Prepare; before starting dialysis : outcomes in patients with CKD stage 4-5

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PREPARE; BEFORE STARTING DIALYSIS

Outcomes in patients with CKD stage 4-5

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1

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

Chronic kidney disease

Healthy kidneys remove waste products and excess water from the body, regulate mineral composition and acidity of the blood, and produce enzymes and hormones. When there are abnormalities in the kidney structure or function for at least three months, with implications for health, patients are diagnosed with chronic kidney disease (CKD).[1] With a worldwide prevalence of 13.4% CKD is a major public health problem.[2]

CKD is classified based on cause, estimated glomerular filtration rate (eGFR) category, and albuminuria category.[1] In general, we define five CKD stages. In stage 1 patients are asymptomatic, have a normal eGFR and only a mildly increased albuminuria, while stage 5 CKD is characterized by kidney failure with an eGFR<15ml/min/1.73m^2. Stage 5 CKD is also called end-stage renal disease (ESRD) and in this stage renal replacement therapy (RRT) can become necessary to replace the function of the kidney and thereby improve quality of life and postpone death. RRT consists either of receiving a kidney transplantation, or dialysis. Although kidney transplantation is the best treatment for ESRD, not all patients can receive a donor kidney due to waiting lists, severe cardiovascular morbidity, or unsuitability to undergo surgery.[3, 4] These patients depend on dialysis for survival.

There are two dialysis treatment modalities; hemodialysis and peritoneal dialysis. During hemodialysis, waste products and excess water are removed from the body by using a non-biological membrane in an artificial kidney (hemodialysis machine) outside the body. Patients undergo this treatment approximately three times a week for several hours. Peritoneal dialysis is a treatment that uses the peritoneum as an endogenous membrane to remove waste products and excess water. This is done via a catheter implanted in the abdominal cavity of the patient, through which fluid has to be instilled and refreshed several times a day. Peritoneal dialysis in general takes place at home opposed to hemodialysis which most often takes place at the hospital.

Pre–dialysis stage

Ideal preparation for RRT starts with referral to a multidisciplinary team when reaching CKD stage 4 (eGFR<30 ml/min/1.73m^2), for so-called pre-dialysis care, to optimize care and slow down CKD progression. During pre-dialysis, patients are in the care of a nephrologist, nurse, dietician, and a social worker at an outpatient clinic. This team tries to retard kidney function decline by treating risk factors for kidney function decline, prevents and treats complications of CKD, and educates patients with regard to RRT. This approach has shown to be effective in multiple studies.[5-7] Patients on pre-dialysis care for example, have a lower risk of starting dialysis as compared with patients on regular care. After starting dialysis, patients who have received pre-dialysis care have a lower mortality as compared with patients on regular care.[5]

In this advanced stage of CKD, biological processes are changing and therefore treatment effects are changing too. Unfortunately, trials and large cohort studies, both in general and in CKD patients, often exclude pre-dialysis patients or include a very small proportion of

these patients for whom results are not analysed separately.[8-10] As a consequence there is a lack of knowledge on the optimal treatment of several risk factors for kidney function decline in pre-dialysis patients. More knowledge could positively affect the prevention and postponing of negative outcomes in this patient group.

Health related quality of life

Traditional outcomes in patients with CKD are mortality, morbidity, start of dialysis, and kidney function decline. However, patients with CKD suffer from a great range of physical and psychological symptoms and are known to have a lower health related quality of life (further referred to as quality of life), especially in the later stages of CKD.[11, 12] Focus is shifting from only attempting to improve prognosis (the traditional outcomes) in CKD stage 4-5 patients, towards also improving symptom burden and quality of life. Although these latter outcomes seem more subjective and may seem less specific as compared with traditional outcomes, for patients, especially with chronic conditions, these are very relevant outcomes representing the burden of their disease in daily life. Insights in these outcomes can increase the understanding of treatment effects and will improve patient care.[13, 14] In addition, a low quality of life in CKD stage 4-5 patients is associated with an increased risk of ESRD and mortality.[15, 16] In dialysis patients a low quality of life is associated with hospitalization, lower residual kidney function and mortality.[17, 18]

Quality of life can be defined in many ways, but a very common definition is “the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient” which is determined by an individual’s capacity to cope and to adapt.[19, 20] Quality of life can be measured with questionnaires completed by patients. Currently, several measurement tools are used, of different sizes and with different content. Not all of them are developed for the same population. Therefore, these questionnaires should be validated before using them in a population that differs from the original population in which the questionnaire was developed (**chapter 3**).

Several clinical variables are considered to be determinants of quality of life.[12, 21-24] However, kidney function, the most important biological factor in CKD and determinant for many treatment choices, does not influence quality of life as much as expected.[12, 25] A possible explanation for this can be found in the conceptual model by Wilson ***et al***. which portrays quality of life as the result of a chain of consecutive elements, passing from biological variables through symptom status to quality of life.[26] From this model it could be inferred that factors earlier in the chain – affecting quality of life through more intermediate variables – will have a weaker effect. The effect of biological factors, such as kidney function, is mediated by symptoms, which may thus be more important determining quality of life (**chapter 2**).

Cardiovascular risk factors and traditional outcomes

Even though there appears to be a careful shift of focus towards quality of life, treatment is still primarily aimed at delaying progression of the disease, and thus delaying kidney function decline and trying to prevent the need for a kidney transplant or start of dialysis.[27] Treatment is aimed at risk factors that are associated with disease progression as well as general lifestyle changes. With hypertension and diabetes mellitus causing over 50% of all CKD cases, many interventions are aimed at these diseases and their associated risk factors.[28]

As a result, many of the treatment targets in CKD address cardiovascular disease. As CKD progresses there is an increasing risk of cardiovascular disease and mortality. For example, patients with CKD stage 4 have a three times higher cardiovascular mortality risk as compared with individuals without CKD.[28] It is thought that addressing cardiovascular risk factors may directly and indirectly slow down CKD progression. Important treatment targets and thus risk factors for CKD and cardiovascular disease are blood pressure, the renin-angiotensin system (RAS), metabolic parameters (blood sugar, uric acid, and acidosis), and dyslipidemia (**chapter 4, 5 and 6**).[27] Non-traditional risk factors, such as FGF-23 and hyperhomocysteinemia, are beyond the scope of this thesis.

When a patient has reached ESRD, the treatment aim shifts towards preventing cardiovascular morbidity and postponing death. During dialysis, mortality rates are up to eight times higher as compared with persons without ESRD in the same age range and of the same sex.[28-30] With increasing age the difference in mortality rate becomes smaller but remains substantial. Cardiovascular events are the main cause of death, and the incidence of coronary artery disease, congestive heart failure, and left ventricular hypertrophy is elevated in these patients.[31] Therefore, research into cardiovascular risk factors remains an important topic in dialysis patients (**chapter 7**).

Aims of this thesis

The aims of this thesis were firstly to provide insight in quality of life as an outcome in pre-dialysis patients by investigating appropriate ways to measure this construct and by investigating factors affecting quality of life, and secondly to increase the understanding of the different associations between several cardiovascular risk factors and traditional outcomes in pre-dialysis and dialysis patients. The results can improve pre-dialysis patient care directly, provide supporting evidence for current guidelines for pre-dialysis and dialysis patients, or provide information to change current guidelines.

Description of the cohorts used in this thesis

EQUAL

The European Quality study on treatment in advanced chronic kidney disease (EQUAL), is a prospective cohort study performed in elderly patients with CKD progressing towards

ESRD in six European countries (the Netherlands, Sweden, Germany, United Kingdom, Italy, Poland). Study enrolment started in 2012 end will continue until 2020. Patients aged ≥65 years and an eGFR ≤ 20 ml/min/1.73m^2 (stage 4 and 5 CKD) for a maximum of six months are included in this study. These patients are followed for at least 4 years. A subset of the included patients (1500 patients, all patients included before December 2015) was used to perform the study in **chapter 2**.

PREPARE

The PREdialysis Patient Record (PREPARE) study is a multicenter follow-up study in 1049 patients aged ≥18 years, starting specialized pre-dialysis care in the Netherlands. The PREPARE study consists of a retrospective and a prospective part. In the retrospective part (PREPARE-I), incident patients who started pre-dialysis care (stage 4 CKD) in one of eight participating nephrology outpatient clinics between 1999 and 2001 were included. In the prospective part (PREPARE-II), incident patients who started pre-dialysis care in one of 25 participating nephrology outpatient clinics between 2004 and 2011 were included. The PREPARE-II population was used in **chapter 3, 4 and 5**. The entire PREPARE study was used for **chapter 6**.

NECOSAD

The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) is a prospective Dutch multicenter study in 38 dialysis centers, which included incident ESRD patients, aged ≥18 years, starting dialysis between January 1997 and January 2007. Over 2000 dialysis patients were included. After inclusion, patients were followed over time during which events of death and censoring due to other reasons were recorded. Follow up of events of death are continued to this day via the national registry. The NECOSAD population was used in chapter 7.

Outline of this thesis

In **chapter 2** we determined the relation between symptoms and quality of life in pre-dialysis patients.[12] The association of quality of life with negative outcomes, such as an increased risk of ESRD and mortality, emphasizes its importance and thereby the need to investigate determinants of quality of life in CKD patients.[15-18]

Since quality of life is an important outcome there is a need for adequate and efficient questionnaires to measure this. The most frequently used questionnaire to assess quality of life is the Short Form 36 (SF-36). The SF-36 measures health on eight dimensions as well as overall physical- and mental component scores.[32] However, the SF-36 can take up to 12 minutes to complete and is often considered too long for inclusion in large scale monitoring efforts. Therefore, shorter questionnaires are needed. In **chapter 3** we validated two of the most often used shorter quality of life questionnaires, the Short Form-12 (SF-12) and the EuroQol questionnaire (EQ-5D), in pre-dialysis patients.

In **chapter 4** we focused on the traditional outcome start of dialysis. We investigated the association between dyslipidemia and start of dialysis. This is one of the main risk factors aimed at in the treatment to delay CKD progression, although knowledge on the effects of dyslipidemia in pre-dialysis patients is lacking.

In **chapter 5 and 6** we investigated associations with the traditional outcomes start of dialysis and kidney function decline in pre-dialysis patients. In **chapter 5** the association with the risk factors angiotensin converting enzyme inhibitor use or/and angiotensin II receptor blocker use was investigated, which influence the RAS, an important target in the treatment to delay CKD progression. In **chapter 6** we investigated the association between vitamin K antagonists and start of dialysis and kidney function decline in pre-dialysis patients.

In **chapter 7** we shift focus from pre-dialysis to dialysis patients. We investigated the risk factor vitamin K antagonist again, but this time we investigated the association with mortality in dialysis patients.

In **chapter 8** the results of the previous chapters are discussed and summarized.

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2

THE IMPACT OF SYMPTOMS ON HEALTH RELATED QUALITY OF LIFE IN ELDERLY PRE–DIALYSIS PATIENTS; EFFECT AND IMPORTANCE IN THE EQUAL STUDY

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Nephrol Dial Transplant 2018

Abstract

Introduction: Quality of life (QoL) is an important outcome in chronic kidney disease (CKD). Patients feel symptoms are an important determinant of QoL. However, this relation is unknown. The aims of this study were to investigate the impact of the number and severity of symptoms on quality of life in elderly pre-dialysis patients, assessed by both the effect of symptoms and their importance relative to kidney function, and other clinical variables on QoL.

Methods: The EQUAL Study is an ongoing European prospective follow-up study in late stage 4/5 CKD patients aged ≥65 years. We used patients included between March 2012 and December 2015. Patients scored their symptoms with the Dialysis Symptom Index, and QoL with the RAND-36 item Health Survey (RAND-36). The RAND-36 results in a physical component summary (PCS) and a mental component summary (MCS). We used linear regression to estimate the relation between symptoms and QoL at baseline and after six months, and to calculate the variance in QoL explained by symptoms.

Results: 1079 (73%) patients had a baseline questionnaire (median age 75, 66% male, 98% Caucasian) and 627 (42%) patients a follow- up questionnaire. At baseline, every additional symptom changed MCS with -0.81 (95% CI -0.91;-0.71), and PCS with -0.50 (95% CI-0.62;-0.39). In univariable analyses number of symptoms explained 22% of MCS variance and 11% of PCS variance, whereas eGFR only explained 1%.

Conclusions: In elderly CKD stage 4/5 patients symptoms have a substantial impact on QoL. This indicates symptoms should have a more prominent role in clinical decision making.

Introduction

Elderly patients with advanced chronic kidney disease (CKD) often have a poor quality of life (QoL).[1, 2] This is an important outcome in these patients since it predicts mortality and morbidity.[3-5] Although many definitions of QoL exist, it is commonly defined as "the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient" which is determined by an individual's capacity to cope and to adapt.[6, 7]

In CKD patients clinical variables are considered important determinants for QoL.[8-12] However, kidney function, the most important biological factor in CKD and determinant for many treatment choices, does not influence QoL as much as expected. [12, 13] Although Pagels ***et al.*** and Chin ***et al.*** found a difference in QoL between patients with moderately severe versus severe CKD, no linear effect of eGFR on QoL has been observed.[12, 13] A possible explanation for this can be found in the conceptual model by Wilson ***et al***. which portrays QoL as the result of a chain of consecutive elements, passing from biological variables through symptom status through functional status to QoL.[14] From this model it could be inferred that factors earlier in the chain – affecting QoL through more intermediate variables – will have a weaker effect. The effect of biological factors, such as kidney function, is mediated by symptoms, which may thus be more important in determining QoL. The IDEAL study, where a large part of the CKD patients initiated dialysis based on symptoms instead of planned kidney function, illustrates this idea.[15]

CKD patients suffer from a wide range of physical and psychological symptoms. They can range from tiredness and itching to feeling anxious or irritable. Patients consider symptoms as one of the most important aspects of their disease, and both patients and nephrologists believe symptoms should be one of the main focuses in CKD research.[16-18] Nonetheless, research on symptoms and their effect on QoL in pre-dialysis patients is limited.[19, 20] A few notable exceptions suggest that an increase in symptoms is associated with a decrease in QoL. De Goeij ***et al***. found an increase in symptoms over time accompanied by a decrease in QoL in 436 pre-dialysis patients.[1] In a cross-sectional study by Abdel-Kader ***et al.*** symptoms were negatively correlated with QoL in 87 CKD stage 4/5 patients.[11]

This study aimed to fill this knowledge gap by investigating the impact of number and severity of symptoms on quality of life in pre-dialysis patients, assessed by both the effect of symptoms and their importance relative to kidney function and other clinical variables. In this study the word effect is used to investigate the relation between symptoms and QoL, an etiological research aim. The term relative importance is used when investigating the part of QoL that is determined by symptoms, a research aim more at the edge of etiological research.

Methods

Study design and population

The European Quality study on treatment in advanced chronic kidney disease (EQUAL study) is an ongoing prospective cohort study in advanced CKD patients in six European countries: Germany, Italy, Poland, Sweden, The Netherlands and the United Kingdom. We included patients of 65 years and older with an eGFR that had dropped to 20 ml/min/1.73m^2 or lower for the first time during the last six months in patients referred to a nephrologist. Patients were eligible when they were followed in a nephrology clinic, but were excluded if the drop in eGFR resulted from an acute event, or if the patient had received any form of renal replacement therapy (RRT) in the past. Patients were followed until kidney transplantation, death, refusal for further participation, moving to a center not participating in the EQUAL study, loss to follow-up, or end of follow-up. For the current study end of follow-up was determined at the 29th of November 2016 and patients were censored when starting dialysis. A full description of the study has been published elsewhere.[21]

For our analyses we used the baseline and six months follow-up data of the patients who were recruited for the EQUAL study between March 2012 and December 2015 and filled in at least the QoL part of the patient questionnaire at baseline. The study was approved by the medical ethics committee or institutional review boards (as appropriate) of all participating centers. Written informed consent was obtained from all patients.

Data collection

The EQUAL study followed patients receiving routine medical care as provided by the nephrology clinic. Data were collected and entered into a web-based clinical record form that was developed for this specific purpose. The information included patients' demographics, ethnicity, kidney disease, comorbid conditions, diet and medication, physical examination, and laboratory data.

The eGFR was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) formula, taking into account age, sex, race, and serum creatinine.[22] Primary kidney disease was classified by the treating nephrologist according to the codes of the European Renal Association-European Dialysis and Transplantation Association.[23] We grouped patients into four classes of primary kidney disease: glomerulonephritis, diabetes mellitus, renal vascular disease, and other kidney diseases. Educational level was classified into low (no education or primary school only), intermediate (primary and secondary school), and high (academic education).

All laboratory investigations and physical examinations were performed through standard protocols and procedures according to routine care at the local participating sites. In order to standardize these data, all participating centers completed a questionnaire to capture details on local laboratory methods, units of measurement and normal ranges. All data were then recalculated into one uniform unit of choice.

Additionally, data regarding the patient's lifestyle, marital status, QoL, as well as the presence and severity of uraemic symptoms were obtained via self-administered paper patient questionnaires. The list of uraemic symptoms was based on the Dialysis Symptom Index, which consists of 30 symptoms, and was complemented with the items bleeding, loss of weight, and loss of strength.[24] The patients had to score the presence of these symptoms over the past month. For each symptom experienced, patients subsequently rated how much they had been bothered by that symptom using a 5-point Likert scale with the options "not at all", "a little bit", "somewhat", "quite a bit", or "very much". The total number of symptoms resulted in a score that ranged from 0 to 33. The reported symptom severity was summarized in a score that ranged from 0 to 165 by counting the Likert scale points. Unreported symptoms were assigned a severity score of zero.[11]

QoL was measured with the RAND-36, a 36 item questionnaire measuring QoL on eight dimensions, resulting in an overall physical component score (PCS) and mental component score (MCS). The eight dimensions are physical functioning, role limitations due to physical problems, bodily pain, social functioning, role limitations due to emotional problems, mental health, general health, and vitality. To score a dimension at least half of the items in that dimension had to be completed.[25] The PCS and MCS were calculated using norm based scoring, which employs linear transformation to achieve standardized scores with a mean of 50 and a standard deviation of 10 for each dimension by using the United States population as a reference group.[26] Research has shown using the United States reference group is as good as using a Dutch reference group.[26]

Statistical analysis

Baseline characteristics were presented as mean ± standard deviation (SD) for normally distributed continuous variables, skewed continuous variables as median with interquartile range (IQR), and categorical variables as percentages.

Multiple imputation was used to minimize the risk of bias.[27] Missing values of number of symptoms, and symptom severity at baseline and after six months, as well as potential confounders at baseline were imputed (using 10 repetitions).

We conducted linear regression analyses to estimate the effect of number and severity of symptoms on the outcomes PCS and MCS. This was performed both at baseline and after six months of follow-up. All residuals were plotted to check the linearity assumption. To check the direction of the effect of symptoms on QoL we estimated the effect of baseline determinants on six months QoL, adjusted for baseline QoL using a linear regression analysis. Next, the effect of the difference in symptoms between baseline and six months of follow-up (delta symptoms) on the difference in QoL between baseline and six months of follow-up (delta QoL) was estimated with linear regression. All analyses were adjusted for the potential confounders: age, sex, ethnicity, country of residence, educational level, diabetes mellitus, cerebrovascular disease, myocardial infarction, hypertension, malignancy, psychiatric disease, body mass index, primary kidney disease, albumin, and eGFR.

All analyses including only baseline variables were performed in patients with a QoL patient questionnaire at baseline. Analyses including baseline and six months follow-up variables were performed in patients with a QoL patient questionnaire at baseline and after six months of follow-up. To simplify clinical interpretation we have added the effects of number and severity of symptoms on PCS and MCS per quartile, using the interquartile range for number and severity of symptoms.

Lastly, we calculated the impact of symptoms on QoL using linear regression analysis to calculate the explained variance as a measure of importance. In this analysis we defined different variable clusters: demographics (sex, age, ethnicity, education level, country of residence), comorbidities (diabetes mellitus, cardiovascular disease, myocardial infarction, malignancy, psychiatric disease) and primary kidney disease, eGFR, other laboratory measurements (albumin, hemoglobin, proteinuria), symptom number, and symptom severity. These clusters were included both separately with a univariable analysis and stepwise with a multivariable analysis. This way, the impact of each of these variables as well as their additive effect could be calculated. In addition to the estimated associations, this analysis gives more clinical context and demonstrates the relative importance of different determinants of QoL. The explained variance was calculated at baseline, after six months, and for change in symptoms and change in QoL.

To test the robustness of the results we performed several sensitivity analyses. First, we stratified all analyses by sex, since the occurrence of symptoms as well as the perceived QoL might differ between men and women and thereby affect the associations between symptoms and QoL. Second, we repeated all analyses without using multiple imputation for missing values. Third, we repeated all analyses only using multiple imputation for baseline confounders, not for symptom number or severity. Fourth, we repeated the linear regression analysis at baseline only including patients with a patient questionnaire at baseline and after 6 months of follow-up. Finally, we calculated the explained variance without the symptoms fatigue, feeling sad, feeling nervous, and feeling anxious since these are both symptoms and part of the SF-36 and thereby might influence the explained variance. P-values <0.05 were considered statistically significant. All analyses were performed using SPSS version 23.0 for Windows.

Results

Patient characteristics

Of the 1486 patients in EQUAL by the 31th of December 2015, 1079 (73%) filled in the QoL part of the baseline patient questionnaire and 627 (42%) filled in the QoL part of the patient questionnaire at baseline and after six months of follow-up. Missing symptom number and symptom severity were imputed. Of the 452 patients missing QoL at 6 months of follow-up, 40 already started dialysis, 61 died, 29 withdrew from the study, 7 received a kidney

Table 1. Baseline characteristics in patients with a patient questionnaire at baseline (n=1079) and in patients with a patient questionnaire at baseline and follow–up (n=627)

	QoL questionnaire at baseline, n=1079	QoL questionnaire both at baseline and 6 months, n=627
Sex, male	66	65
Age, years	75 (70-80)	76 (70-80)
Ethnicity		
Caucasian	98	98
Black	1	1
Other	1	1
Primary Kidney Disease		
Glomerular disease	10	9
Tubulo-interstitial disease	9	10
Diabetes Mellitus	20	18
Hypertension	35	37
Other/ unknown	28	26
Education [a]		
Low	30	28
Intermediate	48	48
High	17	21
Other	3	3
Marital status, married or living together	64	64
Diabetes Mellitus, yes [b]	40	37
Hypertension, yes [c]	89	90
Cerebrovascular Disease, yes	15	15
Myocardial Infarction, yes	18	17
Malignancy, yes	21	22
Psychiatric disease, yes	7	6
Body Mass Index, kg/m^2	28 (25-31)	29 (25-31)
Index eGFR, ml/min/1.73m^2 [d]	17.1 (3.1)	17.4 (2.7)
eGFR baseline, ml/min/1.73m^2 [d]	19.0 (5.5)	19.7 (5.3)
Serum albumin, g/L	37.6 (5.8)	37.7 (5.4)
Hemoglobin, mmol/L	7.2 (1.0)	7.3 (1.0)
Proteinuria, g/24h	1.9 (0.6-6.3)	1.6 (0.5-4.9)

Values are given as a percentage, means (±SD) or median (IQR).
Missings: baseline group; marital status 15, education 14, proteinuria 852, albumin 101, BMI 63, hemoglobin 12; baseline and six months group: marital status 9, proteinuria 517, albumin 56 BMI 32, hemoglobin 7 [a] Defined as: low, no education or primary school only; intermediate, primary and secondary school; high, academic education. [b] Defined as the presence of diabetes mellitus as primary kidney disease or a history of diabetes mellitus. [c] Defined as either the presence of hypertension as primary kidney disease or a history of hypertension. [d] eGFR was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) formula. Index eGFR; eGFR at time of study inclusion, eGFR baseline; eGFR at baseline measurement.
QoL: Quality of life

transplantation, and 3 patients had not yet reached the 6 months follow-up measurement. The other 312 (29%) patients were defined as non-responders. Patients with complete follow-up had a median age of 76 (IQR 70-80), 65% were male, and 98% were Caucasian (table 1). Sixty-four percent of these patients were married or living together, 28% had a low education level, 48% an intermediate education level, and 21% a high education level. Hypertension was present in 90%, a malignancy in 22%, and a psychiatric disease in 6% of these patients. In the 1079 patients with a baseline questionnaire these numbers were virtually the same. Supplemental table 1 shows the baseline characteristics for the 312 patients where follow-up questionnaires were missing.

Table 2 shows the number of symptoms, symptom severity, MCS, and PCS at baseline and after six months of follow-up for complete cases. The numbers showed only small changes over the first six months. In figure 1 the prevalence of symptoms with the severity score per symptom at baseline are shown. The most prevalent symptoms at baseline were fatigue, a decreased interest in sex, and loss of strength. “A decreased interest in sex” and “difficulty becoming sexually aroused” were the symptoms that scored the most “very much bother” as symptom severity score. After six months (figure 2) the most prevalent symptoms and the most severe symptoms remained unchanged.

Table 2. Symptom and QoL descriptives at baseline and after 6 months

	QoL questionnaire at baseline, n=1079	QoL questionnaire at baseline and 6 months, n=627		
	Baseline	Baseline	6 months	Scale
Symptom number	12.6 (6.5) n=819	12.4 (6.2) n=460	13.5 (7.2) n=460	0-33
Symptom severity	33 (18 to 51) n=720	33 (19 to 48) n=407	36 (19 to 57) n=407	0-165
MCS	50.3 (10.9) n=1079	50.6 (10.4) n=627	48.3 (11.7) n=627	50 (10)*
PCS	34.8 (12.1) n=1079	35.1 (11.4) n=627	36.5 (9.8) n=627	50 (10)*

Values are given as means ± SD or median (interquartile range)

*standardized score mean (standard deviation)

QoL; quality of life, MCS; Mental Component Summary, PCS: Physical Component Summary

Example questions: Symptom number: In the past month have you experienced any of the following symptoms? Muscle cramps; yes/no

Symptom severity: In the past month have you experienced any of the following symptoms? If yes, how much did it bother you

MCS: During the past 4 weeks, have you had any of the following problems with your work or other regular activities as a result of any emotional problems (such as feeling depressed or anxious)?

PCS: During the past 4 weeks, have you had any of the following problems with your work or other regular activities as a result of your physical health?

The effect of symptoms on QoL

Table 3 shows the association between symptoms and QoL at baseline. With every additional symptom the MCS changed with -0.81 (95% CI -0.91 to -0.71) and the PCS with -0.50 (95% CI -0.62 to -0.39). The association between symptom severity and MCS was -0.23

Figure 1. Symptom prevalence and scoring according to 5 Likert scale at baseline (n=1079)

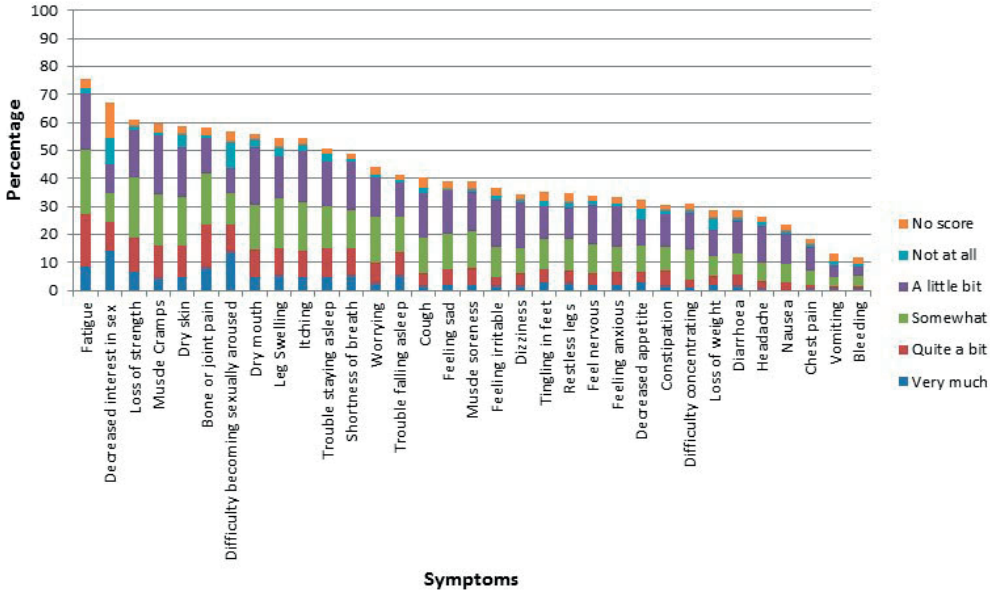

Figure 2. Symptom prevalence and scoring according to 5 Likert scale at six months follow-up (n=627)

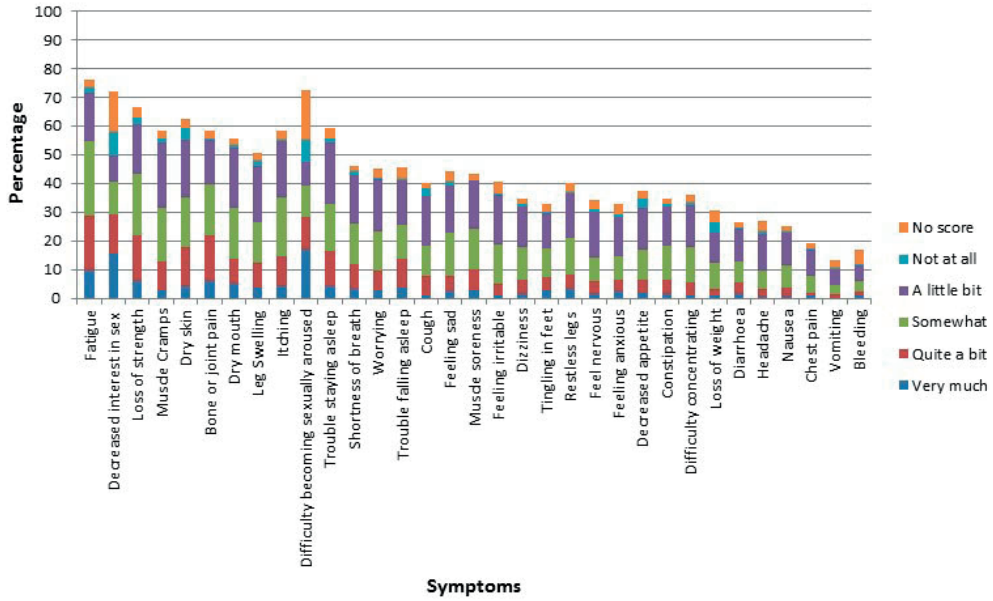

Table 3. Effect size per point increase of symptom number and severity on MCS and PCS at baseline (n=1079)

	MCS	PCS
Symptom number, crude	-0.80 (-0.90 to -0.70)	-0.64 (-0.76 to -0.53)
Symptom number, adjusted*	-0.81 (-0.91 to -0.71)	-0.50 (-0.62 to -0.39)
Symptom severity, crude	-0.22 (-0.25 to -0.19)	-0.22 (-0.25 to -0.19)
Symptom severity, adjusted*	-0.23 (-0.26 to -0.20)	-0.18 (-0.21 to -0.15)

*Adjusted for: age, sex, ethnicity, country of residence, educational level, diabetes mellitus, cerebrovascular disease, myocardial infarction, hypertension, malignancy, psychiatric disease, BMI, primary kidney disease, albumin, and eGFR.
MCS; Mental Component Summary, PCS: Physical Component Summary

(95% CI -0.26 to -0.20) and -0.18 (95% CI -0.21 to -0.15) for PCS. After six months results were similar (results not shown). Table 4 shows the effect of symptom number and severity on QoL over time. After adjustment, one extra symptom at baseline changed MCS at six months of follow-up with -0.42 (95% CI -0.59 to -0.25), and PCS with -0.15 (95% CI -0.24 to -0.05). With every point increase in symptom severity at baseline the change in MCS at six months of follow-up was -0.14 (95% CI -0.19 to -0.09), and for PCS this was -0.05 (95%

Table 4. Effect size per point increase in symptom number and severity on MCS and PCS six month changes (n=627)

	M6 MCS	M6 PCS
Baseline symptom number, crude*	-0.42 (-0.58 to -0.26)	-0.16 (-0.26 to -0.06)
Baseline symptom number, adjusted**	-0.42 (-0.59 to -0.25)	-0.15 (-0.24 to -0.05)
Baseline symptom severity, crude*	-0.13 (-0.18 to -0.09)	-0.05 (-0.08 to -0.02)
Baseline symptom severity, adjusted**	-0.14 (-0.19 to -0.09)	-0.05 (-0.07 to -0.02)

*Adjusted for: baseline QoL
**Adjusted for: baseline QoL, age, sex, ethnicity, country of residence, educational level, diabetes mellitus, cerebrovascular disease, myocardial infarction, hypertension, malignancy, psychiatric disease, BMI, primary kidney disease, albumin, and eGFR.
MCS; Mental Component Summary, PCS: Physical Component Summary, QoL; Quality of Life

Table 5. Linear regression; effect size of change in symptom number and severity on change in MCS and PCS (n=627)

	Change in MCS	Change in PCS
Change in symptom number, crude	-0.48 (-0.67 to -0.29)	-0.22 (-0.35 to -0.09)
Change in symptom number, adjusted	-0.51 (-0.71 to -0.31)	-0.22 (-0.36 to -0.08)
Change in symptom severity, crude	-0.18 (-0.24 to -0.11)	-0.09 (-0.14 to -0.05)
Change in symptom severity, adjusted	-0.18 (-0.25 to -0.12)	-0.09 (-0.14 to -0.04)

Adjusted for: age, sex, ethnicity, country of residence, educational level, diabetes mellitus, cerebrovascular disease, myocardial infarction, hypertension, malignancy, psychiatric disease, BMI, primary kidney disease, albumin, and eGFR.
MCS; Mental Component Summary, PCS: Physical Component Summary

CI -0.07 to -0.02). Table 5 shows the association between the change in symptom number and severity during the first six months of follow-up and the change in QoL during those six months. The association was -0.51 (-0.71 to -0.31) for symptom number and MCS, -0.22 (-0.36 to -0.08) for symptom number and PCS, -0.18 (-0.25 to -0.12) for symptom severity and MCS, and -0.09 (-0.14 to -0.04) for symptom severity and PCS. All negative numbers indicate a decrease in QoL.

Although these effect sizes seem quite small, they are clinically relevant effects. This is illustrated by the changes in QoL per quartile of symptom number and symptom severity. For example, the change from quartile one to quartile three for symptom number and MCS at baseline is over 8 points (Supplemental table 2, 3 and 4).

The importance of symptoms in explaining QoL

Tables 6a and 6b show the R^2 for the different variable clusters that influence QoL, both separately and stepwise at baseline. In the univariable analysis symptom number and

Table 6a. Explained variance for MCS and PCS, for the separate variable clusters (n=1079)

	R^2 MCS	R^2 PCS
Demographics	0.02	0.12
Comorbidities+ PKD	0.02	0.04
eGFR	0.01	0.01
Other lab measurements	0.02	0.01
Symptom number	0.22	0.11
Symptom severity	0.21	0.16

Demographics: sex, age, ethnicity, education level, country of residence
Comorbidities + PKD: diabetes mellitus, cerebrovascular disease, myocardial infarction, malignancy, psychiatric disease, primary kidney disease
Other laboratory measurements: albumin, hemoglobin, proteinuria
MCS; Mental Component Summary, PCS: Physical Component Summary

Table 6b. Explained variance for MCS and PCS, for the stepwise combined variable clusters (n=1079)

	R^2 MCS	R^2 PCS
1.Demographics	0.02	0.12
2. 1+Comorbidities+ PKD	0.04	0.16
3. 2+ eGFR	0.04	0.16
4. 3+Other lab measurements	0.06	0.17
5. 4+symptom number	0.26	0.24
6. 5+symptom severity	0.26	0.28

Demographics: sex, age, ethnicity, education level, country of residence.
Comorbidities + PKD: diabetes mellitus, cerebrovascular disease, myocardial infarction, malignancy, psychiatric disease, primary kidney disease
Other laboratory measurements: albumin, hemoglobin, proteinuria.
DM; diabetes mellitus, CVD; cardiovascular disease, MI; myocardial infarction, PKD; primary kidney disease

severity have an R^2 of 0.22 and 0.21 for MCS respectively, while eGFR has an R^2 of 0.01 and the other variables have a maximum R^2 of 0.02. For PCS the R^2 for symptom number and severity is smaller, 0.11 and 0.16, and demographic variables also explain a large part of the variance with an R^2 of 0.12. The R^2 for eGFR is again 0.01. When adding the variables stepwise in a multivariable analysis for MCS, symptom number significantly adds to the R^2 in addition to demographic and clinical variables, increasing the R^2 from 0.06 to 0.26. Symptom severity does not add more to this correlation. For PCS, the contribution of symptoms is smaller but also substantial. The R^2 increased from 0.17 to 0.24 with symptom number and up to 0.28 with symptom severity. In contrast, eGFR did not add to the R^2 in multivariable analyses, neither for MCS nor for PCS. Both after six months and for change between baseline and six months of follow-up symptom number and severity remained the variables with the largest R^2 in univariable analyses and contributed most to the R^2 in multivariable analyses. In these analyses eGFR did not contribute to the R^2 either.

Sensitivity analyses

Stratifying by sex showed a higher number and severity of symptoms and a lower QoL in women compared to men (supplemental table 5). The effect of symptoms on QoL did not show large differences between the different sexes (supplemental table 6, 7, 8). Repeating the analyses without multiple imputation showed similar results, as did the analyses when only using multiple imputation for baseline confounders. Repeating the baseline linear regression analysis with only the 627 patients who had a QoL questionnaire at baseline and after six months of follow-up showed no substantial differences in the results (supplemental table 9). Removing symptoms that are also part of the SF-36 changed the R^2 to 0.17 (symptom number) and 0.16 (symptom severity) in the univariable analysis for MCS at baseline. For PCS the R^2 changed to 0.12 and 0.18 in the univariable analysis. In the multivariable analysis the R^2 changed to 0.19 (symptom number) and 0.21 (symptom severity) for MCS, and to 0.25 and 0.29 for PCS.

Discussion

In this cohort of 1079 incident elderly pre-dialysis patients we found a wide range of symptom occurrence and severity. Most prevalent symptoms were fatigue, a decreased interest in sex, and loss of strength. Symptoms on sexuality scored highest on severity. Both an increase in number of symptoms and in symptom severity were associated with a decrease in QoL. In addition, baseline symptoms were related to QoL after six months of follow-up. The impact of symptoms on QoL is substantial, especially compared to eGFR which did not impact MCS or PCS at all.

Overall, effects on MCS were larger as compared with effects on PCS. We hypothesize this might be due to depressive symptoms having more impact on mental QoL as compared with physical QoL, due to the fact that a part of these symptoms are heavily reflected in MCS

questions, while the other symptoms do not have that much overlap with PCS questions. The sensitivity analysis in which the explained variance is calculated without overlapping symptoms seems to support this hypothesis. However, the analyses show only small changes as compared with the analyses including these overlapping symptoms.

The difference in impact on QoL between symptoms and eGFR we found supports the conceptual model by Wilson ***et al***. showing symptoms are a more determinant for QoL.[14] With this knowledge on symptom impact, a more prominent role for symptoms in clinical decision making in the pre-dialysis phase seems justifiable. That this is already happening has been illustrated by IDEAL, where symptoms overruled eGFR on the decision when to start RRT.[15] As far as we know there is no other research on the impact of symptoms on QoL in pre-dialysis patients.

Our results on the number of symptoms and symptom severity are in line with existing research in CKD patients.[17, 28-30] Almutary ***et al.*** performed a systematic review investigating symptom burden in CKD stage 4 and 5. They found seven studies on symptom burden in pre-dialysis patients. These studies showed a wide range of symptoms, with fatigue being the most common symptom, followed by pruritus and dry skin. Pre-dialysis patients had more psychological problems compared to patients on dialysis. The average number of symptoms ranged from 6 to 20, compared to 13 in our population.[17] Other research in 436 CKD patients of which 24.5% were in the pre-dialysis phase (mean age 52, 55% male), showed an average symptom number of 13 with fatigue and pain as most common symptoms. In this study "difficulty becoming sexually aroused" and "decreased interest in sex" were two of the most severe symptoms when experienced, which is in concordance with our study.[28]

Yong ***et al.*** performed a study in 179 end stage renal disease patients of which 45 were treated conservatively (mean age 73), looking both at symptom burden and at its relation to QoL. They found a negative correlation between symptom burden and QoL, which is similar to our study, although the CKD stage in this population differs from our population.[31] In a study by Abdel-Kader ***et al.*** symptom burden was negatively correlated with MCS but not with PCS, while symptom severity was negatively correlated with both MCS and PCS in 87 CKD stage 4/5 patients.[11] The lack of correlation between symptom burden and PCS in the latter study could be explained by the small population or by the lack of correction for confounding.

There is only one other study we know of that looks at symptoms and QoL over time.[1] De Goeij ***et al***. studied this relation in 436 pre-dialysis patients (median age 69, 66% male, mean eGFR 16.9ml/min/1.73 m^2). They found an increase in symptoms over time, and a decrease in QoL (both MCS and PCS). However, they did not directly assess the relation between symptoms and QoL over time. Although de Goeij ***et al.*** studied a longer period of time, their findings on symptoms and QoL are quite similar to our results.

The main strength of this study is the size of the study population. As far as we know this is the largest population of pre-dialysis patients in which the relation between symptoms

and quality of life has been evaluated. Another strength is the inclusion of incident pre-dialysis patients (who for the first time passed a pre-specified eGFR level), which decreased the risk of survival bias. In addition, the exclusion criteria for EQUAL are minimal, ensuring a wide range of elderly pre-dialysis patients were included, making the results generalizable to the clinical practice of pre-dialysis care for elderly patients.

The main limitation of this study is the duration of follow-up. In the future follow-up will be extended to at least four years, but for this study only the first six months of follow-up were available. Although this is a limitation, it is one of the first studies researching symptoms and QoL over time and thereby still an important contribution to the body of evidence on this subject. A second limitation is the number of non-responders after six months of follow-up. Due to this problem we had to restrict the number of patients in analyses involving the six months follow-up measurement. Another limitation is the use of the Dialysis Symptom Index as symptom questionnaire. This symptom questionnaire was developed and validated in dialysis patients. Since patient's follow-up continues during dialysis this questionnaire is a good choice for the entire EQUAL study. For this particular study in pre-dialysis patients the lack of validation in this group is a limitation. However, the Dialysis Symptom Index has been used in pre-dialysis populations before, with valid results.[32, 33] Finally, based on the model of Wilson which implies symptoms result in QoL, and on the measurements over time which gave us the opportunity to measure symptoms at an earlier moment compared to QoL, we interpreted our results as effects. However, we would like to emphasize the caution needed when interpreting our results as causal, and the possibility of methodological limitations, such as residual confounding, which could make causal interpretation very difficult.

In conclusion, this study showed an effect of symptoms on QoL, and quantified their relative importance. The prevalence and severity of symptoms in our population emphasizes the need for attention on symptoms during outpatient clinic visits. The effect of symptoms on a clinically relevant outcome measure indicates symptoms should have a more prominent role in clinical decision making and guidelines in CKD should emphasize this. Opportunities for future research include studying the impact of individual symptoms on QoL and testing whether interventions on symptoms improve QoL. Future results of the EQUAL study on the start of dialysis will give the opportunity to investigate the role of symptoms in that period more thoroughly.

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3

MEASURING QUALITY OF LIFE IN PRE–DIALYSIS PATIENTS; COMPARING THE SF–12 AND EQ–5D TO THE SF–36

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Abstract

Introduction: The influence of chronic kidney disease on quality of life (QoL) is usually measured with the Short Form-36 (SF-36) questionnaire. Frequently used shorter QoL questionnaires are the Short Form-12 (SF-12) and the EuroQol (EQ-5D), but these have not yet been validated in pre-dialysis patients. The aim of this study was to validate the SF-12 and the EQ-5D questionnaire in pre-dialysis patients.

Methods: In a multi-center cohort study, incident pre-dialysis patients (>18y) were included between 2004-2011 and followed until renal replacement therapy, death, or October 2016. These patients completed QoL questionnaires every 6 months. Pearson correlation coefficients between the SF-12 and the SF-36, and between the EQ-5D and the SF-36 were calculated. Bland-Altman plots were used to assess limits of agreement, using Z-scores. Associations between the different measurement tools with time to start of dialysis and death were assessed with Cox regression analyses.

Results: The correlation between the Mental Component Score (MCS)-12 – MCS-36 and the Physical Component Score (PCS)-12 – PCS-36 were both 0.95, for EQ-5D – MCS-36 this was 0.37, and for EQ-5D – PCS-36 this was 0.57. All mean differences were 0, limits of agreement ranged from -0.60 to 0.60 for MCS-12 – MCS-36 to -2.05 to 2.05 for EQ-5D – MCS-36. The adjusted HRs for start of dialysis and for death were similar using the SF-36 and the SF-12. The EQ-5D HR for start of dialysis was similar to the PCS-36 association. The EQ-5D HR for death was similar to the MCS-36.

Conclusion: The SF-12 has better agreement with the SF-36 compared to the EQ-5D and can be used as a substitute for the SF-36 in pre-dialysis patients.

Introduction

Chronic kidney disease (CKD) is a leading cause of premature death and also an important disabling factor in daily life.[1-3] Patients with Chronic Kidney Disease, especially those with an estimated glomerular filtration rate (eGFR) below 30 ml/min/1.73m^2 suffer from a great range of physical and psychological symptoms and are known to have a lower quality of life.[4, 5] Currently, focus is shifting from only attempting to improve prognosis in CKD patients towards also improving these so called patient reported outcomes.

One of the most essential patient reported outcomes is the health related quality of life (HRQoL). In CKD patients a decrease in HRQoL is associated with an increased risk of end stage renal disease (ESRD) and mortality.[6, 7] In dialysis patients a lower HRQoL is associated with hospitalization, dialysis vintage, lower residual kidney function and mortality.[8, 9]

The most frequently used questionnaire to assess HRQoL is the Short Form 36 (SF-36). The SF-36 contains 36 items, which measure health on eight dimensions, as well as overall physical and mental component scores (PCS-36 and MCS-36).[10] Unfortunately, the SF-36 can take up to 12 minutes for a patient to complete and is therefore often considered too long for inclusion in large scale monitoring efforts. Therefore, shorter questionnaires are used when patients are asked to fill in multiple questionnaires.

Two frequently used shorter HRQoL questionnaires are the Short Form-12 (SF-12) and the EuroQol questionnaire (EQ-5D).[11-15] The SF-12 is an abbreviated version of the SF-36, reducing the number of items down to 12. In contrast to the SF-36, which measures eight health domains, the SF-12 measures health only by physical and mental component scores (PCS-12 and MCS-12). The EQ-5D consists of a health valuation questionnaire and a visual analogue scale (VAS). The EQ-5D questionnaire results in a single index score based on five questions covering; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The VAS records the patient's self-reported health valuation on a vertical axis ranging from 0 to 100. The questionnaire of the EQ-5D is the part that is generally used as a HRQoL measurement tool.[13, 16, 17]

Ideally, a short questionnaire improves efficiency while remaining almost as valid as a long questionnaire, such as the standard SF-36. The SF-12 and EQ-5D have been validated for multiple chronic diseases in multiple populations, including dialysis and kidney transplant patients, but have not yet been validated in pre-dialysis patients.[13, 18, 19] Since pre-dialysis patients differ from the aforementioned patients and have a specific medical treatment, perceived physical and mental health may be dissimilar. Therefore, the aim of this study is to validate the SF-12 and the EQ-5D questionnaire in pre-dialysis patients using the SF-36 as a reference.

Methods

Study design and population

The PREPARE-2 study is a prospective cohort study of incident pre-dialysis care patients (≥18 y) who had an estimated glomerular filtration rate (eGFR) of less than 30 ml/min/1.73m^2 and progressive renal function loss. Patients with a failing kidney transplant who were transplanted at least one year ago were also eligible for inclusion. For this study all patients with complete SF-36 component scores were included. The PREPARE-2 study has been described in detail elsewhere.[20] In brief, patients were recruited in one of 25 nephrology specialized pre-dialysis outpatient clinics in the Netherlands between July 2004 and June 2011. All patients were treated by their nephrologist in accordance with the treatment guidelines of the Dutch Federation of Nephrology, guidelines partly based on the K/DOQI and EBPG guidelines.[21-24] Patients were followed from the start of pre-dialysis care until start of dialysis, kidney transplantation, death or censoring. Censoring was applied in case of: refusal for further participation, recovery of kidney function, moving to an outpatient clinic not participating in the PREPARE-2 study, loss to follow up or October 2016 (end of follow up), whichever came first. This study was approved by the medical ethics committee or institutional review boards (as appropriate) of all participating centers. Written informed consent was obtained from all patients.

Health Related Quality of Life Questionnaires

Both the SF-36 and the EQ-5D were part of the HRQoL questionnaire in the PREPARE-2 study, and were measured every six months. The SF-36 Health Survey consists of 36 multiple choice questions with standardized responses, of which 35 are organized into eight multi item domains (supplemental table 1).[25] The 36th question asks how health has changed over a specified time period (in this study: three months), this question is not included in the eight domains. These eight domains are used to form two component scores, referred to as the PCS-36, consisting of physical functioning, role limitations due to physical problems and bodily pain dimensions, and the MCS-36, consisting of social functioning, role limitations due to emotional problems and mental health dimensions. The component scores share the domains general health and vitality. At least half of the items per domain have to be complete for a domain to be scored. The component scores are a weighted summary score of the domains.[26] The PCS-36 and MCS-36 are calculated using norm based scoring, which employs linear transformation to achieve standardized scores with a mean of 50 and a standard deviation of 10.[27] A score over 50 can be interpreted as above average. We used the United States (US) population as a reference group.[28] We used the first version of the SF-36 questionnaire.[25] The SF-12 is obtained by extracting 12 questions from the SF-36 (supplemental table 1). The SF-12 does not have enough items to assess eight domains but solely calculates the two component scores. In the SF-12 all items have to be complete in order to calculate physical and mental component scores.

[29] The PCS-12 and MCS-12 regression weights were calculated with norm based scoring to achieve standardized scores with a mean of 50 and a standard deviation of 10, using the US population as the reference group.[29, 30]

The EQ-5D questionnaire measures quality of life by five dimensions (supplemental table 2a).[31] The five dimensions are scored as follows: no, some, or extreme problems. The five dimensions are summarized in a single score by applying a weight to each dimension score according to the time trade-off valuation technique (TTO), explained in detail elsewhere.[32] In short, the TTO creates a set of values based on the opinion of a group Dutch citizens. This value set results in a so-called tariff score ranging from -0.33 to 1.00. Higher scores indicate a better quality of life. A score of zero indicates that the quality of life is equal to death.

Statistical analyses

Baseline characteristics were presented as mean ± standard deviation (SD) for normally distributed continuous variables, skewed continuous variables as median with interquartile range (IQR). Multiple imputation was used to minimize the risk of bias and obtain correct standard errors.[33] Missing values of PCS-12 and MCS-12 scores, EQ-5D scores at baseline, and of possible confounders were imputed (using 10 repetitions).

Both construct validity and external validity were investigated. We defined construct validity as the extent to which the short questionnaires actually measure QoL. We defined external validity as the performance of the short questionnaires when measuring external constructs. Construct validity was measured by comparing the SF-12 and EQ-5D with our reference, the SF-36. External validity was assessed by using symptoms, the VAS part of EuroQol, the health change question from the SF-36, start of dialysis and death as external constructs.

First, for construct validity, Pearson correlation coefficients were calculated for the MCS-12 and PCS-12 and the EQ-5D on the one hand with the MCS-36 and PCS-36 on the other hand. This was done at baseline, after six months and after 12 months of follow-up. In all analyses, the MCS-12 was compared to the MCS-36 and the PCS-12 was compared to the PCS-36. The EQ-5D scores were compared with both the MCS-36 and the PCS-36. Changes over time in the aforementioned questionnaire scores were calculated and Pearson correlation coefficients were calculated for these changes. The Pearson correlation coefficient was favored over the intra-class correlation coefficient, since the EQ-5D has a different scoring system as compared with the SF questionnaires. This results in a systematic error which is not of interest for validating the questionnaires, which is ignored when using a Pearson correlation coefficient.[34] Second, agreement between the SF-12 and the EQ-5D on the one hand and the SF-36 on the other was assessed with Bland –Altman plots.[35] In this plot individual differences in scores are plotted against the mean of two different questionnaire measurements (e.g. MCS-12 ***vs*** MCS-36, PCS-12 ***vs*** PCS-36, EQ-5D ***vs*** MCS-36, EQ-5D ***vs*** PCS-36). Horizontal lines show the population average of all individual differ-

ences and the 95% limits of agreement (mean difference ±1.96 standard deviation of the differences). To create comparable scores for all questionnaires, and take the systematic error caused by the different scoring systems into account, Z-scores were calculated for the five different questionnaire components.

Next, for external validation, Pearson or Spearman correlation coefficients were calculated for the different questionnaire components as appropriate for our three numerical and ordinal external constructs, in this case symptom frequency, the VAS part of the EuroQol, and the health change question from the SF-36. Symptom frequency was measured in the patient questionnaires by evaluating the occurrence of 14 different symptoms, which resulted in a symptom frequency score ranging from 0 to 14. The VAS is the second part of the EuroQol, not used to measure HRQoL (supplemental table 2b). This is a thermometer on which patients can mark their own current health status from zero (worst imaginable health state) to 100 (best imaginable health state).[31] The health change question in the SF-36 ranges from 1; large increase in health over the past three months, to 5; large decrease in health over the past three months. The correlations with these three external constructs were calculated at baseline, after six months, and after 12 months of follow-up. The correlation for changes between baseline and six months of follow-up were calculated as well. Correlations with the external constructs should be similar for questionnaire scores measuring the same construct, in this case HRQoL.

Finally, the association between the five questionnaire components (MCS-36, PCS-36, MCS-12, PCS-12, and EQ-5D) and our two time to event external measurements start of dialysis and mortality were estimated with Cox proportional hazard regression analyses. Analyses were adjusted for the confounders age, sex, ethnicity, and primary kidney disease. For these analyses the different questionnaire components were transformed into Z-scores. This should result in similar hazard ratios for questionnaire scores measuring the same construct. Follow-up time was defined as time between baseline visit of the patient and the start of dialysis, renal replacement therapy (RRT), death, withdrawal or end of follow-up (October 2016). To estimate the median follow up time, a reversed Kaplan-Meier was used.

In a sensitivity analysis we repeated all analyses without using multiple imputation for missing values. All analyses were performed using SPSS version 23.0 for Windows.

Results

Of the 502 pre-dialysis patients in PREPARE-2, 433 patients had complete SF-36 component scores at baseline. Table 1 shows the baseline characteristics for the 433 patients with complete component scores and for the 69 patients with incomplete component scores. Patients with complete SF-36 component scores at baseline were more often women, less often had diabetes mellitus as primary kidney disease, suffered more often from cardiovascular disease, and had a higher kidney function as compared with patients with

Table 1. Baseline characteristics of 502 pre–dialysis patients with complete and incomplete SF–36 component scores

	Patients with complete SF-scores (N=433)	Patients with incomplete SF-scores (N=69)
Sex, men	287 (66)	54 (78)
Age, years	69 (56-76)	66 (49-75)
Ethnicity, Caucasian	401 (93)	61 (88)
Marital status, married or living together	304 (70)	-
Education		
Low	97 (23)	-
Intermediate	254 (59)	-
High	60 (14)	-
Other	13 (3)	-
Children, yes	358 (83)	-
Employment, yes	108 (25)	-
Primary kidney disease		
Diabetes Mellitus	57 (13)	15 (22)
Glomerulonephritis	58 (13)	9 (13)
Renal vascular disease	133 (31)	21 (31)
Other	185 (43)	24 (35)
Cardiovascular disease, yes [a]	182 (42)	25 (36)
Diabetes Mellitus, yes [b]	111 (26)	19 (28)
Congestive heart failure, yes [c]	51 (12)	10 (15)
Systolic blood pressure, mmHg	142 (22)	147 (21)
Hemoglobin, mmol/l	7.7 (0.9)	7.6 (0.8)
Serum creatinine, μmol/l	350 (112)	402 (130)
eGFR, ml/min/1.73 m^2 [d]	14.5 (11.4-18.9)	13.2 (10.0-16.3)
Proteinuria, g/24h	1.0 (0.4-2.1)	1.3 (0.6-2.6)

SF; Short Form

Values are given as number (percentage of the total), means ± SD or median (interquartile range).

[a] Defined as presence of coronary artery disease, a history of cardiovascular accident, peripheral vascular disease, or myocardial infarction. [b] Defined as the presence of diabetes mellitus as primary kidney disease or a history of diabetes mellitus. [c] Defined as a history of congestive heart failure [d] eGFR (estimated glomerular filtration rate) is calculated with the CKD EPI (Chronic Kidney Disease Epidemiology Collaboration) formula 2009.

Number of missings: Complete SF-36 component scores; marital status 2, children 4, education 9, employment 8, hemoglobin 54, proteinuria 218, eGFR 51, creatinine 51, systolic blood pressure 4. Incomplete SF-36 component scores; marital status 66, children 66, education 66, employment 66 hemoglobin 6, proteinuria 37, eGFR 13, creatinine 13t

an incomplete questionnaire. Education, current employment and having children were incomparable for the two groups, since these questions were part of the questionnaire and therefore missing for almost all patients with an incomplete questionnaire. All further analyses were performed in the 433 patients with complete SF-36 component scores.

Construct validity

At baseline correlations between the SF-12 and the SF-36 were high, with a Pearson correlation coefficient of 0.95 for both the MCS and the PCS (table 2a). The correlations between the EQ-5D and the SF-36 were lower, with a lower correlation between the EQ-5D and the MCS as compared with the correlation with the PCS. After 6 and 12 months of follow-up correlations were comparable (table 2a). The correlations for change over time in component scores were all slightly weaker as compared with the cross-sectional correlations (table 2b). However, the correlations between the SF-12 and SF-36 remained high (0.92 for the MCS, 0.88 for the PCS).

Table 2a. Pearson correlation coefficients of the SF–36 component scores at baseline, after 6 and 12 months with the time corresponding SF–12 component scores and EQ–5D score

	Baseline		6 months follow-up		12 months follow-up	
	SF-36 MCS	SF-36 PCS	SF-36 MCS	SF-36 PCS	SF-36 MCS	SF-36 PCS
SF-12 MCS	0.95	-	0.96	-	0.96	-
SF-12 PCS	-	0.95	-	0.96	-	0.95
EQ-5D	0.37	0.57	0.45	0.62	0.47	0.60

SF; Short Form, EQ-5D; EuroQol 5D, MCS; mental component summary, PCS; physical component summary

Table 2b. Pearson correlation coefficients of the changes in SF–36 component scores with the changes in the SF–12 component scores and EQ–5D score during follow–up

	0-6 months		6-12 months	
	SF-36 MCS	SF-36 PCS	SF-36 MCS	SF-36 PCS
SF-12 MCS	0.92	-	0.91	-
SF-12 PCS	-	0.88	-	0.89
EQ-5D	0.30	0.31	0.39	0.26

SF; Short Form, EQ-5D; EuroQol 5D, MCS; mental component summary, PCS; physical component summary

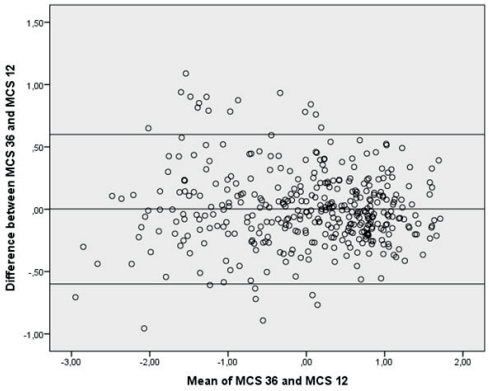
In order to create Z-scores the SD was calculated for each score. This was 9.4 for the MCS-36, 10.2 for the PCS-36, 9.4 for the MCS-12, 9.9 for the PCS-12, and 0.2 for the EQ-5D. In figure 1 the Bland-Altman plots show the individual Z-score differences between the different SF-12 and EQ-5D with the SF-36 components at baseline. Limits of agreement ranged from -0.60 to 0.60 SD for the MCS-12 scores, from -0.58 to 0.62 SD for the PCS-12 scores, from -2.05 to 2.05 SD for the EQ-5D and the MCS-36, and from -1.69 to 1.73 SD for the EQ-5D and the PCS-36. For changes over time in the component scores the limits of agreement were somewhat wider for all comparisons (Supplemental figure 1).

External validity

Table 3 shows the Pearson and Spearman correlation coefficients for the SF-36, SF-12 components, and the EQ-5D with the external constructs symptom frequency, VAS, and the health change question. The negative correlations indicate that an increase in HRQoL

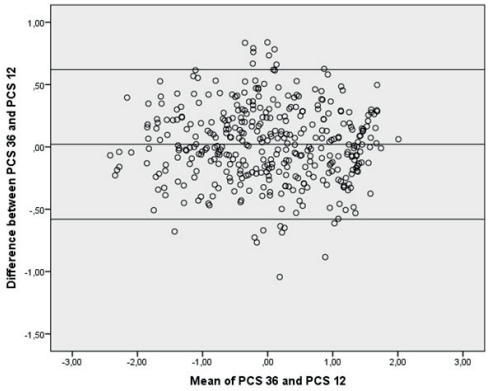
Figure 1. Bland–Altman plots showing mean difference and 95% limits of agreement between Z–scores of the SF–36, SF–12, and EQ–5D

a. MCS-36 and MCS-12 (n=381)



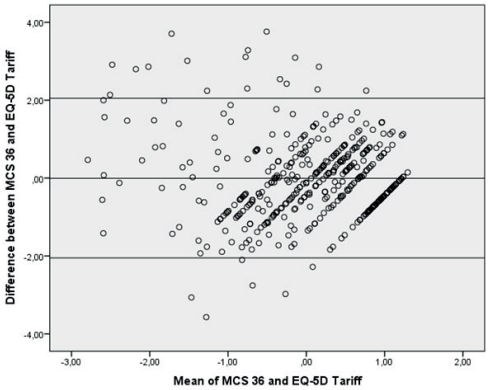
Horizontal lines show the population average of all individual differences (mean: 0.00) and the 95% limits of agreement (mean difference ±1.96 standard deviation of the differences): -0.60, +0.60

b. PCS-36 and PCS-12 (n=381)



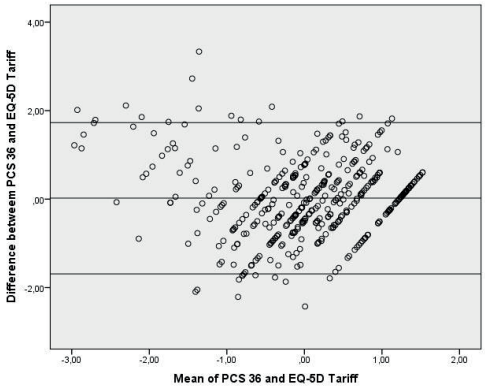
Horizontal lines show the population average of all individual differences (mean: 0.02) and the 95% limits of agreement (mean difference ±1.96 standard deviation of the differences): -0.58, 0.62

c. MCS-36 and EQ-5D score (n=413)



Horizontal lines show the population average of all individual differences (mean: 0.00) and the 95% limits of agreement (mean difference ±1.96 standard deviation of the differences): -2.05, 2.05

d. PCS-36 and EQ-5D score (n=413)



Horizontal lines show the population average of all individual differences (mean: 0.02) and the 95% limits of agreement (mean difference ±1.96 standard deviation of the differences): - 1.69, 1.73

is correlated with a decrease in respectively symptoms and the health change question (in which a low score is the most positive). The positive correlations indicate that an increase in HRQoL is correlated with an increase in the VAS score. The correlations for the SF-36 and SF-12 PCS and MCS were virtually the same. At baseline, the EQ-5D showed a correlation comparable to the PCS-36 correlation with symptom frequency, had a correlation with the VAS in between the PCS-36 and MCS-36 correlations, and had a somewhat lower correlation with the health change question compared to both the PCS-36 and MCS-36 correlations.

Table 3. Pearson and Spearman correlation coefficients between a. symptom frequency, b. EuroQol Visual Analogue Scale, c. the health change question at baseline, after 6 and 12 months with the time corresponding SF–36 component scores, SF–12 component scores, and EQ–5D score

	Baseline	6 months follow-up	12 months follow-up
a. Symptom frequency			
SF-36 MCS	-0.29	-0.32	-0.38
SF-36 PCS	-0.38	-0.33	-0.42
SF-12 MCS	-0.30	-0.33	-0.38
SF-12 PCS	-0.37	-0.32	-0.44
EQ-5D	-0.39	-0.41	-0.43
b. EuroQol Visual Analogue Scale			
SF-36 MCS	0.38	0.39	0.55
SF-36 PCS	0.60	0.60	0.65
SF-12 MCS	0.42	0.38	0.55
SF-12 PCS	0.60	0.62	0.68
EQ-5D	0.47	0.49	0.61
c. Health change question			
SF-36 MCS	-0.36	-0.32	-0.32
SF-36 PCS	-0.39	-0.37	-0.42
SF-12 MCS	-0.38	-0.36	-0.31
SF-12 PCS	-0.42	-0.42	-0.40
EQ-5D	-0.31	-0.32	-0.44

SF; Short Form, EQ-5D; EuroQol 5D, MCS; mental component summary, PCS; physical component summary

The calculated correlations for change in components and symptom frequency over time were very low for all components. The correlation of change in EQ-5D with change in symptom frequency was very similar to that of change in PCS-36. Correlations with change in VAS between 0 and 6 months were similar for change in SF-36 and SF-12 component scores, the change in EQ-5D correlation was similar to that of the change in PCS-36. Correlations with change in the health change question were very similar for change in SF-36 and SF-12 components, the change in EQ-5D had a correlation similar to that of the change in MCS-36.

Median follow-up time was 51 (38-63) months. Table 4a shows the association between the different questionnaire components with start of dialysis in a Cox regression analysis. An increase in MCS, PCS, and in EQ-5D score were all associated with a lower risk to start dialysis. This decrease was significant for the MCS in both the SF-36 and the SF-12. The SF-36 and SF-12 showed the same associations with start of dialysis. The EQ-5D showed the same association as the PCS-36. All 95% CIs overlapped. All five questionnaire components were associated with a lower mortality when increasing (table 4b). The MCS-12 and EQ-5D scores had the same association as compared with the MCS-36. The PCS-12 had similar associations as compared with the PCS-36.

Repeating all analyses without multiple imputation did not essentially change the results.

Table 4a. Crude and adjusted hazard ratio (95%CI) for start of dialysis per 1 SD increase in SF–36 component scores, SF–12 component scores, and EQ–5D scores

	HR (95% CI) Crude	HR (95% CI) Adjusted*
SF-36 MCS	0.83 (0.73-0.93)	0.83 (0.73-0.94)
SF-36 PCS	0.94 (0.84-1.05)	0.92 (0.82-1.04)
SF-12 MCS	0.83 (0.74-0.94)	0.83 (0.74-0.94)
SF-12 PCS	0.94 (0.84-1.06)	0.92 (0.82-1.04)
EQ-5D	0.93 (0.83-1.04)	0.92 (0.82-1.04)

SF; Short Form, EQ-5D; EuroQol 5D, SD; standard deviation, MCS; mental component summary, PCS; physical component summary, HR; hazard ratio, CI; confidence interval
*Adjusted for: Age, sex, race, primary kidney disease

Table 4b. Crude and adjusted hazard ratio (95% CI) for mortality per 1 SD increase in SF–36 component scores, SF–12 component scores, and EQ–5D scores

	HR (95% CI) Crude	HR (95% CI) Adjusted*
SF-36 MCS	0.88 (0.63-1.21)	0.82 (0.60-1.12)
SF-36 PCS	0.61 (0.45-0.81)	0.68 (0.51-0.92)
SF-12 MCS	0.83 (0.61-1.14)	0.81 (0.60-1.10)
SF-12 PCS	0.60 (0.44-0.81)	0.67 (0.49-0.91)
EQ-5D	0.84 (0.64-1.11)	0.84 (0.63-1.13)

SF; Short Form, EQ-5D; EuroQol 5D, SD; standard deviation, MCS; mental component summary, PCS; physical component summary, HR; hazard ratio, CI; confidence interval *Adjusted for: Age, sex, race, primary kidney disease

Discussion

In this study we found a better agreement between the SF-12 and the SF-36 as compared with the agreement between the EQ-5D and the SF-36, both for measurements at a single point in time and for changes over time. This was most pronounced in direct comparisons with the SF-36. In external validations the EQ-5D largely corresponded with the PCS-36.

In more detail, the Pearson correlation coefficient was high between the PCS-12 and PCS-36, as well as between the MCS-12 and MCS-36. The correlation was much lower between the EQ-5D and MCS-36. Between the EQ-5D and the PCS-36 the correlation was moderate. Over time correlations remained the same, except for the correlation between the EQ-5D and MCS-36 which improved slightly. The correlations for change over time were lower for most comparisons between the scores. In contrast, the correlations between the SF-12 and SF-36 remained very high. The Bland-Altman plots showed the largest 95% limits of agreement when comparing the EQ-5D with the SF-36 components and thus the lowest agreement.

Validating the questionnaires externally with symptom frequency, the VAS, and the health change question resulted in similar correlations for the SF-12 and SF-36, both for

a single point in time and for change over time. The EQ-5D had correlations comparable to the SF-36 PCS score. The correlation between the EQ-5D and VAS was in between the correlations for VAS with PCS-36 and VAS with MCS-36, and the correlation of EQ-5D with the health change question was somewhat lower compared to the health change question with PCS-36 and MCS-36 correlations. Calculating associations with start of dialysis resulted in similar HRs for the SF-12 and the SF-36, the EQ-5D associations were comparable to the SF-36 PCS association. The associations with death were similar for the SF-12 and the SF-36. The EQ-5D association with death was comparable to that of the MCS-36.

The type of questions in the EQ-5D could explain why most comparisons show a similarity to the PCS-36 score, and to a lesser extent to the MCS-36 score. The five questions that result in the tariff score mainly reflect physical limitations, with just one question on anxiety and depression. Most likely, as a consequence this results in more similarities with the physical part of the SF-36 as compared with the mental part. Given this explanation, the similarity with MCS-36 for the association with death seems counterintuitive. However, the associations with death are simply lower for both the EQ-5D and the MCS-36 as compared with the PCS-36 score. This can be explained by the type of questions in the MCS-36, since it is likely that physical suffering has a higher association with death as compared with mental problems.

As far as we know this is the first study validating the SF-12 and EQ-5D in pre-dialysis patients. In dialysis patients the SF-12 has been validated multiple times.[18, 19, 36] Both cross-sectional validation and validation over time showed a good agreement between the SF-12 and the SF-36 in these studies which is in concordance with our study. The EQ-5D has not been completely validated in dialysis patients, but change over time in EQ-5D scores has been compared with change over time in SF-36 and SF-12 scores by Loosman ***et al***.[19] The correlations between the change in SF-scores and change in EQ-5D scores were moderate and equal for both the SF-36 and SF-12, which is similar to the results in our study. In kidney transplant patients the EQ-5D has been validated.[13] When testing concurrent validity, Cleemput ***et al***. found a larger agreement between the EQ-5D and the PCS as compared with the agreement between the EQ-5D and the MCS, this is similar in our study.[13]

Our study had several limitations. First, we decided to use the SF-36 as our reference. Although this is not formally established as being the gold standard to measure QoL, QoL cannot be measured directly and the use of a questionnaire is necessary. When searching PubMed for QoL questionnaires the SF-36 is by far the most often used questionnaire. Choosing the SF-36 as a reference results in two component scores as an outcome, namely the MCS and PCS. When comparing the SF-12 with the SF-36, both questionnaires have the same component scores which makes comparisons easy. In contrast, the EQ-5D generates one single score which makes the comparison with the SF-36 more cumbersome. The total score of the EQ-5D consists of 4 questions regarding physical problems and 1 question regarding mental problems, making the higher correlations with the PCS understandable.

Finally, some of the baseline characteristics between patients with and patients without a QoL questionnaire differed. It is not likely this influenced the correlations between the questionnaires, but this affects generalizability.

Main strength is that this is the first study validating the SF-12 and EQ-5D in pre-dialysis patients. This an important step in achieving large scale monitoring in this patient group with the use of validated questionnaires with limited time consumption for the patient. Another strength is the extensive validation of the questionnaires, not only comparing to our golden standard the SF-36, but also with different external constructs, such as symptom frequency, the VAS from the EuroQol, and start of dialysis. Finally, we had a large sample of pre-dialysis patients who were followed over time, providing us with the opportunity to expand the validation with measurements over time.

In conclusion, the SF-12 had good agreement with the SF-36 and can be used as a substitute for the SF-36 when this questionnaire is considered too long. The EQ-5D in general had lower agreement with the SF-36 as compared with the SF-12 and should not be first choice to substitute the SF-36 when measuring quality of life in pre-dialysis patients.

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DYSLIPIDEMIA AND RISK OF RENAL REPLACEMENT THERAPY OR DEATH IN INCIDENT PRE–DIALYSIS PATIENTS

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Abstract

Introduction: Globally the number of patients on renal replacement therapy (RRT) is rising. Dyslipidemia is a potential modifiable cardiovascular risk factor, but its effect on risk of RRT or death in pre-dialysis patients is unclear. The aim of this study was to assess the association between dyslipidemia and risk of RRT or death among patients with CKD stage 4-5 receiving specialized pre-dialysis care, an often underrepresented group in clinical trials.

Methods & results: Of the 502 incident pre-dialysis patients (>18y) in the Dutch PREPARE-2 study, lipid levels were available in 284 patients and imputed for the other patients. During follow up 376 (75%) patients started RRT and 47 (9%) patients died. Dyslipidemia was defined as total cholesterol ≥5.00 mmol/L, LDL cholesterol ≥2.50 mmol/L, HDL cholesterol <1.00 mmol/L, HDL/LDL ratio<0.4, or triglycerides (TG) ≥2.25 mmol/L, and was present in 181 patients and absent in 93 patients. After multivariable adjustment Cox regression analyses showed a HR (95% CI) for the combined endpoint for dyslipidemia of 1.12 (0.85 to 1.47), for high total cholesterol of 1.01 (0.70-1.46), for high LDL of 1.20 (0.89-1.61), for high HDL of 1.02 (0.69-1.51), for high HDL/LDL ratio of 0.99 (0.66-1.48), and for high TG of 0.91 (0.68-1.22).

Conclusions: We did not find an association between dyslipidemia or the separate serum lipid levels and RRT or death in CKD patients on specialized pre-dialysis care.

Introduction

Patients with chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2, have an increased risk of cardiovascular and non-cardiovascular mortality compared to the general population.[1] In the general population dyslipidemia is an important risk factor for cardiovascular morbidity and mortality due to its key role in the development of atherosclerosis.[2-4] Furthermore, dyslipidemia is associated with an increased risk of CKD by accelerating processes that contribute to glomerulosclerosis.[5-8]

CKD patients display a different lipid profile compared to the general population, characterized by e.g. more atherogenic low-density lipoprotein (LDL), low plasma high-density lipoprotein (HDL) cholesterol concentrations with impaired HDL maturation and function, and elevated plasma levels of triglycerides (TG) due to an impaired clearance of VLDL and chylomicrons.[9-11] Hence, dyslipidemia in CKD patients could be a contributing factor to the increased risk on mortality and could accelerate kidney function decline.

Observational studies in patients with CKD stage 1-4, thus far, have shown no or a slightly reversed association between dyslipidemia and mortality.[12-14] In contrast, the Study of Heart and Renal Protection (SHARP), an RCT with simvastatin plus ezetimibe in patients with CKD, showed in a sub-analysis in patients (N=1200) on statin therapy with an eGFR between 15 and 30 ml/min/1.73m^2 a significant reduction of 22% of major atherosclerotic events.[15, 16]

All in all, the effects of dyslipidemia on start of dialysis and mortality in the later CKD stages remain unclear, while dyslipidemia is a potential modifiable cardiovascular risk factor. Therefore, the aim of the present study is to assess the association between dyslipidemia and risk of renal replacement therapy (RRT) or death among patients with CKD stage 4-5 receiving specialized pre-dialysis care. These data reflect specialized nephrology care and allow us to evaluate the real-world association between dyslipidemia and outcome in pre-dialysis patients, often under-represented or excluded from clinical trials.

Methods

Study design and population

The PREPARE-2 study is a prospective cohort study of incident pre-dialysis care patients (≥18 y) who had an estimated glomerular filtration rate (eGFR) of less than 20 - 30 ml/min/1.73m^2 and progressive renal function loss. Patients with a failing kidney transplant, who were transplanted at least one year ago, were also eligible for inclusion. The study has been described in detail elsewhere.[17] In brief, patients were recruited in one of 25 nephrology specialized pre-dialysis outpatient clinics in the Netherlands between July 2004 and June 2011. All patients were treated by their nephrologist in accordance with the treatment guidelines of the Dutch Federation of Nephrology, guidelines partly based

on the K/DOQI and EBPG guidelines.[18-21] Patients were followed from the start of pre-dialysis care until start of dialysis, kidney transplantation, death or censoring. Censoring was defined as: refusal for further participation, recovery of kidney function, moving to an outpatient clinic not participating in the PREPARE-2 study, loss to follow up, or October 2016 (end of follow up), whichever came first. This study was approved by the medical ethics committee or institutional review boards (as appropriate) of all participating centers. Written informed consent was obtained from all patients.

Demographic and clinical data

Data on demography, primary kidney disease, comorbidities, medication use, and laboratory values were collected during routine visits to pre-dialysis outpatient clinics. These visits took place at the start of specialized pre-dialysis care, at the moment of reaching one of the study endpoints as described previously, and every intermediate 6-month interval. Laboratory data were extracted from the electronic hospital information systems or medical records. The closest laboratory measurement performed within 90 days before or after the date of a visit was appointed to that visit. HDL cholesterol and TG levels were directly measured following standard procedure in the participating outpatient clinics. LDL cholesterol was either directly measured or estimated with the Friedewald equation: total cholesterol – HDL cholesterol – TG/2.2.[22] This formula was not applied in patients with serum TG levels>8.0 mmol/L. Information regarding the fasting state of the patients was not available. The eGFR was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula from 2009, taking into account age, sex, race, and serum creatinine.[23] Hypertension was defined as either a history of hypertension, antihypertensive drug use, a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90mmHg at baseline.[24] Nutritional status was scored with the Subjective Global Assessment (SGA), a tool that uses medical history and physical examination to create a score ranging from '1' indicating severe protein energy wasting, to '7' indicating a normal nutritional status.[25] Primary kidney disease was classified according to the codes of the European Renal Association-European Dialysis and Transplantation Association.[26] We grouped patients into four classes of primary kidney disease: glomerulonephritis, diabetes mellitus, renal vascular disease, and other kidney diseases.

Exposure and outcomes

Dyslipidemia was defined as total cholesterol ≥5.00 mmol/L, LDL cholesterol ≥2.50 mmol/L, HDL cholesterol <1.00 mmol/L, HDL/LDL ratio<0.4, or TG ≥2.25 mmol/L. Outcomes were start of dialysis, start of RRT and the combined endpoint start of RRT or death. Start of dialysis was defined as starting hemodialysis or peritoneal dialysis during follow up. Start of RRT was defined as start of dialysis or receiving a kidney transplant during follow up.

Statistical analysis

Baseline characteristics were presented as mean ± standard deviation (SD) for normally distributed continuous variables, skewed continuous variables as median with interquartile range (IQR). Categorical variables were presented as number and percentages. Total cholesterol, LDL cholesterol, HDL cholesterol levels, HDL/LDL ratio, and TG were used as determinants, and categorized based on the target goals recommended by the Dutch and international pre-dialysis guidelines, being <5.00 mmol/L, <2.50 mmol/L, ≥1.00 mmol/L, ≥0.4, and <2.25 mmol/L, respectively.[20, 27, 28] Baseline characteristics were presented for the total population and according to presence or absence of dyslipidemia. Absolute crude incidence rates of the primary outcomes were calculated for the total population and separately for patients with and without dyslipidemia.

We conducted Cox proportional hazards regression analysis, obtaining hazard ratios (HR) with 95% confidence intervals (95%CI) to estimate the effect of dyslipidemia and the different components of dyslipidemia on the three primary outcomes. Because dyslipidemia shows its detrimental effects after long term exposure, we studied dyslipidemia as a fixed risk factor at baseline. The separate components of dyslipidemia were analyzed as categorical and continuous variables. Analyses were adjusted for age, sex, ethnicity, body mass index, diabetes mellitus, hypertension, primary kidney disease, proteinuria and current smoking (model 1). In addition to model 1 we also adjusted for malnutrition-inflammation factors: serum albumin, serum C-Reactive Protein, the SGA score (model 2), as well as for lipid-lowering medication use (statin use, fibrate use, or cholesterol absorption medication use) (model 3). Follow-up time was defined as time between baseline visit of the patient and the start of dialysis, RRT, death, withdrawal or end of follow-up (October 2016). The proportional hazard assumption was tested using a log minus log plot. To estimate the median follow up time, a reversed Kaplan-Meier was used.

Multiple imputation was used to avoid bias and to maintain power.[29, 30] Missing values of total cholesterol, LDL cholesterol, HDL cholesterol and TG at baseline, as well as potential confounders at baseline were imputed (using 10 repetitions). The imputed data were predicted based on the available information of each patient.

We performed multiple sensitivity analyses to test the robustness of our findings. First, we added kidney function at baseline into the multivariable models. Since kidney function could be in the causal pathway between dyslipidemia and the outcomes we did not add this variable in the main model. Second, we stratified for statin use, because statins may have a pleiotropioc, non-lipid lowering effect, independent of the effect on lipid levels. Third, we stratified for baseline eGFR (≤15 ***vs.*** >15 ml/min/1.73 m^2) to study effect modification between kidney functon and dyslipidemia with regard to the outcome. Fourth, we restricted our analysis to patients who were persistent users or non-users of lipid-lowering medication during the entire study period (adjusted for model 3), since changes in lipid-lowering therapy during the follow up period might dilute treatment effects. Fifth, we studied short and long term effects from baseline dyslipidemia seperately by restricting our follow up

Table 1. Baseline characteristics of all 502 pre–dialysis patients of the PREPARE–2 Study and according to the presence of dyslipidemia

	Total population (n=502)	Patients with dyslipidemia (n=181)	Patients without dyslipidemia (n=93)
Men	341 (68)	129 (71)	55 (59)
Age, years	69 (56-76)	66 (55-75)	70 (59-78)
Ethnicity			
Caucasian	462 (92)	168 (93)	86 (93)
Negroid	29 (6)	11 (6)	2 (2)
Other	11 (2)	2 (1)	5 (5)
Primary Kidney Disease			
Renal vascular disease	154 (31)	60 (33)	30 (32)
Diabetes	72 (14)	20 (11)	14 (15)
Glomerulonephritis	67 (13)	60 (33)	14 (15)
Other	209 (42)	74 (41)	35 (38)
Current smoker, yes	99 (20)	40 (22)	15 (16)
Diabetes Mellitus, yes [a]	130 (26)	45 (25)	25 (27)
Cardiovascular Disease, yes [b]	207 (41)	75 (41)	44 (47)
Hypertension, yes [c]	445 (89)	163 (90)	81 (87)
Systolic blood pressure, mmHg	142 (22)	144 (23)	142 (21)
Diastolic blood pressure, mmHg	78 (12)	79 (11)	77 (11)
Body Mass Index, kg/m^2 [g]	26 (23-30)	26 (23-30)	25 (23-30)
Subjective Global Assessment [dg]			
Well nourished	336 (67)	120 (66)	58 (62)
Moderately well nourished	43 (9)	13 (7)	9 (10)
Anti-hypertensive drug use	413 (82)	151 (83)	75 (81)
Lipid lowering drug use [eg]	273 (54)	96 (53)	55 (59)
Statin use	263 (52)	91 (50)	55 (59)
Serum creatinine, μmol/L [g]	357 (115)	348 (112)	360 (101)
eGFR, ml/min/1.73 m^2 [fg]	15 (6)	16 (6)	14 (6)
Total cholesterol, mmol/L [g]	4.45 (1.20)	4.76 (1.19)	3.87 (0.93)
LDL, mmol/L [g]	2.49 (0.93)	2.77 (0.94)	1.87 (0.44)
HDL, mmol/L [g]	1.28 (0.45)	1.22 (0.47)	1.42 (0.38)
Triglycerides, mmol/L [g]	1.52 (1.11-2.20)	1.87 (1.34-2.60)	1.20 (0.98-1.50)
Albumin, g/L [g]	40.7 (4.6)	41.2 (4.5)	41.1 (4.2)
C-Reactive Protein, mg/L [g]	4 (2-9)	4 (3-10)	3 (1-8)
Proteinuria, g/24h [g]	1.08 (0.37-2.20)	1.09 (0.38-2.23)	1.01 (0.41-1.50)

Values are given as mean ± SD or median and interquartile range (IQR).

[a] Defined as the presence of diabetes mellitus as primary kidney disease or a history of diabetes mellitus. [b] Defined as presence of coronary artery disease, a history of cardiovascular accident, peripheral vascular disease, or myocardial infarction. [c] Defined as either a history of hypertension, antihypertensive drug use, a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg at baseline. [d] Defined as well-nourished

[subjective global assessment (SGA) 6 – 7], moderately well-nourished (SGA 3 – 5), and severely malnourished (SGA 1 – 2).
[e] Defined as the prescription of statins, fibrates, or cholesterol absorption inhibitors. [f] eGFR (estimated glomerular filtration rate) is calculated with the CKD EPI (Chronic Kidney Disease Epidemiology Collaboration) formula 2009. [g] Body Mass Index was known for 492 patients, Subjective Global Assessment for 379, Serum creatinine and eGFR for 438, proteinuria for 247, total cholesterol for 230, LDL cholesterol for 201, HDL cholesterol for 207, triglycerides for 211, albumin for 403, C-reactive protein for 198, and lipid lowering drug use for 398 patients.

time to 12 months (short term) and by restricting our analyses to patients who were still in the study after 12 months (long term). Finally, we repeated all analyses applying multiple imputation confined to patients with at least one serum total cholesterol, LDL cholesterol, HDL cholesterol or TG measurement during the first 6 months of their study participation. A p-value <0.05 was considered statistically significant. All analyses were performed using SPSS version 23.0 for Windows.

Results

Patient characteristics

The PREPARE-2 cohort consists of 502 pre-dialysis patients. Of these patients, dyslipidemia could be determined in 274 patients, using the cholesterol measurements (total cholesterol, LDL, HDL, HDL/LDL ratio or TG) from the first 6 months of the study. Of these 274 patients, 181 had dyslipidemia, and 93 did not have dyslipidemia. Baseline characteristics of the patients of the cohort are shown in Table 1. Patients had a median age of 69 (IQR 56-76), 68% were men, 92% were Caucasian, 54% used lipid lowering drugs, and 52% used statins. Patients with dyslipidemia had more often glomerulonephritis as their primary kidney disease, were more frequent a current smoker, had cardiovascular disease as a co-morbidity less often, had lower HDL levels, and had higher levels of total cholesterol, LDL, and triglycerides. Of all patients with or without dyslipidemia 50% and 59%, respectively, used a statin at baseline. During the study 91 patients switched statin use from users to non-users or vice versa.

Start of dialysis, renal replacement therapy and death

Of all patients the median follow up time was 66 months (IQR 61-71). During follow up 376 patients (75%) started RRT and 47 patients (9%) died. The crude incidence rate for the combined endpoint RRT or death in patients with or without dyslipidemia was 35/100 py and 31/100 py, respectively (Table 2). For all Cox proportional hazards regression analyses the proportional hazards assumption was fulfilled (plots not shown). The crude and adjusted hazard ratios (HR) for the outcomes for dyslipidemia and for each serum lipid category (outside or within target range) are presented in Table 3. After multivariable adjustment, including statin therapy, the HR for dyslipidemia was 1.12 (0.85 to 1.47). We only found a

Table 2. Crude incidence rates (95% CIs) of primary outcomes according to the presence of dyslipidemia (n=502)

	Total (n=502)	Patients with dyslipidemia (n=181)	Patients without dyslipidemia (n=93)
Person years (py)	950.9	337.5	191.7
Start dialysis, n (%)	327 (65)	117 (65)	60 (65)
Incidence rate/100 py	34.4	34.7	31.3
95% CI	23.5 to 47.5	28.7 to 41.5	23.9 to 40.3
Start RRT, n (%)	376 (75)	137 (76)	71 (76)
Incidence rate/100 py	39.5	40.6	37.0
95% CI	28.6 to 54.5	34.1 to 48.0	28.9 to 46.7
Combined RRT or death, n (%)	423 (84)	155 (85)	76 (82)
Incidence rate/100 py	44.5	45.9	39.6
95% CI	32.0 to 59.1	39.0 to 53.8	31.2 to 49.6

CI: confidence interval, n: number, py: person year, RRT: Renal Replacement Therapy

weak positive association between LDL and RRT or death with a HR of 1.20 (95% CI 0.89 to 1.61) for high LDL compared to a LDL level within target range. We found no association between RRT or death and the lipid levels when analyzed as continuous variables (Table 4).

Sensitivity analyses

Adding kidney function to model 3 changed the HR for start of dialysis for dyslipidemia to 1.16 (0.80 to 1.67), for RRT to 1.18 (0.82 to 1.69), and for RRT or death to 1.21 (0.87 to 1.69). For LDL (<2.5 *vs* ≥2.5 mmol/L) the HR changed to 1.12 (0.60-2.08) for start of dialysis, 1.17 (0.66 to 2.05) for RRT and 1.27 (0.77 to 2.11) for RRT or death. The HRs for high TG were 1.25 (95% CI 0.80 to 1.95) for start of dialysis, 1.20 (0.79 to 1.00) for RRT and 1.17 (0.79 to 1.73) for RRT or death. The HR for the continuous HDL/LDL ratio changed to 0.85 (95% CI 0.45 to 1.58) for start of dialysis, 0.83 (0.49-1.40) for RRT and 0.81 (0.49 to 1.33) for RRT or death. The HRs for total cholesterol and HDL cholesterol, both categorical and continuous, remained unchanged. When stratifying for statin use at baseline, the HRs for dyslipidemia were higher in non-statin users as compared with statin users. the HRs for the separate lipid categories were higher in statin users compared to non-statin users, except for the category exposure HDL and TG and the continuous exposure HDL/LDL ratio. When stratifying for baseline eGFR (≤15 *vs* >15 ml/min/1.73 m^2) the HR for the combined endpoint RRT or death was 1.02 (0.68 to 1.53) *vs* 1.36 (0.73 to 2.52) for the presence of dyslipidemia, 0.99 (0.63 to 1.56) *vs* 1.23 (0.72 to 2.11) for total cholesterol, 1.09 (0.75 to 1.59) *vs* 1.46 (0.82 to 2.60) for LDL, 1.10 (0.72 to 1.69) *vs* 0.92 (0.54 to 1.58) for HDL, 0.90 (0.57 to 1.43) *vs* 0.90 (0.53 to 1.56) for triglycerides, and 0.91 (0.55 to 1.51) *vs* 0.92 (0.50 to 1.72) for the HDL/LDL ratio. Restricting the analyses to persistent users and non-users of lipid-lowering medication, the HR for the combined endpoint RRT or death for dyslipidemia decreased to 1.05 (0.77 to 1.43). The HR for the categorical lipid variables increased to 1.33 (0.91 to 1.92) for LDL, decreased to

Table 3. Crude and adjusted hazard ratio (95%CI) according to the presence of dyslipidemia, serum lipids or triglycerides category for start of dialysis, RRT and combined endpoint (n=502)

	Start of dialysis HR (95% CI) (n=327)	RRT HR (95% CI) (n=376)	RRT or death HR (95% CI) (n=423)
Dyslipidemia			
No	Ref	Ref	Ref
Yes	1.08 (0.81 to 1.44)	1.11 (0.85 to 1.44)	1.16 (0.90 to 1.50)
Model 1[a]	0.97 (0.71 to 1.32)	1.00 (0.74 to 1.35)	1.07 (0.79 to 1.44)
Model 2[b]	0.95 (0.70 to 1.29)	0.98 (0.72 to 1.34)	1.06 (0.79 to 1.43)
Model 3[c]	1.07 (0.78 to 1.46)	1.06 (0.79 to 1.42)	1.12 (0.85 to 1.47)
Total cholesterol			
< 5mmol/L	Ref	Ref	Ref
≥ 5 mmol/L	0.90 (0.68 to 1.19)	0.95 (0.73 to 1.24)	0.99 (0.76 to 1.30)
Model 1[a]	0.85 (0.59 to 1.21)	0.87 (0.62 to 1.23)	0.92 (0.66 to 1.30)
Model 2[b]	0.84 (0.58 to 1.21)	0.87 (0.61 to 1.24)	0.92 (0.65 to 1.31)
Model 3[c]	0.98 (0.65 to 1.47)	0.98 (0.67 to 1.44)	1.01 (0.70 to 1.46)
LDL			
< 2.50 mmol/l	Ref	Ref	Ref
≥ 2.50 mmol/l	1.04 (0.80 to 1.34)	1.10 (0.85 to 1.42)	1.19 (0.93 to 1.50)
Model 1[a]	1.01 (0.76 to 1.32)	1.05 (0.79 to 1.39)	1.13 (0.86 to 1.48)
Model 2[b]	1.00 (0.75 to 1.33)	1.04 (0.78 to 1.40)	1.13 (0.86 to 1.49)
Model 3[c]	1.08 (0.78 to 1.49)	1.11 (0.82 to 1.52)	1.20 (0.89 to 1.61)
HDL			
< 1.00 mmol/l	Ref	Ref	Ref
≥ 1.00 mmol/l	1.13 (0.76 to 1.69)	1.06 (0.74 to 1.53)	1.03 (0.73 to 1.46)
Model 1[a]	1.10 (0.72 to 1.69)	1.07 (0.73 to 1.57)	1.02 (0.70 to 1.49)
Model 2[b]	1.10 (0.73 to 1.67)	1.07 (0.74 to 1.55)	1.02 (0.71 to 1.47)
Model 3[c]	1.10 (0.69 to 1.75)	1.08 (0.71 to 1.65)	1.02 (0.69 to 1.51)
HDL/LDL ratio			
< 0.4	Ref	Ref	Ref
≥ 0.4	0.96 (0.67 to 1.37)	0.97 (0.74 to 1.27)	0.98 (0.78 to 1.24)
Model 1[a]	1.03 (0.68 to 1.58)	1.01 (0.68 to 1.48)	0.99 (0.69 to 1.44)
Model 2[b]	1.04 (0.69 to 1.56)	1.00 (0.69 to 1.46)	0.99 (0.69 to 1.43)
Model 3[c]	1.00 (0.63 to 1.59)	0.98 (0.64 to 1.48)	0.99 (0.66 to 1.48)
Triglycerides			
< 2.25 mmol/l	Ref	Ref	Ref
≥ 2.25 mmol/l	1.00 (0.75 to 1.32)	0.97 (0.74 to 1.27)	0.98 (0.78 to 1.24)
Model 1[a]	0.85 (0.63 to 1.15)	0.84 (0.64 to 1.09)	0.87 (0.67 to 1.13)
Model 2[b]	0.87 (0.64 to 1.17)	0.85 (0.64 to 1.13)	0.88 (0.67 to 1.15)
Model 3[c]	0.91 (0.64 to 1.31)	0.90 (0.65 to 1.23)	0.91 (0.68 to 1.22)

[a]Model 1 was adjusted for; age, sex, ethnicity, current smoker, body mass index, diabetes mellitus, hypertension, proteinuria and primary kidney disease.
[b]Model 2 was adjusted for: model 1 + CRP, Albumin, Subjective Global Assessment
[c]Model 3 was adjusted for: model 2 + Lipid-lowering medication use
RRT: Renal Replacement Therapy

0.76 (0.51 to 1.14) for the HDL/LDL ratio, and to 0.68 (0.44-1.04) for triglycerides. The HRs for the combined endpoint for total cholesterol and HDL did not change when analyzed as a categorical variable. The HRs for the combined endpoint when analyzing lipids as continuous variables did not change. When we confined all analyses to patients with at least one cholesterol measurement during the first 6 months of their study participation the results did not change essentially.

To account for changes of serum lipids over time, we examined the short term (≤12 months) and long term (>12 months) association between serum lipids and outcomes separately. Table 5 and 6 show the adjusted hazard ratios for the outcomes for dyslipidemia, and for the serum lipids as a categorical and continuous variable for short and long term follow-up. For dyslipidemia, the short term HRs were lower as compared with the long term HRs, 0.97 (0.63 to 1.49) *vs* 1.23 (0.80 to 1.88) for the combined outcome. For the

Table 4. Crude and adjusted hazard ratio (95%CI) according to continuous levels of serum lipids or triglycerides for start of dialysis, RRT and combined endpoint (n=502)

	Start of dialysis HR (95% CI) (n=327)	RRT HR (95% CI) (n=376)	RRT or death HR (95% CI) (n=423)
Total cholesterol (per 1 mmol/L increment)	1.00 (0.90 to 1.11)	1.02 (0.92 to 1.12)	1.04 (0.95 to 1.14)
Model 1[a]	0.96 (0.83 to 1.10)	0.97 (0.85 to 1.10)	0.99 (0.88 to 1.12)
Model 2[b]	0.95 (0.83 to 1.10)	0.96 (0.84 to 1.11)	0.99 (0.87 to 1.13)
Model 3[c]	1.01 (0.87 to 1.18)	1.01 (0.88 to 1.17)	1.03 (0.90 to 1.17)
LDL (per 1 mmol/L increment)	0.97 (0.83 to 1.13)	1.01 (0.88 to 1.17)	1.05 (0.92 to 1.20)
Model 1[a]	0.95 (0.80 to 1.12)	0.99 (0.84 to 1.16)	1.02 (0.87 to 1.20)
Model 2[b]	0.94 (0.79 to 1.12)	0.98 (0.83 to 1.17)	1.02 (0.86 to 1.20)
Model 3[c]	1.00 (0.83 to 1.21)	1.03 (0.86 to 1.24)	1.06 (0.89 to 1.26)
HDL (per 1 mmol/L increment)	0.98 (0.68 to 1.40)	1.02 (0.74 to 1.39)	1.05 (0.79 to 1.41)
Model 1[a]	1.03 (0.72 to 1.48)	1.06 (0.76 to 1.47)	1.09 (0.80 to 1.47)
Model 2[b]	1.03 (0.71 to 1.49)	1.05 (0.75 to 1.48)	1.08 (0.79 to 1.49)
Model 3[c]	1.07 (0.72 to 1.60)	1.09 (0.76 to 1.56)	1.13 (0.81 to 1.57)
HDL/LDL ratio (per 1 point increment)	1.01 (0.67 to 1.51)	0.99 (0.69 to 1.41)	0.96 (0.70 to 1.32)
Model 1[a]	1.07 (0.76 to 1.51)	1.04 (0.74 to 1.45)	1.02 (0.74 to 1.38)
Model 2[b]	1.06 (0.74 to 1.52)	1.03 (0.73 to 1.44)	1.01 (0.73 to 1.39)
Model 3[c]	1.01 (0.62 to 1.67)	0.99 (0.62 to 1.58)	0.98 (0.61 to 1.55)
Tri-glycerides (per 1 mmol/L increment)	1.02 (0.92 to 1.14)	1.01 (0.91 to 1.11)	1.01 (0.92 to 1.11)
Model 1[a]	0.96 (0.85 to 1.07)	0.94 (0.85 to 1.04)	0.95 (0.86 to 1.06)
Model 2[b]	0.96 (0.86 to 1.06)	0.94 (0.85 to 1.04)	0.96 (0.87 to 1.06)
Model 3[c]	0.98 (0.87 to 1.10)	0.96 (0.86 to 1.07)	0.97 (0.87 to 1.08)

[a]Model 1 was adjusted for; age, sex, ethnicity, current smoker, body mass index, diabetes mellitus, hypertension, proteinuria and primary kidney disease.
[b]Model 2 was adjusted for: model 1 + CRP, Albumin, Subjective Global Assessment
[c]Model 3 was adjusted for: model 2 + Lipid-lowering medication use
RRT: Renal Replacement Therapy

separate lipid categories and levels short term effects were stronger than long term effects, but without any significant differences since all 95% confidence intervals overlapped.

Table 5. Adjusted hazard ratio (95%CI) according to the presence of dyslipidemia, serum lipids or triglycerides category for start of dialysis, RRT and combined endpoint after 12 months and after a minimum of 12 months of follow–up

	Start of dialysis HR[a] (95% CI)	RRT HR[a] (95% CI)	RRT or death HR[a] (95% CI)
Dyslipidemia			
No	Ref	Ref	Ref
Yes			
FU≤12 months	0.88 (0.55 to 1.40)	0.93 (0.59 to 1.47)	0.97 (0.63 to 1.49)
FU>12 months	1.21 (0.75 to 1.95)	1.16 (0.75 to 1.80)	1.23 (0.80 to 1.88)
Total cholesterol			
< 5mmol/L	Ref	Ref	Ref
≥ 5 mmol/L			
FU≤12 months	0.88 (0.55 to 1.41)	0.92 (0.59 to 1.41)	0.97 (0.63 to 1.49)
FU>12 months	1.06 (0.59 to 1.90)	1.04 (0.57 to 1.88)	1.04 (0.61 to 1.78)
LDL			
< 2.50 mmol/l	Ref	Ref	Ref
≥ 2.50 mmol/l			
FU≤12 months	1.08 (0.63 to 1.84)	1.13 (0.67 to 1.90)	1.19 (0.72 to 1.98)
FU>12 months	1.07 (0.61 to 1.86)	1.09 (0.64 to 1.85)	1.20 (0.74 to 1.93)
HDL			
< 1.00 mmol/l	Ref	Ref	Ref
≥ 1.00 mmol/l			
FU≤12 months	1.11 (0.62 to 1.97)	1.10 (0.63 to 1.91)	1.04 (0.58 to 1.84)
FU>12 months	1.15 (0.65 to 2.01)	1.12 (0.68 to 1.85)	1.05 (0.66 to 1.68)
HDL/LDL ratio			
< 0.4	Ref	Ref	Ref
≥ 0.4			
FU≤12 months	0.92 (0.51 to 1.67)	0.87 (0.50 to 1.52)	0.93 (0.56 to 1.56)
FU>12 months	1.05 (0.59 to 1.89)	1.05 (0.62 to 1.77)	1.01 (0.61 to 1.70)
Triglycerides			
< 2.25 mmol/l	Ref	Ref	Ref
≥ 2.25 mmol/l			
FU≤12 months	0.69 (0.36 to 1.31)	0.69 (0.39 to 1.21)	0.71 (0.40 to 1.24)
FU>12 months	1.14 (0.75 to 1.73)	1.08 (0.74 to 1.58)	1.09 (0.76 to 1.55)

[a]All analyses were adjusted for: age, sex, ethnicity, current smoker, body mass index, diabetes mellitus, hypertension, proteinuria and primary kidney disease, CRP, Albumin, Subjective Global Assessment, Lipid-lowering medication use

RRT: Renal Replacement Therapy, FU: follow-up

Table 6. Adjusted hazard ratio (95%CI) according to continuous levels of serum lipids or triglycerides for start of dialysis, RRT and combined endpoint after 12 months and after a minimum of 12 months of follow–up

	Start of dialysis HR[a] (95% CI)	RRT HR[a] (95% CI)	RRT or death HR[a] (95% CI)
Total cholesterol (per 1 mmol/L increment)			
FU≤12 months	0.98 (0.81 to 1.18)	0.99 (0.83 to 1.18)	1.01 (0.85 to 1.20)
FU>12 months	1.03 (0.80 to 1.31)	1.02 (0.81 to 1.28)	1.04 (0.85 to 1.27)
LDL (per 1 mmol/L increment)			
FU≤12 months	1.02 (0.78 to 1.34)	1.07 (0.82 to 1.40)	1.08 (0.84 to 1.38)
FU>12 months	0.95 (0.72 to 1.26)	0.98 (0.76 to 1.27)	1.04 (0.81 to 1.32)
HDL (per 1 mmol/L increment)			
FU≤12 months	1.15 (0.69 to 1.93)	1.13 (0.69 to 1.84)	1.20 (0.76 to 1.90)
FU>12 months	0.99 (0.57 to 1.70)	1.05 (0.66 to 1.66)	1.05 (0.69 to 1.60)
HDL/LDL ratio (per 1 point increment)			
FU≤12 months	1.08 (0.53 to 2.18)	1.03 (0.50 to 2.12)	1.04 (0.52 to 2.09)
FU>12 months	0.96 (0.51 to 1.82)	0.95 (0.57 to 1.58)	0.91 (0.55 to 1.49)
Tri-glycerides (per 1 mmol/L increment)			
FU≤12 months	0.88 (0.73 to 1.05)	0.87 (0.73 to 1.04)	0.88 (0.74 to 1.05)
FU>12 months	1.08 (0.92 to 1.26)	1.05 (0.91 to 1.21)	1.06 (0.92 to 1.22)

[a]All analyses were adjusted for: age, sex, ethnicity, current smoker, body mass index, diabetes mellitus, hypertension, proteinuria and primary kidney disease, CRP, Albumin, Subjective Global Assessment, Lipid-lowering medication use

RRT: Renal Replacement Therapy, FU: follow-up

Discussion

We found no association between dyslipidemia and start of dialysis, RRT or death in incident pre-dialysis patients.

Our finding is in line with several other studies in CKD patients.[7, 13, 31] The CRIC study (mean age 58 y, mean eGFR 45 ml/min/1.73m^2, 42% non-Hispanic black) showed no association between lipoprotein levels and risk of end-stage renal disease (ESRD) after multivariable adjustment.[7, 31] Chawla ***et al***. found no association between lipid levels and 10-year mortality in 840 CKD stage 3-4 non diabetic patients (mean age 52 y, mean GFR 33 ml/min/1.73m^2, 85% white patients).[13]

Kovesdy ***et al.*** found in 986 patients (mean age 67y, mean eGFR 37 ml/min/1.73m^2, 40% statin usage) after multivariable adjustment, including controlling for case-mix and malnutrition-inflammation factors, no association between total cholesterol, LDL and TG, and mortality.[12] In our study additional adjustment for malnutrition-inflammation factors did not essentially change the results, which can be explained by the characteristics of our population. Almost all patients of our cohort were well nourished (SGA of 6 or 7), only less than 10% had a moderate nourishment status. Unfortunately, in 25% of all patients

the SGA measurement was not performed. Therefore, we cannot exclude that some pre-dialysis patients were severely malnourished. On the other hand, only 2% of all patients in our cohort had a very low BMI<18.5 kg/m^2. To adjust for residual confounding due to under nutrition we added serum albumin as a nutritional marker to our analyses, which essentially did not change the results.

Our results are in concordance with a recent guideline, stating that CKD patients ≥50y should be treated with a statin, independent of lipid or triglyceride levels, without aiming at a target level.[32, 33] This shows a paradigm shift moving away from LDL based therapy, towards treatment based on atherosclerotic cardiovascular risks. This shift is caused by the lack of evidence that changing lipid levels affects cardiovascular risk in CKD patients.[34-36]

The guideline advice to start statin therapy independent of lipid levels is based on results of subanalyses of large trials.[32, 33] For example the SHARP trial, including 9270 patients with a mean eGFR of 27 ml/min/1.73m^2 (mean age 62y, 63% men, and 23% diabetics), showed that patients treated with statins compared to no statins had a 17% lower risk of cardiovascular outcome.[15, 16] More advanced CKD may attenuate statin efficacy, as evidenced by negative statin trials in dialysis patients, such as the 4D study and AURORA. A recent meta-analysis by the CCT Collaboration[15, 37-39], including 28 trials - totaling 183,419 patients, studied the effect of statin therapy on major cardiovascular events and death per eGFR category (eGFR ≥60, 45 to <60, 30 to <45, <30 ml/min/1.73 m^2, including dialysis patients). They found a progressive smaller beneficial effect from statin therapy on major vascular events with decreasing eGFR. In patients with an eGFR ≥60 ml/min/1.73m^2 compared to dialysis patients, the beneficial effect of statins on risk of major vascular events was 0.74 (95% CI 0.70-0.79) and 0.89 (95% CI 0.70-1.14), respectively.[39]

Several hypotheses have been suggested to explain the lack of association between dyslipidemia and cardiovascular morbidity and mortality in patients with impaired kidney function. First, uremia may transform HDL into a promotor of inflammation and atherogenesis.[40-43] In addition, Bauer ***et al***. found that HDL functionality (HDL cholesterol efflux capacity) is not associated with cardiovascular events in CKD patients (mean eGFR 46 ml/min/1.73m^2).[44] This is in line with our finding that high HDL level was weakly associated with an increased risk of adverse outcome. If uremia induced, one would expect a dose-response relation, and as a result a decreasing beneficial effect of high levels of HDL in the later CKD stages. After stratification for baseline eGFR (≤15 or >15 ml/min/1.73m^2) we found a HR for the combined endpoint of 1.10 (95% CI 0.72 to 1.69) and 0.92 (95% CI 0.54 to 1.58) for high versus low HDL.[44] Second, although we adjusted for malnutrition-inflammation factors, we cannot exclude residual confounding by coexistent wasting and/or inflammation that led to both lower lipid levels and an increased risk of adverse outcome. Finally, severe atherosclerosis, as present in most pre-dialysis patients, is multifactorial, and might be too advanced to achieve disease regression by lower lipid levels. In addition, non-

traditional cardiovascular risk factors such as a disturbed calcium-phosphate balance may play a more important role than dyslipidemia in the progression of atherosclerosis.[45-47]

Main strength of this study is the specific selection of pre-dialysis patients who were treated according to the current CKD guidelines by nephrologists. Pre-dialysis patients form a special group in chronic kidney disease care and cannot be compared to patients in the early stages of CKD. Since no exclusion criteria were used for the PREPARE cohort a wide range of incident pre-dialysis patients were included and all patient information was used to perform the analyses, our results can be generalized to the clinical practice of pre-dialysis care.

This study has limitations. The main limitation of this study are the missing data. Even though we used multiple imputation to deal with this in the best possible way, it is possible that the amount of predictors was insufficient to complete the data. However, in a sensitivity analysis where multiple imputation was restricted to patients with at least one lipid measurement during the first 6 months of study participation, results did not change materially. Second, information regarding the fasting state of patients was not available, resulting in a lack of distinction between patients with fasting or post-prandial elevated TG levels. Finally we used two different methods to measure LDL. Under normal circumstances the Friedewald equation correlates very well with the direct measurement of LDL. [48] However, we cannot exclude the occurrence of chylomicrons or a combination with high plasma TG, both causes of under- and overestimation of LDL levels.

In conclusion, we found no clear association between dyslipidemia and start of dialysis, RRT or death.

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5

EFFECT OF DUAL COMPARED TO NO OR SINGLE RENIN–ANGIOTENSIN SYSTEM BLOCKADE ON RISK OF RENAL REPLACEMENT THERAPY OR DEATH IN PRE–DIALYSIS PATIENTS: PREPARE–2 STUDY

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Abstract

Introduction: Current guidelines on hypertension treatment in chronic kidney disease (CKD) patients discourage combined angiotensin converting enzyme inhibitor (ACEi) and angiotensin II receptor blocker (ARB) use due to the risk of an increased kidney function decline. However, dual compared to single renin-angiotensin system (RAS) blockade may have more efficacy with regard to hypertension and proteinuria. Among incident pre-dialysis patients (CKD 4-5) we compared dual with no or single RAS blockade regarding kidney function decline, and risk of renal replacement therapy (RRT) or death.

Methods: In a multi-center cohort study, 495 incident pre-dialysis patients (>18y) were included between 2004-2011 and followed until RRT, death or October 2016. At baseline, patients were divided into four categories: non-user, single or dual user of ACEi and/or ARB. Cox models were used to estimate the hazard ratio (HR) for the combined endpoint RRT or death. Differences in decline of kidney function among the four drug groups were compared with a linear mixed model.

Results: 119 patients were non-users, 164 ACEi-users, 133 ARB-users, and 79 dual RAS users. Compared to non-users, the multivariable adjusted HR (95% CI) for the combined endpoint was 0.75 (0.65-0.86) for ACEi-users, 0.87 (0.76-1.00) for ARB-users, and 0.79 (0.67-0.94) for dual RAS users. The average annual decline in kidney function did not differ among the four groups.

Conclusions: We observed in pre-dialysis patients that compared to no RAS blockade both dual RAS blockade and single ACEi-use were associated with about 20-25% lower risk of RRT or death, without difference in kidney function decline.

Introduction

Hypertension is one of the major risk factors of accelerated loss of kidney function in chronic kidney disease (CKD). CKD is a leading cause of death due to premature cardiovascular disease.[1] Therefore, prevention of kidney function decline is important to improve life expectancy. Globally, the prevalence rates of CKD are >20% among men and women aged 65-74 year and >30% among those aged 75-84 year.[2, 3] Current therapies in CKD patients aim at improving modifiable cardiovascular risk factors, such as hypertension, to slow down kidney function decline, and prevent or postpone end stage renal disease (ESRD).

To manage hypertension in patients with CKD, the use of renin–angiotensin system (RAS) inhibitors to a goal of <140/90 mmHg is recommended by international guidelines such as the Joint National Committee 8 guidelines (JNC8) and the Kidney Disease Improving Global Outcomes 2012 (KDIGO).[4, 5] RAS inhibitors, such as angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB), both lower systolic and diastolic blood pressure, without cardiac dysfunction, and have extensively been proven to be renoprotective agents.[6-11] ACEi down regulate the level of angiotensin II and aldosterone by blocking ACE, ARBs mainly block the angiotensin I receptor.

Cellular effects in the kidney and alterations in glomerular hemodynamics due to RAS inhibitors, probably prevent the development or reduce proteinuria, and delay the progression of CKD to ESRD.[12] Possible negative consequences of ACEi and ARBs include hypotension, decline in kidney function, and hyperkalemia. In patients with severe impaired renal perfusion, ACEi and ARBs can compromise glomerular perfusion pressure and glomerular filtration rate (GFR).[12]

Since ACEi or ARBs alone do not block the entire RAS and work via different pathways, it has been hypothesized that dual RAS blockade can improve renoprotective and antihypertensive effects.[13, 14] However, until now trials, such as the ONTARGET (Ongoing Telmisartan alone an in combination with Ramipril Global Endpoint Trial) trial, have not been able to prove this hypothesis and only found negative consequences, such as an increased risk of kidney function decline and hyperkalemia for which dialysis is required in dual RAS compared to single users.[6-11] Unfortunately, due to a lack of power to detect differences in renal outcome and small number of included patients with CKD (ONTARGET: mean eGFR 74 ml/min/1.73m^2), so far these trials have not been able to provide a definite conclusion for patients with CKD.[15, 16] Therefore, current guidelines discourage combined ACEi and ARB usage in CKD patients, based on expert opinion. When using a single RAS inhibitor both ACEi and ARBs are equally valued.[4] The aim of our prospective cohort study is to investigate in incident pre-dialysis patients whether dual compared to single use and non-use of ACEi and ARBs is associated with an increased risk of RRT or death, or an accelerated kidney function decline. These data reflect specialized nephrological care and allow us to evaluate real-world effectiveness and safety of ACEi and ARB in pre-dialysis patients often under-represented or excluded from clinical trials.

Methods

Study design and population

The PRE-dialysis Patient Record-2 (PREPARE-2) study is a prospective cohort study of incident pre-dialysis care patients (≥18 y) who had an estimated glomerular filtration rate (eGFR) of less than 30 ml/min/1.73m^2 and progressive renal function loss. Patients with a failing kidney transplant who were transplanted at least one year ago were also eligible for inclusion. The PREPARE-2 study has been described in detail elsewhere.[17] In brief, patients were recruited in one of 25 nephrology specialized pre-dialysis outpatient clinics in the Netherlands between July 2004 and June 2011. All patients were treated by their nephrologist in accordance with the treatment guidelines of the Dutch Federation of Nephrology, guidelines partly based on the K/DOQI and EBPG guidelines.[18-21] Patients were followed from the start of pre-dialysis care until start of dialysis, kidney transplantation, death or censoring. Censoring was defined as: refusal for further participation, recovery of kidney function, moving to an outpatient clinic not participating in the PREPARE-2 study, loss to follow up or October, 2016 (end of follow up), whichever came first. This study was approved by the medical ethics committee or institutional review boards (as appropriate) of all participating centers. Written informed consent was obtained from all patients.

Demographic and clinical data

Data on demography, primary kidney disease, comorbidities, medication use, and laboratory values were collected at baseline and during routine visits to pre-dialysis outpatient clinics. These visits took place at the start of specialized pre-dialysis care, at the moment of reaching one of the study endpoints as described previously, and every intermediate 6-month interval. Laboratory data were extracted from the electronic hospital information systems or medical records. The closest laboratory measurement performed within 90 days before or after the date of a visit was appointed to that visit. Patients were categorized as non-users or users (single or dual) of ACEi and/or ARB medication based on medication use at baseline. The eGFR was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula from 2009, taking into account age, sex, race, and serum creatinine.[22] Hypertension was defined as either a history of hypertension, antihypertensive drug use, a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90mmHg at baseline.[4] Primary kidney disease was classified according to the codes of the European Renal Association-European Dialysis and Transplantation Association.[23] We grouped patients into four classes of primary kidney disease: glomerulonephritis, diabetes mellitus, renal vascular disease, and other kidney diseases.

Outcomes

Our primary outcomes were start of dialysis, start of renal replacement therapy (RRT), and the combined endpoint RRT or death. Start of RRT was defined as start of dialysis

(hemodialysis or peritoneal dialysis) or receiving a kidney transplant during follow up. Secondary outcomes was the change in rate of decline in kidney function for the four ACEi-ARB categories. To calculate the kidney function decline rate, all available eGFR measurements from inclusion until two years of follow-up were used. Complete follow-up data were not used because the healthy and stable patients, who are still on pre-dialysis care after 2 years, would then provide a relatively large contribution to the overall renal function decline, possibly leading to a dilution of the estimated decline.

Statistical analysis

Baseline characteristics are presented according to the four ACEi-ARB categories: no ACEi or ARB use (non-users), only ACEi use, only ARB use, and dual ACEi and ARB use. Continuous variables are described with their mean ± standard deviation (SD), skewed variables with their median and interquartile range (IQR), and categorical variables are presented as number (proportion). First, absolute event rates of the primary outcomes were calculated for the four ACEi-ARB categories. To estimate the median follow up time, a reversed Kaplan-Meier was used. Second, we conducted Cox proportional hazards regression analysis, obtaining hazard ratios (HR) with 95% confidence intervals (95%CI) to estimate the effect of the four ACEi-ARB categories on the three primary outcomes. Analyses were adjusted for the potential confounders: age, sex, race, diabetes mellitus, primary kidney disease and current smoking. Follow-up time was defined as time between baseline visit of the patient and the start of dialysis, RRT, death, withdrawal or end of follow-up (October, 2016). The proportional hazard assumption was tested using a log minus log plot. Third, a Kaplan-Meier analysis was performed to produce a survival plot for the combined endpoint.

To estimate the change in rate of decline in renal function during two years of follow-up in each ACEi-ARB category a linear mixed model (LMM) was used. This model takes the correlation between the eGFR in each patient into account. In the LMM adjustments were made for the same confounders as in the Cox regression analyses.

Since severe hyperkalemia (potassium level ≥6.0 mmol/l) is a side effect of ACEi and ARB use we counted the occurrence at baseline and during follow up. We compared the prevalence and incidence of severe hyperkalemia among the four ACEi-ARB groups with a Chi Square test. Multiple imputation was used to impute missing potential confounders at baseline. The imputed data were predicted based on outcome, follow-up time, age, sex, race, smoking habits, presence of diabetes mellitus, primary kidney disease, ACEi and ARB usage during the study after baseline, and blood pressure at baseline. To test the robustness of our findings, multiple sensitivity analyses were performed. First, we expanded the Cox hazard models simultaneously with baseline proteinuria, eGFR, and cholesterol. The presence of (severe) proteinuria is an indication for combined ACEi and ARB therapy, and therefore a proxy of dual RAS blockade as well as a confounder. EGFR could be both a confounder as well as part of the causal pathway. Second, we stratified the Cox regression analysis for eGFR, at an eGFR level of 15 ml/min/1.73 m^2. In clinical practice a low eGFR

(below 15 ml/min/1.73 m^2) might be an indication to stop ACEi and/or ARB use. Third, we restricted our analysis to patients who were persistent users or non-users of ACEi and/or ARB during the entire study period, since changes in therapy during the follow up period might dilute treatment effects. Fourth, we added nephrology center into our model to remove any confounding from treatment preferences per center. Finally, we repeated all analyses without using multiple imputation for missing values. P-values <0.05 were considered statistically significant. All analyses were performed using SPSS version 23.0 for Windows.

Results

Patient characteristics

In total, 502 incident pre-dialysis patients were included in the PREPARE-2 study. Baseline ACEi and ARB use was known in 495 patients. Of these patients, 119 (24%) were non-users of ACEi or ARB, 164 (33%) used an ACEi alone, 133 (27%) used an ARB alone and 79 (16%) patients used both an ACEi and ARB. A total of 354 (72%) patients were persistent users or non-users of ACEi and/or ARB during the entire study period. Of the ACEi only users 24 (15%) stopped using ACEi completely during follow-up, in ARB users this were 17 (13%) patients and in dual users this were 2 (3%) patients. Table 1 shows the baseline characteristics of the four ACEi-ARB categories. Dual ACEi and ARB users were younger, had more often diabetes mellitus, less often renal vascular disease and more often glomerulonephritis as primary kidney disease than the other categories. Median eGFR and proteinuria were higher in patients with dual RAS blockade. The number of patients with severe CKD at baseline (eGFR< 10ml/min/1.73m2) did not differ significantly among the four ACEi-ARB categories.

Start of dialysis, renal replacement therapy and death

Of all patients the median (IQR) follow-up time was 66 months (61 to 71). During follow up 321 (65%) patients started dialysis, 370 (75%) patients started RRT and 47 (10%) patients died. Table 2 shows the primary outcomes per ACEi-ARB category with their incidence rate per 100 person years (py). The incidence rate of the combined outcome RRT or death in the ACEi and dual user group was substantially lower compared to the non-users. Figure 1 shows the Kaplan-Meier for start of RRT or death for each ACEi-ARB category.

The proportional hazards assumption was fulfilled (plots not shown). The crude and adjusted hazard ratios (HR) for the outcomes are presented in Table 3. Compared with no RAS blockade (reference category) pre-dialysis patients who used ACEi or dual RAS blockade, had a 20-30% lower risk of start of dialysis and RRT. For the combined endpoint RRT or death we found a HR of 0.75 in ACEi users and 0.79 in dual RAS users after multivariable adjustment, corresponding to a 25% and 21% lower risk for RRT or death.

Table 1. Baseline characteristics according to ACEi or ARB drug use at baseline (n=495)

	No ACEi or ARB (n=119)	ACEi only (n=164)	ARB only (n=133)	ACEi and ARB (n=79)
Men	72 (61)	122 (74)	78 (59)	64 (81)
Age, years	72 (59-80)	67 (56-76)	68 (55-75)	63 (49-74)
Ethnicity				
Caucasian	117 (98)	155 (95)	119 (90)	66 (84)
Black	2 (2)	7 (4)	11 (8)	8 (10)
Other	0 (0)	2 (1)	1 (2)	5 (6)
Primary Kidney Disease				
Renal vascular disease	39 (33)	52 (32)	49 (37)	11 (14)
Diabetes	7 (6)	24 (15)	17 (13)	22 (28)
Glomerulonephritis	9 (8)	24 (15)	11 (8)	22 (28)
Other	64 (54)	64 (39)	56 (42)	24 (30)
Hypertension, yes[a]	96 (81)	145 (88)	121 (91)	76 (96)
Diabetes Mellitus, yes[b]	17 (14)	43 (26)	35 (26)	31 (39)
Cardio Vascular Disease, yes[c]	48 (40)	70 (43)	52 (39)	32 (41)
Current smoker, yes	30 (25)	22 (13)	28 (21)	18 (23)
Body Mass Index, kg/m^2 [e]	26 (23-29)	25 (22-30)	26 (24-30)	27 (24-30)
Systolic blood pressure, mmHg	140 (20)	140 (22)	143 (23)	149 (22)
Diastolic blood pressure, mmHg	78 (10)	77 (13)	78 (12)	79 (11)
Pulse pressure, mmHg	60 (50-71)	60 (53-72)	61 (50-80)	65 (57-80)
Serum creatinine, μmol/L	354 (282-447)	347 (256-407)	332 (270-426)	321 (270-429)
eGFR, ml/min/1.73m^2[de]	12.8 (10.1-17.3)	14.7 (11.7-19.1)	14.5 (11.1-18.0)	16.5 (11.7-19.7)
eGFR <10.0 ml/min/1.73m^2, yes	24 (20)	20 (12)	20 (15)	9 (11)
Proteinuria, g/24h[e]	1.0 (0.4-2.1)	1.0 (0.3-2.0)	0.9 (0.3-2.0)	1.7 (0.6-3.6)
Total cholesterol, mmol/L	4.3 (3.7-5.0)	4.4 (3.6-4.8)	4.7 (3.6-5.6)	3.9 (3.6-4.8)
Potassium, mmol/L[e]	4.60 (4.00-4.90)	4.90 (4.45-5.25)	4.80 (4.40-5.10)	4.70 (4.30-5.25)
Antihypertensive drug use				
Beta-blocker	57 (48)	84 (51)	77 (58)	48 (61)
Calcium antagonist	57 (48)	74 (45)	63 (47)	35 (44)
Diuretics	55 (46)	89 (54)	74 (56)	56 (71)
Other	12 (10)	13 (8)	17 (13)	17 (22)
Statin use	58 (49)	96 (59)	80 (60)	57 (72)

Values are given as number (percentage of the total), means ± SD or median (interquartile range).
[a]Defined as either a history of hypertension, antihypertensive drug use, a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg at baseline. [b]Defined as the presence of diabetes mellitus as primary kidney disease or a history of diabetes mellitus. [c]Defined as presence of coronary artery disease, a history of cardiovascular accident, peripheral vascular disease, or myocardial infarction. [d]eGFR (estimated glomerular filtration rate) is calculated with the CKD EPI (Chronic Kidney Disease Epidemiology Collaboration) formula 2009.
[e]Body mass index available for 485, eGFR for 431, proteinuria for 244, potassium for 428 patients.
ACEi; Angiotensin Converting Enzyme Inhibitor, ARB; Angiotensin II Receptor Blocker

Table 2. Dialysis, RRT and combined RRT–death incidence rates (95% CIs) according to ACEi and/or ARB drug use at baseline (n=495)

	No ACEi or ARB (n=119)	ACEi only (n=164)	ARB only (n=133)	ACEi and ARB (n=79)
Person years (py)	194.6	329.2	253.0	161.1
Start dialysis, n (%)	79 (66)	97 (59)	88 (66)	57 (72)
Incidence rate /100 py (95% CI)	40.6 (29.4 to 55.6)	29.5 (20.2 to 42.8)	34.8 (24.4 to 48.7)	35.4 (24.4 to 48.7)
Start RRT, n (%)	89 (75)	116 (71)	102 (77)	63 (80)
Incidence rate/100 py (95% CI)	45.7 (33.7 to 61.4)	35.2 (24.4 to 48.7)	40.3 (28.6 to 54.5)	39.1 (27.7 to 53.3)
Combined RRT/death, n (%)	98 (82)	132 (81)	117 (88)	70 (89)
Incidence rate/100 py (95% CI)	50.4 (37.1 to 65.9)	40.1 (28.6 to 54.4)	46.2 (33.7 to 61.4)	43.5 (32.0 to 59.1)

ACEi; Angiotensin Converting Enzyme Inhibitor, ARB; Angiotensin II Receptor Blocker, CI; Confidence Interval, RRT; Renal Replacement Therapy

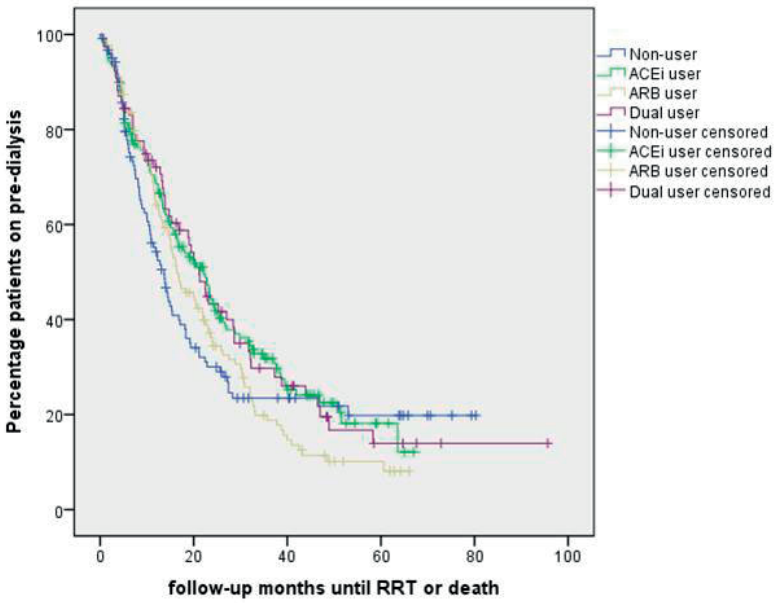

Figure 1. Kaplan Meier for the combined endpoint RRT or death for each medication category

Kidney function decline

During follow up patients had on average 2.5 (SD 1.2) measurements of serum creatinine. The mean decline in kidney function was -1.79 (95%CI -2.21 to -1.37) ml/min/1.73 m^2/year. Table 4 shows the difference in kidney function decline in the three ACEi-ARB categories compared to the non-users. After adjustment for confounding ACEi users had an extra change in kidney function of -0.16 (95% CI -1.47 to 1.16), ARB users of 0.05 (95% CI -1.26 to 1.35), and dual users of 0.63 (95% CI -0.95 to 2.20) per year. The negative number indicates

Table 3. Crude and adjusted hazard ratios (95% CI) for start of dialysis, RRT and combined RRT–death according to ACEi and/or ARB drug use at baseline (n=495)

	Start of dialysis (n=277)	RRT (n=318)	RRT or death (n=359)
No ACEi or ARB	Reference	Reference	Reference
ACEi only, crude	0.72 (0.54 to 0.98)	0.76 (0.58 to 1.00)	0.78 (0.60 to 1.02)
ACEi only, adjusted	0.69 (0.59 to 0.81)	0.70 (0.61 to 0.81)	0.75 (0.65 to 0.86)
ARB only, crude	0.85 (0.63 to 1.15)	0.86 (0.65 to 1.15)	0.90 (0.69 to 1.18)
ARB only, adjusted	0.81 (0.69 to 0.95)	0.82 (0.71 to 0.95)	0.87 (0.76 to 1.00)
ACEi and ARB, crude	0.87 (0.62 to 1.22)	0.85 (0.61 to 1.17)	0.85 (0.63 to 1.16)
ACEi and ARB, adjusted	0.81 (0.67 to 0.98)	0.78 (0.65 to 0.93)	0.79 (0.67 to 0.94)

Adjustments were made for; age, sex, ethnicity, current smoker, diabetes mellitus, and primary kidney disease. ACEi; Angiotensin Converting Enzyme Inhibitor, ARB; Angiotensin II Receptor Blocker, CI; Confidence Interval, RRT; Renal Replacement Therapy

a faster decline in ACEi users, the positive numbers a slower decline in ARB and dual users (all non-significant).

Hyperkalemia

At baseline 2 non-users (2%), 6 ACEi users (4%), 3 ARB users (3%), and 4 dual users (6%) had severe hyperkalemia (P=0.48). During follow-up 3 additional non-users (2%), 7 other ACEi users (4%), 6 other ARB users (5%), and 2 other dual users (3%) developed severe hyperkalemia (P=0.76).

Sensitivity analyses

The sensitivity analyses showed robustness of the results. Results without multiple imputation were similar for LMM and resulted in similar point estimates with wider 95%-CIs in the Cox proportional hazard analyses. Adding nephrology center as a confounder into the model did not change the results. After additional adjustment for baseline proteinuria, eGFR, and serum cholesterol into the basic model the HR (95%CI) was 1.08 (0.72 to 1.61) in ACEi users, 0.90 (95% CI 0.57 to 1.41) in ARB users, and 0.63 (95% CI 0.36 to 1.08) in dual RAS users for the combined endpoint in comparison to non-users. Stratification for baseline eGFR (<15 or ≥ 15 ml/min/1.73 m^2) revealed no differences between low and high baseline eGFR, except for the association of dual use with the combined endpoint of RRT and death. The protective effect of dual use was attenuated in patients with high baseline eGFR. Restricting the analyses to persistent users and non-users changed the adjusted HR for the combined endpoint to 0.78 (95% CI 0.67 to 0.92) in ACEi users and to 0.81 (0.66 to 0.99) in dual RAS users.

Table 4. Annual rate of decline of kidney function according to ACEi and/or ARB drug use at baseline (n=495)

Mean decline in eGFR (ml/min/1.73 m^2/y)	-1.79 (95%CI -2.21 to -1.37)	
Change in decline in eGFR ml/min/1.73m^2 per year	Crude (95%CI)	Adjusted (95%CI)
No ACEi or ARB	Reference	Reference
ACEi only	-0.23 (-1.37 to 0.91)	-0.16 (-1.47 to 1.16)
ARB only	-0.07 (-1.23 to 1.09)	0.05 (-1.26 to 1.35)
ACEi and ARB	0.19 (-1.22 to 1.59)	0.63 (-0.95 to 2.20)

Adjustments were made for; age, sex, ethnicity, current smoker, diabetes mellitus, and primary kidney disease. ACEi; angiotensin converting enzyme inhibitor, ARB; angiotensin II receptor blocker, CI; Confidence Interval

Discussion

We found in a cohort of almost 500 incident pre-dialysis patients a 20-25% lower risk of renal replacement therapy or death in patients treated with dual RAS blockade or single ACEi-users compared to non-RAS blockade-users. Dual RAS blockade medication use did not accelerate kidney function decline compared to patients with single or no RAS blockade.

There are no RCTs specifically designed among pre-dialysis patients to study the effect on renal outcome of dual RAS blockade compared to no or single use. Hsu ***et al.*** showed in a large cohort study of adults (>28,000, mean age 65y) with CKD stage 5, a 6% lower risk of dialysis or death in ACEi or ARB users compared to non RAS blockade users.[24] The only RCT in patients with advanced CKD (serum creatinine between 274 to 442 μmol/L) and proteinuria showed that starting either ACEi or ARB lowered risk of death and slowed progression of kidney function decline (doubling serum creatinine or ESRD).[25] Another study showed that treatment with ACEi or ARB in patients with CKD lowered proteinuria, an independent predictor of progression of kidney function decline.[26, 27] Taken together, these studies support continuing ACEi or ARB usage in patients with advanced kidney disease, especially if they have proteinuria.

Our study is in line with a recent meta-analysis that included nine trials on the differences between dual and single RAS inhibition in all stages of the CKD population.[15] In this meta-analysis a total of 17,750 CKD stage 2-5 patients were included, with a mean age of 65y, and a mean follow up of 3.4 years. Dual compared to single RAS inhibition resulted in a 5% lower risk for all cause death. Since only a limited number of patients included in this meta-analysis had CKD stage 4-5, the results cannot be generalized to the pre-dialysis population. Unfortunately, a sub analysis among pre-dialysis patients was not performed. Fernandez-Juarez ***et al***. showed in an RCT in 133 patients with diabetic nephropathy (mean eGFR 49 mL/min/1.73m^2) an equal risk for RRT, death or kidney function decline in dual and single RAS blockade users.[28] The ORIENT Study showed in patients with type 2 diabetes (mean age 59y, mean serum creatinine 143 μmol/L) and proteinuria that dual RAS block-

ade compared to ACEi alone was more effective with regard to reduction of proteinuria and blood pressure, but did not lower risk of ESRD or death.[29]

In the ONTARGET trial the effect of dual compared to single RAS blockade was studied in 25,620 pre-dominantly non-proteinuric individuals with preserved kidney function (mean eGFR 74 ml/min/1.73 m^2) at low risk of CKD progression (annual rate of GFR decline of <1 ml/min/1.73m^2).[7] No sub analysis in CKD stage 4-5 patients was performed. After 5 years kidney function decline in dual, single ACEi and ARB users was 6.1, 2.8 and 4.1 mL/min/1.73m^2, respectively. Start of dialysis (acute and chronic) and death were more frequent in dual RAS blockade users with an increased risk of 9%. After removal of acute hemodialysis from the renal endpoint, there was no significant difference in secondary outcome (doubling of serum creatinine or risk of chronic hemodialysis) among the three groups.[7, 16]

We found in our cohort a mean annual eGFR decline of 1.79 mL/min/1.73m^2 , which is almost similar with the finding in a study among Taiwanese patients with comparable baseline characteristics.[30] Chen ***et al.*** showed in a prospective cohort study involving >500 Taiwanese patients with CDK stage 3-5, who received a multi-disciplinary care approach (mean eGFR 33 ml/min, mean age 65 y, 77% ACEi or ARB users, 49% diabetes mellitus) a yearly kidney function decline of 1.85 ml/min/1.73m^2.[30]

We found a slightly stronger beneficial effect in single ACEi users as compared with single ARB users with regard to reducing risk of RRT or death. A larger magnitude of a beneficial effect of ACEi compared to ARB has been found in other studies.[15, 31] A possible explanation for this difference might be the different effects of ACEi and ARBs in the RAS pathway. It is possible that by blocking the angiotensin-I receptor with an ARB more alternative pathways remain open in the RAS, while with ACE inhibition both angiotensin-II and aldosterone are down regulated and less alternative pathways remain open.[12]

We found that single ACEi or ARB use did not change the annual kidney function decline compared to non-users in our cohort of pre-dialysis patients. However, the rate of kidney function decline was studied only during two years of follow-up. We assume that a longer period of follow-up would have shown a slower rate of kidney function decline in RAS-blockade users compared to non-users.

Finally, we found that additional adjustment for baseline proteinuria, eGFR, and cholesterol resulted in a smaller effect in ACEi users with wider confidence intervals, due to over-correction of factors in the causal pathway.

Main strength of this study is the specific selection of pre-dialysis patients. Pre-dialysis patients form a special group in CKD care and cannot be compared to patients in the early stages of CKD. They require special attention, often different care and are all treated according to the previously mentioned guidelines by a nephrologist.[21] Since no exclusion criteria were used for the PREPARE cohort a wide range of incident pre-dialysis patients were included, making our results generalizable to the clinical practice of pre-dialysis care. This is in contrast to RCTs with strict in- and exclusion criteria and optimized settings which

may result in lack of generalizability. Another strength is the prospective longitudinal design of the PREPARE-2 study, resulting in specific, complete information and the opportunity to track kidney function over time.

The present study also has limitations. Main limitation is the possibility of confounding by indication. The indication for prescribing dual RAS blockade is a patient's increased risk of kidney function decline based on the presence of certain risk factors.[32-34] Thus, these risk factors are associated with the probability of receiving dual RAS blockade therapy and with the probability of kidney function decline. Therefore, patients receiving dual RAS blockade have a higher probability of developing ESRD, not because of the dual RAS blockade, but because of their increased intrinsic risk.[35] Nevertheless, although patients with dual RAS blockade had more severe proteinuria compared to the non-ARB users, we found a beneficial effect on outcome. Additional correction for the known important confounders most likely limited residual confounding. Another limitation is that we included patients who were prevalent users or non-users of RAS-blockade medication. We had no information about the duration of ACEi and ARB use or a history of intolerance of RAS blockade in these patients. However, in the non-users 29 (24%) patients started an ACEi or ARB during follow-up, which may have resulted in underestimation of the beneficial effect of ACEi- or ARB use. A third limitation is that we had no information about the cause of discontinuation of RAS blockade in patients who did use ACEi and/or ARB medication at baseline but stopped using either of these drugs during follow-up. If anything, this may have resulted in an underestimation of the effect that we found. Finally, we had no information on side effects such as hospital admittance due to syncope or dizziness. The incidence of severe hyperkalemia was low and did not differ among the four ACEi-ARB groups. Unfortunately, we could not study the side effect acute kidney injury defined as a 50% reduction in kidney function within hours or days. However, in our cohort of pre-dialysis patients a reduction of 50% of kidney function would have most likely resulted in start of RRT. If anything, the risk of RRT in patients who used RAS blockade was lower compared to non-users.

In conclusion, we observed in pre-dialysis patients that compared to no RAS blockade, both dual RAS blockade as well as single ACEi-use were associated with about 20-25% lower risk of RRT or death. We did not find an accelerated kidney function decline in the single or dual RAS inhibition groups compared to non-RAS inhibition drug users. This lack of an increased RRT or mortality risk in dual RAS inhibition users suggests that there might be room for dual RAS inhibition when treating severe hypertension or proteinuria in CKD 4-5 patients.

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6

VITAMIN K ANTAGONIST USE AND RENAL FUNCTION IN PRE–DIALYSIS PATIENTS

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Abstract

Introduction: A post-hoc analysis of a recent trial on direct oral anticoagulants versus vitamin K antagonists showed that amongst patients with a mildly decreased kidney function, use of vitamin K antagonists was associated with a greater decline in renal function than use of direct oral anticoagulants. Whether these vitamin K antagonist effects are the same in pre-dialysis patients is unknown. Therefore, the aim of this study was to investigate the association between vitamin K antagonist use and rate of renal function decline and time until start of dialysis in incident pre-dialysis patients.

Methods: Data from 984 patients from the PREdialysis PAtient REcord study, a multicenter follow-up study of patients with chronic kidney disease who started pre-dialysis care in The Netherlands (1999–2011), were analysed. Of these patients, 101 used a vitamin K antagonist. Linear mixed models were used to compare renal function decline between vitamin K antagonist users and non-users. Cox proportional hazards models were used to estimate the hazard ratio (HR) with 95% confidence intervals (95% CIs) for starting dialysis.

Results: Vitamin K antagonist use was associated with an extra change in renal function of -0.09 (95% CI (-1.32 to 1.13) ml/min/1.73m^2 per year after adjustment for confounding. The adjusted hazard ratio for start of dialysis was 1.20 (95% CI 0.85 to 1.69) in vitamin K antagonist users, compared to non-users.

Conclusions: In incident pre-dialysis patients the use of vitamin K antagonists was not associated with an accelerated kidney function decline or an earlier start of dialysis compared to non-use.

Introduction

Vitamin K antagonists are used to prevent and treat thrombotic complications. Several clinical trials performed in patients with thrombotic complications and a normal kidney function, have shown that the benefits of vitamin K antagonists outweigh the side-effects such as bleeding.[1-4]

Recent studies have debated whether the benefits of vitamin K antagonists also outweigh the risks in patients with early stage chronic kidney disease or in dialysis patients.[5-11] A post-hoc analysis of a recent trial comparing direct oral anticoagulants with vitamin K antagonists, showed that patients with a mildly decreased kidney function receiving vitamin K antagonists exhibited a greater decline in renal function than patients receiving direct oral anticoagulants.[12] Furthermore, most studies in dialysis patient have failed to show a protective effect of vitamin K antagonists on stroke risk or all-cause mortality,[5-9, 13] with the exception of two studies that showed a decreased risk of stroke and a survival benefit for vitamin K antagonists in dialysis patients.[10, 14] The proposed hypotheses of these negative effects due to vitamin K antagonists are that the medication could either cause damage to the kidneys by vascular calcifications due to the inhibition of matrix Gla protein or cause damage by glomerular haemorrhage which could lead to tubular obstruction.[11, 15-19]

As patients with chronic kidney disease are often prescribed vitamin K antagonists, adequate insight into the benefits and risks of vitamin K antagonist use is crucial.[20] To our knowledge, there are no existing studies that investigated the association between vitamin K antagonist use and decline of glomerular filtration rate or time until start of dialysis in pre-dialysis patients. From a clinical point of view, withholding medication that could lead to kidney function decline is very important to postpone or prevent dialysis in pre-dialysis patients.

Therefore, the aim of this study was to investigate the association between vitamin K antagonist use and rate of kidney function decline and time until start of dialysis in incident pre-dialysis patients.

Methods

Study design and population

The PREdialysis PAtient REcord (PREPARE) study is a multicenter follow-up study of incident patients starting specialized pre-dialysis care (age ≥18 years) in the Netherlands. At inclusion, these patients had an estimated GFR (eGFR) between 20 and 30 ml/min per 1.73 m^2 (CKD stages 4–5). The PREPARE study consists of a retrospective and a prospective cohort. In the retrospective cohort (PREPARE-I), incident pre-dialysis patients who had their first pre-dialysis visit between 1999 and 2001 were included from eight outpatient clinics. In the prospective cohort (PREPARE-II), incident pre-dialysis patients who started

pre-dialysis care in one of the 25 participating outpatient clinics between 2004 and 2011, and understood the Dutch language were included. In PREPARE-I, patients who experienced kidney failure from a kidney transplant were excluded. In PREPARE-II, patients who experienced kidney failure from a kidney transplant that was received within a year before referral to pre-dialysis care were excluded. The study was approved by the medical ethics committee or the institutional review board of the participating centers. Patients included in PREPARE-II gave written informed consent before study inclusion.

Demographic and clinical data

Data were collected from medical records and extracted from the hospital information systems. Data on demography, primary kidney disease, comorbidities, medication use including vitamin K antagonist use (phenprocoumon or acenocoumarol), and laboratory values were collected at baseline and during routine visits to the pre-dialysis outpatient clinics. These visits took place at the start of specialized pre-dialysis care and when one of the study endpoints was reached. In PREPARE-II, data were also collected every 6 months at follow-up visits. The closest laboratory measurement performed within 90 days before or after the date of a visit was appointed to that visit. Patients were categorized as non-users or users of vitamin K antagonists based on medication use at baseline. We had no information on the indication for vitamin K antagonist use. The eGFR was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula from 2009, taking age, sex, race, and serum creatinine into account.[21] Hypertension was defined as either a history of hypertension, a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90mmHg at baseline.[22] Cardiovascular disease (CVD) was defined as angina pectoris, myocardial infarction, heart failure, ischemic stroke, or claudication. Primary kidney disease was classified according to the codes of the European Renal Association-European Dialysis and Transplantation Association.[23] Patients were grouped into four classes of primary kidney disease: glomerulonephritis, diabetes mellitus, renal vascular disease, and other kidney diseases.

Outcomes

In the PREPARE study, patients were followed until the start of renal replacement therapy (defined as dialysis or renal transplantation), death, loss to follow-up, refusal to further participate in the study (PREPARE-II), recovery of renal function, or the end of the study period (January 2008 for PREPARE-I and October 2016 for PREPARE-II), whichever came first. Main outcomes were change in rate of kidney function decline and start of dialysis within two years. For the current study follow-up time was restricted to two years, after this period the number of patients at risk became too small.[24, 25] The date of dialysis initiation was collected from medical records. To calculate the kidney function decline rate, all available eGFR measurements from three months prior to inclusion until two years of follow up were used.

Statistical analyses

Baseline characteristics are presented stratified for vitamin K antagonist use. Continuous variables are described by their median and interquartile range (IQR), and categorical variables are presented as percentages.

Follow-up time was defined as the time between baseline and the start of dialysis, other renal replacement therapy, death, withdrawal or end of follow-up (two years). To estimate the change of renal function decline rate in vitamin K antagonist users, compared to non-users, a linear mixed model (LMM) was used. This model takes the correlation between eGFR measurements within each individual patient into account. Multivariable analyses were used to adjust for age, sex, race, diabetes mellitus, hypertension, cardiovascular disease, malignancy, gastro-intestinal problems, antiplatelet drug use, primary kidney disease, and hemoglobin levels.

The proportional hazard assumption was tested using a log minus log plot. Incidence rates of dialysis initiation within two years of follow-up were calculated for both vitamin K antagonist users and non-users. Survival curves for start of dialysis were determined with the Kaplan Meier method, stratifying for vitamin K antagonist use. We conducted Cox proportional hazards regression analyses, obtaining hazard ratios (HR) with 95% confidence intervals (95%CI) to estimate the effect of vitamin K antagonist use on start of dialysis. Analyses were adjusted for potential confounders, including: age, sex, race, diabetes mellitus, hypertension, cardiovascular disease, malignancy, gastro-intestinal problems, antiplatelet drug use, primary kidney disease, hemoglobin levels, and eGFR levels.

Multiple imputation was used to impute missing potential confounders at baseline. To test the robustness of the results, several sensitivity analyses were performed. Analyses were repeated with stratification by PREPARE-I and PREPARE-II. Furthermore, we repeated the analyses without correcting for cardiovascular disease, since cardiovascular disease could be both a confounder and part of the causal pathway. Next, we added angiotensin converting enzyme inhibitor (ACEi), angiotensin II receptor blocker (ARB), systolic blood pressure, and diastolic blood pressure to our linear mixed model. These variables could be both a confounder or part of the causal pathway. For the same reason C-reactive protein (CRP), body mass index (BMI), albumin, and proteinuria were added as confounders in a sensitivity analysis.

Fifth, we restricted our analysis to patients who were persistent users or non-users of vitamin K antagonists during the entire study period, since changes in therapy during the follow- up period might dilute treatment effects. Sixth, we restricted our analyses to patients with cardiovascular disease. This could give an indication of the effects of confounding by indication. Finally, we performed our analyses with a follow-up period of five years. All analyses were performed using SPSS version 23.0 for Windows.

Results

Baseline characteristics

Of the 1049 patients in PREPARE, 547 patients originate from PREPARE-I and 502 patients originate from PREPARE-II. Vitamin K antagonist use was known for all PREPARE-I patients and for 437 PREPARE-II patients, resulting in 984 patients. Of these patients, 101 used a vitamin K antagonist and 883 did not use a vitamin K antagonist. The baseline characteristics of these 984 patients are shown in table 1. Vitamin K antagonist users were older, more often male, had more cardiovascular disease and used antiplatelet drugs less often than vitamin K antagonist non-users. A total of 846 (96%) patients were persistent vitamin K antagonist non-users, and 86 (85%) patients were persistent vitamin K antagonist users during the entire study period.

During follow-up the occurrence of vascular cerebral complications was recorded. A total of six brain infarctions occurred, all in vitamin K antagonist non-users. A cerebral hematoma was diagnosed in five vitamin K antagonist non-users and in one vitamin K antagonist user.

Table 1. Baseline characteristics vitamin K antagonist users and vitamin K antagonist non–users (N=984)

	Vitamin K antagonist users N=101	Vitamin K antagonist Non-users N=883
Age (years)	74 (68-79)	63 (51-74)
Sex, female	29%	39%
Primary kidney disease		
Diabetes mellitus	21%	15%
Glomerulonephritis	9%	12%
Renal vascular disease	39%	26%
Other	32%	48%
Cardiovascular disease[a]	71%	47%
Malignancy	20%	11%
Gastro-intestinal disease	26%	31%
Hypertension	83%	90%
Antiplatelet drug use	2%	16%
eGFR (ml/min)[b]	14.1 (10.5-18.0)	12.5 (9.6-16.7)
Hemoglobin (mmol/L)	7.4 (6.7-8.1)	7.2 (6.5-7.9)

Continuous variables; median (interquartile range), categorical variables; percentages

[a]Cardiovascular disease was defined as angina pectoris, myocardial infarction, heart failure, ischemic stroke, or claudication.

[b]eGFR; estimated glomerular filtration rate, calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula from 2009

Missings: Users: Malignancy; 60, Gastro-intestinal disease; 63, eGFR; 20, Hemoglobin; 22. Non-users: Malignancy; 379, Gastro-intestinal disease; 383, Hypertension; 1, eGFR; 93, Hemoglobin; 89.

Vitamin K antagonist and decline of kidney function

During the first two years of follow-up, patients had on average of 1.5 (SD 1.2) serum creatinine measurements. The mean change in kidney function was -1.45 (95% CI -1.80 to -1.10) ml/min/1.73 m^2/year for the total group. Table 2 shows the difference in kidney function change between vitamin K antagonist users and non-users. The difference in kidney function change was -0.09 (95% CI -1.32 to 1.13) ml/min/1.73 m^2/year after adjustment (the minus indicates an extra change of 0.09 units in the vitamin K antagonist users). In absolute numbers this means the change in vitamin K antagonist non-users was -3.23 ml/min/1.73 m^2/year, and -3.32 ml/min/1.73 m^2/year in vitamin K antagonist users.

Table 2. Vitamin K antagonist use and renal function decline

Mean decline in eGFR (ml/min/1.73 m^2/y)	-1.45 (95%CI -1.80 to -1.10)
	Change in decline in eGFR ml/min/1.73m^2 per year (95% CI)
Vitamin K antagonist non-users	Reference
Vitamin K antagonist users, crude	0.43 (-0.74 to 1.60)
Vitamin K antagonist users, adjusted*	-0.09 (-1.29 to 1.11)
Vitamin K antagonist users, adjusted**	-0.09 (-1.32 to 1.13)

*Adjusted for: age, sex, race, diabetes mellitus, hypertension, cardiovascular disease, malignancy, gastro-intestinal problems, antiplatelet drug use, and primary kidney disease
** Additionally adjusted for hemoglobin levels

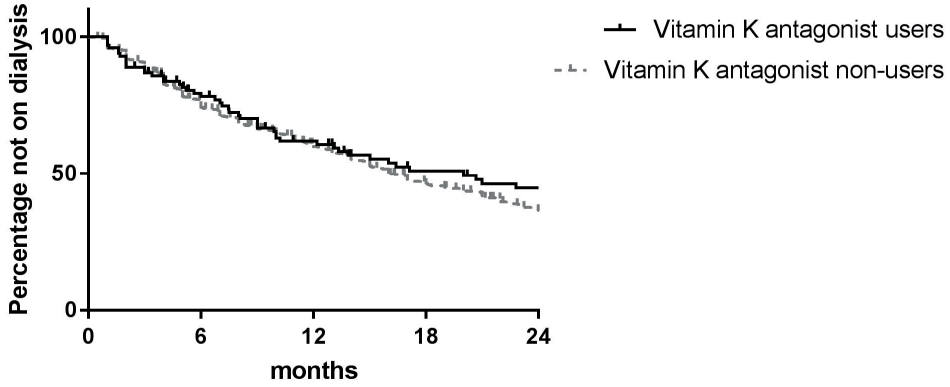
Vitamin K antagonists and start of dialysis within two years

Incidence rates for start of dialysis were 47/100 person years for vitamin K antagonist users and 46/100 person years for non-users. During the two years of follow-up, 48 (48%) vitamin K antagonist users started dialysis, and 520 (59%) non-users started dialysis. Figure 1 shows the Kaplan Meier for start of dialysis for vitamin K antagonist users and non-users. The crude and adjusted hazard ratios (HR) for start of dialysis are presented in Table 3. As compared with no vitamin K antagonist use (reference category), pre-dialysis patients who used vitamin K antagonists did not have an increased risk of start of dialysis (HR 1.20 (95% CI 0.85 to 1.69)), adjusted for age, sex, race, diabetes mellitus, hypertension, cardiovascular disease, malignancy, gastro-intestinal problems, antiplatelet drug use, primary kidney disease, hemoglobin levels, and eGFR at baseline.

Sensitivity analyses

After stratification for study cohort, the extra change in kidney function in vitamin K antagonist users was 1.11 (-0.86 to 3.07) ml/min/1.73 m^2/year in PREPARE-I, and -0.40 (-1.89 to 1.09) ml/min/1.73 m^2/year in PREPARE-II. Vitamin K antagonist users in PREPARE-I had a HR for start of dialysis of 1.38 (95% CI 0.87 to 2.18) as compared with non-users, in PREPARE-II this was 1.09 (95% CI 0.63 to 1.86). Performing the analyses without correction for cardiovascular disease resulted in an extra change in kidney function of -0.12 (95% CI -1.30 to

Figure 1. Kaplan-Meier curves for start of dialysis stratified for vitamin K atagonist use



Month	0	6	12	18	24
Number at risk vitamin K antagonist users	101	70	50	34	29
Number at risk vitamin K antagonist non-users	883	632	470	336	248

1.05) in vitamin K antagonist users and a HR for start of dialysis of 1.23 (0.88 to 1.73) as compared with non-users. Adding ACEi, ARB, systolic blood pressure, and diastolic blood pressure to the linear mixed model changed the change in kidney function to -0.17 (95% CI -1.42 to 1.08). The addition of CRP, BMI, Albumin, and proteinuria changed the change in kidney function to 0.23 (95% CI -1.74 to 2.20). The HR for start if dialysis changed to 0.80 (95% CI 0.37-1.74).Restricting the analyses to persistent users and non-users changed the adjusted change in kidney function to 0.15 (95% CI -1.17 to 1.47), in absolute numbers this means the change in vitamin K antagonist non-users was -2.41 ml/min/1.73 m^2/year, and -2.26 ml/min/1.73 m^2/year in vitamin K antagonist users. The adjusted HR for start of dialysis changed to 1.36 (95% CI 0.96 to 1.93) in vitamin K antagonist users. Restricting the analyses to patients with cardiovascular disease (417 non-users and 72 users) resulted in an adjusted change in kidney function of 0.07 (95% CI -1.50 to 1.64), which is -1.25 ml/min/1.73 m^2/year in vitamin K antagonist non-users and -1.18 ml/min/1.73 m^2/year in vitamin K antagonist users. The adjusted HR for start of dialysis was 1.04 (0.66 to 1.65) in vitamin K antagonist users. Using a follow-up period of five years changed the adjusted change in kidney function to 0.09 (95% CI -0.97 to 1.15) which means the absolute change in vitamin K antagonist non-users was -0.55 ml/min/1.73 m^2/year, in vitamin K antagonist users this was -0.46 ml/min/1.73 m^2/year. The adjusted HR for start of dialysis was 0.99 (95% CI 0.98 to 0.99) for vitamin K antagonist users shows the Kaplan Meier for start of dialysis stratified for vitamin K antagonist use for five years of follow-up.

Table 3. Vitamin K antagonist use and hazard ratios for start of dialysis

	Person years	Number of events	HR (95% CI)
Vitamin K antagonist non-users, n=883	988.7	65	1 (reference)
Vitamin K antagonist users, crude, n=101	107.6	632	0.84 (0.62 to 1.13)
Vitamin K antagonist users, adjusted*, n=101			0.91 (0.65 to 1.28)
Vitamin K antagonist users, adjusted**, n=101			1.20 (0.85 to 1.69)

*Adjusted for: age, sex, race, diabetes mellitus, hypertension, cardiovascular disease, malignancy, gastro-intestinal problems, antiplatelet drug use, and primary kidney disease
** Additionally adjusted for hemoglobin and eGFR levels

Discussion

Key findings

In this cohort of 984 incident pre-dialysis patients with a follow-up of two years, we found no difference in annual kidney function decline between vitamin K antagonist users and non-users. Furthermore, vitamin K antagonist use as compared with non-use was not associated with an increased risk of start of dialysis within two years of follow-up. Restricting the population to patients with cardiovascular disease shows the same lack of an association for kidney function decline and risk od start of dialysis.

Previous studies on the association between vitamin K antagonist use and kidney function decline and start of dialysis

To our knowledge, there are no previous studies that investigated the association between vitamin K antagonist use and kidney function decline in pre-dialysis patients. However, a post-hoc analysis of the RE-LY trial (warfarin versus dabigatran), in which patients with an eGFR <30 ml/min were excluded, showed that warfarin users had more kidney function decline over the first 30 months (-3.68 ml/min/1.73m^2) than dabigatran users (-2.57 ml/min/1.73m^2 with 110 milligram and -2.46 ml/min/1.73m^2 with 150 milligram). The long-term effects of vitamin K antagonists on kidney function have not yet been investigated.

Vitamin K antagonists and start of dialysis

Although we did not find an association between vitamin K antagonist and start of dialysis within two years of follow-up, we did find a 1.2-fold increased risk with a wide confidence interval. It could be that vitamin K antagonist use, which is a marker for cardiovascular disease, is associated with dialysis initiation through other pathways than kidney function decline, including fluid overload.

Pathophysiological effects of vitamin K antagonists on kidney

There are several pathophysiological mechanisms through which vitamin K antagonists could influence kidney function. Firstly, vitamin K antagonists are associated with in-

creased arterial calcifications and accelerate pre-existing vascular calcifications due to the inhibition of matrix Gla protein. This could potentially lead to an acceleration of kidney dysfunction decline.[17-19] Furthermore, vitamin K antagonist use can cause glomerular haemorrhage, with dysmorphic red blood cells and tubular red blood cell casts causing tubular obstruction and thereby kidney damage.[11, 15, 16] However, in our pre-dialysis patients we did not find an association between vitamin K antagonist use and kidney function decline.

Clinical implications

Our study results suggest that the effect of vitamin K antagonist use on kidney function decline and start of dialysis probably is limited. Therefore, based on our study, we do not recommend withholding vitamin K antagonists to slow kidney function decline or postpone dialysis. However, the possibility of confounding by indication should be taken into account when interpreting these results. Other benefits and risks of vitamin K antagonist use in pre-dialysis patients are not known, since existing trials have excluded these patients due to their high bleeding risk. Guidelines mention this knowledge gap concerning risks and benefits of anticoagulation with vitamin K antagonists for stroke prevention, especially in dialysis patients.[26]

Strengths and limitations of this study

The main strength of this study is the well-defined cohort of incident pre-dialysis patients who received standardized treatments and check-ups by nephrologists. A wide range of incident pre-dialysis patients was included and all patient information was used to perform the analyses making the results generalizable to the clinical practice of pre-dialysis care. The main limitation of this study is the possibility of confounding-by-indication when comparing vitamin K antagonist users with non-users in an observational study design. We cannot exclude the possibility that doctors anticipate renal effects when prescribing or withholding vitamin K antagonists. In that case patients with a worse kidney function would receive vitamin K antagonists less often leading to a possible underestimation of negative effects of vitamin K antagonists. We tried to minimize this problem by correcting for multiple confounders, but cannot exclude residual confounding. Another limitation is the lack of information on the indication for vitamin K antagonist use in our population. Therefore, it could be that vitamin K antagonists were used for other indications than atrial fibrillation. However, since atrial fibrillation has a 2-3 times higher prevalence in CKD patients compared to the general population, it is likely the indication for vitamin K antagonist use in most of our population was atrial fibrillation.[27] Another limitation is the possible non-adherence of the vitamin K antagonist users. Medication adherence often is not 100%, which is very likely to be the case in this study too. Non-adherence can lead to an underestimation of the true effects of vitamin K antagonists. However, the adherence in this study is a representation of adherence in clinical practice and therefore gives an

estimate of the expected effects in clinical practice. In addition, we had no information on the number of patients that experienced kidney failure after receiving a kidney transplant. A final limitation is the inclusion of prevalent vitamin K antagonist users which could have led to an underestimation of the negative effects on kidney function and start of dialysis in vitamin K antagonist users.

Conclusion

In conclusion, there was no association between vitamin K antagonist use and rate of renal function decline. Furthermore, this study showed no association between vitamin K antagonist use and time until start of dialysis in incident pre-dialysis patients. This study emphasizes the need for randomized controlled trials comparing vitamin K antagonists with placebo or direct oral anticoagulants in pre-dialysis patients to investigate their effect on kidney function decline. This would provide better insight into the adverse effects of vitamin K antagonists and more personalized prescription of anticoagulant drugs in pre-dialysis patients.

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VITAMIN K ANTAGONIST USE AND MORTALITY IN DIALYSIS PATIENTS

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Abstract

Introduction: The risk-benefit ratio of vitamin K antagonists for different CHA_2DS_2-VASc scores in patients with end-stage renal disease treated with dialysis is unknown. The aim of this study was to investigate the association between vitamin K antagonist use and mortality for different CHA_2DS_2-VASc scores in a cohort of end-stage renal disease patients receiving dialysis treatment.

Methods: We prospectively followed 1718 incident hemodialysis patients. Hazard ratios (HRs) were calculated for all-cause and cause-specific (stroke, bleeding, cardiovascular and other) mortality associated with vitamin K antagonist use.

Results: Vitamin K antagonist use as compared with no vitamin K antagonist use was associated with a 1.2-fold (95% CI 1.0-1.5) increased all-cause mortality risk, a 1.5-fold (95% CI 0.6-4.0) increased stroke mortality risk, a 1.3-fold (95% CI 0.4-4.2) increased bleeding mortality risk, a 1.2-fold (95% CI 0.9-1.8) increased cardiovascular mortality risk and a 1.2-fold (95% CI 0.8-1.6) increased other mortality risk after adjustment. Within patients with a CHA_2DS_2-VASc score of equal to or less than one, vitamin K antagonist use was associated with a 2.8-fold (95% CI 1.0-7.8) increased all-cause mortality risk as compared with no vitamin K antagonist use, while vitamin K antagonist use within patients with a CHA_2DS_2-VASc score of two or more was not associated with an increased mortality risk after adjustment.

Conclusion: Vitamin K antagonist use was not associated with a protective effect on mortality in the different CHA_2DS_2-VASc scores. The lack of knowledge on the indication for vitamin K antagonist use could lead to confounding by indication.

Introduction

Vitamin K antagonists are used to prevent stroke in patients with an increased risk of stroke due to atrial fibrillation [1,2]. Current American College of Cardiology/American Heart Association atrial fibrillation guidelines and European Society of Cardiology guidelines for the management of atrial fibrillation suggest the consideration of vitamin K antagonist prescription for those with high stroke risks based on increased CHA_2DS_2-VASc scores (score of two or more) [1,2]. These guidelines are based on several clinical trials in the general population, in which benefits of vitamin K antagonists outweigh the risks of bleeding for patients with an increased stroke risk [3,4].

The risk-benefit ratio of vitamin K antagonists in patients with end-stage renal disease treated with dialysis and atrial fibrillation is unknown. This is under scribed by the 2016 European Society of Cardiology guideline stating the need for research in this patient group [2]. Previous studies that investigated the effect of vitamin K antagonists in dialysis patients showed conflicting results [5-13]. Only two of these studies showed a decreased risk of stroke [5] or survival benefit [6] for vitamin K antagonist use as compared with no vitamin K antagonist use in dialysis patients, while all other studies did not show a protective effect of vitamin K antagonists on stroke risk or all-cause mortality [9-14]. The studies showing a decreased risk had several limitations, including limited adjustment for confounders. Furthermore, these studies also included transplantation patients. A meta-analysis performed in over 9800 dialysis patients with atrial fibrillation showed that vitamin K antagonist treatment was associated with a 1.2-fold (95% CI 0.8-1.9) increased stroke risk [7]. Several studies showed an increased bleeding risk for vitamin K antagonists [13,15]. It is plausible that pre-existing platelet dysfunction, routine heparin use during hemodialysis treatment and a suboptimal time in therapeutic range leads to increased risks of bleeding complications in dialysis patients [16,17]. Because of the higher bleeding risk in dialysis patients compared to the general population, it could be that vitamin K antagonists are only beneficial in higher CHA_2DS_2-VASc scores (i.e. higher stroke risks) than the cut-off score of two used in the general population. However, studies investigating the association between vitamin K antagonist use and mortality for different CHA_2DS_2-VASc scores in dialysis patients are lacking.

Therefore, the aim of this study was to investigate the association between vitamin K antagonist use and mortality for different CHA_2DS_2-VASc scores in a cohort of end-stage renal disease patients with and without atrial fibrillation receiving dialysis treatment.

Methods

Patients

The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) is a prospective multicenter cohort study in which incident adult end-stage renal disease patients in the

Netherlands were included. Eligibility included age older than 18 years, and no previous renal replacement therapy. All patients gave informed consent and the study was approved by all local medical ethics committees. We followed patients until death or censoring, i.e. transfer to a nonparticipating dialysis center, withdrawal from the study, transplantation, or end of the follow-up period (February 2015).

Demographic and clinical data

Data on age, sex, primary kidney disease, dialysis modality, gastro-intestinal problems including bleeding, malignancy and cardiovascular disease (angina pectoris, myocardial infarction, heart failure, ischemic stroke, or claudication) were collected at the start of dialysis treatment. Primary kidney disease was classified according to the codes of the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) [18]. We grouped patients into four classes of primary kidney disease: glomerulonephritis, diabetes mellitus, renal vascular disease, and other kidney diseases. Antiplatelet drug use, vitamin K antagonist use, blood pressure and laboratory data were collected at three months after the start of dialysis, which was defined as baseline. Blood pressure was measured in the sitting position. Hypertension was defined as a systolic blood pressure ≥140mmHg or use of anti-hypertensive agents. CHA_2DS_2-VASc scores were calculated (Congestive heart failure=1 point, hypertension=1 point, age ≥75 years=2 points, age 65-74 years=1 point, diabetes mellitus=1 point, prior stroke=2 point, vascular disease including peripheral artery disease or myocardial infarction=1 point and female sex=1 point) [19,20], as were HAS-BLED scores (hypertension=1 point, kidney disease=1 point, liver cirrhosis=1 point, prior stroke=1 point, prior bleeding=1 point, age >65 years=1 point, predisposing medication use=1 point, drug or alcohol abuse history=1 point). The HAS-BLED score lacks 1 possible point for labile International Normalized Ratio (INR), since we had no data on INR. We had no data on the presence of atrial fibrillation. Serum hemoglobin, urea and creatinine were routinely measured in the dialysis centers at three months after start of dialysis. Residual glomerular filtration rate (GFR) was calculated as the mean of creatinine and urea clearance corrected for body surface area (ml/min per 1.73 m^2).

Mortality

We classified causes of death according to the codes of the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA) which is a standardized classification of death causes in dialysis patients [18]. We grouped death causes into stroke, bleeding, cardiovascular and other. Stroke mortality was defined as death due to cerebrovascular accident (code 22). Bleeding mortality was defined as death due to hemorrhagic pericarditis (code 13), gastro-intestinal hemorrhage (code 23), hemorrhage from graft site (code 24), hemorrhage from vascular access or dialysis circuit (code 25), hemorrhage from ruptured vascular aneurysm (code 26), hemorrhage from surgery (code 27), other hemorrhage (code 28) and perforation of peptic ulcer (code 71). Cardiovascular

mortality was defined as death due to myocardial ischemia and infarction (code 11), cardiac arrest/ sudden death (code 15), cardiac failure/ fluid overload/ pulmonary edema (codes 14,16,18), hyperkalemia /hypokalemia (code 12,17), pulmonary embolism (code 21), mesenteric infarction (code 29) and cause of death uncertain/unknown (code 0). Other mortality was defined as death caused by pulmonary infection (code 31-33), infections elsewhere (code 34), septicemia (code 35), tuberculosis (code 36-37), generalized viral infection (code 38), peritonitis (code 39), suicide (code 52), treatment cessation (code 51, 53-54), cachexia (code 64), malignancies (codes 66-68) and miscellaneous (codes 41-46, 61-63, 69-70, 72-73, 81-82, 99-102).

Statistical analysis

Continuous variables are presented as median and interquartile range (IQR). Categorical variables are presented as percentages. Survival curves were determined with the Kaplan-Meier method and mortality rates per 1000 person-years were calculated for vitamin K antagonist users and vitamin K antagonist non-users. We calculated crude and adjusted hazard ratios (HRs) with 95% confidence intervals (95% CIs) for all-cause and cause-specific (stroke, bleeding, cardiovascular and other) mortality within five-years of follow-up using Cox proportional hazard regression analysis. In an additional analysis, we calculated HRs with 95% CIs for all-cause and cause-specific mortality for dialysis patients with a CHA_2DS_2-VASc score of two, a CHA_2DS_2-VASc score of three and a CHA_2DS_2-VASc score of four or more as compared with a CHA_2DS_2-VASc score of equal to or less than one. Furthermore, we calculated crude and adjusted HRs with 95% CIs for all-cause mortality within five-years of follow-up for vitamin K antagonist users as compared with vitamin K antagonist non-users within patients with a CHA_2DS_2-VASc score of equal to or less than one, a CHA_2DS_2-VASc score of two, a CHA_2DS_2-VASc score of three and a CHA_2DS_2-VASc score of four or more. Finally, we calculated HR's with 95% CIs for all-cause mortality for vitamin K antagonist users as compared with vitamin K antagonist non-users for patients with a low CHA_2DS_2-VASc score (<2) and a low HAS-BLED score (≤3), a low CHA_2DS_2-VASc score and a high HAS-BLED score, a high CHA_2DS_2-VASc score and a low HAS-BLED score, and a high CHA_2DS_2-VASc score and a high HAS-BLED score. As a sensitivity analysis we repeated the analyses for all-cause mortality stratifying for dialysis modality. HRs were adjusted for age, sex, primary kidney disease, dialysis modality, hypertension, antiplatelet drug use, gastro-intestinal problems including bleeding, malignancy, cardiovascular disease (angina pectoris, myocardial infarction, heart failure, ischemic stroke, or claudication), GFR and hemoglobin levels. All analyses were performed in SPSS statistical software version 23.0 (IBM SPSS Statistics).

Results

Baseline characteristics

Baseline characteristics are shown in Table 1. Of the 1718 patients, 244 patients used vitamin K antagonists and 1474 patients did not use vitamin K antagonists. Vitamin K antagonist users were older, had more often hemodialysis as dialysis modality, had higher CHA_2DS_2-VASc scores, had more often cardiovascular diseases, less often used antiplatelet drugs and had lower hemoglobin levels than patients who did not use vitamin K antagonists.

Table 1. Baseline characteristics

	Vitamin K antagonist users N=244		Vitamin K antagonist non-users N=1474	
Age (years) (IQR)	67.6	(56.4-75.2)	61.3	(48.3-71.0)
Sex, female (%)	40.2		38.4	
Primary kidney disease (%)				
Diabetes mellitus	17.6		15.8	
Glomerulonephritis	7.0		14.9	
Renal vascular disease	32.8		16.3	
Other	42.6		53.0	
Dialysis modality				
Hemodialysis	87.3		60.6	
Peritoneal dialysis	12.7		39.4	
CHA_2DS_2-VASc score				
0-1	10.7		28.9	
2	22.1		29.2	
3	22.1		20.6	
≥4	45.1		21.2	
Cardiovascular disease (%)	59.0		31.7	
Malignancy (%)	12.4		9.1	
Gastro-intestinal diseases (%)	6.2		5.7	
Hypertension (%)	88.1		89.1	
Antiplatelet drugs use (%)	9.8		25.7	
GFR (ml/min) (IQR)	3.4	(1.6-5.2)	3.3	(1.7-5.3)
Hemoglobin (mmol/L) (IQR)	6.7	(6.1-7.3)	6.9	(6.3-7.6)

IQR; interquartile range, GFR; glomerular filtration rate

Vitamin K antagonist use and mortality

During the five-years of follow-up, 141 of the 244 vitamin K antagonist users and 540 of the 1476 vitamin K antagonist non-users died, 66 vitamin K antagonist users and 700 vitamin K antagonist non-users were censored. Figure 1 shows the Kaplan-Meier survival curve with

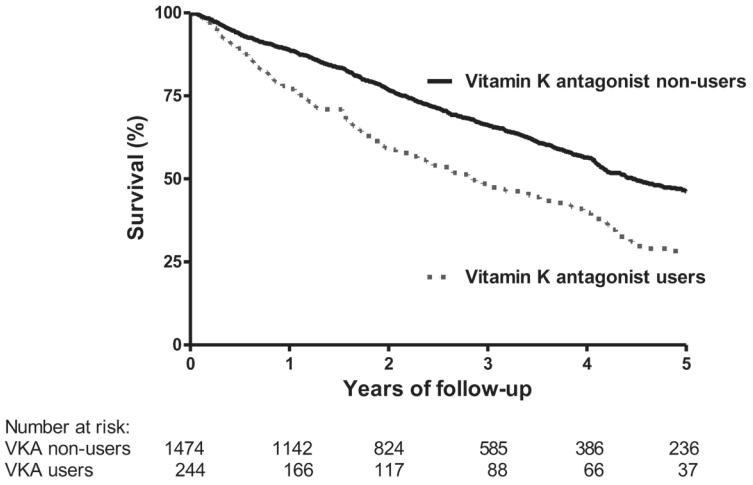

Figure 1. Kaplan–Meier curves for mortality of vitamin K antagonist users and non–users

five-years mortality as outcome. The five-year cumulative survival was 27.9% for vitamin K antagonist users and 46.2% for vitamin K antagonist non-users.

The mortality rate was 250 per 1000 person-years for vitamin K antagonist users and 144 per 1000 person-years for vitamin K antagonist non-users. Vitamin K antagonist use as compared with no vitamin K antagonist use was associated with a 1.2-fold (95% CI 1.0-1.5) increased five-years mortality risk after adjustment for age, sex, primary kidney disease, dialysis modality, cardiovascular disease, hypertension, malignancy, gastro-intestinal disease, antiplatelet drug use, GFR and hemoglobin levels (Table 2). Table 3 shows adjusted hazard ratios for patients who used vitamin K antagonists as compared with patients who did not use vitamin K antagonists for stroke mortality (HR 1.5; 95% CI 0.6-4.0), bleeding mortality (HR 1.3; 95% CI 0.4-4.2), cardiovascular mortality (HR 1.2; 95% CI 0.9-1.8), and for other mortality (HR 1.2; 95% CI 0.8-1.6).

Table 2. Vitamin K antagonist use versus no vitamin K antagonist use and all–cause mortality

		Mortality rate per 1000 person-years	Crude HR (95% CI)	Adjusted* HR (95% CI)	Adjusted** HR (95% CI)	
Vitamin K antagonist non-users	(N=1474)	144	1 (reference)	1 (reference)	1 (reference)	(reference)
Vitamin K antagonist users	(N=244)	250	1.7 (1.4-2.1)	1.3 (1.0-1.5)	1.2 (1.0-1.5)	(1.0-1.5)

HR; hazard ratio, CI; confidence interval. *Adjusted for age, sex, primary kidney disease, dialysis modality, cardiovascular disease, hypertension, malignancy, gastro-intestinal disease, antiplatelet drug use **Additionally adjusted for laboratory measurements (GFR and hemoglobin)

Table 3. Vitamin K antagonist use versus no vitamin K antagonist and cause–specific mortality

			Stroke Mortality	Bleeding Mortality	Cardiovascular Mortality	Other mortality
Vitamin K antagonist non-users	(N=1474)		1 (reference)	1 (reference)	1 (reference)	1 (reference)
Vitamin K antagonist users	(N=244)	Crude HR (95% CI)	1.7 (0.8-3.7)	2.3 (0.8-6.4)	1.6 (1.2-2.2)	1.8 (1.4-2.4)
		Adjusted* HR (95% CI)	1.5 (0.6-4.0)	1.3 (0.4-4.2)	1.2 (0.9-1.8)	1.2 (0.8-1.6)

HR; hazard ratio, CI; confidence interval. *Adjusted for age, sex, primary kidney disease, dialysis modality, cardiovascular disease, hypertension, malignancy, gastro-intestinal disease, antiplatelet drug use, GFR and hemoglobin levels

Vitamin K antagonist use and mortality in patients with low and high CHA2DS2–VASc scores

The risk of all-cause mortality, stroke mortality, bleeding mortality, cardiovascular mortality, and other mortality increased with increasing CHA_2DS_2-VASc scores (Table 4). The risk of all-cause mortality increased with increasing CHA_2DS_2-VASc scores in both vitamin K antagonist users and non-users. Within patients with a low CHA_2DS_2-VASc score (score of equal to or less than one), vitamin K antagonist use was associated with a 2.8-fold (95% CI 1.1-7.9) increased mortality risk as compared with no vitamin K antagonist use after adjustment. There was no association between vitamin K antagonist use as compared with no vitamin K antagonist use within patients with a high CHA_2DS_2-VASc score (score of two and more). Within dialysis patients with a high CHA_2DS_2-VASc score, HRs were 0.9 (95% CI 0.5-

Table 4. CHA_2DS_2–VASc scores and mortality

CHA_2DS_2-VASc Scores		All-cause Mortality		Stroke Mortality		Bleeding Mortality	
		HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
0-1	(N=452)	1	(reference)	1	(reference)	1	(reference)
2	(N=485)	2.2	(1.6-3.0)	10.6	(1.4-81.2)	3.5	(0.4-31.6)
3	(N=358)	4.4	(3.2-6.0)	15.4	(2.0-118.3)	6.5	(0.8-55.7)
≥4	(N=423)	7.6	(5.7-10.1)	18.8	(2.5-142.8)	12.0	(1.5-94.8)

CHA_2DS_2-VASc Scores		Cardiovascular mortality		Other mortality	
		HR	(95% CI)	HR	(95% CI)
0-1	(N=452)	1	(reference)	1	(reference)
2	(N=485)	1.9	(1.1-3.1)	2.2	(1.4-3.4)
3	(N=358)	4.0	(2.5-6.4)	4.3	(2.8-6.4)
≥4	(N=423)	7.6	(4.9-11.8)	7.0	(4.7-10.4)

HR; crude hazard ratio, CI; confidence interval

1.6) for patients with a CHA_2DS_2-VASc score of two, 1.2 (95% CI 0.7-2.0) for patients with a CHA_2DS_2-VASc score of three and 1.2 (95% CI 0.8-1.6) for patients with a CHA_2DS_2-VASc score of four or more (Table 5). Due to a low number of events it was not possible to investigate the association between vitamin K antagonists and cause-specific mortality for the different CHA_2DS_2-VASc scores.

Table 5. Hazard ratios for vitamin K antagonist use versus no vitamin K antagonist use for different CHA_2DS_2–VASc scores

CHA_2DS_2-VASc Scores			All-cause mortality	
			HR	(95% CI)
0-1	Vitamin K antagonist non-users		1	(reference)
	Vitamin K antagonist users	Crude HR	1.8	(0.8-4.2)
		Adjusted* HR	2.8	(1.0-7.8)
2	Vitamin K antagonist non-users		1	(reference)
	Vitamin K antagonist users	Crude HR	1.5	(1.0-2.4)
		Adjusted* HR	0.9	(0.5-1.6)
3	Vitamin K antagonist non-users		1	(reference)
	Vitamin K antagonist users	Crude HR	1.5	(1.0-2.1)
		Adjusted* HR	1.2	(0.7-2.0)
≥4	Vitamin K antagonist non-users		1	(reference)
	Vitamin K antagonist users	Crude HR	1.1	(0.8-1.4)
		Adjusted* HR	1.1	(0.8-1.6)

HR; hazard ratio, CI; confidence interval. *Adjusted for age, sex, primary kidney disease, dialysis modality, cardiovascular disease, hypertension, malignancy, gastro-intestinal disease, antiplatelet drug use, GFR and hemoglobin

We calculated the all-cause mortality risks for vitamin K antagonist users as compared with vitamin K antagonist non-users for low and high CHA_2DS_2-VASc and HAS-BLED scores. The adjusted HR for all-cause mortality in patients with a CHA_2DS_2-VASc score<2 and a HAS-BLED score ≤3 was 2.8 (95% CI 1.0-7.8), in patients with a CHA_2DS_2-VASc score≥2 and a HAS-BLED score ≤3 this was 1.2 (95% CI 0.9-1.5) and in patients with a CHA_2DS_2-VASc score≥2 and a HAS-BLED score >3 this was 1.0 (95% CI 0.3-2.9). There were no patients with a CHA_2DS_2-VASc score<2 and a HAS-BLED score >3.

Dialysis modality stratification

Stratifying for dialysis modality did not show any differences in the five-years mortality risk between the two modalities for all-cause mortality. In hemodialysis patients the adjusted HR was 1.2 (95% CI 0.9–1.5) and in peritoneal dialysis patients the adjusted HR was 1.4 (0.8-2.6). The risk of all-cause mortality increased in both dialysis modalities with increasing CHA_2DS_2-VASc scores (Table 6).

Table 6. CHA_2DS_2–VASc scores and all–cause mortality separated by dialysis modality

CHA_2DS_2-VASc		All-cause mortality			
Scores		Hemodialysis		Peritoneal dialysis	
		HR	(95% CI)	HR	(95% CI)
0-1	(N=452)	1	(reference)	1	(reference)
2	(N=485)	2.3	(1.5-3.5)	1.9	(1.2-3.1)
3	(N=358)	4.0	(2.6-6.0)	4.9	(3.0-7.8)
≥4	(N=423)	6.7	(4.5-10.0)	9.0	(5.7-14.2)

HR; crude hazard ratio, CI; confidence interval

Discussion

In this prospective cohort study of 1718 incident dialysis patients with and without atrial fibrillation, we did not find a protective effect on mortality of vitamin K antagonists. Furthermore, we showed that the mortality risk increased with increasing CHA_2DS_2-VASc scores. In addition, it was shown that within patients with a CHA_2DS_2-VASc score equal to or less than one, vitamin K antagonist use was associated with an increased mortality risk as compared with no vitamin K antagonist use, while vitamin K antagonist use within patients with a CHA_2DS_2-VASc score of two or more was not associated with a protective effect on mortality.

Most of the previous studies that investigated the effect of vitamin K antagonists in dialysis patients with atrial fibrillation did not show a protective effect of vitamin K antagonists on stroke risk or survival [7-13], while only two studies showed a decreased risk of stroke [5] or survival benefit [6] for vitamin K antagonist in dialysis patients with atrial fibrillation. The different conclusion in these two studies might be due to the lack of adjustment for confounding, and the inclusion of transplant patients in both studies. In our study, we found an increased all-cause mortality risk.

As recommended by international guidelines, the CHA_2DS_2-VASc score is frequently used as risk stratification for stroke and to guide the decision to start oral anticoagulation therapy [1,2]. These guidelines advise vitamin K antagonist use in patients with atrial fibrillation and a CHA_2DS_2-VASc score of two or more [1,2]. In our study, we found that stroke risks increased with increasing CHA_2DS_2-VASc scores which is in line with previous studies in the general population [19,20]. Since dialysis patients have an increased stroke risk, the same CHA_2DS_2-VASc scores probably reflect higher stroke risks in dialysis patients than subjects in the general population [21-23]. In our study, we found an increased mortality risk for vitamin K antagonist use in dialysis patients with a low CHA_2DS_2-VASc score. To our knowledge, we are the first to report an increased mortality risk for vitamin K antagonist use in dialysis patients with a CHA_2DS_2-VASc score of equal to or less than one. We did not find an association between vitamin K antagonist use and mortality in patients with a CHA_2DS_2-VASc score of two of more.

Unfortunately, we had no data on the indication for vitamin K antagonist use to investigate whether differences were influenced by the indication for vitamin K antagonist use.

Stratification based on HAS-BLED scores did not show a change in mortality risk for the vitamin K antagonist users as compared with non-users. Vitamin K antagonist use versus non-use was not associated with a protective effect on mortality for patients with a low CHA_2DS_2-VASc score (<2) and a low HAS-BLED score ≤3, for patients with a high CHA_2DS_2-VASc score (≥2) and a low HAS-BLED score ≤3 and for patients with a high CHA_2DS_2-VASc score (≥2) and a high HAS-BLED score (>3).

Since hemodialysis patients receive heparin during dialysis sessions, this might influence the mortality risk. However, we did not find different effects of vitamin K antagonist use in the different dialysis modalities on all-cause mortality.

There could be several pathophysiological explanations why vitamin K antagonist use in dialysis patients is not associated with a protective effect on mortality. This could be explained by an accelerated vascular calcification in dialysis patients due to the inhibition of matrix Gla protein induced by vitamin K antagonists [24]. Therefore, it could be that vitamin K antagonists are less effective in preventing stroke events in dialysis patients than in the general population [25]. Furthermore, pre-existing platelet dysfunction, altered clot properties resulting in denser clots with thinner fibrin fibers, routine heparin use during hemodialysis treatment and a suboptimal time in therapeutic range of vitamin K antagonists could lead to an increased bleeding risk in dialysis patients [16,17,26].

Generally, the benefits of vitamin K antagonists for stroke prevention in atrial fibrillation needs to be outweighed against bleeding risks. Since there are no clinical trials that investigated stroke and bleeding outcomes associated with vitamin K antagonist use in dialysis patients, guideline recommendations of vitamin K antagonist use in dialysis patients are based on observational studies. These guidelines have reported conflicting recommendations for vitamin K antagonist use in dialysis patients [1,27,28]. Current American College of Cardiology/American Heart Association atrial fibrillation Guidelines report that in dialysis patients with a CHA_2DS_2-VASc score of two or more is reasonable to prescribe vitamin K antagonists. In contrast, the Canadian guidelines [27] and the Kidney Disease Improving Global Outcomes guidelines [28] do not recommend routine anticoagulation treatment for dialysis patients with atrial fibrillation for the primary prevention of stroke events. Therefore, randomized controlled trials comparing vitamin K antagonists with placebo or direct oral anticoagulants are needed.

The general strength of this study was the large and well-defined Dutch cohort of incident dialysis patients with available data on many patient characteristics, laboratory measurements, and death. However, our study has several potential limitations. The comparison between vitamin K antagonist use versus non-use in an observational design makes confounding-by-indication the most important limitation. In our analyses, we took this into account by correcting for several confounders, but this cannot exclude possible residual confounding. Furthermore, ERA-EDTA death codes make no distinction between death due

to ischemic or hemorrhagic stroke. Therefore, we could not investigate the association between vitamin K antagonist use and hemorrhagic or ischemic stroke separately and we could not evaluate whether there was a shift from ischemic stroke events towards hemorrhagic stroke events in patients with CHA_2DS_2-VASc scores of two and more. In addition, we had no information about the indication of vitamin K antagonist use in dialysis patients. Therefore, it could be that vitamin K antagonists were used for other indications than atrial fibrillation in dialysis patients with a low CHA_2DS_2-VASc score. However, based on the high risk of atrial fibrillation in dialysis patients, it is likely that an important proportion of these patients had atrial fibrillation[13]. In addition, it could be that at initiation of vitamin K antagonist use (before dialysis), the CHA_2DS_2-VASc score was higher than at baseline of start of dialysis. Furthermore, we had no information about the presence of atrial fibrillation in vitamin K antagonist non-users. However, more than one third of dialysis patients without a diagnosis of atrial fibrillation suffer from paroxysmal atrial fibrillation [29]. These patients with undiagnosed atrial fibrillation who do not use vitamin K antagonists probably have an increased stroke risk, since other therapeutic options such as electric cardioversion or medication for rhythm control are not considered. Therefore, it could be that we overestimated the risk of stroke for vitamin K non-users. Another potential limitation is that we included dialysis patients who already used vitamin K antagonists which could have led to an underestimation of the mortality risks associated with vitamin K antagonist use. Finally, we did not have enough power to investigate the association between vitamin K antagonists and cause-specific mortality for different CHA_2DS_2-VASc scores.

In conclusion, we showed that vitamin K antagonist use compared to no vitamin K antagonist use was associated with an increased all-cause mortality risk in dialysis patients. Furthermore, we showed that the mortality risk increased with increasing CHA_2DS_2-VASc scores. In addition, it was shown that within patients with a CHA_2DS_2-VASc score of equal to or less than one, vitamin K antagonist use was associated with an increased mortality risk as compared with no vitamin K antagonist use, while vitamin K antagonist use within patients with a CHA_2DS_2-VASc score of two or more was not associated with an increased mortality risk. Randomized controlled trials comparing vitamin K antagonists with placebo or direct oral anticoagulants are needed to provide better insight into the adverse effects of vitamin K antagonists and to provide more personalized prescription of anticoagulant drugs in dialysis patients.

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8

SUMMARY AND GENERAL DISCUSSION

In this thesis, which focuses on outcomes in patients with CKD stage 4 and 5, our aim was twofold. First, we aimed to provide insight in health related quality of life (further referred to as quality of life) as an outcome in pre-dialysis patients by investigating appropriate ways to measure this construct and by investigating factors affecting quality of life. Second, we aimed to increase the understanding of the different associations between several cardiovascular risk factors and traditional outcomes in pre-dialysis and dialysis patients. In this chapter we present a summary of our main findings, discuss strengths and limitations of our research and consider its implications. We also provide recommendations for future research and end the chapter with our main conclusions.

Summary of main findings

In **chapter 2** we investigated the impact of the number and severity of symptoms on quality of life in 1079 elderly pre-dialysis patients. We assessed this by investigating both the effect of symptoms and their importance relative to kidney function, and other clinical variables on quality of life. We found that both an increase in number of symptoms and in symptom severity were associated with a decrease in quality of life. In addition, baseline symptoms were related to quality of life after six months of follow-up. The impact of symptoms on quality of life was substantial, explaining 21 and 22% of the variance in quality of life, especially compared to eGFR which did not impact any of the components of quality of life.

Subsequently, we studied the validity of the SF-12 and EQ-5D questionnaire in pre-dialysis patients in **chapter 3**. The PREPARE-2 population was used to investigate whether these two questionnaires could substitute the SF-36 as quality of life measurement tool whenever this questionnaire is impractical to use, for example in larger questionnaires when the SF-36 is too time consuming. We found a better agreement between the SF-12 and the SF-36 as compared with the agreement between the EQ-5D and the SF-36, both for measurements at a single point in time and for changes over time. This was most pronounced in direct comparisons with the SF-36, while in external validations, relating the different questionnaires to external constructs, the EQ-5D largely corresponded with the physical component summary of the SF-36. Overall, the SF-12 had good agreement with the SF-36 and, although losing some information, can be used as a substitute for the SF-36 when a shorter questionnaire is needed.

In **chapter 4** we focus on traditional outcomes. First, we assessed the association between dyslipidemia and start of dialysis, kidney transplantation or death among the 502 pre-dialysis patients in PREPARE-2. During the study 376 (75%) patients started dialysis or had a kidney transplantation, and 47 (9%) patients died. Dyslipidemia was defined based on the levels of total cholesterol, LDL cholesterol, HDL cholesterol, HDL/LDL ratio, and triglycerides. We used continuous values of these lipid levels and determined thresholds, creating categories, to investigate the association with start of dialysis, kidney transplantation or death. Our results indicate there is no association between dyslipidemia and these traditional outcomes.

In **chapter 5** our focus was on the cardiovascular risk factor hypertension and the traditional outcomes start of dialysis, kidney transplantation, death and kidney function decline. More specifically, we compared dual with no or single renin–angiotensin system (RAS) blockade regarding kidney function decline, and risk of renal replacement therapy or death among incident pre-dialysis patients. RAS inhibitors, such as angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB), both lower systolic and diastolic blood pressure, and have extensively been proven to be renoprotective agents.[1-6] Since ACEi or ARBs alone do not block the entire RAS and work via different pathways, it has been hypothesized that dual RAS blockade can improve renoprotective and anti-hypertensive effects.[7, 8] However, so far only negative effects of dual RAS blockade use have been found.[1-6] In the PREPARE-2 population we found a 20-25% lower risk of renal replacement therapy or death in patients treated with dual RAS blockade or single ACEi-users compared to non-RAS blockade-users. Dual RAS blockade medication use did not accelerate kidney function decline compared to patients with single or no RAS blockade. This lack of an increased risk of renal replacement therapy or mortality in dual RAS inhibition users suggests that there might be room for dual RAS inhibition when treating severe hypertension or proteinuria in pre-dialysis patients.

In **chapter 6 and 7** our focus was on vitamin K antagonists in both pre-dialysis and dialysis patients. This drug is used to decrease the risk for cardiovascular events in patients with increased clotting of the blood. However, vitamin K antagonists could cause damage to the kidneys by vascular calcifications due to the inhibition of matrix Gla protein or by glomerular haemorrhage which could lead to tubular obstruction.[9-14] In **chapter 6** we investigated the association between vitamin K antagonist use and the traditional outcomes rate of kidney function decline and time until start of dialysis in incident pre-dialysis patients. In the cohort of 984 pre-dialysis patients from PREPARE-1 and 2, we found no difference in annual kidney function decline between vitamin K antagonist users and non-users. Furthermore, vitamin K antagonist use as compared with non-use was not associated with an increased risk of start of dialysis within two years of follow-up.

In **chapter 7** we shifted focus to dialysis patients. It is plausible that pre-existing platelet dysfunction, routine heparin use during hemodialysis treatment and a suboptimal dose of vitamin K antagonists leads to increased risks of bleeding complications in dialysis patients.[15, 16] Because of the higher bleeding risk in dialysis patients compared to the general population, it could be that vitamin K antagonists are only beneficial in dialysis patients with higher stroke risks (estimated by CHA_2DS_2-VASc scores). Therefore, we investigated the association between vitamin K antagonist use and mortality for different CHA_2DS_2-VASc scores in a cohort of end-stage renal disease patients receiving dialysis treatment. We found that vitamin K antagonist use compared to no vitamin K antagonist use was associated with an increased all-cause mortality risk in dialysis patients. Furthermore, we showed that the mortality risk increased with increasing CHA_2DS_2-VASc scores. In addition, it was shown that within patients with a low CHA_2DS_2-VASc score (equal to or less than one),

vitamin K antagonist use was associated with an increased mortality risk as compared with no vitamin K antagonist use, while vitamin K antagonist use within patients with a higher CHA_2DS_2-VASc score (two or more) was not associated with an increased mortality risk.

The bigger picture

Quality of life

There is a substantial body of literature studying low quality of life as a risk factor in patients with CKD. These studies show that a low quality of life is associated with important outcomes such as impaired renal function, risk of end stage renal disease, and mortality in both pre-dialysis and dialysis patients.[17-21] As an outcome, however, quality of life has been largely neglected in renal literature.[22, 23] The main reason offered for this is the claim that quality of life is too subjective as a clinically relevant outcome. However, patients stress the need for more research into quality of life, since this reflects their health status and the impact their disease has on their daily life, which is much more relevant than traditional, more objective outcomes from their point of view.[22, 24] In this thesis we found that symptoms are a risk factor for quality of life, and impact quality of life much more than clinical factors such as eGFR, albumin, proteinuria, demographics or comorbidities. Earlier cross-sectional research did show similar associations between symptoms and quality of life. The comparison with clinical variables, however, has not been made before.[21, 25, 26]

A possible mechanism explaining the contrasting effects of symptoms versus clinical variables on quality of life can be found in the common-sense model of self-regulation of health and illness by Leventhal, Nerenz and Steele.[27] In this model patients develop their own cognitive and emotional perceptions of a health threat to make sense of this threat. These perceptions determine how a patient copes with their disease, which will determine outcomes, including quality of life. The development of the perceptions is determined by multiple factors, such as the cause, the timeline, and the consequences of the illness, the symptoms that are associated with the illness, and the influence of the patient's behaviour and treatment on the control of the illness.[27, 28] In this model, symptoms have a prominent role in determining the outcome quality of life. Clinical variables however, are not of any significance in this model. This is further confirmed by the later developed model of Wilson ***et al.*** where clinical variables only affect quality of life through intermediate variables, such as symptom status and functional status.[29] Both reflect and support the results we found in **chapter 2**.

To enhance the possibilities to investigate the outcome quality of life in patients with CKD, we validated the SF-12 and EuroQol in a pre-dialysis population. The SF-12 has already been validated in dialysis patients, and the EuroQol has been validated in patients with a kidney transplant. With the results from **chapter 3** we widen the range of possibili-

ties to measure quality of life on a large scale in patients with different stages of CKD. This step enables quality of life to gain more attention and thereby fulfil patient research aims.

Cardiovascular risk factors and traditional outcomes

Classic modifiable cardiovascular risk factors such as hypertension and diabetes are important drivers for the development of CKD. The association between high cholesterol LDL levels and kidney function decline is less clear. Lifestyle factors, such as smoking of cigarettes and adiposity, may increase the risk of hypertension and diabetes. All previous mentioned risk factors can have an unfavourable effect on kidney function owing to increased inflammation, oxidative stress, endothelial dysfunction, and disturbed coagulation, which may contribute to glomerular and interstitial fibrosis.

Our rationale to explore the effect of cardiovascular risk factors and pharmacotherapy in pre-dialysis patients, is the fact that pre-dialysis patients are a special group of patients, who might respond differently to cardiovascular risk factors and medication as compared with patients in the earlier CKD stages, due to different pathophysiological mechanisms. Pre-dialysis patients on specialized nephrological care are often under-represented or excluded from clinical trials. The PREPARE study allowed us to evaluate real world effectiveness of cardiovascular risk factors and medication in pre-dialysis patients. Given the results of the performed studies, the effects of the investigated cardiovascular risk factors seems to be comparable to the effects in patients in earlier CKD stages, especially the effects of dyslipidemia and dual RAS blockade.

In **chapter 4** we did not find an association between dyslipidemia and start of RRT or death. Other studies, performed in patients with a less impaired renal function showed the same lack of an association between lipoprotein levels and risk of ESRD.[30, 31] This is in concordance with a recent guideline, stating that CKD patients ≥50y should be treated with a statin, independent of lipid or triglyceride levels, without aiming at a target level.[32, 33]

In **chapter 5** the focus was on hypertension by investigating the use of ACE inhibitors and/ or ARBs and their association with the start of RRT or death and renal function decline. We found that incident pre-dialysis patients had a 20-25% lower risk of RRT when treated with dual RAS blockade or single ACEi-users compared to non-RAS blockade-users. Renal function decline in dual RAS blockade users did not accelerate as compared with single or no RAS blockade users. Similar results have been found in other studies in patients with a less impaired renal function, where dual RAS blockade was as effective as single RAS blockade.[34, 35] This implies there might be room for dual RAS blockade when treating severe hypertension or proteinuria in pre-dialysis patients.

Finally, we found no association between vitamin K antagonists and start of RRT or rate of renal function decline in vitamin K antagonist users as compared with non-users (**chapter 6**). Other benefits and risks of vitamin K antagonist use in pre-dialysis patients are not known, since trials exclude these patients because of a high bleeding risk. Guidelines mention this knowledge gap concerning risks and benefits of anticoagulation with vitamin K antagonists for stroke prevention.[36]

The overlap in results between the outcomes RRT and renal function decline is not surprising (**chapter 5 and 6**), since a major part of the decision to start RRT is based on renal function. However, it could be that RAS blockade use and vitamin K antagonist use were associated with RRT initiation through other pathways than renal function decline. For example, initiation of vitamin K antagonist use could be involved in the development of fluid overload, leading up to the decision to start RRT.

In **chapter 7** risk of mortality was the main outcome and compared for vitamin K antagonist users and non-users in incident dialysis patients. There was no protective effect on mortality of vitamin K antagonists in this population. Most of the previous studies that investigated the effect of vitamin K antagonists in dialysis patients with atrial fibrillation did not show a beneficial effect of vitamin K antagonists on survival.[37-39] In addition, we found an increased mortality risk for vitamin K antagonist use in dialysis patients with a low CHA_2DS_2-VASc score, which to our knowledge has not been investigated before.

Although all chapters in this thesis provide additional evidence for guidelines in pre-dialysis and dialysis patients, **chapter 5, 6, and 7** add information that is either missing in current guidelines, or provide conflicting evidence. This can either be a welcome addition, like the results in **chapter 7**, or a challenge to decide how much impact one additional observational study (**chapter 5**) has on current beliefs and guidelines.

Study strengths and limitations

In this section the strengths and limitations of our studies in the EQUAL study, PREPARE-I study, PREPARE-II study, and NECOSAD study are discussed.

Strengths

Chapter 2 was performed with data from the EQUAL study. The EQUAL study is a prospective cohort study performed in elderly patients with CKD progressing towards ESRD. Main strength of this study is the large size of the study population, especially for pre-dialysis 1486 patients is a large cohort. Additional strengths are the longitudinal character of the study, the inclusion of incident pre-dialysis patients (who for the first time passed a pre-specified eGFR level), and the collection of detailed information on quite a wide range of subjects. Finally, the generalizability of the study due to the low number of exclusion criteria and the participation of multiple European countries is an important strength.

The PREPARE-II population was used in **chapter 3, 4 and 5**. The entire PREPARE study, combining PREPARE-I and PREPARE-II, was used for **chapter 6**. The PREPARE study is a multicenter follow-up study in 1049 patients, starting specialized pre-dialysis care in the Netherlands. The PREPARE study consists of a retrospective (PREPARE-I) and a prospective part (PREPARE-II). Main strength of this study is the well-defined cohort of incident pre-dialysis patients who received standardized treatments and check-ups by nephrologists. A wide range of incident pre-dialysis patients was included, making the results generalizable

to the clinical practice of pre-dialysis care. An extra strength of PREPARE-I is that the retrospective character made it possible to include all consecutive patients resulting in a high generalizability. An extra strength of the PREPARE-II study is its prospective longitudinal design, resulting in specific, complete information and the opportunity to track kidney function over time. Finally, the measurements of both the SF-36 and the EuroQol (over time) in PREPARE-II make it possible to validate the SF-12 and the EuroQol questionnaire in pre-dialysis patients, which we did in **chapter 3**.

Data from the NECOSAD study were used in **chapter 7**. NECOSAD is a prospective Dutch multicenter study, which included over 2000 incident dialysis patients. After inclusion, patients were followed up to ten years during which clinical variables were collected every six months, and events of death and censoring due to other reasons were recorded. The general strength of this study was the large and well-defined Dutch cohort of incident dialysis patients with available data on an extensive range of patient characteristics, laboratory measurements, quality of life, and death. An extra strength is the fact that follow-up of events of death, transplants and modality changes are continued to this day via linkage to the Dutch national renal registry, resulting in an extremely complete registration of outcomes.

Limitations

Study design limitations

All studies used in this thesis are observational follow-up studies. Inherent to this study design are several methodological limitations.

The first important limitation in observational aetiological studies is (residual) confounding. In every study there are factors that influence the outcome in addition to the investigated exposure. When these factors also affect the exposure - a so-called common cause - they are called confounders. As confounders are unequally divided over the compared patient groups they will disturb the relation between the exposure and the outcome. In well- performed randomized controlled trials patients by design are randomly divided into different groups with concealed allocation, which is expected to result in a balanced division of confounders. In the observational studies used in this thesis we try to solve confounding after performing the study by adjusting the models for all measured confounders and stratifying results. However, this is no guarantee that all confounding is solved. It is impossible to measure every confounder, simply because there are too many, they are subjective and thereby hard to measure, or they are unknown, leaving the possibility of residual confounding in any observational study. This is especially a concern when intended effects are studied, since unintended effects are less influenced by unmeasured confounding, such as expectations from the treating nephrologist. However, with adjusting for confounding and the use of sensitivity analyses it is often possible to show the limited effect residual confounding could have on the conclusions in the performed observational

research. Therefore, when performed correctly, observational research is often a good alternative for a randomized controlled trial. Especially since randomized controlled trials are often not feasible, due to ethical problems, sample size problems, a lack of randomization possibilities, or other practical problems.

A second limitation is the occurrence of missing data, a problem in all study designs. There are three types of missing data; data missing completely at random (MCAR), data missing at random (MAR), and data missing not at random (MNAR). There are several ways to deal with missing data MCAR and MAR.[40] The best way to handle these and the method used in this thesis is by using multiple imputation. This way, the risk of bias is minimized.[41, 42] There are some sophisticated methods to deal with MNAR. However, in this thesis we did not use these methods.

A final limitation is the selection of patients for all three studies. Although the aim was to include consecutive patients in outpatient clinics and consecutive incident dialysis patients in the dialysis centers, treating nephrologists could always decide not to include a patient, for example due to the severity of a patients illness. In addition, patients were asked for a written informed consent before inclusion and could refuse to participate. Sicker patients might find study participation too much of a burden, which might lead to a higher refusal rate as compared with the refusal rate in healthier patients. Both issues might have affected the generalizability of the cohorts, since included patients might be healthier than the average population of pre-dialysis patients and dialysis patients.

Medication study limitations

In **chapter 5, 6, and 7** of this thesis the investigated exposure is medication use. This type of study is associated with some extra limitations.

The main limitation in these studies is the possibility of confounding by indication. The indication for prescribing dual RAS blockade as well as vitamin K antagonists is based on the presence of certain risk factors, as well as the (immeasurable) experience and gut feeling of the treating nephrologist.[43-45] All these factors are associated with the probability of receiving dual RAS blockade or vitamin K antagonists and with the risk of kidney function decline. Therefore, patients receiving dual RAS blockade have a higher probability of developing ESRD, not because of the dual RAS blockade, but because of their increased intrinsic risk.[35] For example, patients with a worse kidney function would receive vitamin K antagonists less often leading to a possible underestimation of negative effects of vitamin K antagonists. However, confounding by indication is less of a problem when the outcome is an unintended effect, since the immeasurable factors that influence the nephrologists decisions do not apply to unintended effects. Since RAS inhibition is mainly prescribed for blood pressure control and vitamin K antagonists for thrombosis prevention, the effect on kidney function and start of RRT are for the largest part unintended effects. In combination with the correction for multiple confounders, this reduced the possible confounding by indication. In **chapter 7** preventing premature death is an indirect goal of prescribing

vitamin K antagonists, the main aim remains thrombosis prevention, making death at least a partial unintended effect.[46]

Another limitation is the inclusion of patients who were prevalent users or non-users of RAS-blockade medication in **chapter 5** and vitamin K antagonists in **chapter 6 and 7**. We had no information about the duration of medication use in these patients. However, in **chapter 5** 29 (24%) of the non-users started an ACEi or ARB during follow-up, which may have resulted in underestimation of the beneficial effect of ACEi-use or ARB-use. The inclusion of prevalent vitamin K antagonist users in **chapter 6** could have led to an underestimation of the negative effects on kidney function and start of dialysis in vitamin K antagonist users. In **chapter 7** this could have led to an underestimation of the mortality risks associated with vitamin K antagonist use. However, since there is no positive effect of the vitamin K antagonist use, and even a negative effect in patients with low CHA_2DS_2-VASc scores this could only result in larger negative effects.

A third limitation is the possible lack of therapy adherence. It is known that adherence to pharmacotherapy is rarely 100%.[47] A lack of therapy adherence in a study could lead to an underestimation of effects. However, it does represent clinical practice resulting in a realistic estimation of the effects in clinical practice. This means an RCT could result in an overestimation of effects when adherence is monitored closely.

Finally, we had no information about the indication of vitamin K antagonist use in our patients in **chapter 6 and 7**. Therefore, it could be that vitamin K antagonists were used for other indications than atrial fibrillation in dialysis patients with a low risk score (CHA_2DS_2-VASc) for thrombotic events. However, based on the high risk of atrial fibrillation in dialysis patients, it is likely that an important proportion of the patients had atrial fibrillation and that the impact on the found results is minimal.[48]

Implications and recommendations

In this thesis we showed the importance of symptoms and relative unimportance of clinical variables in determining quality of life. Both the prevalence and severity of symptoms emphasize the need for attention on symptoms during outpatient clinic visits. The effect of symptoms on a clinically relevant outcome measure which in turn affects other important outcomes, indicates that symptoms should have a more prominent role in clinical decision making and guidelines in CKD should emphasize this.

After the validation of the SF-12 and the EuroQol, we would recommend to use the SF-12 as a shorter substitute for the SF-36, since this questionnaire has a better agreement with the SF-36 as compared with the EuroQol. Since both are now validated, use of the SF-12 and the EuroQol to measure quality of life in pre-dialysis patients could now be justified, however, additional validations in different countries would enhance this first evidence. In clinical practice the use of these shorter questionnaires is useful when large amounts of patients are asked to fill in multiple questionnaires. To measure quality of life and re-

lated topics more in depth, such as its relation with coping, illness perceptions, or coping mechanisms, a larger questionnaire such as the SF-36, is more appropriate.

For future research on quality of life in patients with CKD, we would recommend to broaden research on factors influencing quality of life. This could be achieved by intensifying research on symptoms, for example by studying the impact of individual symptoms or clusters of symptoms on QoL or testing whether interventions on symptoms improve QoL. A second method to achieve this is by investigating other aspects of the common-sense model by Leventhal, Nerenz and Steele, for example illness perceptions.[27]

In this thesis we also investigated several cardiovascular risk factors and their association with the traditional outcomes renal function decline, start of RRT and mortality. Finding no clear association between dyslipidemia and start of dialysis, RRT or death, we suggest focusing on the direct effects and mechanisms of lipid lowering drugs in pre-dialysis patients instead of the absolute lipid and triglyceride levels. The lack of a negative association between dual RAS blockade and start of RRT and renal function decline suggests that there might be room for dual RAS blockade when treating severe hypertension or proteinuria in CKD 4-5 patients with single RAS blockade.

The results in our studies on vitamin K antagonist use emphasize the need for randomized controlled trials comparing vitamin K antagonists with placebo or direct oral anticoagulants. This would provide better insight into the adverse effects of vitamin K antagonists and more personalized prescription of anticoagulant drugs in pre-dialysis and dialysis patients.

Conclusion

In elderly pre-dialysis patients symptoms have a substantial impact on quality of life. The effect of symptoms on a clinically relevant outcome measure indicates that these symptoms, which in turn affect other important outcomes, should have a more prominent role in clinical decision making, and guidelines in CKD should emphasize this. An appropriate way to measure the construct quality of life in pre-dialysis patients with a short questionnaire is by using the SF-12. In the future additional validation of this questionnaire in different countries could strengthen this evidence.

No association between dyslipidemia and start of dialysis, RRT or death in pre-dialysis patients was found. In pre-dialysis patients, both dual RAS blockade as well as single ACEi-use were associated with a lower risk of RRT or death, as compared with no RAS blockade. Kidney function decline in the single or dual RAS inhibition groups was not accelerated as compared with non-RAS inhibition drug users. This implies there there might be room for dual RAS blockade when treating severe hypertension or proteinuria in CKD 4-5 patients with single RAS blockade. There is no association between vitamin K antagonist use and rate of renal function decline or time until start of dialysis in the pre-dialysis population, which provides support to continue the use of vitamin K antagonists in this population.

Vitamin K antagonist use compared to no vitamin K antagonist use is associated with an increased all-cause mortality risk in dialysis patients, which increases with increasing CHA2DS2-VASc scores. Within patients with a CHA2DS2-VASc score of equal to or less than one, vitamin K antagonist use is associated with an increased mortality risk as compared with no vitamin K antagonist use. This implies the need to evaluate the indication for vitamin K antagonist use when starting dialysis.

In short, in pre-dialysis patients quality of life is an important outcome measure which can be measured with the SF-12 in addition to the SF-36, and which is affected by the symptom burden of a patient. Cardiovascular risk factors remain important treatment targets in pre-dialysis and dialysis patients, and often have similar effects on traditional outcomes compared to their effects in earlier CKD stages.

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9

NEDERLANDSE SAMENVATTING

DANKWOORD

CURRICULUM VITAE

PUBLICATIELIJST

Nederlandse samenvatting

Inleiding

Gezonde nieren verwijderen afvalstoffen en overtollig water uit het lichaam en produceren enzymen en hormonen. Wanneer er gedurende minimaal drie maanden afwijkingen zijn in de nierstructuur of van de nierfunctie met gevolgen voor de gezondheid, spreekt men van een chronische nierziekte. Met een wereldwijd voorkomen van meer dan 13% zijn chronische nierziekten een groot probleem voor de internationale gezondheidszorg.

Chronische nierziekten worden verdeeld in vijf stadia, van zeer mild in stadium 1 tot zeer ernstig in stadium 5. Tijdens stadium 1 heeft een patiënt geen symptomen en een normale nierfunctie, maar verliest eiwit in de urine. In stadium 5 is de nierfunctie bij patiënten zo ernstig verminderd dat nierfunctievervangende therapie, namelijk dialyse of een niertransplantatie, noodzakelijk is. Stadium 4 is de fase waarin patiënten worden voorbereid op eventuele nierfunctievervangende therapie en waarin wordt geprobeerd progressie naar stadium 5 zo lang mogelijk uit te stellen. Stadium 4 wordt ook wel de pre-dialyse fase genoemd. In dit proefschrift richt ik mij specifiek op patiënten met een chronische nierziekte in stadium 4 of 5.

Traditioneel wordt bij onderzoek naar chronische nierziekten de overleving van patiënten bestudeerd, de tijd tot het starten van dialyse, of de daling van de nierfunctie. De laatste jaren verschuift de focus van alleen het verbeteren van deze uitkomsten (de traditionele uitkomsten) naar het ook verbeteren van de kwaliteit van leven voor deze patiënten. Een van de redenen voor deze verschuiving is de toename van de invloed van patiënten op wetenschappelijk onderzoek, die het belang van kwaliteit van leven benadrukken.

Het doel van dit proefschrift is tweeledig. Ten eerste het verkrijgen van meer inzicht in kwaliteit van leven als uitkomstmaat bij pre-dialyse patiënten door het onderzoeken van meetmethoden voor kwaliteit van leven en factoren die kwaliteit van leven beïnvloeden. Ten tweede het vergroten van het inzicht van de samenhang tussen verschillende risicofactoren voor hart- en vaatziekten en traditionele uitkomsten bij pre-dialyse en bij dialyse patiënten.

Overzicht van de belangrijkste resultaten van dit proefschrift

In **hoofdstuk 2** wordt de impact van fysieke en mentale symptomen en de ernst van symptomen op kwaliteit van leven in 1079 oudere pre-dialyse patiënten beschreven. Ik heb dit onderzocht door het effect van symptomen te bestuderen en naar hun belang in het bepalen van kwaliteit van leven in vergelijking met andere klinische variabelen, zoals de nierfunctie. In dit onderzoek bleek een toename van het aantal en van de ernst van symptomen samen te hangen met een slechtere kwaliteit van leven. Daarnaast zijn symptomen bij start van de studie van invloed op de kwaliteit van leven zes maanden later. De impact van symptomen op kwaliteit van leven was substantieel, de verklaarde variantie was 21% voor het aantal symptomen en 22% voor de ernst van de symptomen. De klinische varia-

bele voor nierfunctie, glomerulaire filtratie snelheid (eGFR), had geen enkele impact op de kwaliteit van leven.

In **hoofdstuk 3** worden vervolgens de kwaliteit van leven vragenlijsten Short Form-12 (SF-12) en EuroQol-5D (EQ-5D) gevalideerd in pre-dialyse patiënten. Gebruikmakend van de pre-dialyse populatie uit de PREPARE-2 studie heb ik onderzocht of de korte SF-12 en EQ-5D vragenlijsten de lange, tijdrovende kwaliteit van leven vragenlijst Short Form-36 (SF-36) kunnen vervangen als kwaliteit van leven meetinstrument. In deze studie bleken de SF-12 en SF-36 beter onderling overeen te komen dan de EQ-5D en de SF-36, zowel op een vast moment in de tijd als voor veranderingen over de tijd. Dit kwam het duidelijkst naar voren wanneer de vragenlijsten direct vergeleken werden met de SF-36. Bij het bestuderen van de relatie met bijvoorbeeld start van dialyse of symptomen kwam de EQ-5D vaak overeen met het somatische gedeelte van de SF-36. Over het algemeen kwam de SF-12 goed overeen met de SF-36 en deze kan dan ook als vervanging voor de SF-36 gebruikt worden.

In **hoofdstuk 4** heb ik mijn aandacht verschoven van kwaliteit van leven naar meer traditionele uitkomsten. In dit hoofdstuk heb ik de associatie tussen dyslipidemie en start van dialyse, niertransplantatie of sterfte bestudeerd bij de 502 pre-dialyse patiënten van de PREPARE-2 populatie. Gedurende de studie zijn 376 (75%) patiënten gestart met dialyse of hebben een niertransplantatie ondergaan en zijn 47 (9%) patiënten overleden. Dyslipidemie werd gedefinieerd op basis van de waarden van het totale cholesterol, het LDL cholesterol, het HDL cholesterol, de HDL/LDL ratio en de waarde van de triglyceriden. Op basis van deze continue waarden werden drempelwaarden vastgesteld waarmee categorieën werden gecreëerd die ik heb gebruikt om de associatie met start van dialyse, niertransplantatie of sterfte te bepalen. De resultaten van dit onderzoek lieten geen associatie zien tussen dyslipidemie en de traditionele uitkomsten.

In **hoofdstuk 5** heb ik de samenhang tussen hoge bloeddruk en de traditionele uitkomsten start van dialyse, niertransplantatie, sterfte en nierfunctieachteruitgang onderzocht. In deze studie heb ik het effect van dubbele renine- angiotensine systeem (RAS) blokkade (het gebruik van 2 soorten RAS blokkade) in nieuw ontdekte pre-dialyse patiënten vergeleken met dat van enkele RAS blokkade. RAS blokkers, zoals angiotensine converterend enzym inhibitoren (ACEi) en angiotensine II receptor blokkers (ARB) verlagen de systolische en diastolische bloeddruk en beschermen de nier. Aangezien enkel ACEi of ARB gebruik niet het gehele RAS blokkeren en via verschillende paden werken, wordt er verondersteld dat dubbele RAS blokkade de antihypertensieve werking en bescherming van de nier zou kunnen verbeteren. In tegenstelling tot deze hypothese zijn er tot nu toe voornamelijk negatieve effecten van dubbele RAS blokkade gevonden. In de PREPARE-2 studie vonden we een 20 tot 25% lager risico op nierfunctievervangende therapie of sterfte in patiënten die behandeld waren met dubbele RAS blokkade of alleen met ACEi remmers in vergelijking met patiënten zonder RAS blokkers. Dubbele RAS blokkade versnelde de achteruitgang van de nierfunctie niet in vergelijking met enkele RAS blokkade of zonder RAS blokkade. Deze uitkomst biedt perspectief op het gebruik van dubbele RAS blokkade bij het behandelen

van ernstige hypertensie of proteïnurie in pre-dialyse patiënten, omdat er waarschijnlijk geen negatieve effecten zijn ten opzichte van enkele blokkade en er mogelijk wel een extra gunstig effect is op de bloeddruk en op proteïnurie (niet onderzocht in dit proefschrift).

In **hoofdstuk 6 en 7** lag de aandacht op vitamine K-antagonisten in zowel pre-dialyse als dialyse patiënten. Vitamine K-antagonisten worden gebruikt om het risico op hart- en vaatziekten bij patiënten met een verhoogd stollingsrisico (een cardiovasculaire risicofactor) te verlagen. Ondanks dit gunstige effect zouden vitamine K-antagonisten de nieren kunnen beschadigen ten gevolge van vaatverkalkingen of door glomerulaire bloedingen die tot obstructies zouden kunnen leiden. In **hoofdstuk 6** heb ik de associatie tussen vitamine K-antagonisten en de traditionele uitkomsten nierfunctie achteruitgang en tijd tot de start van dialyse in nieuwe pre-dialyse patiënten onderzocht. In het cohort van 984 pre-dialyse patiënten van de PREPARE-1 en PREPARE-2 populatie vond ik geen verschil tussen de jaarlijkse achteruitgang in nierfunctie tussen vitamine K-antagonist gebruikers en niet gebruikers. Daarbij was vitamine K-antagonist gebruik niet geassocieerd met een verhoogd risico op de start van dialyse in vergelijking met niet gebruikers gedurende de eerste twee jaar waarin de patiënten gevolgd werden.

In **hoofdstuk 7** werd gebruik gemaakt van een cohort dialyse patiënten. Het is plausibel dat bloedplaatjes dysfunctie, het routinematige gebruik van heparine tijdens hemodialyse en een suboptimale tijd in de therapeutische range tot een verhoogd risico op bloedingscomplicaties in dialyse patiënten kunnen leiden. Vanwege het verhoogde bloedingsrisico in dialyse patiënten in vergelijking met de algemene populatie is het mogelijk dat het gebruik van vitamine K-antagonisten alleen voordeel biedt voor deze patiënten bij een hoger risico op een herseninfarct (dit risico wordt weergegeven met de CHA2DS2-VASc score). In dit hoofdstuk heb ik de associatie tussen vitamine K-antagonist gebruik en de mortaliteit bij verschillende CHA2DS2-VASc scores in een cohort met eindstadium nierfalen patiënten die behandeld worden met dialyse onderzocht. In deze studie vond ik een associatie tussen vitamine K-antagonist gebruik en sterfte in dialyse patiënten die niet aanwezig is bij niet gebruikers van vitamine K-antagonisten. Daarnaast vond ik een hoger sterfterisico bij hogere CHA2DS2-VASc scores. In patiënten met een lage CHA2DS2-VASc score was vitamine K-antagonisten gebruik geassocieerd met een verhoogd sterfte risico in vergelijking met niet gebruikers, terwijl vitamine K-antagonist gebruik bij hogere CHA2DS2-VASc scores niet geassocieerd is met een hoger risico op sterfte.

Aanbevelingen en conclusies

Bij oudere pre-dialyse patiënten hebben symptomen een substantieel effect op de kwaliteit van leven. Het effect van symptomen op een klinisch relevante uitkomst impliceert dat symptomen een prominentere rol in de klinische besluitvorming omtrent pre-dialyse patiënten zouden moeten hebben en richtlijnen voor deze populatie zouden dit moeten benadrukken. Een geschikte manier om de kwaliteit van leven met een korte vragenlijst

te meten in pre-dialyse patiënten is door gebruik te maken van de SF-12. Aanvullende validatie van de SF-12 in andere landen zou deze aanbeveling versterken.

In dit proefschrift vond ik geen associatie tussen dyslipidemie en de start van dialyse, nierfunctie vervangende therapie of sterfte in pre-dialyse patiënten. Het is daarom nuttiger om de directe effecten en mechanismen van lipiden verlagende medicatie te onderzoeken. Ik vond een lager risico op nierfunctie vervangende therapie of sterfte bij enkel of dubbele RAS blokkade in vergelijking met pre-dialyse patiënten zonder RAS blokkade. De achteruitgang van de nierfunctie was niet groter bij dubbele of enkele RAS blokkade ten opzichte van patiënten zonder RAS blokkade. Dit impliceert dat er mogelijk ruimte is voor dubbele RAS blokkade bij het behandelen van ernstige hypertensie of proteïnurie bij pre-dialyse patiënten. Er is geen associatie tussen vitamine K-antagonisten gebruik en nierfunctie achteruitgang of de tijd tot de start van dialyse in pre-dialyse patiënten, wat het gebruik van vitamine K-antagonisten in deze populatie ondersteunt. In patiënten met een CHA2DS2-VASc score van 0 of 1 was vitamine K-antagonisten gebruik geassocieerd met een verhoogd mortaliteitsrisico in vergelijking met niet gebruikers. In patiënten met hogere CHA2DS2-VASc scores vonden we geen verhoogd risico op sterfte in vitamine K-antagonist gebruikers. Dit benadrukt de noodzaak om de indicatie voor vitamine K-antagonisten te evalueren bij het starten van dialyse.

Concluderend onderschrijft dit proefschrift het belang van kwaliteit van leven als uitkomstmaat in pre-dialyse patiënten, wat naast de SF-36 ook met de SF-12 gemeten kan worden en wat beïnvloed wordt door symptomen van de patiënt. Het behandelen van risicofactoren voor hart- en vaatziekten blijft een belangrijk therapiedoel in patiënten met een chronische nierziekte stadium 4 of 5. In dit proefschrift blijken deze risicofactoren in stadium 4 en 5 vaak hetzelfde effect op traditionele uitkomsten te hebben als in de vroege stadia van chronische nierziekten.

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Curriculum Vitae

Pauline Voskamp werd geboren op 12 juni 1988 in Hendrik Ido Ambacht. In 2006 behaalde zij haar gymnasium diploma aan het Marnix Gymnasium in Rotterdam, waarna zij geneeskunde ging studeren aan de Erasmus Universiteit Rotterdam. Tijdens haar studie heeft zij zich verdiept in de neurologie, waar zij haar wetenschappelijke stage deed en haar oudste coschap liep. Na haar afstuderen in 2012 heeft zij twee jaar ervaring opgedaan als arts-assistent niet in opleiding bij de neurologie in het Albert Schweitzer ziekenhuis in Dordrecht.

Eind 2014 is zij aan een promotietraject begonnen op de afdeling Klinische Epidemiologie van het LUMC, onder supervisie van Prof. Dr. Friedo Dekker, dr. Merel van Diepen en dr. Ellen Hoogeveen. De resultaten hiervan staan beschreven in dit proefschrift. Naast haar promotietraject was Pauline de Nederlandse coördinator van de EQUAL studie, een Europese studie naar het beste moment voor patiënten met een chronische nierziekte om dialyse te starten. Tijdens haar promotietraject heeft zij de opleiding tot Epidemioloog B gevolgd en onderwijs gegeven aan (bio)medische studenten. Sinds 1 januari 2018 is zij werkzaam als arts-assistent niet in opleiding bij de neurologie in het Elisabeth-TweeSteden Ziekenhuis in Tilburg.

Publicatielijst

Dit proefschrift:

Effect of dual compared to no or single Renin-Angiotensin System blockade on risk of renal replacement therapy or death in pre-dialysis patients: PREPARE-2 study. PWM Voskamp, FW Dekker, M van Diepen, EK Hoogeveen. J Am Soc Hypertension 2017;11:635-643

Dyslipidemia and risk of renal replacement therapy or death in incident pre-dialysis patients: PREPARE-2 study. PWM Voskamp, M van Diepen, FW Dekker, EK Hoogeveen. Scientific reports 2018;8:3130

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Measuring quality of life in pre-dialysis patients; comparing the SF-12 and EQ-5D to the SF-36. PWM Voskamp, M van Diepen, C Grim, EK Hoogeveen, FW Dekker

Submitted

Overig:

Prediction models for the mortality risk in chronic dialysis patients: A systematic review and independent external validation study. CL Ramspek, PWM Voskamp, FJ van Ittersum, RT Krediet, FW Dekker, M van Diepen. Clin Epidemiol 2017;9:451-464

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Health valuation of dialysis with the EQ-5D: determinants of discrepancy between patients and society. A Beby, PWM Voskamp, AH Zamanipoor Najafabadi, M van Diepen, FW Dekker Submitted

Association between serum phosphate, start of dialysis and renal function decline in incident pre-dialysis patients. EL Fu, MG Vervloet, PWM Voskamp, M van Diepen, FW Dekker Submitted