From DEPARTMENT OF CLINICAL SCIENCE,
INTERVENTION AND TECHNOLOGY, CLINTEC
DIVISION OF RENAL MEDICINE

Karolinska Institutet, Stockholm, Sweden

RENAL FUNCTION DECLINE AND OPTIMIZED PLANNING FOR KIDNEY REPLACEMENT THERAPY

Ulrika Hahn Lundström

Karolinska Institutet

Stockholm 2022

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2022

ISBN 978-91-8016-602-7
Cover illustration: Design by Dr. John Sandberg, access- and transplant surgeon

RENAL FUNCTION DECLINE AND OPTIMIZED PLANNING FOR KIDNEY REPLACEMENT THERAPY
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Ulrika Hahn Lundström

The thesis will be defended in public in the Rolf Luft Auditorium, L1:00 CMM Karolinska University Hospital, June 10, 2022 at 9:00.

Principal Supervisor:
Associate Professor Marie Evans
Karolinska Institutet
Department of Clinical Science, Intervention and Technology
Division of Renal Medicine

Co-supervisor(s):
Professor Ulf Hedin
Karolinska Institutet
Department of Molecular Medicine and Surgery
Division of Vascular Surgery

Professor Juan Jesus Carrero
Karolinska Institutet
Department of Medical Epidemiology and Biostatistics

Professor Peter Stenvinkel
Department of Clinical Science, Intervention and Technology
Division of Renal Medicine

Opponent:
Professor Björn Odvar Eriksen
UiT The Arctic University of Norway
Institute of Clinical Medicine, Metabolic and Renal Research Group

Examination Board:
Associate Professor Sandra Eloranta
Karolinska Institutet
Department of Medicine
Division of Clinical Epidemiology

Associate Professor Naomi Clyne
Lund University
Department of Clinical Sciences
Division of Nephrology

Professor Håkan Pärsson University of Linköping Department of Biomedicine and Clinical Sciences
Division of Surgery, Orthopedics and Oncology

Till min älskade familj.

POPULAR SCIENCE SUMMARY OF THE THESIS

Chronic kidney disease (CKD) is a common, but silent condition that increases with age. My thesis studies the kidney progression rate, its influence on prognosis, planning for Kidney Replacement Therapy (KRT), dialysis accesses and survival. KRT include transplantation, dialysis or conservative care. Compare to downhill skiing, where slope and speed correlate to both the ride and the approach to the lift area. With predialysis information the patient develops an increased understanding and participation in their own care. This shared decision-making provides a personalized care, with future treatment choices based on individual values and conditions. In younger CKD patients, kidney transplantation and self-dialysis often improve the prognosis and survival. However, in elderly patients with more diseases, conservative care without dialysis may provide increased life quality. The goal is "The right access for the right patient at the right time and for the right reason." Research on the natural course and prognosis of kidney disease is important to offer our patients the best possible care.

Study I examined the influence of progression rate, age and kidney function on prognosis, risk of KRT and survival. Previous studies; in Italy the risk for KRT prevailed, regardless of age. In American veterans after a certain age, the risk of death outweighed the risk of dialysis. We found that fast progression rate increased the risk for KRT. Especially if the patients are younger, have low renal function or diabetes.

Study II examined if arteriovenous (AV) access creation could influence the progression rate. Two previous studies associated AV access creation for hemodialysis to reduced progression, their hypothesis involved the blood vessel wall. We compared patients who received accesses for hemo- or peritoneal dialysis (PD). The PD access in the abdominal wall has no blood vessel wall contact whereas the hemodialysis access has. All patients in our study received the same pre-dialysis care. We found access creation was associated to slower progression rate, with no significant differences between the two types of accesses.

Study III examined hemodialysis patients with AV accesses thrombosis and compared open surgery to endovascular intervention, via the blood stream. The outcome was access survival, this is important since the AV access is considered the lifeline of the hemodialysis patient. Previous studies and guidelines offer no consensus. In our study endovascular thrombosis intervention was associated to improved access survival, particularly in younger patients, women and in forearm accesses.

Study IV examined a risk model, the Kidney Failure Risk Equation, (KFRE). We studied the development and role of KFRE to optimize access creation. The goal is to start dialysis in a planned functioning access since acute accesses have worse prognosis. The AV access needs time and often interventions to develop. The timing is crucial; late access creation is a time jeopardy, whereas early access creation increases the risk for an access never used. A KFRE >40% threshold for dialysis in two years has been proposed by others, but never studied in reality. In our results, using a KFRE>40% threshold for surgery increased the chance of hemodialysis start in a planned functioning access. The majority of all patients initiated dialysis within a year from KFRE>40%.

We used data from the Swedish Renal Registry (SRR), the Swedish Renal Registry- Chronic Kidney Disease (SRR-CKD), the Swedish Renal Registry-Access (SRR-Access) and the Stockholm CREAtinine Measurements, (SCREAM) for the studies included in this thesis. SRR is our national registry for patients in KRT whereas SRR-CKD includes patients in out-patient nephrology care. SRR-Access contains data on each individual dialysis access. The SCREAM contains data on all Stockholm inhabitants where creatinine ever was measured, linked to several other databases. We used STATA, for statistical calculations.

In summary, an individualized predialysis care considering the kidney progression rate and age is important to optimize the planning for future care. We found no evidence of a specific effect of AV access surgery on the kidney progression rate, which may open up for alternative hypotheses. Endovascular methods for thrombosis intervention increased the proportion of patients with a functioning AV access at 3-6 months. KFRE>40% could be a valuable tool to improve the share of patients starting hemodialysis in a functioning access. KFRE>40% may serve as a flag that the patient enters the last lap of the predialysis race, time for action and planning. Altogether our results emphasizes that predialysis personalized care and close team collaboration may improve the CKD prognosis, and hopefully also the quality of life for our patients.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Kronisk njursvikt är en tyst folksjukdom som blir allt vanligare med ökande ålder. Min avhandling studerar hur njurens försämringstakt inverkar på prognos, planering för njurersättande behandling och överlevnad. I njurersättande behandling ingår transplantation, dialys eller konservativ vård. Man kan jämföra med utförsåkning, hur lutning och hastighet påverkar både åkning och hur det ska gå. Med predialysinformation får patienten mer kunskap och delaktighet i sin vård. Ett delat beslutfattande medför en mer personanpassad vård, där valet av framtida behandling baseras på individens egna värderingar och förutsättningar. Hos yngre patienter kan njurtransplantation och självdialys förbättra prognos och överlevnad. Däremot hos äldre patienter med ytterligare sjukdomar kan en konservativ vård, medföra en ökad livskvalitet. Målet är ”rätt access för rätt patient, vid rätt tidpunkt och av rätt anledning.” Forskningen om njursjukdomens naturalförlopp och prognos är viktig för att kunna erbjuda våra patienter bästa möjliga vård.

Studie I undersökte hur försämringstakt, ålder och njurfunktion inverkar på prognos, risk för njurersättande behandling och överlevnad. Tidigare studier; i Italien övervägde risken för dialysbehandling, oavsett ålder. Hos amerikanska krigsveteraner efter en viss ålder övervägde istället risken för död. I våra resultat fann vi att snabb försämringstakt ökade risken för njurersättande behandling, speciellt hos yngre patienter, med låg njurfunktion eller diabetes.
Studie II undersökte hur försämringstakten påverkas av en accessoperation. Två tidigare studier hade visat att arteriovenös (AV) accessoperation bromsar in försämringstakten, med hypotesen att faktorer från blodkärlsväggen inverkar. Vi jämförde patienter som accessopererats inför blod- eller peritonealdialys, (PD). PD- accessen i bukväggen saknar kontakt med blodkärlsväggen, emedan båda grupperna erhåller samma predialysvård. Vi fann att accessoperation bromsade in försämringstakten, vilken sorts access medförde däremot ingen signifikant skillnad.
Studie III undersökte bloddialyspatienter med trombos, stopp i AV accessen och jämförde öppen kirurgi med endovaskulär åtgärd, via blodbanan. Utfallet var accessöverlevnad, som är viktig då AV accessen anses vara dialyspatientens livlina. Tidigare studier och guidelines ger ingen konsensus. Våra resultat visade att endovaskulära åtgärder av trombosen ökade accessens överlevnad, speciellt hos yngre patienter, kvinnor och i underarmsaccesser.
Studie IV undersökte en riskanalysmodell, Kidney Failure Risk Equation KFRE, dess utveckling och roll i accessplanering. Målet är att starta dialys i en planerad fungerande access, då akutaccesser har sämre prognos. AV accessen behöver tid och ofta åtgärder för att utvecklas. Timingen är viktig, en sen accessoperation kan innebära tidsnöd, emedan en för tidig accessoperation ökar risken för att accessen aldrig används. En KFRE- risk på >40% för dialysstart inom två år har föreslagits, men aldrig studerats på verkliga patienter. Vi fann att om vi använde KFRE>40% som tröskel så ökade chansen för dialysstart i en planerad fungerande access och att många patienter startade dialys inom ett år från den gränsen.

Vi använde data från Svenskt Njurregister, (SRR), Svenskt Njurregister-kronisk njursvikt, (SRR-CKD), Svenska Accessregistret (SRR-Access) och Stockholm CREAtinine

Measurements, (SCREAM). SRR är vårt nationella register på patienter i njurersättande behandling och SRR-CKD innehåller patienter som följs på njurmedicinsk mottagning. SRR-Access innehåller data om varje dialysaccess. SCREAM innehåller data på personer i Stockholm där njurvärdet kreatinin kontrollerats och är kopplat till flera andra databaser. Statistiska beräkningar har vi gjort i STATA.

Sammanfattningsvis är en individuell predialysvård som tar hänsyn till njurarnas försämringstakt och patientens ålder viktigt för att optimera planeringen av framtida vård. Vi fann ingen specifik effekt av en AV accessoperation på försämringstakten, vilket kan öppna upp för andra förklaringsmodeller. Endovaskulär åtgärder vid access-stopp ökade andelen patienter med fungerande access efter 3–6 månader. KFRE>40% kan vara ett verktyg som bidrar öka andelen patienter som startar hemodialys i en fungerande access. KFRE>40% kan vara en varningsflagg att patientens sista varv på predialysracet inleds, dags för omedelbar planering och åtgärder. Slutligen betonar våra sammantagna resultat att en personlig predialysvård, med nära samarbete i teamet kan förbättra prognosen och förhoppnings även livskvaliteten hos våra patienter.

ABSTRACT

Chronic Kidney disease (CKD) is an increasing health problem world-wide, and the prevalence increases with age. CKD is a life-threatening condition, with high risk of cardiovascular disease and mortality. Patients with advanced CKD often need Kidney Replacement Therapy, (KRT), this includes transplantation, dialysis or conservative care. Education and follow-up of patients with advanced CKD is often referred to as predialysis care. This increases patient knowledge and enables more individualized treatment choices. Research on the natural course, and prognosis of CKD is necessary to be able to offer our patients best possible care. This thesis studies the influence of kidney progression rate on prognosis, planning for KRT, vascular access and patient survival.

All studies were observational cohort studies. Patients were included from the Swedish Renal Registry, (SRR), SRR-CKD, SRR-Access and Stockholm CREAtinin Measurement (SCREAM) during 2005-2020.

Study I described the impact of progression rate and age on the absolute risk for KRT and death. We used an unselected nephrology- referred CKD population, (n=8,771) with at least two creatinine measurements within a year. We used competing risk models and compared fast to slow progressors with regard to outcomes. Fast progression was associated to increased KRT risk in all ages and CKD stages, but the prognosis was affected by the age and eGFR of the patient.

Study II studied the progression rate following access creation, comparing Arteriovenous (AV) to peritoneal dialysis (PD) access placement in patients with severe CKD. Data were collected at 100 days before and after surgery, (n=744). We used linear mixed models with random intercept and slope. Access surgery was associated to a slower progression rate, but without any significant differences in AV compared to PD accesses. This study emphasizes the importance of predialysis care, but the need for dialysis remains the main determinant for access creation.

Study III compared the influence of open surgical versus endovascular intervention for AV access thrombosis on time to access abandonment and next intervention, (n=904). We also compared several categories of each intervention. The outcome; time to access abandonment were described in Kaplan-Mayer curves and compared with log-rank statistics. There was a statistically significant benefit of endovascular intervention on both short- and long-term access survival, albeit small in absolute terms

Study IV evaluated the use of Kidney Failure Risk Equation, (KFRE) versus eGFR15 as a threshold for optimized timing of AV access creation. We used cumulative incidences to describe the outcomes of KRT, death and test diagnostics. KFRE>40% had superior specificity and positive predictive value compared to eGFR15 and were superior to predict KRT initiation and death.

To summarize, an individualized predialysis care considering progression rate and age is important to optimize the plan for future care. We found no evidence of a specific effect of AV access creation on the eGFR decline, and endovascular methods for vascular access thrombosis were shown to increase the proportion of people with a functioning access after 3-6 months. The use of KFRE>40% could be a valuable tool to improve the proportion of patients starting hemodialysis with a working access.

LIST OF SCIENTIFIC PAPERS

I. HAHN LUNDSTRÖM ULRIKA, Alessandro Gasparini, Rino Bellocco, Abdul Rashid Qureshi, Juan-Jesus Carrero Marie Evans

Low renal replacement therapy incidence among slowly progressing elderly chronic kidney disease patients referred to nephrology care: an observational study.

BMC Nephrol. 2017 Feb 10;18(1):59.

II. HAHN LUNDSTRÖM ULRIKA, Ulf Hedin, Alessandro Gasparini, Fergus J. Caskey, Juan-Jesus Carrero, Marie Evans

Influence of Arterio Venous Access Placement on renal function decline.

Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association 2021;36:275-80.

III. HAHN LUNDSTRÖM ULRIKA, Gunilla Welander, Juan Jesus Carrero, Ulf Hedin, Marie Evans

Surgical versus endovascular intervention for vascular access thrombosis: a nationwide observational study

Nephrology, dialysis, transplantation: Manuscript accepted for publication Jan 25, 2022

IV. HAHN LUNDSTRÖM ULRIKA, Chava L. Ramspek, Friedo W. Dekker, Juan-Jesus Carrero, Ulf Hedin, Marie Evans

Kidney Failure Risk Equation for Arterio Venous access planning: a nationwide cohort study, in manuscript

Scientific papers not included in the thesis:

HAHN LUNDSTRÖM, U., et al., *Barriers and opportunities to increase PD incidence and prevalence: Lessons from a European Survey.* Perit Dial Int, 2021: p. 8968608211034988.

Xu, H., Lindholm, B.; HAHN LUNDSTROM, U.; et al., *Treatment practices and outcomes in incident peritoneal dialysis patients: the Swedish Renal Registry 2006-2015.* Clin Kidney J, 2021.14 (12): p. 2539-2547

van Eck van der Sluijs A, van Jaarsveld BC, Allen J, Altabas K, Béchade C, Bonenkamp AA, Burkhalter F, Clause AL, Corbett RW, Dekker FW, Eden G, François K, Gudmundsdottir H, HAHN LUNDSTRÖM U, de Laforcade L, Lambie M, Martin H, Pajek J, Panuccio V, Ros-Ruiz S, Steubl D, Vega A, Wojtaszek E, Davies SJ, Van Biesen W, Abrahams AC. *Assisted peritoneal dialysis across Europe: Practice variation and factors associated with availability*. Perit. Dial Int 2021; 41:533-541

CONTENTS

LIST OF ABBREVIATIONS

ACEi	Angiotensin Converting Enzyme Inhibitor
ACR	Albumine-creatinine ratio
ARB	Angiotensin Receptor Blocker
AV	Arterio Venous
AVF	Arterio Venous Fistula
AVG	Arterio Venous Graft
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CVC	Central Venous Catheter
CVD	Cardo Vascular Disease
ESA	Erythropoiesis-stimulating agents
ESKD	End Stage Kidney Disease
ESRD	End Stage Renal Disease
eGFR	Estimated Glomerular Filtration Rate
KDOQI	Kidney Disease Outcome Quality Initiative
KFRE	Kidney Failure Risk Equation
KRT	Kidney Replacement Therapy
MDRD	Modification of Diet in Renal Disease Study
mGFR	Measured Glomerular Filtration Rate
NDD	Non-Dialysis Dependent
OR	Odds Ratio
PD	Peritoneal Dialysis
PDC	Peritoneal Dialysis Catheter
ROC	Receiver Operator Characteristics
RRT	Renal Replacement Therapy
SCREAM	Stockholm CREAtinine Measurement
SRR	Swedish Renal Registry
SRR-Access	Swedish Renal Registry- Access
SRR-CKD	Swedish Renal Registry-Chronic Kidney Disease

1 INTRODUCTION

To be a nephrologist, meeting chronic kidney disease patients approaching end stage kidney disease, means working with terminally ill patients. The spectrum involves the younger patients with reduced kidney function, fast progression rate and high risk for end stage kidney disease. On the other end the elderly patients with low, but often stable kidney function for years. They rarely reach end stage kidney disease, however they are more prone to cardiovascular disease and mortality. Kidney replacement therapy includes dialysis, transplantation, or conservative care. The prior two are lifesaving treatments, whereas timely preparations are important to improve the prognosis and quality of life for all three treatment options. The progression rate and its interaction with age, prognosis and cardiovascular mortality is a new concept. My research is geared to offer our patients the best possible advice on available treatment options to optimize their care and quality of life.

2 LITERATURE REVIEW

2.1 CHRONIC KIDNEY DISEASE AND STAGES, A BRIEF BACKGROUND

Chronic Kidney Disease (CKD), the definition requires glomerular filtration rate (GFR) <60ml/min/1.73m² OR other structural or functional abnormalities persisting >3 months.[1] Markers of kidney damage are; albuminuria or urine sediment abnormalities, electrolyte disturbances due to tubular disorders, morphological/pathological signs or a history of kidney transplantation. Glomerular filtration rate, when estimated from calibrated serum creatinine and estimating equations is referred to as eGFR.

There are 5 stages of CKD based on GFR and albuminuria. The classification originates from the National Kidney Foundation-Kidney Disease Outcome Quality Initiative (NKF-KDOQI or KDOQI) from 2002.[2] The CKD definition was updated 2012 and proteinuria was added as a marker of kidney damage. Since albumin is the main urinary protein, the quantification measures the Albumin Creatinine Ratio (ACR), but the definition holds true for all proteinuria. The albuminuria categories in CKD are; A1 normal to mildly increased <3 mg/mmol, A2 moderately increased 3-30mg/mmol and A3 severely increased >30mg/mmol.[1]

CKD stage 1-2 means albuminuria and normal to slightly reduced GFR. CKD stage 3 is moderately reduced GFR 30-59 ml/min/1.73m² (stage 3a 45-59, 3b 30-44 ml/min/1.73 m²) and stage 4 is severely reduced GFR 15-29 ml/min/1.72 m². End Stage Kidney Disease (ESKD), stage 5, is very severely reduced kidney function, with or without dialysis, GFR <15 ml/min/1.73 m². CKD stage 3-5 are associated with several complications: fluid retention with hypertension and potential heart failure, inflammation, metabolic acidosis, anemia, disturbances in bone-mineral metabolism and malnutrition.[2]

2.2 METHODS FOR MEASUREMENT OF GLOMERULAR FILTRATION RATE

Measurements of kidney function are central in nephrology and in the classification of CKD. Inulin was the original gold standard GFR measurement from 1951. The inulin polysaccharide was injected intravenously and then measured in blood and urine after a certain time period. Today we often use Iohexol, a contrast agent for the measured GFR (mGFR).[3] Various equations have been used to calculate estimated GFR (eGFR) from creatinine over time; the Cockcroft-Gault formula calculated filtration with creatinine based on uncorrected Jaffe.[4] In the MDRD equation from Modification of Diet in Renal Disease, eGFR was standardized to body surface area (ml/min/1.73m²). The MDRD equation did not include body weight, whereas ethnicity and standardized creatinine were added in 2006.[5] In elderly patients with better eGFR, >60 ml/min/1.73m², the MDRD-eGFR is less reliable.[6] Then in 2009, the Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI) was developed, with less false positive CKD diagnoses and improved risk predictions.[7] The formula was recently updated to not include race, in CKD-EPI 2021.[8] In clinical practice

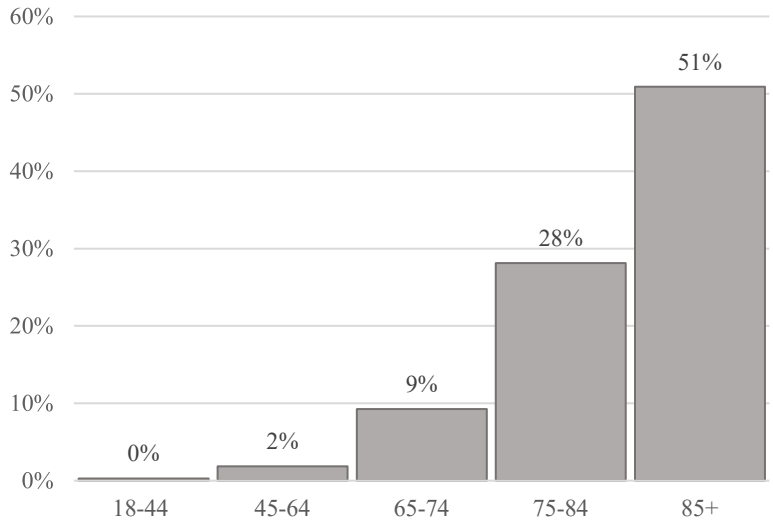
today we use eGFR from both creatinine and Cystatin C, or more often the average of the two. These are endogenous substances with different sources of errors, such as hydration status, muscle mass and medication.[9] Clinicians need to be aware of when to question the eGFR reliability and encourage the use of mGFR.[10] The eGFR methods are calculated in an average patient, therefore not as reliable in the elderly patients where low muscle mass, low meat intake, thyroid disease, corticosteroids and other medications are more frequent. Hence, the elderly patient experiences an increased risk of overestimation of eGFR from creatinine with subsequent overdosage of drugs with renal elimination.[11] In severe CKD the tubular secretion of P-cresol sulphate and other solutes may be reduced relatively more than the GFR indicates. According to recent research this may contribute to the increased uremic symptoms in patients approaching ESKD.[12]

2.3 CKD EPIDEMIOLOGY; PREVALENCE, INCIDENCE AND SEX

Prevalence, the occurrence of CKD in the population is increasing worldwide. In the United States it has stabilized, and about 14% of the population is reported to have CKD stage 1-4.[13] The Swedish CKD prevalence is lower, about 6% according to SCREAM. Some hypotheses for the difference are access and quality of primary health care, nephrology referral rates and less diabetes nephropathy in Sweden. [14, 15]

CKD is more common in the elderly, (Figure 1) in females and patients with diabetes, hypertension and cardiovascular disease. [14] Conversely hypertension/ renovascular disease, other specified kidney disease and diabetes are also the most common underlying diagnoses, of importance for the patient prognosis.[16]

Figure 1. Prevalence of CKD in the Stockholm region, stratified by age.



Adapted from Gasparini et al. NDT (2016) 31: 2086–2094

There were 15,189 patients with eGFR<30 included in the Swedish Renal Registry for CKD, (SRR-CKD) in 2020. They receive outpatient nephrology care; a majority is in CKD stage 4 and 38% women. Patients in kidney replacement therapy, (KRT) are increasing, to 10,300 patients in 2020. Most are kidney transplanted patients 6,200, whereas the number of dialysis patients 4,100 have stabilized during the last 5 years.[16] Of the prevalent dialysis population, the majority are in institutionalized hemodialysis, 3044 patients (75%), peritoneal dialysis is increasing to 912 patients (22%) and home hemodialysis in 117 patients (3%). In peritoneal dialysis, first described in 1923 the peritoneum, the lining of the abdomen is used to filter the blood.[17] The peritoneal- and home hemodialysis modalities are encouraged and referred to as selfcare- or home dialysis. The main diagnoses for KRT patients are glomerulonephritis, other specified renal diseases and diabetic nephropathy in decreasing order.[16]

Incidence refers to number of new patients per year, about 3,000 patients were added to the SRR-CKD in 2020. Their median age was 74 years and the median eGFR was 27ml/min/1.73m². The KRT incidence was 107/million/year in Sweden, as compared to the US of 386/million/year.[13] In Sweden 1,103 patients initiated active KRT, at median age 64 years and median eGFR of 6.4 ml/min/1.73m². The KRT incidence by modality; hemodialysis was initiated in 642 patients (58%), PD in 378 patients (34%) and kidney transplantations in 83 patients (7.5%). About 14% of patients in SRR-CKD died without initiating KRT.[18]

There are sex-differences in CKD, men experience more albuminuria, faster eGFR decline and increased cardiovascular mortality. Women are common in early CKD stages, more likely to get diagnosed, yet less referred to nephrology care than men.[19] with this in mind, possibly the referral decision is based on creatinine and not eGFR.[14] Today, there are 38% women in SRR-CKD and 35% in KRT. The KRT incidence rates are 6.4 and 8.0/100 person years for women and men respectively.[16] Elderly women choose or receive more conservative care and dialyses with less permanent accesses. Hypotheses include differences in oxidative stress, nitrogen metabolism and sex-hormones, combined with an unhealthier lifestyle.[19, 20]

2.4 RISKFACTORS AND PROGRESSION OF CKD

Etiology and early diagnosis of kidney disease is important for targeted treatment and prognosis. CKD care can be seen as a staircase; the first step is to identify individuals with increased risk, and the next step is to prevent CKD progression. The CKD progression is important for the CKD prognosis and mortality. The definition of CKD progression is drop of one GFR category, accompanied by >25% drop in eGFR.[1] In clinical studies doubling of creatinine is an often used endpoint, equal to -57% change in eGFR. Already more moderate annual changes of -30% eGFR decline over 2 years were associated to increased ESKD and mortality.[64] KDIGO define *rapid* progression as a yearly decline of >5 ml/min/1.73m².[65] Rapid eGFR-decline before KRT was associated to heart failure, decreased survival and

predicted mortality. [66, 67] The risk factor definition does not require a causal association. Several CKD risk factors are not causal, although they may reflect the severity of the disease.[18]

Various kidney diagnoses differ with regard to progression and prognosis. Patients with hypertension, diabetes or cardiovascular disease are certain risk groups where albuminuria, blood pressure and renal function require extra attention.

Blood pressure and albuminuria are the two most important factors for CKD progression. Antihypertensive treatment is more important in patients with extensive albuminuria according to the MDRD study.[21] The importance of the renin-angiotensin system (RAS) on reduced eGFR decline was first shown in the AASK trial.[22] Today albuminuria and hypertension are established risk factors. The KDIGO recommendation include ARB or ACE inhibitors, target systolic blood pressure <120 mmHg and limited sodium intake. [23]

Diabetes is another important risk factor, also for progression. In diabetes type II heart failure and CKD are the most frequent cardiorenal manifestations, also associated to increased mortality.[24] Studies have found prediabetes to have an independent role in the development of hyperfiltration and albuminuria.[25] A meta-analysis in diabetes type II associated an absolute HbA1c reduction of 0.9% to reduced risk for nephropathy and ESKD.[26] The KDIGO recommendation of target haemoglobinA1c, (HbA1c) is 53 mmol/mol (7%).[27] This need to be balanced to the increased risk for hypoglycemic episodes in CKD.

Recent trials found sodium-glucose co-transporter 2 (SGLT2) inhibitors associated to improve both cardiovascular and renal outcomes of reduced CKD progression and risk for KRT.[28] Through glucosuria with osmotic diuresis and natriuresis, they reduce glomerular hyperfiltration, weight and decrease albuminuria.[29]

Cardiovascular disease (CVD) and CKD are closely related, and already mild CKD predicts cardiovascular mortality. Proteinuria as a marker of kidney damage constitutes a significant risk factor for cardiovascular morbidity and mortality. For CVD there are both traditional risk factors; age, smoking, obesity, hypertension, and diabetes, as well as non-traditional factors; endothelial dysfunction, oxidative stress, vascular calcification, and inflammation.[30, 31] Hypoalbuminemia, protein energy wasting, and inflammation are strongly associated with progression and mortality in CKD.[32, 33] Future research involves epigenetics, genome changes in response to the environment, and their role in the pathogenetic pathways of cardiovascular risk factors in CKD.[30, 31] The CKD-Prognosis Consortium found the traditional cardiovascular risk factors remained to be prognostic also in patients with severely reduced eGFR, (CKD4+) In the patients with CKD4+ the leading cause of death was cardiovascular disease with heart failure. Further, when the CKD4+ patients experienced a CVD event or KRT they had an even higher risk of mortality.[34, 35]

Obesity and waist circumference are associated to increased risk for CKD, eGFR decline and mortality.[36] There is a physiological correlation between obesity, hyperfiltration and

albuminuria.[37] Previous studies found weight reduction associated to reduced albuminuria, further in high-risk groups bariatric surgery were associated with several years of CKD risk reduction.[38] In early CKD stages there is a U-shaped association between obesity and clinical outcome. This is referred to as the obesity paradox in CKD, where overweight to mildly obese patients with BMI 25-30 had superior clinical prognosis.[39] Possible explanations involve a protective nutritional reserve, comorbidity with short lifespan, or lower metabolic rate, less uremic waste products and improved tolerance to CKD morbidity.[39]

An overall healthy lifestyle with regular physical activity, non-smoking and BMI 25-30 kg/m² were associated to improved outcomes in the Chronic Renal Insufficiency cohort, (CRIC).[40] Smoking and low socio-economic status were associated to increased risk for CKD.[41, 42] We studied Uric Acid, (UA) and found high UA associated to mortality in CKD patients, especially in patients with high UA and early CKD.[43] The effect of UA lowering treatment is debated, larger studies did not favor treatment, suggesting a non-causal relationship.[44]

Protein restriction 0,6 g/kg bodyweight/day is recommended by KDOQI to reduce risk for ESKD.[42] Fruit, vegetables and moderate alcohol intake were associated to delayed progression.[43] Mediterranean diet, fruit and vegetables are recommended for lipid-lowering and reduced net acid production in guidelines.[42] A high net endogenous acid production (NEAP) as a measure of dietary acid load was associated to CKD progression.[44] Metabolic acidosis is an independent risk factor for CKD progression, and randomized studies on acidosis correction with bicarbonate reduced the risk of CKD progression and mortality.[45] Treatment of persistent mild anaemia was associated to reduced CKD progression.[46] Gut microflora dysbiosis may be linked to uremic toxins and increased risk for CVD.[47] Small studies associated colostomy to absence of uremic toxins, and prior appendectomy to inferior CKD prognosis.[48, 49]

2.5 CHRONIC KIDNEY DISEASE IN THE ELDERLY AND CONSERVATIVE CARE

CKD prevalence increases with age, it is debated whether CKD is a disease or part of normal aging. Normal aging includes reduced kidney volume, increased tubulointerstitial atrophy, glomerulosclerosis and fewer nephrons.[45] Also in the elderly low eGFR and albuminuria are associated to ESKD and mortality. This is the argument to keep the CKD definition age neutral, although the negative influence of CVD and diabetes diminishes with age.[46, 47] The prognostic role of risk factors; phosphate, albuminuria and anaemia still holds true in elderly patients.[46]

Age is associated to a slower progression rate and modifies the competing risk of ESKD or death with impact on the prognosis.[48] In Italy, ESKD exceeded the risk of death independently of eGFR in patients ≤60 years. The risk of death increased with age, but ESKD

was still the more frequent outcome.[46] To be compared to American war veterans, where the incidence of death was 5 times higher than the risk for ESKD.[48] All Italian patients experienced >1 year of nephrology care. In contrast to the American cohort; 26% had received <3 months, and one third had not experienced any nephrology care at all before start of KRT.[46, 48] Studies in elderly diabetic patients associated nephrology care to improved CKD prognosis and decreased mortality over time.[49]

A patient-centered approach is extra important in the frail elderly patient with multiple chronic conditions, and limited life expectancy. The potential survival advantage of KRT, was lost with high comorbidity, age ≥80 or impaired Activities of Daily Living (ADL).[50] KRT initiation was associated to ADL decline, cardiovascular events, and mortality. [51, 52] Conservative care can be an option when the CKD constitutes only a part of the total disease burden. Symptoms like fatigue, restless legs, low appetite, decreased mobility, sleep problems and dementia may worsen on dialysis and subsequently impair the quality of life. In conservative care, symptoms can be relieved with medication, diet, physiotherapy and psychosocial support. A recently suggested treatment goal was do no harm.[53] According to guidelines, counseling for KRT would ideally be risk-based, patient-centered, tailored to the cultural setting, psychosocial needs, mindful to health literacy and possible presence of cognitive impairment. Individual preferences of the patient need to be considered in counseling about treatment options and likely outcomes before dialysis initiation. [54]

2.6 THE HEMO- AND PERITONEAL DIALYSIS ACCESS AND VASCULAR ACCESS THROMBOSIS

In 1960 Scribner invented an AV access and Cimino, Brescia and Appel created the AV fistula in 1966. Since then, synthetic AV graft and the central venous catheter (CVC) have been added. The timing of the AV access creation is important, especially in the elderly were delayed access maturation may occur. The average time from AV fistula creation to develop is 3-4 months for an AV fistula, faster in grafts and within days for fast-cannulation grafts.[55] Late AV access creation increases the risk of dialysis start in a CVC, associated with inferior prognosis due to infections and mortality.[56-58] . Early access creation enables time for access maturation yet increases the probability of an access never used.[59]

The access decision has to be individualized; in older patients, women, and diabetics, AV grafts have comparable or better outcomes regarding fistula maturation, mortality and costs.[60] There is no survival difference for AV grafts or AV fistulas as the initial access in patients ≥80 years.[59]

Patient factors and selection bias affecting AVF placement is said to in part explain the survival benefit in AVF patients.[61] The CVC patients are often associated with later referrals, more acute illnesses and less pre-dialysis care.[57] When incident patients in CVC receive either AV graft /fistula or stay on CVC, the AV fistula strategy was superior in young, non-diabetic men. The AV graft strategy improved outcome especially in women with

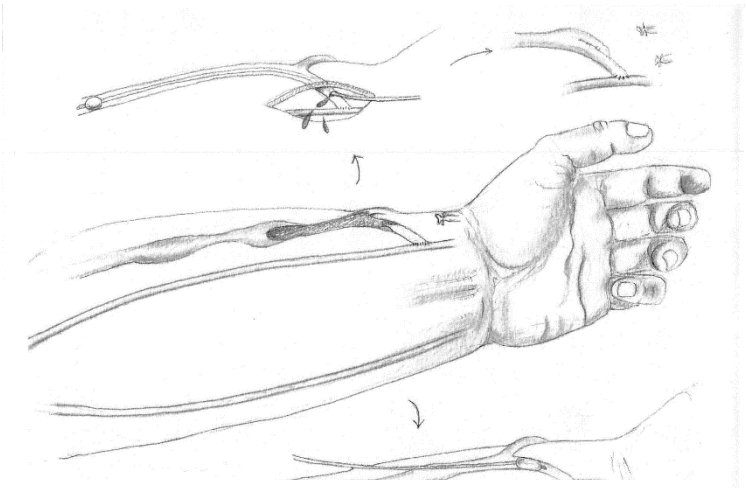
diabetes, compared to CVC.[62] There are no randomized trials comparing AV access strategies observational data is often affected by confounding by indication, where elderly sicker patients more often receive a CVC.[62] Patient characteristics; age, vascular anatomy, functional status, diabetes and CVD influence the vascular access outcome. These factors need be considered when deciding the optimal vascular access for a particular patient. “The right vascular access- at the right time- for the right patient- and for the right reason!”[63]

In peritoneal dialysis a break-in period of >2 weeks is recommended before elective start of PD treatment.[64] If a more acute start is needed, the recommendation is a supine position of the patient and use of low volume exchanges.[64] Urgent start of PD has proven effective, early cannulation grafts could also be considered in order to limit the need for acute CVC. [65]

The AVF placement has been discussed as a possible nephroprotective intervention.[66] Two previous studies found AV creation associated to reduced eGFR decline. One study lacked control group, and the other compared to CVC patients.[67, 68] The underlying mechanism for the slower eGFR decline following AV access creation is unknown, hypotheses involve physiological explanations, related to microcirculatory and cardiovascular changes, or more optimized compliance due to closer follow-up.[69] There is also a possibility of regression towards the mean, with the decision of access placement more likely to occur following a transient period of faster decline.

AV access dysfunction is often accompanied by underlying stenosis or thrombosis. KDOQI recommends clinical physical examination for access surveillance.[70] Other surveillance methods used in addition, increased the stenosis detection and intervention rates without improved access survival.[71] For access thrombosis there is no preference in guidelines for either endovascular or open surgical approach, the methods are seen as complementary (Figure 2).[70] A randomized trial of endovascular to open surgical AV graft thrombectomy found no significant difference.[72] Prior studies in AV grafts have supported open surgical intervention, while newer studies find improved endovascular outcomes.[73, 74] Early thrombectomy is encouraged, especially in AV fistulas to minimize inflammation and also to minimize the need for CVCs for the next dialysis session.[70]

Figure 2. Access thrombosis with open surgery or endovascular intervention

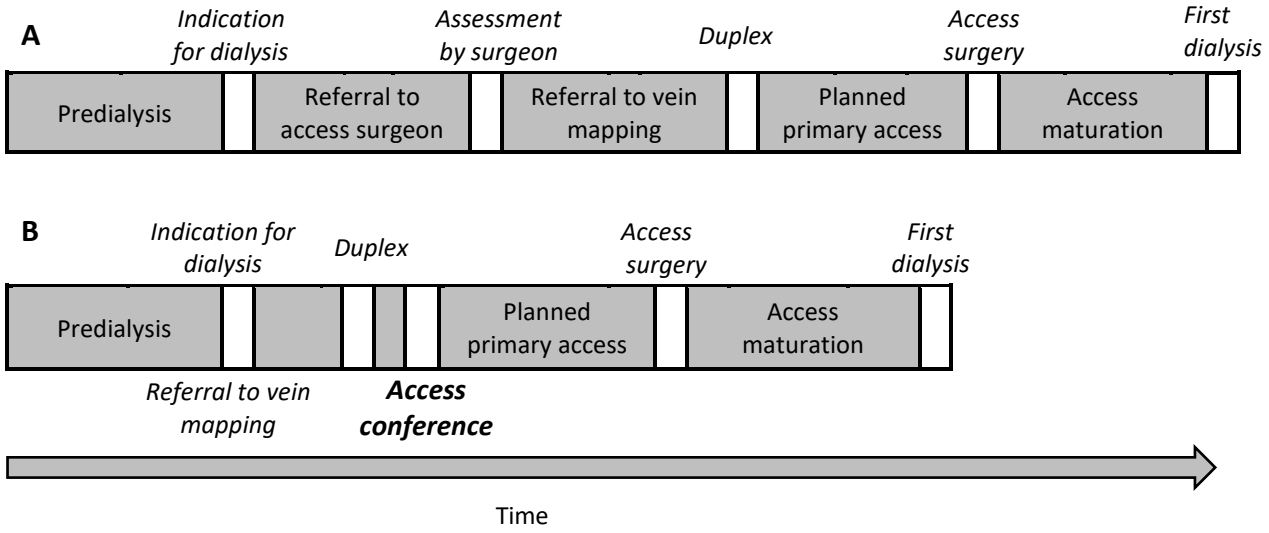


Design by Dr John Sandberg

2.7 MULTIDISCIPLINARY PRE-DIALYSIS CARE

Multidisciplinary care (MDC) is defined by KDOQI as access to dietary counselling, education about KRT modalities, transplant options, access surgery and ethical, psychological and social care.[70] The goal for the MDC team is to facilitate the timely creation of a functioning permanent access and to preserve the access function for as long as possible. The MDC team may through collaboration provide a more efficient time plan for the access process (Figure 3).[75]

Figure 3. Schematic figure of improved access care and optimized time plan from dialysis decision to functioning access.



A: The patient is referred to the access surgeon, put on waiting lists for surgical assessment, duplex examination, and surgery.
B: The patient is referred to duplex examination by the nephrologist and selection of primary access are then decided in MDC team conference.

Adapted with permission from Prof.Hedin; J Cardiovasc Surgery (Torino). 2014 Dec;55(6):793-801

The Incident Management of Patients, Actions Centered on Treatment (IMPACT) study reported decreased mortality, less CVCs and improved nutritional status compared to regular care.[76] Research on pre-dialysis MDC often originates in Asia, small cohort studies associate MDC to improved guidelines adherence, reduced eGFR decline, less urgent dialysis, cardiovascular events, infections, and reduced mortality compared to regular care.[77, 78] In a randomized study in elderly patients, MDC were associated to reduced mortality.[79] At Karolinska a randomized nurse predialysis initiative were associated to improved rates of both permanent accesses and self-care dialysis.[80] In line with previous metanalyses MDC was associated to reduced eGFR progression, mortality, KRT initiation and CVC use.[81, 82] With a shared decision-making taking patient preferences, values and prognosis into account the outcome potentially can be improved. Then the recommendations

are that the discussions should be revisited at intervals to ensure that the circumstances are unchanged.[35]

The KDOQI guidelines from 2019 recommends an individualized ESKD Life-PLAN as a strategy for ESKD care. The PLAN; Patient, Life-plan, Access, and Needs, is ideally created with the patient together with a CKD team of nephrologist, access surgeon, radiologist, nurse-coordinator, family or another supporter. Each access should have a plan for; vessel preservation, insertion/creation, contingency, and succession. KDOQI recommends every dialysis facility to treat according to PLAN, and also monitor patient satisfaction, unnecessary accesses, vascular procedures, and infections for research.[70]

The concept of certain transition clinics, specialized to prepare the patients for KRT have been suggested. With a risk-based approach, the transition clinic could provide patient counselling with planning for kidney transplantation, dialysis or conservative care.[83] A recent European study on >7,800 dialysis patients in 38 countries; 25% of the patients on hemodialysis had never received any information on other dialysis modalities, 33% had never heard about conservative care. Only 6% of the patients were on PD and 2% on home-hemodialysis, although self-dialysis were available options at the centers according to their doctors.[84-86] The access to any pre-dialysis information and the decision-making practices differ across Europe. With this in mind we collaborate to improve the availability of predialysis information.

2.8 RISK EQUATIONS AND PREDICTIVE ACCESS PLANNING

Prediction tools are needed to optimize the patient care regarding referral, prognosis, level of care, education, and treatment options. There is no ideal prognostic tool. When nephrologists aim for vascular access creation 6 months prior need for dialysis, one year later only 50% of the patients had started.[87] KDIGO 2013 recommended for access referral at 10-20% risk for ESKD according to risk prediction tools. NKF-KDOQI 2019 recommended access referral, assessment and subsequent surgery in CKD patients with progressive disease at eGFR15-20ml/min.[70]

Tangri developed the Kidney Failure Risk Equation (KFRE) in a Canadian cohort of CKD patients stage 3-5 in 2011 to stratify ESKD risk in 2 and 5 years.[88] The overall aim of KFRE was to guide referral, prognosis and decisions regarding level of care, dialysis/transplant education and timely planning for vascular access. The model uses 4 or 8 variables: age, sex, eGFR, albuminuria, plus calcium, phosphate, bicarbonate, and albumin. KFRE was validated in the CKD-Prognosis Consortium in 31 multinational cohorts.[89] The use of common laboratory variables enables an updated automated risk report whenever labs are taken. This risk- versus eGFR-based approach has led to a 35% reduction in new referrals in Canada, based on KFRE risk >3% in 5 years.[90]

The dialysis access is often referred to as the patient lifeline, to emphasize the life sustaining function of dialysis. In 2014 the Tangri group developed a risk-based AV access strategy tested in simulation models. They suggested a KFRE risk> 40% in two years as threshold to be evaluated in clinical practice.[90] In conclusion, predictive access planning would ideally improve the decisions in the multidisciplinary team, tailoring the access plan for the individual patient. In line with “the right access, in the right patient, at the right time, for the right reason.”

3 RESEARCH AIMS

The overall aim of this thesis was to study factors influencing the planning for kidney replacement therapy including vascular accesses, in order to improve the prognosis and quality of life for the CKD patient.

The specific research aims were:

1. To describe the impact of progression rate and age on absolute and relative risk for ESKD and mortality among unselected referred patients with chronic kidney disease.

2. To study the association between AV access placement and kidney function progression among patients with severe chronic kidney failure.

3. To compare the influence of surgical versus endovascular intervention for an AV access thrombosis on post-thrombectomy patency.

4. To evaluate the use of a risk prediction model for optimizing timing of AV access creation in our Swedish cohort of nephrology patients.

3.1 RESEARCH FRAMEWORK

Table 1. Overview of the main research questions and related study areas.

Focus area	Research questions	Methodological approach	Study/Outcome
CKD-progression and prognosis	CKD- (3b-5) patients risk of advancing to KRT, impact of age and progression rate.	SRR-CKD 2005-2011	I. Cumulative incidence of start of KRT or mortality by age and eGFR decline within 5 years.
	The association between access placement and eGFR decline, AV compared to Peritoneal Dialysis access	SRR-CKD 2005-2011 SCREAM Predialysis patients in Stockholm 2006-2012; receiving AVA or PDC 100 days before and after surgery	II. Difference in eGFR decline after surgery for AVA compared to PDC.
AV Access patency	Influence of surgical vs endovascular intervention for AV access thrombosis.	SRR, SRR-Access 2008-2020	III. Time to access abandonement
AV access creation	Evaluate use of KFRE>40% versus eGFR 15 threshold as decision tool for timing of AV access creation	SRR, SRR-CKD, SRR-Access 2008-2020	IV. Cumulative incidence of KRT initiation or mortality within 2 years.

4 MATERIALS AND METHODS

Table 2. A summary of the studies included in the thesis.

	I	II	III	IV
Design	Observational cohort study	Observational cohort study	Observational cohort study	Observational cohort study
Study population/ Data source	SRR-CKD 2005-2011 CKD 3b-5, >18 years	SRR-CKD 2006-2012 SCREAM >18 years	SRR, SRR-Access 2008-2020 >18 years	SRR, SRR-CKD, SRR-Access 2008–2020 >18 years
Main factors analyzed	Risk for KRT and death	Renal function decline	AV access patency	KFRE for AV access timing
Statistical analyses	Competing risk models	Linear mixed models with random intercept and slope, before and after surgery. Propensity matched analysis	Multivariable logistic regression Log-rank statistics Cox proportional hazard regression Competing risk models (Fine and Gray)	C-statistics (ROC) Mixed models Competing risk models

4.1 SETTING

The Nordic countries and Sweden have the advantage of both census registers and nationwide registers on health care and hospitalization held by Statistics Sweden and the National Board of Health and Welfare. Our general access to health care mandates quality registries, most often created by the medical profession. The registries are used to evaluate the quality of care and outcome on group level, along with providing decision support to the clinician. They also constitute an excellent source for epidemiological research, with detailed information not only on diagnoses, but also the characteristics of patients.[91] The registries with individual-based clinical data, together with Swedish residents having a unique personal identity offers possibilities for linkage between the registries. Patients are informed about their participation in the registries, they have the possibility to opt out and erase previous entries. Written consent in not required since the registries are considered quality control of public health care under Swedish law.

4.2 DATA SOURCES USED

4.2.1 Swedish Renal Registry

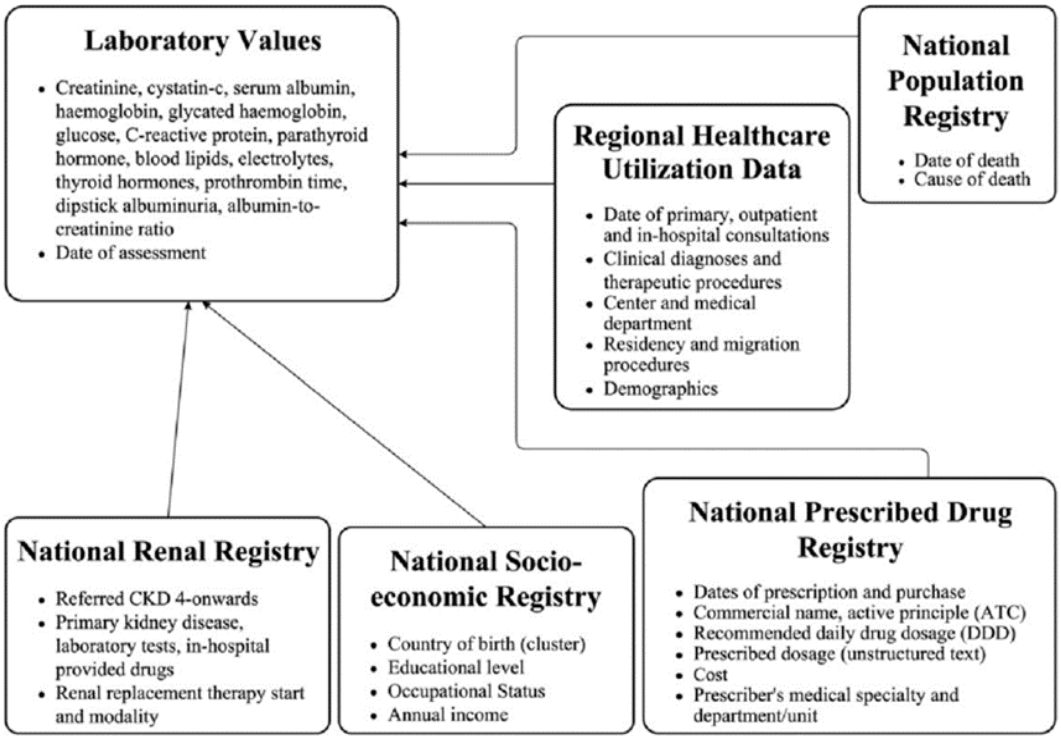
The SRR is the main source for this thesis, created in 2007 originating in the Swedish Registry for Active Uremic care, (SRAU), from 1991. Two other registries on non-dialysis dependent CKD were added to create SRR-CKD, the national renal registry of nephrology-referred patients. Nephrology clinics are requested to register patients with renal function below ≤30 ml/min/1.73m², while registration from eGFR ≤ 45 ml/min/1.73m² is optional. Patients are informed about their participation upon referral to the nephrology clinic.

SRR-Access was established as national access registry in 2011, originating in a regional access registry from 2005. It includes information on access placement, type of access, complications and procedures for access patency. In recent years three additional registries has been added; for renal transplantation, renal biopsies and patient related outcome measures, (RAND 36). The overall completeness of SRR is 97%, although it varies in different parts of the registries, the coverage of SRR for KRT is nearly 100%.[92] For SRR-CKD there is 98% adherence to the mandatory request of one registration per year, although reporting all visits are encouraged.[19]

4.2.2 Stockholm CREAtinine Measurements (SCREAM) project

SCREAM is a repository of creatinine and other laboratory measurements of people living or using healthcare in the Stockholm Region, linked to several other databases with information on demographics, socioeconomics, healthcare usage, diagnoses, dispensed medications and vital status (Figure 4). The aim was to study the burden of CKD and safe use of medications. Its coverage is complete for people undergoing creatinine testing. Reasons for testing also provide high coverage of complete population segments: For instance, 98% of patients with diabetes, and 97% of patients with CVD got creatinine tested.[93]

Figure 4. Data sources and information linked to the Stockholm CREAtinine Measurements.



4.2.3 National registers

Some National registers were used in this thesis, all held by the National Board of Health and Welfare.

4.2.3.1 The National Patient Register

Includes information on inpatient and hospital diagnoses, the diagnoses coded according to the Swedish International Classification of Disease System (ICD).

4.2.3.2 The Cause of Death Register

Includes information on cause of death statistics.

4.2.3.3 The Prescribed Drug Register

Includes information on prescribed and dispensed drugs in Swedish pharmacies.

4.3 STUDY DESIGNS AND POPULATIONS

4.3.1 Low renal replacement therapy incidence among slowly progressing elderly chronic kidney disease patients referred to nephrology care (Study I)

4.3.1.1 Study design and population

We identified a cohort of patients with CKD 3b-5, <45ml/min/1.73m², in SRR-CKD between 2005-2011, (n=8,771). To be included patients had to survive one year and have at least two creatinine measurements. Patients were then followed until death, start of KRT or end of study, (Figure 5-7).

Figure 5. Schematic presentation of study design, study I.

4.3.1.2 Exposure and progression

The exposure was progression rate, measured as relative difference in eGFR during a one-year period and rescaled to yearly % change. (Figure 7.) Patients were divided into three groups; "fast progressors", the tertial with the fastest progression rate, all others were considered "slow progressors". This decision was made based on two reasons; to match the definition of fast renal progression (≥ 5ml/min/1.73m²/ year), and to be in line with previous studies. The outcome was KRT, death before KRT, or no event within 5 years.

Figure 6. Inclusion, study I.

Figure 7. Progression rate per year %

$$\text{Progression rate} = \frac{\text{last eGFR} - \text{first eGFR}}{\text{first eGFR}} \%$$

4.3.1.3 Statistical analysis

The two outcomes were analyzed with Cox proportional hazard regression models to estimate the 5-year cause-specific probabilities of events for the combinations of age, CKD and renal progression. We created cumulative incidence curves using estimated coefficients from Fine and Gray models for age, CKD and renal progression. Both models were adjusted for remaining covariates to understand the association of covariates with cause-specific hazards and cumulative incidence. The adjustment variables were age, renal diagnosis, morbidity, comorbidity, blood pressure, body mass index (BMI), laboratory variables, medications and low protein diet (≤ 0.6 g/kg/day).

4.3.2 Arteriovenous access placement and renal function decline (Study II)

4.3.2.1 Study design and population

We identified a cohort of non-dialysis patients in Stockholm >18 years, who underwent primary surgery for a dialysis access (n=797) from SRR-CKD and SCREAM, between 2006-2012. We used registry linkages; hospitalization records to match for comorbidities and the National Registry for Dispensed Drugs to match for ongoing medication.

4.3.2.2 Exposure and outcome

Patients were divided into 3 groups based on access surgery; AVA (n=435), PDC (n=309) and central venous catheter (CVC), (n=53). The day of surgery was considered the index date and we hypothesized the eGFR trajectory closest prior to surgery was associated to the timing of the access creation. The main outcome was differences in eGFR decline (ml/min/1.73m²/year) before and after access surgery as well as median time (days) to start of dialysis, stratified on eGFR at the time of surgery.

4.3.2.3 Statistical analysis

We estimated eGFR decline with linear mixed models, with random intercept and slope before and after surgery. With the intention to treat approach, patients were categorized to the treatment they initially received. In the final model, we included variables we a priori considered to be of importance, or significantly associated to treatment decision or outcome. Data on covariates were collected at 100 days before and after surgery. We adjusted for covariates; model 1 included eGFR slope and last eGFR before surgery. Model 2 were also adjusted for age, sex, primary renal disease, and BMI. Model 3 were additionally adjusted for medications, p-albumin and albuminuria. Further, we estimated the post-surgery ORs of a 30% slower eGFR decline/year with logistic regression and adjusted for the same variables. As sensitivity analysis we did a propensity matched analysis for differences in eGFR slope before and after surgery.

4.3.3 Surgical versus endovascular intervention for vascular access thrombosis (Study III)

4.3.3.1 Study design and population

We identified a cohort of hemodialysis patients with a working AV access >18 years, experiencing their first thrombosis, treated with open surgical or endovascular intervention (n= 904) between 2008-2020. Patient characteristics and dialysis start were obtained from SRR, access information was collected from SRR-Access.

4.3.3.2 Exposure and outcome

The exposure was open surgical (n=368), or endovascular (n=536) intervention, including several categories of each type of intervention. We studied the primary outcome of secondary patency, (the permanent cessation of use of the access for dialysis) following AV access intervention at 30, 60, 90 days, 1 and 5 years. Secondary outcomes were primary patency, (time from declotting to next intervention) along with mortality.

4.3.3.3 Statistical analysis

The outcomes were computed and adjusted for patient characteristics and access type with logistic regression. Secondary access patency, time to event up to 5 years were described with Kaplan-Meier curves and compared with log-rank statistics. The primary and secondary outcomes were evaluated with Cox proportional hazard regression, we included time from access intervention to abandonment in the unadjusted model and censored for kidney transplant or death. Covariates; model 1 were adjusted for age and sex, whereas model 2 were also adjusted for comorbidities. In model 3 we additionally adjusted for more access related variables such as time from first cannulation to thrombosis, number of interventions before thrombosis, access type (AVG/AVF) and location. Missingness for any variable was very low, consequently analyses were performed on complete cases. Sensitivity analyses; First, we excluded patients who underwent anastomosis revision. Second, we stratified on prevalent/ incident patients in dialysis after 2008. Third, we stratified based on year of first cannulation. Lastly, we analyzed based on competing risk of death with Fine and Gray models.

4.3.4 Kidney Failure Risk Equation for vascular access planning; a nationwide observational cohort study from Sweden (Study IV)

4.3.4.1 Study design and population

We included patients >18 years in SRR-CKD 2008-2020 (n= 28,798) experiencing either a KFRE >40% risk for KRT in 2 years (n=7,229) or eGFR <15 ml/min/1.73m² (n=9,281) for the first time. Patients were followed until KRT initiation, death or end of follow-up. From SRR-Access we obtained information on type of access at KRT initiation.

4.3.4.2 Exposure and outcome

The exposure was KFRE>40% and the comparator was the eGFR 15 ml/min/1.73m² threshold. There were repeated measurements of KFRE over a 10-year period. eGFR decline, modality and type of access at KRT initiation were also compared. The outcome was initiation of KRT, mortality before KRT and test diagnostics.

4.3.4.3 Statistical analysis

KRT and mortality before KRT, as well as diagnostics were compared. We described the cumulative incidence of KRT and death before KRT for both cohorts. The curves are based on cumulative incidence function plots up to two years. We used competing risk regression (Fine and Gray) to assess both outcomes. We estimated C-statistics for KFRE using the ROC curve at baseline and for the two cohorts respectively. We estimated diagnostic test statistics; sensitivity, specificity and positive predictive value. The eGFR slopes were estimated with linear mixed models and compared with Kruskal-Wallis nonparametric test.

4.3.5 Covariates

The covariates we used in our studies I-IV were age, sex, clinical variables including BMI and blood pressure, laboratory measurements, medications, primary renal disease and comorbidities. The more study specific relevant covariates are listed for each study. The categorizations most often used are listed in Table 3.

Table 3. Categorization study I-IV.

Variable	Categorization
Age (years)	<50, 50-64, 65-75, >75
Sex	Male, female
CKD stage	3b, 4, 5
Blood pressure (mmHg)	Systolic, diastolic blood pressure
BMI kg/m²	<18.5, 18.5–25, 25–30, >30
Laboratory measurements	P-Albumin (g/l), S-Calcium (mmol/l), CRP (mmol/l), P-Phosphate (mmol/l), S-Creatinine (mmol/l), B-Hemoglobin (g/l), S-PTH (ng/ml)
ACR (mg/mmol)	<3, 3-30, >30
Comorbidities	Diabetes mellitus, Cardiovascular disease, Heart failure and other heart disease, Peripheral artery disease, Cancer
Diagnosis	Hypertension/renovascular, Diabetes nephropathy, Polycystic kidney disease, Glomerulonephritis, Pyelonephritis, other specified, unknown.
Medications	Antihypertensives; ACE/ARB, Beta-blockers ESA, Diuretics, Statins, Vitamin-D supplement, Iron, Phosphate binders/Calcium supplement Protein-restricted diet
Type of access	AVG/AVF

4.3.6 Comorbidity score

We used the Charlson comorbidity index to account for overall comorbidity burden since it is applicable to use in registry data. This Charlson comorbidity index is based on 19 diagnoses, each assigned a certain weight based on severity. The sum of the weights (1-6) adds up to a score, which then is translated into an index.[94] In study I, the minimum score was 2 since all patients had CKD. In this study centered the score at 2 and used the score as additional comorbidities to CKD.

4.4 ETHICAL CONSIDERATION

The ethical considerations include to reflect on all aspects involved in the clinical research, from project planning, patient meetings, the handling of clinical and research data, then to analyze and communicate the results, to implement the new insights into the clinic work. All studies in my thesis are performed in line with the Helsinki declaration and the ethical approvals are in place.

The ethical aspect of register studies and observational data provides an opportunity to a large population, together with little to no risk for the individual participant. Patients are informed about inclusion in SRR-CKD upon their first visit to the nephrology department. This is an informed consent in line with the guidelines for national quality registers. In accordance with the Personal Data Act, the persons are entitled to extracts of the information about themselves, however the individual participant cannot be traced in the register. For the patient self, there is no direct benefit to be included in the registry moreover the treating doctor have no knowledge about the patient´s choice to participate or not. For the participating patient the registry research implies very limited ethical risk, nevertheless they contribute to improve our healthcare, resource utilization and guidelines. It is of importance to distribute and share the research and publish the results in international journals.

My research questions involve the clinical, ethical dilemma about to advise elderly patients in their choice of future potential dialysis treatment or conservative care. Dialysis treatment is life-sustaining, easier to refrain from starting than to withdraw. Conservative care on the other hand is renouncing dialysis and receive good palliative care. If the elderly patient, possibly would survive a little longer time on dialysis, this added time should maintain quality of life. This important choice of dialysis treatment or conservative care do qualify as an ethical problem. The conflict here is genuine, even though all the underlying facts are acknowledged, in the individual case there is always uncertainty. The decision involves an evaluation of medical facts and the patient´s value of their life-quality and what is most important in their life, then leading up to a common decision. As doctors, we use virtue ethics to create trust, to convey and always prioritize what is best for the individual patient, if not to cure, to always try to offer relief and comfort. We should also pursue the shared decision-making and refrain from medical paternalism. From a utilitarian perspective, our actions should also benefit the patient and provide the best possible outcome with no undue expense for neither the patient nor the society. This right to an informed consent may conflict with patient autonomy, as the survival data in elderly patients with chronic kidney disease are often pessimistic and patient integrity may be threatened if we as professionals convey this to the patient, since we are always expected to offer hope.

5 RESULTS, DISCUSSION, METHODOLOGICAL CONSIDERATION AND IMPLICATIONS

5.1 BASELINE CHARACTERISTICS

5.1.1 Sex

The majority of patients in the study cohorts were men, (63-75%) corresponding to the male dominance in SRR 2021, with 65% men.[16] However, the study cohort in study III is an exception with 60% women.

5.1.2 Age

The study cohorts from SRR-CKD in study I and IV where older (72-73 years) compared to the more access-oriented studies II-III (63-69 years). This again corresponds to the average age at KRT initiation of 64 and 63 years for men and women in SRR 2021.[16]

5.1.3 Primary renal disease

The primary renal disease in all our studies were hypertension, diabetes mellitus and other disease. Study III is an exception with less hypertension 13% (vs 25% and 27% in study I and IV respectively) and more diabetes 25% (vs 21-22%).

5.1.4 Comorbid diseases

The most common comorbidities in all studies were diabetes mellitus and cardiovascular disease including ischemic heart disease, hypertension and obesity. Also, here study III was an exception with less cardiovascular disease 18% (vs 38-41%) and less diabetes 33% compared to (37-42%) in the other studies. Study II on access creation had the highest prevalence of diabetes and cardiovascular comorbidities. Again, this mirrors the different composition of the study population in study III on access thrombosis.

5.2 CHRONIC KIDNEY DISEASE PROGRESSION AND PROGNOSIS (STUDY I AND II)

5.2.1 Results, discussion, methodological considerations and implications

In study I the final cohort consisted of 8771 patients, a majority in CKD stage 4. Their median eGFR was 20.2 ml/min/1.73m², with a median eGFR decline of -1.71 ml/min/1.73m²/year, equal to -8.8%. Patients in the fast progression group (> -18.7% decline per year) were younger, had lower eGFR and higher ACR compared to the slow progression group. A notable 35% of patients experienced a stable or improved eGFR during the first year. Median follow-up time was 2.8 years, after the initial year. At the end of follow-up, the

rates of KRT initiation and mortality were 24% and 24% respectively, while 52% remained event-free.

Fast progression rate was associated to increased cumulative risk for KRT in all ages and CKD stages.

Risk for KRT initiation was high in late CKD stage, in younger individuals and fast progressors, also in the competing risk setting. The risk of KRT increased up to 13 times in CKD 5 compared to CKD 3a. High comorbidity score and diabetic kidney disease were associated to increased risk of KRT in the adjusted model. Risk for KRT was low in elderly slow progressors, and slightly higher in elderly fast progressors. In the final adjusted model women had a lower KRT incidence.

Risk for mortality increased with age, in patients >75 years, the risk was almost 6 times higher compared to patients <65 years. Lower mortality was associated to female sex, a BMI > 30 kg/m², diabetic kidney disease and glomerulonephritis.

Table 4. Cause-specific hazard from Cox models for initiation of kidney replacement therapy and death before initiation of kidney replacement therapy.

Demographics	**KRT initiation**			**Death before KRT initiation**		
	HR	**95 % CI**	**P-value**	**HR**	**95 % CI**	**P-value**
Age (years)						
<65	1.00	ref		1.00	ref	
65–75	**0.64**	0.57-0.72	<0.01	**2.48**	2.07-2.97	<0.01
>75	**0.449**	0.40-0.51	<0.01	**5.47**	4.61-6.49	<0.01
Sex, women	**0.72**	0.66–0.80	<0.01	**0.77**	0.70–0.85	<0.01
Primary renal disease						
Hypertensive kidney disease	1.00	ref		1.00	ref	
Diabetes nephropathy	**1.21**	1.03-1.41	0.020	**0.57**	0.45-0.72	<0.01
Glomerulonephritis	1.04	0.91-1.19	0.59	**0.78**	0.67–0.90	<0.01
Fast progressor (> 18.7% decline/year)	**2.24**	2.00-2.51	<0.01	**1.27**	1.13-1.43	<0.01
CKD stage*						
G3b	1.00	ref		1.00	ref	
G4	2.04	1.52-2.75	<0.01	0.94	0.80-1.09	0.40
G5	**4.05**	2.89–5.67	<0.01	0.94	0.75-1.19	0.61
Charlson Score above kidney disease (per 1 unit increase)	**1.15**	1.04-1.28	0.01	1.06	0.95-1.17	0.31
Body Mass Index (kg/m²)						
<18.5	1.08	0.72–1.62	0.72	1.39	0.98–1.96	0.06
18.5-25	1.00	ref		1.00	ref	
25-30	0.91	0.81-1.02	0.11	0.96	0.85-1.07	0.46
>30	0.90	0.80-1.02	0.11	0.86	0.76-0.98	0.02

Chronic Kidney Disease (CKD), Kidney replacement therapy (KRT), Cause-specific hazard ratio (HR), Confidence interval (CI). All variables, estimates are adjusted for all other variables, eGFR after the initial follow-up, current medication, laboratory data, hospital status, region and diet.

There were mainly two previous studies that increased our curiosity to study these research questions in the Swedish cohort; De Nicola studied a cohort of Italian nephrology-referred patients and found an increasing risk for KRT with decreasing renal function. This overcame the risk of death even in patients of advanced age.[70] On the other hand, O´Hare studied American veterans, CKD III-V, where the eGFR when the risk for KRT exceeded the risk of death varied with age, from 45 to 15 ml/min/1.73m². The risk of death always exceeded the risk of KRT in elderly patients over 85 years.[72] During our work with this study, the large meta-analysis from the CKD-PC consortium with research questions in line with ours were released. They found already moderate changes of -30% in eGFR over 2 years associated to increased ESKD and mortality.[95] The release of the CKD-PC study made our research more into a comparison. Our results in a national unselected population with access to free health care were in line with their findings. The meta-analysis led the FDA to accept reduced progression rate, 40% eGFR decline compared to >0.5-1ml/min/1.73m²/year as valid outcomes in clinical investigations.[96] The notion that every patient has a slope, entails eGFR decline a valid maker of outcome.

In relation to these previous studies, we found a high mortality risk before KRT initiation, in line with the American study. This is despite the similarities with the nephrology-referred population in the Italian study. Possibly the study also reflects the different treatment traditions between our countries, not just the natural course of CKD. In Sweden, 15% of patients choose conservative care, whereas according to professor De Nicola they do not do conservative care in Italy. Conservative care is also very limited also in the US.[97] The higher mean age of our and the American study cohorts, (72 and 73 years) versus the younger Italian cohort (67 years) could be one factor to the similar outcome. The increased cardio-vascular mortality in northern Europe could be another factor, but all females in our study population compared to the American veteran cohort (3%) would possibly have balanced this.

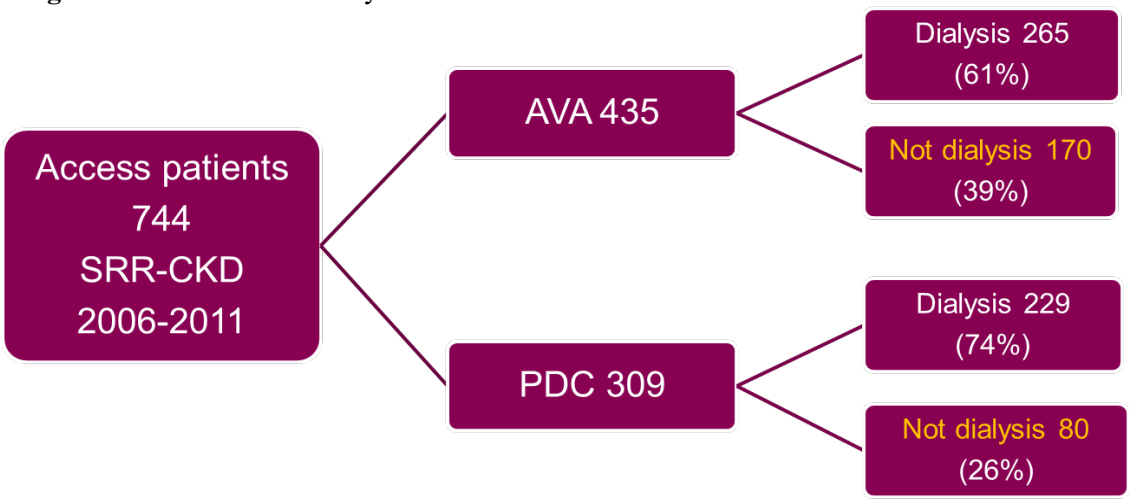
Some methodological considerations would involve generalizability. The coverage of SRR-CKD is >95% and our study refers to the nephrology-referred population. The patients in SRR-CKD are referred and considered to need nephrological follow-up. They constitute a risk-population compared to patients in primary care. Our results can be compared to the CKD cohort in the CKD-PC study, not the general population cohort. There is a risk that doctors are less prone to initiate KRT in the elderly patients with slow progression rate, which may affect the 5-year outcome of elderly patients. Age is a confounder since it has an impact on both kidney progression rate and KRT, the outcome. For this study, the outcome also depends on the setting. The later eGFR when KRT is initiated and our different views on conservative care could be considered as misclassification bias.

The implications of this study lead us to the importance of an individualized predialysis assessment to optimize our advice and treatment. When planning for future care we need to consider the progression rate and the age of the patient.

5.2.2 Results, discussion, methodological considerations and implications

In study II the cohort consisted of 744 predialysis patients; 435 received AV access, 309 PDC catheter (Figure 8), and 53 patients had CVC. Patients who received an AVA were somewhat older, more often men and suffered more diabetes and cardiovascular disease. The AVA patients were less often treated with ESA and ACEi/ ARB compared to the PDC group. The patients receiving a CVC were even older, more men, and suffered more comorbid diseases and laboratory abnormalities than the AVA patients.

Figure 8. Patient cohorts study II.



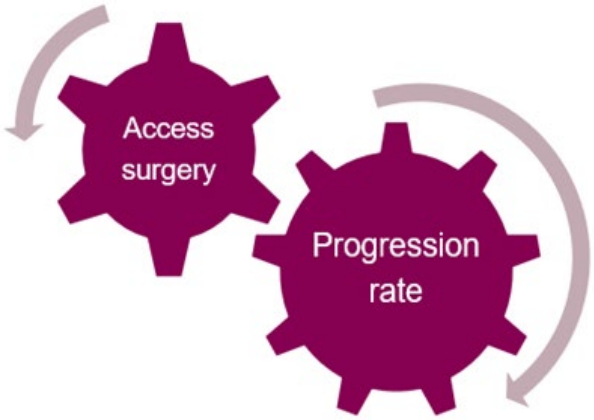
The median eGFR at surgery was 8.1 vs 7.0 ml/min/1.73m² for AVA and PDC respectively. AVA patients had a less rapid decline before surgery (-5.6 vs -6.7 ml/min/1.73m²/year for PDC). The CVC-cohort had the lowest eGFR at the time of surgery (5.6 ml/min/1.73m²) and the fastest eGFR decline, (-11.2 ml/min/1.73m²/year). In the unadjusted model, both AVA and PDC experienced a slower decline in eGFR after compared to before the access surgery. The median slope difference was 0.56 ml/min/1.73m²/year in AVA compared to PDC. No significant difference was seen in the adjusted model. The median time to KRT initiation was 59 and 154 days in PDC and AVA respectively. There were 250 patients (34%) receiving an access without initiating KRT during the follow-up period, (of median 0.5 years). The median number of eGFR measurements were 6,5 before and 5 after access surgery.

In addition, we did several sensitivity analyses to test the robustness of our results. We did a logistic regression analyzing the odds ratios of a 30% slower yearly eGFR decline. We also did a propensity score matched analysis of the slope difference before and after access surgery, without any significant difference.

In study II we continued to study the progression rate, this time in relation to access creation (Figure 9). Previous studies had suggested AV access creation per se to slow down eGFR decline. [65, 66] In line with previous studies we found access surgery overall associated to a reduced eGFR decline, however we found no significant differences between AVA and PDC.

Our results led us to believe that although some physiological effect of AVA creation may occur, it did not influence the eGFR decline in our study population. There are also previous articles of eGFR decline independent of AVA maturation status and changes in blood pressure and ejection fraction already two weeks after surgery. [68, 98]This opens up to alternative explanations; the closer overall monitoring may increase the patient´s compliance to diet, medication and exercise. Possibly the accompanying hospital visits, and frequent lab tests impose the seriousness to the patient. We also believe that there could be a statistical explanation; regression towards the mean. Maybe then access decision is made following a period of faster progression, which then slows down. We may then place the accesses at a symptomatic tipping point, when the patient experiences more uremic symptoms including reduced appetite, with loss of weight and muscle mass. We performed a sensitivity analysis on dialysis start with AVF without impact on the results. Neither did the slope at 100 days before and after surgery have any impact.

Figure 9.



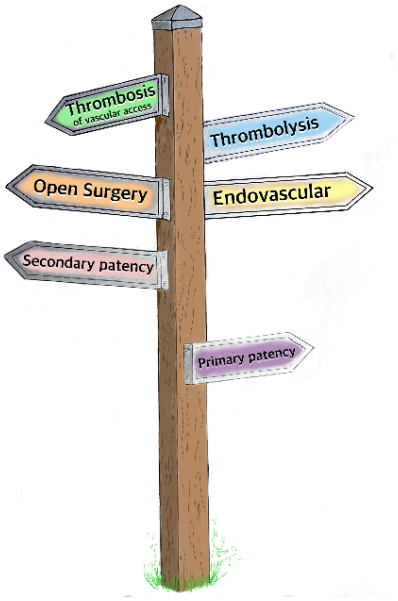
We thought about the optimal comparison group. We used patients planned for future peritoneal dialysis as our control group. At this time the PD catheters were placed earlier, and patients received the same pre-dialysis treatment. Today this is not the case anymore, we opt for PD catheter placement at two weeks before anticipated start of dialysis. Patients receiving AV accesses with poor maturation could have constituted another control group. We studied this option in the sensitivity analysis to further evaluate the physiological hypothesis.

Some methodological considerations in regard to other studies could be our later timing of access creation and KRT initiation. Selection bias is always a consideration and sometimes difficult to adjust for in registry data. A randomized trial would solve this problem. Possible selection biases in this study would be if different patients were selected for AVA and PDC. A possible cofounding could be that the accesses were placed at different time points with regard to KRT initiation. A differential misclassification could be if there were differences in the number of creatinine measurements in between the cohorts. To increase the precision and possibility of a significant difference between our cohorts a larger study population, with more patients and maybe earlier access placements would be needed.

The implication of this study would emphasize the importance of pre-dialysis care, although there is no reason for an early access creation to reduce progression of the advancing kidney failure.

5.3 ARTERIOVENOUS ACCESS PATENCY

5.3.1 Results, discussion, methodological considerations and implications



Artist Dr. John Sandberg

In study III, the final cohort included 904 prevalent hemodialysis patients experiencing AV access thrombosis. The intervention was endovascular in 368 patients (41%) and open surgical in 536 patients (59%). Their median follow-up time was 1.1 years. The endovascular intervention cohort had more cardiovascular disease and diabetes, while the surgical intervention group suffered more hypertension. There was a female dominance of 60%, more endovascular interventions were done in AVFs (60 vs 49% surgical) and in upper arm accesses (39 vs 32% surgical). The endovascular adjunctive procedures involved stents 11%, cutting balloon 14%, drug eluting balloon 3% and coiling of venous side branches in 1%. Surgical intervention included surgical thrombectomy 58%, anastomosis revision 11%, and also hybrid interventions in 31%; cutting balloon 2%, thrombolysis 2% stent 1% and drug eluted balloon (DEB) in 0.2%. Despite being registered as an access thrombosis, information on thrombolysis was missing in the registry for 61% of the endovascular and in 11% of the surgically treated patients.

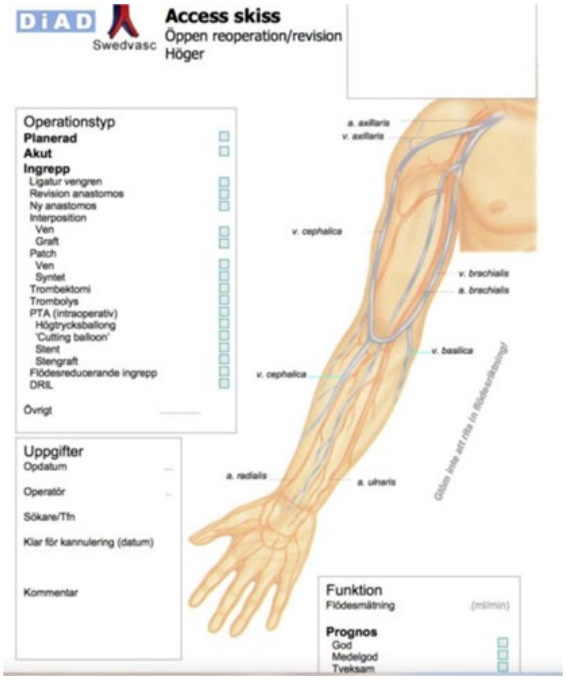
The open surgical intervention was associated to a higher risk of access abandonment at 30 days (OR 1.63), 60 days (OR 1.44) and 90 days (OR 1.44) compared to the endovascular group. The results prevailed over time, with a hazard ratio of 1.2 (1.03-1.44) for surgical vs endovascular intervention, in the fully adjusted model. Also, over 5 years the time to access abandonment was superior for endovascular interventions. Endovascular interventions were significantly more successful in recent years, in patients with first cannulation after 2017 (HR 2.39 [1.19-4.79]) or intervention during 2018-2020, (HR 1.68 [1.02-2.77]). We found no difference in the immediate success rates. When looking at time to next intervention, only 16% of the patients were intervention-free at one year, with no significant differences between the cohorts. In our subgroups analysis we found younger patients, those with AVF, fore-arm accesses and fewer prior interventions had longer time to access abandonment. In sensitivity analyses further comparing surgical to hybrid intervention, there was inferior short-term access survival (at 30 days) for surgical versus hybrid interventions.

In study III we demonstrated a statistically significant benefit of endovascular intervention. In previous studies, with more heterogenous endovascular methods, the results more often advocate surgical intervention.[72, 73] However, a systematic review found comparable short-term success rates for treatment of the underlying thrombosis lesion for the two interventions.[99] In line with previous studies we found hybrid interventions could complement to surgery to improve patency.[100]

Guidelines of today offer no preference on intervention, but they stress the importance of a fast, safe thrombus removal to get the patient ready for the next dialysis.[70] The choice of intervention is often based on local availability and resources. With time, endovascular results have improved, probably due to technical advances in visualization as well as treatment of the underlying causing lesion. Our study included more women and younger patients as compared to previous studies. We included patients with thrombosis and women experience more access thromboses. Women overall are known to have a more complicated access situation.

Our study setting is prospectively included real-life patients, undergoing routine care endovascular interventions of today. The study size and a more diverse population allows us to compare the outcome in various access types, both AV grafts and fistulas, locations and subgroups. We adjust for several confounders, including previous interventions, with a complete and long follow-up. Compared to previous smaller studies our findings add to the results of previous studies in this field.

Figure 10. The Access sketch.



There is always an issue with the representativeness of real-life registries such as the SRR-Access. We have to rely on the data of interventions reported to the registry. The registration is often performed by a dialysis nurse. The missing registration of thrombolysis method in the endovascular group reflects it is not mandatory to register, despite all patients being registered as access thrombosis. Possibly larger centers are more behind in their registration. Possibly complicated interventions with subsequent complicated registrations are less often reported, however this would not differ in between the cohorts. The access sketch (Figure 10), is important for clarity in the registrations. There could be a risk for misclassification if for example radiologists were more prone than access surgeons to report exact interventions. If vascular calcification has an impact on both choice of intervention, the exposure and at the same time increases the risk for access abandonment, the outcome it could be a confounder. The possibility of inequal registration rates across the country is possible, but a recent validation study found a 95% match between the registry and medical records. [101]

The implication of this study is our finding that endovascular methods are not inferior to surgical interventions. The endovascular methods and the possibility of both interventions methods should be available in more centers.

5.4 TIMING OF ARTERIOVENOUS ACCESS CREATION

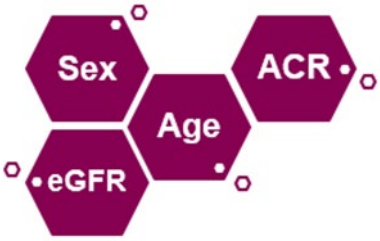
5.4.1 Results, discussion, methodological considerations and implications

In study IV we included 28,798 patients from SRR-CKD with available KFRE measurements. Upon inclusion in SRR-CKD the mean eGFR was 27.4 ml/min/1.73m², with a mean eGFR decline of -1,64 ml/min/1.73 m²/year. During follow-up 29% of the patients died and 23% initiated KRT; whereof 56% hemodialysis, 35% peritoneal dialysis and 8% received a pre-emptive kidney transplant. Patients in the KFRE>40% cohort (n=7,229) were younger (66 vs 71) years, included more men (69 vs 65%) and had higher ACR (1,929 vs 880 mg/g) compared to the eGFR15 cohort. Of the patients we had information on type of access when they started hemodialysis, 56% did so in a CVC and 44% with an AV access. Of the patients initiating KRT only 73% ever had KFRE >40% while 86% ever had eGFR15 in planned outpatient visits. Patients initiating KRT with a CVC had lower KFRE and higher eGFR one year before initiation. The KFRE>40% cohort experienced a shorter median time to KRT initiation, (0.9 vs 1 year) compared to eGFR15, consistent to the more rapid eGFR decline in the KFRE>40% cohort (-2.0 vs -0.95 ml/min/1.73m²/year. Test diagnostics; For KFRE>40% the specificity (90 vs 79%) and the positive predictive value were superior (56 vs 44%) compared to eGFR15. Sensitivity was superior for eGFR15 (88 vs 75%) compared to KFRE>40%.

In study IV we found that although eGFR had a higher sensitivity, the use of an eGFR threshold for AV access timing would result in a substantial larger share of patients undergoing unnecessary access creation. Although eGFR would identify people at risk for KRT, the lower eGFR decline and higher mortality in the eGFR cohort may contribute. If we used KFRE>40% alone as a threshold, the higher positive predictive value would improve the share of patients starting KRT in a working access. Nevertheless, as for eGFR15, it would also cause a quite high share of unnecessary AV access surgery. Ultimately, the use of KFRE>40% plus a registered plan for future dialysis were superior to predict both KRT initiation and death.

In this study we noted increasing KFRE estimates over time, especially in the year leading up to dialysis. KFRE>40% showed lower discrimination measured with c-statistics closer to KRT initiation. This is understandable since prediction models in this homogenous population with a smaller range of eGFR, would cause a lower discrimination (Figure 11).

Figure 11. Variables in the Kidney Failure Risk Equation.



The timing of vascular access creation is essential to reach the goal of initiating KRT in a working AV access (Figure 12). Even though nephrologists follow their patients in out-patients clinics with regular eGFR measurements, only 21% of Swedish patients start KRT in a working AV access. Patients with unnecessary access surgery also include those who live with an access never used or did not survive. In our results about 35% of the patients included

in the two cohorts did not need to initiate KRT within two years. Thus, nephrologists are excellent in identifying the surviving patients who will live until KRT initiation. However, we also oversee a lot of patients eventually needing KRT, without being referred for access creation in time.

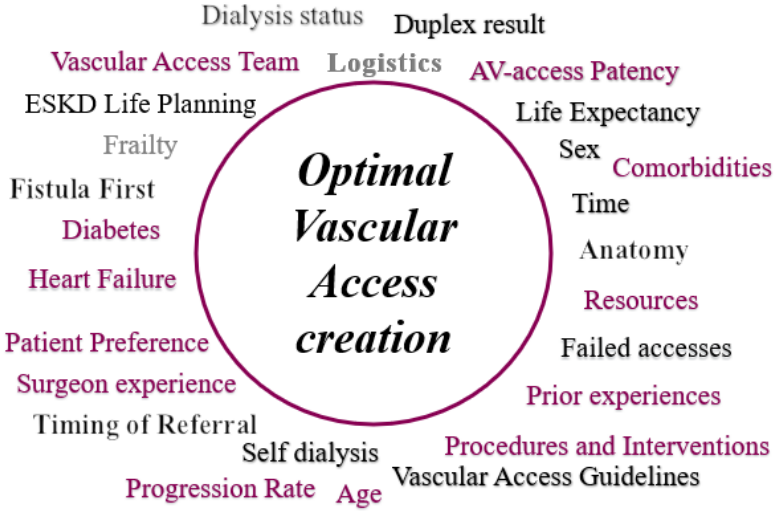
In summary, the clinical problem to be solved is not the patients who are referred for access surgery, but those who are not referred. The patients with a registered plan may represent someone who was identified by the doctor to have a high risk of both progression and survival. Our results suggests that a KFRE >40% threshold could serve as the warning-flag that the patient is entering the last lap of the pre-dialysis race, with need for an access action plan.

Another important finding is that we found the median time to KRT initiation was less than one year from entering any of the two cohorts. This further emphasizes the importance of multi-disciplinary predialysis care to establish a fast and efficient vascular access procedure.

Some methodological consideration would include that albuminuria measurement was missing in about one third of the 42,000 included patients. However, one ACR measurement was required for inclusion into both cohorts, not just the KFRE>40%. If some centers never include ACR in their registrations, it could be non-differential misclassification. If patients with faster progression, or more extensive albuminuria have their labs taken more often, this could lead to higher precision. A possible confounding would be if the referral decision to nephrology was influenced by the level of ACR.

The implication of this study supports the use of KFRE>40% as an eye-opener in nephrological pre-dialysis care. To combine KFRE>40% with clinical judgement with a decision plan for future dialysis would optimize the AV access creation timing and increase the patients starting in a working AV access.

Figure 12. Factors of importance for Optimal Vascular Access creation



Adapted from Woo, Clin J Am Soc Nephrol 11: 1487–1494, 2016

5.5 GENERAL DISCUSSION AND METHODOLOGICAL CONSIDERATIONS

Epidemiology derives from the Greek words Epi (upon) Demos (people) and Logos (science), and the definition is "The study of the distribution and determinants of disease frequency." It is quantitative research about the occurrence of illness, or in short, who gets sick and why?[102]

There are 3 possible explanations to a study result; true, random error, or systematical error. Several types of systematic errors may apply to research and cohort studies, these need to be considered when planning, conducting and analyzing a study.

5.5.1 Study design

Cohors derives from Latin, translates to "a group of people". Recruited study participants share a common characteristic and at start all of the participants are "at risk" for a certain outcome. Cohort studies are longitudinal, the participants are followed for a certain time. During this follow up some of the participants will be exposed to a specific risk factor. By measuring outcomes over time and compare the exposed to the unexposed cohorts, it is then possible to explore the impact of the specific risk factor on the outcome.

All studies in this thesis are nationwide registry-based observational cohort studies on nephrology referred patients, >18 years of age. Study I and IV are more descriptive and follow the natural history of renal progression. Study II and III are more analytical in comparing the outcome of two different interventions. Register studies are per definition often considered retrospective, although data were registered prospectively, before the occurrence of the exposure.

5.5.2 Validity

The word valid is derived from the Latin validus, strong. Validity in research means to what extent the study performed is able to measure what it is intended to measure. The validity of a study then encompasses two domains; external and internal validity.[103] External validity; how the study results apply to other settings than those studied, the generalizability. Internal validity; can the results be trusted and are not due to systematical errors, bias. The major threats to internal validity are selection bias, information bias and confounding.

5.5.2.1 Selection bias

Selection bias is a systematic error that stems from the procedure to select subjects and factors that influence study participation.[102] The association between exposure and disease may differ between the participants and non-participants in a study. We used internal comparisons with unexposed individuals taken from the same population, to diminish any differences in between the study groups, except for the exposure of interest. All of the studies in this thesis would have been difficult to perform in a randomized setting. Study III would be an exception, whereas availability of both interventions at the local level would be the limiting factor.

The use of eGFR for inclusion in the SRR registry instead of only creatinine is important. Creatinine is derived from muscle mass; men have superior muscle mass and are possibly therefor more often referred to nephrology. Another advantage is the eGFR <30 ml/min limit, this diminishes the risk of survival bias of prevalent patients. It is uncommon to have access to an incidence registry in CKD research of today.

5.5.2.2 Misclassification, information bias

Information bias results from incorrect measurement of exposure or outcome. Misclassification can be differential or non-differential, this is related or unrelated to other variables, outcome or exposure.[102] Any differences between different study cohorts in our studies however seem unlikely. Different creatinine measurements originating in testing in different labs, could be a non-differential misclassification. Nevertheless, we studied the progression rates over time and most patients tend to use the same laboratory for every testing.

6.1.2.3 Confounding

Confounding is referred to as "confusion of effects" in the textbook of Epidemiology.[102] The effect of the exposure could be mixed with the effect of another variable, leading to a bias. A confounder must be associated with both the disease and the exposure, although not be an effect of the exposure or a mediator between exposure and outcome. The confounding factors have an unbalanced effect between the compared exposure groups. Confounding could be handled be randomization, restriction, stratification, regression and matching.

Sometimes, despite extensive adjusting, it is not possible to adjust for every factor that possibly affect the outcome, for example the choice of future treatment. These remaining differences, after confounding has been adjusted for, is referred to as residual confounding. Confounding by indication is when the reason to choose a treatment involves a difference in the outcome.

5.5.3 Precision

Random error is the remaining error when systematic error is eliminated, the variability of data that may be due to chance or cannot be readily explained. A point estimate refers to an estimate presented as a single value, hence do not express the statistical variation, the amount of random error in the estimation. Confidence interval (CI) is used to indicate the precision of the point estimate, where a narrow CI indicates high precision with little random error in the estimate[102] The standard error decreases with increasing size of the population, while the precision do not infer about bias.

P-value is the statistics used for hypothesis testing, a probability measure. In hypothesis testing the null hypothesis is defined and an alternative hypothesis where either hypothesis can be true, but not both of them. When data are very discrepant with the null hypothesis, the P-value is low, the null hypothesis can be rejected, although it does not address whether the null hypothesis is true or correct. Power is the probability of rejecting the null hypothesis

(H0) when the alternative hypothesis (HA) is valid. (Table 5.) Type I error, false positive, is rejecting the H0 when there is no true difference. Type II error is not rejecting H0 although there is a difference. Power is the complement of the risk of type II error, to be sure to detect a difference between the groups if there is one.

Table 5. Overview of type I and type II errors.

	H0 is true	**HA is true**
Reject H0	Type I error	
Do not reject H0		Type II error

.

6 CONCLUSIONS

I. The risk for Kidney Replacement Therapy varied with progression rate and age. There is a low risk for KRT in elderly patients with slow progression rate, and a high risk for KRT in younger patients with a fast progression rate.

II. The progression rate and other risk factors for progression are important to consider when individualizing the planning and decision about future treatment

III. Both arteriovenous and peritoneal dialysis access placement were associated to reduced eGFR decline, with no significant difference between the two.

IV. The need for dialysis remains the main determinant for timing of access surgery.

V. Endovascular intervention was associated to superior access survival, both in the short- and long-term. This is compared to open surgical intervention in patients on hemodialysis experiencing their first arteriovenous access thrombosis.

VI. The combination of risk prediction models and clinical judgement with a plan for future kidney replacement therapy would optimize the timing of access creation. Thereby increasing the share of patients starting dialysis in a working arteriovenous access.

VII. The use of KFRE>40% as decision threshold were associated to superior specificity and positive prediction value as compared to eGFR15 to predict kidney replacement therapy initiation in two years.

VIII. There is a need for a new prediction model incorporating both eGFR deline and survival to further improve access related outcomes.

7 POINTS OF PERSPECTIVE

This thesis has discussed the impact of progression rate and factors related to access survival. The research projects have followed the development of CKD care, and we have revised the research questions over time. My understanding of clinical research and epidemiology has developed during the work with the thesis and has added dimensions to me as a doctor. This is clinical nephrological research, some of the results are already implemented in our every-day work.

In dialogue with the patients, we refer to progression rate, age and CKD stage regarding their future prognosis. The pre-dialysis information and recurring nurse-coordinator visits are crucial in the transition clinic. Together with the patient we consider the various treatment options; kidney transplantation, conservative care or dialysis. When dialysis is needed, the self-care modalities are encouraged whenever possible. Keeping the overall arteriovenous access patencies in mind, we consider PD or assisted PD when suitable. We opt for a more risk-based approach to optimize the timing of accesses and kidney transplantation. The collaboration in our multidisciplinary team facilitates the access care, and the use of endovascular procedures is increasing.

Based on the findings in this thesis some new research questions have arisen. The Swedish renal registries are invaluable for nephrological research. To further evaluate the study questions of endovascular or surgical thrombosis intervention as well as progression rate following access surgery, randomized studies are necessary. The SRR-Access is a unique source of routine-care, real-life data with opportunities for future studies. One currently undeveloped area of research is the renal transplant patients with high flow accesses and their risk for heart failure, transplant- and patient survival. Further research ideas involve; KFRE with regard to nephrology referral from the primary care. KFRE for early CKD diagnosis in primary care, and new interventions to reduce eGFR decline.

For the future, with chronic kidney disease increasing world-wide, we need to increase the awareness about CKD and the risk factors for progression. As professionals, we collaborate to increase the availability of information. With pre-dialysis information including multi-disciplinary care, our aim is to improve the prognosis and quality of life for our patients. The ambition is for every patient to be able to engage in their own journey with chronic kidney disease.

8 ACKNOWLEDGEMENTS

Marie Evans, main supervisor. Thanks for taking me on as your PhD candidate and so generously share your extensive knowledge in research and statistics. You are a very appreciated colleague, a true inspiration and most of all a dear friend.
Ulf Hedin, I am so grateful for your invaluable support and all doors you have opened. You got me engaged in the Swedish Access Meeting initiative, which sparked my research interest. Your hands-on engagement in my writing, always striving for perfection.
Juan Jesus Carrero, Thanks for always improving our research ideas, your immediate statistical advice and finishing touches to all our manuscripts.
Peter Stenvinkel, as well as my co-authors, *Alessandro Gasparini*, *Fergus Caskey, Rino Bellocco, Abdul Rashid Qureshi, Gunilla Welander, Friedo Dekker, Chava Ramspek* and more, thanks for superb collaboration and support!

To all my colleagues at Renal Medicine, Karolinska University Hospital;
Mats Söderhäll, dear boss, thanks for creating an open-minded atmosphere and workplace. I toast mastered your doctoral dinner, great to have you back. *Helena Rydell* and *Sara Lind af Hageby*, clinical supervisors, thanks for creating a workplace where research is encouraged, you always care for me and my patients´ best. *Carl-Gustaf Elinder* prior boss, now knowledgeable colleague. Our coffee breaks add life-quality and so does your friendship. *Olle Heimburger* my experienced PD colleague- what you do not know about PD and wine is probably not worth knowing. *Mårten Ståhl* you embody being an empathetic, knowledgeable doctor and friend. *Hassan Magin* your clinical skills are amazing, I value our cooperation. *Pälle Hedman* hope you are back for life this time. We need your clinical skills, your calm Luleå-spirit, and you need all of us plus coffee. *Julia Wijkström* and *Jim Alkas* I know I owe you for your hard work with my patients while I have been away. Good luck on your research Jim, Julia you are a star. *Charikleia Chrysostomou*, *Joakim Österman* and *Emelie Westergren*; my prior residents. You juggle family-life, work and research, besides being brilliant clinicians! *Helen* good luck next week! *Peter, Krassimir, Elisabeth, Annette, Grazyna, Luay, Xiang, Alexandra, Samiha, Ehab, Anna, Hovak, Amel, Juha, Oskar, Markus, Salim, Peter B, Stefania,* and all the rest; your friendship and collegial collaboration means a lot to me. *John Sandberg,* what an artist, you are amazing!

Maria A, Jenny, Erika, Maria, Mina, Hanna, Ellen, David and *Irene*; the great team at our PD clinic, thanks for your hard work and for making every day at work so special! *Marie, Helena, Ailie, Agneta, Michaela, Ewa* all of my long-term so close colleagues; we work hard, and since forever are you there for me, I hope you know how much that means. *Eva-Marie, Inger, Anneli, Marita and Anne-Carin* you are great. *Nina, Gudrun* and *Sanna*, medical secretaries. Thanks for so creatively filling in my blanks, I will try my best to learn how to dictate. *Monica, Helen, Nina, Brittis, Pia, Kristina, Ida, Helen, Yvonne, Lisa, Julia* and all you other colleagues in hemodialysis; you are the best!

All friends in the Swedish Access meeting; *Frida Fondelius*, my co-organizer through thick and thin, my dear friend. *Gunilla Welander* thanks for creating the SRR-Access and your commitment! *John Softeland, Pelle Carlsson, Mattias, Laszlo* and the rest of you professionals, I am so lucky for our gang, science, work and pleasure as its best! *Helga Gudmundsdottir*, always there for science, clinical issues, chats, I appreciate your LV taste. *Professor Wim van Biesen*, our mentor, the EuroPD dialysis leadership program. Thanks for introducing me to all European colleagues, to research, lectures and our manuscript. Professors *Monika Niemierko* and *Edwina Brown* you are my inspiration.

Britta Hylander Rössner, thanks for employing me at KS in -99. Your way of seeing both the patients and us, always with time for questions. The safe, caring environment were made for clinical development. I try my best to live up to your standards. *Martin Glimåker* the one doctor making the greatest impression during Med school, and Almunecar neighbor. *Ann-Sofie Backman* our friendship started with all the medical students. We are indeed the most understanding moms, wives, colleagues and cultural ladies ever... *Katarina Öhrling* dear med-school friend, forever UCLA& California girl. Thanks for being my outside mentor for this thesis.

The KI research school in epidemiology, director of studies *Anna Sandström.* PhD-student colleagues, *Lina Ivert* and *Caroline De Visscher* for support along the way, networking and friendships! *Jessika Norrbom* and all friends on Fortasana and Free Nature.

The neighbors at Pink Hill; it takes a village to raise a thesis. Thanks for all support, AWs and dinners. *Marie & Henrik*, exercise partner and wine dealer all-inclusive, organizer of our parties. *Johan & Linn-Marie*, for all deep talks and school-pickups. *Åsa & Anders*, for all your advice over the years. *Inger Andersson*, my professional role model, thanks for your and *Martin´s* support.

Moberg, *Kjellsson, Landholm, Berinder, Florinus, Sjödin and Frantzén* all good friends-finally it´s time to party! *Eva, Erik* and *Felicia* thanks for all fun over the years, and *Royne* who encouraged me to try research. *Pia* thanks for always caring and checking in, and *Mikael* for my company name, KidneyPie.

My sisters in law *Helen,* your work ethics to for troubled schoolkids is amazing and *Peter*, I appreciate your energy! *Marina* one more Medical specialty than I have. *Sonja & Herbert,* mina svärföräldrar. Ni har lärt oss alla att våga satsa, att man står för sitt ord och hugger i när det behövs. *Titti och Bettan*, kära kusiner. *Fredrik & Catharina*, det är en trygghet att ni alltid finns där för oss med *Elsa och Edvin*. *Margareta & Göran*, kära mamma och pappa. Jag älskar er! Tack för ovärderligt stöd och all hjälp genom åren. *Mamma* för alla läxförhör och all omtanke. *Pappa* för en trygg grund att stå på och alla våra samtal. Det här hade nog farmor Frida gillat. *Karl och Frida* mina kära, världens allra bästa och underbaraste barn. Jag är så oändligt stolt över vilka bra människor verkar bli! Följ era drömmar så blir de sanna! Grattis på 22-årsdagen *Karl*!! *Peter*, min egen älskade make- inget hade varit om inte Du varit den du är, min trygghet som alltid finns där för mig.

Thanks to all my patients. This project would not have been possible without the support of Njurfonden, Njurstiftelsen, Westmans Stipendiefond and Svensk Njurmedicinsk förening.

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