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IMPLICATIONS OF CHRONIC KIDNEY DISEASE ON PRESENTATION TREATMENT AND OUTCOMES IN PATIENTS WITH AORTIC STENOSIS

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IMPLICATIONS OF CHRONIC KIDNEY DISEASE ON PRESENTATION, TREATMENT, AND OUTCOMES INPATIENTS WITH AORTIC STENOSIS

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Georgios Vavilis

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To the persons thanks to Them I got the chance for a better quality of life

"A science is possible if and only if there are knowable objects"

Aristotle (384 – 322 BC)

POPULAR SCIENCE SUMMARY OF THE THESIS

Kidney disease is a highly prevalent condition associated with high risk for cardiovascular morbidity and mortality. The knowledge of the epidemiology and management of aortic stenosis in patients with concomitant chronic kidney disease is limited. In this thesis, we evaluated kidney dysfunction as a risk factor for aortic stenosis, risk of new kidney injury after aortic valve replacement, and assessed the management in dialysis patients.

There is scarcity of data regarding whether kidney disease is associated with higher risk for new onset aortic stenosis. We used a regional registry consisting of individuals in a general population to explore the association between aortic stenosis and kidney dysfunction. Our findings suggest that kidney dysfunction is a risk factor for aortic stenosis, and the risk is present already in patients with mild to moderate kidney dysfunction.

The survival after transcatheter aortic valve replacement and new kidney dysfunction was assessed in a national registry of aortic valve replacement. New kidney dysfunction among patients treated with transcatheter aortic valve replacement was more common in those who had pre-operative kidney dysfunction. When kidney dysfunction was still present at the time of discharge it was associated with worse survival.

In a contemporary nation-wide cohort of dialysis patients, we explored the point prevalence of aortic stenosis and the incidence of new onset aortic stenosis. Despite recent advances in dialysis treatment, we identified high rates of new diagnosed aortic stenosis with less frequent use of aortic valve replacement.

Among dialysis patients who underwent aortic valve replacement we compared mortality among those treated with mechanical compared to bioprosthetic valve. There was no significant difference in mortality between the two valve types. There was also no difference in other complications such as bleeding events, stroke and aortic valve reoperation. These findings suggest that bioprosthetic valves can be used safely in dialysis patients.

ABSTRACT

Background

Aortic valve stenosis (AS) is the most common valvular heart disease in the western world. No pharmacological treatment has been proved to halt the progression to severe disease and after symptom debut, the prognosis is poor with a high mortality, if left untreated. Hence, surgical or transcatheter aortic valve replacement (AVR) is the only therapeutic option for severe AS. AS is prevalent with rapid evolution among patients with chronic kidney disease (CKD). Concomitant AS and CKD is accompanied with high risk of death and cardiovascular events.

The aims of this thesis were to:

1. Assess whether CKD is associated with the risk of developing AS in a general population
2. Determine the risk factors of worsening renal function following transcutaneous AVR (TAVR) and its association with the short and long-term mortality
3. Evaluate the point prevalence of AS and AVR at dialysis start, and to assess the incidence rates and associated risk factors for new onset AS after dialysis initiation.
4. Compare the long-term complication rates after surgical AVR (SAVR) with mechanical (MAV) or bioprosthetic aortic valve (BAV) in dialysis patients

Methods and results

Study I: Kidney Dysfunction and the risk of developing Aortic stenosis

The study included all adult Stockholm citizens from the Stockholm CREAtinine Measurement project (SCREAM) with known kidney function and without prior diagnosis of AS, and the aim was to study the risk of AS in relation to kidney function. Kidney dysfunction was found to be independently associated with higher risk of developing AS. This risk increased linearly with lower estimated Glomerular Filtration Rate (eGFR) and was present after adjustments of covariates.

Study II: Risk factors for worsening renal function and their association with long-term mortality following transcatheter aortic valve implantation: data from the SWEDEHEART registry

We used the The SWEdish traNscatheter cardiac intervention regisTRY (SWENTRY), part of Swedish Web-system for Enhancement and Development of Evidence -based care in Heart disease Evaluated According to Recommended Therapies (SWEDHEART) to identify all patients with severe AS who underwent TAVR. Risk factors associated with persistent acute kidney injury (pAKI) were explored, and their association to short- and long-term mortality was explored. pAKI occurred in 6.1% of AS patients who underwent TAVR and was associated with a doubled short- and long-term risk of death, independent of baseline kidney function. Male gender, baseline kidney function and transapical access were found to be independently associated with pAKI.

Study III: Epidemiology of aortic stenosis/aortic valve replacement in the nationwide Swedish Renal Registry

The Swedish Renal Registry (SNR), a national registry of all patients who commenced dialysis or received a kidney transplant in Sweden between 1993 and 2018, was used to identify the point prevalence of AS and AVR at dialysis start, and to explore the incidence

and associated factors for developing AS and AVR after dialysis initiation. We found that patients initiating dialysis have high prevalence and occurrence of AS. Older age, male gender, hypertension, and peritoneal dialysis were strongly associated with new onset AS. Only 20% of new cases with incident AS underwent AVR.

Study IV: Prognosis after aortic valve replacement in dialysis patients – a report from the Swedish Renal Registry

We identified all dialysis patients in the SNR registry who had undergone surgical AVR with MAV or BAV. We compared the long-term complication rates of the composite end-point of all-cause death, bleeding, stroke and aortic valve reoperation, and separately, the end-point all-cause death. The main finding was that BAV- and MAV-recipients had comparable mortality and complication rates.

Conclusions

Kidney dysfunction is independently associated with new onset AS in a general population. This association was attenuated, but remained significant after adjustments, and the association increased linearly with lower eGFR categories. In unselected patients with severe AS undergoing TAVR, worsening kidney function occurred often, and was predicted by male gender, baseline kidney dysfunction and access type. pAKI was strongly associated with higher risk of all-cause death. Among dialysis patients, the prevalence at initiation and occurrence of clinically detected AS was high, but few underwent AVR. Dialysis patients who underwent surgical AVR with MAV or BAV had similar rates of all-cause death and overall complication rates.

LIST OF SCIENTIFIC PAPERS

I. **Georgios Vavilis**, Magnus Bäck, Giuseppe Occhino, Marco Trevisan, Rino Bellocco, Marie Evans, Bengt Lindholm, Karolina Szummer, Juan-Jesus Carrero. Kidney Dysfunction and the Risk of Aortic Stenosis
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IV. **Georgios Vavilis**, Magnus Bäck, Peter Bárány, Marie Evans, Andreas Rück, Karolina Szummer. Prognosis after aortic valve replacement in dialysis patients – A report from the Swedish Renal Registry
Manuscript

CONTENTS

LIST OF ABBREVIATIONS

AHA/ACC	American Heart Association/American College of Cardiology
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
ARB	Angiotensin Receptor Blockers
AVA	Aortic valve area
AS	Aortic valve stenosis
AVR	Aortic valve replacement
BAV	Bioprosthetic Aortic Valve
BMI	Body mass index
BSA	Body surface area
CAVD	Calcific aortic valve disease
CKD	Chronic kidney disease
CMR	Cardiac Magnetic Resonance
CT	Computed tomography
EF	Ejection fraction
ESC	European Society of Cardiology
EuroSCORE II	European System for Cardiac Operative risk Evaluation
eGFR	estimated Glomerular Filtration Rate
FGF-23	Fibroblast growth factor 23
γ-MPG	Gamma-carboxyglutamic (GLA)-protein
FH	Familiar Hyperlipidemia
HR	Hazards Ratio
ICD - 10	International Classification of Disease 10^{th} Revision Codes
IHD	Ischemic heart disease
IR	Incidence Rate
IQR	Interquartile Range
KDIGO	Kidney Disease: Improving Global Outcomes
LV	Left ventricle
LVH	Left ventricular hypertrophy
LVOT	Left Ventricle Outlet
Lpa	Lipoprotein (a)
LDL-C	Low-Density Lipoprotein Cholesterol
MAV	Mechanical Aortic Valve
MDCT	Multidetector Computed Tomography
NF-κB	Nuclear Factor kappa-B

PTH	Parathyroid hormone
pAKI	Persistent acute kidney injury
PCSK9	Proprotein Convertase Subtilisin/Kexin type 9
RANKL	Receptor Activator of Nuclear Factor κB Ligand
RANK	Receptor of Nuclear Factor κB
SAVR	Surgical Aortic Valve Replacement
SCREAM	Stockholm CREAtinine Measurement project
STS-PROME	Society of Thoracic Surgeons Predicted Risk of Mortality
TAVR	Transcutaneous Aortic Valve Replacement
SNR	Swedish Renal Registry
SVD	Structural valve deterioration
SWENTRY	SWEdish traNscatheter cardiac intervention regisTRY
SWEDHEART	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated According to Recommended Therapies
TGF-β1	Transforming growth factor-β1
TAVR	Transcutaneous AVR
TTE	Transthoracic echocardiography
ucMGP	Uncarboxylated matrix gamma-carboxyglutamic-acid
VEC	Valvular endothelial cells
VICs	Valvular InterstitialCells
VARC-2	Valve Academic Research Consortium 2
VKA	Vitamin K Antagonists

1 INTRODUCTION

1.1 BACKGROUND

AS is the most common valvular heart disease affecting 0.3% to 0.5% of general population with a markedly higher prevalence with advanced age[1]. In the western world it is the third most common cardiovascular morbidity after ischemic heart disease (IHD) and arterial hypertension[2]. It arises from fibrocalcific changes and over time as the disease progresses, results in reduced cusp motion and hemodynamic obstruction of the left ventricular outlet (LVOT)[3].

Dialysis patients have a particularly high prevalence of AS[4] compared to a general population[5-7]. Few studies have explored the association of kidney dysfunction as a risk factor for the development of AS among non-dialysis patients and those that have found contradictory results[8,9]. CKD affects 8 - 13% of the general population[10] with high prevalence of cardiovascular diseases, atherosclerosis[11] and disturbances in bone mineral metabolism[12]. Moreover, one third of patients admitted for AVR have CKD[13]. However, there is limited evidence as to whether the risk of AS is associated with the degree of kidney dysfunction.

Patients with symptomatic AS, have poor prognosis, with annual mortality of more than 50% if left untreated[14]. There is presently no medical treatment to prevent or attenuate the AS progression. Although current management is limited to replacement of the valve, and transcutaneous techniques have evolved rapidly over the past decade, AS continues to be a major cause of morbidity and mortality[15,16].

Two interventional methods are recommended for the replacement of the stenotic aortic valve: i) open cardiac surgery with replacement of aortic valve with MAV or BAV. Current guidelines recommend surgical AVR (SAVR) as a class I indication for appropriate patients. ii) Transcatheter aortic valve replacement (TAVR) is the percutaneous implantation of a bioprosthetic valve and is recommended for symptomatic patients with AS, ineligible for SAVR due to high surgical risk and periprocedural mortality[17,18]. However, several ongoing trials are currently investigating if TAVR can be an option in intermediate-risk patients[19]. TAVR nowadays has become an alternative treatment to conventional SAVR especially for inoperable and high-risk patients[20]. Several studies have shown that patients undergoing TAVR are at high risk for acute deterioration of kidney function, that is associated with poor clinical outcomes and high mortality rates[21,22]. The most commonly used definition of acute kidney injury (AKI) for patients undergoing TAVR is based on Valve Academic Research Consortium 2 (VARC-2) definition[23]. Factors that have been identified to be associated with AKI are: lower kidney function at baseline, larger contrast volume, red blood cells transfusion and high logistic Euroscore[21,22,24,25]. However, there is limited knowledge on the prevalence, the predictors and the implications on short- and long-term mortality, of irreversible AKI after TAVR, that persists until the time of discharge.

Aortic valve calcification is common in dialysis patients[7,26,27]. The metabolic milieu in patients with kidney failure, disturbances of bone mineral metabolism with increased circulated levels of calcium and phosphate product promotes early atherosclerosis and valvular calcification. The presence of aortic valve calcification has been independently associated with higher risk of death in dialysis patients[28]. Nevertheless, there is a scarcity of longitudinal data examining the point prevalence and the occurrence of new onset AS in dialysis patients. The reported incidence and prevalence of AS is based on small, single center and cross-sectional studies, performed several decades ago. Consequently, a comprehensive approach for the epidemiology and clinical outcomes of AS in dialysis patients in required.

The optimal prosthetic valve selection (MAV vs BAV) or the more appropriate intervention choice (SAVR vs TAVR) for dialysis patients who are candidates to undergo AVR remains unknown as they are typically excluded from large prospective and randomized trials.

The process of patient evaluation by the Heart Team regarding appropriate type of intervention (SAVR or TAVR) and prosthetic valve selection (mechanical or bioprosthetic) is based on the patient's age and preference, co-morbidities, patient's life expectancy, need for anticoagulant therapy and expected durability of the valve. The European and American guidelines have conflicting recommendations for prosthetic valve selection in dialysis patients. After 2006, the AHA/ACC ceased to have explicit criteria for valve selection in dialysis patients. In contrast, the most recently published European guidelines from 2021 still suggest that a MAV should be considered in patients on maintenance hemodialysis, because of the higher risk of accelerated structural valve deterioration. However, the prognosis of dialysis patients after AVR with MAV or BAV has not yet been well investigated. Few small and single center studies have explored the incidence of clinical outcomes after AVR. Thus, the evidence on the management of these patients is limited and the recommendations for best prosthetic valve selection in this challenging group of patients is based on extrapolation of data from the general population.

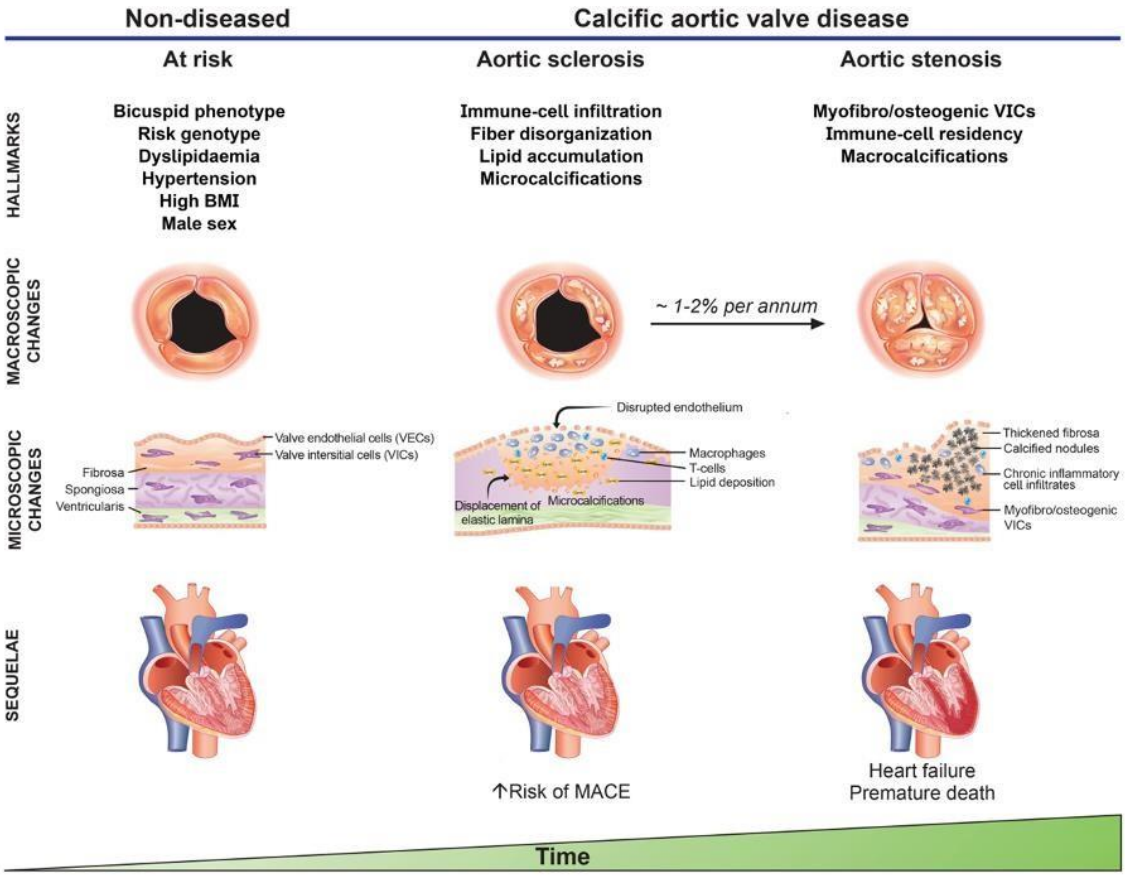
1.2 THE AORTIC VALVE

1.2.1 The structure of the Aortic valve

The aortic valve is an avascular structure composed of tree leaflets (cusps) named the left coronary, right coronary, and noncoronary according to their location in relation to the coronary artery ostia[29]. Behind each cusp the aortic wall bulges to form the aortic sinus of Valsalva. The leaflets which are normally less than 1mm in thickness, attach with their base to the aortic root. Coaptation of their free edges ensures complete closure of the valve and maintains unidirectional blood flow from the left ventricle to aorta, protecting retrograde flow during the left ventricular diastole[30]. During the ventricular systole the aortic valve opens to an average area of 4 cm^2.

Each leaflet has normally a trilaminar structure[31]: the fibrosa, spongiosa and ventricularis[30]. The fibrosa, which provides structural integrity, facing the aortic side of the valve, is composed of circumferential aligned type I and III collagen fibers[30]. The ventricularis layer, facing the LVOT, is composed of collagen and elastin fibers and reduces the radial strain[30]. The spongiosa residing in-between the former two, with function to link and lubricate them, consists of proteoglycans and collagen fibers[31]. In non-diseased aortic valves, all three layers are populated by valvular interstitial cells (VICs)[32] with the majority of them to be fibroblast like cells[33]. A physical barrier on the surface area of the aortic valve is formed by circumferentially aligned valvular endothelial cells (VEC). They interact with the valvular endothelial cells, through the secretion of endothelial-cell derived nitric oxide signaling, in order to maintain the valvular homeostasis[34] (Figure 1).

Figure 1. Risk factors, structural changes and sequelae of calcific aortic valve disease at different disease stages



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1.2.2 Epidemiology of AS in patients with CKD

AS, the most common valvular heart disease[36], is recognized as a degenerative process with increasing prevalence in elderly[37]. The mean age of AS diagnosis increased in the last two decades from 68 years in 2000 to 78 years in 2017[38]. The older age has been associated with an almost 3-times higher prevalence of AS and a 10-fold increased volume of AVR[38]. In Sweden between 2003 and 2010 there were 34582 individuals in total with newly diagnosed valvular heart diseases. Of these, 18890 (47.2%) individuals with median age 74 (Interquartile Range [IQR]: 64 - 81) were diagnosed with AS. The overall incidence rate of the disease was 37.8 per 100000 person-years (95% Confidence Interval [CI]: 37.3 - 38.3).

Aortic valve calcification is highly prevalent in CKD and in patients with kidney failure. The prevalence of aortic valve calcification ranges from 28% - 85% in CKD patients, and from 28% to 76.5% in dialysis patients[39,40]. This prevalence is significantly higher than in aged individuals > 65 years from the general population, where 25% of them have calcified aortic valves[41]. Severe AS is present in 3% in elderly patients ≥ 75 years[42]. In a large echocardiography-based cohort the prevalence of AS in the CKD group was 9.5% versus 3.5% in non-CKD group[43]. The occurrence of AS in dialysis patients ranges from 4% - 13%, with 60% to be low-flow, low-gradient AS[40].

1.3 MECHANISMS OF VALVULAR CALCIFICATION IN CKD PATIENTS

The exact mechanism by which aortic valve becomes calcified and stenotic is unknown. According to available research, traditional cardiometabolic risk factors such as hyperlipidemia, obesity[44], hypertension[45], diabetes[46], and smoking[47] have been shown to increase the risk of AS in retrospective studies. A Mendelian randomization study, showed that increased plasma lipoprotein(a) concentration was a genetically determined, causal risk factor for AS[48].

The hallmarks of calcific aortic valve disease (CAVD) are the fibrosis and the calcification that change the biomechanical properties, the organization, and composition of the aortic valve leaflets. The histological changes in aortic stenosis (AS) are characterized by cellular and molecular mechanisms involved in the pathophysiology of aortic valve calcification. Some of them include:

i) inflammatory cell infiltration caused by the presence of macrophages and T-cells and secretion of cytokines[49],
ii) the oxidization of low-density lipoprotein deposits[50] and the elevated oxidative stress[51],
iii) the mineralization process promoted by neo-angiogenesis[52],
iv) the appearance of myofibroblasts[49], osteoclasts[53], and other ectopic mesenchymal cells[54].

AS is the most common valvular heart disease in patients with kidney disease with premature manifestation and accelerated progression[5,9]. Multiple and complex mechanisms have been identified to be involved in the pathophysiology of AS in patients with kidney dysfunction. Although these are related to traditional mechanisms of AS, the uremic milieu and the frequent occurrence of bone metabolism dysregulation, the exact contribution and synergy between them has to be further explored[41].

1.3.1 Disturbances of flow patterns

The VECs of the aortic valve, are exposed to hemodynamic and deformation forces during the cardiac cycle[31]. Disturbances of flow patterns and hypertension alter shear stress, on the endothelial cells on the aortic side of the valve[39]. This is more prominent in HD-dependent patients due to fluid overload, anemia, shunts across AV-fistula, increased LV-afterload which results in further valvular endothelial damage.

1.3.2 Endothelial dysfunction

Impaired endothelial function and structure of the overlying basement membrane in areas with low shear stress of the leaflets, enhance coagulation process, leucocyte adhesion and smooth muscle cell proliferation[55]. Altered endothelial barrier function promotes the uptake and deposition of circulating lipids and inflammatory cells infiltration in aortic leaflets[56] (Figure 2).

1.3.3 Lipid infiltration and oxidation

Abnormalities in lipid metabolism have a central role in the enhancement of inflammation which predisposes the mineralization process in calcific AS[57]. Early lesions of calcific AS are characterized by the presence of a low-grade inflammatory process. Histological studies have shown the presence of apoB, apoE, apoA1 and apo(a)[49] in surgically removed stenotic aortic valves. Studies have shown that hemodialysis patients have higher levels of lipoprotein (a)[58] associated with increased risk for CAVD[48] that progresses in a linear manner to more severe forms of valvular disease[59].

Increased oxidative stress with elevated concentration of superoxide and hydrogen peroxide has been found in calcific aortic valves in humans[51]. The oxidative stress is associated with the activation and trans-differentiation of fibroblasts to osteoblast-like cells[51]. Patients with CKD have high circulating levels of molecules (i.e. asymmetric dimethylarginine) that enhance the oxidation process by reduction in the nitric oxide production and increase of reactive oxygen species[39] (Figure 2).

1.3.4 Systemic and local inflammation

The lipid deposits, the oxidative stress and the endothelial dysfunction activates the release of proinflammatory cytokines (TNF-α, transforming growth factor β1, nuclear factor κB) which promote the infiltration of VICs with circulating inflammatory cells (T-Lymphocytes, mast cells, macrophages, lipid-laden foam cells).

Systemic inflammation is frequent in dialysis patients associated with vascular calcification and bone mineral disturbances[60]. The systemic uremic inflammation is related to the activation of interleukin-6, tumor necrosis factor α (TNF-α), nuclear factor κB and malnutrition[39].

Kidney dysfunction enhances serum accumulation of uremic toxins such as the indoxyl sulphate. The indoxyl sulphate is produced in the liver from proteins absorbed from intestine and excreted in urine[61]. It is associated with accentuated loss of kidney function and increased vascular cell proliferation, inflammatory cytokine release and production of reactive oxygen species[62].

1.3.5 Bone metabolism regulation

The inflammatory phase, with lipid deposition and inflammation that initiates the calcification of the aortic valve, is followed by the calcification process. The valvular interstitial cells are differentiated in myofibroblasts and osteoblastic-like cells. Ossification of the aortic valve is characterized by the formation of lamellar bone and occurs in advanced kidney failure[53].

The calcification process is promoted by osteoblastic markers[39]. These include the osteopontin, osteocalcin, LDL, receptor-related protein-5, osteoprotegerin/receptor activator of nuclear factor κB ligand (RANKL)/receptor of nuclear factor κB (RANK), bone morphogenetic protein 2 and core binding factor 1/Runt-related transcription factor 2[39]. Elevated plasma concentrations of Angiotensin II have been found in patients with AS. In animal studies it has been shown that administration of angiotensin II was associated with strong fibrosis of the aortic valve[63].

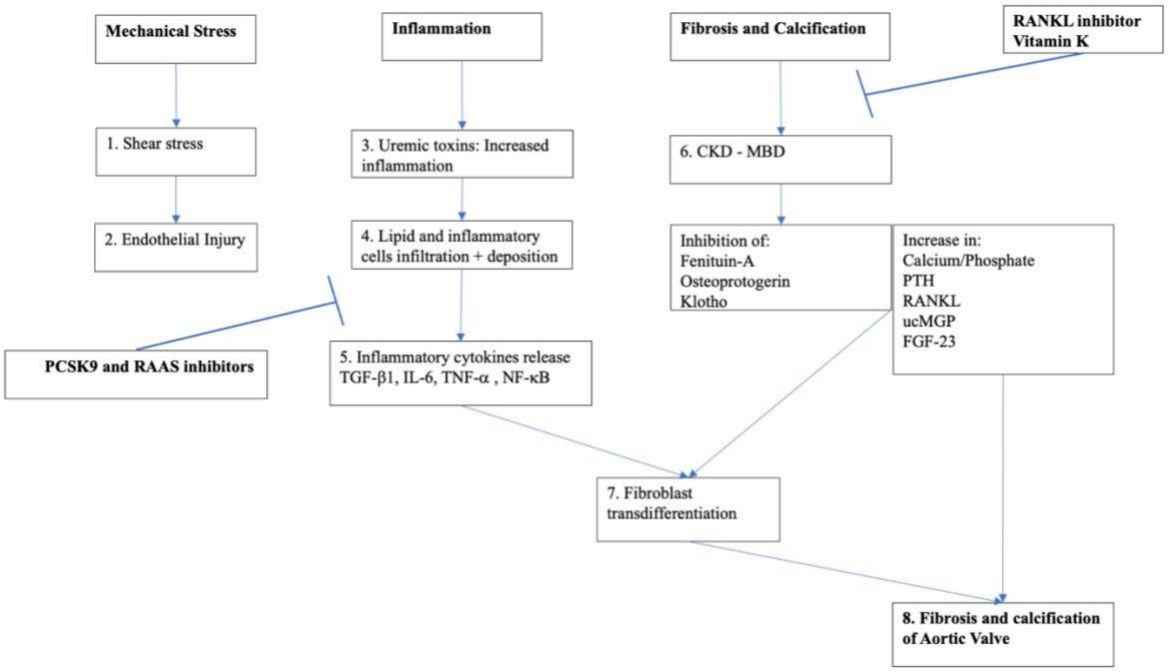
Another pathway involved in cardiovascular calcification is enhanced by circulating inhibitors of vascular and soft tissue calcification[39]: osteoprotegerin, fetuin and gamma-carboxyglutamic (GLA)-protein (MPG)[64]. Osteoprotegerin is a recoy receptor of RANKL produced by osteoblasts. Its main function is the prevention of osteoclast formation and bone reabsorption through the inhibition of osteoblastic markers[65]. Fetuin is a calcium-binding glycoprotein that inhibits tissue calcification[64], and its low concentration in CKD patients has been associated with adverse clinical outcomes[66]. When blood is supersaturated with calcium-phosphate fetuin absorbs the precipitates to form calciprotein particles. When fetuin levels are low, more calciprotein particles undergo crystalline transition which associate with extra-skeletal calcification[67]. MGP (uncarboxylated matrix gamma-carboxyglutamic-acid) is activated by carboxylation and phosphorylation, in a vitamin K- dependent manner[68]. Deficiency of vitamin-K leads to inefficient activation of MGP and more calcification[69].

1.3.6 Calcium/phosphate homeostasis

Phosphate is essential structural and functional component in its organic and inorganic form, and ensures optimal cell function[35]. CKD is associated with generation of inorganic phosphates from the organic form present in extracellular nucleotides, and transport of intracellular phosphate to extracellular matrix[70]. Hyperphosphatemia and hypocalcemia increase parathyroid hormone (PTH) secretion[12] that stimulates bone reabsorption by osteoclasts and activates vitamin D in its active metabolite (25-Hydroxycholecalciferol)[12]. The PTH dysregulation and hyperphosphatemia results in osteoporosis and ectopic vascular and valvular calcifications[70]. Extracellular phosphate has been shown to provoke valvular calcification and activates apoptotic mechanisms in valvular interstitial cells of valvular tissue[71].

An intrinsic preventive regulator of hyperphosphatemia is Klotho, a co-receptor of fibroblast growth factor 23 (FGF-23). FGF-23 maintains the mineral homeostasis by inducing urinary elimination, lowering intestinal absorption of phosphate and reduction of active vitamin D levels[70,72]. FGF-23 requires the presence of Klotho. Klotho deficiency has been shown to be associated with aortic valve inflammation, and dysregulation of hyperphosphatemia and secondary hyperparathyroidism[73,74]

Figure 2. Phases in pathophysiological pathways involved in aortic valve stenosis in patients with chronic kidney disease.



FGF-23: Fibroblast growth factor-23; IL-6: interleukin 6; Lp(a): lipoprotein a; MGP: matrix gamma-carboxyglutamic-acid; NF-κB, nuclear factor kappa-B; PTH: parathyroid hormone; RANKL: receptor activator of nuclear factor kappa-B; TGF-β1: transforming growth factor-β1; ucMGP uncarboxylated matrix gamma-carboxyglutamic-acid.

1.4 DEFINITION AND DIAGNOSIS OF AORTIC STENOSIS

CVAS is caused by superimposed fibrocalcific changes of an initially normal tricuspid or in a congenital bicuspid aortic valve[75]. The pathologic thickening and fusion of the aortic valve leaflets results in stiffness, reduced leaflet mobility and a decrease in the effective aortic valve area (AVA), leading to AS and blood flow obstruction[29].

1.4.1 Clinical diagnosis

The classical symptoms of AS are angina[76], dyspnea and syncope on exertion[77]. The onset of symptoms differs among patients with some remaining asymptomatic for many years despite the presence of a hemodynamically severe disease[78].

The clinical manifestation of AS in CKD stage 4 to 5 may vary from the general population and moreover may be masked by other conditions. Dyspnea and presyncope can be due to volume overload, pulmonary congestion or anemia[79].

The physical examination of patients can be helpful to suspect AS and can be used to identify patients with a hemodynamically severe grade of stenosis. The parvus et tardus sign, identified on palpation of the carotid upstroke and radial artery is defined by a small arterial pulse with reduced stroke volume and can be present in patients with severe AS[80]. Another physical finding is a harsh and rasping systolic murmur, crescendo-decrescendo in intensity, heard at the second intercostal space that radiates towards to the apex and is transmitted to the carotid arteries[81]. When the murmur is a high-pitched a thrill may be palpated on the precordium[82]. In CKD patients systolic murmur can result from increased stroke volume, fluid overload and left ventricle (LV) hypertrophy[83].

1.4.2 Echocardiography

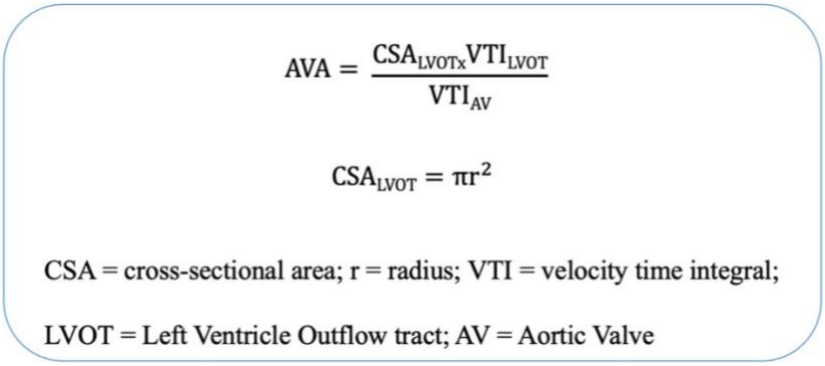
Transthoracic echocardiography (TTE) is the standard diagnostic method in the initial evaluation of patients with known or suspected AS either by the presence of a systolic murmur identified during the heart auscultation or by the onset of exertional dyspnea, angina or syncope[84]. The acquisition and interpretation of echocardiographic images is quick, non-invasive, free of radiation and inexpensive, making echocardiography ideal for routine follow-up[86].

Echocardiographic imaging provides reliable evaluation of heart and valve anatomy, quantifies the degree of AS severity, assesses the valve calcification, leaflets motion and blood flow parameters in aortic valve, the presence of concomitant valvular diseases and the LV response to the pressure overload as well as important prognostic findings such as degree of LV hypertrophy, presence of mitral regurgitation and pulmonary artery pressure[87,88].

The hemodynamic parameters recorded for the evaluation of AS in normotensive patients are: a) the peak jet systolic velocity across the aortic valve measured with continuous-wave Doppler b) mean pressure gradient defined as the average difference in pressure between the LV and aorta during systole and calculated by Bernoulli equation c) effective aortic valve orifice area as determined by continuity equation (Figure 3)[86]. The continuity equation is based on the concept that the stroke volume ejected through the LV outflow tract (LVOT) and the aortic valve are equal[86].

The application of continuity equation in the calculation of the AVA has some theoretical limitations. First, the equation measures the effective valve area that is lower that the anatomical one. This measurement is based on the flow contraction through the stenotic valve (vena contracta)[89]. Secondly, the calculated area changes with flow rate. The resting AVA measured in adults with normal left ventricular function is accurate. However, left ventricular dysfunction results in decreased valve opening and subsequently lower effective orifice AVA[90].

Figure 3. The continuity equation used to calculate aortic valve orifice area



1.4.3 Determination of AS-severity by echocardiography

AS is suspected when thickened aortic valve leaflets with a reduced opening are detected. The diagnosis has to be based on an integrative approach combining all the information obtained from Doppler and 2D imaging as well as clinical presentation[86]. TTE allows accurate assessment of valve anatomy and determination of hemodynamic parameters, essential for patient management and clinical decision making[86]. Severe AS is suspected in the basis of any one of the three criteria: a peak aortic jet velocity ≥ 4 m/s, mean gradient (ΔPm) ≥ 40 mmHg and effective AVA using the continuity equation < 1 cm^2 or ≤ 0.6 cm^2/m^2) when indexed to body surface area (BSA)[84]. Ideally, all criteria should be fulfilled in severe AS[84].

However, the accuracy of these measurements may be influenced by several factors in CKD patients with AS, including measurement errors, low- or high- flow states and increased afterload by hypertension[91]. The echocardiographic assessment of AS in dialysis patients should be planned for the day after dialysis[83]. Temporary arteriovenous fistula compression for the assessment of AS severity should be avoided, as complications like thrombosis can occur[79]. Several secondary parameters can be measured to confirm AS severity including the Doppler velocity index, the anatomic AVA measured by planimetry, and ejection dynamics such as acceleration time or the ratio of acceleration time to ejection time[86,92]. The anatomic AVA obtained by planimetry in CKD patients is often challenging and inaccurate due to extensive calcification of aortic valve and basal septum hypertrophy. Compared to 2D echocardiography, 3-D modalities allow more accurate quantification of the aortic valve as it permits measurement of the smallest and more restrictive valve orifice, avoiding underestimation of AS severity[93].

1.4.4 Measurement errors leading to low-gradient AS in CKD patients

LVOT measurement is challenging in CKD patients with AS due to severe aortic valve calcification extending to the LVOT and to basal septum hypertrophy[39]. These abnormalities may cause higher peak jet velocities and gradients resulting in errors in AVA calculation by the continuity equation. Measurement errors of velocity and gradients by doppler echocardiography result in underestimation of gradient, overestimation of the AVA, and underestimation of the AS severity[94]. The underestimation of the anteroposterior LVOT diameter at peak systole, results in underestimation of the stroke volume and AVA, and overestimation of the AS severity. The LVOT has an oval rather than circular shape. The anteroposterior diameter, used to measure the LVOT area by 2D echocardiography is smaller than the septal to lateral diameter[95]. A hybrid approach in the estimation of LVOT has been used to overcome the ascertainments in the AVA measurement by 2D echocardiography.

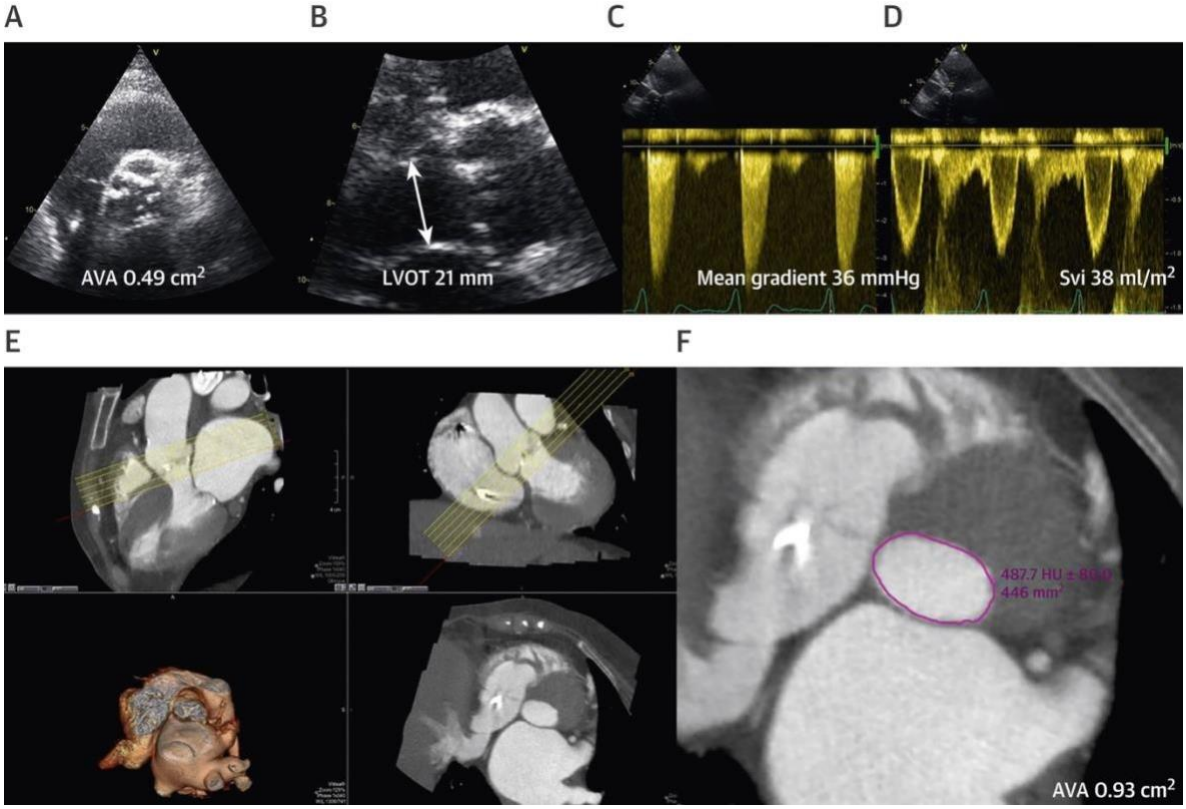
Table 1. Echocardiographic parameters used to assess the severity of Aortic Stenosis

	Mild	**Moderate**	**Severe**
Structural assessment	Mild leaflet calcification OR thickening with some reduction in systolic motion	Mild to moderate leaflet calcification with reduction in systolic motion or Rheumatic valve changes with commissural fusion	Severe leaflet calcification with severe reduced leaflet opening Planimetered AVA < 1.0 cm^2
Quantitative parameters (flow-dependent)			
Peak velocity	2.0 – 2.9 m/sec	3.0 – 3.9 m/sec	≥ 4 m/sec
Median Gradient	< 20 mmHg	20 – 39 mmHg	≥ 40 mmHg
Quantitative parameters (flow-independent)			
Doppler Velocity Index	> 0.5	0.25 – 05	< 0.25
AVA	> 1.5 cm^2	1.0 – 1.5 cm^2	< 1.0 cm^2
AVA index	> 0.90 cm^2/m^2	0.60 – 0.90 cm^2/m^2	< 0.6 cm^2/m^2

The use of 3D imaging techniques, including 3D TTE, multidetector computed tomography (MDCT), or cardiac magnetic resonance (CMR), allows the reconstruction of the LVOT where the cross-sectional area can be measured. This value is introduced in the continuity equation and a hybrid AVA can be calculated and to confirm the severity of AS in in patients with discordant grading.

However, larger severity cut-point values have to be applied when hybrid imaging is used, because hybrid MDCT-Doppler imaging measures larger values of AVA compared to Doppler echocardiography[96]. A recent study shown that there is a comparable correlation between TTE AVA and hybrid MDCT-Doppler AVA without significant reclassification of patients[96] (Figure 4). Furthermore, the prognostic value of the hybrid AVA was similar to the standard AVA. However, larger hybrid AVA cut-points (AVA > 1.2 cm^2) are used to predictmortality compared to Doppler - echocardiography[96,97].

Figure 4. Measure of Aortic Valve Area by Hybrid Imaging



Example of a patient with low-gradient normal flow severe aortic stenosis, with a calculated AVA of 0.49 cm^2 based on 2-dimensional transthoracic echocardiography. **(A)**Tricuspid aortic valve with limited opening. **(B)** The LVOT is measured on a zoomed parasternal view. **(C, D)** The mean transvalvular gradient and the pulsed wave recording of the LVOT and stroke volume index, respectively. **(E)** After aligning the multiplanar reformation planes on the multidetector row computed tomography data, **(F)** the cross-sectional area of the LVOT can be measured and included in the continuity equation. AVA = aortic valve area; Svi = stroke volume index

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1.4.5 Implications of volume states

CKD patients have several conditions, that result in a reduction of transvalvular flow including: left ventricular remodeling (hypertrophy and dilatation), myocardial fibrosis, impaired relaxation with increased filling pressure, systolic dysfunction and low flow state, valvular insufficiencies, right ventricle impairment, and atrial fibrillation[40,98].

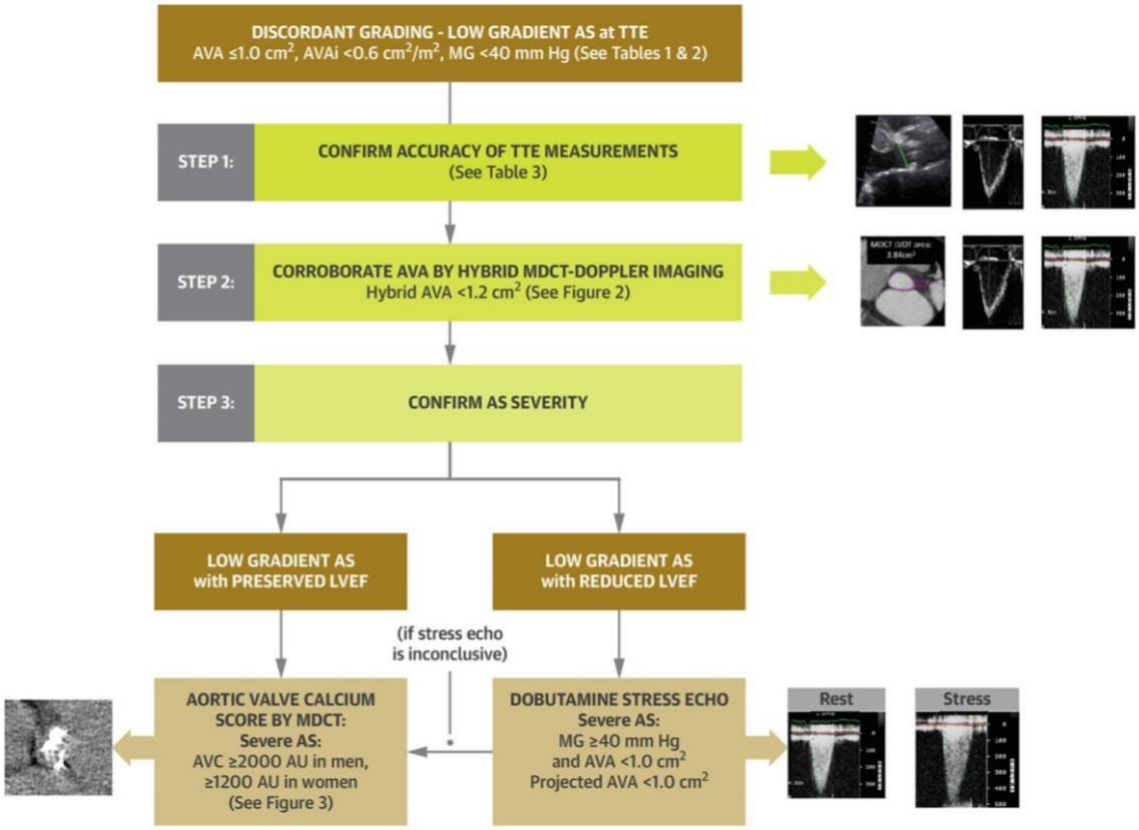
A substantial proportion of dialysis patients with AS (≈ 60%) have a low-flow state[40], classified as low-flow with preserved (EF ≥ 50%) or reduced EF (≤ 50%)[86]. A low-flow state is defined as a volume index < 35 ml/m^2[17,99] and mean transvalvular flow rate (stroke volume/Ejection Fraction) < 200 ml/s[100]. There are two main types of low-flow, low gradient AS:

1.4.5.1 Low-flow, low-gradient AS with reduced EF

The classical low-flow, low-gradient AS is defined by the following conditions: i) stroke volume index ≤ 35 ml/m^2 ii) low gradient with mean gradient < 40 mmHg, and iii) reduced EF (< 50%). The decrease in stroke volume and transvalvular flow rate, are attributable to myocardial dysfunction[86]. Dobutamine stress echocardiography is helpful to differentiate a

truly severe AS from a pseudo-severe AS, providing information on changes in aortic jet velocity, mean gradient, valve area, contractile response and flow reserve measured by the change in EF and stroke volume[101](Figure 5,6). The aim with dobutamine stress echocardiography is to distinguish a severe AS causing LV dysfunction from moderate AS with other underlying causes of LV dysfunction[86]. An increase in effective AVA area > 1 cm^2, with > 20% increase in stroke volume from baseline, suggests that the AS is not severe[102] (Figure 5, 6). Failure to increase the LV stroke volume ≥ 20% complicates the interpretation of AS severity. The projected AVA in normal flow state can be used to overcome this limitation[103].

Figure 5. Algorithm for the Multimodality Imaging Assessment of Patients with Discordant Grading of AS Severity at Doppler Echocardiography



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1.4.5.2 "Paradoxal" low-flow, low gradient AS

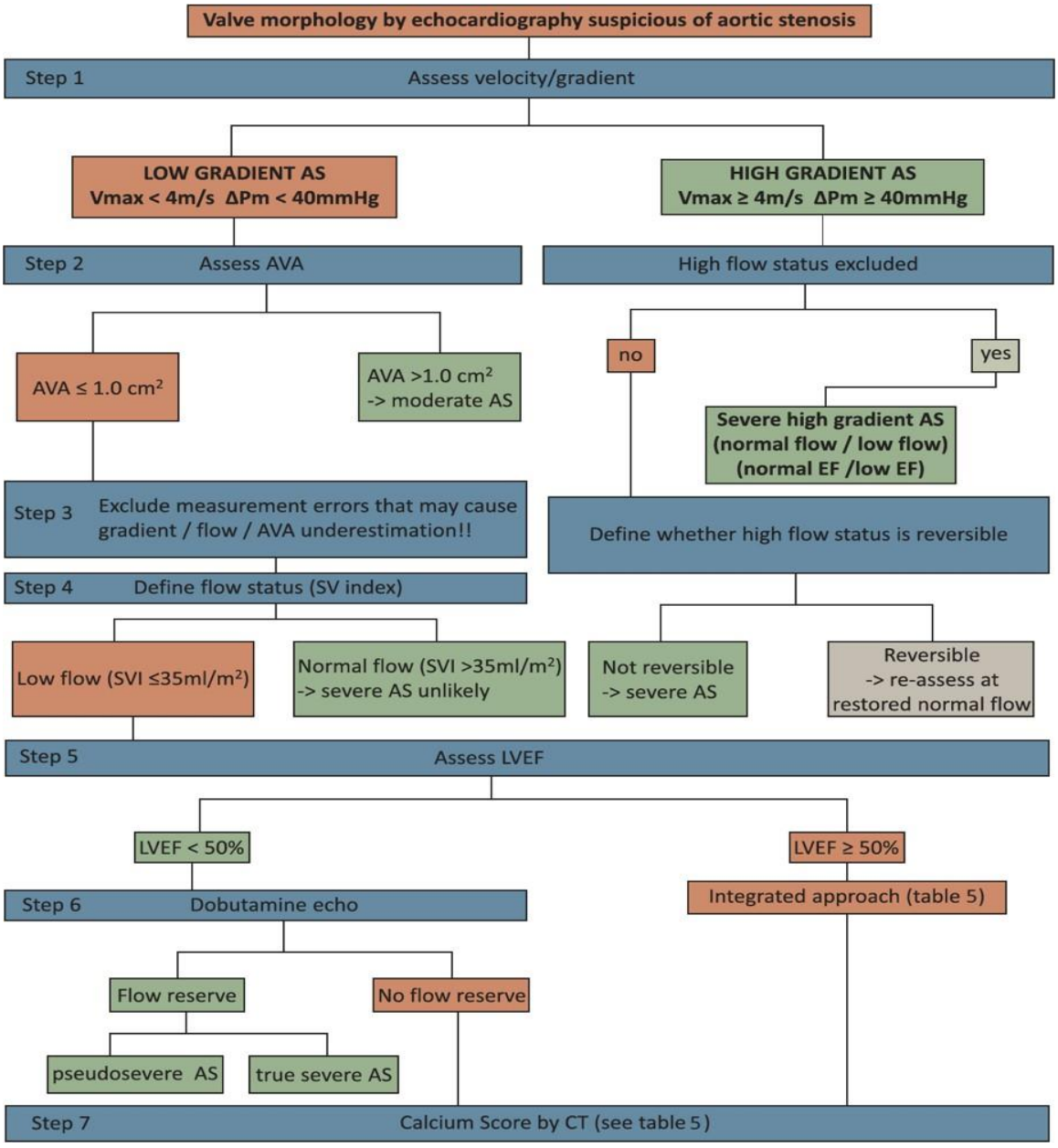
Low-flow, low-gradient AS with preserved EF includes the following conditions: i) stroke volume index ≤ 35 ml/m^2, ii) low-gradient with mean gradient < 40 mmHg, and iii) normal EF (> 50%). The paradoxal low-flow state has been found in patients with small and hypertrophic LV due to remodeling[104] with impaired diastolic filling[100,105]. Most of these patients have a history of hypertension[91], severe mitral or tricuspid regurgitations[106], tachycardias[107], pulmonary hypertension and right ventricular failure[108].

1.4.6 Quantification of aortic valve calcification by Multidetector Computed Tomography (MDCT)

Aortic valve calcium scoring by MDCT correlates with the hemodynamic severity of AS and clinical outcomes[109]. American[18] and European[17] guidelines recommend the use of CT aortic valve calcium scoring to confirm AS severity in patients with classical low-flow, low- gradient

AS, or paradoxal low-flow, low gradient AS, when dobutamine stress echocardiography is contraindicated or inconclusive (Figure 5, 6). Different sex-specific Agaston Units cut-offs values are used in women (> 1200 AU) compared to men (> 2000 AC)[110], as women achieve similar hemodynamic severity of AS as men with less calcification and higher fibrosis degree. However, defining AS severity with aortic valve calcium scoring has not been validated in CKD/dialysis patients[79]. In CKD patients, extra-valvular aortic valve calcium deposits, should be excluded from the estimation of aortic valve calcium to avoid overestimation of AS severity[111]. Aortic valve calcium scoring is a strong prognostic marker of fast disease progression and mortality[112] in general population. Previous studies have shown that valvular and coronary calcium in CKD[113] and dialysis patients[114] are associated with increased cardiovascular and all-cause mortality.

Figure 6. Stepwise approach to grading AS



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1.5 DEFINITION AND STAGING OF KIDNEY DISEASE

1.5.1 Definition

Kidney disease is a global public health problem with increasing prevalence and incidence. It is associated not only with adverse kidney outcomes but also with increased risk of cardiovascular morbidity and mortality[115]. According to KDIGO guidelines the definition of kidney disease is based on structural and functional abnormalities of the kidneys and on their complications linked with worsening health outcomes. Kidney disease is defined by the presence of:

- sustained reduction in estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 for > 3 months

- increased albumin with creatinine/ albumin ratio (ACR) >3 mg/mmol

- pathological abnormalities of kidney structure detecting by imaging, biopsy or function (electrolyte abnormalities)

- preserved GFR with evidence of abnormalities on urinalysis (urine sediment analysis with hematuria, red cast cells)

- history of kidney transplantation[116]

1.5.2 The classification of kidney disease

CKD patients account, according to previous reports, for 8 - 13% of the global population[10] and is classified according to eGFR categories and urine ACR levels. Figure 7 shows the prevalence estimates based on eGFR and urine ACR from the yellow to red categories: 73% for yellow, 18% for orange, and 9% for red[117-119]. Patients are classified to G1- G5 and A1- A3 (Figure 7), since both eGFR and albuminuria should be included in risk prediction models. The colors in the heat map indicate groups of patients at progressively higher risk for major clinical outcomes[119].

1.6 ASSESSMENT OF KIDNEY FUNCTION

The GFR is currently considered the best overall index of kidney function estimation, diagnosis and classification of kidney disease. The GFR is also a strong prognostic marker as it has been independently associated with, adverse kidney outcomes, all-cause and cardiovascular mortality [120,121]. The more accurate tests for the determination of kidney function are to get an estimate of the GFR and to check for proteinuria. Inulin clearance has been the golden standard method for GFR estimation with acceptable precision of radionuclides and iohexol clearance (^{125}I-iothalamate, ^{51}Cr-EDTA, ^{99m}DTPA), they are non-protein bounded, non-metabolized, freely filtered from the glomerulus and without any tubular secretion, maintaining stable plasma concentrations[122-124]. However, this method is time and cost ineffective and not suitable in clinical practice.

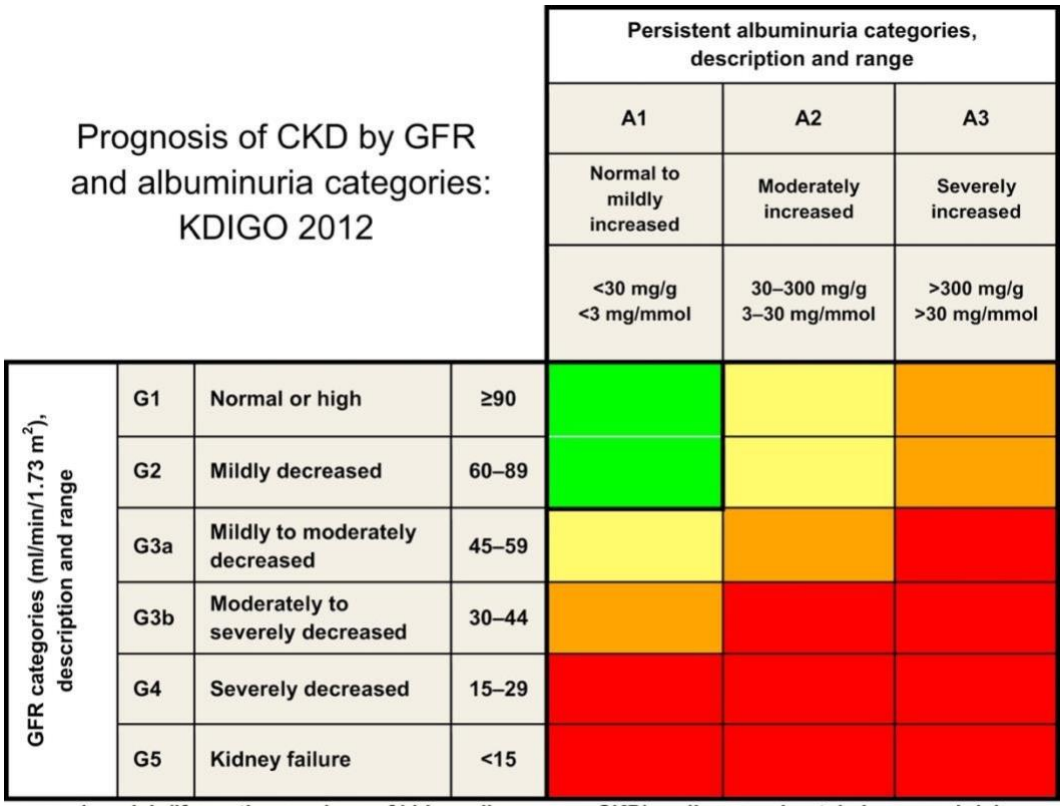
According to clinical guidelines the eGFR has to be reported when serum creatinine is measured[116]. Serum creatinine is a widely used biomarker for the assessment of kidney function and GFR estimation. However, serum creatinine is inaccurate in several situations[125] since it is produced during protein metabolism and excreted almost completely by kidneys.

Kidney disease results in higher tubular secretion of creatinine, but several drugs have an inhibitory action. Changes in muscle mass and protein metabolism, gender, hydration and

nutritional status affect the serum creatinine levels. Older age is associated with loss of kidney function and a steadily increased plasma creatinine concentration[126].

An alternative to serum creatinine is the measurement of Cystatin C, produced by all nucleated cells. It has a low biological variation, and is used as an intrinsic biomarker of kidney function and GFR estimation. Plasma concentrations of Cystatin C are sensitive to kidney function changes, its half-life is shorter compared to creatinine, and it is less influenced by muscular mass, making it a more accurate biomarker in the estimation of kidney function[127]. However, its accuracy is limited in endocrine disturbances such as thyroid dysfunction, steroid administration and inflammatory reactions[128].

Figure 7. Prognosis of CKD stratified by eGFR (Glomerular Filtration Rate) category (G1 - G5) and ACR (albumin/creatinine ratio) category (A1 - A3).



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1.6.1 Equations used in the estimation and prediction of GFR

The National Kidney Foundation Disease Outcomes Quality Initiative recognized the inaccuracies in plasma creatinine and creatinine clearance and suggested estimation of GFR from mathematical predictive equations based on plasma creatinine[130]. Various mathematical and well validated equations, using the serum creatinine concentration, and demographic data, have been developed to estimate kidney function and to assess the burden of chronic kidney disease in epidemiological studies[117].

The most commonly used equations are the Cockcroft-Gault formula[131], the Modification of Diet in Renal Disease Study equation (MDRD)[132] and the Chronic Kidney Disease Epidemiology equation (CKD-EPI)[117]. A Swedish Agency for Health Technology Assessment concluded that Equations based on IDMS-traceable creatinine analyses2 (MDRD, CKD-EPI,

and Lund-Malmö-rev) should be used[133]. Lund-Malmö-rev is developed in Sweden, has good performance as the above mentioned formulas, and is more accurate in the elderly[134] and in individuals with advanced CKD[133]. The Cockcroft-Gault creatinine-based equation is substantially less accurate and should not be used.

2 IDMS = Isotope dilution mass spectrometry, an internationally certified standard for plasma creatinine analysis[124].

Table 2. Equations used in the estimation of kidney function

Name - Unit	**Equation**	**Author, Year**	**Cohort used**
Cockcroft – Gault – ml/min	CrCl = [(140 – age) x weight (kg)] x constant*/ S_Creatinine (µmol/L)	Cockcroft – Gault, 1976[135]	N = 249, 100% males, mean
Modification of Diet in Renal Disease Study equation (MDRD) (ml/min/1.73m^2)	eGFR = 175 x [Serum_Creatinine (µmol/L)/88.4]$^{-1.154}$ x age$^{-0.203}$ x 0.742 (*if female*) x 1.210 (i*f African- American*)	Levey at. al. 1999[132]	N = 1628, Mean age: 50.9 ± 12.7 years, Males: 60%, Mean eGFR: 39.8
Chronic Kidney Disease Epidemiology equation (CKD – EPI) - (ml/min/1.73m^2)	GFR = 141 x min(Serum_Creatinine /κ**,1)$^{\alpha}$ x max(Scr/κ, 1)$^{-1.209}$ x 0.993^{Age} x 1.018 (if female) x 1.159 (if black)	Levey at. al. 2009[117]	N = 5502, mean age: 47 ± 15 years, Males: 57% Mean eGFR: 68 ± 40
Lund - Malmö Formula***	GFR = e$^{X-0.0124 \times Age + 0.339 \times \ln(Age) - 0.226}$	Björk at. al.[136]	N = 850, median Age: 60 (IQR: 26 - 85), Males: 55.8% Median eGFR: 107 (IQR: 45 - 545)
* The published constants are 1.23 for males of any age, and 1.05 for females of any age **For females, the following values are used: Sex = 1.018; α = -0.329; κ = 0.7 For males, the following values are used: Sex = 1; α = -0.411; κ = 0.9[117] CrCl: Creatinine Clearence; eGFR: estimated Glomerular Filtration Rate			
*** pCr < 150: X = 4.62–0.0112 x Plasma_Creatinine pCr ≥ 150: X = 8.17 +0.0005 x Plasma_Creatinine - 1.07 x ln(Plasma_Creatinine)			

The Cockcroft-Gault formula was developed in 1976 to predict the creatinine clearance based on age, weight, height, and plasma creatinine, expressed in ml/min (Table 2). The main limitations of this formula are: i) it has been derived from a small number of elderly and hospitalized population (N = 294), predominantly men, with CKD[131], (Table 2) and ii) the requirement of anthropometric measurements in order to be reported by the laboratories.

The MDRD Study, based on a multicenter trial with 1628 African - American, CKD patients developed an equation that improved the prediction of the GFR from plasma creatinine[132]. After stepwise multiple logistic regression analysis, a simplified 4-variable equation was developed which included the serum creatinine and age, presented on the log scale, gender and race differentiation and was expressed in ml/min/1.73m^2 [132], (Table 2). Compared to Cockcroft-Gault formula, the MDRD Study equation predicted better with less bias and with better accuracy in patients with kidney dysfunction (eGFR < 60 ml/min/1.73m^2)[137]. However, the MDRD Study equation performs more poorly in subjects with normal kidney function. An important limitation of the MDRD formula is the systematic underestimation of measured GFR at higher values, indicated by high negative bias and imprecision[138]. The impact of creatinine variability from laboratory to laboratory, was reduced by the introduction of standardized creatinine assays to the reference isotope dilution mass spectrometry. Thus, further improvement of the MDRD formula was generated[139].

Given the limited precision of the MDRD equation, the systematic underestimations of measured GFR at higher levels, and the overestimation of the CKD prevalence, the CKD-Epidemiology Collaboration group developed and validated a new equation based on serum creatinine that matched the accuracy of MDRD formula at GFR < ml/min/1.73m^2 and was more accurate at GFR > 90 ml/min/1.73m^2 [(117)].

The CKD-EPI equation was developed based on pooled data from several research and clinical populations, encompassed in excess of 8000 individuals, and included the log serum creatinine in a 2-slope linear spline with sex specific knots, sex, race, and age on the natural logarithmic scale[117] (Table 2). The application of CKD-EPI equation in an Australian cohort study of general population leads to a lower estimation of CKD prevalence than the MDRD Study equation, due to reclassification of low-risk individuals to the normal kidney function category[140].

1.6.2 The clinical consequences of eGFR estimated by the different mathematical equations

Many studies have investigated the impact of CKD stage reclassification by the different equations and its impact on the prognosis of patients with concomitant cardiovascular diseases. A meta-analysis of 1.1 million adults evaluated the inferences of estimated GFR using the CKD-EPI equation compared with MDRD Study equation. The authors reported that almost 25% of participants were recategorized to a higher estimated GFR strata than did the MDRD

Study equation, lowering the prevalence of CKD in all the cohorts except for elderly. The reclassified individuals had lower risk for mortality and kidney failure compared to non-reclassified population. Consequently, CKD-EPI equation provides more accurate risk stratification and should therefore be a better choice for risk prediction[141].

However, when the same hypothesis was tested in an unselected cohort of 12394 patients with cardiovascular diseases, Tarantini at. al. found that 15% of participants were reclassified into lower GFR strata, and had a 2-fold higher mortality rate, if the CKD-EPI equation was used, providing a more accurate risk stratification, than MDRD Study equation did. The reclassified

patients were older and had multiple comorbidities[142]. These results were confirmed by a meta-analysis on >20000 heart failure patients. The use of CKD-EPI equation, rather the MDRD Study equation, increased the prevalence of kidney disease in patients with heart failure with preserved and reduced ejection fraction. However, the eGFR was strongly associated with the all-cause death only in heart failure patients with reduced ejection fraction[143].

A recent prospective, multicenter statewide registry study, compared the accuracy and risk prediction of eGFR equations in the risk for adverse outcomes (AKI, new requirement of dialysis, in-hospital mortality and transfusion) following PCI and the impact of eGFR by the various equations in drug dosing recommendations. More than 128000 patients with ischemic heart disease who underwent emergent or elective percutaneous coronary intervention, were included[144]. CKD-EPI equation was more accurate in the prediction of mortality and stratification for the kidney outcomes. Moreover, the study found noticeable disagreements up to 45% between CKD-EPI and Cockcroft-Gault equation, and only 15% between CKD- EPI and MDRD Study equation, in eGFR estimation, and drug dose adjustment between the various equations. The Food and Drug Administration recommends the use of CKD-EPI equation for the GFR estimation, with the difference that the eGFR will be individualized for drug dosing and expressed in ml/min (https://www.fda.gov/media/78573/download).

1.7 DIALYSIS

Kidney failure is associated with declined body functions, coma and death if left untreated. Kidney replacement therapy (KRT) by dialysis or renal transplantation are the only means to extend survival[145]. Previous studies reported in 2010, that 4.9 - 9.7 million people worldwide were estimated to require kidney replacement therapy, but only half or less of them had access to it[146]. The prevalence of kidney failure and the demand for dialysis is growing due to aging of population and higher prevalence of hypertension and diabetes mellitus[10,147]. Hemodialysis and peritoneal dialysis are the main dialysis modalities. Hemodialysis is usually performed thrice per week over 4 hours, whereas peritoneal dialysis is performed continuously. The KRT maintains a kidney equivalent function to anuric patient of only 5 - 10 ml/min for urea and creatinine[148]. Oral phosphate binders are indicated to maintain phosphate concentrations close to normal range. Hemodiafiltration, based on convective transport, enhances the removal of middle-sized molecules such as b2-microglobulin and FGF-23, but still their hemodiafiltration is still far from normal kidney removal rates[149].

1.8 CARDIOVASCULAR DISORDERS AND PROGNOSIS OF CKD PATIENTS

Cardiovascular disorders are very common but are more frequently unrecognized and undertreated in CKD patients than in general population[150]. Hypertension and diabetes mellitus are common causes of CKD[151]. However, the associations of kidney function and albuminuria with cardiovascular risk are independent of these traditional factors[152]. The cardiac remodeling in CKD patients is characterized by left ventricular hypertrophy (LVH), interstitial fibrosis, diastolic impairment and capillary dysfunction. More than 80% of patients who initiate dialysis have developed LVH promoted by anemia and arterial stiffness. LVH is associated with deteriorated systolic and diastolic function, and congestive heart failure in CKD patients. Dyslipidemia in patients with kidney dysfunction and albuminuria becomes atherogenic[153]. In a population-based study of > 1.1 million people with GFR < 60 ml/min/1.73m^2, the prevalence of ischemic cardiomyopathy (IHD) was 14.9% and 7.1% had congestive heart failure[154]. IHD is the leading cause of morbidity and death in CKD patients. CKD has been independently associated with higher mortality risk with an inverse graded relationship between worsening eGFR and mortality rate[154]. Even a mild reduction of kidney function with 5 ml/min/1,73m^2 has been associated with 22% higher risk of cardiovascular death[155].

1.9 CARDIOVASCULAR OUTCOMES OF DIALYSIS PATIENTS

Many cardiovascular risk factors are prevalent in dialysis patients, including hypertension[156], diabetes mellitus[157], fluid overload and congestion[158]. However, many factors that are affected by the uremic milieu including inflammation, oxidative stress, macrophage infiltration, endothelial dysfunction, arterial calcification or osteodystrophy, have been associated with higher risk for cardiovascular diseases[150]. Although, dialysis and transplantation improve life expectancy in dialysis patients, cardiovascular and non-cardiovascular mortality remains higher than in age-matched populations with normal kidney function[159]. The prevalence of cardiovascular diseases in hemodialysis patients is over 60%[160] while the reported cardiovascular mortality is > 50%[161]. Compared to general population, dialysis patients have 20-fold higher cardiovascular mortality, associated to LVH[162] and other non-traditional risk factors such as anemia, chronic volume overload, inflammation and mineral bone disorders[158]. Recent studies of implantable loop recorders in patients with kidney failure have shown that in > 50% of cases, the main cause of cardiovascular related death is fatal arrythmias such as bradycardic arrythmias or pulseless electrical activity and only 25% of cases, have been attributed to myocardial infarction[160].

1.10 MANAGEMENT OF AS

The only management available to patients with symptomatic severe AS is mechanical relief of valvular obstruction with implantation of prosthetic valve either surgically or transcutaneously. Moreover, there is no medical therapy to prevent leaflet calcification or to attenuate disease progression[17].

1.10.1 PHARMACOLOGICAL THERAPIES

Recent studies have found multiple pathophysiological mechanisms that are involved in the development of aortic valve calcification and progression to AS including atherosclerosis, inflammation, lipid deposition, oxidation, mineralization, bone deformation and genetic factors with elevated lipoprotein(a)[48,50,163,164]. New insights in the valve biology and development of novel therapeutic agents for calcific AS may be possible to prevent or attenuate the progression to severe AS. Recent research has focused to the development of pharmacotherapies that are directed at targets implicated in the pathogenesis of AS, but further research is required to evaluate their clinical effectiveness.

1.10.1.1 Low-density lipoprotein cholesterol (LDL-C) and Lipoprotein (a) [Lp(a)]

Familiar Hyperlipidemia (FH) has been strongly associated with AS[165]. The SAFEHEART study identified a higher incidence of AVR in patients with FH[166]. In contrast to lipoprotein(a), LDL-C, has not been associated with hemodynamic progression of AS[167]. Randomized clinical trials have shown progression of AS despite aggressive LDL-C lowering. In SALTIRE trial over 50% reduction of LDL-C with atorvastatin 80 mg had no impact on AS progression[168]. Similarly, in the SEAS randomized trial treatment of hyperlipidemia with simvastatin and ezetimibe or placebo, did not reduce the composite outcome of combined aortic valve events in patients with AS[169]. In the ASTRONOMER trial LDL-C lowering with rosuvastatin by 55% had no effect on disease progression in patients with moderate to severe AS[170].

Studies on Mendelian randomization have shown a causal role for Lp(a) in AS[48]. A post hoc analysis of the FOURIER trial suggested that the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor[171], by a simultaneous lowering of LDL-C and more than 30% reduction of Lp(a) showed protective effects against the calcification of aortic valve[172]. This strategy has been beneficial only to a minority of patients as, increased Lp(a) concentration accounts for only up to 7% of AS cases[173].

1.10.1.2 Activators of γ-MGP

Vitamin K a fat-soluble vitamin, is composed of two types:

-The K1, essential in the integration of functional coagulation factors II, VII, IX, and X and the

- The K2, that is involved in the inhibition of arterial calcification and is crucial for the activation of γ-MGP an inhibitor of cardiovascular calcification. It has been observed in animal models that loss of γ-MGP promotes valvular calcification[174]. Epidemiological studies indicate that vitamin K (the K2 form) has protective effect against vascular calcification and might retard the progression of aortic valve calcification[175]. Treatment with vitamin K antagonists (VKA) results in accentuated calcification of aortic valve. DANCAVAS trial demonstrated, that VKA treatment was associated with a raise in non-contrast enhanced CT detected aortic valve calcium by 6%/year[176]. A small prospective proof of concept trial evaluated the anti-calcification effect of daily vitamin K supplementation, on calcific aortic valve disease of 99 patients. The study demonstrated a slower progression of aortic valve calcification in the vitamin K group[177].

1.10.1.3 Renin Angiotensin Blockers

Angiotensin Converting Enzyme Inhibitors (ACEI) have been suggested from American and European Guidelines in patients with AS to control hypertension and to reduce the myocardial fibrosis in AS patients[17,18]. Angiotensin Receptor Blockers (ARB) exerts antifibrotic and protective properties in the endothelia integrity. In animal studies where hyperlipidemic rabbits were used, the ARBs inhibited the trans-differentiation of valvular fibroblasts to myofibroblasts, protecting the aortic valve leaflets from lesions[178]. Clinical studies have reported attenuated remodeling of aortic valve, slower progress to hemodynamic disease[179], and better clinical outcome following AVR among patients treated with ARB[180]. More specific treatment with ARB in AS-patients following TAVR, was associated with significantly lower 1-year mortality, with up to 50% relative risk reduction, and 5% absolute risk reduction[181].

1.10.1.4 Phosphate/calcium -metabolism associate targets

Epidemiological studies have demonstrated a positive association between increased serum phosphate levels withing normal range and the risk for new onset AS[182-184], implying that mineral-targeted treatment can be a preventive strategy. CaLIPSO trial showed that treatment with SNF-472 (inhibitor of hydroxyapatite formation) attenuated aortic valve calcium score in long-term hemodialysis patients, but the effects on hemodynamic disease progression and clinical endpoints in patients at high risk for vulnerable outcomes following AVR have to be further evaluated[79]. In another study of 360 patients with kidney failure and secondary hyperparathyroidism, the use of calcimimetic drug cinacalcet with lower dose vitamin D was found to be associated with slower progression of aortic valve calcification. But it remains unknown whether this drug combination would prevent or halt hemodynamic progression of AS in this population[185].

Preclinical research suggested that the effectiveness of pharmaceutical strategies directed at targets inferring with RANKL/RANK/osteoprotegerin axis (denosumab) or osteoclastic activity (bisphosphonates), conditions linked with bone turnover, osteoporosis and aortic valve calcification[186,187]. In SALTIRE trial, it was evaluated whether target medication against calcification process could slow the progression of AS. In this double blind randomized controlled trial, 150 AS-patients were randomized to treatment with denosumab vs placebo injection and alendronate vs placebo capsule. The study concluded that neither denosumab or alendronate acid were shown to affect the progression of aortic valve calcification by any change in aortic valve calcium load or peak jet velocity[188]. All these studies have examined

potential interventional targets for AS and further research is needed to evaluate potential treatment strategies.

1.10.2 AORTIC VALVE REPLACEMENT

AVR with implantation of a prosthetic valve surgically or transcutaneously, is the only available treatment for suitable patients with severe, symptomatic and high-gradient AS regardless of LVEF[17,18] Since TAVR appeared, the number of AVR has increased, with a decreasing proportion of SAVR closed to 6/4, in favour to TAVR[189]. The life expectancy in middle aged patients < 65 year after AVR is similar to that of the general population[190].

However, the findings from the VALVENOR study indicated that inoperable AS-patients have increased cardiovascular mortality close to ≈ 45%, associated mainly with congestive heart failure and sudden death[191]. The increased cardiovascular mortality risk of the inoperable patients paralleled the severity of AS. Those with moderate and severe AS had 47% and 3.5-fold higher cardiovascular mortality risk than those with mild AS. The life expectancy in middle aged patients < 65 year after AVR is similar to that of the general population[190]

1.10.3 TIME TO INTERVENE

AVR either with SAVR or TAVR is accompanied by improved survival, quality of life, symptoms relief and exercise capacity[192,193]. Two interventional modes are recommended: i) open cardiac surgery with replacement of aortic valve with mechanical or bioprosthetic valve. Current guidelines recommend surgical SAVR as a class I indication for symptomatic patients with severe AS and low surgical risk, and ii) percutaneous implantation of a new aortic valve recommended for symptomatic patients with AS ineligible for surgical intervention due to high surgical risk and periprocedural mortality scoring[17,18].

Patients with indication for AVR require well-timed treatment. According to the results of a recent study based on ≈ 23000 patients with severe AS referred for AVR, mortality was significantly higher on the waiting list for SAVR or TAVR[194] indicating that expanding efficient practices and developing a rational classification that prioritizes the sickest AS-patients is essential to meet the demands of a the growing AS population[38]. The requirement to have symptoms to qualify for surgery is currently being investigated. As many as 50% of patients with severe AS at the time of diagnosis are asymptomatic.

Guidelines recommend AVR in selected asymptomatic patients with severe AS either with pathologic exercise test or LV dysfunction (LVEF < 50%)[17,18]. Meanwhile, a watchful waiting or active surveillance strategy is recommended for the majority of asymptomatic patients. Intervention is planned when symptoms emerge or left ventricular impairment develops. A retrospective analysis of ≈ 1520 conservatively treated patients with severe AS reported that only ¾ of them were alive at 5-year of follow-up[195].

Recently the results of the AVATAR (Aortic Valve ReplAcemenT versus conservative management in Asymtomatic seveRe aortic stenosis)[196] on 157 patients with severe asymptomatic AS, randomly allocated to early surgery or conservative treatment, documented significantly lower rates of the primary composite endpoint (all-cause mortality, acute myocardial infarction, stroke or unplanned hospitalization for heart failure) in the surgical group. Although, these results need to be further corroborated from larger studies and over a longer period of follow-up, they suggest that early AVR strategy might improve outcomes in patients with asymptomatic AS.

1.10.4 MODE OF INTERVENTION

The decision to intervene as well as the type of procedure recommended is based on the pre-procedural evaluation, and short- and long-term risk assessment of patients with AS. Several factors affect the choice of interventional method, including age, patient preference, bioprosthetic valve durability, avoidance of patient-prosthesis mismatch, surgical or interventional risk, the risk for reintervention and risks associated with long-term anticoagulation treatment.

The European recommendations[17] suggest SAVR for low-surgical risk (STS-PROME (Society of Thoracic Surgeons Predicted Risk of Mortality)/EuroSCORE II (European System for Cardiac Operative risk Evaluation) < 4%) patients ≤ 75 while the American guidelines recommend SAVR for patients < 65 years with life expectancy > 20 years[18]. Conversely, TAVR is recommended for severe symptomatic patients with AS, ineligible for surgical intervention due to high surgical risk (STS-PROME/EuroSCORE II > 8%) and periprocedural mortality scoring, aged ≥ 75 years and ≥ 65 years according to European recommendations and American guidelines respectively[17,18]

The choice between TAVR and SAVR remains a matter of controversy in patients suitable for both methods and is of particular importance as TAVR utilization expands to younger and lower-risk patients. The long-term safety and efficacy of TAVR has been evaluated but still there is a paucity of data on the longer-term comparison with SAVR. The SURTAVI trial compared the mid-term clinical outcomes after TAVR and SAVR among patients who were at intermediate surgical risk. The CoreValve and Evolut R bioprostheses were used. The 2-years non-inferiority analysis showed no-difference in the combined endpoint of all-cause mortality and disabling stroke. The authors reported differences in the procedural complications; SAVR was associated with higher risk of atrial fibrillation and acute kidney injury, where TAVR was related with higher incidence of vascular complications and need for permanent pacemaker[197].

1.10.4.1 AVR in intermediate risk patients

The PARTNER 2 cohort trial compared the 5-year long-term clinical outcomes, valve function and quality of life in AS-patients with intermediate surgical risk, randomized to TAVR or SAVR. The balloon-expandable SAPIEN XT heart valve was used. The authors found similar rates of death from any cause or disabling stroke between the two groups during the 5-years of follow-up period, with higher incidence of all-degrees paravalvular aortic regurgitation in the TAVR group[198]. The results from the analysis from 2 to 5 years showed significant higher incidence of the combined endpoint of all-cause death and stroke and higher rates of all-cause death in the TAVR group. Possible explanations for this observation included higher rates of more than mild paravalvular regurgitation after TAVR, and higher incidence of untreated significant coronary artery disease in the TAVR than in the surgery group, that affected the long-term outcomes[198]. These findings raised concerns regarding the long-term outcomes after TAVR, and were confirmed from a meta-analysis of 4 available randomized trials by Zhang at. al[199]. While the 2-year results for all-cause mortality, and the combined outcome of all-cause mortality and cardiovascular mortality were comparable for the two methods, the late differences in the 2- to 5-years results, favoured surgery.

1.10.4.2 AVR in low-risk patients

The continuous improvements in TAVR, the lower occurrence of periprocedural complications (less paravalvular regurgitation, permanent pacemaker, stroke, and vascular complications) and the evidence of similar clinical outcomes and valve hemodynamics, comparing SAVR and TAVR in high and intermediate risk patients, have extended the indication for TAVR[18]. Two randomized trials in low surgical risk patients have shown superior or similar clinical outcomes

for TAVR versus SAVR[200]. The 2-year results from the PARTNER 3 low-risk trial that compared the SAPIEN 3 TAVR versus the standard SAVR found a lower but still significant difference in favour of TAVR for the composite of death, stroke and rehospitalization for heart failure, but no significant difference for death or stroke alone[200]. The 5-year follow-up from the NOTION study compared the clinical and echocardiographic outcomes between CoreValve self-expanding prosthesis versus SAVR, in patients with severe isolated AS at low surgical risk. The authors did not demonstrate significant difference in the composite of all-cause death, stroke or myocardial infarction between TAVR and SAVR[201], although higher rates of prosthetic valve regurgitation and higher incidence of new pacemaker implantation were found in the TAVR group[201]. The 8-years analysis from the same low-risk trial, so far, the longest follow-up for a randomized trial, reported non-inferiority compared to SAVR, with similar rates in all-cause death or the composite of all-cause death, stroke and myocardial infarction[202]. Hemodynamic results were significantly better for TAVR with a lower rate of valvular deterioration and similar rates of prosthetic valve failure between the two groups[202].

One-half of TAVR recipients develop coronary artery disease with 50% of them having multivessel disease[203] and the limited access to the coronary arteries with failure of percutaneous intervention close to 10% remains a matter of concern[204,205]. Moreover, patients with ST-elevation myocardial infarction after TAVR have significantly prolonged door - to balloon time and four-times higher PCI failure rates compared to patients without TAVR[206]. Thus, the TAVR implanted valve durability with still higher rates of conduction disturbances and paravalvular regurgitation together with failure in cannulation of coronary arteries after TAVR raises major concerns and has to be evaluated with caution, before the extensive utilization of the method in younger and low risk population.

1.10.5 MECHANICAL VS BIOPROSTHETIC VALVES

Prosthetic valve selection in AS-patients is a complex decision based on surgical risk, potential need for anticoagulation and bleeding risk, valve durability and potential risks for reoperation, life longevity and comorbidities, patient preference and plans of pregnancy in women in childbearing age, and finally expected hemodynamics for valve type and size[17,18]. Overall, recipients of MAV experience higher risk of bleeding complications due to anticoagulation[207,208] whereas those who received BAV might experience higher hazards of reoperation[209,210]. While structural valve deterioration decreases with advanced pre-operative age, the risk of bleeding increases with advanced age[211]. Therefore, pre-operative age is one of the most important factors when selecting prosthetic valves, showing the time-dependent benefit/risk ratio between bleeding complications and need for reoperation. The recent European Society of Cardiology guidelines (ESC 2021)[17] is in line with the American Heart Association/American College of Cardiology (AHA/ACC) guidelines[18], takes in consideration the differences in valve relating complications, although their differences in age limits, regarding the selection of MAV or BAV[212]. Therefore, the risk/benefit ratio between major bleedings, thromboembolic events and the risk for reoperation favours the implantation of MAV in patients younger that 50 years according to the American guidelines[18] and under 60 years in the European guidelines unless anticoagulation is undesired, contraindicated or cannot be appropriately monitored[17,18]. Conversely, both American and European guidelines are consistent in their recommendation of BAV implantation in patients > 65 years of age[17,18]. For middle aged patients both mechanical or bioprosthetic valves are acceptable and the choice should be individualized through a shared decision process on advantages and limitations, depending on the patients' characteristics and preferences.

VKA requires regular monitoring of International Normalized Ratio, interacts with both food and several drugs, and can be harmful in case of accidents during physical or occupational activities. In general, recipients of BAV do not require chronic anticoagulation treatment but

patients < 50 years of age experience higher and earlier incidence of bioprosthetic valve deterioration[209]. The predicted 15-year risk of bioprosthetic valve reoperation due to structural deterioration increases from 22% for patients at 50 years, to 50% for those at 20 years[18]. The likelihood of BAV deterioration in patients > 65 years at 15 - 20 years following AVR, is only 10%. Reoperation of BAV is associated with increased in hospital and long-term mortality due to advanced age and higher burden of comorbidities[213,214]

Regular anticoagulant therapy is indicated in all patients with mechanical valves, to prevent valve thrombosis and thromboembolic events[215,216]. A BAV is preferred in women of childbearing age, given the risks related to anticoagulation treatment and thromboembolism during pregnancy if a MAV is implanted[17]. Generally, the risks related to anticoagulation treatment are acceptable in patients with good adherence to their anticoagulation regime[217]. MAV may be favoured in patients with other indications for permanent anticoagulation like atrial fibrillation, or high risk of reoperation due to porcelain aorta or prior radiation mediastinal damage[16,218].

Risk scores including the EuroSCORE II (http://www.euroscore.org) and the STS risk calculator (http://www.riskcalc.sts.org) are used to estimate the perioperative mortality during AVR. However, these scores are imperfect as they do not include information on patients' frailty, prior mediastinal radiation or porcelain aorta[29]. Skills and experience of the surgical team affect the periprocedural mortality during AVR[219].

Older age and multiple concomitant comorbidities are associated with both increased periprocedural and long-term mortality[220,221]. The extended utilization of BAV in younger and low-risk patients may result in future reoperation at a higher age with poor impact on survival[222]. However, transcatheter valve-in-valve implantation gives the potential to replace surgical reoperations in patients with bioprosthetic valve deterioration, although it could result in an intervention at higher older, with poor prognosis[223] and suboptimal hemodynamics with higher post-implantation gradients[222,224]. This option influences the discussions regarding the trade-offs between mechanical and bioprosthetic valves.

1.11 AORTIC VALVE REPLACEMENT IN CKD PATIENTS

1.11.1 Prognosis of CKD patients with AS

Kidney disease is common in patients undergoing AVR and its presence has been independently associated with major complications and poor outcomes[225]. The reported prevalence of CKD in patients undergoing SAVR varies from 33.7% to 38%, with 7.2% to 17% of them having moderate or severe kidney disease[13]. In the inoperable and high-risk cohort of PARTNER trial, 70% of patients present with moderate or severe CKD[226].

The presence of AS in CKD patients is associated with a higher than 50% mortality at 4 years of follow-up[226]. Although CKD patients with AS are more symptomatic compared to non-CKD individuals[227], AVR is offered less frequently to them, due to high surgical risk, frequent occurrence of periprocedural complications, raised in-patient mortality and poor long-term outcomes after AVR[228].

1.11.2 Aortic Valve Replacement in Kidney Disease patients

AVR is recommended in CKD patients, even though there is limited evidence whether to intervene, when (before or after symptoms debut) or how (surgical or transcutaneous replacement)[83]. SAVR remains the main treatment of AS but TAVR has emerged as the preferred alternative modality. However, any large randomized controlled trial that compared SAVR with TAVR have excluded patients with severe CKD[20,83,193,197] limiting the

generalizability of their results to this population. Recent advances in TAVR and SAVR have extended AVR to elderly patients with comorbidities, considered previously inoperable[198,229]. Patients with advanced CKD and AS have long been considered not to be candidates for AVR as the potential benefit of AVR is still uncertain in this challenging group[230] due to high surgical risk[228,231,232]. The American and European guidelines for valvular heart diseases lack specific recommendations regarding the optimal selection of prosthetic valve (mechanical, bioprosthetic or transcatheter) in CKD and dialysis patients with concomitant AS[18,84].The available findings indicate that AVR in CKD patients is superior to conservative management as it has been associated with significant reduction of all-cause and cardiovascular mortality[227,228] The determination of interventional risk and the correct choice of method for CKD patients requires multidisciplinary approach including assessments of ischemic cardiomyopathy, other valvular lesions, life expectancy and frailty[79]. The pre-procedural evaluation has to be performed by multidisciplinary teams of clinicians, cardiac surgeons, nephrologists, and anesthetists. Such teams can perform an individualized risk-benefit analysis of the available alternatives[79]. In a shared decision-making process, patient preferences should also be included[3]. However, there are conflicting results regarding the prognosis after AVR in CKD patients[233,234].

1.11.3 IN-HOSPITAL OUTCOMES AFTER TAVR IN CKD PATIENTS

Several periprocedural complications are common in CKD patients during AVR including stroke[235], major vascular complications[236], paravalvular insufficiency[237], conduction disturbances that need permanent pacemaker implantation[238] and the occurrence of AKI[239]. Mohananey at. al. explored the effect of pre-procedural CKD on in-hospital outcomes following TAVR[240]. In a total of more than 42000 patients, 33.7% had CKD or kidney failure. The authors reported significantly higher rates of in-hospital mortality, AKI, longer hospital length of stay, conduction disturbances requiring permanent pacemaker implantation and major bleedings requiring blood transfusions compared to no-CKD patients. CKD patients were more likely to have cardiac and vascular complications compared to their non - CKD counterparts[240].

TAVR versus SAVR in patients with moderate kidney dysfunction is associated with lower rates of early death and periprocedural mortality. Observational data from Kumar at. al. compared the short-term primary outcome of in- hospital mortality, AKI, dialysis requiring AKI, and stroke after TAVR or SAVR in CKD patients[241]. The study included 2820 and 4054 CKD patients who underwent TAVR or SAVR respectively[241]. In propensity match analysis, TAVR was associated with significantly lower odds ratio of in-hospital and 30-day mortality, dialysis required AKI and stroke[241]. A higher but not statistically significant risk for conduction disturbances requiring permanent pacemaker implantation was observed in the TAVR group.

Cheng at. al. in a meta-analysis of 9619 patients with CKD stage 3 defined as eGFR $\leq$ 60 ml/min/1.73m^2 showed that CKD patients who underwent TAVR had lower mortality rates (6.1 vs 10.2%)[242] and lower risk of blood transfusions and dialysis requiring AKI. On the contrary, patients who underwent TAVR had higher risk of conduction disturbances requiring permanent pacemaker implantation[242].

1.11.4 Short-term mortality after AVR in CKD patients

Preoperative kidney dysfunction has been strongly associated with the short- and mid- term outcomes following TAVR with reported 30-day mortality of 10% and a 1-year mortality of 26%. The short- and midterm outcomes after AVR in CKD patients are more amplified in the lower eGFR categories[243-245]. Results from a meta-analysis of more than 42000 CKD patients and > 51000 controls who underwent TAVR demonstrated a steep increase in 30-day risk and long-term mortality in CKD patients compared to non-CKD controls[246]. Compared to CKD stage 3, the 30-days mortality risk raised from 26% to 89% for those with CKD stage 4. Given

the high burden of cardiovascular risk factors and cardiovascular diseases such as ischemic cardiomyopathy and heart failure in CKD patients with severe AS, although they are often younger[226] they present an inverse graded relationship between more advanced pre-procedural CKD stages and risk of cardiovascular mortality[225,247]

1.11.5 Long-term mortality after AVR in CKD patients

Both SAVR and TAVR are associated with improved survival and quality of life, but the long-term mortality following AVR in CKD patients with AS remains high. Pre-operative CKD is independently associated with higher overall mortality rates in AS-patients after either SAVR or TAVR. The risk of death after AVR has been significantly increased with reduced kidney function. Allende at. al. found that pre-existed CKD (defined as eGFR < 60 ml/min/1.73m^2) was associated with higher risk of death, while mortality increased significantly with eGFR < 30 ml/min/1.73m^2. The presence of atrial fibrillation was associated with 2-year mortality rates > 70% [225].

Thourani at. al. analyzed the all-cause mortality after SAVR in 2408 patients with various stages of baseline kidney function varying from normal to kidney failure[13]. The study found that SAVR provided a 5- and 10- year survival rate of 65% and 42% in patients with CKD stage 3, compared with 79% and 59% in those with mild kidney disease. Interestingly, the mortality rates between recipients of BAV or MAV valves did not differ significantly[248]. Analogous findings were reported in another group of CKD patients who underwent AVR with SAVR or TAVR[43].

In the randomized part of the US Pivotal High Risk Trial, of 797 patients with overall CKD stages 3 - 4 (69.7%), 391 patients were allocated to TAVR and 359 to SAVR[249]. Self- expanded valve was used in the TAVR group without difference of CKD prevalence between the groups (patients with eGFR < 20 ml/min/1.73m^2 were excluded). At 3 years of follow-up there were lower rates of the primary composite endpoint of all-cause mortality, stroke, myocardial infarction and need of dialysis in the CKD patients who underwent TAVR[249]. The study showed that TAVR was associated with lower incidence of AKI and life-threatening bleedings but higher rates of vascular complications and conduction disturbances requiring pacemaker implantation[249].

1.11.6 SAVR versus TAVR in CKD patients

When considering SAVR or TAVR in the settings of severe AS, the presence of CKD raises concerns as it is associated with increased risk of AKI and structural valve deterioration mainly in bioprosthetic valves[250,251].

1.11.6.1 Acute kidney injury after Aortic Valve replacement

The development of AKI during AVR is associated with high mortality and increased risk for kidney replacement treatment[252]. Many comparative randomized trials[19,20,197] have shown an increased risk of AKI with SAVR but comparable rates of AKI requiring dialysis between SAVR and TAVR[253]. The expanding indication of TAVR has reduced by 50% the occurrence of periprocedural AKI events[254]. SAVR is associated with higher levels of systemic inflammatory reaction caused by extracorporeal circulation, lower incidence of bleeding and blood product transfusion. Moreover, AKI during SAVR can be caused by hypothermic and ischemia-reperfusion injury or kidney embolic events after aortic cannulation[255-257].

AKI after TAVR is a common complication that occurs in 12% - 57% of patients and has been associated with increased risk of dialysis and mortality[258]. The reported incidence of AKI is significantly lower after TAVR than SAVR[253], and varies widely among previous studies who

have used different definitions of AKI, making it difficult to compare AKI incidence across different studies[259]. Despite the recommendations of guidelines for preventive measures once AKI occurs the therapeutic options used to reverse it are limited[17].

Several potential mechanisms contribute to the development of AKI such as, history of hypertension[260], lower kidney function at baseline[261], suprarenal aortic atheroma burden[262], periprocedural larger contrast volume[263], red blood cell transfusion[24], transapical approach[264], and higher logistic EuroSCORE[265].

Earlier studies have demonstrated that resolved AKI and worsening CKD in patients undergoing TAVR is associated with a two-times higher mortality rates compared to those who did not experienced AKI[266]. Every 10 ml/min/1.73m^2 reduction in eGFR has been associated with 18% increase of risk of death[228].

Findings from observational studies including high and low risk patients undergoing TAVR demonstrated that 89% of CKD participants either stabilized or improved their kidney function post-TAVR[233,267]. Witberg at. al. found that TAVR was associated with more than 10% higher eGFR compared to baseline in 30% of study participants[266]. A possible explanation for this finding is that TAVR enhances kidney hemodynamics and many patients may improve their kidney function until they will be discharged from the ward[233]. Variables associated with improved post-TAVR eGFR were higher baseline eGFR, transfemoral access[233] and female sex[266].

1.11.6.2 Management of AKI

Some commonly used periprocedural strategies can reduce the risk of acute kidney insult. These are according to the latest recommendations by the Kidney Disease: Improving Global Outcomes group[268]:

- Patients with pre-procedural CKD should be discussed with the nephrologists for optimal management of cardiorenal syndrome[269]
- Avoidance of hemodynamic instability by volume expansion through the administration of isotonic crystalloids[79] and diuretics or ultrafiltration
- Minimize the risk of contrast induced AKI and prevent systemic atheromatic embolization or bleeding events[269]. Contrast should be minimized with preferential use of iso-osmolar or low-osmolar contrast[268]
- Avoidance of hypoglycemia[270] or administration of other nephrotoxic drugs[268].

1.11.6.3 Structural valve Deterioration after AVR in CKD patients

The presence of pre-procedural CKD is an established risk factor for structural valve deterioration (SVD)[271] that appears as thickening, calcification or tearing of the bioprosthetic material leading in hemodynamic impairment and bioprosthetic valve deterioration[272,273]. The presence of extensive calcification of the device landing zone for TAVR may lead to under-expansion and asymmetry of the self-expanding devices that results in higher degrees of paravalvular regurgitation and thrombosis[274]. Garcia at. al. in analysis of PARTNER 2A trial and SAPIEN 3 Intermediate Risk Registry compared the rates of primary composite endpoint of major adverse cardiac and renal events as well as the secondary endpoint of bioprosthetic durability at 5- years among CKD patients who received bioprosthetic valves transcutaneously (SAPIEN XT, SAPIENT) or surgically (PARAMOUNT)[275]. Worse clinical valve related outcomes were more likely to occur in the second generation SAPIEN XT. Conversely, comparable rates of the primary endpoint were found between recipients of SAPIEN 3 and surgical bioprosthetic valves[275]. The 5-year incidence of bioprosthetic valve failure was low

without significant differences between surgical and transcutaneous implanted bioprosthetic valves. Predictors of bioprosthetic valve failure were female gender, diabetes and younger age[275].

The latest advances in TAVR technology may explain these findings as a better valve patency is achieved with the SAPIEN 3 and surgical bioprosthetic valves[251]. Additionally, the tissue used for the current TAVR models is more durable and similar to that used for surgical bioprostheses with equivalent anti-calcification treatment[251].

1.12 AVR IN DIALYSIS PATIENTS

Patients who commence dialysis are a challenging group with high burden of comorbidities and short anticipated survival with mortality rate which is 40% at 5 years after dialysis start[276]. Dialysis patients differ from general population in terms of higher bleeding rates and thromboembolic complications[277]. The prognosis of dialysis patients with untreated AS is poor and the mortality exceeds 80% if left untreated[277]. The debate regarding optimal aortic valve prosthesis is focused mainly on the assumption that anticoagulant use and its complications can be prevented by the implantation of a bioprosthetic valve[278]

Specific considerations before AVR in dialysis patients are similar to those in a general population with the addition of concerns regarding their short life expectancy[279] increased perioperative morbidity and mortality[280], the thrombotic and hemorrhagic risk[281], as well as the potential adverse events related to warfarin as it is related with raised occurrence of bleeding, calciphylaxis and ectopic calcification[282]. Platelet dysfunction is common in kidney failure patients with imbalance between thrombotic and hemorrhagic events due to hypercoagulable state, leading to higher risk of hemorrhagic events especially in those receiving antiplatelet or anticoagulant treatments[283]

BAV have long been considered not to be used in dialysis patients due to faster structural deterioration[284]. Thus, the AHA/ACC since 1998 recommended mechanical valves in all dialysis patients who underwent AVR[285]. However, on the basis of a report from Herzog at. al. who included ≈ 5990 dialysis patients undergoing SAVR (of whom 3500 underwent isolated AVR) and showed overall 2-years survival at 39% with comparable rates between recipients of MAV and BAV[286], the guidelines changed their recommendation and ceased to have explicit criteria for prosthetic valve selection[287]. AVR is recommended in dialysis patients as it is associated with significantly improved survival compared to those with conservative management[28,288].

Current practice guidelines have contradictory recommendations concerning prosthetic valve selection in dialysis patients with AS. The American guidelines suggest that a mechanical valve should be considered in patients < 65 years of age with life expectancy of more than 20 years[18]. In general population the life expectancy at 65 years is > 15 years and only 5 years in dialysis patients[289]. Therefore, the prosthetic valve choice in dialysis patients should be individualized[18]. However, the European guidelines still recommend mechanical valve placement in dialysis patients on the basis that BAVs have a higher risk of structural deterioration secondary to advanced calcification and hemodynamic changes[17].

The reported evidence for optimal choice of aortic valve prosthesis in dialysis patients is mainly based on small single center retrospective observational studies with mixed aortic and mitral valve cohorts[290-292] with conflicting results[293,294].

1.12.1 TAVI vs SAVR in dialysis: Periprocedural complications

Although SAVR is being utilized more frequently in dialysis patients with AS during the recent years, the in-hospital mortality is almost 2-times higher when compared with non-dialysis patients in propensity matched cohorts[280]. Following the TAVR-trend in general population, TAVR has become a less invasive alternative for AVR in dialysis patients who should otherwise be considered inoperable due to high periprocedural risk[295]. Aljohani at. al. reported statistically significant higher incidence of blood transfusion and cardiac tamponade, in dialysis patients who underwent SAVR whereas conduction disturbances requiring pacemaker implantation occurred more often in the TAVR group[280]. The in-hospital mortality was improved for those who underwent transfemoral TAVR compared to SAVR.

1.12.2 TAVI vs SAVR in dialysis patients: Short- and mid- term outcomes

A recent propensity-match study of dialysis patients who underwent AVR either with SAVR or TAVR reported significantly lower 30-days mortality in the TAVR group (3% vs 12.5%). However, during the mid- term follow-up, SAVR when compared to TAVR in dialysis patients was found to be associated with higher complication rates of infective endocarditis (3.5% vs 0.4%) and stroke, without difference in all-cause mortality[288]. The same study reported significantly improved survival after AVR with 50% reduction in mortality compared to those who received conservative management. AVR mainly with TAVR was associated with significant reduction in hospital admissions due decompensated heart failure[288].

Patients CKD stage 4 and 5 had improved functional status after AVR[225]. The findings from Ogami at. al. showed that median overall survival of dialysis patients following AVR is 1.8 years, with 5-year mortality closed to 90%[296]. Szerlip at. al. evaluated the safety of TAVR in dialysis patients utilizing data from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapies registry. The authors compared the short- and mid-term outcomes after TAVR between dialysis (n = 3053) and non-dialysis patients (69578) with AS[297]. Dialysis patients had significantly higher in-patient mortality compared to non-dialysis patients (5.1 vs 3.4%) and although their younger age, they had two-fold higher mid-term mortality after TAVR, with a parallel increase with the number of comorbidities. Interestingly, the anatomical characteristics and the need of alternative access other than the transfemoral (transapical access in this case) influenced the feasibility of TAVR and were linked to higher mortality risk. Dialysis patients were more susceptible to peri-procedural complications frequently longer in-hospital stay. Vascular complications were similar in the two groups but major bleedings were more common in the dialysis group.

1.12.3 Valvular degeneration after TAVR and SAVR in dialysis patients

Bioprosthetic valves used during SAVR or TAVR have limited durability due to structural valve deterioration. Valve longevity is a major issue in dialysis patients, given the high risk of bioprosthetic valve structural deterioration and the short life expectancy in this group [285]. A study by Kuroda at. al. showed that dialysis patients who underwent SAVR with BAV present significantly higher incidence of structural valve deterioration compared to their non-dialysis counterparts. The 5-year incidence of structural valve deterioration was 10% in the dialysis group, but interestingly, it was not associated with higher mortality[298]. Conversely, Allende at.al., in patients who underwent TAVR, reported similar hemodynamics without findings of BAV deterioration 1 year after the procedure[225]. Given the short life longevity of dialysis patients following AVR, more data are necessary to identify those patients on maintenance dialysis with AS who can benefit from AVR. Consequently, BAV in the aortic position should be recommended since these patients are not expected to outlive their bioprosthetic valves[284].

The latest scientific statement from AHA recommends TAVR for dialysis patients > 55 years of age with expected longevity of life > 2 years[299], and with suitable transfemoral access that is the preferable approach[79]. Heart - Kidney multidisciplinary team-based approach has been recommended to valve selection and choice of intervention, as well assessment of surgical risk, suitability of transfemoral access and extend of coronary artery disease before AVR in dialysis patients[79].

2 RESEARCH AIMS

The overall aim of this thesis was to evaluate the occurrence of AS in patients with CKD and to investigate kidney outcome after TAVR and its association with the short - and long- term mortality. The secondary objective was to compare the net adverse event rates and mortality in dialysis patients who underwent AVR with different aortic valve prostheses.

2.1 STUDY-SPECIFIC AIMS

Study I: Aimed to assess whether CKD was associated with the risk to develop incident AS

Study II: Evaluated the prevalence of pAKI following TAVR in patients with AS, and assessed whether pAKI was associated with short and long-term mortality.

Study III: Investigated i) the point prevalence of known AS and prior AVR for patients who initiated dialysis and ii) the incidence and associated factors of new onset AS and AVR after dialysis initiation

Study IV: Compared the all-cause mortality and rates of bleeding events (intracranial, gastrointestinal, urogenital and other unspecified types), stroke and aortic valve reoperation between dialysis patients who underwent AVR with a mechanical or bioprosthetic valve.

3 THESIS AT A GLANCE - TABLE 3

Study	I	II	III	IV
Design	Cohort Study	Cohort Study	Cohort Study	Cohort Study
Data source	SCREAM	SWENTRY	SNR	SNR
Time of data collection	2006 - 2011	2008 - 2015	2005 - 2018	2005 - 2018
Study Population	Adults Stockholm citizens with known kidney function	High risk patients with AS who underwent TAVR	Patients on maintenance dialysis	Dialysis patients with AS who underwent SAVR or TAVR
Numbers included in analysis	N = 1121875	N = 1540	N = 14550	N = 294
Follow – up time	5.1 years (IQR: 3.3 to 6.1)	1.8 years (IQR 0.7–3.0)	2.7 years (IQR 1.1 to 5.7)	1.49 years (IQR: 0.66 to 2.83)
Outcomes	Aortic Stenosis	pAKI and short and long-term mortality	AS and AVR	All-cause death, bleeding events (intracranial, gastrointestinal, urogenital and other unclassified types), stroke and aortic valve reoperation
Main statistical analysis	Cox regression analysis	Logistic regression and Cox regression analysis	Logistic regression and Cox regression analysis	Logistic regression and Cox regression analysis
Conclusions	There is a higher AS risk in individuals with mild to severe CKD	Worsening kidney function present at discharge occurred in 6.1% of patients and it was associated with a double short - and long-term mortality, independent of baseline kidney function	Patients initiating dialysis have high prevalence of known AS and higher incidence of new onset AS but they have lower likelihood to be considered candidates for AVR.	Dialysis patients with AS who underwent AVR with MAV vs. BAV had similar rates of the composite outcome of all-cause mortality, bleeding events, stroke and aortic valve reoperation. Prosthetic valve type was not associated with higher mortality rates

4 MATERIALS AND METHODS

4.1 DATA SOURCES

Study I was conducted using data from the Stockholm CREAtinine Measurement project (SCREAM)[300]. In order to receive complete information on health care use such as diagnosis, dispended drugs, data on kidney replacement therapy, follow-up and death, the laboratory data were linked to regional and national administrative datasets. All linkages were performed centrally by the Swedish National Board of Welfare. The SWEdish traNscatheter cardiac intervention regisTRY (SWENTRY) was used in study II. To carry out studies III - IV the Swedish Renal Registry (SRR) was utilized. This registry was merged with the National Patient Registry (to obtain co-morbidities and outcome diagnosis), the Swedish Prescribed Drug Register (https://www.socialstyrelsen.se/statistik-och-data/register/lakemedelsregistret/) and the Population Register to obtain information on demographic data. All data sources used in this thesis are shown on table 3.

4.1.1 SCREAM

The SCREAM project is a health care cohort initiated in collaboration with the healthcare provider of Stockholm County. The goals were to evaluate the burden of CKD and to point out considerations regarding the implications of kidney function into the medical decision-making process and prescription of medication[300]. The SCREAM project was initiated in 2010. In the first update it covered the period 2006 - 2011, included data for 1,357,156 residents since 1997, the year that the international Classification of Disease Version 10 (ICD-10) was introduced. Inclusion criteria to enter the SCREAM were the Stockholm residency and the presence of at least one undertaken creatinine or albuminuria measurement with additional details about date, time (fasting non-fasting measurement), units, as well as reference interval, method of analysis and commends on the presence of haemolysis.

SCREAM is composed of three components:

- The first one contains demographic information (i.e. sex and date of birth) and administrative health data of Stockholm citizens with consultations in primary, specialist and even hospital outpatient care. Each record comprises information on date, center and medical department, clinical diagnoses and undertaken therapeutic measurements.
- The second core component, is a warehouse of laboratory data provided from the laboratories of Aleris, Unilabs and Karolinska University Hospital, who perform all biochemical tests in the Stockholm Region. The surveillance, for quality and harmonization of these laboratories by EQUALIS, an independent national organization provider of external quality assessment in laboratory medicine, insures the absence of inter- and intra-laboratory variation[300].
- The third part of SCREAM is provided by the Swedish National Board of Welfare after the linkage of SCREAM dataset to regional and national administrative datasets. In order to receive complete information on health care use the SCREAM dataset was linked with the Swedish Population Registry, Swedish Dispensed Drug Registry, LISA registry (the Longitudinal Integration Database for Health Insurance and Labour Market Studies) (Table 4). All linkages were performed centrally by the Swedish National Board of Welfare, which created a de-identified database.

The estimated coverage varies from 54% for the age group from 18 - 44 to 92% for individuals ≥65 years old. The SCREAM project has been approved by the Ethical Committee of Stockholm.

Table 4. Available linkages and key information for Regional, National and Quality registries used in this thesis

Region Stockholm **data sources**	**National Registries**	**Quality Registries**
Regional Health Utilization Database Includes information on: • Demographics • Residency and migration • Consultation centre • Clinical diagnoses and treatment	**Prescribe Drug Register** • Dispensation Date • Commercial name • Prescribe and daily drug dosage • Prescriber's specialist and type of centre	**SWEDEHEART** • Patients admitted for coronary artery disease • Clinical data • In-hospital procedures and drugs • Life style
Routinine laboratory measurements provided by: • Karolinska University Hospital • Aleris • Unilabs	**Death Register** • Date of death • Causes of death (ICD-10)	**SWENTRY** • Patients admitted for transcatheter valve intervention • Preprocedural data • patient Demographics • Drugs • Life style • Echocardiographic variables
		SRR • Nephrologist – referred CKD-4 patients • Primary kidney disease and drugs • Dialysis characteristics • Kidney replacement therapy and modality

4.1.2 SWEDEHEART

The SWEDEHEART registry is a national registry developed in December 2009 after incorporated the Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS - HIA), the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), the Swedish Heart Surgery Registry and the National Registry of Secondary Prevention (SEPHIA)[301]. Moreover, SWEDEHEART contains the cardiogenetic Registry and the national percutaneous valve device registry, The SWENTRY[301].

4.1.2.1 SWENTRY REGISTRY

SWEDEHEART contains information of all hospitalized patients for acute coronary syndrome or undergoing coronary or valvular intervention for any indication. The SWENTRY, developed in 2010, is part of the nationwide SWEDEHEART registry and includes all patients undergoing TAVR in all 8 centers in Sweden[302]. The first TAVR in Sweden was performed in 2008 and therefore data for the years 2008 - 2009 were entered retrospectively. Monitoring of the recorded data occurs continuously and reaches an agreement > 95%[301]. Comprehensive information in SWENTRY is collected prospectively since 2010[302]. The registry contains

preprocedural data including patient demographics, past medical history, medication before aortic valve intervention, body mass index, smoking, laboratory values, echocardiographic variables and procedural data. The registry is updated on a weekly basis[302]. All centres performing TAVR enter all procedures performed. All collected variables in the SWENTRY are based on the European System for Cardiac Operative Risk Evaluation (EuroSCORE II). Major complications are site-reported reported and according to VARC-2 during index hospitalisation[303].

Plasma concentration of creatinine is used to measure the patient kidney function in patients admitted for TAVR. Collection of creatinine variable at once during hospital stay and by treating physician, is mandatory in SWEDEHEART and SWENTRY since 2003. The SWENTRY registry has been merged with the Patient Registry, to enrich data on comorbidities before the valvular replacement as well as post procedural complications. Information about mortality data is gathered from the NPR, which is 100% completed for our patients[301].

4.1.3 The Swedish Renal Registry (SNR)

The SRR (https://www.medscinet.net/snr/), a national registry of all patients who commence dialysis or receive a kidney transplant in Sweden. The registry was launched on a national level in 2008. Renal registries were developed as regional registries since 1999. The nation-wide Swedish Renal Registry keeps two linked registries: the first one is the SRR - CKD in which nephrology clinics report information on outpatient visits in patients followed at the clinic with eGFR < 30 ml/min/1.73m^2. The second SRR cohort registers yearly information on all patients with chronic dialysis. The national coverage in 2013 was 96.4%[304].

This national registry contains all dialysis patients that started kidney replacement therapy from 1991 - 2011 in Sweden. The selection of patients is based on the first kidney replacement treatment start date. Variables include data on primary kidney disease, laboratory tests and in-hospital provided medication for kidney disease treatment.

Cross-sectional measurements are performed yearly, to evaluate the national coverage. They consist of random analysis between September 15 and October 15. According to recent annual reports > 96% of records are completed in all fields, in the SRR in a national level.

4.1.4 National Patient Register

The National Patient Register was launched in 1964 and since 1987 has complete coverage that is almost 99%. Information from all somatic and psychiatric hospital discharges is included. The diagnoses are coded according to the ICD system. The validity of the National Patient Register is examined by the National Board of Health and Welfare and is generally between 85 - 95%[305]. Individual data are linked to the personal identity number and patient-related data, data about the care-provider, administrative data and medical data are registered. The high validity and the long follow-up of the Swedish Patient Registry make the register suitable for large-scale population-based research[305].

4.1.5 Swedish Personal Identity Number

The personal identity number is a ten-digit number maintained by the National Tax Board for all residents in Sweden. It is used in the Swedish health care to trace the patient medical records, to promote the medical care and to enable linkages between medical registers that allows a 100% coverage of the Swedish health care system[306]

4.2 DEFINITIONS

4.2.1 Definition of aortic stenosis

The main outcome in studies I and III was the occurrence of clinically detected AS during the follow-up as primary or secondary diagnosis. The record of the disease in the NPR was based on the International Classification of Disease 10th Revision Codes (ICD - 10) that was used in Sweden since 1997 and onwards. AS diagnosis in NPR is based on echocardiographic assessment and mainly represents moderate to severe rating of disease[48]. The diagnosis was ascertained by the diagnostic codes I35.0 or I35.2.

4.2.2 Definition of kidney function

Index creatinine values and creatinine values at discharge in studies I and II, were used to calculate the eGFR. Since 2005, all laboratory providers implemented methods for creatinine analysis (enzymatic or corrected Jaffe method), traceable to isotope dilution mass spectroscopy[300]. In this thesis we lack information on duration of any previous kidney disease, since we only had a single creatinine measurement.

The kidney function was defined by eGFR in ml/min/1.73m^2 derived from the creatinine-based Chronic Kidney Disease - Epidemiology Collaboration (CKD - EPI) equation[307] (Figure 8). Kidney function was defined by the stratified eGFR categories according to Kidney Disease: Improving Global Outcomes (KDIGO) classification[307]. In study I patients were stratified according to eGFR (ml/min/1.73m^2) in the following stages:

i) eGFR $\geq$ 90 ml/min/1.73m^2
ii) eGFR 60 – 90 ml/min/1.73m^2
iii) eGFR 45 – 60 ml/min/1.73m^2
iv) eGFR 30 – 45 ml/min/1.73m^2
v) eGFR $\leq$ 30 ml/min/1.73m^2.

In study II we defined four CKD-groups at baseline:

i) > 60 ml/min/1.73m^2
ii) 45 – 59 ml/min/1.73m^2
iii) 30 – 44 ml/min/1.73m^2 and
iv) 15 -29 ml/min/m^2.

Figure 8. CKD - EPI formula

$$eGFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} *$$

eGFR is estimated Glomerular Filtration Rate

S_{Cr} is serum creatinine in μmol/lt

$\kappa = 61.9$ (females) or 79.6 (males)

$\alpha = -0.329$ (females) or -0.411 (males)

min = indicates the minimum of S_{Cr}/κ or 1

max = indicates the maximum of S_{Cr}/κ or 1

*We did not perform adjustments for race since information on race is not available in Sweden by law. It was assumed that all patients were of Caucasian origin.

4.2.3 Definition and Classification of Acute Kidney Injury

Creatinine values at admission and discharge were extracted from the SWENTRY. Early assessment of increased creatinine values within 72 hours to 7 days following TAVR, with additional serial measures until the creatinine declined from its peak value, were not available in SWENTY. The definition of AKI proposed by VARC-2 is based on the Acute Kidney Injury Network (AKIN) system which is a modified version of the widely recognized KDIGO definition of AKI (Table 5). The definition of AKI with worsening kidney function present at discharge encompassed the VARC-2 criteria[273] with the modification that due to lack of information on peak creatinine value within 72 hours to 7 days, the creatinine value at discharged was used. The robustness of the main results was assessed by sensitivity analysis where two other definitions of pAKI were applied:

a) A relative ≥ 25% increase in creatinine from baseline to discharge or initiation of dialysis
b) RIFLE criteria with either a ≥ 25% increase in eGFR calculated by the CKD – EPI equation.

The therapeutic decision for TAVI versus SAVR was discussed by the Heart team, which was consisted by interventional cardiologist, cardiac imaging specialist and cardiothoracic surgeons. The study population consisted of patients with severe native AS as diagnosed by echocardiography and using an integrative evaluation according to guidelines[17].

Table 5. Classification and staging of acute kidney injury according to different definitions

VARC – 2 CRITERIA		RIFLE CRITERIA		AKIN CRITERIA	
Increase in Serum creatinine	**Urine output**	**Glomerular Filtration Rate Criteria (GFR)**	**Urine Output**	**Serum Creatinine**	**Urine output**
Stage 1 Increase in serum creatinine 1.5-1.99 from baseline within 7 days or ≥ 0.3mg/dl (> 26.4 µmol/l) increase within 48 hours	<0.5 ml/kg/h for 6-12 hours	Increased serum creatinine x1.5 or GFR decrease > 25%	<0.5 ml/kg/h x 6 hours	Increase in serum creatinine ≥ 0.3mg/dl (26.4 µmol/l) or increase ≥ 150 – 200% from baseline within 48 hours	<0.5 ml/kg/h for ≥ 6 hours
Stage 2 Increase in serum creatinine 2.0-2.99 from baseline	<0.3 ml/kg/h for 12-24 hours	Increased serum creatinine x2 or GFR decrease > 50%	<0.5 ml/kg/h x12 hours	Increase in serum creatinine > 200 – 300% from baseline	<0.5 ml/kg/h for ≥ 12 hours
Stage 3 Increase in serum creatinine > 3.0 from baseline or serum creatinine ≥ 4 mg/dl (≥ 354 µmol with an acute increase of at least 0.5 mg/dl (44mmol/l)	<0.3 ml/kg/h for ≥24hours or anuria for ≥12hours	Increase serum creatinine x3 or GFR decrease 75% or serum creatinine 4 mg/dl (= 355 µmol/dl) with an acute increase of at least 0.5 mg/dl (44mmol/l)	<0.3 ml/kg/h for ≥24hours or anuria for ≥12hours	Serum creatinine increased > 300% from baseline (or serum creatinine > increase in serum creatinine ≥ 4 mg/dl ≥ 354 µmol/dl) with an acute increase of at least 0.5 mg/dl (44mmol/l)	<0.3 ml/kg/h for ≥ 24hours or anuria for ≥12hours
		Persistent acute kidney failure; complete loss of kidney function for longer than 4 weeks			
		End-stage renal disease (> 3 months)			

4.2.4 Definition of Aortic Valve Replacement

AVR in study III was defined as secondary outcome and in the IV study was the exposure. In both studies AVR was defined by the procedural codes FM00 (mechanical aortic valve prosthesis), FMD10 (bioprosthetic aortic valve), FMD12 (transcatheter aortic valve implantation) and FMD13 (apical transcatheter aortic valve implantation). Most common transcatheter valve types used, in the second study, were Medtronic CoreValve and Edwards SAPIEN.

4.2.5 Definition of bleeding, stroke, reoperation

The periprocedural bleeding events in study II were defined according to VARC-2 criteria (Table 6), based on the Bleeding Academic Research Consortium classification (BARC)[308].

In study IV the outcome was the occurrence of any adverse clinical event defined as the composite of all-cause death and readmission due bleeding events (intracranial, gastrointestinal, urogenital or other unspecified bleedings), ischemic stroke and aortic valve reoperation. For these composite endpoints the earliest event was selected. The search was made in the NPR. The ICD-10 diagnostic codes were used to identify the adverse clinical events (Table 4)

Table 6. BARC definitions

Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek treatment
Type 2	Any clinically overt sign of hemorrhage that "is actionable" and requires diagnostic studies, hospitalization, or treatment by a health care professional
Type 3	a. Overt bleeding plus haemoglobin drop of 3 to < 5 g/dl (provided haemoglobin drop is related to bleed); transfusion with overt bleeding b. Overt bleeding plus haemoglobin drop < 5 g/dl (provided haemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring IV vasoactive agents c. Intracranial haemorrhage confirmed by autopsy, imaging, or lumbar puncture; intraocular bleed compromising vision
Type 4	CABG – related bleedings
Type 5	a. Probable fatal bleeding b. Definite fatal bleeding (overt or autopsy or imaging confirmation)

Table 7. Definition of the bleeding events and stroke based on ICD-codes

Bleeding Events		**ICD-10 codes used to identify bleeding events**
Intracranial bleedings		
	Subarachnoid haemorrhages	I60
	Intracerebral haemorrhages	I61
	Sub- and epidural haemorrhages	I62
	Traumatic epidural haemorrhages	S064
	Traumatic subdural haemorrhages	S065
	Traumatic subarachnoid haemorrhages	S066
Gastrointestinal bleedings		
	Gastro-oesophageal laceration-haemorrhage syndrome	K226
	Bleeding gastric ulcer (subcodes 0,2,4,6 only)	K25
	Gastric ulcer with perforation	K252
	Bleeding duodenal ulcer (subcodes 0,2,4,6 only)	K26
	Bleeding peptic ulcer unspecified (subcodes 0,2,4,6 only)	K27
	Bleeding gastro-jejunal ulcer (subcodes 0,2,4,6 only)	K28
	Acute haemorrhagic gastritis	K290
	Haemorrhage of anus and rectum	K625
	Hemoperitoneum	K661
	Haematemesis, melena and unspecified GI bleeding	K920-K922
	Oesophageal varices with bleeding	I850, I983
Urogenital bleedings		
	Haematuria	N02
	Haematuria, unspecified	R319
	Abnormal uterine and vaginal bleeding	N938, N939
	Postmenopausal bleeding	N950

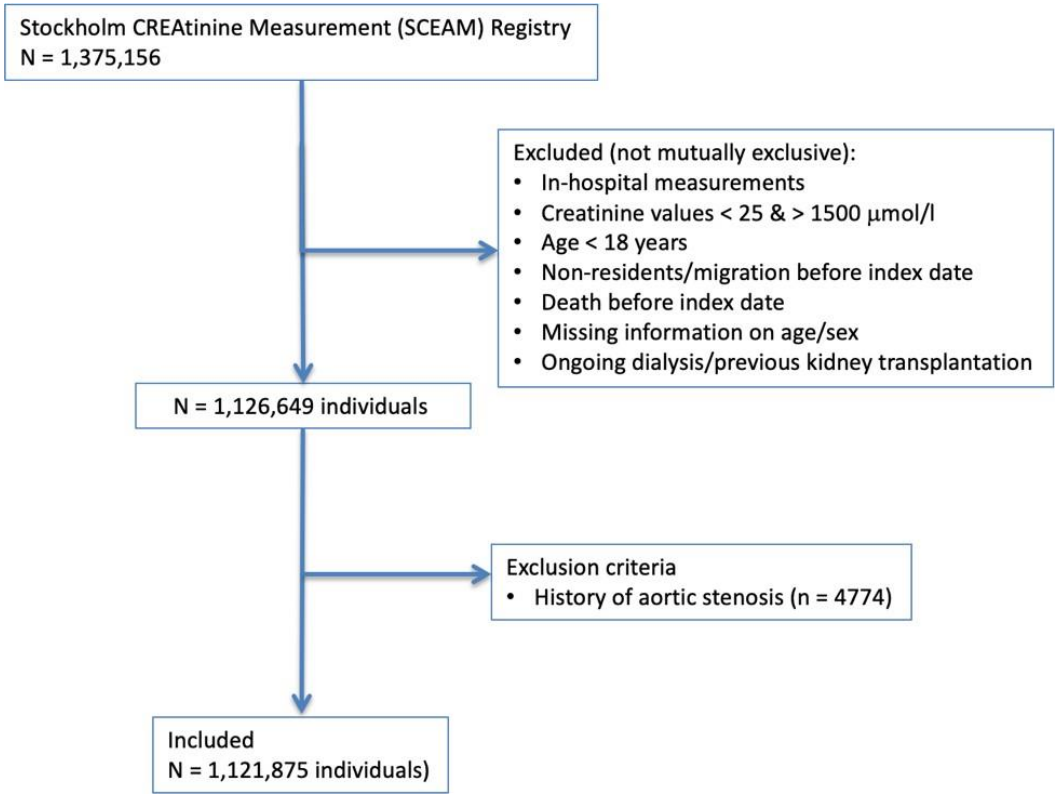
	Haemorrhage in male genital organ	N501A, N421
Other types of clinically significant bleeding		
	Conjunctival haemorrhage	H113
	Choroidal haemorrhage	H313
	Retinal haemorrhage	H356
	Vitreous haemorrhage	H431
	Vitreous haemorrhage in diseases classified elsewhere	H450
	Ear bleeding	H922
	Hemopericardium	I312, I230
	Haemothorax	J942
	Hemarthrosis	M250
	Nose bleeding (subcodes 1, 2, 8, 9 only)	R04
	Haemorrhage not elsewhere classified	R58
	Haemorrhage and haematoma complicating a procedure not elsewhere classified	T810
	Iron deficiency anaemia secondary to blood loss (chronic)	D500
	Anaemia after acute major bleeding	D629
	Procedure codes for transfusion	DR029, DR033 Z513
Cerebrovascular diseases		
	Cerebral infarction	I63
	Stroke unspecified	I64
	Sequelae of cerebrovascular disease	I69
	Transitory ischemic attack	G45.9

4.3 STUDY POPULATION

4.3.1 Study I

Study I was an observational longitudinal population-based cohort study. Eligible participants in the main analysis were all Stockholm citizens included the SCREAM with available plasma creatinine tests in any form of healthcare provider, undertaken between January 1, 2006 and July 1, 2011. Inclusion and exclusion criteria are shown in figure 9.

Figure 9. Flowchart of study I



4.3.2 Study II

The study II was an exploratory patient-based nationwide cohort study. The cohort consisted of all the consecutive patients registered in SWENTRY who underwent elective or urgent TAVR between January 1, 2008 and October 4, 2015. Those with severe CKD treated with maintenance dialysis or with preoperative eGFR < 15 ml/min/1.73m^2 before TAVR were excluded. A flowchart with inclusion and exclusion criteria is displayed in figure 10.

4.3.3 Study III

Study III is an exploratory observational, patient-based, nationwide cohort study. The study population comprised all patients in the Swedish Renal Registry who initiated dialysis between January 1, 2005, and August 2018. Figure 11 presents the flowchart containing the inclusion and exclusion criteria.

4.3.4 Study IV

The study population in study IV, consisted all consecutive adults in the SRR with a diagnosis of AS who underwent AVR in the period between 1st January 2005 and 3rd August 2018. Figure 12 presents the inclusion and exclusion criteria.

Figure 10. Flowchart of study II

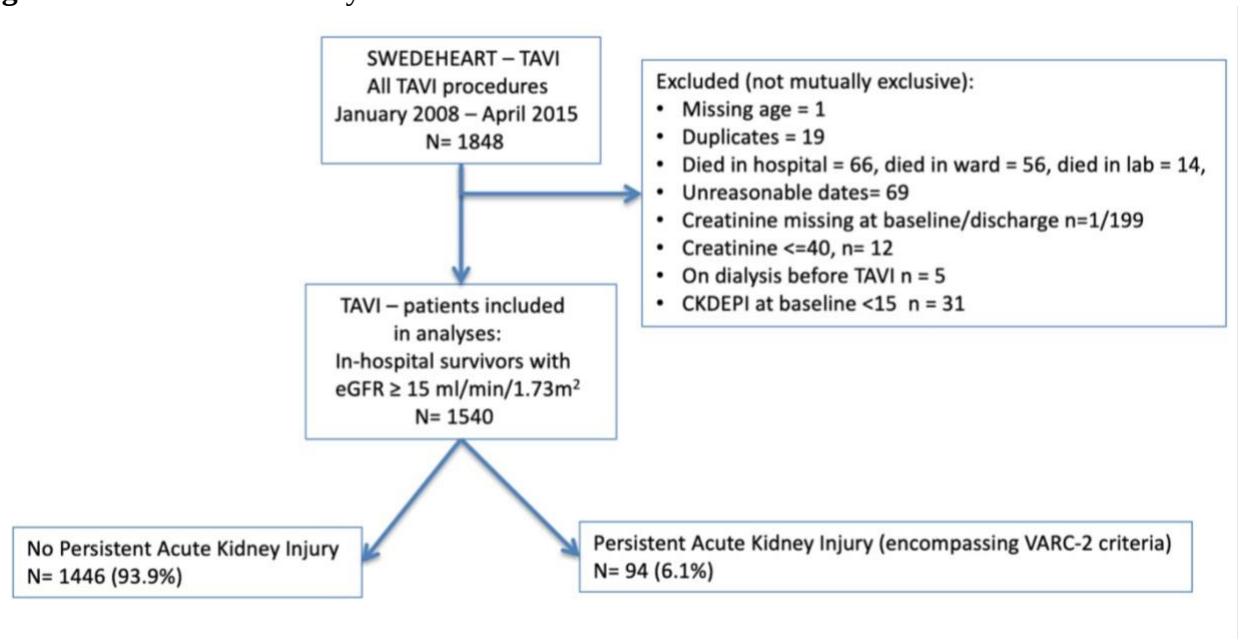
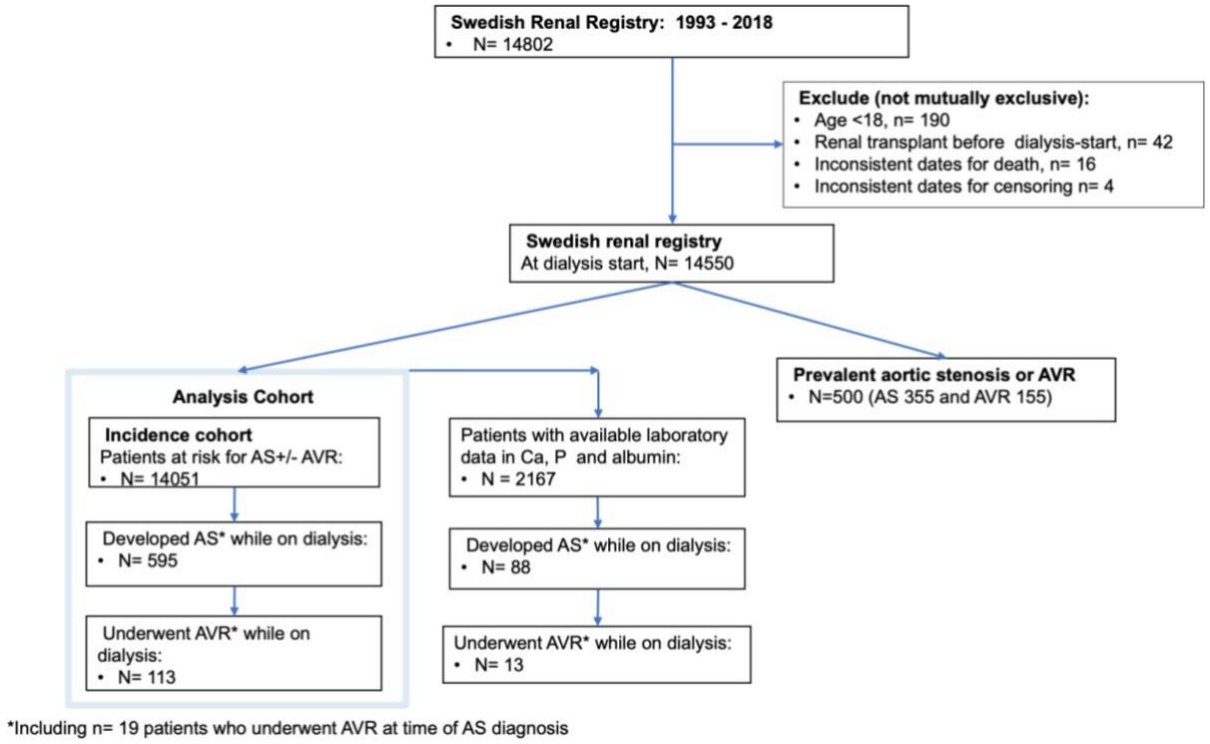
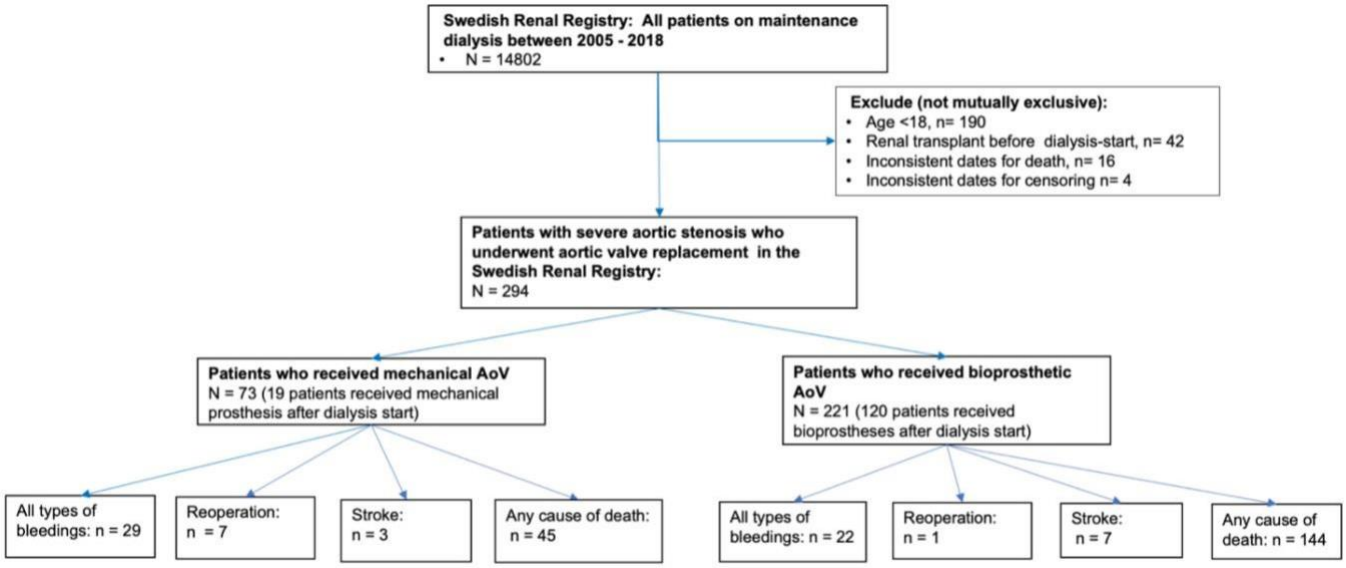


Figure 11. Flowchart of study III



*Including n= 19 patients who underwent AVR at time of AS diagnosis

Figure 12. Flowchart of study IV



4.4 STATISTICS

Categorical data at baseline were expressed as number (n) and proportion (%). Continuous data are presented as medians with interquartile range (IQR) (studies I, III & IV) or means with standard deviation (SD) (Study II). In all analysis, a p - value < 0.05 was considered statistically significant. Statistical analyses were performed with using R software in study I, Stata Software version 13.1 in study II and Stata Software version 15.1 in studies III and IV.

4.4.1 Study I

Person-time was calculated as time from the date that the creatinine test was undertaken until the date the study outcome was reached, the patient died or emigrated or until the end of data collection (December 31, 2012). Kaplan-Meier method was used to calculate the overall and stratified cumulative incidence of AS across the different eGFR categories and the 10-years strata of age. Crude incidence rates (IR) and 95% Confidence Intervals (95%CI) were also calculated. Cox proportional hazards models, expressed as Hazards Ratios (HR) and 95% Confidence Intervals, were used to assess the association between kidney function categories and risk of AS. The variables of age, sex, cardiovascular diseases (ischemic heart disease, peripheral arterial disease, cerebrovascular diseases, heart failure) hypertension and hyperlipidaemia were adjusted in a stepwise manner. The proportionality assumption of hazards on the basis of Schoenfeld residuals against ranks of time was assessed and plotted. Restricted cubic splines were used to assess the dose response multivariable-adjusted association between the included covariates and incident AS.

Subgroup analysis was conducted to evaluate the consistency of the main results across age groups and covariates (sex, ischemic heart disease, hypertension, diabetes mellitous and heart failure). Falsification analysis was performed to evaluate the possibility that the observed association was the result of residual confounding. Myocardial infarction was a positive control, car accidents and the composite of gallstones with cholecystectomy were the negative controls. The incidence rates and the hazards ratios with 95% Confidence Intervals of the

control outcomes were estimated in the different categories of kidney function. Sensitivity analysis was performed to evaluate the likelihood of reverse causation, that undiagnosed AS present at the enrolment caused the kidney dysfunction. A separate analysis was performed by delaying the start of follow-up of the cohort during differed exclusion periods of increasing length (6 months, 1 and 2 years). Censored individuals or participants who developed AS during the exclusion periods were rejected from the main analysis. The role of clinically diagnosed congestive heart failure in the early detection of AS was evaluated in another sensitivity analysis. Patients with known heart failure before their enrolment were excluded from the analysis. The incidence rates and the hazards ratios with 95% Confidence Intervals of AS were estimated in individuals without congestive heart failure at baseline.

4.4.2 Study II

Univariate and multivariate logistic regression analysis was used to calculate patients' odds to develop pAKI at discharge. The adjustments were performed for age/10 years increase, baseline kidney function (eGFR/10ml/min/1.73m^2), contrast volume/10ml increase, gender, diabetes mellitous, left ventricle ejection fraction categories, logistic EuroSCORE I, prosthesis make, COPD, bleeding complication. Kaplan-Meier models were used to calculate the mortality rates between the different categories of kidney function at discharge by the occurrence of pAKI. Multivariable Cox proportional hazards models were used to assess the adjusted associations between covariates and short- and long- term mortality. Sensitivity analyses were assessed to evaluate the assumption that the different definitions of AKI altered the associations of covariates with the persistent acute kidney injury. The statistical analyses were repeated with the pAKI as: i) the 25%-change in creatinine from baseline to discharge and ii) and according to the RIFLE criteria. These new definitions of pAKI were then used to explore the associations of covariates with all-cause mortality in multivariable Cox regression models.

4.4.3 Study III

The person-time was calculated from the date of dialysis start until the date of AS diagnosis, death, kidney transplantation or the end of data collection (August 3, 2018). Crude incidence rates with 95% Confidence Intervals of AS and AVR were estimated. The Kaplan-Meier models were used to calculate the cumulative incidence and to construct incidence curves. Cox proportional hazards were used to assess the associations between AS and covariates. Adjustments were made for age (as a continuous variable), gender, ischemic heart disease, peripheral arterial disease, cerebrovascular diseases, heart failure, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, hyperlipidemia, and dialysis modality. Stratified incidence rates of the outcome were calculated for sex categories and dialysis modalities. The number of missing values in the biochemical covariates was > 80%. The association between biochemical data at dialysis start with the outcome was evaluated in multivariable Cox regression analysis in a subgroup of patients with complete data. A sensitivity analysis with the same models was performed to assess the role of atrial fibrillation in the early detection of aortic stenosis. Consequently, patients with atrial fibrillation before dialysis start were excluded.

4.4.1 Study IV

The index date was the date of dialysis start, for patients with AVR before dialysis start, and the date of aortic valve intervention for patients who underwent AVR after dialysis start.

Patients were censored until the date of kidney transplantation, date of death or end of follow-up (August 3, 2018). Crude incidence rates and 95% presented with Confidence Intervals and Cumulative Incidence rates were calculated to compare the occurrence net adverse clinical events defined as the composite endpoint of all-cause mortality, all bleeding events (intracranial, gastrointestinal, urogenital or other types) in recipients of mechanical and bioprosthetic aortic valve recipients. Kaplan-Meier curves were used to display the proportion of patients in each group, compared by the log-rank test. Cox proportional hazard regression was used to assess the relation of covariates with the primary endpoint and mortality. Adjustments were made for age (as continues variable), gender, diabetes mellitus, atrial fibrillation, hypertension, ischemic heart disease, heart failure, prosthetic valve type, AVR before or after dialysis start and dialysis modality. Univariate and multivariate models were used to evaluate the association between baseline covariates and choice of mechanical versus bioprosthetic valves.

Age stratified analysis at age cut-off ≤ 72 versus ≥ 72 was conducted to compare the differences in the primary end-point and all-cause mortality after aortic valve replacement in dialysis patients. We performed separate analysis: the rates of primary and secondary endpoint were explored in dialysis patients aged ≤ 72 and ≥ 72 years. A sensitivity analysis was performed to compare the rates of primary and secondary endpoints among patients who underwent AVR before and after dialysis start. For trend analysis, Cochrane - Armitage test was used. A two-sided p-value < 0.05 was considered statistically significant.

4.5 ETHICAL CONSIDERATIONS

The present work used laboratory and registry-based databases. Patients received information about their participation in the SWEDEHEART registry during their hospital stay and had the possibility to opt out. In accordance with the Personal Data Act in Sweden and with the European General Data Protection Regulation, personal data were anonymized at the Swedish Board of Health and Welfare before they were given to researchers and safely stored. informed consent is not mandatory, according to Swedish law, for anonymized registry-based data. All studies were approved by the regional ethical board in Stockholm and conducted in accordance with the declaration of Helsinki[309]. Data were only analyzed on a group level and the results cannot be linked back to an individual patient.

5 RESULTS

5.1 STUDY I

There were 1121875 Stockholm citizens with available creatinine test undertaken in outpatient care from the SCREAM project who were included in the analysis, after applying exclusion criteria. The median age was 50 years IQR: 36 - 64 years), 54% were women and the median eGFR rate was 96 ml/min/1.73m^2. It was 6% of the study population with eGFR < 60 ml/min/1.73m^2. These participants had more often comorbidities, such as hypertension, hyperlipidaemia and diabetes mellitus.

During a median follow-up period of 5.1 years (IQR: 3.3 - 6.1 years) there were 5858 individuals (0.5%) who were diagnosed with AS. The unadjusted incidence of AS, compared to participants with normal eGFR (> 90 ml/min/1.73 m^2), increased linearly from 0.34/1000 person-years (95%CI: 0.32 - 036) to 8.27/1000 person-years (95% CI: 7.05 - 9.64) to those with severe reduced eGFR < 30 ml/min/1.73 m^2 (Table 8, Figure 13).

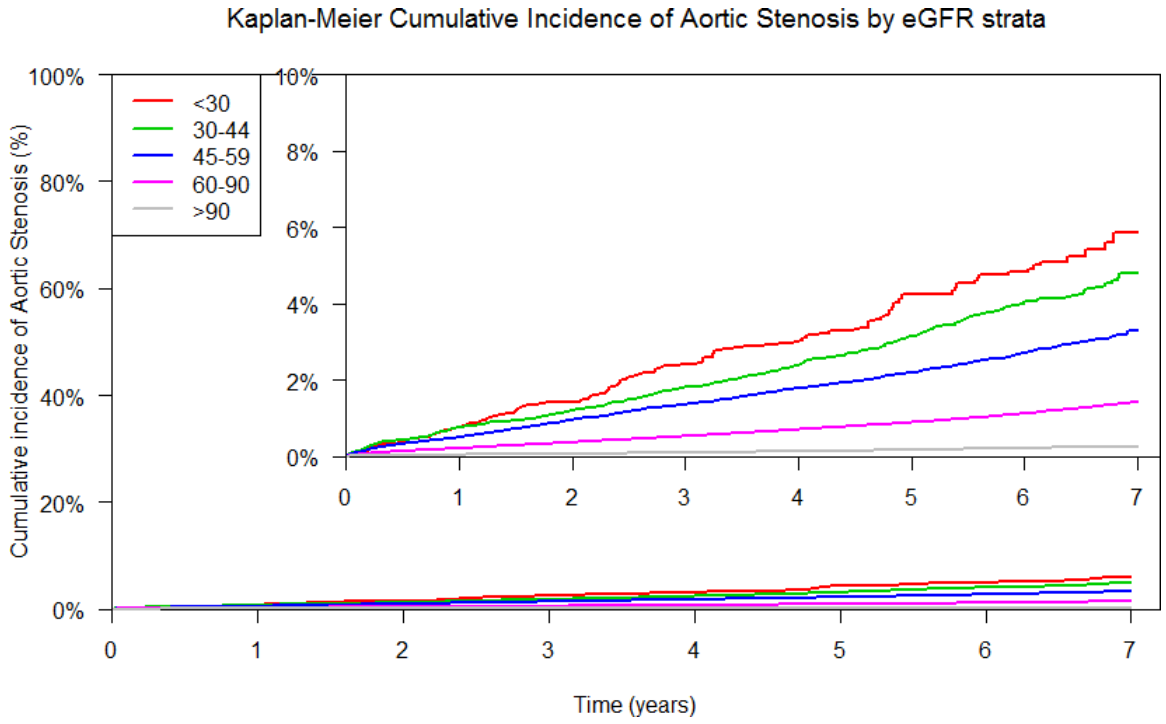
Table 8. Incidence Rates and Hazard ratios for Aortic Stenosis

	Person-years	**Number of events**	**Incidence rate per 1000 person-years (95% CI)**	**Crude hazard ratio (95% CI)**	**Adjusted* hazard ratio (95% CI)**
Overall	5197763	5858	1.13 (1.10-1.16)		
eGFR categories					
>90	3187089	1092	0.34 (0.32-0.36)	1	1
60-90	1720092	3227	1.88 (1.81-1.94)	5.43 (5.07- 5.82)	1.14 (1.05- 1.23)
45-59	206142	950	4.61 (4.32-4.91)	13.29 (12.18-14.50)	1.17 (1.05- 1.30)
30-44	66296	439	6.62 (6.03-7.26)	19.11 (17.11-21.35)	1.22 (1.07- 1.39)
<30	18143	150	8.27 (7.05-9.64)	23.78 (20.05-28.20)	1.56 (1.29- 1.87)

eGFR (ml/min/1.73 m^2): estimated glomerular filtration rate strata

*Adjustments were made for age, sex, ischemic heart disease, peripheral arterial disease, cerebrovascular diseases, heart failure, diabetes mellitus, hypertension, chronic obstructive pulmonary disease and hyperlipidemia.

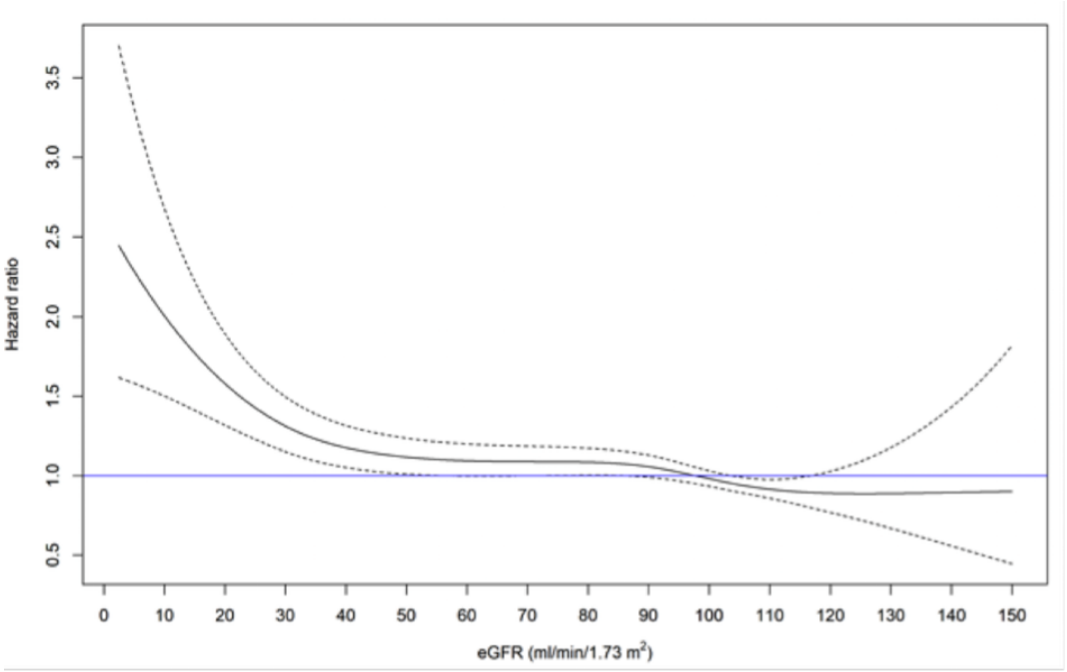
Figure 13. Cumulative Incidence of aortic stenosis by categories of estimated glomerular filtration rate



The adjusted hazards for AS were proportionally distributed in the different eGFR categories and a linear increase was observed from 14% (adjusted HR: 1.14;95% CI:1.29 - 1.87) among participants with eGFR 60 - 90 ml/min/1.73m^2, to 56% (adjusted HR: 1.56; 95% CI: 1.29 - 1.87) among participants with eGFR < 30 ml/min/1.73m^2. In figure 14 the adjusted hazards are shown between the eGFR and risk for AS.

In the subgroup analysis, women with kidney disease had 20% higher risk of AS (HR: 1.20; 95%CI: 1.11 - 1.31) than those with normal kidney function. Lower eGFR categories were strongly associated with AS in the absence rather than in the presence of co-morbidities, such as ischemic heart disease, hypertension, diabetes mellitus and heart failure.

Figure 14. Restricted cubic splines showing the multivariable - adjusted hazard risk of aortic stenosis associated with estimated glomerular filtration rate (eGFR). The graph is truncated at an eGFR ≥ 150ml/min/1.73m^2.



5.2 STUDY II

In study II, 1540 consecutive patients with severe AS who underwent TAVR between 2005 - 2015 were included. Patients were excluded if they had an eGFR < 15 ml/min/1.73m^2 or preoperative dialysis. After a median follow-up of 1.8 years (IQR: 0.7 - 3.0), 94 (6.1%), patients developed pAKI. Compared to patients without acute kidney disease, those who developed AKI were more often males (71.3%), with higher baseline creatinine levels (Figure 15), had more often chronic obstructive pulmonary disease, underwent TAVR via apical vascular access and had longer hospital stay.

At 1.8-years after discharge (IQR: 0.7 - 3.0), the cumulative mortality was 27%. The presence of pAKI following TAVR was associated with higher mortality rates (50% vs 25%, P < 0.001) (Figure 16). In Cox multivariable regression analysis, pAKI at the time of discharge was an independent predictor of 1-year and long-term mortality. After multivariable adjustments, pAKI was associated with a double risk of 1-year and long-term mortality in all kidney function categories (Table 9).

Figure 15. Creatinine changes: **A)** From baseline to discharge **B)** Distribution of baseline creatinine among patients with pAKI.

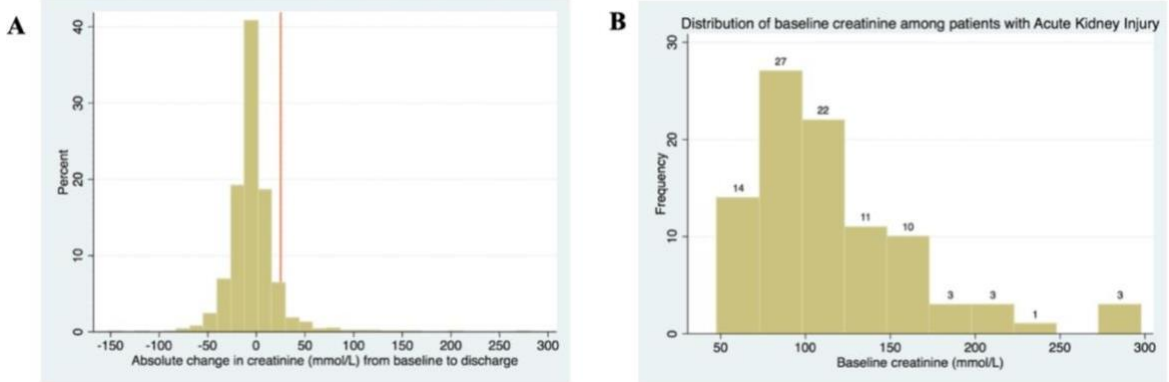


Figure 16. Kaplan - Meier curves with the mortality rates of patients following TAVR

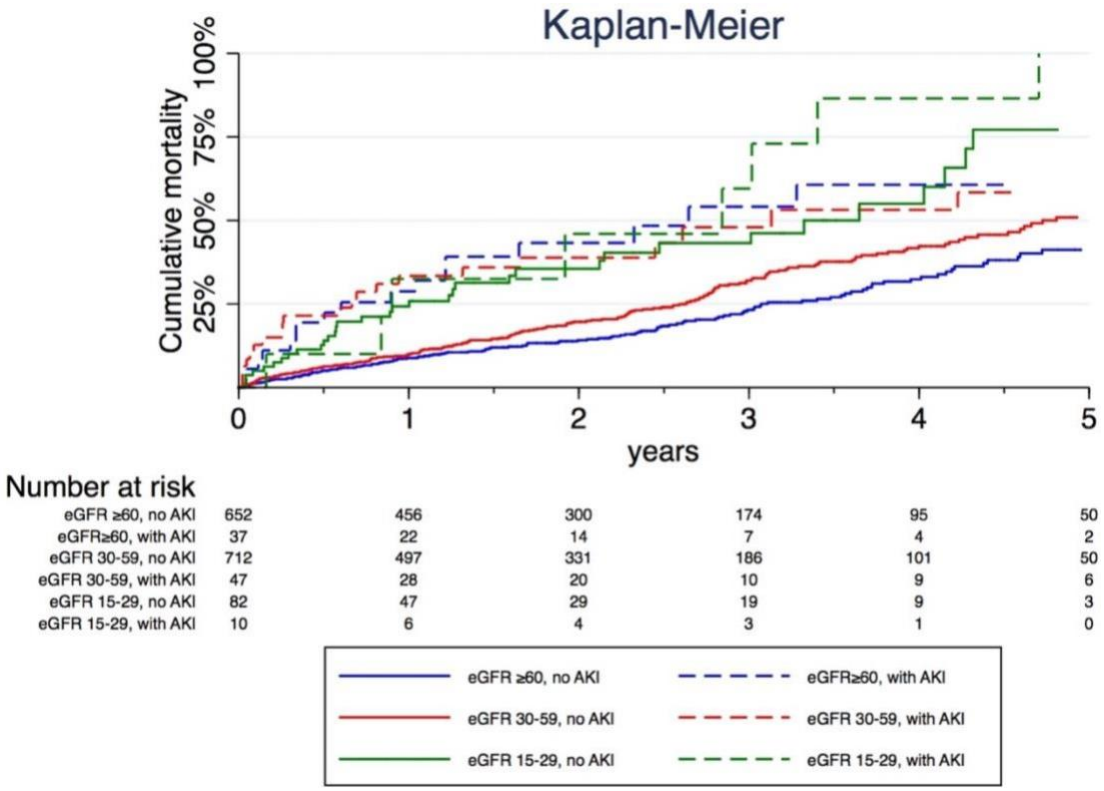


Table 9. Cox regression analysis of 1-year and long-term mortality

	Univariate HR (95%CI)	**P-value**	**1-year mortality** **Multivariable HR (95%CI)**	**P-value**	**Long-term mortality** **Multivariable HR (95%CI)**	**P-value**
Age (per 1 year increase)	1.12 (0.97-1.29)	0.132	1.01 (0.98-1.03)	0.497	1.19 (1.01-1.41)	0.038
Persistent Acute Kidney Injury	2.12 (1.57-2.88)	<0.001	2.74 (1.80-4.16)	<0.001	2.04 (1.49-2.81)	<0.001
eGFR (per 1 ml/min/1.73m^2 increase)	0.93 (0.88-0.97)	0.002	0.99 (0.99-1.00)	0.102	0.94 (0.90-0.99)	0.031
Male	1.42 (1.17-1.73)	<0.001	1.54 (1.09-2.18)	0.015	1.50 (1.22-1.86)	<0.001
NYHA Class (Ref. NYHA I)						
NYHA II	1.17 (0.16-8.68)	0.878	N/A	N/A	N/A	N/A
NYHA III	1.30 (0.18-9.23)	0.796	N/A	N/A	N/A	N/A

NYHA IV	1.93 (0.27-13.8)	0.514	N/A	N/A	N/A	N/A
LVEF >50%	ref		Ref 1.0			
LVEF 40-49%	1.47 (1.15-1.87)	0.002	1.69 (1.13-2.53)	0.011	1.36 (1.06-1.75)	0.018
LVEF 30-39%	1.43 (1.10-1.88)	0.009	1.52 (0.97-2.38)	0.070	1.33 (1.00-1.76)	0.049
LVEF<30%	1.54 (1.09-2.19)	0.014	1.99 (1.22-3.20)	0.005	1.36 (0.96-1.94)	0.088
Prior stroke	1.26 (0.98-1.62)	0.073	1.14 (0.75-1.72)	0.482	1.14 (0.87-1.48)	0.341
Known diabetes	1.36 (1.09-1.69)	0.007	1.47 (1.01-2.11)	0.040	1.46 (1.15-1.85)	0.002
Known hypertension	0.82 (0.67-1.01)	0.069	0.71 (0.50-1.00)	0.052	0.76 (0.61-0.95)	0.014
Prior cardiac surgery/Prior PCI			0.59 (0.42-0.82)	0.002	0.66 (0.53-0.82)	<0.001
Prior cardiac surgery	0.70 (0.57- 0.87)	0.001	N/A	N/A	N/A	N/A
Prior PCI	0.94 (0.76-1.16)	0.578	N/A	N/A	N/A	N/A
Prior COPD	1.28 (1.02-1.61)	0.034	1.04 (0.71-1.52)	0.842	1.18 (0.93-1.50)	0.175
Peripheral arterial disease	1.22 (0.97-1.51)	0.084	1.48 (1.02-2.16)	0.041	1.24 (0.97-1.58)	0.082
Atrial fibrillation	1.33 (1.09-1.62)	0.004	1.39 (1.01-1.91)	0.044	1.28 (1.05-1.57)	0.016
Logistic EuroSCORE I (n=1332)	2.48 (1.21-5.07)	0.013	N/A	N/A	N/A	N/A
Prosthesis make (Ref. CoreValve)						
Edwards	0.92 (0.76-1.12)	0.418	0.83 (0.60-1.15)	0.276	0.90 (0.73-1.11)	0.315
Other	0.54 (0.20-1.48)	0.236	0.60 (0.22-1.65)	0.322	0.59 (0.22-1.61)	0.305

5.3 STUDY III

Between January 1st, 2005 and August 3rd 2018 there were 14550 patients included in the analysis cohort. Of these 500 (3.4%) had confirmed AS and 155 (1.1%) had undergone AVR before dialysis start. In a multivariable logistic regression analysis, older age, hypertension, ischemic heart disease, atrial fibrillation, heart failure and peripheral arterial disease were independently associated with prevalent AS. In multivariable Cox regression analysis, patients with known AS (adjusted HR: 1.45, 95%CI: 1.27 - 1.65, p < 0.001) and undergone AVR before dialysis start (adjusted HR: 1.26, 95%CI: 1.04 - 1.53, p < 0.038) had higher risk of death.

When patients with known AS and prior AVR were excluded, there were 14050 dialysis patients included in the main analysis (Figure 11). The median age was 68 years (IQR: 56 - 75) and 66.3% were males. During a median follow-up of 2.7 (1.1 - 5.7) years, 595 (4.2%) patients developed AS. The corresponding crude incidence rate was 16.3/1000 person-years (95%CI: 15.1 - 17.7) (Figure 17). In subgroup analyses males than females (18.5/1000 person-years; 95% CI: 16.9 - 20.3 vs 11.8/1000 person-years; 95% CI: 10.1 - 13.9, p <0.001) and patients treated with peritoneal- rather haemo- dialysis (IR 17.90/1000 person-year; 95% CI: 15.62 - 20.54 vs IR 15.60/1000 person-year, 95% CI: 14.10 - 17.21, p = 0.039) had significantly higher incidence rates of incident AS. Several comorbidities such as ischemic heart disease, previous coronary artery by-pass graft surgery and atrial fibrillation were more common in dialysis patients who developed new onset AS compared to those who did not.

In adjusted Cox regression analysis, higher age (adjusted HR: 1.03/year, 95%CI: 1.02 - 1.04, p < 0.001), male gender (adjusted HR: 1.51, 95%CI: 1.25 - 1.83), atrial fibrillation (adjusted HR: 1.32, 95%CI: 1.06 - 1.64, p = 0.011) and hypertension (adjusted HR: 1.65, 95%CI: 1.03 - 2.65, p = 0.037) were strongly associated with increased risk for incident AS. Compared to haemodialysis, peritoneal dialysis was associated with 18% higher, but non-significant, AS risk (adjusted HR:1.18, 95%CI: 0.99 - 1.40, p = 0.055), (Table 7).

Patients who underwent AVR were younger, more often males and had higher prevalence of coronary heart disease treated with percutaneous coronary intervention. In multivariable adjusted Cox regression analysis, only male gender was associated with a two-fold higher likelihood than females to undergo AVR (adjusted HR: 2.07, 95%CI: 1.30 - 3.30, p = 0.002).

There were 113 patients (20%) of those with incident aortic stenosis, who underwent AVR during 2.7 years of follow-up period (IQR: 1.1 - 5.7 years). The crude incidence rate of AVR was 3.1/1000 person-years (95%CI: 2.6 – 3.7), (Figure 18).

Table 10. Associations of covariates with incident aortic stenosis

	Crude Hazard Ratio* (95% CI)	P-value	Adjusted Hazard Ratio* (95% CI)	P-value
Age (continuous)	1.04 (1.03 – 1.05)	<0.001	1.03 (1.02 – 1.04)	<0.001
Men	1.58 (1.31 – 1.91)	<0.001	1.51 (1.25 – 1.83)	<0.001
Coronary heart disease	1.51 (1.25- 1.83)	<0.001	1.18 (0.96 – 1.44)	0.110
Diabetes	1.11 (0.94 – 1.31)	0.207	1.06 (0.89 – 1.25)	0.532
Atrial fibrillation	1.80 (1.46 – 2.20)	<0.001	1.32 (1.06 – 1.64)	0.011
Heart failure	1.31 (1.03 – 1.68)	0.027	0.97 (0.75 – 1.26)	0.809
Hypertension	2.64 (1.67 – 4.17)	<0.001	1.65 (1.03 – 2.65)	0.037
Peripheral arterial disease	1.21 (0.93 – 1.57)	0.150	0.93 (0.71 – 1.21)	0.592
Hyperlipidaemia	0.94 (0.66 – 1.35)	0.744	0.95 (0.67 – 1.36)	0.785
COPD	1.45 (1.04 – 2.18)	0.030	1.26 (0.90 – 1.76)	0.186
Haemodialysis (ref) vs Peritoneal dialysis	1.19 (1.01 – 1.42)	0.039	1.18 (0.99- 1.40)	0.055

Figure 17. 3-years risk of aortic stenosis and aortic valve replacement in dialysis patients

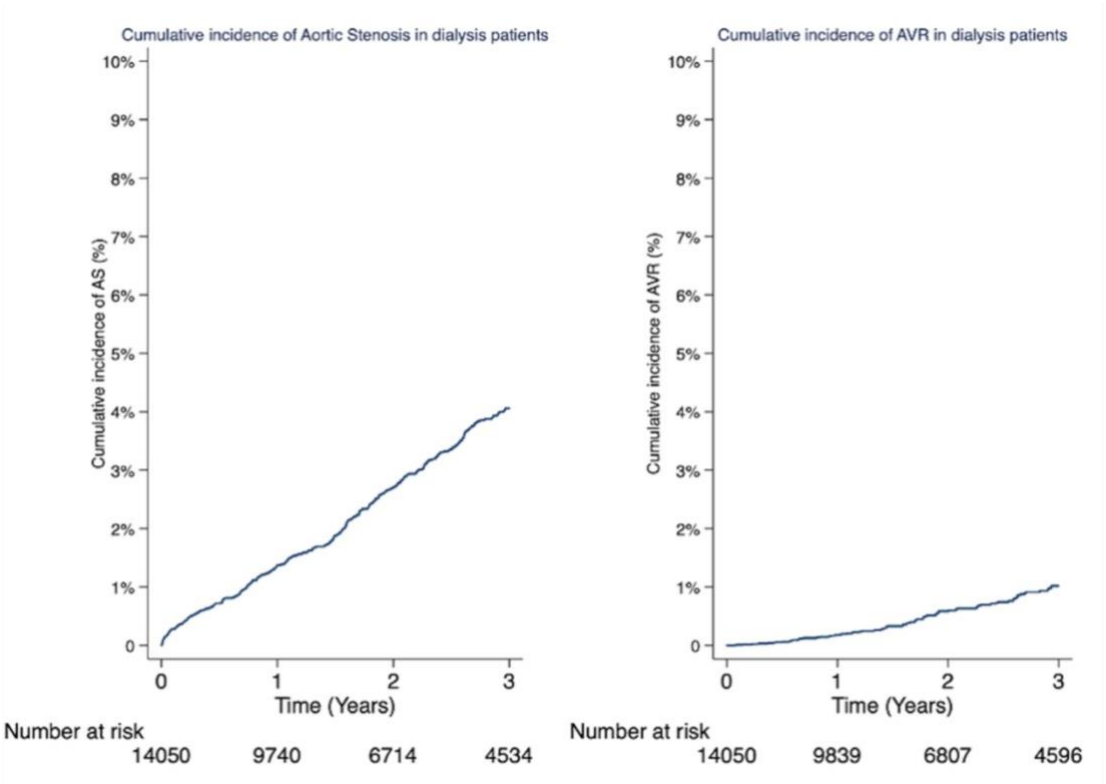
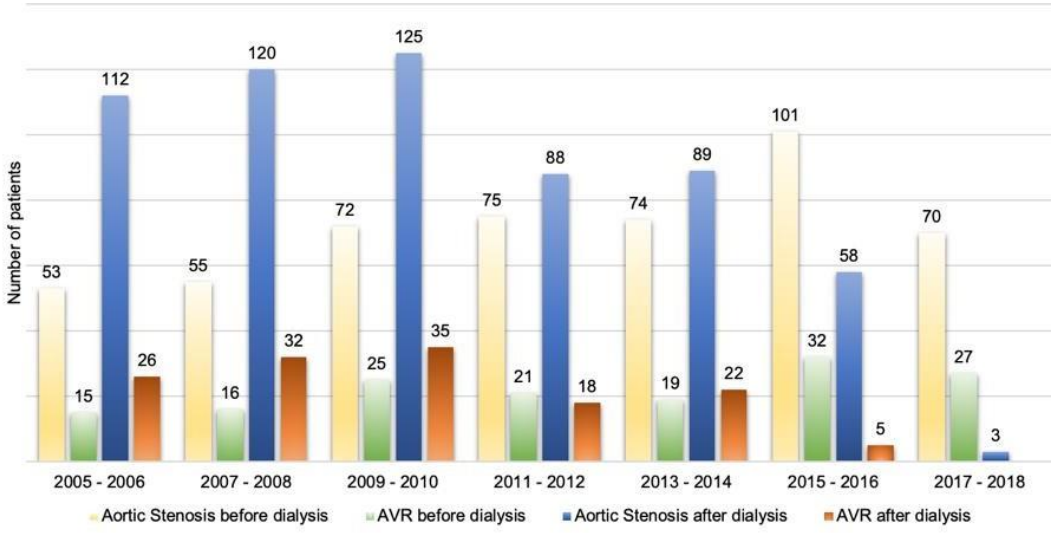


Figure 18. Number of patients in the Swedish Renal Registry with known aortic stenosis and aortic valve replacement at time of dialysis initiation, as well as new cases after dialysis initiation of aortic stenosis diagnosis and aortic valve replacement. (p-trend = 0.244 for aortic valve replacement over different time periods; p-trend = 0.001 for aortic stenosis diagnosis over different time periods).



Time periods	**2005 - 2006**	**2007 - 2008**	**2009 - 2010**	**2011 - 2012**	**2013 - 2014**	**2015 - 2016**	**2017 - 2018***
Number of patients who started dialysis	2193	2215	2172	2101	2117	2215	1537

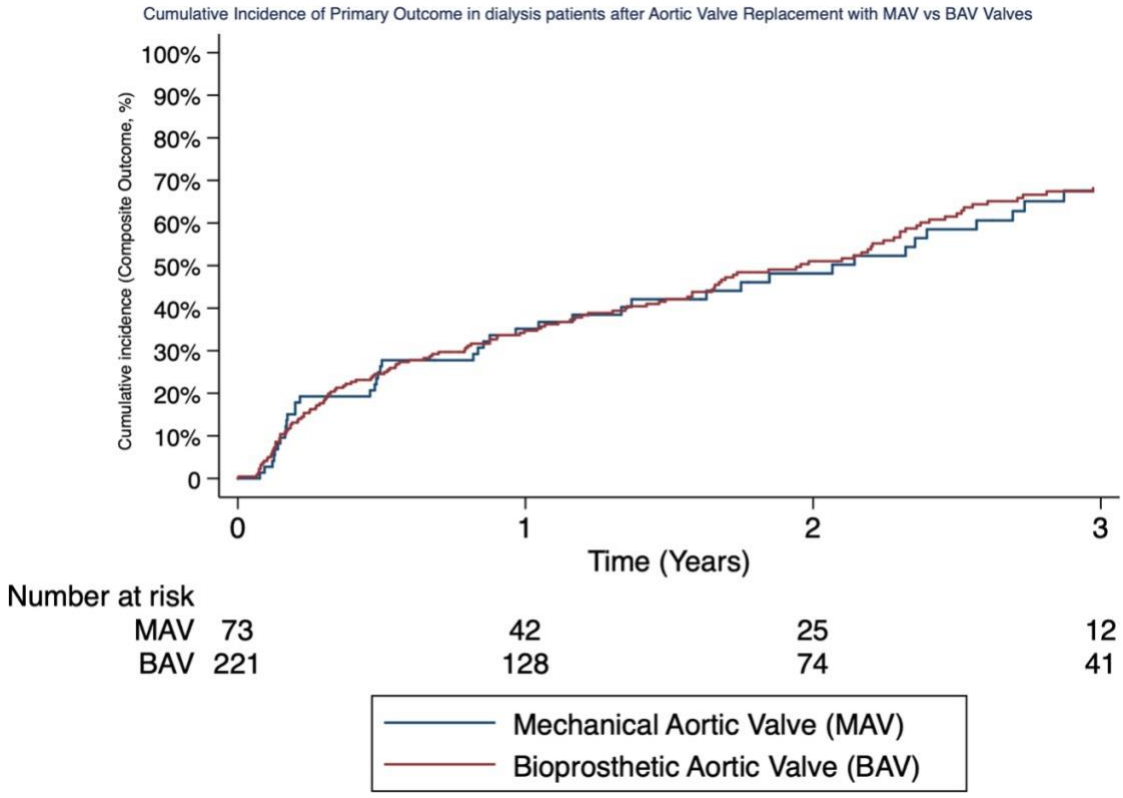
*Data in the Swedish Renal Registry are collected till August 3rd, 2018

5.4 STUDY IV

There were 294 consecutive patients in the SRR between January 2005 and August 2018, who underwent AVR either before (n = 155) or after (n = 139) dialysis start. In the total population, the median age was 71.7 years (IQR: 63.9 - 77.3) and 77.6% were males. Overall, more patients received bioprosthetic valves (75.2% vs 24.8%). Nonetheless, if AVR was undergone before or after dialysis, older age was independently associated with the section of bioprosthetic valve.

Over a median follow-up of 1.49 years (IQR: 0.66 - 2.83), a total of 202 primary end-points (comprising all-cause death and valve related complications bleeding events, stroke, aortic valve reoperation and all-cause death) occurred. Compared with patients who received bioprosthetic valves, recipients of mechanical valves had similar rates (69.7% vs 65.8% of primary end-point, IR: 39.5/100 person-years; 95%CI: 33.7 - 46.2) vs IR: 35.9/100 person-years; 95%CI: 27.0 - 47.6, P = 0.359) (Figure 19). Significant interaction was found between prosthetic valve type and age (p = 0.033). Several subgroup analyses were undertaken (gender, dialysis modality and age cut-off of ≤ 72 versus >72 years), but no difference was found compared to the main analysis.

Figure 19. Kaplan - Meier curves for time to first clinical adverse event (all-cause death, bleeding, stroke or reoperation) after aortic valve replacement with mechanical or bioprosthetic aortic valves in dialysis patients, p = 0.359, log-rank test.



After a median follow-up period of 1.49 years (IQR: 0.66 - 2.83), a total of 189 patients died; 61.2%; 45/73 in the mechanical group and 65.1%; 144/221in the bioprosthetic group. The overall mortality at 1-year follow-up was 28.9%. Recipients of bioprosthetic and mechanical valves had comparable mortality rates (IR: 32.1/100 person-year; (95%CI: 27.3 - 37.8), vs 27.4/100 person-year; (95%CI: 20.5 - 36.7), p = 0.183) (Figure 20). No association between co-morbidities and all-cause death was found.

Bioprosthetic valves were widely selected in dialysis patients (Figure 21). TAVR in dialysis patients began in 2011 in Sweden and till the end of follow-up period its use increased 2 to 3-fold. Patients undergoing TAVI were older and had higher comorbidity burden with ischemic heart disease, hypertension and chronic obstructive pulmonary disease.

Figure 20. Mortality rate in dialysis patients (N = 294) after aortic valve replacement with mechanical or bioprosthetic aortic valves, p = 0.312, log-rank test

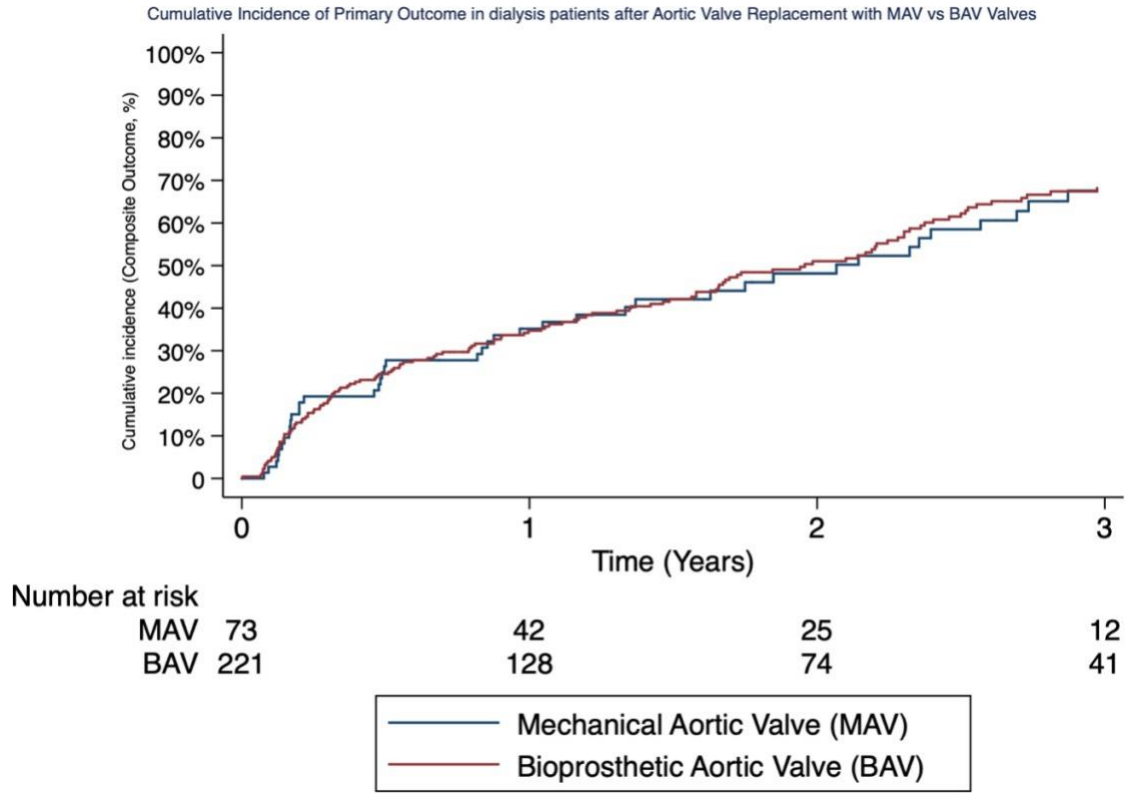
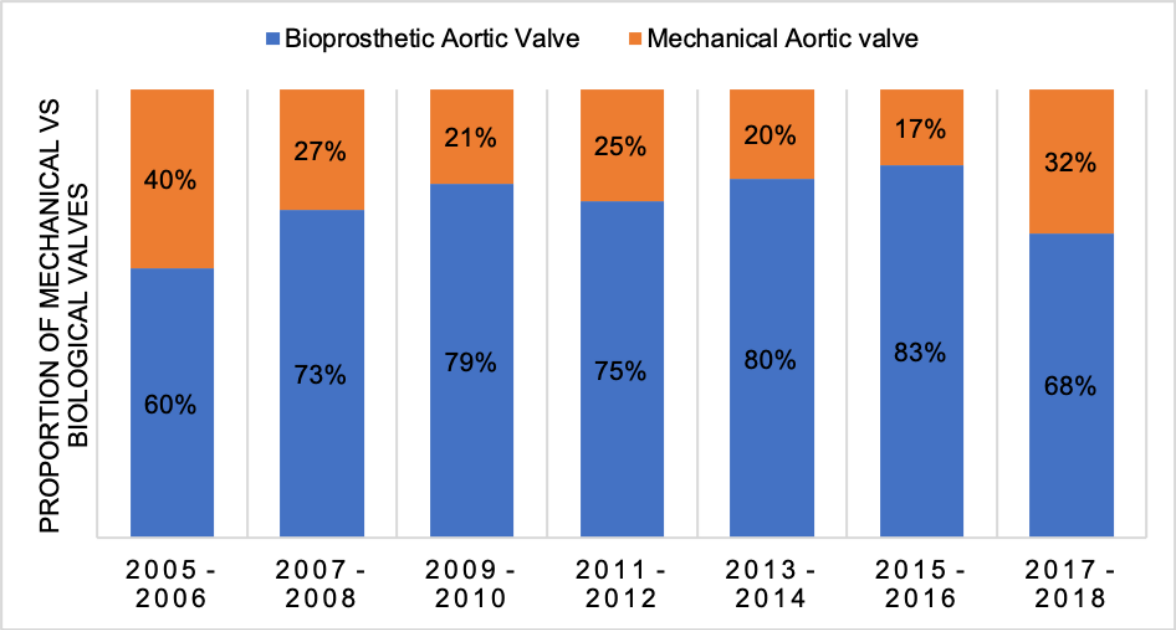


Figure 21. Changes in the proportions of bioprosthetic aortic valve utilization by two years period, among all patients with aortic stenosis in the Swedish Renal Registry who underwent aortic valve replacement, $p_{\text{-trend}} = 0.39$



6 DISCUSSION

6.1 MAJOR FINDINGS

Study I: In an unselected cohort of patients from the SCREAM database, encompassing patients with all CKD levels, an association between kidney dysfunction and AS was found, that remained significant after adjustments with covariates. The increase in risk appeared already in individuals with mild-to-moderate kidney dysfunction and seemed to be linear. Our findings suggest that kidney dysfunction is an independent predictor for AS.

Study II: In the national SWEDEHEART registry, where all patients in Sweden who underwent TAVR were included, we found that the presence of pre-procedural kidney dysfunction and the transapical approach were independently associated with the risk of persistent AKI, which was present at the time of discharge. pAKI occurred in 6% of patients and was associated with a double-fold high risk for long-term mortality.

Study III: Our study based on a contemporary nation-wide register determined that more than 3% of all patients who commence dialysis treatment are diagnosed with AS and almost one third of them had undergone AVR. During a median follow-up period of 3 years the cumulative incidence of AS was 4.1%. Older age, male gender, arterial hypertension and peritoneal dialysis, were independently associated with higher risk for clinically detected AS in dialysis patients. Only 20% of the patients underwent AVR.

Study IV: During 1.4 years of median follow-up, the complication rates of all-cause mortality, bleedings, stroke and aortic valve reoperation were comparable among dialysis patients who received MAV vs BAV. The 1-year mortality rate of dialysis patients who underwent AVR was 28.9%, with similar incidence between recipients of either MAV or BAV. The type of the implanted prosthetic aortic valve was not independently associated with long-term mortality.

6.2 INFLUENCE OF CKD ON THE DEVELOPMENT OF NEW-ONSET AS

AS is prevalent among patients requiring dialysis[5,8] and the progression to severe disease is accelerated compared to non-dialysis individuals[310]. Renal dysfunction has only been indicated as a weak risk factor for early changes in the aortic valve, but its role in the progression to more severe AS has not been established[311,312].

In this large population-based cohort study that included more than 1 million residents of Stockholm we explored whether CKD was associated with incident AS. Overall, CKD (defined as eGFR < 60 ml/min/1.73m^2) and AS were found in similar proportions as in previous studies[29,313]. The prevalence of CKD at baseline in the SCREAM cohort was 6% and during the follow-up period 0.5% of participants developed clinically diagnosed AS.

Our study revealed that kidney dysfunction was independently related with the development of incident AS, with a "dose response association" between lower eGFR strata and higher risk for new-onset AS in non-dialysis dependent individuals. This association was present even in patients with mild degrees of kidney dysfunction and after adjustments for covariates was attenuated but still present[314].

Previous studies in non-dialysis CKD individuals with cross-sectional evidence have shown contradictory results regarding the association of kidney dysfunction and aortic valve sclerosis or calcification[8,9,315]. The Chronic Renal Insufficiency Cohort (CRIC) study reported higher aortic valve calcium score across lower kidney function levels in individuals with different

kidney function categories who underwent aortic valve CT-scanning[315]. Additionally, the Multi-Ethnic Atherosclerosis (MESA) study reported a moderate association between kidney dysfunction and aortic valve calcification by computer tomography[8]. Finally, the Framingham off-spring study failed to observe an association between CKD and aortic valve calcification detected by echocardiography[9].

The definition of AS in our study was based on clinical diagnosis, as per clinical indication and current practice, where the diagnosis of AS is based on the quantification of effective AVA and the recording of blood flow hemodynamic parameters on echocardiogram of individuals with cardiac symptoms or significant systolic heart murmur. Validation studies have shown that the identification of AS diagnosis by diagnostic codes has an accuracy > 90%, as mainly moderate and severe AS are captured[48]. This outcome definition differs from prior studies[8,9,315] where aortic calcification was the primary outcome detected by imaging modalities providing morphological description of the aortic valve with quantification of valvular calcification, without information on hemodynamic performance or clinical significance of AS.

The mechanisms behind this association are not fully elucidated. Multiple and complex mechanisms have been identified to be involved in the pathophysiology of AS in patients with kidney dysfunction and dialysis. These are related to traditional atherosclerotic risk factors[311,316,317], cardiovascular diseases[318,319], uremic milieu and the frequent occurrence of bone metabolism dysregulation[12,320] and hemodynamic changes[6,27,310,321,322]. All these factors are well-established promoters of cardiovascular calcification with unknown contribution and synergy between them[41]. However, an important unexpected finding in our study is that the association of kidney dysfunction and AS was more attenuated in elderly and in the presence of cardiovascular morbidities. Recent population-based studies, have revealed an independent association between elevated serum phosphate and new-onset AS[12,182]. Further research is needed to explore potential associated etiologies behind lesser degrees of kidney dysfunction and AS.

Severe AS has dismal prognosis if left untreated and there are currently limited preventive and therapeutic strategies for this condition. This study on region-representative population was not designed to explore treatment outcomes. Nevertheless, it has provided strong evidence that even mild degrees of kidney dysfunction are linear associated with higher risk of clinically diagnosed AS.

6.3 MANAGEMENT OF AS: KIDNEY OUTCOMES AND PROGNOSIS AFTER TAVR

TAVR has emerged as an effective treatment for inoperable high-risk patients with severe AS[17]. However, AKI is a common complication, following TAVR, associated with increased risk of adverse outcomes[323]. Study II expands beyond these findings by providing real-world registry data on the clinical implications of unresolved AKI present at the time of discharge. In this large nationwide real-world registry of patients with AS who underwent elective or emergency TAVR in Sweden between 2008 and 2015, the overall incidence of pAKI was 6.1%; 83% of them developed stage 1 pAKI. Patients who developed pAKI were more likely to have pre-procedural kidney dysfunction, and to be of male gender. The only procedural characteristic associated with pAKI was transapical access. Interestingly, when assessing the out-of-hospital short- and midterms outcomes, pAKI was significantly associated with two-fold higher 1-year mortality risk[324].

In general, the occurrence of AKI following TAVR has decreased since approval, likely due to improved pre-procedural patient evaluation and procedural advances, but despite these

advances 10% of patients still will develop AKI after TAVR[323]. Our study confirmed prior findings demonstrating an increased risk for pAKI among patients undergoing TAVR via non-transfemoral access[325,326]. In these studies, patients selected for transapical TAVR often had porcelain aorta with advanced atherosclerotic burden and peripheral vascular arteriopathy. The potential mechanisms may be explained by atherosclerotic plaque embolization during catheter manipulation throughout balloon pre-dilatation, valve positioning, and implantation[250]. Additionally, TAVR via transapical access is performed under general anesthesia which may cause kidney hypoperfusion[327].

According to our findings, contrast medium volume did not reach statistical significance as predictor of AKI. Previous studies have suggested that vulnerable patients with extensive atherosclerotic disease are at high risk to develop AKI[328]. Recent meta-analyses[329,330] are in agreement with our results. They have demonstrated an insufficient association between increased iodinated contrast volume and incident AKI, and rare need of dialysis due substantial decrements in kidney function following TAVR[331]. Hence, although the current lack of data that ionized contrast agents are nephrotoxic, evidence-based preventive care is recommended for patients undergoing contrast-enhanced procedures and who are identified to be at higher risk for AKI[331].

Interestingly, we reported significant sex disparities in the occurrence of important periprocedural complications that accounted for differences in the short and mid-term mortality following TAVR. Overall, there were no trend differences, and similar number of men and women underwent TAVR. For men, however, there was significantly higher risk to develop pAKI, but women experienced higher rates of periprocedural complications[324]. The sex differences in the early periprocedural outcomes are mainly driven by differences in the baseline characteristics. In our cohort, men were significantly younger but more likely to have important comorbidities, including higher burden of atherosclerotic diseases, higher creatinine values at baseline, cardiovascular and cerebrovascular comorbidities and had undergone more often percutaneous interventions for ischemic heart diseases, compared to women who were referred for TAVR. These results are consistent with previous studies and metanalyses, showing higher prevalence of comorbidities in men compared to women[332-335].

Additionally, in a sensitivity analysis, where two different definitions of AKI were used, we found that pAKI predictors that were identified with the VARC-2 definition, differed based on the AKI definition. Men, who presented higher baseline creatinine values, were more likely to develop pAKI when pAKI was defined as an absolute than relative increase in creatinine values at discharge by 26 mmol/L rather 25%-point, respectively[336].

In our study, all the AKI definitions used were strongly associated with two-fold both short- and long-term higher mortality in all baseline kidney function categories[303]. According to the VARC-2[303] and even the updated version of VARC 3 criteria[273], the KDIGO criteria have better accuracy in the diagnosis of AKI, than the RIFLE criteria[259].

Regardless of the definition used, in multivariable Cox-regression analysis, pre-procedural kidney dysfunction, male gender and pAKI were strongly associated with higher mortality risk[324]. Allende at. al. described a graded inverse relationship between pre-procedural eGFR and short- and long-term mortality[225]. The presence of atrial fibrillation was associated with 2-year mortality rates > 70%[225]. In our report the mortality risk appears to be further amplified by the presence of pAKI, regardless the baseline kidney function, with 1-year mortality two-fold higher compared to those without pAKI[324].

Although men were less prone to vascular complications, they had significantly higher risk for all-cause mortality. These results are in line with sex-specific analysis from PARTNER trial, which included 2500 patients[337]. The authors demonstrated that even if women had higher risk for vascular complications, men had less favorable late outcomes after TAVR, explained mainly by the higher incidence of atherosclerotic comorbidities at baseline[337]. A possible explanation for the survival benefit for women after TAVR is that women with AS more often develop myocardial hypertrophy with less fibrosis compared to men, with a rapid regression after AVR[337,338].

6.4 INCIDENCE AND NATURAL HISTORY OF NEW-ONSET AS IN DIALYSIS PATIENTS

AS is the most prevalent valvular heart disease in dialysis patients associated with poor prognosis in untreated patients[14]. The current knowledge on the prevalence and the incidence of the disease in dialysis patients is based on results from single-center cohorts, collected several decades ago[5-7]. Study III explored the modern epidemiology of AS in a large contemporary cohort of unselected patients who commenced dialysis in Sweden. We found a higher point prevalence of AS in dialysis patients[339] than that reported in general population[44].

Our findings are based on a contemporary longitudinal cohort representing the nation-wide renal registry in Sweden, with full coverage of study population. In addition, the definitionof the outcome differed compared to previous studies, where the AS diagnosis was based on outdated criteria such as cusp separation and aortic valve calcification detected by echocardiography[5-7]. In the presented study, AS was diagnosed based on the hemodynamic performance of aortic valve according to the current recommendations[18]. Patients with more severe form of the disease were referred to local heart-teams for multidisciplinary preoperative assessment.

The methodological differences in the study design and definition of outcome may explain the discrepancies in the reported results. For example, in 1987 Maher et. al. reported that in a total of 87 hemodialysis patients aged 35 - 70 years, 28% (n = 24) had aortic valve calcification[5]. In a recent cross-sectional study including end-stage renal disease patients (only half on dialysis) the prevalence of aortic calcification was about 40% on computed tomography[340]. Older age, longer duration of hemodialysis and higher concentrations of calcium phosphate product were associated with the presence of aortic valve calcification. The prevalence of AS was 6% (n = 5) and 2 of them had severe AS confirmed by cardiac catheterization. This is a much higher prevalence than in our nationwide study. Similarly, Straumann et. al. reported an AS prevalence of 13% among 62 patients on hemodialysis[7]. The report was based on echocardiographic measurement of cusp-separation (< 1.5 cm) and peak aortic flow (>2.2 m/s). In a single-center study based on data from 110 dialysis patients between 1990 – 1996, Urena et al reported, based on indexed aortic valve area criteria (< 0.8 cm2/m2), a cumulative incidence of 3.3%/year[6]. The cumulative incidence of AS in the present study was 4.2% in the first 3 years of follow-up period. Even though we report a lower incidence than in previous studies, the rate of AS is still much higher than in a general population or among patients with chronic kidney disease[44].

Our study highlights sex differences in dialysis patients with AS. Indeed, male gender was associated with a 50% higher risk of being diagnosed with AS or undergoing AVR. These findings are consistent with the results from Larsson at. al. in general population[44]. Prospective studies in general population based on modern diagnostic modalities have tried to elucidate the

sex differences in the pathophysiology of AS. Findings from a multicenter cardiac magnetic resonance study confirmed that the sex differences in AS may be partially explained by the higher atherosclerotic disease burden in men than in women[341]. Further imaging studies that evaluated the sex differences in aortic valve calcium load with multidetector CT demonstrated increased and faster annual rates of aortic valve calcium loads in men compared to women[342,343]. Conversely, following the results from study I we reported a 20% significantly higher risk in women with CKD to develop AS compared to those with normal kidney function[314]. Thus, men on dialysis are more likely to develop AS, as they display higher levels of aortic valve calcification promoted by dialysis[340].

In this study, atrial fibrillation was present in one fifth of dialysis patients who developed AS and was associated with 32% higher risk for the development of new onset AS[339]. As previously reported by Zhang at. al. the presence of atrial fibrillation in AS patients has to be considered as a clinical marker instead of risk factor, denoting the presence of other underlying myocardial structural diseases[344], associated with dismal prognosis[345].

Hypertension is a known risk factor of AS in the general population[45] and among obese individuals[44]. Our study confirmed and extended these findings in a contemporary nation-wide cohort of dialysis patients, where hypertension was found to be the most prevalent comorbidity, associated with a twice-fold higher risk of AS[339]. Potential explanations for this association are the high tensile stress on aortic valve leaflets and the turbulent blood flow that results in low shear stress and valvular endothelial damage[346-348].

We identified, that patients on peritoneal dialysis had a non-significant trend towards higher risk to develop AS over those on maintenance hemodialysis[339]. More recent research has shown increased circulating Lp(a) levels in peritoneal dialysis patients[349]. Thanasoulis at. al. showed that increased plasma Lp(a) concentration is a genetically determined, causal risk factor for AS[48]. Although, the general consensus from the AHA Scientific Statement[79] is that the risk of AS may be lower with peritoneal than with hemo-dialysis, the aforementioned data indicate a trend in the opposite direction.

AVR before dialysis initiation was performed in a similar proportion of individuals as in the general population[44]. For dialysis patients who developed incident AS only one of fifth of them underwent AVR. A possible explanation for this finding is the limited life expectancy and the presence of comorbidities that makes them more vulnerable to peri-procedural complications associated with AVR[297].

6.5 MANAGEMENT OF AORTIC STENOSIS IN DIALYSIS PATIENTS

Following the results of study III, we explored the survival and complication rates of dialysis patients who underwent AVR with mechanical or bioprosthetic valves.

Our results showed similar all-cause mortality and complication rates in dialysis patients who underwent AVR with MAV or BAV. In multivariable Cox regression analysis prosthetic valve type was not associated with the outcomes. The 1-year mortality was 29%. A recent study from Perrotta at. al. analyzing the same cohort, reported similar short- mid- and long- term mortality and complication rates in dialysis patients who underwent AVR between 1997-2017. Interestingly, the unadjusted 10-years survival was lower for the recipients of bioprosthetic valves compared to those who received MAV (24% vs 38%)[350]. Aljohani at. al. compared the rates of in-hospital mortality and periprocedural complications in propensity matched cohort of hemodialysis and non-hemodialysis patients. The in-hospital mortality of dialysis patients who underwent AVR, was mainly driven by the occurrence of cardiogenic shock, concomitant

cardiac surgery and male gender and was found to be improved during the follow-up time but still 2-times higher when compared withnon-dialysis patients[280].

Considerations before AVR in dialysis patients are similar to those in a general population, but with the addition of concerns regarding their short-anticipated life expectancy[279], increased perioperative morbidity and mortality[280], increased thrombotic and hemorrhagic risk[281], and the potential adverse events related to anticoagulation treatment as it is associated with high bleeding and calciphylaxis risk[282].

The pre-operative age is an important determinant related with the postoperative outcomes. However, in our study age was not significantly associated with the outcomes. The complication and mortality rates were comparable when the analysis was performed at the median age. Dialysis patients have significantly higher mortality compared to non–dialysis patients and although they are younger, the perioperative mortality risk after AVR, increases linearly with the number of comorbidities[297,350].

6.5.1 TAVR as alternative modality to SAVR in dialysis patients.

BAV were most commonly used throughout all time periods in our cohort. TAVR in dialysis patients began in 2011 in Sweden, and the utilization of TAVR in dialysis patients increased 2 to 3-fold between 2011 - 2018. The temporal trends seen in our study were similar with those from Aljohani at. al.[280]

Nowadays, TAVR has become the preferred choice for AVR in dialysis patients, as it is a less invasive alternative. These patients should otherwise be considered inoperable, due to high periprocedural risk[295]. The in-hospital mortality has improved for dialysis patients with suitable transfemoral access compared to SAVR. The current literature suggests that SAVR in dialysis patients is related to higher incidence of blood transfusion and cardiac tamponade, whereas conduction disturbances requiring pacemaker implantation occurred more often in theTAVR group[280].

Data from the Medicare and Analysis Preview have reported significantly lower short-term mortality in the TAVR group compared to SAVR (3% vs 12.5%). During the mid-term follow-up, SAVR was associated with higher incidence of valve related complications like infective endocarditis (3.5% vs 0.4%) and stroke, without differences in all–cause mortality[288]. The latest scientific statement from AHA suggests that TAVR should be used in dialysis patients > 55 years of age with expected longevity of life > 2 years[299], and with suitable transfemoral access[79].

Prosthesis durability is an important concern in dialysis patients, given the high risk of bioprosthetic valves structural deterioration and the short life expectancy in this group[285]. Bioprosthetic valves have long been considered not to be used in dialysis patients due to faster structural deterioration[284]. Evidence from retrospective observational studies of mixed cohorts with aortic and mitral valve surgery, have shown comparable survival and complication rates in dialysis patients who received BAV or MAV[286,291,351]. Perrotta at. al. identified low incidence of structural valve deterioration in a Swedish nationwide dialysis cohort, with similar rates between the MAV and BAV group[350]. The cumulative incidence of structural valve deterioration in general population varies from 2 - 9% at 7 - 8 years of follow-up[352]. Results from Kuroda at. al. showed dialysis patients who underwent AVR with bioprosthetic valves had 6-times higher rate of structural valve deterioration compared to general population[298]. Conversely, the presence of kidney failure was not linked with higher rates of transcutaneous BAV deterioration 1 year after theprocedure[225].

6.6 LIMITATIONS

All studies in this thesis are entirely observational and register based. The Swedish national registers have repeatedly been shown to have high quality and accuracy of the diagnostic codes, and due to cross-linkage with the National Cause of Death Register complete follow-up for death. Pharmacological therapies and demographical data are documented accurately. The external validity of the epidemiological studies is improved by using large cohorts with long follow-up periods. The larger and more representative the cohort is, the higher the generalizability of the results. However, the absence of randomization and selection criteria is a major limitation of the observational studies. The internal validity is affected by, confounding, immortal time bias, information and selection bias. Despite adjustments for a large number of confounders, only variables that are measured can be adjusted, residual confounding is still present and observational studies can prove associations and not causality.

Specific limitations of individual studies are discussed in brief bellow.

Study I

The outcome of AS in the present study takes a long time to develop. The median follow- up in this study was 5.1 years, which may not be long enough to capture the first stages of the disease. Due to lack of echocardiographic data, we were unable to define the grade of AS severity, the cause and the anatomical variations of the aortic valve and the rate of progression. Kidney dysfunction at baseline could be secondary to the presence of asymptomatic AS by reducing cardiac output and was defined based on a single creatinine measurement. Thus, transient variations of creatinine due to acute illness could not be captured at inclusion period.

Study II

An important endpoint in this study is the CKD progression following TAVI, based on laboratory changes of creatinine values. However, the availability of creatinine on discharge and the absence of the peak creatinine within 72 hours to 7 days has introduced information bias, non-differential misclassification of the outcome and underestimation of the AKI occurrence. Additionally, patients at high risk to develop dialysis required AKI with kidney failure and eGFR <15 mL/min/1.73 m^2, were excluded.

Study III

As in study I, the definition of AS in study III was based on ICD-10 diagnostic codes. However, they do not give any information for valvular condition as hemodynamic performance, severity, aetiology and anatomical variations of the disease. Doppler echocardiography is the gold standard method used to assess the severity of AS. Moreover, we were unable to capture the initiation or the rate of progression of AS. Another important limitation in this study is the high degree of missing laboratory values. We were unable to make adjustments and to evaluate associations for important comorbidities in dialysis patients such as, hyperphosphatemia, hyperparathyroidism or hypercalcemia.

Study IV

The low number of study population merits caution in the interpretation of results, even more in subgroup analysis. For instance, we could not control for patient frailty, etiology of aortic stenosis, severity of other valve lesions, extend of ventricular dysfunction and missing information on the type of prostheses implanted. Beside the lack of information on the patients' INR, the 1.4 years of follow up is too short to capture the longer effects of anticoagulation

therapy on the incidence of bleeding rates as well as the indication of reoperation in recipients of bioprosthetic aortic valve.

7 CONCLUSIONS

Study I

Patients with mild or moderate CKD had increased risk for new onset AS. This risk was more attenuated in the absence than in the presence of older age and other cardiovascular comorbidities.

Study II

Men with AS with lower baseline kidney function who underwent TAVR through transapical approach were more likely to develop pAKI. The presence of worsened kidney function at the time of discharge was associated with two-fold higher early and late mortality risk.

Study III

Patients who commence dialysis have both a high prevalence and incidence of AS. In this study, higher age, male gender, hypertension and peritoneal dialysis were associated to AS. Although the increased incidence of newly diagnosed AS, were infrequently treated as only one fifth underwent AVR.

Study IV

Among dialysis patients who underwent AVR with MAV compared to BAV, there was no significant difference in the overall death or the composite endpoint of all-cause mortality and the valve related complications such as all bleeding types, stroke and aortic valve reoperation, without higher mortality rates between the groups. Prosthetic aortic valves were not independent predictors of long-term survival. These findings suggest that bioprosthetic valves can be used with safety in dialysis patients.

8 POINTS OF PERSPECTIVE

Study I

Severe AS is common in CKD and dialysis patients and is associated with increased cardiovascular mortality. Timely diagnosis of AS may be improved, and aortic valve calcium scoring may be an additional tool in evaluation but need further evaluation in CKD patients[79,315]. A better understanding of the multifactorial mechanisms involved in AS disease progression overall, but also mechanisms specific to CKD patients, is an important research topic, which may help in finding both biomarkers that can predict progression of AS in CKD[353], and also targets for early intervention. We still lack treatments to prevent the AS disease, both in the general population as well as in the CKD patient.

Study II

AKI is an important negative prognostic sign. Finding patients at risk before TAVR is important, and assessing whether specific nephroprotective treatments can be used to reduce this risk are underway. It is still unknown, whether any treatment can reduce the risk after AKI has occurred after TAVR.

Study III

Despite the advances in dialysis techniques, dialysis patients are at risk of AS. Further research is needed to understand the underlying pathophysiological mechanisms that influences the initiation and progression of valvular calcification in dialysis patients. It is unknown, whether different dialysis techniques, modalities and the metabolic milieu obtained through dialysis, affect AS development.

Study IV

Life expectancy of dialysis patients with AVR is short. Therefore, BAV may be preferred in the aortic position since these patients are not expected to outlive their bioprosthetic valves[284]. TAVR is used increasingly in dialysis patients, and evaluation of its durability and complications is important. Due to the low number of patients, it is unlikely that any randomized trial will be undertaken in this patient group. Hence, continued surveillance of complications, durability and outcomes through registries remains important.

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