the fibrinolytic system, and platelet-vessel wall interaction defects.[116] It is not known at what stage of renal failure these coagulation disorders start. Previous studies have found a higher risk of major bleeding events after AVR in patients with ESRD.[80] In line with these results, we found a higher risk of bleeding events after AVR in patients with moderately reduced kidney function, but this difference did not reach statistical significance (HR 1.18, 95% CI 1.03–1.39, p=0.051).

Survival in Patients with Moderately Reduced Kidney Function

Patients with ESRD have a higher risk of both bleeding events and SVD after AVR, and therefore, it has been debated whether these patients benefit from biological or mechanical valve prostheses.[117,118] We did not find a difference in survival between patients with moderately reduced kidney function who received biological versus

mechanical valve prostheses. However, these results should be interpreted with caution because of the small numbers of patients and events.

Clinical Implications

Our results provide knowledge about outcomes after AVR in patients with moderately reduced kidney function. The results can be used for preoperative risk stratification and reference when designing future studies. Given the pessimistic prognosis after AVR in patients with moderately reduced kidney function, it is important with careful observation of these patients after surgery.

Study V

Prosthetic Valve Endocarditis

In Study V, we found a yearly PVE rate of 0.57%. The incidence was highest during the first year after surgery and thereafter remained stable during follow-up. PVE was more common in patients who received bioprostheses compared to those who received mechanical valve prostheses. Previous studies of patients who underwent surgical AVR have reported a cumulative incidence of PVE of approximately 3% at 12 months.[119,120] These studies were however performed during the 1970s, which limits their generalizability to contemporary patients. A more recent study found an incidence rate of 0.7% per person-year after AVR.[121] Regueiro et al.[122] reported a yearly PVE rate of 1.1% in patients after TAVI, and similar incidence rates have been reported after mitral valve replacement.[123]

According to the European Society of Cardiology's guidelines for the management of infective endocarditis[39], there is no difference in PVE rates between patients who receive mechanical compared with biological valves. However, there are no references to support this statement. Brennan et al.[124] performed a cohort study of 39 199 patients aged 65–80 years who underwent AVR in 605 hospital centers in the United States from 1991 to 1999. Their primary endpoint was all-cause mortality, but they also reported a higher risk of PVE in patients with biological compared with mechanical valve prostheses (HR 1.60, 95% CI 1.31–1.94), which is in line with our results. They found a 1.8% cumulative incidence rate of PVE 10 years after AVR. The cumulative incidence rate of PVE in our study was 0.47% at 10 years. Because Brennan et al.[124] only included patients until 1999, and because their study population was older than ours, it is difficult to compare the results directly. A nationwide study of the Danish population performed by Østergaard et al. also found that patients with bioprostheses had higher risk of PVE than patients with mechanical valves after AVR.[121] A small number of previous studies found no difference in PVE risk between biological and mechanical valves.[70,108,125] However, these studies were limited by non-contemporary, small patient cohorts and small numbers of events.

Biological valve prostheses are expected to calcify gradually throughout a patient's life. It is possible that the gradual degeneration of bioprostheses makes them susceptible to bacterial implantation and infection. Two previous studies found a higher incidence of PVE in patients with mechanical valves during the early follow-up period, and a higher risk of PVE in patients with biological valves during late follow-up,[120,126] which strengthens this theory. However, we found a higher risk of PVE in patients with biological valve prostheses in both the early and late follow-up periods.

Mortality after Prosthetic Valve Endocarditis

The reported short-term mortality ranges from 6%–12% in patients with native valve infective endocarditis[40,127,128] and from 12%–23% in patients with PVE.[40,45,127,128] The previously reported short-term mortality after PVE is consistent with our findings, which showed a 30-day mortality after PVE of 12%–17% depending on treatment. In contrast to prior studies,[129] we did not find a difference in mortality between patients who underwent surgery for PVE and those who were treated conservatively. However, these results should be interpreted with caution because of the small number of patients who underwent surgery for PVE in our study.

Clinical Implications

Our study provides a robust estimation of PVE incidence after AVR. The results extend the existing knowledge about possible complications after AVR with biological and mechanical valves. This study has direct clinical implications because it can facilitate diagnosis of PVE and prosthetic choice in selected patients. Furthermore, the numbers provided can function as reference values when designing future studies.

Study VI

In Study VI, we found no difference in long-term survival between patients who underwent AVR with bovine compared to porcine bioprostheses. Yap et al. performed a systematic review of articles comparing bovine and porcine aortic valve prostheses in 2013.[130] They found that bovine prostheses had advantageous hemodynamics compared with porcine prostheses, but they found no difference in survival between the two groups. However, none of the articles we included in our systematic review and meta-analysis were included in the study by Yap et al.[130]

In line with previous studies,[56,57] we found no difference in survival between patients who underwent AVR with bovine versus porcine bioprostheses. Initially, we also wanted to compare the rate of aortic valve reoperations and the prevalence of PPM. However, the small number of eligible articles and difficulties finding comparable articles required that we limit our study to survival. One of the included articles in our study found slightly better survival in patients with porcine prostheses, whereas the remaining six articles found no statistically significant between-group differences in

survival. One study that did not report HR, and therefore was not included in our study, reported a survival benefit for patients with bovine prostheses.[4] Our study does not prove causality, and thus, the question of whether survival is the same after AVR with bovine and porcine prostheses cannot be entirely answered by our study. However, when summarizing the available evidence, the superior hemodynamics, higher degree of left ventricular mass regression, and the lower frequency of PPM previously reported with bovine prostheses[4,131] do not seem to translate into better survival. However, whether bovine prostheses lead to higher rates of aortic valve reoperations, lower functional status, or lower quality of life remains unknown.

Clinical Implications

This study contributes to the existing knowledge about different types of aortic valve bioprostheses by summarizing the scientific evidence in the field. The results can be used as quality indicators, and they suggest that both bovine and porcine bioprostheses are good alternatives for AVR.

Strengths and Limitations

Methodological Considerations

All studies were observational studies except Study VI, which was a systematic review and meta-analysis. However, even Study VI has the disadvantages that come with observational studies because all the included studies in the systematic review and meta-analysis were themselves observational. First, observational studies can prove only association rather than causality. Second, group allocation is not random in observational studies, and therefore, it is likely that the groups are different at baseline. In Study I–V, we used multivariable regression models to adjust for differences in baseline characteristics between the groups. In Study III–IV, we also used propensity score methods to further account for these differences. Nevertheless, in observational studies, there is always a risk of residual confounding (i.e., that some factors were unknown or unmeasured and therefore could not be adjusted for).

Another type of inevitable error that can be present in all study designs is random error. Random error reflects the role of chance. The smaller the study size, the larger the risk of random error. In Study III–V, the study populations were large, and there were many events, which decreases the risk of random errors. However, large sample sizes are associated with smaller detectable differences, and therefore, it is important to consider clinically significant differences rather than statistically significant differences.

Study I–V were population-based, meaning that all eligible patients that lived in a specific region were included in the study. In population-based cohort studies, the risk of selection bias (i.e., that the people included in the study are different from those not included in the study) is smaller than if only a sample of the population is included in

the study. Furthermore, including all eligible people in one region increases the study's external validity (i.e., its generalizability). The larger and more representative the region is, the higher the external validity is. Study III–V were also nationwide. It is therefore likely that the results of our studies can be generalized to both Sweden and other countries with similar healthcare standards to those of Sweden.

In Study I–II, we used medical records and national registers to obtain information about the study population, and Study III–V were entirely register-based. The Swedish national registers have repeatedly been shown to have high quality, which is a particular strength of our studies. Other strengths include complete follow-up for death (the data availability of which is 100% thanks to the completeness of the national registers) and a large number of patients.

Study I–II

These studies were single-center studies, which might decrease their external validity. However, differences in pre-, peri-, and postoperative care were minimized because all patients were operated in the same center. Data regarding patient characteristics and outcomes were obtained manually from medical records. Consequently, existing data could have been missed, and data that were not available from medical records were not included.

In Study II, long-term hemodynamic data were only available for 161 (45%) patients of the total cohort of 355 patients. Of these, approximately two-thirds underwent echocardiography as part of their clinical care. It is possible that patients with symptoms, and consequently affected hemodynamics, were more likely to undergo late echocardiography than patients without symptoms were. This could have biased the results towards higher postoperative gradients. Furthermore, the echocardiography performed as part of the patients´ clinical care was performed by different people, not according to a predefined study protocol. However, most echocardiography in Sweden is performed by clinical physiologists in accordance with a standardized protocol, which decreases the risk of information bias (i.e., a systematic error caused by erroneous information collected about or from the study subjects[132]).

Study III

We did not have information about the different types of biological and mechanical prostheses used in this study. It is possible that patients receiving certain types of prostheses have better outcomes than patients receiving other types of prostheses. Furthermore, we did not have information about implanted valve size or the prevalence of PPM.

Study IV

Because kidney function constituted the exposure groups in this study, patients with missing creatinine were excluded. This may have introduced selection bias, which in turn might limit generalizability. To account for this possibility, we analyzed the prognosis of patients with missing creatinine and found similar results to those of patients with creatinine values present. This indicates that the difference between included and excluded patients was not important. We used the most recent preoperative creatinine value to calculate each patient's eGFR. However, the creatinine value might differ in the same individual depending on factors such as hydration status, protein intake, and exercise level. Therefore, some patients might have erroneously ended up in the incorrect kidney function groups. Furthermore, we did not have information about implanted valve size, cardiopulmonary bypass time, cause of CKD, or degree of frailty, which might have been a cause of residual confounding.

Study V

The criteria for diagnosing a patient with endocarditis might differ between hospitals and treating physicians, which might have introduced information bias in this study. Also, it is often difficult to diagnose endocarditis. Not all patients have positive blood cultures (e.g., those with recent use of antibiotics, immunosuppressed patients, and patients with bacteria that require different culture techniques), and older or frail patients may be underdiagnosed. Consequently, we might have underestimated the incidence of PVE. However, it is likely that the incidence of PVE was equally underestimated in patients with biological and mechanical valves, and therefore, the relative risk was probably not affected. Furthermore, we could not distinguish between infection affecting the aortic valve prostheses and other heart valves or cardiac implantable electronic devices. This might have led to an overestimation of the incidence of PVE. We did not have information about patient frailty, dental hygiene, antibiotic use, echocardiographic or other imaging data, or frequency of infections such as dental infections, pneumonia, mediastinitis, or urinary tract infections before, at the time of, or after surgery. For example, it is possible that patients with a higher degree of frailty and worse dental hygiene may have been more likely to receive bioprostheses and therefore had a higher risk of PVE. Furthermore, for patients with diagnosed PVE, the time from symptoms to hospital admission and surgery, if performed, is not known. A time delay between disease onset and treatment might have influenced mortality after PVE negatively. However, the data come from real-world experience, which increases generalizability.

Study VI

Even though systematic reviews and meta-analyses are often considered to have the potential to provide the highest level of evidence, the quality of the systematic review always depends on the quality of the included studies. In our study, all of the included

studies were observational, with the inherited limitation of possible residual confounding. Furthermore, because prosthetic choice was not randomly allocated, it is possible that the operating surgeon chose a certain prosthesis type for certain patients, which could lead to differences between the groups at baseline. For example, it is possible that a bovine prosthesis was chosen for younger and healthier patients or for patients with a smaller aortic annulus if the surgeon believed the bovine prostheses to have better hemodynamics and a lower degree of PPM. In that case, the mortality of patients who received bovine prostheses might have been underestimated. Further, we found moderate heterogeneity in our study, which might reflect important differences between the studies. For example, different types and brands of bovine and porcine prostheses were used in the different studies. It is possible that that the true effect differs between different types of prostheses, and therefore, this distinction might have influenced the results. As with Study I–II, it is possible that the follow-up was not long enough to detect a survival difference between the groups.

Even though we performed a thorough literature search, it is not certain that we found all eligible articles. Further, it is possible that mainly studies with positive results have been published, which could lead to an under- or overestimation of the effect measure. The largest advantage of this study is that it is, to the best of my knowledge, the first complete systematic review and meta-analysis performed on this topic. Other strengths include the large number of patients and the strict inclusion criteria, which make the articles more comparable.

Future Perspectives

The primary outcome in all studies except Study II and V was all-cause mortality. This is an important endpoint, but other factors, such as functional status, quality of life, and repeat hospitalizations might be equally important to individual patients. More information about these factors would be helpful when choosing the optimal valve prosthesis for each patient, and studies evaluating outcomes other than survival are needed.

To provide causality rather than associations, large RCTs are in demand. Because patient preference is of the utmost importance when choosing valve type, random allocation of biological and mechanical valves will be difficult. However, it might be feasible to conduct an RCT comparing bovine and porcine aortic valve prostheses, which could be facilitated with register-based randomization. The information provided from such a trial could also be useful in the era of TAVI, in which both bovine and porcine prostheses are used. Furthermore, future studies with longer follow-up, both for bovine versus porcine and biological versus mechanical prostheses, would provide useful information.

Moderately reduced kidney function is present in one-quarter of patients who undergo AVR. The majority of studies that evaluate outcomes, prosthesis choice, and prognosis after AVR in patients with CKD are performed in patients with ESRD. More studies evaluating operation-related outcomes in patients with moderately reduced kidney function instead of ESRD are needed. It would also be interesting to investigate at what GFR level alterations in the coagulation system occur.

We found a higher incidence of PVE in patients with bioprostheses than mechanical valves. However, the mechanism behind these results is not clear, and it is not certain that the association found resulted from a causal relationship. More studies evaluating this possible association in different patient cohorts are needed.

The continued development of mechanical valves with less thrombogenic properties and biological valves that are less prone to SVD will greatly benefit all patients who undergo AVR. The dream scenario would be to find a perfect valve prosthesis that does not require anticoagulation treatment AND has excellent durability.

CONCLUSIONS

Study I Long-term, all-cause mortality after AVR was similar in patients with Perimount and Mosaic bioprostheses. Both Perimount and Mosaic bioprostheses are acceptable valve choices for AVR.

Study II Mosaic bioprostheses had acceptable hemodynamic function after AVR. A substantial proportion of the patients who underwent AVR with a Mosaic bioprosthesis had increased postoperative gradients or moderate to severe PPM. However, this was not associated with increased mortality in our cohort.

Study III In patients aged 50–69 years, survival after AVR was better for those who received mechanical valve than biological prostheses. The increased use of bioprostheses in this age group does not have sufficient scientific support.

Study IV Mortality after AVR was higher in patients with moderately reduced kidney function than in those with normal kidney function. Patients with reduced kidney function warrant careful observation after AVR.

Study V After AVR, the yearly rate of PVE was 0.57%. We found a higher relative risk for PVE in patients with biological than mechanical valve prostheses in both the early and late postoperative periods. These results can facilitate diagnosis of PVE and prosthetic choice in selected patients.

Study VI Long-term, all-cause mortality after surgical AVR was similar in patients with bovine and porcine bioprostheses. Both bovine and porcine bioprostheses are acceptable valve choices for AVR.

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