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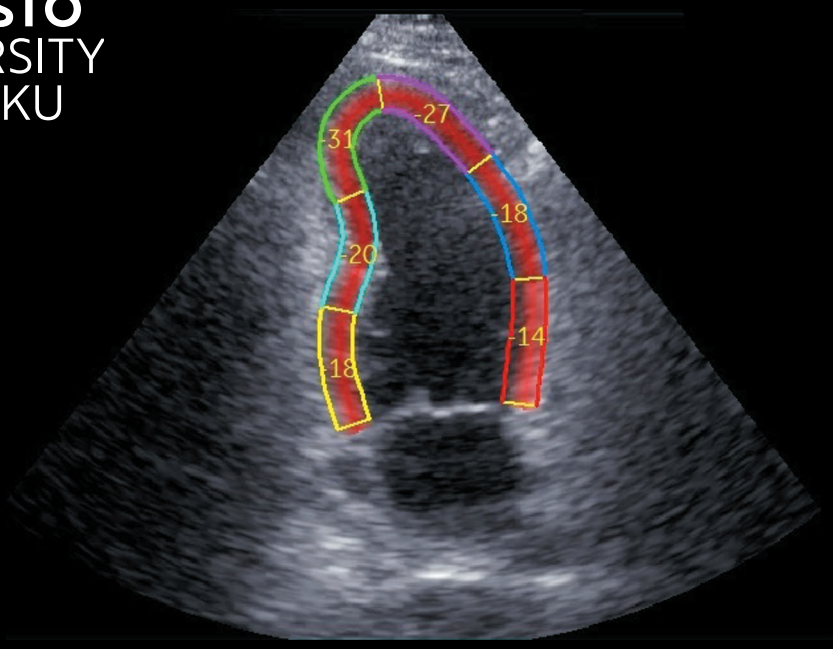

QUALITY OF LIFE, CARDIOVASCULAR DISEASE AND MORTALITY IN ADVANCED CHRONIC KIDNEY DISEASE

Markus Hakamäki

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ABSTRACT

Chronic kidney disease (CKD) patients suffer from impaired Health-related Quality of Life (HRQoL). Impaired HRQoL has important implications for their prognosis. Cardiovascular disease (CVD) is common in CKD patients, leading to excess morbidity and mortality in this population. Risk factors unique to the CKD population add to the traditional risk factors. A multi-faceted treatment approach to improve the HRQoL and prognosis of CKD patients is needed. Correctly assessing a patient's prognosis would be helpful in tailoring treatment.

A Chronic Arterial Disease, Quality of Life and Mortality in Chronic Kidney Injury (CADKID) Study enrolled 210 participants with advanced non-dialysis CKD. The cardiovascular system was assessed by exercise test, echocardiography, evaluation of abdominal aortic calcification (AAC) and vascular ultrasound. A wide selection of biomarkers and HRQoL were measured.

HRQoL was associated with cardiac biomarkers, Troponin T (TnT), N-terminal Pro-B-type Natriuretic Peptide (proBNP) and echocardiographic measure of cardiac systolic function, global longitudinal strain (GLS). A measure of the physical aspect of HRQoL, Physical Component Summary, was associated with mortality. In the longitudinal study of HRQoL, kidney transplantation improved kidney disease-specific aspects compared to dialysis.

Cardiovascular determinants of mortality in the CADKID study were TnT, proBNP, serum albumin, AAC, exercise performance and an echocardiographic measure of cardiac diastolic function, E/e'. The incidence and prevalence of atrial fibrillation in the study cohort were high. Age, elevated TnT and increased left atrial volume index were associated with the incidence of atrial fibrillation.

HRQoL is associated with biochemical and echocardiographic markers of cardiac function. Kidney transplantation is the renal replacement therapy of choice for the eligible CKD patients. Readily available methods investigating cardiovascular health help to determine the prognosis in advanced CKD and thus guide treatment.

KEYWORDS: Chronic Kidney Disease, Quality of Life, Mortality, Cardiovascular Disease, Echocardiography, Ergometry Stress Test, Aortic Calcification, Troponin T, Renal Replacement Therapy, Kidney Transplantation, Atrial Fibrillation, Left Atrial Volume Index

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
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TIIVISTELMÄ

Krooninen munuaistauti heikentää elämänlaatua vaikuttaen potilaiden jokapäiväisen elämän lisäksi heidän ennusteeseensa. Sydän- ja verisuonitaudit ovat yleisiä kroonista munuaistautia sairastavilla ja aiheuttavat ylimääräistä kuolleisuutta ja sairastavuutta. Tavanomaisten riskitekijöiden lisäksi krooniseen munuaistautiin liittyvät tekijät lisäävät riskiä. Näiden potilaiden elämänlaadun ja ennusteen parantamiseksi tarvitaan monitahoista hoitostrategiaa. Olisi tärkeää pystyä arvioimaan potilaan ennuste oikein, jotta hoito voitaisiin sovittaa yksilöllisesti.

Krooninen valtimotauti, elämänlaatu ja mortaliteetti vaikeaa munuaisten vajaatoimintaa sairastavilla (CADKID) –tutkimukseen osallistui 210 potilasta, joilla oli pitkälle edennyt krooninen munuaistauti mutta ei vielä dialyysihoitoa tutkimuksen alkaessa. Sydäntä ja verisuonistoa tutkittiin rasituskokeella, ultraäänitutkimuksilla ja vatsa-aortan kalkkiutumisen aste (AAC) arvioitiin. Verikokeita tutkittiin laajalti ja elämänlaatua mitattiin.

Elämänlaatu oli yhteydessä sydänmerkkiaineisiin troponiini T (TnT) ja B-tyypin natriureettisen peptidin esiaste (proBNP) sekä sydämen systolisen toiminnan mittariin, pitkittäissupistuvuuteen (GLS). Elämänlaatumittarin fyysisen osan yhteenvetopisteet olivat yhteydessä kuolleisuuteen. Seurantatutkimuksessa munuaissiirto paransi munuaistautiin liittyvää elämänlaatua merkitsevästi verrattuna dialyysiin.

CADKID-tutkimuksessa kuolleisuutta ennustivat TnT, proBNP, matala albumiini, AAC, suorituskyky rasituskokeessa ja sydämen diastolisen toiminnan mittari, E/e'. Eteisvärinän esiintyvyys ja ilmaantuvuus oli suurta tutkimusaineistossa. Ikä, koholla oleva TnT ja suurentunut sydämen vasemman eteisen tilavuusindeksi olivat yhteydessä eteisvärinän ilmaantuvuuteen.

Elämänlaatu on yhteydessä sydämen toimintaa kuvaaviin merkkiaineisiin ja ultraäänilöydöksiin. Munuaisensiirto on elämänlaadullisesti paras hoitomuoto loppuvaiheen munuaisten vajaatoimintaan. Yleisesti saatavilla olevilla tutkimuksilla voidaan määrittää potilaan ennuste ja ohjata hoitoa.

AVAINSANAT: krooninen munuaistauti, elämänlaatu, kuolleisuus, sydän- ja verisuonitauti, sydämen ultraäänitutkimus, rasituskoe, aortan kalkkiutuminen, troponiini T, munuaiskorvaushoito, munuaisensiirto, eteisvärinä, vasemman eteisen tilavuusindeksi

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Abbreviations

15D-HRQoL	15-dimensional Health-Related Quality of Life
AAC	Abdominal Aortic Calcification
AASK	African American Study of Kidney Disease and Hypertension
ACCORD	Action to Control Cardiovascular Risk in Diabetes Study
ACE	Angiotensin-Converting Enzyme
ACR	Urine Albumin-to-Creatinine Ratio
AF	Atrial Fibrillation
AMI	Acute Myocardial Infarction
ANOVA	Analysis of Variance
APD	Automated Peritoneal Dialysis
ARB	Angiotensin II Receptor Blocker
ARIC	Atherosclerosis Risk in Communities Study
BMI	Body Mass Index
BP	Blood Pressure
CAC	Coronary Artery Calcification
CAD	Coronary Artery Disease
CADKID	Chronic Arterial Disease, Quality of Life and Mortality in Chronic Kidney Injury
CAPD	Continuous Ambulatory Peritoneal Dialysis
CHF	Congestive Heart Failure
cIMT	Carotid Intima-Media Thickness
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CKD-MBD	Chronic Kidney Disease Mineral and Bone Disorder
COPD	Chronic Obstructive Pulmonary Disease
CRIC	Chronic Renal Insufficiency Cohort
CRP	C-Reactive Protein
CT	Computed Tomography
CV	Cardiovascular
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure

DCCT	Diabetes Control and Complications Trial
DKD	Diabetic Kidney Disease
DM	Diabetes Mellitus
DOPPS	Dialysis Outcomes and Practice Patterns Study
E/A	Ratio of the Early to Late Ventricular Filling Velocities
ECG	Electrocardiogram
EDIC	Epidemiology of Diabetes Interventions and Complications Study
E/e'	Ratio Between Early Mitral Inflow Velocity and Mitral Annular Early Diastolic Velocity
eGFR	estimated Glomerular Filtration Rate
EPO	Erythropoietin
EQ-5D	EuroQoL-5-Dimension
ESA	Erythropoiesis-Stimulating Agent
ESKD	End-Stage Kidney Disease
FGF23	Fibroblast Growth Factor 23
fIMT	Femoral Intima-Media Thickness
FMD	Flow-Mediated Dilatation
GFR	Glomerular Filtration Rate
GLP-1	Glucagon-Like Peptide-1
GLP-1RA	Glucagon-Like Peptide-1 Receptor Agonist
GLS	Global Longitudinal Strain
Hb	Hemoglobin
HbA1c	Glycated Hemoglobin
HD	Hemodialysis
HDF	Hemodiafiltration
HF	Heart Failure
HHD	Home Hemodialysis
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
ICD	Implantable Cardiac Defibrillator
ICHD	In-Center Hemodialysis
IL-6	Interleukin-6
IMT	Intima-Media Thickness
IQR	Interquartile Range
KDCS	Kidney Disease Component Summary
KDIGO	Kidney Disease: Improving Global Outcomes
KDQOL	Kidney Disease and Quality of Life
KDQOL-36	Kidney Disease and Quality of Life-36
KDQOL-SF	Kidney Disease and Quality of Life Short Form
KTR	Kidney Transplant Recipient

KTx	Kidney Transplantation
LAVI	Left Atrial Volume Index
LVEDD	Left Ventricular End-Diastolic Diameter
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricular Hypertrophy
LVMI	Left Ventricular Mass Index
MACE	Major Adverse Cardiovascular Event
MCID	Minimal Clinically Important Difference
MCS	Mental Component Summary of the Short Form 36
MDRD	Modification of Diet in Renal Disease
MI	Myocardial Infarction
MRA	Mineralocorticoid receptor antagonist
NHANES	National Health and Nutrition Examination Surveys
OR	Odds Ratio
PAD	Peripheral Artery Disease
PCS	Physical Component Summary of the Short Form 36
PD	Peritoneal Dialysis
PDOPPS	Peritoneal Dialysis Outcomes and Practice Patterns Study
proBNP	N-terminal Pro-B-type Natriuretic Peptide
PTH	Parathyroid Hormone
QoL	Quality of Life
RAS	Renin-Angiotensin System
RCT	Randomized Controlled Trial
RRF	Residual Renal Function
RRT	Renal Replacement Therapy
SBP	Systolic Blood Pressure
SCD	Sudden Cardiac Death
SD	Standard Deviation
SF-12	Short Form 12
SF-36	Short Form 36
SGLT-2	Sodium-Glucose Co-Transporter 2
SGLT-2i	Sodium-Glucose Co-Transporter 2 Inhibitor
SPRINT	Systolic Blood Pressure Intervention Trial
TnT	Troponin T
Wmax	Mean Work Load of the Last Four Minutes of Exercise

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Hakamäki M, Lankinen R, Hellman T, Koivuviita N, Pärkkä JP, Saarenhovi M, Metsärinne K & Järvisalo MJ. Quality of Life Is Associated with Cardiac Biomarkers, Echocardiographic Indices, and Mortality in CKD Stage 4-5 Patients Not on Dialysis. *Blood Purif*. 2021;50(3):347-354.

II Hakamäki M, Järvisalo MJ, Lankinen R, Koivuviita N, Pärkkä JP, Kozak-Barany A, Hellman T & Metsärinne K. Evolution of Quality of Life in Chronic Kidney Disease Stage 4-5 Patients Transitioning to Dialysis and Transplantation. *Nephron*. 2022;146(5):439-448.

III Lankinen R, Hakamäki M, Metsärinne K, Koivuviita NS, Pärkkä JP, Hellman T, Kartiosuo N, Raitakari OT & Järvisalo MJ. Cardiovascular Determinants of Mortality in Advanced Chronic Kidney Disease. *Am J Nephrol.* 2020;51(9):726-735.

IV Hakamäki M, Hellman T, Lankinen R, Koivuviita N, Pärkkä J, Kallio P, Kiviniemi T, Airaksinen KEJ, Järvisalo MJ & Metsärinne K. Elevated Troponin T and Enlarged Left Atrium Are Associated with the Incidence of Atrial Fibrillation in Patients with CKD Stage 4-5. *Nephron.* 2021;145(1):71-77.

1 Introduction

Chronic Kidney Disease (CKD) is a significant worldwide health burden affecting the life of millions of people every day. Estimates of its prevalence vary between geographical regions, reaching over 15% of the adult population in many developed countries(1) and increasing with age. CKD is often initially asymptomatic, so many affected are unaware of the diagnosis. However, CKD has many important implications for the patients. Cardiovascular (CV) morbidity and mortality are more common than in the general population.(2,3) Furthermore, CKD patients' Health-related Quality of Life (HRQoL) is inferior compared to the general population.(4–6)

Diabetes mellitus (DM) and hypertension are common causes of CKD. Obesity can cause CKD, mainly indirectly by causing impaired glucose metabolism and elevated blood pressure. However, these conditions, and other traditional risk factors, such as smoking and hyperlipidemia, offer only a partial explanation of excess cardiovascular disease (CVD)-associated morbidity and mortality among CKD patients.

CV risk factors directly linked to CKD include disturbance of mineral and bone metabolism called Chronic Kidney Disease Mineral and Bone Disorder (CKD-MBD). Hyperphosphatemia, secondary hyperparathyroidism and associated vascular calcification are important manifestations of CKD-MBD.(7) Contrary to intimal atherosclerosis, the vascular calcification linked to CKD-MBD affects the media layer of the arteries by stiffening the vessels. This results in increased pulse pressure and contributes to development of left ventricular hypertrophy (LVH) and diastolic dysfunction of the heart.(8)

Anemia is a frequent finding in advanced CKD. Anemia in CKD is associated with LVH and heart failure as well as mortality.(9) Low-grade inflammation is recognized as a key component contributing to CV morbidity and mortality of CKD patients via a plethora of inflammatory cytokines and other mediators that are also important in the development of protein-energy wasting often encountered in end-stage kidney disease (ESKD).(10)

Through these traditional and CKD-specific risk factors and pathogenetic mechanisms, there is a manifold increase in cardiovascular morbidity and mortality

risks in the CKD population. Sudden cardiac death (SCD) is among the most dramatic manifestations of cardiovascular disease. CKD patients are at an increased risk for SCD that is most often caused by sudden arrhythmias. Pathogenetic mechanisms are thought to be related to structural changes in the heart induced by CKD as well as electrolyte abnormalities, mainly dyskalemias and fluid balance disturbances.(11) The same pathogenetic mechanisms could also lead to increased prevalence of other arrhythmias, such as atrial fibrillation (AF).

The HRQoL of CKD patients has been mainly studied among dialysis patients and in cross-sectional settings. HRQoL is increasingly recognized as an essential measure of quality of care. Measuring HRQoL gives information on patients' functioning in daily life and their symptom burden. Furthermore, HRQoL is associated with hospitalisations and mortality in CKD patients.(12–14)

In the Chronic Arterial Disease, Quality of Life and Mortality in Chronic Kidney Injury (CADKID) study, we prospectively studied 210 CKD patients initially not on dialysis with emphasis on CVD manifestations, quality of life and determinants of mortality. The specific aim of this thesis was to shed light on predialysis patients' quality of life and its evolution as the patients transitioned to dialysis and kidney transplantation (KTx) as well as determinants of mortality in this population. Furthermore, we studied the epidemiology and predictors of AF.

2 Review of the Literature

2.1 Definition and Classification of Chronic Kidney Disease

The commonly used Kidney Disease: Improving Global Outcomes (KDIGO) definition characterizes Chronic Kidney Disease (CKD) as abnormalities of kidney structure or function, with implications for health, lasting more than three months. CKD is divided into six categories according to glomerular filtration rate (GFR) and three categories according to albuminuria. GFR category G1 indicates normal or high GFR, G2 mildly decreased GFR, whereas G4 indicates severely decreased GFR and G5 indicates kidney failure. The G3 category is divided in two, namely G3a (mildly to moderately decreased GFR) and G3b (moderately to severely decreased GFR). Albuminuria categories A1, A2 and A3 indicate normal to mildly increased, moderately increased and severely increased albuminuria, respectively. Figure 1 shows the KDIGO classification of CKD and its associated risk.

The estimated GFR (eGFR) is used in clinical practice for CKD categorisation or staging. Multiple equations for eGFR calculations have been presented, including the Cockcroft-Gault formula and the Modification of Diet in Renal Disease (MDRD) formula. However, they have been largely replaced by the more accurate Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which is also recommended by KDIGO Guideline.(15) In addition to serum creatinine, age, ethnic origin and sex are needed for the eGFR calculation. A new CKD-EPI (2021) equation was introduced in 2021. This equation does not require information on ethnic origin. The American Society of Nephrology and the National Kidney Foundation recommend immediate implementation of the new equation in the United States. Using the equation with both creatinine and Cystatin C as variables further enhances the accuracy of estimating GFR.(16)

Albuminuria is graded preferably by the urine albumin-to-creatinine ratio (ACR) obtained from a morning urine sample.

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min per 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	⩾90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red, very high risk.

Figure 1. CKD staging by GFR and albuminuria categories and prognosis of CKD. Reprinted from Kidney International 85, Levin A and Stevens PE, Summary of KDIGO 2012 CKD Guideline: behind the scenes, need for guidance, and a framework for moving forward, 49–61, Copyright (2013), with permission from Elsevier

2.2 Epidemiology of Chronic Kidney Disease

CKD is a common worldwide health problem. Its mean global prevalence is estimated to be 13.4%. Its prevalence varies in different geographical regions, being generally higher in developed countries. A meta-analysis estimated a prevalence of 15.45% in North America and as high as 18.4% in Europe, all CKD stages considered, whereas in Africa its prevalence was 8.7%, although fewer data were available from African countries.(1) A cross-sectional analysis of National Health and Nutrition Examination Surveys (NHANES) by Coresh et al. observed an increase in prevalence of CKD stages G1 to G4 from 10.0% to 13.1% in the United States in 1999-2004 compared to 1988-1994.(17)

Considerable differences were observed in the prevalence of CKD in different study populations from different countries in the European adult general population. The age- and sex-adjusted prevalence of CKD stages G1-5 was 3.3% in Norway, whereas it was 17.3% in northeast Germany. The adjusted prevalence of CKD stages

G3-5 in the population aged 45-74 years varied from 1.7% in Switzerland to 11.5% in northeast Germany, Finland being in the middle with a 4.5% prevalence in this group.(18)

2.3 Chronic Kidney Disease and Mortality

CKD patients have an increased mortality risk, starting from eGFR <60 ml/min/1.73 m^2. Albuminuria increases mortality risk linearly starting from albuminuria levels considered normal. The death risk was inversely associated with eGFR in a large community-based population of over 1.1 million adults. The Hazard Ratio (HR) was 1.2 for those classified by eGFR to CKD stage G3a, 1.8 in stage G3b, 3.2 in stage G4 and the HR was as high as 5.9 in CKD stage G5 not in dialysis. The risk of CV events and hospitalisation followed a similar pattern in this study, i.e., higher HRs were associated with lower eGFRs.(19) In the NHANES II study, the risk of all-cause mortality was 68% higher in those with an eGFR <70 ml/min/1.73 m^2 compared to those with an eGFR >90 ml/min/1.73 m^2, whereas the CV mortality risk was 51% higher, respectively.(20) Anavekar et al. reported in 2004 that CKD is an independent predictor of worse outcomes after acute myocardial infarction (AMI). The risk of death and nonfatal adverse cardiovascular outcomes increased; each 10-unit decrease in eGFR below 81 ml/min/1.73 m^2 was associated with an HR of 1.10 regarding these outcomes.(21)

A collaborative meta-analysis of cohorts representing the general population found a comparable inverse relation between all-cause and CV mortality and eGFR. The risk was significantly increased at eGFR levels of 60 ml/min/1.73 m^2 and below. Furthermore, a linear association between albuminuria and both all-cause mortality and CV mortality was observed. Strikingly, the mortality risk was already increased within normal range of ACR.(3) Thus, albuminuria seems to be a sensitive measure of mortality risk in CKD patients.

CVD is the most frequent cause of death among CKD patients. Any stage of CKD increased the risk of CV death 100% (HR 2.0) compared to those without CKD in a Taiwanese population cohort of nearly half a million people. The increase was more marked in CKD stages G3b-5, indicating an eGFR <45 ml/min/1.73 m^2 (HR 3.3-10.3).(22) A retrospective study of a Canadian population-based cohort of more than 47000 adults with an eGFR <30 ml/min/1.73 m^2 reported a higher mortality risk, compared to kidney failure requiring renal replacement therapy (RRT), in all age groups.(23) There are mixed results in studies of subjects with severe CKD, although it is clear that the risk of dying, mainly of CV causes, is substantially higher than the risk of kidney failure in people with less severe CKD.(24)

A Canadian study concerning causes of death reported that the most common cause of death in those with no CKD was cancer, whereas those with an eGFR <60

ml/min/1.73 m^2 died most commonly because of CVD. The proportion of deaths from a cardiovascular cause increased as eGFR decreased. The most common CV cause of death, accounting for 52-58% of CV mortality, was ischemic heart disease regardless of eGFR. The proportion of heart failure and valvular heart disease as CV causes of death increased in the lower eGFR categories, whereas the proportion of cerebrovascular disease diminished. The proportion of cancer, the second-most common cause of death in CKD patients, diminished as eGFR decreased, and the proportion of infection-related deaths increased, respectively.(25)

Cancer was the most common cause of death overall in the Korean Heart Study population of ca. 370000 adults. Approximately 17000 patients were identified as having CKD. Albuminuria was associated with CV mortality and cancer mortality when the effect of albuminuria and GFR on cause of death was studied. Lower GFR was associated with CV deaths and non-CVD/non-cancer deaths. The causes of death associated with CKD in this population were coronary heart disease, infectious diseases, kidney failure and diabetic complications. The novel finding in this study was the association of albuminuria and cancer as a cause of death.(26)

An interesting study from Japan found that in a general-population cohort of 338000 persons with annual health check-ups, a finding of only transiently positive dipstick proteinuria increased the HR of CV death significantly to 1.94 in men and 2.78 in women. Transiently decreased GFR did not affect mortality. The finding highlights the significance of albuminuria, even if only transient, as a marker of increased CV risk.(27)

A study of 45000 hypertensive CKD patients found that both high and low systolic blood pressure (SBP) (<120 mmHg and >150 mmHg) were associated with all-cause and CV mortality. Diastolic blood pressure (DBP) >90 mmHg was associated with CV mortality, whereas DBP <60 mmHg with non-CVD/non-malignancy mortality and all-cause mortality. These findings underscore the role of hypertension as an important factor associated with increased CV mortality in CKD patients. However, low blood pressure (BP) is also associated with excess mortality.(28)

The effect of AF on causes of death was studied in a CKD stage G2-4 population of 62459 patients. 11% of patients had a diagnosis of AF. More than 19000 patients died during a follow-up of 4.1 years. AF was associated with higher all-cause mortality (adjusted HR 1.23). CV mortality was 45% higher and malignancy-related mortality 13% lower. Ischemic heart disease and congestive heart failure (CHF), in addition to stroke, also contributed to excess CV mortality, which seems to be the main driver of excess all-cause mortality in this study.(29) The high mortality risk in the CKD population was further augmented by the presence of AF.

The mortality rate of CKD patients remains high, although its prognosis has improved over the years. The Finnish Registry for Kidney Diseases Annual Report

compared patient survival in different periods. In 2000-2004, 74% of Finnish patients were alive 2 years after initiating RRT, while survival had improved to 82% in 2015-2018 despite the fact that the median age of patients initiating RRT was higher in the latter period. The underlying diagnosis leading to CKD affects the prognosis. The highest survival in those initiating RRT in 2014-2018 was observed in those with polycystic kidney disease or glomerulonephritis. Patients with amyloidosis and type 2 diabetes had the highest risk of death.(30)

2.4 Epidemiology of Cardiovascular Disease in Chronic Kidney Disease Patients

There are risk factors unique to the CKD population, in addition to traditional cardiovascular risk factors, such as hypertension and hyperlipidemia, that are partly responsible for the high CVD burden among these patients. These CKD-specific risk factors include CKD-MBD, anemia and low-grade inflammation. The consequence of multiple risk factors is that CKD patients are at a risk of acquiring CVD manifestations earlier in life than the general population. The distribution of CVD manifestations differs from the general population. For instance, SCD is, by far, more common among the maintenance dialysis population but also in CKD patients not on dialysis(11) than in the general population.

2.4.1 Heart Failure

The incidence of heart failure (HF) among the CKD population with an eGFR <60 ml/min/1.73 m^2 is markedly higher than that of the non-CKD population. Among nearly 15000 Atherosclerosis Risk in Communities (ARIC) study participants, the incidence of HF was three-fold higher in those with an eGFR <60 ml/min/1.73 m^2 than in those with normal kidney function during a mean follow-up of 13.2 years.(31) Bansal et al. found an adjusted risk difference of 2.3 for HF in those with an eGFR <60 ml/min/1.73 m^2 in a pooled analysis of three community-based cohort studies. The risk difference was more marked in males and non-white ethnicities.(32)

2.4.2 Stroke

The risk of stroke in CKD patients is increased compared to the general population. The mechanisms are manifold, including traditional risk factors such as hypertension. However, an independent association of CKD with stroke has been noted in studies. The adjusted HR for stroke was 1.81 in the middle-aged ARIC study population. In those participants with an eGFR <60 ml/min/1.73 m^2 but no anemia, the HR was 1.41, suggesting that CKD-associated anemia contributes to the stroke

risk in this population.(33) The incidence of stroke is even higher in dialysis patients. The adjusted HR for ischemic stroke was approximately 3 for both hemodialysis (HD) and peritoneal dialysis (PD) patients compared to a matched reference cohort in a Taiwanese study. The HR for hemorrhagic stroke was even higher, 6.8 and 6.2 for HD and PD patients, respectively.(34) A meta-analysis of 21 articles by Lee et al. found a 43% greater risk of future stroke in patients with an eGFR <60 ml/min/1.73 m^2 compared to those with an eGFR >90 ml/min/1.73 m^2. The risk of incident stroke was not significantly increased in those with an eGFR 60-90 ml/min/1.73 m^2.(35) Albuminuria is also associated with an increased stroke risk. In a prospective, observational study of 6252 Japanese American men aged 45-69 years, the relative risk of stroke was 2.84 for those with persistent proteinuria in a urine dipstick screening compared to those without proteinuria over a 27-year follow-up.(36) A British population-based prospective cohort study of nearly 24000 subjects aged 40-79 years noted a 49% increased stroke risk in those with moderately increased albuminuria and a 143% increased risk in those with severely increased albuminuria. The mean follow-up was 7.2 years. Strikingly, the risk of stroke already increased in the two highest tertiles of normoalbuminuria.(37)

2.4.3 Peripheral Artery Disease

Peripheral artery disease (PAD) and its consequences, such as lower limb amputations, are notoriously common among dialysis patients. The epidemiology of PAD among CKD patients has been assessed, e.g., in NHANES 1999-2000. The prevalence of PAD among the United States population over 40 years of age was 4.3%, whereas the prevalence was 18.2% in the CKD population as defined by an eGFR <60 ml/min/1.73 m^2.(38) In another report of the NHANES population, 2229 participants with an available ankle-brachial index (ABI) and serum creatinine were studied. The Odds Ratio (OR) of having ABI <0.9 after adjustment for demographic characteristics and comorbid conditions was 2.5 for those with a decreased eGFR (<60 ml/min/1.73 m^2) compared to eGFR >60 ml/min/1.73m^2.(39) The prevalence of PAD was 4.5% in the whole population in a retrospective cohort study of over 453000 Canadians. 30% of PAD patients had also CKD, whereas 10% of the non-PAD population had CKD.(40)

2.4.4 Coronary Artery Disease

The risk of adverse cardiovascular events rises as eGFR declines with the highest event rates in those with CKD stage G5.(19) The clinical picture of coronary artery disease (CAD) may be modified by kidney disease-specific pathogenetic mechanisms leading to arteriosclerosis in tunica media instead of the typical

atherosclerotic disease of tunica intima. The presence of diabetic and/or uremic neuropathy may also modify the clinical picture of atherosclerotic CAD. Coronary artery calcification diagnosed by computed tomography (CT) was already present in 88% of dialysis patients aged 20-30 years in a study by Goodman et al.(41) An angiographic study of 261 elderly male participants with 83 (31.8%) of the subjects having CKD stage G3-G5 demonstrated an association between CKD and an angiographic finding of significant CAD. Patients with CKD were also more likely to have three-vessel or left main disease.(42)

2.4.5 Atrial Fibrillation

AF is the most common significant cardiac arrhythmia. It is usually classified into four categories. Paroxysmal AF terminates spontaneously within 7 days, whereas persistent AF fails to self-terminate within 7 days. Long-standing AF lasts over 12 months and permanent AF is a permanent condition, and restoring the sinus rhythm is no longer pursued.(43)

The prevalence of AF in the population has been widely studied, but estimates vary substantially and many study populations are affected by selection bias. A Dutch study of more than 6800 inhabitants of a Rotterdam suburb, aged over 55 years, reported a 5.5% prevalence of atrial fibrillation.(44) In Germany, among 8.3 million statutory health insurance fund members who can be regarded as a more truthful representation of the general population, the prevalence of AF was 2.1% and the incidence was 4.1 cases in 1000 person-years. Both the prevalence and the incidence of AF are higher among men than women and increase significantly with age. The prevalence was over 10% in those over 80 years of age in this German study.(45) AF is more common in developed countries, with the highest prevalence in North America. According to the Global Burden of Disease Study 2017, the global prevalence of AF was 482 per 100 000 person-years. Compared to 1990, the number of individuals living with AF roughly doubled in 27 years to 37.6 million.(46)

The relationship between CKD and AF is considered bidirectional. AF is more common among CKD patients, and AF is associated with CKD progression. In the ARIC study cohort of 10328 individuals free of AF, both decreased eGFR and proteinuria were independently associated with higher risk of AF incidence. The highest incidence was observed in those with an eGFR <30 ml/min/1.73 m^2 and severely increased albuminuria. The HR was 13.1, compared to subjects without albuminuria and a normal eGFR.(47) The prevalence of AF was 21.4% in a retrospective analysis of 1010 consecutive non-dialysis CKD stage G2-5 patients from two community-based hospitals.(48) The REGARDS study of approximately 27000 US adults over 45 years of age reported that the prevalence of AF was 1.0% in those without CKD, increasing with every CKD stage, up to 4.2% in those with

CKD stage G4-5.(49) The Chronic Renal Insufficiency Cohort (CRIC) Study cohort of 3267 adult participants with a mean eGFR of 44 ml/min/1.73 m^2 had a high prevalence of AF, 18%. Adjusted models revealed associations of age, male sex, smoking, CHF and a history of CVD with prevalent AF.(50) The prevalence of AF was even higher, 26.5%, in an Austrian cohort of more than 600 HD patients. AF was associated with age, male sex, CHF, dialysis vintage, previous thromboembolism and cancer.(51) The prevalence of AF increased from 3.5% to 10.7% between 1992 and 2006 in American HD population.(52)

A Taiwanese nationwide cohort study analysed the incidence of new-onset AF in over 400 000 subjects. HD patients had 2.42-fold and 1.66-fold incidence of AF compared to healthy controls and non-dialysis CKD patients, respectively. Independent risk factors for occurrence of new-onset AF in dialysis patients were hypertension, CHF, CAD, PAD and chronic obstructive pulmonary disease (COPD).(53)

A population-based study of 1.4 million individuals with an eGFR <90 ml/min/1.73 m^2 from Canada examined the associations of adverse CV events, CKD progression and mortality with AF. AF was associated with CHF, AMI, mortality and CKD progression to ESKD.(54) Watanabe et al. studied the relations of AF and CKD in 235818 subjects in a prospective setting in Japan. A previous AF diagnosis was associated with development of CKD, and a decreased baseline eGFR was associated with new-onset AF, suggesting a bidirectional relationship with common pathogenetic mechanisms.(55)

2.4.6 Sudden Cardiac Death

Sudden cardiac death is defined as sudden, unexpected cessation of cardiac activity with hemodynamic collapse resulting in death.(11) Ventricular tachyarrhythmias, often due to CAD, are the most common cause of SCD in the general population.(56) SCD is one of the leading causes of death in the HD population, but non-dialysis CKD is also associated with an increased SCD risk.(11) The mechanism behind SCD in the dialysis population is usually bradyarrhythmia.(57,58) The highest rate of clinically significant arrhythmias in HD patients are observed towards the end of the interdialytic interval and in thrice-weekly dialysis, particularly during the long interdialytic interval.(57)

2.5 Risk Factors, Pathogenetic Mechanisms and Pathways Associated with Cardiovascular Disease in Chronic Kidney Disease

Traditional risk factors for CVD, such as hypertension, hyperlipidemia, DM and smoking, are common among CKD patients. However, only a part of excess CV morbidity in these patients can be attributed to traditional risk factors. Two kidney-related mechanisms are contributing to CVD in CKD patients. Enzymes, cytokines and hormones released by the kidney in response to kidney injury cause changes in blood vessels. Hemodynamic alterations and mediators associated with CKD add to cardiac damage.(59) Thus, complications of advanced CKD, such as CKD-MBD, anemia and the inflammatory state associated with CKD, contribute to a high CVD burden through various mechanisms.

2.5.1 CKD-MBD and Vascular Calcification

Less phosphorus is excreted and 1-α-hydroxylase activity in kidney is reduced as kidney function declines. This favours the development of hypocalcemia, which stimulates the release of parathyroid hormone (PTH) from the parathyroid glands. PTH increases 1-α-hydroxylase activity and bone turnover, leading to correction of the serum calcium level. An increase in PTH favours urinary phosphate excretion. A rise in Fibroblast Growth Factor 23 (FGF23) level is an early alteration in the development of CKD-MBD that favours excretion of phosphate. These compensatory mechanisms fail to secure sufficient excretion of phosphate in advanced CKD, and hyperphosphatemia with secondary hyperparathyroidism is a common finding. In addition to detrimental effects on bone metabolism, termed renal osteodystrophy, vascular and valvular calcification occur.(60)

In cellular level, the smooth muscle cells of the tunica media of blood vessels are affected by calcification. A process similar to bone formation occurs as the phenotype of these cells is altered. This medial vascular calcification results in the vessels' stiffening. Pulse wave velocity and, as a result, cardiac afterload are increased, predisposing to LVH and HF. Coronary artery perfusion is also decreased.(59) Calcification of the media layer is also associated with DM, a common cause of CKD, in addition to CKD-MBD.(8)

2.5.2 Anemia

Anemia in CKD patients is the result of relative erythropoietin (EPO) deficiency. Kidneys are the main source of EPO, so anemia is encountered more frequently in patients with advanced CKD. Three major factors, in addition to relative EPO deficiency, contribute to the development of anemia in CKD. Shortened life span of

erythrocytes, inhibitors of erythropoiesis induced by CKD and alterations in iron balance all contribute to low hemoglobin values. Hepcidin, an important regulator of iron homeostasis, is a peptide produced by the liver. Elevated hepcidin levels reduce iron availability in plasma. This normally acts as a defence mechanism against pathogens. However, the inflammatory cytokines present in CKD stimulate a hepcidin expression, contributing to the development of anemia.(61) Anemia in CKD is associated with adverse outcomes. Lower hemoglobin was associated with LVH and HF as well as mortality in a study by Foley et al. of over 430 dialysis patients.(9) Another study found an association between anemia and MI, stroke and all-cause mortality, in diabetic non-dialysis CKD patients.(62) Anemia affects patients' HRQoL, and treatment of anemia with erythropoiesis-stimulating agents (ESAs) is associated with improved HRQoL in most studies.(63–65) Contrary to expectations, ESA treatment showed no benefit in reducing mortality or CV events.(66)

2.5.3 Inflammation

Low-grade inflammation is a component of advanced CKD, especially in dialysis patients. Mechanisms leading to inflammation in CKD patients include not only increased production of cytokines and their decreased clearance but also metabolic acidosis and oxidative stress. Infections contribute to the inflammatory state. Numerous biomarkers of inflammation are elevated in CKD. Of these biomarkers, C-reactive protein (CRP) and interleukin-6 (IL-6) seem to be the best predictors of mortality.(10) Inflammation is also an important mechanism behind protein-energy wasting, a catabolic state often present in advanced CKD and linked to mortality. Both inflammation and malnutrition often contribute to a characteristic low serum albumin level, a strong predictor of mortality in dialysis patients.(67) Inflammation also contributes to the development of anemia in CKD.

2.6 Treatment

CKD treatment can be divided into lifestyle interventions, medical treatment and treatment of ESKD with different RRT methods. Lifestyle interventions and medical treatment aim to prevent or slow the progression of CKD and to prevent the development of comorbidities or relieve their symptoms. Naturally, it is important to discontinue nephrotoxic medications and rule out urinary tract obstruction when CKD is suspected. RRT methods, including hemodialysis, peritoneal dialysis and kidney transplantation, are needed as CKD progresses to ESKD.

2.6.1 Lifestyle Interventions

Some data from randomized controlled trials (RCTs) evaluate lifestyle interventions in CKD. However, most data come from observational studies.

Obesity is a well-known risk factor for CKD. An energy-restricted diet and physical activity group in a Spanish trial fared better than the control group. Intervention led to a 0.58 ml/min/1.73 m^2 smaller annual eGFR decline.(68)

A 2020 Cochrane systematic review summarized 17 RCTs assessing dietary protein intake in non-diabetic CKD patients. Moderate quality evidence supports that very low protein intake in CKD stage G4-5 patients delays progression to ESKD, whereas no such effect was noted in CKD stage G3 patients. However, data were very limited on adverse effects, including malnutrition.(69) Recent observational studies have found an association between plant-derived protein and better preservation of GFR compared to animal-based protein.(70)

Physical activity, as opposed to a sedentary lifestyle, is associated with a lower incidence of CKD, improvement in BP and blood glucose control. Its effect on CKD progression is uncertain.(70)

According to a recent meta-analysis, a higher dietary potassium intake is associated with a lower incidence of CKD and RRT.(71) However, diet restrictions are needed in advanced CKD as part of the management of hyperkalemia and hyperphosphatemia.

Limiting sodium intake is the mainstay of lifestyle modifications in treating hypertension, an important cause of CKD. It is unsurprising that higher sodium intake is associated with incident CKD and the need for RRT. Current or former smokers are also known to have a higher risk of incident CKD and RRT.(71)

2.6.2 Medical Treatment

Medical treatment of CKD has two principal aims - preserving kidney function and reducing comorbidity - particularly cardiovascular morbidity and mortality. The specific medical therapy of an underlying kidney disease, such as glomerulonephritis, offers a chance to preserve kidney function, in addition to the general principles presented here.

2.6.2.1 Antihypertensive Drugs

Higher BP levels are associated with the development of ESKD.(72) Inhibitors of Renin-Angiotensin System (RAS), namely Angiotensin-Converting Enzyme (ACE) inhibitors and Angiotensin II Receptor Blockers (ARBs) slow the decline of GFR in proteinuric CKD(73,74) and are therefore the first-line treatment for hypertension in these patients. No data exist, in the absence of proteinuria, on the superiority of RAS

inhibitors over other categories of BP medications regarding renal protection.(75) The risk of adverse CV outcomes was reduced by ACE inhibitor therapy as reported in a CKD subgroup analysis in the Heart Outcomes and Prevention Evaluation (HOPE) Study.(76) The 2021 KDIGO Guideline for the Management of Blood Pressure in Chronic Kidney Disease states that the use of RAS inhibitors in CKD patients without proteinuria is reasonable because of this cardiovascular protection.(77)

A SBP goal of <120 mmHg is recommended by the same guideline, based on the results of the Systolic Blood Pressure Intervention Trial (SPRINT) CKD subgroup analysis. Treating to this target reduced all-cause mortality and adverse CV events, whereas no effect on CKD progression was noted when compared to the higher SBP target.(78) There is lack of data on a DBP target. However, the KDIGO Guideline states that it seems reasonable to aim at <80 mmHg in young adults.(77)

2.6.2.2 Lipid-Lowering Agents

Dyslipidemia is common among CKD patients. Statins are the drugs with the most data available on dyslipidemia treatment in the general population and in CKD patients. Ezetimibe has also been studied in combination with statin in studies with CKD patients, whereas fibrates are contraindicated in advanced CKD.

A meta-analysis of 8 trials of statin therapy found a decrease in all-cause mortality, CV mortality and CV events in CKD patients not in dialysis.(79) Three large studies have shown no benefit of statin or statin/ezetimibe therapy in dialysis patients.(80–82) According to the aforementioned meta-analysis, statins have no impact on progression of CKD, but they may reduce proteinuria.(79)

2.6.2.3 Diabetes Medications

Diabetic kidney disease (DKD) is the leading cause of CKD worldwide. Several studies have shown the benefit of intensive glucose control in preventing microvascular complications. For instance, the Diabetes Control and Complications Trial (DCCT) and subsequent observational Epidemiology of Diabetes Interventions and Complications (EDIC) Study showed that intensive glucose lowering early in the course of the disease is associated with better eGFR in the long term.(83) However, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study demonstrated increased mortality in the group targeting lower glycated hemoglobin (HbA1c) targets.(84) The 2020 KDIGO Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease recommends individualized HbA1c targets in the range of <6.5% to <8.0%.(85)

Insulin in its different forms has traditionally been the mainstay of diabetes therapy in patients with advanced CKD. However, the newer agents used to treat hyperglycemia in type 2 diabetes, the sodium-glucose co-transporter 2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, are increasingly used after encouraging results in many trials.

Over 7000 diabetic patients with a history of CVD received Empagliflozin or a placebo in the EMPA-REG OUTCOME trial. Its primary outcome were major adverse cardiovascular events (MACE) consisting of CV death, MI or stroke. Empagliflozin reduced the relative risk of the primary outcome by 14%. The relative risk reduction of CV death was as high as 38%.(86) The prespecified secondary outcome in this trial was the incidence or progression of nephropathy. Empagliflozin significantly reduced the occurrence of this outcome, and HR in the empagliflozin group was 0.61.(87)

The renal effect of canagliflozin, another SGLT-2 inhibitor (SGLT-2i), was studied in DKD patients in the CREDENCE trial. The trial was stopped early after recruiting 4401 patients because it was deemed unethical to continue the trial when the canagliflozin group showed a 30% lower relative risk of a primary composite outcome of ESKD, a doubling of creatinine or death from CV or renal causes. The risk of secondary CV outcomes was also reduced by canagliflozin.(88)

GLP-1 receptor agonist (GLP1-RA) injections are used subcutaneously daily or once a week in the case of semaglutide and dulaglutide. They act by stimulating the glucose-dependent release of insulin. They also decrease the secretion of glucagon. Gastric emptying is delayed, which can cause nausea. Weight loss is a desired effect of this category of medications. Liraglutide, semaglutide and dulaglutide studies have shown favourable results regarding both cardiovascular and renal endpoints.(89) According to a 2019 meta-analysis, CV deaths, strokes and myocardial infarctions (MIs) were reduced by 12%, 16% and 9%, respectively. The HR for all-cause mortality was 0.88 and 0.83 for composite kidney outcome. Kidney outcome was mainly driven by a reduction in albuminuria.(90) Of note, the meta-analysis also included exenatide and lixisenatide studies, which were negative regarding cardiovascular protection. However, a 2021 meta-analysis comparing the effects of SGLT-2i and GLP-1RA in CKD patients with eGFR <60 ml/min/1.73 m^2, the risk reduction of MACE consisting of CV death, MI and stroke, was only 9% and not statistically significant. The RR for secondary outcome, namely composite kidney outcome, including a decline in kidney function, albuminuria, ESKD and renal or CV death, was 0.86, which was also not statistically significant. Notably, when Exendin-4 analogue (exenatide and lixisenatide) studies and GLP-1 analogue (liraglutide, semaglutide, dulaglutide and albiglutide) studies were analysed separately, the latter showed a significant reduction in MACE, whereas Exendin-4

analogues did not. Overall, SGLT-2i performed better in reducing both MACE and kidney outcomes.(91)

2.6.2.4 SGLT-2 Inhibitors in Non-Diabetic Chronic Kidney Disease

SGLT-2 inhibitors also seem to benefit non-diabetic CKD patients. The results from registration studies of these agents were encouraging, showing large-scale CV protection in diabetics. SGLT-2is have also been studied lately in patients without diabetes with positive results. Renoprotective effects noted now in many studies are believed to be due in part to intraglomerular pressure reduction.(92)

The DAPA-CKD trial is the first SGLT-2i trial published with a significant proportion of participants having non-diabetic CKD. Approximately two thirds of the enrolled participants had type 2 diabetes and a third were non-diabetics. The eGFR of the participants was in the range of 25-75 ml/min/1.73 m^2 and ACR 200-5000 mg/g. Like CREDENCE, this trial was also stopped early after the data monitoring committee's recommendation. The median follow-up was 2.4 years, and dapagliflozin reduced the primary outcome that was 50% decline in eGFR, ESKD, renal death or CV death (HR 0.61).(93) Trials involving other SGLT-2is in the non-DKD CKD population are ongoing, also including non-proteinuric CKD patients.

After a long wait, a new class of medications benefits a wide population of proteinuric CKD patients, in addition to RAS inhibitors.

2.6.2.5 Mineralocorticoid Receptor Antagonists

The steroidal Mineralocorticoid Receptor Antagonists (MRAs) spironolactone and eplerenone have well-known beneficial effects in CVD, but their use in CKD patients has been limited by the risk of hyperkalemia. Spironolactone and eplerenone have been shown to additionally decrease proteinuria in DKD when used with RAS inhibitors. However, there is no evidence of benefit on hard kidney endpoints.(94) Recent studies with a novel non-steroidal MRA, finerenone, have demonstrated promising results in CKD patients. Finerenone has been beneficial in reducing both CV and kidney endpoints.

The FIDELIO-DKD trial investigated patients with CKD and type 2 diabetes with moderately increased albuminuria and an eGFR between 25-60 ml/min/1.73 m^2 or severely increased albuminuria and an eGFR between 25-75 ml/min/1.73 m^2. All patients were on RAS inhibitor therapy. Finerenone reduced the incidence of composite kidney outcome consisting of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes, and the HR was 0.82.(95) Compared to FIDELIO, the FIGARO-DKD trial recruited patients with preserved eGFR. The mean eGFR was 68 ml/min/1.73 m^2 as opposed to 44

ml/min/1.73 m^2 in the previous study. The primary outcome was CV death, MI, stroke or hospitalisation for HF. Finerenone reduced the incidence of primary outcome, and the HR was 0.87. The benefit was mainly driven by hospitalisation for HF component.(96)

Interestingly, a post hoc analysis of FIDELIO-DKD study observed also a reduction of new-onset AF in finerenone group.(97) A secondary analysis of FIGARO-DKD trial showed a 29% reduction in the risk of hospitalisation for HF, while a 14% risk reduction was observed in the FIDELIO-DKD study that recruited patients with more advanced CKD.(98)

2.6.2.6 Metabolic Acidosis, Hyperkalemia and CKD-MBD Management

Metabolic acidosis in CKD occurs when acid production exceeds the net excretion by the kidneys. The prevalence of metabolic acidosis among CKD patients increases as eGFR declines. In a study with 3939 CKD stage G2-4 patients, metabolic acidosis was defined as serum bicarbonate <22 mmol/l. The prevalence of metabolic acidosis was 7%, 13% and 37% in CKD stage G2, stage G3 and stage G4, respectively.(99) The treatment of metabolic acidosis benefits CKD patients because it seems to slow eGFR decline according to several single-centre studies.(100) A recent Italian multi-centre open label RCT of 740 patients with a diverse etiology of CKD and a mean follow-up of 30 months found that the risk of the doubling of serum creatinine was lower in the sodium bicarbonate-treated group vs. the standard care group, and the HR was as low as 0.36. In those patients who did not reach study endpoints, the annual GFR decline during 3-year follow-up was 1.4 ml/min in the sodium bicarbonate group and 3.4 ml/min in the standard care group.(101) These results further support the treatment of metabolic acidosis in CKD recommended by the 2012 KDIGO Guideline. The KDIGO suggests treating with oral bicarbonate supplementation if serum bicarbonate is less than 22 mmol/l.(15)

Hyperkalemia in CKD is the result of diminished potassium excretion in the kidneys, often further exacerbated by metabolic acidosis and medications that cause hyperkalemia, such as RAS inhibitors. Hyperkalemia is associated with excess mortality. For instance, in a large retrospective cohort, the OR of death within 1 day of a severe measured hyperkalemia of ≥6.0mmol/l differed from 8.0 in CKD stage G5 patients to 19.5 in CKD stage G3 patients.(102) The mainstay of hyperkalemia medical treatment is diuretics that increase potassium excretion through the kidneys. Potassium-binding agents such as sodium polystyrene sulphonate and newer agents, patiromer and sodium zirconium cyclosilicate, bind potassium in the GI tract. Correction of acidosis with sodium bicarbonate may also be useful in correcting hyperkalemia.(103)

CKD-MBD affects patients' bone and blood vessels and may also lead to soft tissue calcifications. CKD-MBD is associated with mortality. Medical treatment consists of phosphate binders, vitamin D and analogues and calcimimetics. Phosphate binders in use include calcium carbonate, lanthanum carbonate and sevelamer. The KDIGO 2017 CKD-MBD Clinical Practice Guideline suggests treating hyperphosphatemia towards the normal range avoiding large doses of calcium. Secondary hyperparathyroidism should be treated with vitamin D analogues or calcimimetics or their combination.(104) Observational data shows association of these treatments with better outcomes but there are no good data from RCTs on hard endpoints.(60)

2.6.3 Renal Replacement Therapy

As individual patients' CKD progress to stage G4-5, it becomes time to consider choosing an RRT method. Conservative management without RRT may be the best option for frail patients with multiple comorbidities and impaired functional capacity. RRT methods include hemodialysis, peritoneal dialysis and kidney transplantation. Home dialysis modalities include continuous ambulatory peritoneal dialysis (CAPD), automated peritoneal dialysis (APD) and home hemodialysis (HHD) and are usually performed by the patient, whereas, in-center hemodialysis (ICHD) is performed in healthcare facility by healthcare professionals.

2.6.3.1 Hemodialysis

Hemodialysis is a procedure in which a patient's blood and dialysate flow in opposite directions in a dialyser, separated by a semipermeable membrane allowing solute and fluid transfer. Thus, excess water and uremic toxins can be removed from a patient's blood to dialysate before blood returns to the patient.(105) Diffusion down a concentration gradient is the main mechanism of solute removal in hemodialysis. The drag of solutes in removed plasma water, so-called "solvent drag" represents convection, another mechanism of removal of solutes in hemodialysis. Convection is particularly important in hemodiafiltration (HDF), in which large amounts of fluid are removed and convection increases solute removal, especially that of larger solutes. The HDF procedure requires infusion of replacement fluid to the patient since much fluid is removed.(106) Four hours is the typical duration of an ICHD session and is usually performed thrice weekly. HHD allows patients to choose their own dialysis schedule. Dialysis sessions of 1.5-3 hours are performed 5-7 times per week in so-called short daily hemodialysis. Nocturnal HD sessions last 6-8 hours or more and can be done thrice weekly or more often. Most, but not all, studies have found better survival among HHD patients compared to ICHD patients. However,

studies comparing these modalities are subject to numerous confounders.(107) A recent Finnish study found survival among patients on HHD similar to those on the APD modality.(108)

2.6.3.2 Peritoneal Dialysis

The human peritoneum serves as a dialysis membrane in PD, allowing passage of excess fluid and uremic toxins from circulation to the peritoneal dialysis solution and out of the body via a PD catheter. CAPD requires a manual exchange of the dialysis solution, usually four times per day, while a cycler machine takes care of the exchanges in APD, usually at night. PD is generally performed by the patient at home, although sometimes assisted PD is needed, in which a family member or a visiting nurse assists the patient.

PD solutions contain glucose as an osmotic agent. Stronger solutions increase ultrafiltration but cause metabolic problems like hyperglycemia, insulin resistance and weight gain. Preservation of residual renal function (RRF), an important prognostic factor for dialysis patients, is better in PD than HD.(109) The survival prognosis of PD and HD patients is generally considered to be similar but, according to some studies, PD might be superior during the first 1-2 years after RRT initiation.(109–113)

2.6.3.3 Kidney Transplantation

Kidney transplantation is the treatment of choice for ESKD. A kidney donated either by a living or deceased donor is placed extraperitoneally to the lower abdomen area in a surgical operation. Circulation is connected to the recipient's iliac vessels and the ureter to the recipient's bladder. Permanent immunosuppressive medication to reduce the risk of rejection is necessary after kidney transplantation.

A study by Wolfe et al. reported that excess mortality associated with the surgical procedure of transplantation and early complications turned to a survival benefit by day 106 after transplantation and that the cumulative likelihood of survival was equal on day 244 after transplantation compared to patients on the transplant waiting list. Overall, those who remained on the transplant waiting list had a 70 % increased annual risk of death compared to kidney transplant recipients.(114)

A systematic review found that, besides mortality, the risk of CV events and infection-related hospitalisations was decreased after transplantation and HRQoL seemed to be better compared to dialysis patients.(115)

2.7 Study Methods

2.7.1 Serum Biomarkers

Several biomarkers are associated with adverse events in CKD patients. Diseases, per se, cause alterations in serum biomarker levels. Reduced, or in some cases, increased renal clearance of biomarkers may contribute to these alterations. For instance, albuminuria may contribute to hypoalbuminemia. A vast array of biomarkers have been linked to prognosis in CKD patients. Selected biomarkers widely used in clinical practice are briefly reviewed herein.

2.7.1.1 Albumin and Biomarkers of Inflammation

Serum albumin is a classic example of a biomarker associated with prognosis in CKD. Malnutrition, in addition to proteinuria, contributes to hypoalbuminemia in advanced CKD and ESKD. Albumin is the strongest predictor of survival in CKD, particularly in dialysis patients.(116) Lower serum albumin was associated with prevalent CVD in a study of over 500 incident dialysis patients. This study showed that IL-6, a biomarker of inflammation, was the only biomarker associated with both prevalent CVD and all-cause mortality.(117) Another marker of inflammation, CRP, was investigated with serum albumin as predictor of mortality in CKD stage G3-4 patients. Both were independent predictors of all-cause mortality, but only CRP predicted CV mortality in this study.(118)

2.7.1.2 Cardiac Biomarkers

Cardiac biomarkers troponin T (TnT) and N-terminal pro-B-type natriuretic peptide (proBNP) are associated with CV events and all-cause mortality in dialysis patients. This was reported in studies from the early 2000s.(119) Later studies have addressed the association of cardiac biomarkers and adverse outcomes in earlier CKD stages. A 2012 Dutch study of a Caucasian population comprising over 8100 subjects reported that more than 1500 had CKD, mainly stages G1-3. Elevated levels of both TnT and proBNP were independently associated with CV events after adjustment for kidney function and traditional CV risk factors.(120) Hayashi et al. reported an association between proBNP and a composite of fatal and non-fatal CV events in CKD stage G2-5 population with a median eGFR of 20 ml/min/1.73 m^2.(121) Wang and coworkers reported an association of baseline TnT and proBNP in a CRIC study population of CKD stage G2-4 patients with CV mortality and all-cause mortality. Declining proBNP levels over time were associated with a lower risk of all-cause mortality.(122) A multi-ethnic population of more than 3200 individuals

participating in the Dallas Heart Study were followed up for 12.5 years. A wide selection of biomarkers, including the TnT, proBNP and coronary artery calcification score measured by CT and LVH in cardiac magnetic resonance imaging were studied as prognosticators of all-cause mortality and, secondarily, CV mortality or CV event. Approximately 9 % of the population had CKD, almost exclusively stages G1-3. TnT, proBNP and LVH were at least as good prognosticators of outcomes in the CKD population as in those without CKD. They also provided further prognostic information added to the traditional risk factors.(119) These cardiac biomarkers, in addition to functioning as powerful markers of prognosis in CKD patients, are associated with echocardiographic parameters (123) and the physical aspects of HRQoL.(124) The two highest quartiles of TnT in the CRIC study population were associated with a higher incidence of new-onset AF compared to the lowest quartile over a 7.1 year follow-up despite adjusting for eGFR and AF's traditional risk factors.(125)

2.7.2 Lateral Lumbar Radiograph

Current KDIGO guideline concerning CKD-MBD suggests lateral abdominal radiograph as a reasonable alternative to CT-based imaging methods in detecting vascular calcification in CKD stage G3-5 patients. Coronary Artery Calcification (CAC) scores obtained by CT have a strong correlation to abdominal aortic calcification (AAC) score calculated from a radiograph, the latter imaging being less costly. The patient is at highest CV risk if calcifications are detected.(7)

The method of calculating the AAC score was described by Kauppila et al. in 1997.(126) The same group studied the association of the AAC score in the Framingham Heart Study population and found that the AAC score is an independent predictor of subsequent CV morbidity and mortality.(127) A prospective study by Lewis et al. made a similar observation in material consisting of over 1000 women aged over 70 years.(128)

The presence of abdominal aortic calcifications in CKD patients seems to increase as kidney function declines and is most common in dialysis patients.(129) The progression of AAC measured by the AAC score in the predialysis population seems to be fastest in CKD stages G4-5 compared to earlier stages.(130) The AAC score of 4 or more was associated with CV events in a Dutch study of 280 predialysis patients with a mean eGFR of 36 ml/min.(131) The progression of AAC in the dialysis population was associated with all-cause and CV mortality in a Dutch study of 384 patients.(132) A meta-analysis of AAC in dialysis patients showed an association between the AAC score and CV events as well as the AAC score and mortality.(133)

2.7.3 Vascular Ultrasound and Flow-mediated Dilatation

Measuring the intima-media thickness (IMT) of arteries by ultrasound is a convenient, non-invasive method of assessing subclinical atherosclerosis since thickening of the arterial walls is a sign of atherosclerosis. IMT is commonly measured in the distal common carotid artery.

Carotid IMT (cIMT) is associated with incident cardiovascular events in the general population.(134) Carotid IMT seems to increase early in the course of CKD. According to a French study, cIMT is already increased in stage G2 CKD.(135) A 2020 meta-analysis indicated that cIMT is associated with CV mortality and all-cause mortality in dialysis patients, but data are too scarce to draw conclusions in CKD patients not on dialysis.(136) cIMT was a predictor of CV events in a univariate analysis in a mixed material of patients with CKD stage G4-5 with about one sixth of patients in predialysis care, but the association was not significant after adjustment for confounders.(137) Femoral IMT (fIMT) measured in the femoral artery is less well studied. In one study it was associated with MACE in a two-year follow-up in a non-CKD population free of pre-existing CVD.(138)

Flow-mediated dilatation (FMD) is another indicator of initial atherosclerosis. FMD is measured in a brachial artery. The artery's diameter is recorded at rest and one minute after releasing a cuff that is inflated to a pressure of 250 mmHg for 5 minutes and then released. FMD is expressed as the relative dilatation of a brachial artery after cuff release compared to resting diameter. FMD was lower the more advanced the CKD stage was in diabetic CKD patients without known CAD.(139) According to a study by Yilmaz and coworkers, FMD and eGFR decrease in parallel, and FMD predicts future CV events in non-dialysis CKD patients.(140)

2.7.4 Stress Ergometry

The cardiopulmonary exercise test provides versatile information on patients' cardiac and pulmonary function. Oxygen uptake is one of the principal parameters obtained in this test. Peak oxygen uptake is among the most important determinants of a patient's prognosis. A stress test performed without a gas analyser using a ramp exercise protocol still provides information on exercise capacity and myocardial ischemia.(141)

Impaired physical performance measured by multiple modalities, including a 6-minute walking test and handgrip strength, is associated with all-cause mortality in CKD stage G2-4 patients. These patients with mainly moderate CKD performed inferiorly in the testing of the lower extremity function compared to the normative values of the general population.(142) Exercise capacity as measured by a cycle ergometry exercise test is associated with survival in hemodialysis patients.(143) Another study enrolled 240 patients with advanced CKD of whom 2/3 of the patients

were on dialysis and 1/3 were not yet on dialysis. Poor exercise capacity, defined by an anaerobic threshold <40% of predicted peak oxygen uptake, predicted mortality. The survival of patients with poor exercise capacity was better in those receiving a kidney transplant during follow-up compared to those who did not.(144) Maximal oxygen uptake was associated with HRQoL in a study of 143 patients with advanced CKD. 75% of the patients were on dialysis. Maximal oxygen uptake was associated with physical summary score. Thus, a subjective evaluation of physical health is correlated to an objective measure of physical performance in this study.(145) Exercise training of HD patients resulted not only in better exercise capacity but also in improved quality of life (146), underscoring the significance of good physical condition in patients with CKD and stress ergometry as a way to measure physical performance. As seen, most data come from ESKD patients. There is less data on CKD patients not on dialysis.

2.7.5 Echocardiography

Echocardiography is a radiation-free and non-invasive way to investigate the heart's structure and function. CKD's consequences and complications, such as hypervolemia, hypertension and cardiac diseases, cause alterations that can be detected by ultrasound examination of the heart.

LVH is a structural change in the heart that is often detected early in the course of CKD and becomes even more common with advanced CKD. In a study of approximately 3500 CRIC participants without overt HF, about one third of CKD stage G2 patients had LVH, and its prevalence increased with progressing CKD to 75% in CKD stage G4-5 patients. Systolic or diastolic functional changes, as measured by the left ventricular ejection fraction (LVEF) or ratio of the early to late ventricular filling velocities (E /A), respectively, did not show an association with kidney function after adjustment for confounders.(147) Bansal et al. conducted a longitudinal study of almost 200 CRIC participants who had echocardiographic data available. Advanced CKD patients with an eGFR <20 ml/min/1.73 m^2 were studied at baseline and again as they advanced to ESKD, defined as HD or PD treatment. 85% of the patients had LVH at baseline, and there was no significant change at ESKD. However, mean LVEF decreased from 53% to 50%, and the proportion of patients with LVEF of 50% or less increased to 48% from 29% at baseline.(148) LVEF is among the most powerful ultrasound measures of the heart, predicting CV morbidity and mortality.(149)

An Australian study of CKD stage G3 patients found that, compared to matched non-CKD controls and healthy subjects, the Left Atrial Volume Index (LAVI) was increased. This early change in cardiac structure in CKD was speculated by the writers to be due to myocardial fibrosis induced by activation of the RAS.

Hypertension, LVH, volume overload and DM are also conditions associated with left atrial enlargement and are common in the CKD population.(150) Left atrial enlargement, as measured by the left atrial diameter, was associated with the incidence of AF in dialysis patients in a retrospective cohort study of about 1000 patients.(151) The left atrial diameter was associated with the presence of AF in a cross-sectional, retrospective setting in non-dialysis CKD patients with a mean eGFR of 34 ml/min/1.73 m^2.(48)

Speckle tracking echocardiography is a novel technique that allows following the motion of cardiac tissue throughout systole and diastole, tracking acoustic reflections, termed speckles. Global longitudinal strain (GLS) of myocardium, obtained using this technique, is a more subtle indicator of systolic dysfunction of the heart than LVEF. In the setting of preserved LVEF, there still seems to be a worsening of systolic function measured by reduced GLS, another measure that is reduced in parallel with declining kidney function.(149) GLS was an independent predictor of all-cause mortality in a study of 447 CKD patients by Krishnasamy and coworkers.(152)

The same group of investigators observed a somewhat surprising association between GLS and the mental component summary of an HRQoL questionnaire.(153) Data on HRQoL and echocardiographic measures in CKD patients are otherwise scarce. There was no association between HRQoL and any echocardiographic parameter in the aforementioned study observing an association between maximal oxygen uptake and HRQoL.(145)

The diastolic function of the heart is assessed echocardiographically by E/A and the ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e'). The prevalence of diastolic dysfunction in CKD is high. The prevalence of diastolic dysfunction was 81% in one study of advanced CKD patients, with about half of the patients already receiving dialysis.(154) An elevated E/e' correlated with CV events and mortality, whereas a decreased LVEF correlated with CV events in a study of 186 CKD stage G3-5 patients.(155)

Echocardiography performed before and after a stress test is called stress echocardiography and is used to diagnose CAD. Ischemia is detected after a stress test as cardiac wall-motion abnormalities, with modest sensitivity in CKD patients. Stress echocardiography is often used as CAD screening in kidney transplant candidates. A stress echocardiography showing no ischemia is associated with a low incidence of CV events.(149)

Valvular calcifications and other forms of vascular calcification are highly prevalent in the CKD population, facilitated by CKD-MBD and other risk factors. Valvular calcifications can also be detected by echocardiography.(156)

2.8 Quality of Life in Chronic Kidney Disease Patients

2.8.1 Definition of Quality of Life

Quality of life (QoL) is defined by the World Health Organization as “an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns”. Thus, QoL is a subjective matter, and an individual with serious disabilities may have a good QoL, whereas a person with no disabilities may experience significantly impaired QoL. Health-related quality of life refers to aspects of quality of life affected by an individual’s health status; therefore, HRQoL is part of a broader concept of QoL. The Centers for Disease Control and Prevention defines HRQoL as “an individual’s or group’s perceived physical and mental health over time.” The social aspects of well-being are also usually assessed when measuring HRQoL. Overall, no single, comprehensive definition of HRQoL has emerged in the literature.(157)

2.8.2 Quality of Life Assessment

Several instruments have been developed for assessment of HRQoL. Among the most popular ones are Short Form 36 (SF-36), EuroQoL-5-dimension (EQ-5D), the World Health Organization Quality of Life-BREF and 15-dimensional Health-related Quality of Life (15D-HRQoL), all of which are generic instruments for measuring HRQoL. Short Form 12 (SF-12) is a 12-item, shortened version of SF-36.(158)

The SF-36 is a 36-item questionnaire comprising eight subdomains that can be summarized in two summary scores: Physical Component Summary (PCS) assessing physical aspects of HRQoL and Mental Component Summary (MCS) assessing mental aspects of HRQoL. EQ-5D comprises five dimensions, which can be summarized into a summary index value. A patient’s self-rated health is also measured on a vertical visual analogue scale of 0 – 100.(158)

Kidney disease-specific instruments for measuring HRQoL among the CKD population are scarcer. According to a systematic review, the most widely used and reliable kidney disease-specific HRQoL instruments are two derivatives of Kidney Disease Quality of Life (KDQOL), a 134-item questionnaire: Kidney Disease Quality of Life Short Form (KDQOL-SF) and Kidney Disease Quality of Life-36 (KDQOL-36). The latter is a 36-item instrument comprising three specific dimensions and the generic SF-12 survey. The specific dimensions are Symptoms/Problems, Burden of Kidney Disease and Effects of Kidney Disease. The

SF-12 can be summarized into a physical component summary and a mental component summary. KDQOL-SF is an 80-item measure that includes the SF-36 as a generic core. There are 10 kidney disease-specific domains and 8 generic SF-36 domains, the latter of which can be summarized into PCS and MCS.(159) Table 1 summarizes the interpretation of the kidney disease-specific domains of KDQOL-SF, including the item on Overall Health.

Table 1. Explanation of the scores of the kidney disease-specific domains of KDQOL-SF. Modified from Jansz et al. 2018. (181)

Domain	Meaning of low score	Meaning of high score
Symptoms/Problems	Extremely bothered by symptoms such as muscle cramps, pruritus, anorexia, and/or dialysis access problems	Not at all bothered
Effects of Kidney Disease	Extremely bothered by fluid and dietary restriction, by an inability to travel, and dependency on doctors	Not at all bothered
Burden of Kidney Disease	Extremely bothered by the time consumed by kidney disease, its intrusiveness, and degree of burden on family	Not at all bothered
Cognitive Function	Affected all of the time by inability to concentrate, confused, with poor reaction time	Not at all bothered
Quality of Social Interaction	Continual irritation and failure to get along with people with virtual isolation	No problems, socially interactive
Sexual Function	Experiencing severe problems with enjoyment and arousal	No problems
Sleep	Very poor sleep with daytime somnolence	No problems with sleep
Social Support	Very dissatisfied	Satisfied with level of social support
Overall Health	Rates health as worst possible	Rates health as best possible

2.8.3 Quality of Life and Stages of CKD

CKD patients suffer from impaired HRQoL. Most data comes from dialysis, mainly HD, patients.(4,160,161) The data are more limited on the HRQoL of predialysis CKD patients. However, the HRQoL of predialysis CKD patients also seems to be inferior to that of the general population.(4,162) Most studies have reported lower HRQoL in more advanced CKD, already beginning in CKD stage G2.(13,163,164) A German population-based study, using the generic SF-36 instrument, reported inferior HRQoL beginning from CKD stage G3a. The physical aspects and general health perceptions were affected by CKD, whereas mental health was not.(165) A Report from a Chinese CKD cohort with 1277 CKD stage G3 patients showed that even stage G3a and stage G3b patients had HRQoL differences. CKD stage G3b patients scored significantly lower in PCS, even after adjustment for confounders. The crude scores were lower in stage G3b patients in all domains compared to stage G3a patients.(166)

The lowest quality of life among CKD patients has been reported in those with the lowest eGFR, i.e., dialysis patients.(4) Kidney transplantation, a procedure that leads to a rise in eGFR, seems to offer better HRQoL than dialysis.(167–169) The vast majority of studies concerning HRQoL and CKD stages are cross-sectional in design.

2.8.4 Factors Associated with Impaired HRQoL Among CKD Patients

2.8.4.1 Comorbidities

Comorbidities have a profound effect on CKD patients' HRQoL. Several studies have identified an association between CVD and an impaired quality of life.(5,163,170) More specifically, CHF, CAD and PAD are associated with CKD patients' impaired HRQoL.(14,164) Some studies have linked hypertension (14,170) and COPD (5) to impaired HRQoL. The existing literature reports quite a uniform association with impaired HRQoL and diabetes(14,162–164,170), and obesity is also associated with lower HRQoL in many studies.(14,171,172) Psychiatric disorders, such as depression, are associated with impaired HRQoL.(5) The use of beta-blockers was associated with inferior HRQoL in one study.(164)

It is clear that the presence of CVD affects the HRQoL of CKD patients, but data on AF's effect are lacking. However, it is known that patients with AF, with no data on CKD status, suffer from impaired HRQoL, and both rate and rhythm-control strategies seem to improve HRQoL. Patients with paroxysmal AF had poorer HRQoL compared to those with permanent AF.(173)

2.8.4.2 Demographic and Socioeconomic Factors

The effect of age on CKD patients' HRQoL is two-fold: The scores of the physical aspects of HRQoL, in many studies, measured for instance by SF-36 PCS, seem to be lower with advancing age, whereas the mental aspects measured, e.g., by SF-36 MCS are actually higher in the elderly.(6,14,164,171,174) This finding probably reflects the adjustment to limitations caused by CKD and a smaller gap between expectations and reality among elderly CKD patients. Female sex is associated with impaired HRQoL compared to males in many studies.(14,164,170) Lower income(174), unemployment(5) and a lower education level are associated with lower HRQoL in some studies.(14) A recent Danish study reported an association with having a partner as opposed to living single having a positive impact on the mental aspect of HRQoL measured by MCS, whereas high educational level was associated with better MCS and PCS scores.(175)

2.8.4.3 Biochemical Parameters

Renal anemia becomes more frequent as eGFR declines. Symptoms of anemia, such as fatigue and impaired physical performance, have an effect on CKD patients' HRQoL. Several studies have shown an association with impaired HRQoL and anemia.(163,164,170) Trials of anemia correction have yielded mixed results. Early treatment of anemia with ESAs to a higher hemoglobin (Hb) target led to improvement of HRQoL in the CREATE trial compared to treatment initiated later to a lower Hb target.(64) Contrary to this finding, in the TREAT trial there was no improvement in HRQoL measured by SF-36 among patients receiving ESAs compared to a placebo group, but there was improvement in the FACT-Fatigue score in those treated with ESAs.(66) HRQoL improved in a similar fashion in the CHOIR trial in those assigned to higher and lower Hb targets, respectively.(65)

CRP is commonly used as a marker of inflammation and/or infection. Low-grade inflammation in CKD patients is often present. Inflammation is believed to be an important factor leading to adverse cardiovascular outcomes, especially so in CKD patients. HRQoL studies have reported an association between CRP and impaired HRQoL in CKD patients.(163,170)

Serum albumin is a strong predictor of CKD patients' prognosis. Its association with HRQoL was examined in a study by Kalantar-Zahed et al. and a strong correlation was found between serum albumin and low PCS and MCS scores in HD patients.(176) Inflammation and, to a lesser degree, diet restrictions may contribute to low albumin levels in CKD.

A recent Korean study of more than 1500 predialysis CKD patients with a mean eGFR of 54 ml/min/1.73 m^2 found an inverse association between serum adiponectin levels and PCS. According to the authors, this seemingly paradoxical finding may

be explained in CKD patients by a previously found association of adiponectin levels and malnutrition as well as adiponectin levels and anemia.(177)

2.8.5 Quality of Life and Renal Replacement Therapy

HRQoL of CKD patients deteriorates as CKD advances, being the lowest among dialysis patients.(4,163,164) The choice of the RRT modality has an impact on patients' HRQoL. However, the topic is a difficult one to study, due to many confounders.

Conservative kidney treatment and dialysis were compared in a systematic review. Elderly patients predominated in the studies with this setting. Regarding HRQoL, dialysis did not seem to offer benefit, and HRQoL was even better in those treated conservatively in some studies.(178)

Many studies have compared PD and HD patients' HRQoL with mixed results. A recent report from The Dialysis Outcomes and Practice Patterns Study (DOPPS) and The Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) did not even try to adjust for confounders but found the absolute Burden of Kidney Disease scores to be higher, indicating better HRQoL in PD patients. The main finding in this study was that impaired functional status is significantly associated with worse HRQoL in multiple domains in both PD and HD patients.(179) A meta-analysis by Zazzeroni et al. tried to clarify the differences in HRQoL offered by these modalities, but the results were inconclusive. Of the seven studies included, four tended to be in favour of PD and two claimed HD to be better regarding HRQoL, while one showed both modalities to be equal. There was a statistically significant difference in favour of PD in the Effects of Kidney Disease domain.(180) A recent meta-analysis on the same subject included studies using three varied HRQoL instruments. The results were in favour of PD in the studies using SF-36, EQ-5D and KDQOL instruments. The KDQOL domains Effects of Kidney Disease and Burden of Kidney Disease and also, to a lesser extent, Symptoms/Problems, differed in favour of PD.(158) However, due to the aforementioned problems in comparing these two modalities, the results do not necessarily reflect the true differences in HRQoL induced by the RRT modalities, per se.

Nocturnal HD and kidney transplantation are assumed to be the RRT modalities offering better HRQoL compared to conventional HD. A study by Jansz and coworkers compared HRQoL between these modalities using the KDQOL-SF instrument. 41 kidney transplant recipients and 31 patients on nocturnal home hemodialysis (who were eligible for kidney transplantation) participated. HRQoL was assessed one year after enrollment in the study. After adjustment, Effects of Kidney Disease was the only domain showing a significant difference in HRQoL. The score was 12 points in favour of kidney transplantation in this domain. Burden

of Kidney Disease, Social Support and PCS were numerically higher in transplant patients, but the difference was not statistically significant.(181)

Kidney transplantation is considered the best RRT modality regarding HRQoL and survival. A Spanish study compared the HRQoL of patients before and after transplantation using the Sickness Impact Profile, a generic HRQoL instrument. Transplantation improved HRQoL, especially in men, younger patients and those with fewer comorbidities.(169) A cross-sectional study observed that HRQoL was better in transplant recipients compared to dialysis patients in all eight SF-36 domains.(168) Kidney transplantation significantly improved HRQoL compared to dialysis in the kidney disease-specific domains Effects of Kidney Disease, Burden of Kidney Disease, Symptoms/Problems, Overall Health and Work Status, whereas no clinically significant change in any of the generic SF-36 domains was observed in a Norwegian study with a longitudinal setting. The HRQoL of the transplant recipients remained inferior to that of the general population.(182) Ortiz and coworkers studied the effect of transplantation on HRQoL according to a previous dialysis modality. PD patients seemed to benefit the most in this study. ICHD patients had the lowest baseline HRQoL and experienced an improvement in HRQoL after transplantation. HHD patients' HRQoL was better than other patients' at baseline, and about a quarter of these patients showed no improvement in HRQoL after transplantation.(167)

An interesting study was recently published comparing HRQoL of patients of similar GFR levels with and without a kidney transplant. Transplanted patients had better PCS and MCS than CKD patients without a transplant at similar renal function corresponding to CKD stages G1-3. Kidney disease-specific domains did not differ between the groups. The writers hypothesized that the better HRQoL of the transplanted patients may be related to their improved kidney function and clinical condition after transplantation, whereas CKD patients without a transplant and declining kidney function may have more anxiety concerning the state of their health.(183)

2.8.6 Quality of Life, Mortality and CKD Progression

The association between impaired HRQoL and mortality in CKD was first reported in patients on hemodialysis. Among larger studies is a report from DOPPS of more than 10000 HD patients. The KDQOL-SF was completed at study entry. PCS, MCS and Kidney Disease Component Summary (KDCS) were all inversely correlated to mortality. The lowest quintile of PCS had adjusted risk of death 93% higher than the highest quintile. PCS had the strongest association followed by MCS and KDCS.(12) A recent Swedish study using SF-36 in a dialysis population, most of whom were incident HD patients, found that one standard deviation (SD) increase in PCS was

associated with lower all-cause mortality, HR 0.65 after adjustments. The median follow-up was 28 months. MCS was not associated with mortality in this population.(184)

A Taiwanese study of 423 non-dialysis CKD patients found an association between impaired HRQoL measured by the World Health Organization Quality of Life-BREF questionnaire and risk of both ESKD and death. The physical and psychological domains and all total scores were strongly associated with dialysis initiation and all-cause mortality. However, the number of deaths was only four during the median follow-up of 410 days.(13) Porter et al. studied the longitudinal quality of life and its correlations in African American Study of Kidney Disease and Hypertension (AASK) study patients. Lower Mental Health Composite and Physical Health Composite scores were associated with a composite of CV events and CV death as well as a composite of CKD progression and death. However, the results concerning CKD progression were variable with different analytic techniques. This analysis of approximately 1000 patients with a mean eGFR of 48 ml/min/1.73 m^2 and a follow-up of 8.8-12.2 years found quite similar associations compared to a previous study with a cross-sectional HRQoL evaluation.(185) A total of 3837 participants completed the KDQOL-36 questionnaire at baseline in a CRIC study and Hispanic CRIC study cohorts. Low HRQoL was defined in this study as a score >1 SD below the mean. The mean baseline eGFR was 45 ml/min/1.73 m^2 and median follow-up of 6.2 years. After adjustment for confounders, MCS and PCS were independently associated with all-cause mortality, the latter also with incident CV events. Contrary to two previous studies, there was no association between CKD progression and impaired HRQoL in this study.(14) A study by Jesky et al. of 745 advanced CKD patients (median eGFR 26 ml/min/1.73 m^2) used EQ-5D as the HRQoL instrument. A lower HRQoL, indicated by the self-care dimension of EQ-5D, and a composite EQ-5D index score were associated with all-cause death. No association between HRQoL and CKD progression was observed in this study either.(186) Overall, data on HRQoL and CKD progression are inconclusive, whereas the association between HRQoL and mortality has been observed in many studies using various HRQoL instruments.

2.8.7 Quality of Life, Cardiovascular Events and Hospitalisations

Worse HRQoL is associated with multiple adverse outcomes besides mortality. In a recent report from a CRIC cohort, the longitudinal scores of KDQOL-36 remained quite stable in the study population, whereas lower baseline scores were characteristic for those who experienced adverse events during a 14-year follow-up. For instance, the PCS score diminished 0.34 points per year, and in Burden of Kidney

Disease, the domain with the most change over years, the score diminished 0.65 points per year. A high risk group with all baseline measures lower than medium and low risk groups also encountered most adverse events, such as CVD, HF, ESKD and death.(187)

An earlier report from a CRIC cohort showed that baseline low PCS was associated with future CV events, highlighting the significance of self-reported physical aspects of HRQoL.(14) A similar finding of an association between physical health composite and CV events was observed in an AASK study of an African American CKD population.(185)

A report of a large HD population from a DOPPS study showed an association of PCS, MCS and KDCS with hospitalisations.(12) Another smaller study with HD patients showed similar results using SF-36 as the HRQoL instrument.(176) Data are scarce on non-dialysis CKD patients' HRQoL and hospitalisations.

2.8.8 Effect of Exercise Programs on HRQoL

Many, but not all, studies involving HD patients have demonstrated benefit in the physical aspects of HRQoL achieved by exercise training programs.(188) A randomized, controlled trial of ca. 100 CKD stage G3-4 patients, randomized the patients for usual care and renal rehabilitation exercise groups for 12 weeks. Physical capacity and HRQoL improved in the latter group. The RAND-36 questionnaire domains with significant improvement were Physical Functioning, Role-Physical, Energy/Fatigue levels and General Health as well as Pain, a component of the Mental Composite score.(189) The generic RAND-36 instrument is similar to the SF-36 questionnaire.

3 Aims

The aims of this thesis were to study the determinants and evolution of quality of life in patients with advanced chronic kidney disease as well as to identify novel factors associated with cardiovascular morbidity and mortality in these patients.

The specific aims were:

1. To identify determinants of health-related quality of life and its association with mortality and chronic kidney disease progression in a CKD stage G4-5 population (I)
2. To longitudinally evaluate the changes in health-related quality of life as patients advance to different renal replacement therapy methods and the determinants of these changes during follow-up (II)
3. To study the cardiovascular system with several methods of imaging and biochemical parameters and determine the association of these measures to mortality during follow-up (III)
4. To study the epidemiology and determinants of atrial fibrillation in advanced chronic kidney disease (IV)

4 Materials and Methods

4.1 Study Population and Protocol

The CADKID study recruited 210 patients with an eGFR lower than 30 ml/min/1.73 m^2. Patients were recruited from the Turku University Hospital Kidney Centre predialysis outpatient clinic starting in August 2013. A minimum target of 200 participants was set. Recruitment was completed in September 2017. All patients were >18 years of age and none were receiving RRT when entering the study. CADKID is a prospective follow-up study assessing cardiovascular disease, mortality and quality of life in advanced CKD. Most participants represented CKD stage G5 at the beginning of the study. Vascular ultrasound, stress ergometry combined with echocardiography (stress echocardiography), lateral lumbar X-ray and HRQoL assessment were performed at baseline and repeated during follow-up. Laboratory parameters were taken at baseline and every three months during follow-up. The researchers extracted the patients' data, including comorbidities (hypertension, DM, AF, CAD, CHF), from the electronic patient records of Turku University Hospital.

4.2 Assessment of the Cardiovascular System

We used a comprehensive set of methods to assess the participants' cardiovascular system, including a stress test and ultrasound of the heart and vasculature as well as a radiograph of the aorta.

4.2.1 Stress Echocardiography

Stress echocardiography was performed at the Department of Clinical Physiology of Turku University Hospital. First, a standardised transthoracic echocardiography was performed at rest, followed by a maximal symptom-limited stress ergometry. An echocardiographic evaluation of wall motion abnormalities then ensued.

A bicycle ergometer was used in maximal stress ergometry. The initial workload and workload increase per minute (10W, 15 W or 20 W) were individualised with the aim to achieve symptom limitation in 6-10 minutes. An initial 30-second warm-

up period to achieve the target speed of 60 rpm was used, and participants were instructed to maintain the same speed until exhaustion. The mean work load of the last four minutes of exercise (Wmax) and also age, sex and body size-adjusted percentage of expected value (Wmax%) were recorded. Normal values were obtained from the Mini-Suomi study, representing a population of apparently healthy Finnish adults.(190)

The echocardiographic values obtained included measurements of the heart's dimensions as well as the functional parameters measuring the heart's systolic and diastolic functions. The thickness of the posterior wall and septum were measured. The left ventricular end-diastolic diameter (LVEDD) was recorded. The Left Ventricular Mass Index (LVMI) was calculated. LVEF and GLS as measures of systolic function were obtained. Measures of diastolic function, E/A and E/e', were determined. The left atrial dimension and volume were measured and LAVI calculated.

4.2.2 Abdominal Aortic Calcification Score

A lateral lumbar radiograph in the standing position was performed at the study baseline to determine the degree of abdominal aortic calcification. The AAC score was independently calculated by two researchers, and the mean of the scores was used for analyses.

The method described by Kauppila et al. in 1997 was used to calculate the AAC score.(126) The anterior and posterior walls of the aorta on the level of each lumbar vertebra L1 to L4 are graded separately on the scale of 0-3. Thus, the maximum score on the level of each vertebra is 6 (3 anterior + 3 posterior) and the total maximum score is 24. The total score is 0 if there are no calcific deposits on the aorta wall between L1 to L4. Calcific deposit corresponding to less than one third of each segment is graded 1, one third to two thirds 2, and more than two thirds 3. AAC score 0 is considered normal.

4.2.3 Vascular Ultrasound

A Sequoia 512 ultrasound mainframe with a 13.0 MHz linear-array transducer was used to perform vascular ultrasound studies. The scans were stored digitally. One researcher manually analysed the scans.

For intima-media thickness measurements, the left common carotid artery approximately 1 cm proximal to the carotid bulb and the right femoral artery approximately 2 cm proximal to the bifurcation of the deep femoral artery were scanned according to a standardized protocol using B-mode.

Corresponding locations of the left common carotid artery and right femoral artery were used to measure arterial compliance. End-systolic and end-diastolic diameters were recorded. Several scans were stored digitally and analysed later. Results were presented as % / mmHg.

The right brachial artery was used for FMD measurements. The artery diameter was assessed at rest and during reactive hyperaemia after 4.5 minutes of applying a pressure of 250 mmHg by inflating a pneumatic tourniquet. Three measurements at 40 seconds, 60 seconds and 80 seconds after releasing the tourniquet were recorded. The mean of the three measurements at each time point was used to assess the maximum FMD.

4.3 Biochemical Parameters

A comprehensive set of biochemical parameters was collected and analysed at study entry. These included complete blood count, C-reactive protein, sodium, potassium, creatinine, urea, albumin, ionized calcium, phosphate, blood glucose, glycated hemoglobin, capillary blood gas analysis, uric acid, alanine aminotransferase, alkaline phosphatase, parathyroid hormone, transferrin saturation, ferritin, TnT and proBNP. Blood lipid levels were taken according to clinical routine. Biochemical analyses were repeated according to clinical routine or at least once in three months during follow-up. The CKD-EPI equation was used to calculate eGFR. The Turku University Hospital Laboratory Division (Tykslab) analysed the blood samples.

4.4 Quality of Life Assessment

HRQoL was assessed by KDQOL-SF version 1.3, a kidney disease-specific HRQoL instrument. The 80-item questionnaire consists of kidney disease-specific items and a generic core of 36 items called SF-36. 80 items are divided into 18 domains, of which 10 are kidney disease-specific and eight are generic (SF-36) domains.

The kidney disease-specific domains are “Symptoms/Problems” consisting of 12 items: “Effects of Kidney Disease” (8 items), “Burden of Kidney Disease” (4 items), “Work status” (2 items), “Cognitive Function” (3 items), “Quality of Social Interaction” (3 items), “Sexual Function” (2 items), “Sleep” (4 items), “Social Support” (2 items) and a single item on overall health on a 0–10 response scale. The generic SF-36 consists of the following domains: “Physical Functioning” (10 items), “Role– Physical” (4 items), “Role – Emotional” (3 items), “Social Functioning” (2 items), “Emotional Well-being” (5 items), “Pain” (2 items), “Energy/Fatigue” (4 items), and “General Health Perceptions” (5 items). Higher scores in all domains reflect a better HRQoL (scale 0–100). PCS and MCS were calculated. The longitudinal change in HRQoL was assessed by subtracting the domain score of the

baseline questionnaire from the score of the follow-up questionnaire. Thus, the subtraction (delta score) was positive if HRQoL regarding the domain in question improved over time.

The KDQOL-SF was self-administered and completed by the participants at study entry and after 2 years of follow-up in this study. The RAND scoring method of the domains was used.

4.5 Statistical Methods

The results are expressed as mean±SD for the normally distributed variables and median (interquartile range [IQR]) for skewed variables.

Statistical analyses were performed using statistical analysis system, SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) in studies I, II and III. IBM SPSS Statistics software version 26.0 was used in study IV. $p < 0.05$ was considered statistically significant.

4.5.1 Study I

Distributions of HRQoL parameters were skewed. We calculated Spearman correlation coefficients between variables of interest and HRQoL domains. We were unable to normalize the distribution using standard transformations. Thus, Kruskal-Wallis test was used for comparisons between groups. We used multivariable regression models to investigate predictors of PCS. The association between PCS, MCS and kidney disease progression to RRT and mortality was studied using univariable and multivariable Cox proportional hazards models.

4.5.2 Study II

Normality in continuous covariates was tested with the Kolmogorov-Smirnov and Shapiro-Wilk tests. We used paired T-test for normally distributed variables and Wilcoxon signed-rank test for skewed variables for comparisons between baseline and follow-up HRQoL measures. Differences between the treatment groups in delta HRQoL measures were studied using Kruskal-Wallis test followed by the Dwass, Steel, Critchlow-Fligner method for pairwise comparisons for skewed variables. Analysis of variance (ANOVA) was used for normally distributed variables. We used a post hoc Bonferroni correction for pairwise comparisons.

Spearman's correlation coefficients for the skewed variables and Pearson's correlation coefficients for the normally distributed variables were used to examine univariate associations between delta HRQoL scores and echocardiographic measures as well as biochemical parameters. Variables with significant univariate

associations with the delta HRQoL domains of the highest interest were included as covariates in respective stepwise multivariable regression models in addition to the treatment group variable.

We used means of biochemical parameters and echocardiographic parameters during follow-up for analyses. The measure of change in kidney function was the change in eGFR from the start of the study to follow-up HRQoL assessment. Associations between change in HRQoL and outcomes of mortality and MACE were studied using univariate Cox proportional hazards models. MACE was defined as a composite of cardiovascular death, myocardial infarction, stroke and coronary artery revascularisation.

4.5.3 Study III

The skewed variables in this study were transformed using the best transformation for each variable to normalize distributions. Log_e-transformation, square root transformation and square transformation were used and normality was tested with Shapiro-Wilk and Kolmogorov-Smirnov tests and visual examination. For variables with negative values, we used $\log(X + a + 1)$ transformation, where X is the value of the variable and a is the minimum value of the variable in the dataset in order to avoid missing values. For the variables that had values between (0, 1), a $\log(X + 1)$ transformation was used. There was no suitable transformation for some of the skewed variables.

We used chi-squared test for categorical variables and ANOVA for continuous variables in comparisons between groups. The nonparametric Kruskal-Wallis test was used for skewed variables that could not be transformed. Bonferroni correction was used to account for multiple comparisons. The association between variables of interest and mortality was investigated using univariable and multivariable Cox proportional hazards models. The multivariable Cox models included age, sex, and previous coronary artery disease as covariates, together with a single variable of interest in each respective model.

4.5.4 Study IV

The normality of continuous covariates was tested with the Kolmogorov-Smirnov and Shapiro-Wilk tests. The unpaired t test or Mann-Whitney test and Pearson's chi-squared test or Fisher's exact test were used to compare continuous covariates and categorical covariates in the study subgroups. We reported absolute and relative (percentage) frequencies of categorical covariates. TnT and LAVI were studied as dichotomous variables. Cutoff points were chosen based on clinical relevance and distribution of variables. The risk factors of prior AF were studied using univariate

logistic regression models, followed by a multivariable regression model. Variables showing univariate associations at $p \leq 0.01$ significance level were included in the multivariable model. We examined associations between variables of interest and incident AF using univariate and multivariable Cox proportional hazards models. Dichotomous variables, TnT and LAVI, were also studied using a Kaplan-Meier time-to-event analysis with the use of a log-rank test. Only the two variables of interest with the highest hazard ratios and significance in the univariate Cox models (elevated TnT and increased LAVI) were included in the multivariate model, in addition to age, to avoid overfitting. The complete case approach was used for Cox models. As a result of missing LAVI and TnT data, 120 patients were included in the univariate and multivariable Cox models. Little's test was used to ensure that the missing data were missing completely at random.

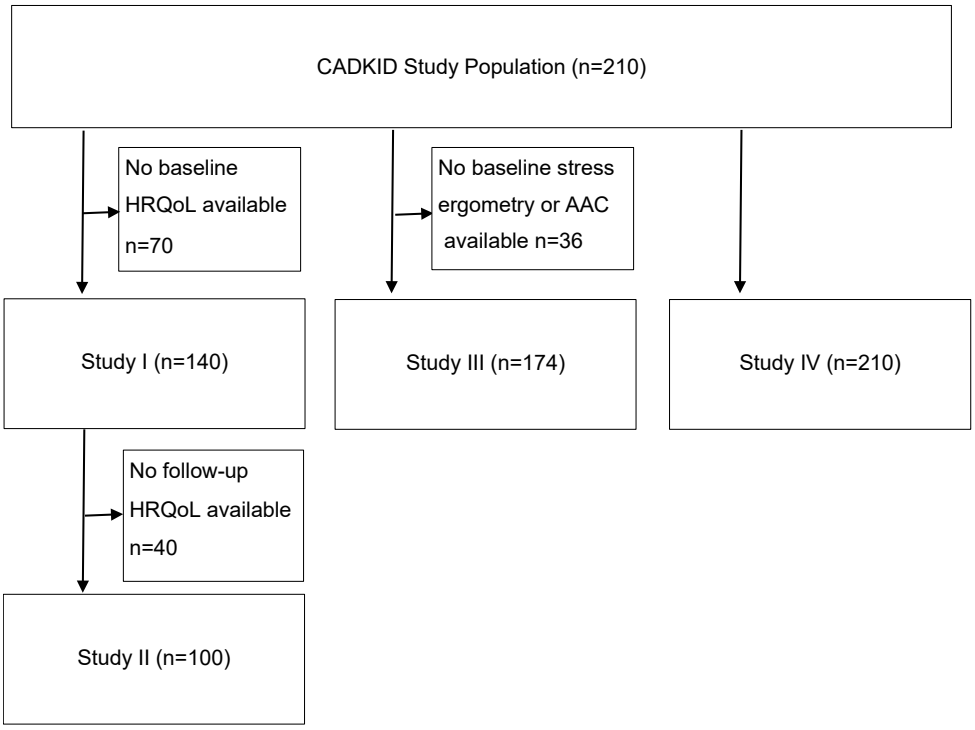
5 Results

Table 2 presents the characteristics of the whole study population of 210 patients. All study patients were included in study IV, whereas studies I-III included 100-174 patients. Figure 2 shows the patient selection in studies I-IV.

Table 2. Baseline characteristics of the CADKID study population (n=210).

Age, years	65 (52-73)
Female	73 (35)
Smoking, Current (n=207)	24 (12)
Ex-smoker (n=207)	68 (33)
Hypertension	205 (98)
Diabetes	94 (45)
Diabetes Type 1 / Type 2	34 / 60 (16 / 29)
Coronary Artery Disease	34 (16)
Heart Failure	48 (23)
Atrial Fibrillation	41 (20)
Body Mass Index, kg/m^2	27.7 (24.1-30.7)
Systolic Blood Pressure, mmHg	150 (136-165)
Diastolic Blood Pressure, mmHg	81±14
Hemoglobin, g/l	114±12
C-Reactive Protein, mg/l	2 (1-5)
Creatinine, µmol/l	396 (332-473)
Albumin, g/l	34.7 (32.1-37.7)
Troponin T, ng/l (n=200)	36 (22-66)
proBNP, ng/l (n=197)	1270 (487-2990)
Abdominal Aortic Calcification Score (n=199)	5.5 (1.0-10.5)
Wmax, W (n=176)	83.5±36.5
Left Ventricular Ejection Fraction, % (n=195)	65 (61-69)

Values are expressed as n (%), mean ± standard deviation, or median (interquartile range). proBNP = N-terminal Pro-B-type Natriuretic Peptide, Wmax = Mean Work Load of the Last Four Minutes of Exercise. Previously unpublished.



HRQoL = Health Related Quality of Life, AAC = Abdominal Aortic Calcification Score. Previously unpublished.

Figure 2. Flowchart of studies I-IV.

5.1 Quality of Life Is Associated with Cardiac Biomarkers, Echocardiographic Indices, and Mortality in Advanced CKD

We investigated the association between baseline HRQoL and echocardiographic and biochemical parameters as well as comorbidities in this study. Furthermore, we studied the association between HRQoL and mortality during a median follow-up of 41.3 months (range 1.9-77.8 months). Of the 210 patients enrolled in the CADKID study, baseline HRQoL data was available for 140 patients (67%) who comprised the study population. Patients with no HRQoL data available (n=70) did not differ from the study population in body mass index (BMI), proportion of diabetics or gender distribution. However, they had higher median eGFR (13 vs 12 ml/min/1.73 m^2) and were younger (61 vs. 66 years).

5.1.1 Correlations Between Comorbidities and Kidney Disease-Specific HRQoL Domains

Obese patients (BMI ≥30) had lower scores in the "Symptoms/Problems" (70.5 vs. 79.5, p = 0.007), "Effects of Kidney Disease" (68.8 vs. 84.4, p = 0.0009) and "Burden of Kidney Disease" (62.5 vs. 75.0, p = 0.047) domains. Diabetics showed significantly lower scores in the "Symptoms/Problems" (71.6 vs. 79.5, p = 0.02) and "Effects of Kidney Disease" domains (71.9 vs. 84.4, p = 0.009). Patients with AF scored lower in the same two domains as diabetics ("Symptoms/Problems" 70.3 vs. 79.5, p = 0.005 and "Effects of Kidney Disease" 70.3 vs. 84.4, p = 0.006). We found no association between CHF and kidney disease-specific domains. Table 3 shows scores of selected kidney disease-specific and generic domains according to BMI and comorbidities.

5.1.2 Correlations Between Demographic, Biochemical, and Echocardiographic Parameters and Kidney Disease-Specific HRQoL Domains

The "Symptoms/Problems" score was inversely associated with E/A (r = −0.25, p = 0.006) and "Effects of Kidney Disease" with left ventricular end-diastolic diameter (r = −0.25, p = 0.004) and left ventricular mass index (LVMI) (r = −0.20, p = 0.02). "Burden of Kidney Disease" had an inverse association with plasma phosphate (r = −0.33, p < 0.0001), LVMI (r = −0.29, p = 0.0009), and creatinine (r = −0.32, p < 0.0001) and a positive association with age (r = 0.22, p = 0.01). There was an inverse association between "Sleep" and plasma phosphate (r = −0.21, p = 0.02) and C-reactive protein (r = −0.22, p = 0.01). "Overall Health" showed multiple associations. A positive correlation was observed with age (r = 0.22, p = 0.009) and GLS (r = 0.29, p = 0.007), while an inverse association was observed with BMI (r = −0.20, p = 0.02), plasma phosphate (r = −0.20, p = 0.02), LVMI (r = −0.24, p = 0.007), E/A (r = −0.21, p = 0.03), and E/e′ (r = −0.21, p = 0.04). There were no significant associations between ionized calcium, parathyroid hormone or albumin and kidney disease-specific domains. TnT was inversely associated with the item on "Overall Health" (r = −0.19, p = 0.03) and proBNP with "Work Status" (r = −0.23, p = 0.007).

The change in eGFR during follow-up (i.e., between baseline and RRT initiation in those who started dialysis or between baseline and death or end of study in those who did not start RRT), divided by the time interval between eGFR assessments (ΔeGFR) was inversely associated with the "Burden of Kidney Disease" (r = −0.30, p = 0.0004) and "Overall Health" (r = −0.23, p = 0.008). Cox models did not show significant associations between kidney disease-specific domains and progression of CKD or mortality.

5.1.3 The Association of PCS and MCS with Comorbidities, Echocardiographic and Biochemical Parameters

Studied comorbidities AF, CHF, diabetes and obesity were all associated with PCS, whereas no association with MCS was detected. Table 3 shows domain scores according to obesity and comorbidities.

Echocardiographic parameters of diastolic cardiac function E/A and E/e´ had an inverse association with PCS ($r = -0.20$, $p = 0.04$ and $r = -0.27$, $p = 0.01$, respectively), and the parameter measuring systolic function, GLS, was positively associated with PCS ($r = 0.38$, $p = 0.0004$). LVEF was not associated with PCS.

TnT, proBNP and CRP were inversely associated with PCS ($r = -0.25$, $p = 0.006$, $r = -0.30$, $p = 0.0008$ and $r = -0.24$, $p = 0.006$, respectively). Hemoglobin and Albumin levels were not associated with PCS.

There was an inverse association between MCS and BMI as well as MCS and phosphate ($r = -0.25$, $p = 0.005$ and $r = -0.21$, $p = 0.02$, respectively).

In multivariable regression models, adjusted for age, BMI and diabetes, proBNP ($\beta = -0.49 \times 10^{-3}$, $p = 0.006$), TnT ($\beta = -0.05$, $p = 0.02$) and GLS ($\beta = 0.73$, $p = 0.02$) remained independent significant predictors for PCS.

Table 3. Quality of life domain scores (0-100) according to BMI group and comorbidities.

Domain	**BMI** <30kg/m^2 n=99	≥30kg/m^2 n=41	**Atrial fibrillation** No n=110	Yes n=30
Symptoms/Problems	79.5 (70.5-90.9)	70.5(56.8-84.1)**	79.5 (70.5-90.9)	70.3(56.8-79.5)**
Effects of Kidney Disease	84.4 (68.8-90.6)	68.8 (59.4-84.4) ‡	84.4 (68.8-90.6)	70.3(59.4-84.4)**
Burden of Kidney Disease	75.0 (50.0-93.8)	62.5 (31.3-81.3) *	68.8 (43.8-87.5)	75.0 (43.8-87.5)
Overall Health	70.0 (50.0-70.0)	50.0 (40.0-70.0) *	60.0 (50.0-70.0)	50.0 (40.0-70.0)
Physical Functioning	75.0 (45.0-85.0)	35.0 (15.0-66.7) ‡	75.0 (37.9-90.0)	32.5 (10.0-60.0)‡
Pain	77.5 (55.0-90.0)	45.0 (22.5-67.5) ‡	67.5 (45.0-90.0)	57.5 (32.5-77.5)*
General Health	43.8 (30.0-55.0)	35.0(20.0-45.0)**	40.0 (30.0-50.0)	37.5 (20.0-50.0)
Energy/Fatigue	57.5 (35.0-75.0)	40.0(30.0-55.0)**	50.0 (32.5-70.0)	40.0 (30.0-60.0)
SF36PCS	38.3±9.9	30.1±10.4‡	37.7±10.5	29.2±8.6‡
SF36MCS	51.2±9.7	47.7±9.6	50.5±9.8	48.8±9.9
Domain	**Diabetes** No n=84	Yes n=56	**Congestive Heart Failure** No n=111	Yes n=29
Symptoms/Problems	79.5 (72.6-88.6)	71.6 (61.4-87.5)*	79.5 (68.2-88.6)	75.0 (59.1-93.2)
Effects of Kidney Disease	84.4 (68.8-90.6)	71.9(59.4-87.5)**	81.3 (68.8-90.6)	81.3 (57.8-90.6)
Burden of Kidney Disease	75.0 (50.0-87.5)	68.8 (37.5-87.5)	71.9 (43.8-87.5)	65.6 (40.6-93.8)
Overall Health	60.0 (50.0-70.0)	50.0 (40.0-70.0)	60.0 (50.0-70.0)	60.0 (40.0-70.0)
Physical Functioning	75.0 (43.8-90.0)	50.0 (20.0-75.0)‡	75.0 (40.0-85.0)	35.0 (15.0-60.0)‡
Pain	67.5 (45.0-90.0)	57.5 (45.0-77.5)	67.5 (45.0-90.0)	72.5 (45.0-88.8)
General Health	40.0 (30.0-55.0)	40.0 (27.5-50.0)	40.0 (30.0-50.0)	40.0 (25.0-50.0)
Energy/Fatigue	55.0 (35.0-70.0)	45.0 (30.0-65.0)	50.0 (35.0-65.0)	42.5 (27.5-60.0)
SF36PCS	38.3±10.2	32.0±10.5**	37.0±10.9	31.2±8.6*
SF36MCS	50.2±9.0	50.0±11.0	50.2±9.4	49.8±11.2

Values expressed as median (interquartile range) for skewed variables and mean±standard deviation for normally distributed variables. *, p<0.05; **, p<0.01; ‡, p<0.001. SF36PCS=Short form 36 Physical component summary, SF36MCS=Short form 36 Mental component summary. Modified from Hakamäki et al, 2021 (I).

5.1.4 HRQoL, Mortality and Kidney Disease Progression

At the end of follow-up, 33 (24%) patients had died and 107 (76%) had initiated RRT. Of the 33 patients who died, 73% had started RRT before death. 12 (36%) patients died of CV causes.

PCS remained an independent predictor of all-cause mortality (HR 0.96 [95% CI 0.92–0.99, p = 0.03]) when multivariable Cox proportional hazards model with age, diabetes and BMI as covariates was applied. The association of PCS with CV mortality did not quite reach statistical significance (HR 0.95 [95% CI 0.89–1.00, p = 0.056]), probably due to the small number of events. There was no association between MCS and mortality.

Neither PCS nor MCS was associated with kidney disease progression to initiation of RRT or change in eGFR during follow-up.

5.2 Evolution of Quality of Life in Advanced CKD Patients Transitioning to Dialysis and Transplantation

Study II investigated the change in HRQoL over time, as the majority of participants initiated RRT. One hundred patients with both baseline and follow-up data on HRQoL were included in this study. Figure 3 shows a flowchart of the study; Table 4 shows the study population's baseline characteristics. The median follow-up was 33 months (range 12-85 months). More than two thirds of the participants (68%) were receiving RRT at the time of the follow-up HRQoL assessment. 30 participants (30%) had initiated HD, whereas 19 (19%) had received a kidney transplant and 19 (19%) were on PD. 39 (39%) of the participants were women. The median age was 65 (53-74) years. None were receiving RRT at baseline, while median eGFR was 12 (IQR 11-15) ml/min/1.73 m^2. Participants receiving transplantation did not differ from those who were on HD, PD or still in predialysis care at the end of follow-up, in prevalence of smoking, AF, CAD, DM or gender distribution. BMI, eGFR and blood pressure were also similar, but those still in predialysis care at the end of follow-up were older than the kidney transplant recipients (KTRs). Baseline HRQoL was similar in all groups, except the SF-36 domain "Physical Functioning" differed significantly in favour of the transplantation group compared to those starting HD during follow-up. The median time to the second HRQoL assessment in KTRs was 40 (35-66) months. This was longer than in those that were on HD (33 [19-42] months, p=0.04), on PD (24 [17-40] months, p=0.01), and not yet receiving RRT (29 [14-40] months, p=0.01). The median time period from transplantation to second HRQoL assessment was 17 (7-40) months in KTRs.

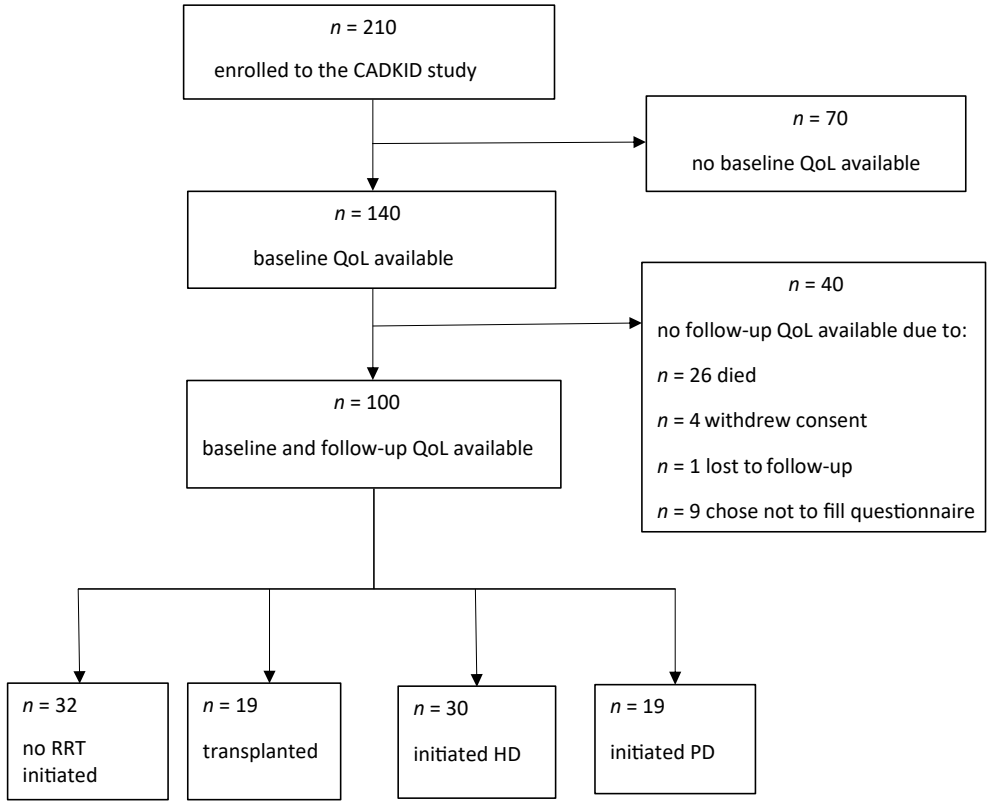


Figure 3. Flowchart of the study. Reprinted with permission from Hakamäki et al, 2022 (II). QoL = Quality of Life, RRT = Renal Replacement Therapy, HD = Hemodialysis, PD = Peritoneal Dialysis.

Table 4. Baseline Characteristics of the study population. Values are expressed as mean ± standard deviation for normally distributed variables and median (interquartile range) for skewed variables. Modified from Hakamäki et al, 2022 (II).

	All patients (n=100)
Age (years)	65 (53-74)
Smoker [n (%)]	6 (6)
Atrial Fibrillation [n (%)]	16 (16)
Coronary Artery Disease [n (%)]	8 (8)
Diabetes Mellitus [n (%)]	35 (35)
Body Mass Index (kg/m^2)	27.8 (24.3-30.6)
Systolic Blood Pressure (mmHg)	148 (135-161)
Diastolic Blood Pressure (mmHg)	80 (71-89)
Estimated Glomerular Filtration Rate (ml/min)	12 (11-15)
Biochemical Parameters	
Hemoglobin (g/l)	116 (108-123)
Creatinine (micromol/l)	393±95
Urea (mmol/l)	21.8±5.7
Potassium (mmol/l)	4.3±0.45
Sodium (mmol/l)	142 (140-144)
Ionized Calcium (mmol/l)	1.21±0.06
Phosphate (mmol/l)	1.41±0.28
Plasma Albumin (g/l)	35.5±3.8
C-reactive protein (mg/l)	2 (1-4)
Ferritin (microg/l)	250±181
Transferrin saturation (%)	24.9±8.5
Parathyroid stimulating hormone (ng/l)	174 (125-287)
Plasma Glucose (mmol/l)	5.6 (5.2-6.4)
HbA1c (%)	5.4 (5.0-5.8)
Total Cholesterol (mmol/l)	4.4 (3.5-4.9)
LDL Cholesterol (mmol/l)	2.2 (1.6-2.9)
Triglycerides (mmol/l)	1.5 (1.2-2.1)
pH	7.39 (7.36-7.42)
Bicarbonate (mmol/l)	22.6±3.0
Echocardiographic Parameters	
Left Ventricular Ejection Fraction (%)	65 (61-69)
Left Ventricular End-Diastolic Diameter (mm)	53.7±5.6
E/A ratio	0.93±0.34
Left Ventricular Mass Index (g/m^2)	98 (85-115)

5.2.1 Correlations of Change in HRQoL and Mean Laboratory and Echocardiographic Parameters

The change from baseline to follow-up HRQoL domain scores (delta domain scores) was examined and the means of biochemical and echocardiographic parameters were used.

Plasma albumin was associated with many delta domain scores, both kidney disease-specific and generic. “Symptoms/Problems”, “Effects of Kidney Disease” and “Overall Health” were associated with plasma albumin ($r = 0.28$, $p = 0.005$, $r = 0.27$, $p = 0.008$ and $r = 0.20$, $p = 0.049$, respectively). Delta SF-36 domains “Pain”, “General Health” and “Energy/Fatigue” ($r = 0.22$, $p = 0.03$, $r = 0.23$, $p = 0.02$ and $r = 0.24$, $p = 0.02$, respectively) showed similar positive associations.

Total cholesterol was associated with delta scores of “Symptoms/Problems”, “Effects of Kidney disease” and “Cognitive Function” ($r = 0.30$, $p = 0.004$, $r = 0.24$, $p = 0.03$ and $r = 0.25$, $p = 0.02$) as well as generic MCS and “Emotional Well-being” ($r = 0.26$, $p = 0.02$ and $r = 0.22$, $p = 0.04$, respectively) domains. There was an association between triglycerides and delta scores of kidney disease-specific domains “Symptoms/Problems” and “Work Status” ($r = 0.22$, $p = 0.04$ and $r = 0.29$, $p = 0.006$, respectively). Associations were also found between triglycerides and following delta scores of generic domains: MCS, “Emotional Well-being” and “Energy/Fatigue” ($r = 0.32$, $p = 0.004$, $r= 0.34$, $p = 0.001$ and $r = 0.22$, $p = 0.04$, respectively).

Other associations of interest included the inverse association of CRP with the delta score of the “Overall Health” domain ($r = −0.24$, $p = 0.02$). Hemoglobin was positively associated with the delta score of the “Work Status” domain, while urea showed an inverse association ($r = 0.24$, $p = 0.02$ and $r = −0.20$, $p = 0.049$).

Mean LVEF was associated with the delta score of the “Overall Health” ($r = 0.22$, $p = 0.04$) and PCS ($r = 0.27$, $p = 0.02$) domains.

Mean serum albumin remained a significant independent explanatory variable for delta scores of “Symptoms/Problems” and “Effects of Kidney Disease” ($\beta = 0.92$, $p = 0.03$ and $\beta = 1.63$, $p = 0.002$, respectively) in the multivariable models. The LVEF and delta score of PCS were also significantly associated in the multivariable model $\beta = 0.45$, $p = 0.004$).

5.2.2 Changes in HRQoL Domains Within RRT Groups

In KTR group, there was improvement in generic “General Health” domain score (baseline: 38.9 ± 15.0 vs. follow-up: 60.8 ± 16.3, $p = 0.0005$) and several kidney disease-specific domain scores: “Symptoms/Problems” (baseline: 74.9 ± 16.6 vs. follow-up: 84.0 ± 10.3, $p = 0.01$), “Effects of Kidney Disease” (baseline: 74.9 ± 18.7 vs. follow-up: 83.9 ± 16.6, $p = 0.04$), “Burden of Kidney Disease” (baseline: $57.9 \pm$

24.6 vs. follow-up: 79.6 ± 17.7, p = 0.0006) and "Overall Health" (baseline: 60 [30–70] vs. follow-up: 70 [70–80], p = 0.002).

The "Effects of Kidney Disease" score was significantly lower after initiation of dialysis (HD or PD) (baseline: 73.9 ± 19.5 vs. follow-up: 65.6 ± 16.9, p = 0.02 for HD and baseline: 77.3 ± 14.9 vs. follow-up: 64.2 ± 20.5, p = 0.04 for PD). A similar change was observed for the "Burden of Kidney Disease" score that was significantly lower after initiation of HD (baseline: 63.3 ± 25.6 vs. follow-up: 40.0 ± 26.4, p = 0.0001); however, the change was not quite statistically significant after initiation of PD (baseline: 65.3 ± 31.1 vs. follow-up: 46.4 ± 25.8, p = 0.06). There was no significant change in any of the domains in the group that remained in predialysis care during the entire follow-up. Notably, PCS and MCS did not change significantly in any of the groups.

5.2.3 Changes in HRQoL Domains Between RRT Modalities

The delta scores of the "Burden of Kidney Disease" and "General Health" domains differed significantly for the better in the transplanted group compared to PD (p = 0.0005 and p = 0.03, respectively), HD (p < 0.0001 and p = 0.007, respectively) and those remaining in predialysis care (p = 0.009 and p = 0.003, respectively). The transplant group also showed a significantly better delta score of "Effects of Kidney Disease" compared to both dialysis groups (p = 0.004 for the HD group and p = 0.002 for the PD group). The delta score of "Overall Health" was better among the KTRs than the HD group (p=0.01) or those remaining in predialysis care (p=0.02). The delta "Cognitive Function" in the KTRs was better than the PD group (p=0.008). There were no significant differences in the change of the domain scores between those who started HD and those who started PD. However, those continuing in predialysis care fared better than the HD group in the delta "Burden of Kidney Disease" score (p=0.03). The delta score of PCS indicated numerically the most change for the better in the KTR group, but the difference compared to other groups was not statistically significant.

5.2.4 Change in PCS Score, Mortality and Major Adverse Cardiovascular Events

There was no significant association between the delta PCS score and major adverse cardiovascular events in the Univariate Cox Proportional Hazards Models (HR = 1.011 [95% CI: 0.967–1.057], p = 0.38). Mortality was not associated with the delta PCS score (HR 0.973 [95% CI: 0.916–1.034], p = 0.38).

5.3 Cardiovascular Determinants of Mortality in Advanced Chronic Kidney Disease

Study III studied the determinants of mortality. Lateral lumbar radiograph and stress echocardiography were performed at baseline for 174 participants and vascular ultrasound studies for 156 participants. Mean follow-up time was 42 ± 17 months and mean age was 61 ± 14 years. 54 (31%) were women. Median eGFR was 12 (11-15) ml/min/1.73 m^2. 36 (21%) participants died during follow-up, three of them during the first 365 days of follow-up. Mean time to death was 835 ± 372 days. 21 (12%) patients had a prior CAD diagnosis and 75 (43%) were diabetics. Dialysis was initiated during follow-up for 139 (80%) participants. 59 (34%) were transplanted. Two of the transplanted participants died during follow-up, whereas 28 (78%) of those deceased during follow-up were on dialysis treatment.

5.3.1 Causes of Death

Of the 36 deaths, 17 (47%) were of cardiovascular causes. Malignancy was the second most common cause of death, 8 cases (22%), followed by infectious causes (5 cases, 14%). The remaining deaths were caused by gastrointestinal causes (2 cases, 6%), trauma (2 cases, 6%) and one death each (3%), was attributed to pulmonary and urinary causes.

5.3.2 Clinical Course of Participants and Mortality

There was no significant difference in mortality between the patients who remained in predialysis care during the entire follow-up period and those who started dialysis (PD or HD) (23.5% vs. 32.1%, p=0.36). Patients who started PD and those who started HD had no difference in mortality (27.8% vs. 35.6%, p=0.46). The KTR group had lower mortality, 3.4%. The difference was significant compared to all the other groups.

5.3.3 Predictors of Mortality

The Univariable Cox Proportional Hazards Models identified 15 significant predictors of all-cause mortality. These included the demographics male sex and age, comorbidities diabetes and CAD. The laboratory parameters with significance in univariable models were TnT, proBNP and low albumin, whereas the significant echocardiographic parameters were left ventricular end-diastolic diameter, global longitudinal strain, E/A ratio and E/e′ ratio. In addition, AAC, carotid IMT, low diastolic blood pressure and low WMAX were associated with all-cause mortality.

Initiating HD or PD during follow-up was not associated with mortality (HR: 0.62 [95% CI: 0.28–1.38], p = 0.24).

The multivariable models were adjusted for age, sex, and CAD. As we added one variable of interest in each respective model, we recognized six significant predictors of mortality (Table 5). The biochemical parameters TnT (HR: 1.81 [95% CI: 1.16–2.82], p= 0.009), proBNP (HR: 2.07 [95% CI: 1.42–3.01], p<0.001) and albumin (HR: 0.61 [95% CI: 0.41–0.91], p= 0.01) remained significant, as well as the E/e' ratio of echocardiography (HR: 1.73 [95% CI: 1.10–2.72], p= 0.02), the AAC score (HR: 1.75 [95% CI: 1.25–2.43], p<0.001) and the ergometric performance measured by Wmax (HR: 0.40 [95% CI: 0.25–0.65], p<0.001). Carotid IMT lost significance after an outlier value (atherosclerotic plaque) was deleted (HR: 1.23 [95% CI: 0.85–1.78], p = 0.28). When 125 patients with baseline eGFR ≤15 ml/min/1.73 m^2 were analysed separately, leaving out the CKD stage G4 patients, E/e' ratio lost significance as an independent determinant of mortality in multivariable analysis (HR: 1.56 [95% CI: 0.87–2.78], p = 0.14), while another five variables remained significant.

Table 5. Multivariable predictors of all-cause mortality. Modified from Lankinen et al, 2020 (III).

Variable	HR (95% CI) Adjusted for age, sex and CAD	p-value
Troponin T	1.81 (1.16–2.82)	0.009
proBNP	2.07 (1.42–3.01)	<0.001
Wmax	0.40 (0.25–0.65)	<0.001
AAC score	1.75 (1.25–2.43)	<0.001
E/e' –ratio	1.73 (1.10–2.72)	0.02
Albumin	0.61 (0.41–0.91)	0.01

5.4 Incidence and Prevalence of AF and Its Determinants in Advanced CKD

We investigated the prevalence and incidence of AF in advanced CKD in study IV. Furthermore, factors associated with the incidence of AF were studied. In this study, all 210 participants enrolled in the CADKID study were included in the analyses regarding the epidemiology of AF. The patients' mean age was 62 years and eGFR 12.8 ml/min/1.73 m^2. 73 (35%) were women. 35 (17%) had a previous diagnosis of CAD and 94 (45%) were diabetics. Transthoracic echocardiography was performed at the beginning of the study.

5.4.1 Prevalence of AF

41 (19.5%) of the 210 participants had AF already at baseline of the study. The mean duration of AF was 76 months. Participants without prevalent AF were younger and had fewer comorbidities than those with an AF diagnosis. CAD and CHF were more common in participants with prior AF. We found an association in the univariate logistic regression models between previous AF and age, CAD, CHD as well as echocardiographic parameters LVEF, left atrial diameter and LAVI. Multivariate logistic regression analysis showed independent associations between prevalent AF and age > 60 years (OR 9.63, [95% CI: 2.17– 42.80], $p < 0.01$) and LAVI > 30 ml/m^2 (OR 4.98, [95% CI: 1.01–22.73], $p = 0.04$).

5.4.2 Incidence of AF

Median follow-up time was 46 [IQR 27] months. New-onset AF was diagnosed in 33 of the 169 (19.5%) participants without diagnosis of AF at the beginning of the study. Thus, the AF incidence rate in this study was 69.9 per 1000 person-years. The median follow-up period to AF diagnosis was 11 [IQR 26] months. The majority of the cases (28/33, 85%) were paroxysmal AF. 12 of the 33 participants with new-onset AF were not yet receiving RRT, whereas 11 were on HD, 8 on PD and two had a kidney transplant at the time of diagnosis. The median time to diagnosis of incident AF after dialysis initiation was 8 [IQR 28] months. Only two of the 33 participants with new-onset AF did not initiate dialysis during follow-up. The ten participants who started dialysis after the diagnosis of new-onset AF, the median time from diagnosis of AF to RRT initiation, was 0.5 [IQR 4.5] months.

5.4.3 Factors Associated with New-Onset AF

Participants with new-onset AF were older and had a higher BMI and a higher proportion of prior stroke and PAD. Their LVMI and LAVI were higher, the myocardium of their posterior wall and septum was thicker, their TnT was higher and both the total and the high-density lipoprotein cholesterol was lower.

Age, previous stroke, elevated TnT, proBNP, left atrial diameter and increased LAVI were associated with new-onset AF in the univariate Cox models. Elevated TnT >50 ng/l (HR 3.61, [95% CI: 1.55–8.37], $p < 0.01$) and increased LAVI >30 mL/m^2 (HR 4.82, [95% CI: 1.11–21.00], $p = 0.04$) remained as significant independent associations with incident AF.

6 Discussion

6.1 Health-Related Quality of Life Is Associated with Markers of Cardiac Disease and Mortality in Advanced Chronic Kidney Disease (I)

Chronic kidney disease, especially in advanced stages, has a marked negative effect on HRQoL.(4) Although HRQoL is a highly subjective perception of an individual's health over time, many studies have shown an association between HRQoL and hard endpoints. Porter et al. found an association between SF-36 composite scores and CKD progression and a composite of CKD progression / Death.(185) Tsai and coworkers reported an association between HRQoL measured by the World Health Organization Quality of Life-BREF and all-cause mortality. HRQoL was also associated with kidney disease progression in this study of non-dialysis CKD patients.(13) An association between HRQoL and mortality was found in a large study using KDQOL-36 as an HRQoL instrument, but no association was found between HRQoL and CKD progression.(14) An association of HRQoL with mortality but not with kidney disease progression was similarly found in a study with EQ-5D HRQoL instrument.(186)

The results of our study further corroborated the association between mortality and HRQoL in CKD patients described in the existing literature. The majority of the earlier studies have been done in the HD population. Most studies with a non-dialysis population have a broader eGFR range. Our results from a cohort of advanced CKD, mainly stage G5 not on dialysis, with a narrow eGFR range, add to the existing evidence. Furthermore, our study used a kidney disease-specific KDQOL-SF instrument, although the association between HRQOL and mortality was found using PCS, a generic summary score.

The association of HRQOL with CKD progression has been investigated in previous studies with mixed results. We did not find an association between PCS and kidney disease progression to RRT initiation in our study. The large study by Porter and coworkers using the KDQOL-based HRQoL instrument similarly found no such association.(14) It seems possible that the choice of HRQoL instrument may influence the detection of this association, although KDQOL-based instruments are

designed for use among CKD patients. The definition of kidney disease progression in the literature is also somewhat variable.

A quite uniform observation in the literature is the association between HRQoL and comorbidities. Mujais et al. noted inferior HRQoL in diabetics and patients with CHF and with previous MI in a population of CKD stage G3-G5 population.(164) A similar observation was made by Aggarwal and coworkers in a cohort of 200 CKD patients representing stages G1-G5. A lower HRQoL was present in diabetics and those with a previous diagnosis of CVD.(170) Our results in a population of mainly CKD stage G5 patients are in line with these results. Of note, AF was associated in our study with inferior HRQoL in both kidney disease-specific domains and the physical component summary PCS.

A novel observation in our study was the association between cardiac biomarkers and HRQoL in advanced CKD. TnT and proBNP were inversely associated with PCS: In multivariable regression analysis, both cardiac biomarkers were still significant as independent predictors for PCS. Prior literature concerning CKD patients has described an association between TnT and two SF-36 domains, namely "Physical Functioning" and "Energy/Fatigue" in new HD patients.(124) No association between cardiac biomarkers and PCS was detected in a small cohort of CKD stage G5 patients, mainly dialysis patients (75%). The only biochemical parameter showing association with PCS in this study was serum albumin.(145) Both TnT and proBNP have previously been linked to CV events and mortality in CKD patients.(191)

There is a scarcity of HRQoL studies with echocardiographic data available in the CKD population. We demonstrated a negative correlation of two echocardiographic parameters of diastolic function, E/A and E/e' with PCS. However, after adjusting for age, BMI and diabetes, E/A lost significance and E/e' ($p=0.07$) likewise. GLS, a subtle indicator of systolic dysfunction, was independently associated with PCS. There have been no previous reports linking echocardiographic parameters and physical aspects of HRQoL in the non-dialysis population with advanced CKD. A small study of CKD patients with a mean eGFR of 45 ml/min/1.73 m^2 found a surprising association between GLS and the mental component summary MCS. The authors speculated that this association was due to a lower energy level and less physical activity because of emotional reasons.(153) Our finding of an association between the systolic function of the left ventricle and the physical aspect of HRQoL seems more plausible. Both GLS and E/e' have been linked to mortality in the CKD population.(152,155)

The kidney disease-specific domains of the KDQOL-SF yielded limited results in this study. We found inverse associations with multiple domains and obesity, DM and AF. Of the biochemical parameters, phosphate was inversely associated with four domains, including sleep, which may indicate the role of phosphate as a cause

of some uremic symptoms, thus reflecting on the results of the kidney disease-specific domains. “Overall Health” is a domain consisting of a single item, namely a person’s own view of their health on a scale of 0-10. This is one of the kidney disease-specific domains, although one might challenge its nature as a specific domain, because CKD patients usually have comorbidities. “Overall Health” was associated with GLS and inversely associated with E/e’, TnT, BMI, LVMI and phosphate. Thus, it seems that a person’s own evaluation of the state of their health is linked to many parameters that reflect their cardiac and vascular health.

6.2 Evolution of Health-Related Quality of Life in Advanced Chronic Kidney Disease Patients Transitioning to Renal Replacement Therapy (II)

Longitudinal studies of HRQoL in CKD patients are few and mainly consist of HD populations. This is probably due to the more demanding setting requiring effort and time to collect follow-up data compared to cross-sectional studies. It is easier to collect follow-up data in an ICHD setting because patients usually visit a dialysis unit thrice weekly.

Our longitudinal HRQoL study (study II) population was enrolled in the study in the predialysis outpatient clinic, and during follow-up, a majority of the patients started to receive RRT of some modality. The vast majority of eventually transplanted patients started dialysis before receiving a transplant due to the previous national policy. Only 1% of the entire CADKID cohort received a pre-emptive kidney transplantation.

HRQoL was assessed in the beginning of the study in the study II population of 100 patients and was sought to be re-assessed in two years. In reality, the median time to the second HRQoL assessment was 33 months, i.e., longer than intended. This was partly due to the transplantation group in which the interval between HRQoL assessments was longest, with a median of 41 months. However, we wanted to study the transplant group after patients had fully recovered from their transplant operation and become accustomed to life as a transplant patient. The transient adverse effects of high-dose immunosuppressive medication during the early post-transplant period could also have an effect on HRQoL. Thus, the longer period between HRQoL assessments is justifiable.

Our study was unique in that it followed patients from predialysis care to different RRT modalities. Another feature of interest was the echocardiographic data that were available in contrast to the majority of HRQoL studies.

A more detailed review of the kidney-disease specific domains is helpful to put our results into context. “Symptoms/Problems” gives information on kidney disease-

related symptoms, such as nausea and lack of appetite, muscle pain and cramps, itchy and dry skin, shortness of breath, dizziness, numbness in limbs and tiredness. Additionally, patients on dialysis express their view on dialysis access problems.(192)

"Effects of Kidney Disease" deals with the bother caused by kidney disease in the patients' daily lives. Items include questions about dietary and fluid restriction, ability to work around the house and to travel as well as the effects on the patients' perception of their own appearance and sex life. The stress and worry caused by kidney disease and being dependent on medical personnel's support is also assessed.(192)

"Burden of Kidney Disease" concerns the interference of kidney disease in the patients' daily lives, the frustration it causes and the perception of how much time dealing with kidney disease consumes. The feeling of being a burden to one's own family is also assessed. The "Sleep" domain comprises four items. They assess the overall perception of one's sleep, being able to get enough sleep, having trouble staying awake during the daytime and finally waking up in the middle of the night and having trouble falling asleep again.(192)

The single item on "Overall Health" asks the patients to rate their health on a scale of 0-10, where 0 equals "as bad or worse than being dead" while 10 is "best possible" health.(192) The rest of the kidney disease-specific domains consist of 2-3 items and showed few associations in our study. The kidney disease-specific domains assess the symptoms, inconvenience and stress caused by CKD, so it is sensible that these domains improve after kidney transplantation.

Our main finding was that kidney transplantation improved HRQoL in the kidney disease-specific domains. Compared to the baseline, "Symptoms/Problems", "Effects of Kidney Disease", "Burden of Kidney Disease" and "Overall Health" improved after transplantation. The only generic SF-36 domain that improved was "General Health". A prospective study comparing HRQoL in dialysis and after transplantation previously had quite similar results, showing clinically relevant improvement in the same domains as in our study and "Work Status". The improvement observed in "Work Status" is likely due to the baseline HRQoL assessment during the dialysis phase in the latter study, as opposed to predialysis care in our study. No clinically significant improvement was observed in any of the generic SF-36 domains in the study by von der Lippe et al.(182)

The PCS of the SF-36 surprisingly did not significantly improve, although the numerical values were higher after transplantation. Besides statistical significance, another way to examine the change in quality of life over time is the concept of minimal clinically important difference (MCID). MCID can be defined as "the smallest difference in score in the domain of interest, which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and

excessive cost, a change in the patient's management".(193) SF-36 is one of the most commonly used HRQoL instruments; thus, the MCID for the domains is well defined. The MCID for CKD patients has not been defined, although it is generally accepted that there is no need to define MCID specifically for different populations, because the previous results among patients with a range of chronic diseases from cancer to chronic lung and heart disease have shown similar results.(194)

The difference in PCS scores of the transplant group at baseline and after transplantation in our study was 3.9, while the MCID in the SF-36 domains is generally 3-5.(194) Thus, there seemed to be meaningful improvement in PCS, although the difference was not statistically significant. The change in PCS did not meet the criteria of MCID in all the other groups.

No significant change in HRQoL was observed in those continuing in predialysis care throughout the follow-up period. This probably reflects the very slow progression of CKD in this group, because the median time between HRQoL assessments in this group was as long as 29 months. The median eGFR of 15 ml/min/1.73 m^2 in the beginning of the study was higher in this group than in other groups, but the difference was not statistically significant, and the baseline eGFR was still quite low.

Dialysis initiation led to inferior HRQoL in the "Effects of Kidney Disease" and "Burden of Kidney Disease" domains. This could reflect the bother and interference caused by frequent dialysis treatment in daily life. Fluid and diet restrictions become even more necessary as residual kidney function diminishes, restricting patients' lives, and dialysis makes traveling more difficult. However, there was no change in the "Symptoms/Problems" domain after dialysis initiation. Although dialysis treats uremic symptoms effectively, intradialytic blood pressure alterations and interdialytic volume changes might induce other symptoms. Additionally, in clinical practice, dialysis is initiated ideally before overt uremic symptoms develop. Dialysis initiation was associated with worse "Effects of Kidney Disease" and "Burden of Kidney Disease" domain scores in a prospective study by Seow and coworkers of elderly CKD stage G5 population with multiple comorbidities, but there was no significant association with the "Symptoms/Problems" score.(195) This is in line with our results. A small prospective study of 38 patients using the generic SF-36 questionnaire observed no statistically significant change in any of the domains during the first year after dialysis initiation compared to 0-1 months before starting dialysis. Half of the patients started PD and the other half started HD.(196) Similarly, no differences were found in the generic HRQoL domains in our study and the study by Seow et al. Kidney disease-specific HRQoL instruments seem to be able to observe these differences better.

KTx induced significantly better delta domain scores in multiple kidney disease-specific domains and the "General Health" domain when we analysed the change in

HRQoL during follow-up according to the RRT modalities. Notably, the delta "Burden of Kidney Disease" score was stable in the continued predialysis care group, whereas those who initiated HD had significantly more change for the worse. We found no differences in change in HRQoL between those who initiated HD or PD. A 2020 meta-analysis by Chuasuwan et al. found moderately better "Effects of Kidney Disease" and "Burden of Kidney Disease" scores in PD patients compared to HD patients, but the studies included were cross-sectional in nature; thus, selection and confounding biases may affect the results.(158)

Contrary to study I, we found no association between PCS and mortality in this study, which studies the change in PCS over time (delta PCS). Similarly, we found no association between delta PCS and MACE. The change in PCS may, understandably, be small after initiation of dialysis or even KTx, because these RRT methods only affect the kidney function, while comorbidities, for instance, remain the same. Similarly, the change in eGFR during follow-up was not associated with delta PCS, while a positive association was found with the change of the kidney disease-specific domains "Symptoms/Problems", "Effects of Kidney Disease" and "Burden of Kidney Disease".

Mean serum albumin during follow-up was associated with the change of the kidney disease-specific domains "Symptoms/Problems" and "Effects of Kidney Disease" in multivariable models. Serum albumin is strongly associated with mortality in CKD.(116) An association between serum albumin and SF-36 PCS and MCS has been previously described.(176) In addition to cardiac biomarkers in study I, serum albumin seems to be the biomarker reflecting the HRQoL of the CKD patients.

6.3 Cardiovascular Determinants of Mortality in Advanced CKD (III)

In study III, we investigated the cardiovascular parameters in the CADKID study population using a wide variety of methods, including biochemical values, carotid and femoral IMT, AAC score and stress ergometry combined with echocardiography. The association of these measures with mortality during follow-up was studied.

The main finding of our study was the association between cardiac biomarkers, echocardiographic parameters, AAC score and stress ergometry performance and all-cause mortality. In addition to these markers of cardiovascular health, serum albumin was linked to mortality.

The excess mortality observed in a majority of studies beginning from CKD stage G3 (eGFR <60 ml/min/1.73 m^2) is attributed mostly to cardiovascular causes. The traditional CV risk factors do not wholly explain this observation. For instance,

in studies of dialysis populations an inverse association exists between cholesterol levels and mortality. This is attributed to the inflammation and malnutrition often present in dialysis populations. However, in the absence of inflammation and/or malnutrition as assessed by IL-6, CRP and albumin levels, higher total cholesterol is also associated with higher all-cause mortality in dialysis patients.(197) Still, large-scale studies have failed to show any benefit of cholesterol-lowering therapy in the dialysis population.(80–82) This example of the complex relation of traditional risk factors and the prognosis of CKD patients, in addition to highlighting the role of non-traditional risk factors such as CKD-MBD and inflammation/malnutrition, underscores the importance of identifying the CKD patients at the highest mortality risk. A single intervention, e.g., statin therapy or phosphate lowering, is unlikely to significantly benefit these patients, so a multifaceted approach should be adopted to improve their prognosis.

The cardiac biomarkers, TnT and proBNP, were associated with all-cause mortality in our study, although more than one half of the deceased patients died of other than cardiovascular causes. Thus, cardiovascular comorbidity is also likely to contribute to deaths not attributed to CV causes. Shortly after the publication of our 2020 study, Wang et al. published a report from a CRIC cohort concerning cardiac biomarkers and mortality. Similar to our study, an elevated baseline proBNP and TnT were associated with all-cause mortality in this large cohort of 3664 CKD patients. Larger sample size allowed the CRIC investigators to detect an association between cardiac biomarkers and CV mortality as well. Kidney function in this study cohort was better than in our study, mean eGFR was 44 ml/min/1.73 m^2 and eGFR of all participants was >20 ml/min/1.73 m^2 at baseline.(122) Thus, our results and those of the CRIC cohort complement each other. Matsushita and coworkers previously showed in a study of an ARIC cohort that TnT and proBNP predict CVD in CKD patients better than kidney markers, such as cystatin C, and the association was actually stronger in those with CKD than in those without CKD.(198) A recent addition to the literature is a Swedish study in an elderly CKD stage G4-5 population, published in 2022, showing an association between serial TnT measurements and mortality risk in a population with similar kidney function to our study.(199)

Serum albumin is a strong predictor of mortality in CKD, as previously discussed. A recent retrospective study found an inverse association between serum albumin assessed three months before the start of RRT and the mortality rate 1 year after RRT initiation.(200) Our results confirm this association in a prospective setting, further confirming the association of low albumin and mortality in CKD.

The AAC score was independently associated with mortality in our study of CKD stage G4-5 patients. Previous studies have shown that AAC is associated with the combined endpoint of CV events and mortality in patients with earlier stages of CKD (131), and a meta-analysis concluded that the AAC score in dialysis patients is

associated with both all-cause mortality and CV events.(133) A recent publication concerning AAC in a large cohort of Chinese patients representing CKD stages G1-4 found an association between not only the AAC score and all-cause mortality but also CV events.(201) The results of the previous studies and our study show that the AAC score is a significant predictor of mortality across the entire CKD population.

CKD stage G2-5 patients' physical function decreases as kidney function declines.(202) The lower limbs are especially affected. Poorer Timed Up and Go–test result and slower gait speed are associated with mortality in CKD stage G2-4 patients.(142) Ting et al. observed an association between ergometric performance and all-cause mortality in a cohort of over 200 patients waitlisted for KTx. 70% of the patients received dialysis treatment.(144) The same observation was made by Sietsema and coworkers among 175 dialysis patients.(143) Our study contributed to these findings using Wmax as a measure of ergometric performance. We observed an independent association between Wmax and all-cause mortality in patients with advanced non-dialysis CKD.

Regular training improves exercise capacity in non-dialysis CKD and dialysis patients, but the effect on hard outcomes is unknown. The "Physical Functioning" domain of the SF-36 improved in dialysis patients.(146,203) Thus, exercise training programs could offer a way to achieve better HRQoL and possibly achieve even a better prognosis for the patients.

The E/e' measure of echocardiography was associated with mortality in our study. It is a measure of the left ventricular filling pressure and is used as a marker of diastolic dysfunction of the left ventricle. LVH, diabetes and reduced distensibility of the aorta are among the causes of elevated E/e'. The association of E/e' with mortality in both non-dialysis CKD and in the dialysis population has been described previously.(154,155) Our results further corroborate this association.

Femoral IMT was not associated with mortality in our study. We are unaware of any previous studies on the subject in CKD populations. Carotid IMT is a more-studied parameter of subclinical atherosclerosis. CKD stage G3-4 patients' cIMT was higher than that of control patients but lower than that of dialysis patients in a cross-sectional study.(204) cIMT was associated with a composite endpoint of CV events or death in approximately 200 participants in an RRI-CKD study with a mean eGFR of 29 ml/min/1.73 m^2.(205) cIMT was predictive of a similar endpoint in univariate analysis in a study on advanced CKD patients, most of whom were already on dialysis. However, after adjustments, the association was not significant.(137) Overall, cIMT seems to increase as CKD advances, but the results on the independent association of cIMT and mortality in the CKD population are inconclusive. A meta-analysis on the subject concluded that cIMT is associated with mortality in HD patients, although the finding was only barely significant. In non-dialysis patients a meta-analysis was not conducted due to a lack of studies.(136)

cIMT appeared to be a significant determinant of mortality in multivariate Cox models in our study, but significance was lost after an outlier caused by an atherosclerotic plaque was removed. This adds to the inconclusive and mixed results in the literature. Brachial artery FMD, a measure of endothelial dysfunction, was not associated with mortality in our study. It is possible that FMD did not have predictive value in our study because we mainly studied CKD stage G5 patients with a long history of kidney disease.

6.4 Epidemiology of Atrial Fibrillation in Advanced CKD and Factors Associated with Incidence and Prevalence of Atrial Fibrillation (IV)

The main finding in study IV was the association of elevated TnT and LAVI with new-onset AF. 19.5 % of the patients (41/210) in the CADKID cohort had a previous diagnosis of AF at the study's baseline. 19.5% of the remaining patients (33 patients) were diagnosed with new-onset AF during a median follow-up of 46 months. Overall, more than one third of the patients were diagnosed with AF at the end of the study. The prevalence of AF was markedly high in this cohort of advanced CKD patients.

The AF incidence rate was 69.9/1000 person-years in our study. The incidence of AF in CKD is known to be higher than in the general population.(206) For instance, compared to a population-based Rotterdam Study cohort, the incidence rate in our study was seven times higher despite the fact that the population in the latter study was older, with a mean age of 69 years.(44)

The prevalence of AF among HD patients was 26.5% in a cross-sectional VIVALDI study, a figure higher than in the beginning but lower than in the end of our study and overall comparable to our study. The prevalence of AF in this study was associated with age, sex, dialysis vintage, cancer and CV comorbidities.(51) Prevalent AF was independently associated with age over 60 years and LAVI >30 ml/m^2 in our study, whereas associations with CV comorbidities were present in the univariate models. The prevalence of AF in the CRIC study population of predialysis CKD patients (mean eGFR 44 ml/min/1.73 m^2) was 18%, and in addition to age, sex and CV comorbidities, smoking was independently associated with AF.(50) Kidney function was poorer and the prevalence of AF higher at baseline in our study.

A retrospective cross-sectional analysis of 1010 CKD patients, representing mainly stage G3-4, had echocardiographic data of approximately 600 patients. The prevalence of AF was 21.2%, similar to our own study. The left atrial diameter was among the significant independent measures associated with prevalent AF in this study.(48) We used LAVI, a more accurate measure of left atrial size. As a novel

finding, increased LAVI was associated with both prior and new-onset AF in our cohort of patients with advanced CKD.

The association of TnT and new-onset AF was assessed in a CRIC cohort of mild-to-moderate CKD. Baseline TnT was associated with new-onset AF during a median follow-up of 7.1 years. The incidence of AF was higher in the two highest quartiles of TnT compared to the lowest quartile.(125) Baseline TnT >50 ng/l was associated with new-onset AF in our study of patients with more advanced CKD. Thus, the association also seems to be accurate in more advanced CKD.

Recognizing the AF risk in CKD patients is important because AF is associated with CV events and mortality as well as kidney disease progression and inferior HRQoL.(54,173) Our study shows that the combination of elevated TnT and increased LAVI is able to recognize many of those patients at risk of developing new-onset AF. Echocardiography and TnT analysis are widely available measures. Our results suggest that measuring LAVI and TnT might be useful in this clinical setting. Echocardiography offers a vast amount of relevant information about patients' cardiac function besides LAVI and is part of routine clinical practice for patients with advanced CKD before initiation of RRT in many centers. Considering this, assessing LAVI and TnT would be easily adopted to practice without significant extra costs.

In addition to the published data, we assessed the predisposing or triggering conditions of AF in our material (Table 6). We found a triggering condition in 67% (22/33) of the new-onset AF cases. 1409 cases of new-onset AF were detected in the Framingham Heart Study. A predisposing factor was found in 31 % of the cases. The most common were cardiothoracic surgery (30%), infection (23%), non-cardiothoracic surgery (20%) and acute myocardial infarction (18%). Thus, half of the cases with a predisposing factor were attributed to surgery.(207) The most common predisposing factor was infection (50% of the cases where a triggering factor was detected) followed by surgery (23 %) and CHF (18 %) in our material on advanced CKD patients. 60% of the cases attributed to surgery were cardiothoracic surgery. Compared to the previous study, the proportion of infections as a triggering factor was higher and the proportion of surgery was lower. This is an interesting observation, because data are scarce on AF triggering factors in the CKD population.

However, the HD procedure is known to be a triggering event for AF. A small study of HD and PD patients with an implantable cardiac defibrillator (ICD) were enrolled. An ICD was implanted without a primary or secondary indication, because the study was designed to evaluate ICDs in the prevention of SCD in dialysis patients. AF episodes were detected using the ICD's remote monitoring function. PD patients experienced fewer episodes of AF, which were not related to weekdays. The frequency of AF episodes in HD patients was three times higher on a dialysis day compared to non-dialysis days, and the risk of AF was 13 times higher during HD

than in the previous 7 hours. Compared to 7 hours after HD, the risk of AF during HD was about twice as high. The onset of AF episodes during the HD procedure increased by the hour, being highest during the last hour of dialysis. Higher ultrafiltration volume and lower dialysate potassium levels were associated with more frequent AF episodes.(208) These findings support the theories of intravascular volume change and change in potassium levels during HD as the factors predisposing to AF episodes. The first detected event of AF in our study was attributed to initiation of HD in 9% of the patients.

Table 6. Predisposing circumstances at the time of detection of the new-onset AF episodes.

New-onset AF cases	Trigger	Care	Other
11	Infection	Hospitalised	
5	Surgery	Hospitalised	2 CABGs, 1 TAVI, 1 laparotomy, 1 AV fistula
4	CHF	Hospitalised	
2	Initiation of HD	Hospitalised	1 case of uremic pericarditis
4	Unknown	Hospitalised	1 case of stroke, 1 case of amaurosis fugax, 1 case of acute vertigo, 1 case of pemphigoid
4	Unknown	Outpatient	Asymptomatic episodes of AF
3	Unknown	Outpatient	Symptomatic episodes of lone AF + ED contact

CABG = coronary artery bypass grafting; TAVI = transcatheter aortic valve implantation; AV fistula = arteriovenous fistula; CHF = congestive heart failure; HD = hemodialysis; AF = atrial fibrillation; ED = emergency department. Previously unpublished data.

6.5 Limitations and Strengths of the Study

Our study has some limitations. As with other observational studies, the determination of causality is not possible in the same manner as in randomized controlled trials. However, its prospective design is one of our study's strengths.

A study population of a minimum of 200 participants was targeted in the beginning of the recruitment, but no power calculations were performed. The study may be underpowered for some of the analyses made. The sample size was relatively small, but study patients were under vigorous follow-up and the data quality were high. The CADKID study is a single-centre study, which may affect the generalisability of our results.

Selection bias may affect the results in the HRQoL studies (Study I and Study II). HRQoL data were unavailable in 33% of the patients in study I, and the respondents were older and their eGFR was slightly lower than that of the participants with no HRQoL data available.

The number of respondents was lower in the longitudinal HRQoL study (Study II), but this was mainly due to mortality during follow-up. The HRQoL instrument used had more items than other widely used instruments. The KDQOL-SF provided versatile data on different aspects of HRQoL, including both generic and kidney disease-specific data. However, it may have affected the response rate negatively considering the amount of time needed to complete the questionnaire. Longitudinal HRQoL data, allowing patients to serve as their own controls, is a rare feature among studies concerning CKD patients, and having longitudinal echocardiographic data makes our study unique. The time between HRQoL assessments in the KTx group was 41 months, longer than in other groups. Successful transplantation possibly affected the patients' adherence to the study protocol. However, we believe that the results depict the true effect of KTx on HRQoL, considering our results are in line with a study using the same HRQoL instrument longitudinally in patients advancing from dialysis to KTx.(182) Furthermore, HRQoL was assessed a minimum of 7 months after KTx. This should reflect the true effect of KTx on HRQoL better than assessing HRQoL in the immediate post-operative period when recovery from the operation continues and the immunosuppressive medication dosage is high, possibly inflicting more side effects. Due to the limited number of participants, we could not analyse ICHD and HHD patients separately, although HHD patients' HRQoL is expected to be better. Similarly, comparing transplant waitlisted dialysis patients to transplanted patients was not possible due to sample size.

Among study III's strengths is the wide variety of methods used to assess the cardiovascular morbidity in the study cohort, but peak oxygen uptake, a measure associated with mortality in CKD (144), was not measured. However, we believe that Wmax reflects the true exercise capacity in our cohort, because the results are in line with a previous study among dialysis patients.(209) Vascular ultrasound data were missing in about one quarter of our cohort. This may have weakened the associations between cIMT, fIMT as well as FMD and mortality. The association between cIMT and mortality remained unclear. Additional data could have clarified the significance of this association.

A more accurate measure of left atrial size, LAVI, a body surface area corrected volume measure, was used in study IV, instead of the left atrial diameter. LAVI was assessed afterwards using ultrasound images saved on a hard disk drive. This led to missing data in 41 study subjects. However, data were missing completely at random, allowing the use of the complete case approach. Thus, it is likely that statistical power was reduced without causing bias to the results; therefore, we

consider our results valid. The prevalence and incidence of AF in our cohort was high. However, due to the often asymptomatic nature of AF, it is possible that true prevalence and incidence is even higher.

Table 7. Main results of the studies.

Study I	Association of HRQoL (PCS) with cardiac systolic function (GLS) and cardiac biomarkers (Troponin T and proBNP) Association between HRQoL (PCS) and mortality
Study II	Improvement of kidney disease-specific HRQoL after kidney transplantation but no change in most generic aspects of HRQoL Kidney transplantation improved kidney disease-specific HRQoL compared to dialysis or continued predialysis care
Study III	Cardiac biomarkers (Troponin T and proBNP), plasma albumin, stress ergometry performance, abdominal aortic calcification score and cardiac diastolic function (E/e') predict mortality
Study IV	Incidence and prevalence of atrial fibrillation is high Elevated Troponin T and increased left atrial volume index are associated with new-onset atrial fibrillation

HRQoL = Health-Related Quality of Life, PCS = Physical Component Summary of the Short Form 36, GLS = Global Longitudinal Strain, proBNP = N-terminal Pro-B-type Natriuretic Peptide, E/e' = Ratio Between Early Mitral Inflow Velocity and Mitral Annular Early Diastolic Velocity

7 Summary/Conclusions

This thesis aimed to elucidate the interrelations between quality of life, cardiovascular disease and mortality in patients with advanced CKD. Table 7 summarizes the studies' main results.

The association of HRQoL and mortality was further corroborated in patients with advanced CKD. There was no association between kidney disease progression and HRQoL in this cohort. There is an association between systolic function of the left ventricle measured by GLS as well as cardiac biomarkers TnT and proBNP and HRQoL. The association between echocardiographic assessment of systolic function of the left ventricle and HRQoL's physical aspect is a novel but plausible finding in CKD. Comorbidities, such as AF, are associated with an inferior HRQoL.

There is a lack of studies concerning longitudinal changes of HRQoL in CKD, and follow-up from predialysis care to different RRT modalities is unique. Kidney transplantation improves HRQoL compared to both dialysis modalities and continuing in predialysis care. The significant changes are limited to kidney disease-specific domains of HRQoL. Mean plasma albumin levels are associated with HRQoL. Kidney transplantation offers the best HRQoL for eligible CKD patients requiring RRT.

Exercise performance, echocardiographic measure of cardiac diastolic dysfunction E/e', AAC score, albumin and cardiac biomarkers TnT and proBNP are associated with mortality during follow-up in the advanced CKD population. These readily available markers can be used to assess patients' prognosis, and they may be helpful in guiding personalised treatment.

AF is associated with morbidity and mortality as well as an inferior HRQoL in CKD patients. The prevalence and incidence of AF is remarkably high in the advanced CKD population. The combination of increased LAVI and elevated TnT help to recognize patients most at risk of developing AF.

Cardiovascular disease, mortality and HRQoL are closely associated in CKD. Patients are able to assess their own mortality risk and convey the information to healthcare professionals by completing HRQoL questionnaires. Exercise performance, aortic calcifications, cardiac biomarkers and echocardiographic measures predict mortality; the latter two also predict the occurrence of AF. Therefore, the use of PROMs and other aforementioned tools in clinical practice may help us reach the ultimate goal of improving CKD patients' HRQoL and prognosis.

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