Chapter 13

Summary and general discussion

Introduction

Chronic kidney disease (CKD) has become a major public health problem worldwide.[1-4] The increasing prevalence of patients with CKD[1;5;6] can be explained by the growing elderly population and lifestyle changes. Renal function has an age-related natural decline[7], leading to a moderately reduced renal function at older age[5]. Lifestyle changes, such as high-fat diets and low physical activity, have led to an increasing prevalence of hypertension[8] and type 2 diabetes mellitus[9]. These morbidities are known to accelerate renal function decline, thereby increasing the risk of developing CKD. CKD is defined by a progressive loss of renal function which may eventually lead to the need for renal replacement therapy (RRT, starting dialysis or receiving a kidney transplant; also defined as end-stage renal disease, ESRD).[10] Ideally, progression towards the start of RRT is slowed down in early stages of the disease process, in which renal function is normal or mildly reduced and albuminuria/proteinuria is present (CKD stages 1 and 2). However, in most patients CKD only becomes symptomatic when renal function deteriorates and drops below 30-60 ml/min/1.73 m^2 (CKD stages 3-5).[11] Screening strategies based on albuminuria/proteinuria to identify patients in earlier stages of the disease process are unfortunately not optimal yet. At this moment, no consensus has been reached regarding the appropriate type of test, which thresholds to use, which patient populations to screen and whether a screening strategy is cost-effective.[4;12-14] Therefore, treatment to slow down the disease progression is mainly performed in more advanced CKD stages and guidelines for this population are important. In The Netherlands young patients (<65 years) with a renal function below 60 ml/min/1.73 m^2 (CKD stages 3-5) should be referred to a nephrologist and treated according to guidelines.[10;15] Elderly patients should only be referred when this moderately reduced renal function coincides with the presence of proteinuria (>1 g/24h) or a progressive loss of renal function (>3 ml/min/1.73 m^2/year). When renal function deteriorates even further (<30 ml/min/1.73 m^2, CKD stages 4-5), both young and elderly patients are referred to an outpatient clinic for multidisciplinary pre-dialysis care. Treatment guidelines for this specific population have been developed in The Netherlands.[16] However, these guidelines are mainly based on studies performed in early- to middle-stage CKD patients and mainly focus on the objectively assessed outcome renal function decline. Studies in the pre-dialysis population are therefore needed to make these guidelines more evidence-based. Therefore, the main goal of this thesis was to investigate the effect of several risk factors on objectively assessed disease progression, defined as renal function decline and time until the start of RRT, and subjectively assessed disease progression, defined as disease-related symptoms and health-related quality of life, in patients on specialized pre-dialysis care. We furthermore tried to explore (un)known mechanisms that determine renal function decline in pre-dialysis patients. For both aims data were used from the PRE-dialysis PAtient REcord (PREPARE) study. We also explored (un)known mechanisms of the age-related renal function decline in the general population and for this aim the Leiden Longevity Study was used. This study consists of subjects with a propensity for longevity and environmentally matched controls without this propensity.[17;18] The exploration of (unknown) mechanisms may

unravel new treatment targets for pre-dialysis patients. A summary of our main findings are presented in the following paragraphs and in Table 1.

Summary of main findings

Outcome: renal function decline

In **chapters 2, 4,** and **5** we used renal function decline as outcome. Renal function was expressed as glomerular filtration rate (GFR) and we used serum creatinine-based formulas to estimate the GFR (eGFR). These chapters provide evidence that current treatment targets for controlling blood pressure (systolic below 130 mmHg and diastolic below 80 mmHg, when proteinuria is present), proteinuria (below 0.3 to 1.0 g/24h) and lipid levels (low density lipoprotein (LDL) cholesterol levels below 2.5 mmol/l and triglyceride levels below 2.25 mmol/l[16]) are clinically well defined regarding the outcome renal function decline. Patients on pre-dialysis care with levels below these targets experience a slower renal function decline compared with patients having levels above the treatment target. For all three important risk factors a dose-response relation was found, indicating that higher levels were associated with a faster renal function decline. Clinically relevant increases of these risk factors (10 mmHg increase in systolic and diastolic blood pressure, 1 g/24h increase in proteinuria, and 1 mmol/l increase in LDL cholesterol and triglyceride levels) resulted in a 0.04 to 0.06 ml/min/1.73 m^2/month faster renal function decline. On a yearly basis this represents a 0.48 to 0.72 ml/min/1.73 m^2 faster decline in renal function. This additional decline is quite large considering the relatively low renal function at the start of pre-dialysis care (~15 ml/min/1.73 m^2). To illustrate the clinical impact of these findings, 17% of all pre-dialysis patients have a systolic blood pressure above 180 mmHg, resulting in a 2.4 ml/min/1.73 m^2/year faster renal function decline compared with patients with their blood pressure on target. For proteinuria, 25% of the patients have levels above 3.8 g/24h, leading to a 1.7 ml/min/1.73 m^2/year faster renal function decline compared with patients with a level of 0.3 g/24h, which is the lower target boundary. Lowering blood pressure, proteinuria, and lipid levels may therefore slow down the rate of renal function decline. Several large randomized controlled trials indeed showed a slower renal function decline when blood pressure and proteinuria were lowered with an angiotensin-converting enzyme inhibitor (ACEi) and/or an angiotensin-II receptor blocker (ARB).[19;20] Lowering lipid levels with statins showed an absent or very small effect on renal function decline.[21-24] However, we have to keep in mind that these randomized controlled trials mainly included patients with moderate CKD (stage 3) instead of patients with advanced CKD (stages 4-5) or used renal endpoints that are very robust (e.g. start of RRT and doubling of serum creatinine).

Outcome: start of renal replacement therapy

For proteinuria, **chapter 4** showed that higher levels resulted in an earlier start of RRT, which is consistent with the outcome renal function decline. Per each 1 g/24h increase, there was a 6% higher rate of starting RRT. This consistency was also present for systolic (≥180 versus 140-

159 mmHg) and diastolic (≥100 versus 80-89 mmHg) blood pressure in young (<65 years) pre-dialysis patients (1.9 and 1.7 fold higher rate, respectively, **chapter 3**). However, **chapter 3** showed contradictory findings with respect to renal function decline in elderly (≥65 years) patients. Low systolic (<120 versus 140-159 mmHg) and diastolic (<70 versus 80-89 mmHg) blood pressure were associated with an earlier start of RRT in elderly patients (2.8 and 1.6 fold higher rate). This finding may indicate that in clinical practice indications are present to start RRT, that do not influence renal function decline. Congestive heart failure is a complication often seen in CKD patients[25] and leads to a reduction in cardiac output. This disease, especially in CKD patients, is often accompanied by volume overload. Fluid overload is one of the most important indications to start RRT. Moreover, a reduced cardiac output will also result in hypo-perfusion of the kidneys and thereby a lower renal function. The loop between cardiac dysfunction and progressive loss of renal function is also called the cardio-renal syndrome.[26] The presence of the renal part of this syndrome is not supported by the results presented in **chapter 3**, showing a similar renal function decline in elderly patients with low compared with normal blood pressure. However, it could be that congestive heart failure leads to a sudden drop of renal function followed by an immediate start of RRT. Such a drop may not be detected when calculating renal function decline with multiple measurements over time.

Outcome: symptoms and health-related quality of life

Chapters 6 and **7** focused on disease-related symptoms and/or health-related quality of life, which are considered subjectively assessed outcome measures. As compared with other medical fields, such as the field of cardiovascular disease[27], in the field of nephrology these outcome measures are not clearly incorporated into clinical guidelines[16]. This is probably caused by the lack of consensus between investigators and clinicians on the meaning, importance, assessment, and interpretation of health-related quality of life[28] and symptoms, implicating the need for more research. During the last years more research has been performed on health-related quality of life in CKD patients. Several studies showed that health-related quality of life deteriorates when renal function declines.[29-31] This could be explained by the fact that disease-related symptoms become more present when kidney function decreases. Together with treatment choices that have to be made, the mental and physical well-being of an individual can be affected. Furthermore, health-related quality of life is a good predictor for mortality and progression to ESRD throughout all stages of CKD.[32] These findings have changed the thought about health-related quality of life and more studies are now focusing on this outcome. Results from **chapter 6** provide further support for the importance of subjectively assessed outcome measures, by showing an increase in symptoms and a decline in health-related quality of life during pre-dialysis care with the sharpest change in the last 6-12 months before starting dialysis. Furthermore, each additional symptom and each 3-point lower physical and mental health-related quality of life score were associated with a respectively 7%, 2%, and 3% higher risk of starting dialysis within the subsequent six months. Besides these changes during pre-dialysis care, it has been shown that in anemic CKD

patients, targeting hemoglobin levels of 11-12 g/dl (recommended target) improves health-related quality of life.[33] However, a debate is ongoing whether targeting higher (≥13 g/dl) hemoglobin levels has more beneficial effects. Evidence supporting this idea is lacking, especially in the specific population of patients on pre-dialysis care. **Chapter 7** showed that only in young (<65 years) patients treated with anemia-medication (an erythropoiesis stimulating agent and/or an iron supplement), high compared with recommended hemoglobin levels (11-12 g/dl) were associated with a better physical and mental health-related quality of life (8.5 and 6 points respectively, 3-5 points are considered clinically relevant[34]). In elderly (≥65 years) patients treated with anemia-medication, no effect of higher hemoglobin levels on health-related quality of life was present.

Risk factors: explore (un)known mechanisms

To identify new treatment strategies for slowing down renal function decline, exploration of (un)known mechanisms that determine renal function decline should be performed. Several studies have shown that black CKD patients who are not dialysis-dependent, experience a faster renal function decline[35] and progression to ESRD[36;37] than whites. The results described in **chapter 8** are in line with this. In this chapter we tried to explore which underlying mechanism(s) is (are) responsible for the faster decline in blacks (additional decline of 0.16 ml/min/1.73 m^2/month). In The Netherlands, a universal healthcare system is present, leading to equal access and comparable quality of care for all patients. Healthcare system related factors could therefore not be the complete explanation for the faster decline found in blacks. Furthermore, results did not change after adjustment for demographic characteristics, co-morbidities/lifestyle, medication, renal damage, renal function, and laboratory values. Therefore, these factors could also not explain the difference in renal function decline between blacks and whites. However, the faster decline in renal function in blacks when compared with whites was only present in patients with diabetes mellitus or proteinuria. This finding could indicate that diabetes mellitus in black patients has more severe consequences for the kidneys than in white patients. **Chapter 9** indicated that at middle-age renal function is higher in men with a propensity for longevity compared with men without such a propensity (eGFR difference of 1.78 ml/min/1.73 m^2). This finding may implicate that subjects from longevity families are less susceptible to risk factors, such as hypertension and cardiovascular events, that further accelerate the age-related natural renal function decline (0.4 ml/min/1.73 m^2/year from the age of eighteen years[7]). An even stronger renal function difference was found in men with a history of hypertension or myocardial infarction/stroke (6.98 and 6.21 ml/min/1.73 m^2, respectively), which may implicate a better handling of systemic inflammation in male longevity subjects. Further research should focus on finding the specific underlying mechanism causing a faster renal function decline in blacks and a lower renal function in middle-aged subjects with a propensity for longevity. By identifying the genetic pathways responsible, our understanding of how the kidneys work increases and new treatments can be identified.[38]

Table 1: Pre-dialysis guidelines: evidence from the PREPARE study

Progression factor / complication	Target	Outcome	Associations present in PREPARE study
Hypertension	Blood pressure <130/80 mmHg	Renal function decline, start of RRT	Below target, <65 years: - Slower renal function decline - Later start RRT Below target, ≥65 years: - Earlier start RRT
Proteinuria	Urinary protein excretion <1 g/24h	Renal function decline, start of RRT	Below target: - Slower renal function decline - Later start RRT
Hyperglycemia	HbA1c <7%		
Anemia	Hemoglobin 6.8-7.4 mmol/l, avoid ≥8.0 mmol/l, serum ferritin 100-500 µg/l	Health-related quality of life	Above target, <65 years: - Better physical and mental health-related quality of life
Mineral bone disorders	Calcium 2.1-2.37 mmol/l, phosphate 0.7-1.3 mmol/l, PTH ~2-7 pmol/l		
Metabolic acidosis	Serum HCO_3 20-22 mmol/l		
Hyperkalemia	Potassium <5.5 mmol/l		
Hyperlipidemia	LDL <2.5 mmol/l, non-HDL <3.4 mmol/l, HDL >1 mmol/l, triglycerides 2.25-4.5 mmol/l	Renal function decline	Below target, LDL: - Slower renal function decline
Lifestyle factors	Stop smoking, balancing nutrition and physical activity		

RRT: renal replacement therapy; HbA1c: hemoglobin A1c; PTH: parathyroid hormone; HCO_3: bicarbonate; LDL: low density lipoprotein; HDL: high density lipoprotein.

Strengths and limitations of the PREPARE study

A great strength of the retrospective PREPARE-1 and prospective PREPARE-2 cohort study is the inclusion of incident instead of prevalent patients in multiple academic and peripheral centers. By following incident patients from the moment of referral, a reliable course of disease progression during pre-dialysis care can be obtained. Furthermore, including prevalent patients may lead to biased results. The chance to be included in a prevalent population not only depends on the occurrence of an event – in this study receiving pre-dialysis care – but also on the duration of the event. Therefore, 'healthier' patients receiving care for a longer period will have a higher chance to be included in a prevalent population. This may lead to selection bias and results cannot be generalized to the entire population of patients on pre-dialysis care. Including patients from multiple centers, both academic and peripheral, results in a good representation of the total pre-dialysis population in The Netherlands and thereby a high generalizability of the results. In the PREPARE-1 study this

generalizability is even more pronounced because data were retrospectively extracted from medical records and thereby all consecutive patients could be included.

The strength of the PREPARE-2 over the PREPARE-1 study is the availability of repeated measurements. In addition to baseline – start of pre-dialysis care – during every six-month interval demographic, anthropometric, and clinical data were collected. Furthermore, health-related quality of life and illness perception questionnaires were filled in by patients. Data on functional status could not be obtained in the PREPARE-1 study due to the retrospective design of the study. With these repeated measurements, changes in clinical factors during pre-dialysis care can be illustrated. Furthermore, changes over time can be related to clinical outcomes on pre-dialysis care, such as the start of RRT or death.

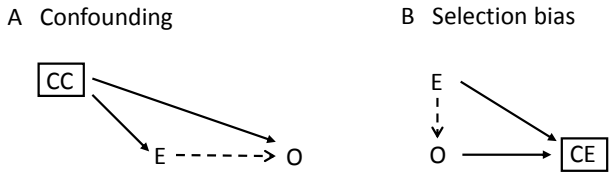
Besides the above mentioned strengths, the PREPARE-1 and PREPARE-2 study have three important methodological limitations, which are discussed in the following three paragraphs.

Confounding

Confounding is a bias that arises when the exposure and the outcome share a common cause.[39] The causal diagram in Figure 1A represents the structure of confounding, depicting two pathways between exposure (E) and outcome (O). The first pathway is the causal effect of exposure on outcome (E → O) and the second pathway between exposure and outcome is via a common cause CC (E → CC → O). If the common cause did not exist the only pathway present would be the causal effect of exposure on outcome. However, the common cause results in an additional association that confounds the causal effect between exposure and outcome. Conditioning on the common cause will block the additional association between exposure and outcome and eliminate confounding. Therefore, all variables that block additional pathways after being conditioned on are called confounders. Confounding is often encountered when answering causal questions in observational studies. In such studies, a causal contrast for the exposure of interest is made – for example high versus low blood pressure – and outcome frequencies – for example mortality rate – are compared. Blood pressure and mortality share many common causes that can confound the causal effect between the two. Elderly patients for example often have a high blood pressure and mortality rates are rising with increasing age. So, when an association is found between high blood pressure and a high mortality rate, this association can be confounded by age. In other words, the higher mortality rate in the high blood pressure category is not completely caused by blood pressure but also by the higher age. Therefore, the analysis should be conditioned on the common cause age to block this additional association. In all chapters of this thesis we used multivariable models to adjust for confounding. Unfortunately, it is difficult to define and measure all common causes (confounders). Residual confounding is therefore unavoidable in observational studies. The optimal method to demonstrate whether a causal relation exists is an interventional randomized controlled trial. Randomization leads to an equal distribution of all (un)known and (un)measured confounders between the trial arms, if the randomization procedure is performed correctly and the sample size is large enough. Only

the assigned intervention will be different between the groups compared. In our example of blood pressure, prescribing anti-hypertensive medication is a possible intervention. However, we have to keep in mind that the results of this trial will tell us something about the causal effect of prescribing anti-hypertensive medication on mortality and not about the causal effect of blood pressure. Most probably, this causal effect of anti-hypertensive medication will act via the lowering of blood pressure, but maybe not entirely. However, for clinical purposes we are more interested in how to treat high blood pressure and what the causal effect is of this treatment than we are interested in the causal effect of blood pressure itself. The prescription of anti-hypertensive medication can be easily randomized and blinded. However, not all exposures in the field of nephrology are easily randomized – such as conservative treatment versus renal replacement therapy – or blinded – such as starting dialysis versus not starting dialysis. A correctly performed observational study is often a good alternative to answer such questions. Furthermore, observational studies are very suitable for answering unintended effects, such as side effect of certain therapies.[40]

Figure 1: Causal diagrams, structure of confounding and selection bias



CC: common cause, E: exposure, O: outcome, CE: common effect,
square: conditioned on this variable.

Selection of patients

Patients with CKD often die of (cardiovascular) complications before reaching pre-dialysis care or ESRD.[41] Therefore, patients who reach the start of pre-dialysis care are a selection of survivors. By conditioning on the start of pre-dialysis care, independent indications to start are then artificially associated with each other. In our study for example, low health-related quality of life and the presence of hypertension are independent indications to start pre-dialysis care. If a physician refers a patient with low blood pressure to an outpatient clinic for specialized pre-dialysis care, the chance that this patient has a low health-related quality of life – another indication for referral – will be greater. We indeed found this association in the PREPARE-2 study (data not shown in thesis), which could be explained by this form of selection bias[42], sometimes called index-event bias. Conditioning on a common effect of exposure and outcome is often encountered in scientific literature (**chapter 11**) and the causal structure of this selection bias is represented in Figure 1B. We cannot account for this problem in our statistical analyses, but we have to keep this in mind when interpreting results. However, many of the chapters in this thesis did not investigate an association between two indications for referral. Only the results in **chapter 7** – investigating the

association of hemoglobin levels with health-related quality of life on each time point during pre-dialysis care – could be biased because of conditioning on the start of pre-dialysis care. Patients treated for anemia towards a high hemoglobin level may be referred to pre-dialysis care because they have a low health-related quality of life. However, if this type of bias plays a role, than our results are an underestimate of the real association.

Missing data

Missing data are a problem that we encountered in every chapter of this thesis. This problem is often encountered in observational studies – cohort or randomized – with routinely collected data. In **chapters 2-4, 8** and **9**, factors at baseline – start of pre-dialysis care – were associated with renal function (decline) and/or time until the start of RRT. In these studies, the exposure – blood pressure, proteinuria, race, and longevity – and/or potential confounders we want to adjust for were missing in some individuals. When performing a complete case analysis, patients with missing data on either the exposure or a confounder are excluded from the analysis. This leads to loss of power due to a smaller sample size and selection bias can occur. Results can be biased if for example the reason of data being missing depends on the prognosis of the patient (i.e. missing data type missing at random). In **chapters 5-7**, factors during pre-dialysis care were associated with renal function (decline), time until the start of RRT, and/or health-related quality of life. A method for dealing with missing follow-up data is the method of last observation carried forward. This method can only be used with repeated measurements because it replaces a missing value of a patient with the last measurement before that time point. However, biased results can occur because the assumption is being made that factors stay constant over time. Especially during pre-dialysis care, this is an assumption that is clinically not very plausible. Therefore, both standard methods for dealing with missing data, complete case analysis and last observation carried forward, are not preferred for the analyses in this thesis.

In this thesis, the method of multiple imputation is used, in which missing values for an individual are predicted based on known data for that individual.[43;44] **Chapter 10** describes the theory behind this method and when to apply. In short, strata are being made based on all variables (baseline and/or follow-up measurements) included in the imputation model. Each individual patient can be categorized into one of these strata based on their patient characteristics. The mean value – of the variable you want to impute – in that stratum is than imputed. Prediction uncertainty is taken into account by adding a random error component and by repeating the imputation procedure several times. We believe that this method results in an imputed value that lies closest to the true value. However, it is important to keep in mind that unknown and unmeasured variables that can predict the missing value very well, cannot be included in the imputation model. Furthermore, the prediction variables included in the imputation model cannot have too much missing values themselves.

In **chapters 2-4, 8** and **9** all patients with available baseline data on the exposure were included in the analyses. We chose the method of multiple imputation to impute missing

baseline confounders because patients with missing confounder data had somewhat different baseline characteristics compared with patients with all data available. Besides loss of power due to a smaller sample size, a complete case analysis would have led to selection bias in this case. Only in **chapter 4** the exposure, proteinuria, was missing in a considerable number of patients (~20%). Furthermore, the patients with missing data on proteinuria had somewhat different baseline characteristics compared with the patients with available data. Therefore, we performed a sensitivity analysis in which proteinuria was additionally imputed to check whether the results of our primary analysis were biased. The analyses presented in **chapters 5-7** have missing baseline and follow-up measurements. For dealing with these missing follow-up measurements we used a linear mixed model.[45] Patients with at least one available exposure and outcome measurement during pre-dialysis care can be included in such a linear mixed model, leading to the exclusion of patients with no data available (varying from 20% to 30% of the total population). Missing baseline confounders were again imputed with multiple imputation to maintain power and avoid selection bias after adjustment. The main reason for not including all patients in the imputation model and thereby not imputing missing baseline and follow-up measurements in these patients is as follows. Including all patients and/or all follow-up measurements would have resulted in prediction variables with too many missing values themselves. It is known that an imputation model does not perform well in such cases. However, if the exclusion of patients leads to selection bias, the not optimal performing imputation model may be preferred. Fortunately, baseline characteristics were very similar between patients with and without at least one exposure and outcome measurement, which excludes the possibility of selection bias. Therefore, excluding patients with no available exposure and outcome data and applying linear mixed models to account for the remaining missing data is in our opinion the preferred method.

Objective versus subjective outcome measures

In this thesis we aimed to find factors that influence the disease progression of patients on specialized pre-dialysis care. But how can we define disease progression in these patients? The most objective manner agreed upon to define progression is by assessing decline in renal function (eGFR) in each individual patient. Renal function is important for defining CKD stages 3-5[10] and is used as a parameter in the decision when to start with dialysis[16]. So, the decline of this parameter reflects progression quite well. But how can we measure renal function? The gold standard for measuring renal function is based on injecting a substance in the blood stream which is freely filtered by the glomerulus and neither secreted nor reabsorbed by the distal tubules, for example inulin[46] or iohexol[47]. After injection, renal function (in ml/min) is determined by measuring the substance concentration in blood and urine at certain time points. Unfortunately, this is an invasive, time-consuming, and expensive procedure. Therefore, several formulas have been developed to estimate renal function based on serum creatinine levels, such as the MDRD[48], CKD-EPI[49], and Cockcroft Gault formula[50]. These formulas experience much inter-variability within and intra-variability between populations[51-53], for example between age categories and CKD stages. This variability may be explained by

the fact that all formulas are based on serum creatinine levels, a waste product of muscles. Serum creatinine levels are not only influenced by the filtration capacity of the kidneys but also by muscle mass, which varies with age, weight, and sex.[54] For example, it is known that patients experiencing cachexia break down their muscles leading to higher serum creatinine levels and thereby a lower estimated renal function than in reality. In contrast, patients who are underweight because of malnutrition will have a low muscle mass, leading to lower serum creatinine levels and thereby a higher estimated renal function than in reality. Moreover, creatinine levels only start rising when a substantial loss of renal function has taken place. Therefore, the formulas will experience more bias in patients with lower creatinine levels.[55] Efforts are made for developing formulas based on other markers of renal function, such as Cystatin-C. However, formulas based on this marker experience similar biases as creatinine-based formulas.[52] So, the estimation of renal function with formulas is perhaps not as objective as we think.

Another outcome used in this thesis is the start of RRT. This outcome is more subjective than the outcome renal function decline. Besides renal function, other factors – such as co-morbidities or other clinical parameters (e.g. hyperkalemia, fluid overload), physicians' or patients' preference, patients' physical or mental status – influence the decision when to start RRT.[56] The actual time until the start of RRT is therefore very subjective to variation. Imagine two patients with a similar renal function at the start of pre-dialysis care (20 ml/min/1.73 m^2), a similar time until the start of RRT (1 year), but a different renal function when starting RRT (10 versus 5 ml/min/1.73 m^2). With regard to the outcome RRT, disease progression is similar, namely one year. However, in the patient with a renal function of 10 ml/min/1.73 m^2 at the start of RRT, renal function decline is slower (10 versus 15 ml/min/1.73 m^2/year). The decision to start at a higher renal function is probably based on other reasons, such as those mentioned before. However, time until the start of RRT is clinically very important because the goal of specialized pre-dialysis care is to postpone the start. According to known factors that accelerate RRT initiation[56], postponement of the start of RRT can be achieved either by the application of therapies that slow down the rate of renal function decline, by regulating clinical parameters/complications, or by improving patients' physical and mental status. For clinical purposes and guideline development, the outcome start of RRT is therefore just as objective as the outcome renal function decline. Research focusing on disease progression should therefore investigate both outcome measures if possible.

Disease-related symptoms and health-related quality of life, both physical and mental, are outcome measures rarely published in the field of nephrology. These outcomes are often classified as subjectively assessed measures and therefore of less value. However, it may well reflect the disease or health status of an individual. Several studies showed that health-related quality of life deteriorates with decreasing renal function.[29-31] Furthermore, it is well established that health-related quality of life at the start of dialysis influences survival, independently of other important risk factors.[57-59] Dialysis patients with a low physical (analyzed categorical, <20 points versus >50, and continuously, per each 10 point increase)

health-related quality of life score experienced respectively a 48% and 22% higher rate of dying. For mental health-related quality of life (analyzed categorical, <30 points versus >50, and continuously, per each 10 points increase) these numbers were 97% and 22% respectively. This effect is also present in CKD patients who are not dialysis-dependent.[32] These studies show that the subjectively assessed health-related quality of life correlates well with objective outcomes. This correlation makes health-related quality of life an objective outcome measure as well.

We believe that for clinical practice all outcome measures used in this thesis are important. During pre-dialysis care, patients should be treated according to guidelines to slow down decline in renal function, decrease symptoms, and improve health-related quality of life, thereby postponing the start of RRT.

Elderly patients

Over the last decades the prevalence and incidence of elderly patients (≥65 years) with CKD or ESRD have increased and these numbers will continue to increase over the coming years.[5] Due to this increasing elderly population, research in the field of healthy ageing becomes more important. Several studies in the field of geriatrics have shown that known risk factors for renal function decline – such as blood pressure, cholesterol, and body mass index – behave differently in the geriatric population.[60-62] In the general population it is known that these risk factors increase the risk for mortality and accelerate renal function decline. However, in the geriatric population a protective effect has been found. It could be hypothesized that decreasing body weight, cholesterol, and blood pressure levels are indicators for a declining cardiovascular and cognitive health (e.g. declining nutritional status or increasing prevalence of congestive heart failure). Such a different association may also be present in elderly CKD patients because the prevalence of malnutrition and congestive heart failure is high in this population. Nowadays, pre-dialysis treatment guidelines[16] are based on studies performed throughout the entire range of age. Therefore, we advocate obtaining more evidence for this specific growing elderly population on pre-dialysis care.

In our pre-dialysis cohort, a less pronounced negative association was found for high systolic and diastolic blood pressure with the start of RRT in elderly (≥65 years) compared with young (<65 years) patients (**chapter 3**). The association between high hemoglobin levels and improved health-related quality of life was also less pronounced in elderly (≥65 years) patients treated with anemia-medication (**chapter 7**). Furthermore, elderly (≥65 years) patients with low systolic and diastolic blood pressure experienced an earlier start of RRT (**chapter 3**), which is a complete opposite association as seen in young (<65 years) pre-dialysis patients. Therefore, our results indicate that some risk factors for renal function decline show a different association with disease progression in elderly (≥65 years) patients on pre-dialysis care.

Several methodological explanations for these contradictory associations in elderly patients on specialized pre-dialysis care can be postulated. First, it is a highly selected population of elderly patients with CKD. Only patients surviving until the start of pre-dialysis care were included. Second, the presence of competing risks may lead to beneficial effects on the short-term but negative effects, as seen in the general population, on the long-term.[63] Third, reverse causation can be an issue, meaning that just before the start of RRT, for example blood pressure decreases. In other words, low blood pressure may be a marker of the impending start of RRT.

Of course, only based on our results we do not advocate discontinuing the prescription of anti-hypertensive medication or anemia-medication in elderly patients on pre-dialysis care. This recommendation cannot be made solely based on observational data. Future studies should proof whether the associations we found are indeed causal. For example, randomized controlled trials in the near future should specify in their study protocol that they want to test the intervention separate for young and elderly patients. Another option would be to pool all available trials on these medications in a meta-analysis and perform subgroup analyses by age.

Risk factors for renal function decline not only behave differently in elderly patients, but also in dialysis-dependent patients. Opposite or absent associations as compared with the general population have been found for cholesterol and body mass index.[63;64] It could therefore well be hypothesized that such an opposite or absent association is already present in patients on pre-dialysis care, who are in the transition phase from early CKD stages to being dialysis-dependent. However, we found a faster renal function decline in patients with high levels of LDL cholesterol or triglycerides (**chapter 5**), which is comparable with the associations seen in the general population.

Conclusions

Chapters 2 and **3:** Young (<65 years) patients on pre-dialysis care with low blood pressure levels experience a slower renal function decline and later start of RRT. Elderly (≥65 years) patients with a low blood pressure experience an earlier start of RRT, but a comparable renal function decline.

Chapter 4: Proteinuria is an important dose-dependent risk marker for CKD progression, defined as a faster renal function decline and an earlier start of RRT, in patients on pre-dialysis care.

Chapter 5: In patients on pre-dialysis care, high levels of LDL cholesterol and triglycerides are associated with a faster renal function decline, independent of the prescription of lipid-lowering medication.

Chapter 6: During pre-dialysis care the prevalence of disease-related symptoms increase and both physical and mental health-related quality of life decrease over time, with the sharpest

change during the last 6-12 months before starting dialysis. This is supported by the finding that patients who report a high number of symptoms and/or a low health-related quality of life experience a higher risk of starting dialysis within six months.

Chapter 7: High hemoglobin levels (≥13 g/dl) in young patients (<65 years) treated with anemia-medication are associated with a higher physical and mental health-related quality of life. However, this association is absent in elderly (≥65 years) patients.

Chapter 8: Black patients on pre-dialysis care experience a faster renal function decline and earlier start of RRT compared with white patients, which may be explained by the greater negative consequences of diabetes mellitus and proteinuria on the kidneys in black patients.

Chapter 9: Middle-aged men with a propensity for longevity have a better renal function compared with men without such a propensity, especially in men with a history of hypertension or cardiovascular disease. A better biological handling of systemic inflammation and atherosclerosis in men from longevity families may be an explanation for this difference.

Chapter 10: When data is missing at random, a correctly specified multiple imputation model is preferred over other conventional methods, such as complete case analysis, mean substitution, or last observation carried forward.

Clinical implications and future research

Chapters 2-4 showed that high baseline blood pressure levels (especially in young (<65 years) patients), proteinuria, and high lipid levels can be useful in predicting the disease progression of patients starting pre-dialysis care. Furthermore, these results indicate that timely referral and well-controlled blood pressure, proteinuria, and lipid levels at the start of pre-dialysis care are important. So, multidisciplinary guidelines and treatment in the phase before pre-dialysis care is just as important. Unfortunately, patients with earlier stages of CKD are difficult to identify due to the absence of clinical symptoms[11] and the lack of appropriate cost-effective screening strategies[4;12]. Randomized controlled trials performed in the specific population of patients on pre-dialysis care are needed to proof whether the lowering of blood pressure, proteinuria, or lipid levels is causally related to a slower disease progression.

The course of symptoms and health-related quality of life during pre-dialysis care is described in **chapter 6**. Currently, a large debate is ongoing about when to start with dialysis. Consensus has been reached that making this decision solely based on renal function is not optimal.[65] In clinical practice, other measures, such as disease-related symptoms and health-related quality of life, are taken into account. However, these measures are not sufficiently incorporated into clinical guidelines because of the lack of knowledge how and when to use them. The results from this study showed that the increase of symptoms and decrease of both physical and mental health-related quality of life was mainly present during the last 6-12 months before starting dialysis. This implicates that these measures could be used in making the decision when to start. They are not useful when the course stays rather stable in the last phase of

pre-dialysis care. Furthermore, the number of symptoms and a low physical and mental health-related quality of life were associated with a higher risk of starting dialysis within six months. Unfortunately, no information was present regarding the exact reasons for starting dialysis in each individual patient. Therefore, we do not know whether the high number of symptoms and low score of health-related quality of life were markers of the underlying indications to start or the actual indications to start. Future research should focus on this relation and follow-up should be continued also after the start of dialysis. In this way, patients can be divided into different groups based on their indications to start; for example four groups based on combinations of high/low renal function and high/low functional status (i.e. symptoms and health-related quality of life). Thereafter, mortality rates during the complete period after referral to pre-dialysis care can be compared between these groups. With this extended follow-up data other clinical factors during pre-dialysis care can also be related to clinical outcomes on dialysis. Such a study, the European QUALity Study on when to start dialysis (EQUAL Study)[47], has been designed and started. The results from the EQUAL study may be used to develop a risk score indicating when to start dialysis for the guidance of nephrologists in this difficult decision.

The results from **chapter 7** implicate that young anemic pre-dialysis patients treated towards higher hemoglobin levels (≥13 g/dl) experience a better health-related quality of life compared with patients treated towards optimal hemoglobin levels (11-12 g/dl). Anemia guidelines were changed in 2007, indicating that the optimal hemoglobin target level is 11-12 g/dl and that targeting high hemoglobin levels (≥13 g/dl) should be avoided.[66] This amendment has been made because several trials showed an increased risk of mortality and morbidities when targeting high hemoglobin levels.[67] These guidelines are applied to all CKD patients, irrespective of age. Our results implicate that these guidelines may indeed be optimal for elderly patients (≥65 years) but need to be adapted for young patients. In clinical practice, a well-considered decision should be made for the best hemoglobin treatment target in each individual patient. This decision should be made by nephrologists together with the patient and should be based on the balance of negative effects – poorer survival – and positive effects – better health-related quality of life – for that individual patient. It could well be that the risk of mortality and morbidities is lower in young patients (<65 years), which would even more advocate targeting high hemoglobin levels in this population. Therefore, future randomized controlled trials investigating the causal effect of targeting high hemoglobin levels in pre-dialysis patients should make subgroups by age and should focus on the balance of negative and positive effects.

Unraveling (un)known biological mechanisms determining renal function decline or time until the start of RRT is important for a better understanding of CKD progression. Additional studies are necessary to investigate whether the finding in **chapter 3** is causal or whether low blood pressure is a marker for complications/mechanisms (e.g. congestive heart failure) that are indications to start RRT. For example, by measuring proBNP, a marker of congestive heart failure, this can be further elucidated. Furthermore, the underlying mechanism explaining the

faster renal function decline in blacks compared with whites (**chapter 8**) and the lower susceptibility to risk factors that accelerate renal function decline in men with a propensity for longevity (**chapter 9**) should also be explored. In both studies we could not find the exact underlying mechanism, but additional information on this may reveal new treatment targets.

We believe that future research should invest more effort in defining subgroups for which certain interventions are most beneficial. Age is an easy and important factor on which these subgroups could be defined. This individualized care is important because the population of patients on pre-dialysis care is very heterogeneous. Furthermore, not all focus should be on performing interventional randomized controlled trials to optimize treatment guidelines for pre-dialysis patients. Research to explore (un)known biological mechanisms that determine a faster renal function decline or an earlier start of RRT may unravel new targets for treatment.

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