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Disease progression in pre-dialysis patients

Renal function, symptoms, and health-related quality of life

Moniek Cornelia Maria de Goeij

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Renal function, symptoms, and health-related quality of life

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Voor mijn ouders

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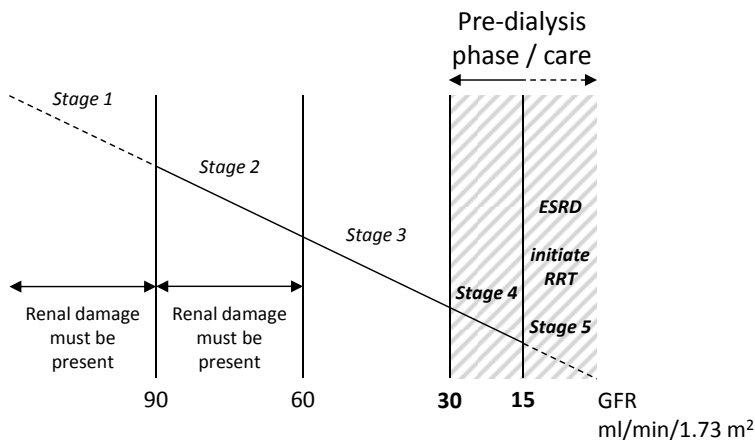
Chapter 1 |

General introduction, aims, and outline of this thesis

Chronic kidney disease

Chronic kidney disease (CKD) is a major public health problem worldwide with a prevalence around 10% in the United States, Europe (including The Netherlands), and Asia.¹⁻⁵ CKD is characterized by a progressive loss of renal function over a period of months or years, leading to inadequate removal of fluid and waste products from the body.⁵ CKD is defined as persistent renal damage (detected by a renal biopsy or markers of renal damage) and/or a glomerular filtration rate (GFR) smaller than 60 ml/min/1.73 m² for three months or longer. CKD can be classified into five clinical stages based on renal damage and GFR, as shown in Figure 1.⁵ Once CKD progresses to stage 5 (end-stage renal disease, ESRD) initiation of renal replacement therapy (RRT), defined as the start of dialysis or receiving a kidney transplant, should be considered.

Figure 1: Classification of chronic kidney disease stages



The prevalence of CKD, with mainly diabetes mellitus and hypertension as underlying cause, is rising.^{1;6;7} This rise can be explained by the ageing population and lifestyle changes (e.g. nutrition) leading to a high worldwide prevalence of diabetes mellitus⁸ and hypertension⁹. Once having developed CKD, the prevalence of cardiovascular events is higher compared with people with a normal renal function.^{10;11} CKD patients are even more likely to die of cardiovascular causes than to reach ESRD.¹² This high cardiovascular burden supports the need for optimal cardiovascular risk-management in CKD patients. Despite the fact that only a small proportion of patients reach ESRD, the prevalence and incidence of ESRD patients receiving RRT has increased dramatically.^{13;14} In the United States, it is expected that ESRD incidence counts will increase with 29% and prevalence counts with 47% in the period 2007 to 2020.⁶ These increasing numbers support the need for actions to slow down progression to ESRD. These actions are preferably initiated in the earlier stages (1-2) of CKD. Unfortunately, CKD is often diagnosed in moderate (stage 3) to advanced stages (4-5) when disease-related symptoms become present.¹⁵ Patients with stage 3 CKD should be under the care of a

nephrologist and treated according to guidelines^{5;16} to slow down progression to ESRD. In The Netherlands, once having progressed to advanced stages of CKD, patients are referred to outpatient clinics for specialized pre-dialysis care (Figure 1).

Pre-dialysis care

Pre-dialysis care in The Netherlands is an intensive and multidisciplinary care program for CKD stage 4 (GFR 15-30 ml/min/1.73 m²) and 5 (GFR <15 ml/min/1.73 m²) patients, not receiving RRT.¹⁷ A nephrologist, dietician, nurse, and social worker will treat and guide these patients in the last phase before starting RRT. During pre-dialysis care, patients are regularly seen by these healthcare workers. Due to the regular check-ups, possibly increasing to once a month in CKD stage 5, individualized care can be provided. The main goals of pre-dialysis care are to slow down renal function decline, prevent and treat metabolic complications (including cardiovascular diseases), and prepare patients for the start of RRT. The effectiveness of multidisciplinary pre-dialysis care on several clinical outcomes has been proven.¹⁸⁻²¹ To illustrate, patients following a multidisciplinary pre-dialysis program had a lower systolic blood pressure and lower mortality and hospitalization rates once having started dialysis, compared with patients receiving standard care.

Slowing down renal function decline can be achieved by treating risk factors of disease progression, such as hypertension, proteinuria, and hyperglycemia. Metabolic complications treated during pre-dialysis care are anemia, hyperkalemia, mineral bone disorders, and metabolic acidosis. Cardiovascular risk-management focuses on both the risk factors of disease progression as metabolic complications, but also on hyperlipidemia and lifestyle factors, such as nutrition, physical activity and smoking. Current treatment options and targets for patients on pre-dialysis care are summarized in guidelines²² and an overview of these Dutch guidelines is presented in Table 1. Preparing patients for the start of RRT includes education on clinical, psychological, and social consequences of different RRT modalities (such as hemodialysis, peritoneal dialysis, and transplantation), or conservative treatment. This guidance contributes to making the best choice for each individual patient and thereby increases the quality of care.

The current Dutch guidelines for pre-dialysis care²² are partly based on the universal K/DOQI⁵ and KDIGO¹⁶ CKD guidelines and partly on clinical experience in The Netherlands. For current pre-dialysis guidelines, the evidence used is mainly based on studies performed in CKD patients with earlier stages of CKD and not on studies performed in the specific population of patients on pre-dialysis care. Furthermore, most studies mainly focused on objective progression outcomes, such as renal function decline and progression to RRT/ESRD. Evidence is lacking on the effect of risk factors of disease progression and metabolic complications on more direct patient-related outcomes, such as self-assessed symptoms and health-related quality of life. Improving health-related quality of life is important because starting dialysis with a better health-related quality of life increases survival.^{23;24} Besides this, not all

guidelines are specified for certain important subgroups (e.g. age), despite the fact that patients receiving specialized pre-dialysis care are a very heterogeneous population.

Table 1: Pre-dialysis guidelines: treatment strategies

Progression factor / complication	Target	Treatment options
<i>Hypertension</i>	Blood pressure <130/80 mmHg	Anti-hypertensive drugs, dietary changes (<2.4 g sodium/day, <6 g salt/day), lifestyle changes
<i>Proteinuria</i>	Urinary protein excretion <1 g/24h	Anti-hypertensive drugs (ACEi/ARB), dietary changes (<2.4 g sodium/day, 0.8 g/kg protein/day)
<i>Hyperglycemia</i>	HbA1c <7%	Balancing medication, diet and lifestyle factors (such as physical activity)
<i>Anemia</i>	Hemoglobin 6.8-7.4 mmol/l, avoid ≥8.0 mmol/l, serum ferritin 100-500 µg/l	Erythropoiesis stimulating agents, iron supplements, dietary changes
<i>Mineral bone disorders</i>	Calcium 2.1-2.37 mmol/l, phosphate 0.7-1.3 mmol/l, PTH ~2-7 pmol/l	Phosphate binders, bisphosphonates, calcium supplements, vitamin D, dietary changes
<i>Metabolic acidosis</i>	Serum HCO ₃ 20-22 mmol/l	Dietary changes (<2.4 g sodium/day, 0.8 g/kg protein/day), sodium bicarbonate
<i>Hyperkalemia</i>	Potassium <5.5 mmol/l	Dietary changes (2-3 g potassium/day), diuretics, cation-exchangers
<i>Hyperlipidemia</i>	LDL <2.5 mmol/l, non-HDL <3.4 mmol/l, HDL >1 mmol/l, triglycerides 2.25-4.5 mmol/l	Statins, dietary changes (<10 energy% and <1 energy% trans fatty acids)
<i>Lifestyle factors</i>	Stop smoking, balancing nutrition and physical activity	Education 'self-management'

ACEi/ARB: angiotensin-converting enzyme inhibitor/angiotensin-II receptor blocker; HbA1c: hemoglobin A1c; PTH: parathyroid hormone; HCO₃: bicarbonate; LDL: low density lipoprotein; HDL: high density lipoprotein.

Clinical studies used in this thesis

PRE-dialysis PATient REcord study (PREPARE)

The PRE-dialysis PATient REcord (PREPARE) study consists of a multi-center retrospective (PREPARE-1) and prospective (PREPARE-2) cohort study. Both studies included incident adult patients referred to an outpatient clinic for specialized pre-dialysis care (547 and 502 patients respectively). In practice, this refers to patients with an estimated GFR of <20-30 ml/min/1.73 m² and a progressive loss of renal function. For the PREPARE-1 study, patients were included between 1999 and 2001 and followed until the start of RRT, death, or January 1, 2008. For the PREPARE-2 study the inclusion period started in 2004 and ended in 2011 and follow-up of patients is still ongoing. In both studies, demographic, anthropometric, and clinical characteristics were collected at baseline and at the end of follow-up. In PREPARE-1 these data were extracted from medical records and in PREPARE-2 information was prospectively collected by the medical staff of each participating center. Additional in PREPARE-2, a health-related quality of life questionnaire was filled in and blood and urine samples were collected.

Besides this, in both studies laboratory values were extracted from the electronic hospital information systems during the whole period of pre-dialysis care. Furthermore, in PREPARE-2 demographic, anthropometric, and clinical characteristics were also collected each six-month interval.

Leiden Longevity Study (LLS)

The Leiden Longevity Study was designed to identify genetic determinants of familial longevity.^{25,26} In total, 421 Dutch families were included, with at least two alive long-lived siblings of 89 years or older for males and 91 years or older for females. Along with the long-lived siblings, 1671 offspring of these families and 744 partners of these offspring, all Caucasian, were included. From these offspring and their partners, non-fasting blood serum samples were drawn and additional information was collected on self-reported lifestyle, information on medical history from the participants' general practitioner, and information on medication use from the participants' pharmacy.

Objective of this thesis

The main objective of this thesis was to estimate the effect of several important risk factors on disease progression in patients on specialized pre-dialysis care. Disease progression was assessed objectively, as renal function decline and time until the start of RRT, and subjectively, as disease-related symptoms and health-related quality of life. These results can provide supporting evidence for current pre-dialysis guidelines or give indications to adapt the guidelines.

The second objective of this thesis was to provide insight in (un)known mechanisms that influence renal function decline. These results may unravel new treatment strategies to slow down disease progression in pre-dialysis patients.

Outline of this thesis

Chapters 2-5 describe the effect of several risk factors on objectively assessed disease progression. In **chapter 2** the effect of reaching the blood pressure target, according to current guidelines for pre-dialysis care, on disease progression is estimated. It was hypothesized that the effect of blood pressure may change in elderly patients due to the age-related increase of the cardiovascular burden. Therefore, **chapter 3** focuses on the effect of blood pressure on disease progression in elderly (≥ 65 year) patients. Whether proteinuria is still a risk marker for disease progression in patients on pre-dialysis care is presented in **chapter 4**. Furthermore, the prescription of proteinuria-lowering medication – angiotensin-converting enzyme inhibitor and angiotensin-II receptor blocker – during pre-dialysis care is described. The idea is that discontinuation of these medications during pre-dialysis care may increase residual renal function and thereby postpone the start of RRT.²⁷ For treating hyperlipidemia evidence is weak and contradictory, and therefore in **chapter 5** the effect of lipid levels on disease progression is estimated.

Chapters 6 and 7 describe the subjectively assessed outcomes. Evidence is lacking on the course of symptoms and health-related quality of life during pre-dialysis care. This information is necessary to decide whether these outcomes are good indicators for disease progression and may be useful as risk markers. Therefore, **chapter 6** describes the course of symptoms and health-related quality of life. Besides this, current guidelines state that targeting high hemoglobin levels in anemic CKD patients increases the risk of mortality and morbidity.²⁸ However, studies on this topic show contradictory effects on health-related quality of life.²⁹ Therefore, more evidence is necessary and **chapter 7** estimates the effect of high hemoglobin levels on health-related quality of life.

The aim of **chapters 8 and 9** is to unravel (un)known mechanisms of renal function decline. Race (black versus white), **chapter 8**, and familial longevity (longevity versus non-longevity families), **chapter 9**, are associated with renal function decline. Both familial circumstances comprise of genetic and early environmental factors that can influence renal function decline. These populations are therefore ideal for revealing new mechanisms.

All previous chapters may contribute to develop more evidence-based guidelines in the near future. However, guidelines can only improve quality of care for CKD patients when these guidelines are actually achieved. In **chapter 10** we comment on an audit-based education program that may increase guideline achievement.

Chapters 11 and 12 are based on methodological issues experienced in the previous chapters. The theoretical and practical principles of multiple imputation, a method that can be used when data is missing, is presented in **chapter 11**. Missing data were encountered in every analysis performed. We experienced that the method of multiple imputation performed better than other conventional methods, such as complete case analysis and mean substitution, when the reason for data being missing was dependent on patient characteristics. Therefore, we used this method in many chapters and the acquired knowledge is illustrated in the educational article presented in this chapter. **Chapter 12** contains a letter to the editor, commenting on statistical analyses performed in an article about the association of body mass index with disease progression in non-diabetic CKD patients.

Chapter 13 discusses and interprets the results presented in all previous chapters.

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Chapter 2 |

Association of blood pressure with decline in renal function and time until the start of renal replacement therapy in pre-dialysis patients: a cohort study

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Abstract

Background: To investigate whether high blood pressure accelerates renal function decline in patients with advanced chronic kidney disease (CKD), we studied the association of systolic (SBP) and diastolic blood pressure (DBP) with decline in renal function and time until the start of renal replacement therapy (RRT) in patients with CKD stages 4-5 on pre-dialysis care.

Methods: In the PRE-dialysis PATient REcord-1 (PREPARE-1) cohort 547 incident pre-dialysis patients, referred as part of the usual care to outpatient clinics of eight Dutch hospitals, were included between 1999 and 2001 and followed until the start of RRT, mortality, or end of follow-up (January 1, 2008). Main outcomes were rate of decline in renal function, estimated as the slope of available eGFR measurements, and time until the start of RRT.

Results: A total of 508 patients, 57% men and median (boundaries of interquartile range) age of 63 (50-73) years, were available for analyses. Mean $\pm$ standard deviation decline in renal function was 0.35 ± 0.75 ml/min/1.73 m²/month. Every 10 mmHg increase in SBP or DBP resulted in an accelerated decline in renal function (adjusted additional decline 0.04 [95% confidence interval (CI) 0.02;0.07] and 0.05 [95% CI 0.00;0.11] ml/min/1.73 m²/month respectively) and an earlier start of RRT (adjusted hazard ratio (HR) 1.09 [95% CI 1.04;1.14] and 1.16 [95% CI 1.05;1.28] respectively). Furthermore, patients with SBP and DBP above the BP target of <130/80 mmHg experienced a faster decline in renal function (adjusted additional decline 0.31 [95% CI 0.08;0.53] ml/min/1.73 m²/month) and an earlier start of RRT (adjusted HR 2.08 [95% CI 1.25;3.44]), compared with patients who achieved the target (11%). Comparing the decline in renal function and rate of starting RRT between patients with only SBP above the target (≥ 130 mmHg) and patients with both SBP and DBP below the target (<130/80 mmHg), showed that the results were almost similar as compared with patients with both SBP and DBP above the target (adjusted additional decline 0.31 [95% CI 0.04;0.58] ml/min/1.73 m²/month and adjusted HR 2.24 [95% CI 1.26;3.97]). Therefore, it seems that especially having SBP above the target is harmful.

Conclusion: In pre-dialysis patients with CKD stages 4-5, having blood pressure (especially SBP) above the target for CKD patients (<130/80 mmHg) was associated with a faster decline in renal function and an earlier start of RRT.

Background

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) are major public health problems worldwide because of rapidly increasing numbers of prevalent and incident cases.¹⁻³ The demand for pre-dialysis care is growing due to the increasing number of patients with late-stage CKD. Patients on pre-dialysis care need to be treated to slow down decline in renal function and to postpone the start of renal replacement therapy (RRT; dialysis and transplantation).

High blood pressure is an important independent predictor of decline in renal function in the general population⁴ and in several subgroups⁵⁻⁸. Furthermore, high blood pressure is also a risk factor for the progression to CKD⁹⁻¹⁰ and ESRD¹¹⁻¹⁴ in the general population. Once a person has developed early-stage CKD, blood pressure has a persisting detrimental effect on decline in renal function resulting in an accelerated progression to ESRD.¹⁵⁻¹⁹ However, little is known about the association of blood pressure with decline in renal function in patients with CKD stages 4-5 on pre-dialysis care.

Therefore, it is important to study the association of blood pressure with progression of CKD in patients with CKD stages 4-5 on pre-dialysis care. Guidelines from the Kidney Disease Outcomes Quality Initiative (K/DOQI), Seventh Report of the Joint National Committee (JNC 7), and the American Heart Association (AHA) propose a blood pressure treatment target of <130/80 mmHg through all stages of CKD.²⁰⁻²² Because the use of this proposed treatment target of <130/80 mmHg in pre-dialysis patients is not evidence-based, it is important to investigate whether this target is indeed beneficial in this specific population. Therefore, the aim of our study was to investigate the association of systolic (SBP) and diastolic blood pressure (DBP) with progression of CKD as assessed by decline in renal function and time until the start of RRT in patients with CKD stages 4-5 on pre-dialysis care.

Methods

Study design and participants

The PRE-dialysis Patient REcord-1 (PREPARE-1) study is a follow-up study in which consecutive incident adult patients with CKD stages 4-5 were included from outpatient clinics of eight Dutch hospitals when referred for pre-dialysis care between 1999 and 2001. Patients had been referred to these outpatient clinics if creatinine clearance was below 20 ml/min. Furthermore, in these patients the need for RRT was expected within one year. Patients who spent less than one month on pre-dialysis care and patients with prior RRT were excluded. The clinical course of pre-dialysis patients was followed through the medical charts until the start of dialysis, transplantation, death, or January 1, 2008, whichever was earliest. Predefined data on demography, anthropometry, and clinical symptoms were extracted from medical charts at inclusion. All available data concerning laboratory measurements during pre-dialysis care were extracted from the hospital information systems. The study was

approved by the Institutional Review Boards of the participating hospitals and conducted in concordance with Good Clinical Practice Guidelines.

Measurements and definitions

Blood pressure and variables used for adjustment in multivariable analyses were assessed at the first pre-dialysis visit (baseline) and measured according to the standard care applied in each individual hospital. The standard procedure for measuring blood pressure is using a device dependent on cuff occlusion of the arm, with the patient in sitting or lying position. The blood pressure treatment target was defined as SBP <130 mmHg and DBP <80 mmHg according to the K/DOQI, JNC 7, and AHA guidelines.²⁰⁻²² Estimated glomerular filtration rate (eGFR) was calculated using the four-variable Modification of Diet in Renal Disease (MDRD) formula, taking into account age, sex, race, and serum creatinine.²³ Baseline serum creatinine measurement was defined as the measurement closest to the start of pre-dialysis care, within 90 days before and 14 days after the start.

Outcomes

For the present analyses, the first year of pre-dialysis care was used as follow-up time because blood pressure was only assessed at baseline and blood pressure levels can change during pre-dialysis care. Therefore, we expect that the effect of baseline blood pressure on progression of CKD weakens after several years of follow-up. Outcomes were decline in renal function and time until the start of RRT. The rate of decline in renal function was estimated by fitting a regression line through the available eGFR measurements for each individual patient. This resulted in slopes expressing the monthly loss of eGFR. eGFR measurements between one month prior to inclusion and one year after inclusion were used and at least two measurements had to be available to estimate the rate of decline. Patients with eGFR measurements only available between one month prior to inclusion and one month thereafter were excluded from the analyses for decline in renal function (n=20). The start of RRT was defined as starting dialysis or being transplanted within the first year of pre-dialysis care.

Statistical analyses

Continuous data were expressed as mean $\pm$ standard deviation (SD) and skewed data as median (boundaries of interquartile range, IQR). Baseline characteristics were presented for the total study population and stratified in patients below or above the blood pressure treatment target. SBP and DBP were both analyzed in steps of 10 mmHg increase and in categories. We used clinically relevant categories for SBP (<130 (reference group), 130-149, 150-169, 170-189, and $\geq$ 190 mmHg) and for DBP (<80 (reference group), 80-89, 90-99, and $\geq$ 100 mmHg). The reference categories chosen were based on the treatment target of <130/80 mmHg. Furthermore, the range of the SBP and DBP categories (steps of 10 and 20 mmHg respectively) were selected by using the distribution of these variables, to end up with enough power in each category. Additionally, SBP and DBP were combined based on the

treatment target of <130/80 mmHg. The additional effect of having DBP above 80 mmHg on top of having SBP above 130 mmHg, compared with the single effect of SBP $\geq$ 130 mmHg or DBP $\geq$ 80 mmHg, was investigated. For this analysis, patients were stratified in four categories based on the combination of SBP and DBP (<130/<80 (reference group), $\geq$ 130/<80, <130/ $\geq$ 80, and $\geq$ 130/ $\geq$ 80 mmHg).

A linear regression analysis was used to assess the association of blood pressure with decline in renal function during the first year of follow-up. Multivariable analyses were used to adjust for the possible confounders age, sex, race, smoking, primary kidney disease, presence of cardiovascular disease (CVD; angina pectoris, coronary disease, and/or myocardial infarction), and presence of diabetes mellitus (DM).

The Kaplan-Meier method was used to estimate the crude rate and a Cox proportional hazard regression analysis was used to estimate the adjusted rate of starting RRT during the first year of pre-dialysis care. The rate of starting RRT was adjusted for the same confounders used in the multivariable linear regression analyses. The time from the first pre-dialysis visit until the start of RRT or end of the first year of follow-up was used in the Cox proportional hazard regression as follow-up time. Mortality and lost to follow-up were censored events. All p-values are two-tailed and $p < 0.05$ was considered statistically significant. Data were analyzed with PASW/SPSS version 17.

Multiple sensitivity analyses were performed. First, sensitivity analyses were performed with only the first six months or with complete follow-up (until January 1, 2008) instead of the first year of follow-up, to investigate whether differences in follow-up time lead to different results. Second, a sensitivity analysis was performed with SBP and DBP stratified in quartiles and quintiles to make sure that the associations found are robust and not dependent on the choice of categories. Third, it can be argued that our analyses should be additionally adjusted for proteinuria, hemoglobin, and baseline eGFR. However, data regarding proteinuria, hemoglobin, and baseline eGFR were not available for all patients included in the analyses ($n=405$, $n=444$, and $n=445$ respectively). Therefore, adjusting for these variables was only performed as a sensitivity analysis, in order to maintain power.

Results

Baseline characteristics

From the 547 incident pre-dialysis patients included, 525 patients had no prior RRT and spent more than one month on pre-dialysis care. SBP and DBP measurements at baseline were present for 508 patients and for 436 patients two or more eGFR measurements were available to estimate the rate of decline in renal function. Of these 508 patients, 89% had SBP and/or DBP above the blood pressure treatment target (SBP $\geq$ 130 mmHg and/or DBP $\geq$ 80 mmHg). Most of the patients on pre-dialysis care were referred by nephrologists (76%). This percentage was the same in patients below and patients above the target (78% and 76% respectively, Table 1). Patients with SBP and/or DBP above the target were older, smoked

more, had a slightly higher body mass index (BMI), lower eGFR, higher levels of proteinuria, and a higher prevalence of CVD (Table 1). At baseline, patients with an available estimated rate of decline in renal function (n=436) were slightly older, had a higher eGFR, lower levels of proteinuria, and less co-morbidities, than patients without available eGFR data (n=72).

Table 1: Demographic, anthropometric, and clinical characteristics at baseline for the total study population and stratified by reaching the blood pressure treatment target

	All n=508	Below target ¹ n=58	Above target ¹ n=450
Age (years)	63 (50-73)	55 (45-71)	64 (50-73)
Sex (% men)	57	57	56
Race (not Black, %)	97	97	96
Body mass index (kg/m ²) ²	26 ± 5	25 ± 4	26 ± 5
Smokers / quitters (%)	56	50	57
Primary kidney disease (%)			
Diabetes mellitus	17	16	17
Glomerulonephritis	10	14	9
Interstitial nephritis	16	17	15
Renal vascular disease/nephrosclerosis	23	17	23
Baseline eGFR (ml/min/1.73 m ²) ³	13.1 ± 5.8	14.0 ± 6.0	13.0 ± 5.7
Proteinuria (g/24h) ⁴	2.0 (0.7-3.9)	1.1 (0.6-2.9)	2.2 (0.8-4.0)
Hemoglobin (g/dl) ⁵	11.3 ± 1.6	11.4 ± 1.8	11.3 ± 1.6
Co-morbidities (%)			
Anemia ⁶	47	46	47
Cardiovascular disease ⁷	36	28	37
Diabetes mellitus	27	24	27
Malignancy	11	10	11
Referral to pre-dialysis care by nephrologist (%)	76	78	76

Median with boundaries of interquartile range is given for age and proteinuria and for the other continuous variables mean ± standard deviation is given. ¹ Below the target was defined as systolic blood pressure (SBP) <130 and diastolic blood pressure (DBP) <80 mmHg and above the target as SBP ≥130 and/or DBP ≥80 mmHg. ² Available for 472 patients. ³ Estimated glomerular filtration rate (eGFR) calculated with the four-variable Modification of Diet in Renal Disease formula and available for 445 patients. ⁴ Available for 405 patients. ⁵ Available for 444 patients. ⁶ Defined as a hemoglobin level <11 g/dl. ⁷ Defined as the presence of angina pectoris, coronary disease, and/or myocardial infarction.

Of all patients, 92% were treated with anti-hypertensive drugs at baseline. Patients below the blood pressure treatment target were primarily prescribed angiotensin-converting enzyme (ACE) inhibitors and/or diuretics whereas patients above the target were prescribed calcium-antagonists and beta-blockers just as often (Table 2). Angiotensin-II inhibitors were prescribed the least. Furthermore, the number of anti-hypertensive drug types was higher in patients above the blood pressure treatment target than in patients below the target. Of the patients treated with anti-hypertensive drugs, only 11% achieved the blood pressure treatment target of <130/80 mmHg.

Table 2: Blood pressure characteristics at baseline for the total study population and stratified by reaching the blood pressure treatment target

	All n=508	Below target ¹ n=58	Above target ¹ n=450
Systolic blood pressure (mmHg)	152 ± 27	114 ± 12	157 ± 25
Diastolic blood pressure (mmHg)	83 ± 14	68 ± 8	85 ± 13
Anti-hypertensive drug types (%)			
ACE-inhibitor	43	60	40
Angiotensin-II inhibitor	20	10	21
Beta-blocker	39	31	40
Calcium antagonist	45	22	48
Diuretics	48	52	48
Other ²	14	7	15
Number of anti-hypertensive drug types (%)			
0	8	9	8
1	26	35	24
2	28	33	28
≥3	38	23	40

ACE: angiotensin-converting enzyme. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) are presented as mean ± standard deviation. ¹ Below the target was defined as SBP <130 and DBP <80 mmHg and above the target as SBP ≥130 and/or DBP ≥80 mmHg. ² Defined as the prescription of alpha blocker, vasodilator, and/or central working agent.

Decline in renal function

The median (IQR) number of available eGFR measurements during the first year of follow-up was 9 (6-13) and 98.6% of the patients had three or more eGFR measurements. In the total group of 436 patients, mean ± SD decline in renal function was 0.35 ± 0.75 ml/min/1.73 m²/month. Mean ± SD decline in renal function was not dependent on the number of eGFR measurements and was 0.37 ± 0.89, 0.38 ± 0.62, 0.41 ± 0.72, and 0.26 ± 0.71 ml/min/1.73 m²/month for patients with 2-6, 7-9, 10-13 and ≥14 eGFR measurements (quartiles) respectively. The analysis of SBP in steps of 10 mmHg showed a linear association, every 10 mmHg increase in SBP resulted in an accelerated decline in renal function (crude additional decline 0.03 [95% confidence interval (CI) 0.01;0.06] ml/min/1.73 m²/month, Table 3). The analysis of SBP stratified in categories showed similar results, every consecutive category above the reference category of <130 mmHg (mean ± SD decline 0.22 ± 0.74 ml/min/1.73 m²/month) resulted in an accelerated decline in renal function (Table 3).

Every 10 mmHg increase in DBP also resulted in an accelerated decline in renal function (crude additional decline 0.07 [95% CI 0.02;0.12] ml/min/1.73 m²/month, Table 3). Furthermore, every consecutive category above the reference category of <80 mmHg (mean ± SD decline of 0.26 ± 0.90 ml/min/1.73 m²/month) resulted in an accelerated decline in renal function. However, the most pronounced decline in renal function was present in patients with DBP ≥100 mmHg.

Using the blood pressure treatment target (SBP <130 mmHg and DBP <80 mmHg) showed that patients with SBP and/or DBP above the target had an accelerated decline in renal

function compared with patients with SBP and DBP below the target (mean $\pm$ SD decline 0.13 ± 0.85 ml/min/1.73 m²/month). Adjustment for confounders did not change these results essentially (Table 3).

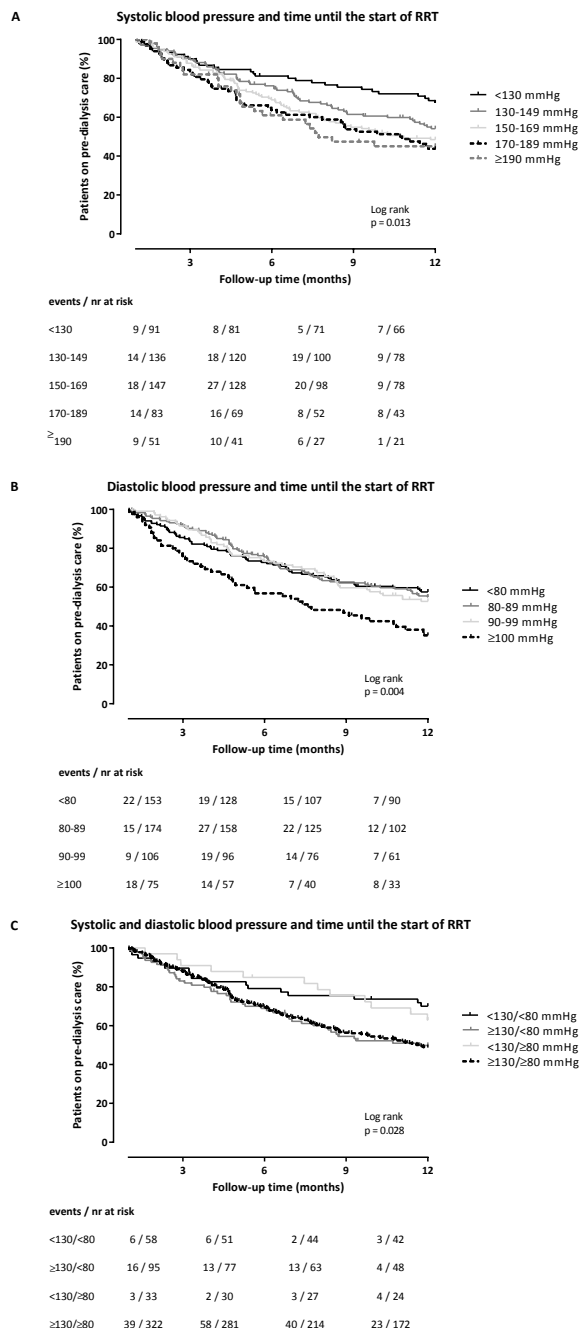
Table 3: Association of systolic and diastolic blood pressure with decline in renal function during the first year of pre-dialysis care

	n	Baseline eGFR ¹ (ml/min/ 1.73 m ²)	Crude additional decline [95% CI] (ml/min/ 1.73 m ² /month)	Adjusted additional decline ² [95% CI] (ml/min/ 1.73 m ² /month)	Adjusted additional decline ³ [95% CI] (ml/min/ 1.73 m ² /month)
<u>Systolic blood pressure (mmHg):</u>					
Per 10	436		0.03 [0.01;0.06]	0.04 [0.02;0.07]	0.04 [0.02;0.07]
<130	79	14.0	0 ⁴	0	0
130-149	116	12.8	0.13 [-0.09;0.34]	0.15 [-0.06;0.36]	0.14 [-0.07;0.35]
150-169	125	12.7	0.14 [-0.08;0.35]	0.19 [-0.02;0.39]	0.17 [-0.04;0.38]
170-189	72	14.2	0.19 [-0.05;0.43]	0.27 [0.04;0.51]	0.24 [0.00;0.48]
≥190	44	13.3	0.34 [0.06;0.61]	0.44 [0.16;0.71]	0.43 [0.15;0.70]
<u>Diastolic blood pressure (mmHg):</u>					
Per 10	436		0.07 [0.02;0.12]	0.05 [0.00;0.10]	0.05 [0.00;0.11]
<80	122	13.4	0 ⁵	0	0
80-89	151	13.7	0.08 [-0.10;0.26]	0.06 [-0.12;0.23]	0.07 [-0.11;0.25]
90-99	98	13.3	0.12 [-0.07;0.32]	0.12 [-0.08;0.31]	0.12 [-0.08;0.32]
≥100	65	11.9	0.29 [0.07;0.52]	0.23 [0.00;0.45]	0.22 [-0.01;0.44]
<u>Blood pressure treatment target (mmHg):</u>					
<130/<80	47	14.2	0 ⁶	0	0
≥130/<80	75	13.0	0.21 [-0.07;0.48]	0.31 [0.04;0.58]	0.31 [0.04;0.58]
<130/≥80	32	13.8	0.22 [-0.12;0.55]	0.21 [-0.12;0.54]	0.26 [-0.08;0.59]
≥130/≥80	282	13.1	0.27 [0.04;0.50]	0.30 [0.08;0.53]	0.31 [0.08;0.53]

The decline [95% confidence interval (CI)] presented for each blood pressure category indicates the additional decline in renal function compared with the reference category (systolic blood pressure (SBP) <130 mmHg, diastolic blood pressure (DBP) <80 mmHg, and SBP/DBP <130/<80 mmHg). A negative decline is equivalent to a slower decline in renal function. ¹ The mean estimated glomerular filtration rate (eGFR) in ml/min/1.73 m² at baseline. ² Adjusted for sex and age. ³ Adjusted for sex, age, race, smoking, primary kidney disease, and the co-morbidities cardiovascular disease and diabetes mellitus. ⁴ The mean $\pm$ standard deviation (SD) decline in renal function is 0.22 ± 0.74 ml/min/1.73 m²/month. ⁵ The mean $\pm$ SD decline in renal function is 0.26 ± 0.90 ml/min/1.73 m²/month. ⁶ The mean $\pm$ SD decline in renal function is 0.13 ± 0.85 ml/min/1.73 m²/month.

Start of renal replacement therapy

During the first year of follow-up, of all patients 23% started hemodialysis and 22% peritoneal dialysis, 1% was transplanted, 5% died, 1% was lost to follow-up while 48% were still on pre-dialysis care. Median (IQR) follow-up time was 351 (144-365) days, while follow-up time in patients starting RRT was 145 (87-234) days. In patients below and above the blood pressure treatment target at baseline, mean eGFR was 6.7 and 8.2 ml/min/1.73 m² at the start of RRT respectively. The crude association of SBP and DBP categories with time until the start of RRT is shown in Figure 1A and 1B respectively.

Figure 1: Kaplan-Meier curve for time until the start of renal replacement therapy

Kaplan-Meier curve for the association of systolic blood pressure (SBP), diastolic blood pressure (DBP) and the combination of SBP and DBP with time until the start of renal replacement therapy (RRT) during the first year of follow-up in pre-dialysis patients. Follow-up time in months (during the first year of follow-up) on the x-axis and the percentage of patients on pre-dialysis care on the y-axis is plotted and stratified by SBP (A), DBP (B), and SBP/DBP (C) blood pressure categories. The numbers below the figures give the number of patients 'at risk' (n) and the events in each blood pressure category for three-month intervals.

Table 4 shows the crude and the adjusted hazard ratios (HRs) for every 10 mmHg increase in SBP and DBP, and for clinically relevant blood pressure categories compared with the reference category of SBP <130 mmHg or DBP <80 mmHg respectively. Patients with higher SBP had an earlier start of RRT. On a continuous scale, every 10 mmHg increase in SBP resulted in an earlier start of RRT (crude HR 1.08 [95% CI 1.03;1.13]). Furthermore, the adjusted rate of starting RRT was 1.60 fold higher [95% CI 1.02;2.50] in patients with SBP 130-149 mmHg compared with patients with SBP <130 mmHg (Table 4). For DBP, every 10 mmHg increase resulted in an earlier start of RRT (crude HR 1.15 [95% CI 1.04;1.27]). The analysis with categories showed that only patients with DBP ≥100 mmHg had a pronounced earlier start of RRT (crude HR 1.84 [95% CI 1.26;2.69], Table 4 and Figure 1B).

Table 4: Association of systolic and diastolic blood pressure with time until the start of renal replacement therapy during the first year of pre-dialysis care

	Events/n	Crude HR [95% CI]	Adjusted HR ¹ [95% CI]	Adjusted HR ² [95% CI]
<u>Systolic blood pressure (mmHg):</u>				
Per 10	235/508	1.08 [1.03;1.13]	1.09 [1.04;1.14]	1.09 [1.04;1.14]
<130	29/91	1	1	1
130-149	60/136	1.52 [0.97;2.36]	1.54 [0.99;2.41]	1.60 [1.02;2.50]
150-169	74/147	1.82 [1.19;2.80]	1.88 [1.22;2.90]	1.96 [1.27;3.02]
170-189	46/83	2.09 [1.31;3.32]	2.20 [1.37;3.53]	2.25 [1.40;3.63]
≥190	26/51	2.10 [1.24;3.57]	2.27 [1.33;3.90]	2.21 [1.28;3.80]
<u>Diastolic blood pressure (mmHg):</u>				
Per 10	235/508	1.15 [1.04;1.27]	1.15 [1.04;1.27]	1.16 [1.05;1.28]
<80	63/153	1	1	1
80-89	76/174	1.02 [0.73;1.43]	1.03 [0.74;1.44]	1.05 [0.75;1.48]
90-99	49/106	1.09 [0.75;1.58]	1.11 [0.76;1.62]	1.11 [0.76;1.62]
≥100	47/75	1.84 [1.26;2.69]	1.85 [1.26;2.71]	1.88 [1.27;2.78]
<u>Blood pressure treatment target (mmHg):</u>				
<130/<80	17/58	1	1	1
≥130/<80	46/95	1.93 [1.11;3.37]	2.03 [1.15;3.57]	2.24 [1.26;3.97]
<130/≥80	12/33	1.18 [0.56;2.47]	1.18 [0.56;2.47]	1.31 [0.62;2.78]
≥130/≥80	160/322	1.91 [1.16;3.16]	1.96 [1.19;3.23]	2.08 [1.25;3.44]

The hazard ratio (HR) [95% confidence interval (CI)] presented for each blood pressure category indicates the increased rate of starting renal replacement therapy compared with the reference category (systolic blood pressure (SBP) <130 mmHg, diastolic blood pressure (DBP) <80 mmHg, and SBP/DBP <130/<80 mmHg). ¹ Adjusted for sex and age. ² Adjusted for sex, age, race, smoking, primary kidney disease, and the co-morbidities cardiovascular disease and diabetes mellitus.

Using the blood pressure treatment target (SBP <130 mmHg and DBP <80 mmHg) showed that patients with SBP above the target and DBP below the target started RRT earlier (crude HR 1.93 [95% CI 1.11;3.37]) compared with patients with both SBP and DBP below the target (Table 4 and Figure 1C). Patients with SBP <130 mmHg (below target) and DBP ≥80 mmHg (above target) had a similar rate of starting RRT as the reference group (patients with SBP <130 mmHg and DBP <80 mmHg). Having both SBP and DBP above the treatment target resulted in a higher rate of starting RRT (crude HR 1.91 [95% CI 1.16;3.16]) compared with having both SBP and DBP below the target. Adjustment for confounders did not change these results essentially (Table 4).

Sensitivity analyses

To test the robustness of our findings, several sensitivity analyses were performed. First, in a sensitivity analysis with only six months of follow-up, results of the primary analyses were confirmed and point estimates were similar. Analyses with complete follow-up showed the same trend as in the primary analyses, however the associations were somewhat diluted. Every 10 mmHg increase in SBP or DBP resulted in an accelerated decline in renal function (adjusted additional decline 0.04 [95% CI 0.01;0.07] and 0.05 [95% CI 0.00;0.11] ml/min/1.73 m²/month respectively) and an earlier start of RRT (HR 1.07 [95% CI 1.03;1.11] and 1.10 [95% CI 1.01;1.19] respectively). Second, other choices of blood pressure categories showed the same results as found in the primary analyses. Third, when including the covariates proteinuria, hemoglobin, and baseline eGFR in the model (sample size of 404 patients), the point estimates for decline in renal function and time until the start of RRT remained similar. With every 10 mmHg increase in SBP or DBP, decline in renal function accelerates (adjusted additional decline 0.04 [95% CI 0.02;0.07] and 0.07 [95% CI 0.02;0.12] ml/min/1.73 m²/month respectively) and the start of RRT is earlier (HR 1.07 [95% CI 1.01;1.13] and 1.17 [95% CI 1.04;1.31] respectively).

Discussion

The results of this study show that 89% of the patients with CKD stages 4-5 starting pre-dialysis care did not reach the blood pressure treatment target of SBP <130 mmHg and DBP <80 mmHg, even though the majority of these patients (92%) were treated with anti-hypertensive drugs. Both higher SBP and DBP were associated with a faster progression of CKD. More specific, patients with SBP ≥130 mmHg or DBP ≥100 mmHg had an accelerated decline in renal function (eGFR) during pre-dialysis care which was accompanied by an earlier start of RRT, compared with patients with SBP <130 mmHg or DBP <100 mmHg. Further analysis showed that in patients with SBP above the target (≥130 mmHg), additionally having DBP above the target (≥80 mmHg) did not result in an accelerated decline in renal function or an earlier start of RRT.

Our study is the first European study to report on the association of both SBP and DBP with the progression of CKD, as assessed by decline in renal function and time until the start of RRT, in a well-defined population of pre-dialysis patients with CKD stages 4-5. Every 10 mmHg increase in SBP or DBP resulted in an accelerated decline in renal function (adjusted additional decline 0.04 [95% CI 0.02;0.07] and 0.05 [95% CI 0.00;0.11] ml/min/1.73 m²/month respectively). Our data are in line with the findings of several observational studies such as the MDRD study,²⁴ which showed that an increased mean arterial pressure is associated with an accelerated decline in renal function in patients with an eGFR between 13 and 24 ml/min/1.73 m². However, CKD patients with an eGFR below 13 ml/min/1.73 m² were excluded from the MDRD study because they were likely to start dialysis before the effect of diet and blood pressure control could be evaluated.²⁵ Furthermore, patients with severe comorbidities were excluded and the patient population in the MDRD study consisted mostly of

patients with polycystic kidney disease. Our patients may therefore be more representative of patient populations as seen by treating physicians in outpatient clinics, as our patient selection did not restrict on etiology of the primary kidney disease, level of eGFR or severity of co-morbidities. The results of our study also showed that every 10 mmHg increase in SBP or DBP respectively resulted in an adjusted 1.09 [95% CI 1.04;1.14] and 1.16 [95% CI 1.05;1.28] fold increased rate of starting RRT earlier. These results are in line with a study performed by Levin *et al.*²⁶, who found that every 5 mmHg increase in SBP or DBP resulted in an earlier start of RRT (HR 1.02 [95% CI 1.00;1.04] and 1.05 [95% CI 1.01;1.09] respectively) in a Canadian cohort of patients on pre-dialysis care (CKD stages 4-5, n=4,231).

Our data are not in line with some previous published interventional trials on the effect of lowering blood pressure in CKD patients.²⁷⁻²⁹ These studies showed that in patients with CKD stages 3-5 intensive blood pressure lowering (<130/80 mmHg versus <140/90 mmHg) was not beneficial on the progression of CKD, defined as decline in renal function or time until the start of dialysis, transplantation, death and/or doubling of serum creatinine. There are several possible explanations for these contradictory findings. First, the study populations of the trials differ from our study population because the trials mainly consist of patients with CKD stage 3 and our observational cohort consists of patients with advanced stages of CKD (4-5). Furthermore, the trials apply many patient exclusion criteria that will result in a relatively more healthy study population compared with our cohort. Second, the achieved blood pressure target in the intensively treated patients (<130/80 mmHg) had a large overlap with the normal treated patients (<140/90 mmHg). This finding suggests that blood pressure control is very difficult in patients with advanced stages of CKD and this can explain the high percentage (89%) of pre-dialysis patients in our cohort not reaching the treatment target, which is in line with another study.³⁰ It can be reasoned that blood pressure control is easier to achieve in patients with early stages of CKD, as shown by Nakayama *et al.*³¹ Finally, the trials found that the effect of lowering blood pressure was beneficial in patients with more severe proteinuria and our cohort mainly consists of patients with proteinuria (89%).

The PREPARE-1 study has potential strengths and limitations. First, in our cohort an equal number of patients started hemodialysis and peritoneal dialysis and therefore the results cannot be generalized to the United States pre-dialysis population. Furthermore, it has been estimated that in the general population 36-65% of the patients with an eGFR below 15 ml/min/1.73 m² are not treated by a nephrologist.³² Therefore, perhaps our results cannot be generalized to all patients with an eGFR below 15 ml/min/1.73 m², but only to those receiving pre-dialysis care. However, for clinical practice our cohort is a very representative and relevant population. Second, for estimating the rate of decline in renal function, we assumed that the decline in renal function is linear in advanced CKD stages. It has been shown previously that linearity of the course in eGFR is a plausible assumption, although on theoretical grounds over a longer period of time an exponential decline could be present.²⁴ Third, SBP and DBP were collected only once at the start of pre-dialysis care. This may lead to less precision and more variability of the SBP and DBP measurement at baseline, possibly

resulting in underestimated effects. Furthermore, blood pressure may change during pre-dialysis care. A time-dependent analysis with time varying blood pressure would be more accurate compared with an analysis with only one blood pressure measurement at baseline. However, such data were not available in our study. As an alternative, we showed that when using follow-up of six months the association of blood pressure with decline in renal function and time until the start of RRT remained similar, whereas the results were somewhat diluted when using complete follow-up. The latter may indeed suggest that blood pressure changes over time. We chose to use the first year of follow-up in our primary analyses in order to have a more precise estimation of the association of blood pressure with decline in renal function and time until the start of RRT. Fourth, it is possible that the association of blood pressure with progression of CKD is confounded by the prognosis of patients. However, baseline characteristics showed that referral of patients is mainly done by nephrologists and this percentage is comparable between patients below and above the blood pressure treatment target, which may give an indication that prognosis is similar. Furthermore, adjustment for sex, age, race, smoking, primary kidney disease, co-morbidities, hemoglobin, eGFR, and proteinuria eliminated a part of this confounding effect, but we cannot exclude some residual confounding of our effect measures. Adjustment for decline in renal function prior to starting pre-dialysis care was not possible because too few eGFR measurements were available. Fifth, the aim of this study was to investigate the association of baseline blood pressure with progression of CKD irrespective of blood pressure control by medication. Therefore, the definition of the blood pressure treatment target was solely based on blood pressure and results were not adjusted for the use of anti-hypertensive drugs. Finally, data regarding proteinuria, hemoglobin, and baseline eGFR were not available for all patients. Therefore, in order to maintain power and to avoid selection bias, we chose not to include these variables into our primary analyses. However, after adjustment for these covariates the point estimates for decline in renal function and time until the start of RRT remained similar.

What could be an explanation for the found association of hypertension with an accelerated decline in renal function and an earlier start of RRT? Endothelial dysfunction is a pathological consequence of hypertension³³ leading to vessel damage, causing atherosclerosis, and subsequently arterial stiffness. Arterial stiffness in turn can lead to an increased afterload, left ventricular hypertrophy, reduced coronary perfusion, congestive heart failure, and altered or reduced blood supply to tissues including the kidney.³⁴ In pre-dialysis patients, arterial stiffness can lead to glomerular hypertension and thereby increased glomerular permeability and excessive filtration of proteins. Protein ultrafiltrates are toxic to the proximal tubules, resulting in tubular damage and scarring. Glomerular hypertension and increased ultrafiltration of proteins contribute to the progression of chronic renal damage and thereby renal function.³⁵ It is also possible that blood pressure increases as the result of an accelerated decline in renal function, resulting in a vicious circle between blood pressure increase and decline in renal function. In our cohort, arterial stiffness seems a plausible explanation because with increasing pulse pressure, which is a marker for arterial stiffness,

decline in renal function accelerated and time until the start of RRT decreased (data not shown).

The proposed blood pressure treatment target for patients with CKD is <130/80 mmHg, according to the K/DOQI, JNC 7, and AHA treatment guidelines for hypertension in CKD patients.²⁰⁻²² The results of our study show that pre-dialysis patients with blood pressure below this target have the slowest decline in renal function and the latest start of RRT. Our results support the beneficial effect of keeping blood pressure levels, especially for SBP, below this treatment target at the start of pre-dialysis care. Randomized controlled trials are necessary to demonstrate whether active blood pressure lowering below this target is beneficial in pre-dialysis patients.

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Chapter 3 |

Association of blood pressure with the start of renal replacement therapy in elderly compared with young patients receiving pre-dialysis care

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Abstract

Background: In the growing elderly pre-dialysis population, little is known about the effect of identified risk factors on the progression to end-stage renal disease. Therefore, we investigated the association of systolic (SBP) and diastolic blood pressure (DBP) with the start of renal replacement therapy (RRT), in elderly (≥ 65 years) compared with young (< 65 years) pre-dialysis patients.

Methods: In the PRE-dialysis PATient REcord-1 (PREPARE-1) cohort, 547 incident pre-dialysis patients, referred as part of the usual care to eight Dutch outpatient clinics, were included (1999-2001) and followed until the start of dialysis, transplantation, death, or until January 1, 2008. The outcome was the start of RRT. All analyses were stratified by age; < 65 years (young) and ≥ 65 years (elderly).

Results: In young pre-dialysis patients ($n=268$) higher SBP (every 20 mmHg increase) and high DBP (DBP ≥ 100 mmHg compared with 80-89 mmHg) were associated with a higher rate of starting RRT (adjusted hazard ratio (HR) 1.21 [95% confidence interval (CI) 1.09;1.34] and 1.74 [95% CI 1.16;2.62] respectively). However, in elderly pre-dialysis patients ($n=240$) only patients with SBP ≥ 180 mmHg had an increased rate compared with patients with 140-159 mmHg (adjusted HR 2.33 [95% CI 1.41;3.87]). Furthermore, patients with DBP < 70 or ≥ 100 mmHg had an increased rate of starting RRT, independent of SBP, compared with patients with 80-89 mmHg (fully-adjusted HR 1.72 [95% CI 1.01;2.94] and 2.05 [95% CI 1.13;3.73] respectively).

Conclusion: The association of SBP and DBP with the start of RRT is different between elderly and young pre-dialysis patients.

Introduction

Worldwide, the elderly population (≥ 65 years) is growing because of increased longevity and better treatment of morbidities.^{1,2} With increasing age, renal function declines with ~ 0.4 ml/min/1.73 m²/year from the age of eighteen years.³ Besides this, in general the prevalence of risk factors that accelerate renal function decline (RFD), such as hypertension⁴ and diabetes mellitus⁵ are rising. Therefore, the prevalence of elderly patients with chronic kidney disease (CKD) and end-stage renal disease has increased over the last decades and will continue to increase.⁶ The demand for pre-dialysis care in elderly CKD patients is growing due to this increasing number of elderly late-stage CKD patients. To formulate evidence-based treatment guidelines for elderly pre-dialysis patients, further studies should focus on the effect of known risk factors for an accelerated progression of CKD in this specific population.

High blood pressure (BP) is a known and important risk factor, independent of other cardiovascular risk factors, for accelerated RFD in the general population⁷ and throughout all stages of CKD⁸⁻¹³. However, studies performed in the 'healthy' elderly population have shown that low rather than high BP is associated with both higher mortality and an accelerated RFD. Moreover, high BP even seems protective for mortality and RFD in elderly 'healthy' subjects.¹⁴⁻¹⁷ Such an inverse association of BP (systolic, SBP, and diastolic, DBP) with mortality is also present in patients on dialysis¹⁸⁻²⁴ and might be present in late-stage CKD (stages 3-5) patients²⁵.

Unfortunately, at the moment an evidence-based BP treatment guideline for the growing elderly pre-dialysis population is lacking. Moreover, there are some indications that low BP may result in an accelerated RFD in elderly pre-dialysis patients. Therefore, target BP levels may differ between the young and elderly. As a consequence, the aim of our study was to investigate the association of BP (SBP and DBP) with the start of renal replacement therapy (RRT; dialysis and transplantation) in patients with CKD stages 4-5 on pre-dialysis care, stratified in young (< 65 years) and elderly (≥ 65 years) patients. Furthermore, we used the rate of RFD as secondary outcome.

Methods

Study design and participants

The PRE-dialysis PATient REcord-1 (PREPARE-1) study is a follow-up study in which incident adult patients with CKD stages 4-5 were included at referral to pre-dialysis care between 1999 and 2001. Referral to these outpatient clinics of eight Dutch hospitals was indicated if patients were expected to need RRT within one year and if their estimated creatinine clearance was below 20 ml/min. Patients who spent less than one month on pre-dialysis care and patients with prior RRT were excluded. The clinical course of pre-dialysis patients was followed through the medical charts from the start of pre-dialysis care until the start of dialysis, transplantation, death, lost to follow-up or end of study (January 1, 2008), whichever was

earliest. Predefined data on demography, anthropometry, and clinical symptoms were extracted from medical charts at inclusion and at the end of follow-up. All available data concerning laboratory measurements during the whole pre-dialysis period were extracted from the hospital information systems until January 1, 2003. The study was approved by the Institutional Review Boards of the participating hospitals and conducted in concordance with Good Clinical Practice Guidelines.

Measurements and definitions

BP and the variables used for adjustment in the multivariable analyses were baseline values assessed at the first pre-dialysis visit and measured according to the standard care applied in each individual outpatient clinic. In The Netherlands, the most standard procedures for measuring BP are the use of cuff occlusion of the arm, auscultation method or occasionally the use of a device, with the patient in sitting position. Hypertension at baseline was defined as SBP ≥ 130 mmHg or DBP ≥ 80 mmHg, and further divided into modest controlled hypertension (SBP 130-149 mmHg or DBP 80-89 mmHg) and poor controlled hypertension (SBP ≥ 150 mmHg or DBP ≥ 90 mmHg).²⁶ Estimated glomerular filtration rate (eGFR) was calculated using the four-variable Modification of Diet in Renal Disease formula, taking into account age, sex, race, and measured serum creatinine.²⁷ Baseline serum creatinine, hemoglobin, and proteinuria measurements were defined as the measurement closest to the start of pre-dialysis care, within 90 days before and 14-30 days after the start.

Outcome

The outcome was the start of RRT during complete follow-up (until January 1, 2008). As a secondary outcome we used rate of RFD (ml/min/1.73 m²/month) during complete follow-up. Not for all included patients this decline was calculated during complete follow-up because eGFR measurements were only extracted until January 1, 2003, and 96 patients had not reached an endpoint on that date. However, it is reliable to assume that the RFD followed a linear pattern²⁸ before and after this date. The method used for the estimation of the rate of RFD has been described in detail previously.¹³ In short, a linear regression line was fitted through the available eGFR measurements for each individual patient. The slope of this line expresses the monthly loss of eGFR.

Statistical analyses

Continuous data were expressed as mean $\pm$ standard deviation (SD) and skewed data as median (boundaries of interquartile range, IQR). All analyses were performed after stratification by age (<65 and ≥ 65 years), and SBP and DBP were analyzed in categories and continuously, only when the association was linear. The cutoff point of 65 years to define young and elderly patients was based both on literature and the median age (63 years) in our cohort. The following categories were used for SBP (<120, 120-139, 140-159 (reference), 160-179, and ≥ 180 mmHg) and for DBP (<70, 70-79, 80-89 (reference), 90-99, and ≥ 100 mmHg). A Cox proportional hazard regression analysis was used to investigate the association of SBP

and DBP with the start of RRT. In all analyses, mortality and lost to follow-up were censored events. For the secondary outcome rate of RFD, the crude median (IQR) rate of RFD was calculated for all categories used in the Cox proportional hazard regression analyses. We reported median (IQR) because RFD was not normally distributed. With a non-parametric test (Kruskal-Wallis) we investigated whether the crude median RFD differed between the categories. For all Cox proportional hazard regression analyses, multivariable models were used to adjust for possible confounders such as age, sex, race, smoking, primary kidney disease, presence of cardiovascular co-morbidities (cardiovascular disease: i.e. angina pectoris, coronary disease, myocardial infarction, left ventricular hypertrophy, and congestive heart failure), diabetes mellitus, malignancy, pulmonary disease, baseline eGFR, proteinuria level, and hemoglobin level. In the fully-adjusted model investigating the association of DBP in categories with the start of RRT, we also included continuous SBP. This was done to check whether the effect of DBP was independent of SBP. For the two age-categories, the correlation between SBP and DBP was 0.628 in young and 0.500 in elderly patients. These values are both below the cutoff point of 0.700 used to check whether collinearity can be of great influence on the results of a regression model.²⁹ For body mass index, baseline eGFR, proteinuria level, and hemoglobin level there were subjects with missing values (n=36, n=63, n=103, and n=64 respectively). These missing values were imputed with multiple imputation (using five repetitions),^{30;31} a recommended technique where missing data for a patient are imputed by a value that is predicted by other known characteristics of this patient (i.e. demographic, anthropometric, clinical characteristics, and outcome). Furthermore, two sensitivity analyses were performed. First, we repeated all analyses using as determinants the average of the BP measurement at the start and at the end of follow-up, both SBP and DBP, divided into the same categories as mentioned above. Second, we repeated all analyses with SBP and DBP as single and quadratic continuous variables to test whether a U-shaped association was present. Including SBP and DBP as a continuous instead of a categorical variable in the model will result in more statistical power. All p-values were two-tailed and $p < 0.05$ was considered statistically significant. Data were analyzed with PASW/SPSS version 17 (SPSS, Chicago, IL).

Results

Baseline characteristics

From the 547 incident pre-dialysis patients included, 525 patients had no prior RRT and spent more than one month on pre-dialysis care. SBP and DBP measurements at baseline were available for 508 patients who were included in our statistical analyses. Of these patients, 53% were younger than 65 years (young) and 47% were 65 years or older (elderly). Elderly compared with young patients had a higher SBP, lower DBP, higher eGFR, lower levels of proteinuria, and higher prevalence of co-morbidities (Tables 1 and 2).

Of all patients, 92% were treated with anti-hypertensive drugs. Of the elderly patients, 45% received three or more different types of anti-hypertensive drugs, while among the young patients this was only 32% (Table 2). According to the type of medication, an angiotensin-converting enzyme inhibitor (ACEi) was prescribed less often, an angiotensin-II receptor blocker (ARB) just as often, and other types of anti-hypertensive medication more frequently in elderly compared with young patients.

The median (IQR) follow-up time was 53 (23-99) weeks in young and 43 (20-99) weeks in elderly patients. For the time until the start of RRT these numbers were 50 (21-81) and 34 (18-89) weeks, respectively. During complete follow-up, 40% of the young patients started hemodialysis and 43% peritoneal dialysis, 7% were transplanted, 4% died, and 6% were lost to follow-up. In elderly patients, 46% started hemodialysis and 27% peritoneal dialysis, 0% was transplanted, 20% died, and 7% were lost to follow-up.

Table 1: Demographic, anthropometric, and clinical characteristics at baseline for the total study population and stratified in young and elderly patients

	Total population n=508	Young patients (<65 years) n=268	Elderly patients (≥65 years) n=240
Age (years)	63 (50-73)	50 (40-57)	73 (69-77)
Sex (% men)	57	53	60
Race (not Black, %)	97	94	99
Body mass index (kg/m ²) ¹	25.8 ± 4.7	25.3 ± 4.8	26.3 ± 4.5
Smokers / quitters (%)	56	52	60
Primary kidney disease (%) ²			
Diabetes mellitus	17	14	20
Glomerulonephritis	10	14	5
Interstitial nephropathy	16	17	14
Renal vascular disease/nephrosclerosis	23	15	31
Baseline eGFR (ml/min/1.73 m ²) ³	13.2 ± 5.8	12.7 ± 5.4	13.8 ± 6.2
Proteinuria (g/24h) ¹	2.0 (0.7-3.9)	2.4 (0.8-4.2)	1.8 (0.7-3.4)
Hemoglobin (g/dl) ¹	11.3 ± 1.6	11.4 ± 1.7	11.3 ± 1.6
Co-morbidities (%)			
Cardiovascular disease ⁴	48	35	64
Diabetes mellitus ⁵	27	17	38
Malignancy	11	6	17
Pulmonary disease	15	10	21

Median (boundaries of interquartile range) is given for age and proteinuria and for the other continuous variables mean ± standard deviation is given. ¹ Body mass index was available for 472, proteinuria for 405, and hemoglobin level for 444 patients. ² Classified into seven categories according to the European Renal Association / European Dialysis and Transplantation Association. ³ Estimated glomerular filtration rate (eGFR) is calculated with the four-variable Modification of Diet in Renal Disease formula and available for 445 patients. ⁴ Defined as presence of angina pectoris, coronary disease, congestive heart failure, left ventricular hypertrophy, and myocardial infarction. ⁵ Defined as the presence of diabetes mellitus as primary kidney disease or co-morbidity.

Table 2: Blood pressure characteristics at baseline for the total study population and stratified in young and elderly patients

	Total population n=508	Young patients (<65 years) n=268	Elderly patients (≥65 years) n=240
Systolic blood pressure (mmHg)	152 ± 27	148 ± 28	157 ± 26
Diastolic blood pressure (mmHg)	83 ± 14	86 ± 14	80 ± 13
Pulse pressure (mmHg)	69 ± 23	62 ± 22	77 ± 23
Hypertension (%) ¹			
Moderate controlled	26	28	24
Poor controlled	63	59	67
Isolated hypertension (%) ²	39	28	51
Anti-hypertensive drug types (%)			
ACE-inhibitor	43	47	38
Angiotensin-II receptor blocker	20	19	20
Beta-blocker	39	36	41
Calcium antagonist	45	42	49
Diuretic	48	43	54
Other ³	14	12	17
Number of anti-hypertensive drug types (%)			
0	8	8	8
1	26	29	22
2	28	31	25
≥3	38	32	45

ACE: angiotensin-converting enzyme. Systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure are given as mean ± standard deviation. ¹ Defined as moderate controlled (SBP 130-149 mmHg or DBP 80-89 mmHg) and poor controlled hypertension (SBP ≥150 mmHg or DBP ≥90 mmHg). ² Defined as SBP ≥140 mmHg and DBP <90 mmHg. ³ Defined as prescription of an alpha blocker, vasodilator, or central working agent.

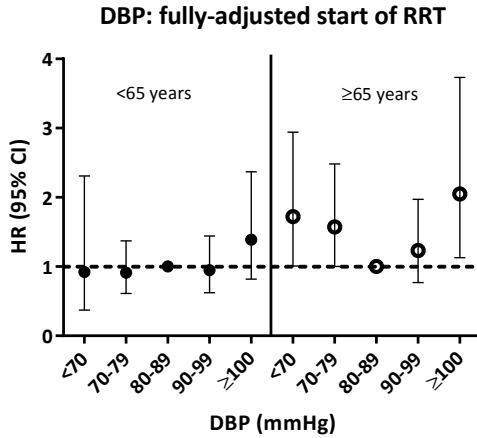
Association of BP with the start of RRT

Young patients with SBP <120 mmHg had a lower rate of starting RRT compared with young patients with SBP 140-159 mmHg (adjusted hazard ratio (HR) 0.81 [95% confidence interval (CI) 0.47;1.42], Table 3). Young patients with a SBP ≥180 mmHg had a higher rate of starting RRT compared with young patients with SBP 140-159 mmHg. Analyzing SBP in categories of 20 mmHg resulted in the same pattern, every 20 mmHg increase in SBP was associated with a higher rate of starting RRT (adjusted HR 1.21 [95% CI 1.09;1.34]). Young patients with DBP ≥100 mmHg had an adjusted 1.74 [95% CI 1.16;2.62] fold increased rate of starting RRT than young patients with DBP 80-89 mmHg (Table 4). This effect was diluted after including SBP in the model (Figure 1).

Elderly patients with SBP <120 mmHg had an increased rate of starting RRT compared with elderly patients with SBP 140-159 mmHg (adjusted HR 2.82 [95% CI 1.21;6.59], Table 3). However, the number of patients (n=12) and events (n=9) in the category SBP <120 mmHg were too small to draw firm conclusions. In line with the results found for young patients with a high SBP, elderly patients with SBP ≥180 mmHg had a higher rate of starting RRT, compared with the reference category (elderly patients with SBP 140-159 mmHg). The association of

DBP with the start of RRT in elderly patients showed a U-shaped pattern because elderly patients with DBP <70 mmHg (adjusted HR 1.60 [95% CI 0.95;2.70]) or ≥100 mmHg (adjusted HR 2.32 [95% CI 1.33;4.04]) had an increased rate compared with elderly patients with DBP 80-89 mmHg (Table 4). Including SBP in the model resulted in an even stronger U-shaped pattern (fully-adjusted HR 1.72 [95% CI 1.01;2.94] and 2.05 [95% CI 1.13;3.73] respectively, Figure 1).

Figure 1: Association of diastolic blood pressure with the rate of starting renal replacement therapy



Association of diastolic blood pressure (DBP) with the rate of starting renal replacement therapy (RRT), fully-adjusted; including systolic blood pressure (SBP), in young (<65 years, left part of graph, closed dots) and elderly (≥65 years, right part of graph, open dots) pre-dialysis patients. The hazard ratio (HR, closed or open black dot) and its 95% confidence interval (95% CI, black lines) gives the increased rate of starting RRT for each category compared to the reference category (80-89 mmHg) stratified by age. The HRs are adjusted for sex, race, smoking, primary kidney disease, cardiovascular disease, diabetes mellitus, malignancy, pulmonary disease, baseline estimated glomerular filtration rate, proteinuria level, hemoglobin level, and SBP.

Table 3: Association of systolic blood pressure with the start of renal replacement therapy, stratified in young and elderly patients

	Events/n	Crude HR [95% CI]	Adjusted HR ¹ [95% CI]	Adjusted HR ² [95% CI]	Median renal function decline (IQR) ³ (ml/min/1.73 m ² /month)
<65 years (young patients)					
<120	20/24	0.69 [0.42;1.14]	0.73 [0.44;1.20]	0.81 [0.47;1.42]	-0.27 (-0.37;-0.03) ⁴
120-139	62/73	0.92 [0.65;1.30]	0.93 [0.66;1.32]	0.96 [0.66;1.41]	-0.32 (-0.48;-0.18)
140-159	68/76	1	1	1	-0.35 (-0.58;-0.17)
160-179	55/56	1.56 [1.09;2.24]	1.53 [1.07;2.20]	1.54 [1.03;2.29]	-0.42 (-0.68;-0.26)
≥180	36/39	1.71 [1.14;2.56]	1.89 [1.25;2.87]	1.88 [1.18;3.00]	-0.51 (-0.99;-0.19)
≥65 years (elderly patients)					
<120	9/12	1.31 [0.64;2.69]	1.42 [0.69;2.93]	2.82 [1.21;6.59]	-0.11 (-0.28;0.47)
120-139	22/36	0.74 [0.44;1.24]	0.72 [0.43;1.22]	1.04 [0.59;1.84]	-0.26 (-0.43;0.13)
140-159	43/61	1	1	1	-0.15 (-0.35;0.02)
160-179	65/85	0.97 [0.66;1.43]	0.96 [0.65;1.42]	1.23 [0.80;1.89]	-0.21 (-0.44;-0.04)
≥180	36/46	1.14 [0.73;1.77]	1.12 [0.72;1.75]	2.33 [1.41;3.87]	-0.34 (-0.65;-0.06)

The hazard ratio (HR) [95% confidence interval (CI)] gives the increased rate of starting renal replacement therapy for each systolic blood pressure (SBP) category compared with the reference category (140-159 mmHg). ¹ Adjusted for sex and age. ² Adjusted for sex, age, race, smoking, primary kidney disease, cardiovascular disease, diabetes mellitus, malignancy, pulmonary disease, baseline estimated glomerular filtration rate, proteinuria, and hemoglobin. ³ Median (boundaries of interquartile range (IQR)) renal function decline (RFD). ⁴ The p-value from the non-parametric (Kruskal-Wallis) test, investigating whether RFD differs between the SBP categories, is ≥0.05-<0.10.

Table 4: Association of diastolic blood pressure with the start of renal replacement therapy, stratified in young and elderly patients

	Events/n	Crude HR [95% CI]	Adjusted HR ¹ [95% CI]	Adjusted HR ² [95% CI]	Median renal function decline (IQR) ³ (ml/min/1.73 m ² /month)
<65 years (young patients)					
<70	7/9	1.07 [0.50;2.32]	1.10 [0.51;2.39]	0.74 [0.29;1.87]	-0.27 (-0.48;0.10) ⁴
70-79	49/55	0.99 [0.70;1.42]	0.97 [0.68;1.39]	0.83 [0.56;1.23]	-0.28 (-0.44;-0.11)
80-89	84/96	1	1	1	-0.35 (-0.62;-0.18)
90-99	53/57	1.27 [0.90;1.80]	1.27 [0.90;1.80]	0.99 [0.66;1.49]	-0.35 (-0.69;-0.21)
≥100	48/51	1.97 [1.38;2.83]	1.94 [1.35;2.78]	1.74 [1.16;2.62]	-0.51 (-1.04;-0.20)
≥65 years (elderly patients)					
<70	27/35	1.39 [0.87;2.22]	1.38 [0.86;2.23]	1.60 [0.95;2.70]	-0.14 (-0.38;0.12)
70-79	39/54	1.15 [0.76;1.75]	1.14 [0.75;1.74]	1.50 [0.96;2.35]	-0.16 (-0.38;0.04)
80-89	52/78	1	1	1	-0.19 (-0.44;-0.03)
90-99	36/49	1.03 [0.67;1.58]	1.03 [0.67;1.58]	1.32 [0.83;2.08]	-0.28 (-0.43;-0.04)
≥100	21/24	1.61 [0.96;2.67]	1.51 [0.90;2.54]	2.32 [1.33;4.04]	-0.27 (-0.70;0.03)

The hazard ratio (HR) [95% confidence interval (CI)] gives the increased rate of starting renal replacement therapy for each diastolic blood pressure (DBP) category compared with the reference category (80-89 mmHg). ¹ Adjusted for sex and age. ² Adjusted for sex, age, race, smoking, primary kidney disease, cardiovascular disease, diabetes mellitus, malignancy, pulmonary disease, baseline estimated glomerular filtration rate, proteinuria, and hemoglobin. ³ Median (boundaries of interquartile range (IQR)) renal function decline (RFD). ⁴ The p-value from the non-parametric (Kruskal-Wallis) test, investigating whether RFD differs between the DBP categories, is ≥ 0.05 - < 0.10 .

Sensitivity analyses

The results remained comparable when taking the average of the SBP and DBP measurements at the start and at the end of follow-up as determinants (ten and twelve young and nine and twelve elderly patients had missing SBP and DBP measurements, respectively, at the end of follow-up and were therefore not included in this analysis). In young patients the HRs for the SBP categories were; 0.68 [95% CI 0.38;1.21] for <120 mmHg, 1.09 [95% CI 0.77;1.54] for 120-139 mmHg, 1.53 [95% CI 1.03;2.28] for 160-179 mmHg, and 2.08 [95% CI 1.15;3.77] for ≥180 mmHg compared with the reference group (140-159 mmHg). In elderly patients these HRs were 2.38 [95% CI 1.02;5.53], 0.79 [95% CI 0.48;1.29], 1.29 [95% CI 0.84;1.97], and 1.91 [95% CI 1.12;3.23] respectively. In young patients the HRs for the DBP categories were; 0.46 [95% CI 0.17;1.26] for <70 mmHg, 0.71 [95% CI 0.49;1.01] for 70-79 mmHg, 1.09 [95% CI 0.75;1.58] for 90-99 mmHg, and 1.54 [95% CI 0.92;2.56] for ≥100 mmHg compared with the reference group (80-89 mmHg). In elderly patients these HRs were 2.27 [95% CI 1.34;3.83], 1.15 [95% CI 0.75;1.76], 1.87 [95% CI 1.07;3.25], and 2.22 [95% CI 0.89;5.50] respectively. Second, the quadratic term for DBP in elderly patients was significant ($p=0.003$) indicating a U-shaped association.

Discussion

The association of BP with the start of RRT was different in elderly (≥65 years) compared with young (<65 years) pre-dialysis patients. In young pre-dialysis patients, the rate of starting RRT increases with increasing SBP and with high DBP (≥100 mmHg). Only elderly patients in the

highest SBP category (≥ 180 mmHg) had an increased rate of starting RRT. DBP showed a U-shaped association with the start of RRT in elderly pre-dialysis patients because elderly patients with DBP < 70 mmHg or ≥ 100 mmHg had a higher rate than patients with DBP 80-89 mmHg. In conclusion, our analyses may indicate that in young pre-dialysis patients a SBP and/or DBP as low as possible is beneficial. In elderly pre-dialysis patients, a moderate increased SBP and DBP does not seem harmful. In this specific patient group only very high SBP and DBP, and low DBP, were associated with a higher rate of starting RRT.

Our study shows that in young pre-dialysis patients high BP (SBP and DBP) accelerates the need to start with RRT, which is in line with several other studies performed in patients with CKD stages 3-5.^{13;28;32} As far as we know, no other study focused on this association in young compared with elderly well defined pre-dialysis patients. We found a smaller effect size, crude and sex- and age-adjusted, of BP with the start of RRT in elderly compared with young pre-dialysis patients. A possible explanation for this smaller effect size could be differences in the composition of factors that influence the decision to start with RRT between elderly and young patients, such as levels of eGFR, the presence of co-morbidities, prognosis, anticipated quality of life, treatment burden, and preference of the patients.^{6;33;34} This explanation seems plausible, as in the elderly pre-dialysis patients the effect sizes became higher and more similar to the young pre-dialysis patients after adjustment for factors influencing prognosis. Furthermore, we found that in elderly pre-dialysis patients both low and high DBP accelerates the need to start with RRT. An association of low DBP with a faster RFD has also been found in the general 'healthy' elderly population.¹⁵ Besides the elderly population, patients with cardiovascular disease also have a higher risk of a second cardiovascular event when they have a low DBP.^{35;36} This harmful effect of DBP is probably due to the fact that a low DBP often coincides with the presence of cardiovascular co-morbidities, such as congestive heart failure, myocardial infarction, and/or valvular heart disease.

The PREPARE-1 study has some limitations. First, our results cannot be generalized to all patients with CKD stages 4-5, only to those patients receiving pre-dialysis care in an outpatient clinic. However, for clinical practice our cohort is a very representative and relevant population. Second, SBP and DBP were collected only once at the start of pre-dialysis care. This type of collection may lead to less precision and more variability of the BP measurements at baseline, and thereby may result in underestimated effects. Furthermore, during pre-dialysis care BP could change due to treatment with anti-hypertensive drugs. Therefore, an analysis with time-varying BP would be interesting, but not possible with the data available (only BP measurement at the start and end of follow-up). Third, we used the complete follow-up in our cohort providing us with enough events in each of the five categories used in our analyses. However, previous analyses¹³ showed that the association of BP with the start of RRT is somewhat diluted when complete instead of six or twelve months of follow-up is being used. Therefore, our results may be an underestimation of the real effect. Fourth, PREPARE-1 is an observational study including pre-dialysis patients when referred to an outpatient clinic. The clinical moment of referral differs between pre-dialysis

patients. Therefore, differences in prognosis at baseline could be present between patients with low and patients with high BP. A part of this problem was eliminated through adjustment for many potential confounders, but residual confounding could still be present. Unfortunately, we could not adjust for RFD before the start of pre-dialysis care.

In elderly pre-dialysis patients, both low and high DBP (U-shape) were associated, independent of SBP, with the start of RRT. Possible biological explanations for this U-shape are an accelerated RFD, the use of ACEi/ARBs, the presence of co-morbidities, arterial stiffness and thereby congestive heart failure, and/or chronic hypoperfusion. First, RFD cannot be the complete explanation because our results in elderly patients showed that RFD was not always consistent with the rate of starting RRT. This is supported by our findings that the residual renal function at the start of RRT was highest in the elderly patients in the lowest DBP and SBP category. Second, a consensus has been reached that ACEi/ARBs can slow down RFD independent of BP lowering. In addition, ACEi/ARBs can also cause a temporary loss of renal function. However, after adjusting our analyses for ACEi and ARB prescriptions the results did not change (data not shown). Possibly, frail elderly patients received a relatively higher dosage of ACEi and ARB prescriptions compared with young patients. Unfortunately, in our cohort no data on dosages were available. Third, although the U-shaped association remained present after adjustment for the most important co-morbidities, we could not control for severity and duration of co-morbidities because these data were not available in the PREPARE-1 study. Therefore, differences in severity and duration of co-morbidities still can be a part of the explanation for the U-shaped association of BP with the start of RRT. Fourth, arterial stiffness of the vessel wall, often accompanied with low DBP, is one of the pathophysiological changes becoming more pronounced with age.^{37;38} These changes can result in isolated systolic hypertension (which is defined as SBP ≥ 140 mmHg and DBP < 90 mmHg²⁶) and thereby an increased pulse pressure (marker for arterial stiffness), an increased afterload, left ventricular hypertrophy, reduced coronary perfusion, congestive heart failure, and altered or reduced blood supply to the tissues.³⁹ These clinical processes are often accompanied with renal damage. In our pre-dialysis population, isolated systolic hypertension was present in 28% of the young and in 51% of the elderly patients. Also angina pectoris and myocardial infarction, consequences of reduced coronary perfusion, and left ventricular hypertrophy were more present in the elderly population. These numbers indicate that the presence of arterial stiffness was higher in elderly compared with young patients. However, both low and high DBP (U-shape) were associated with a higher rate of starting RRT, independent of SBP. Therefore, an increased pulse pressure could not be the entire explanation for the association of low DBP with the start of RRT. Furthermore, after adjustment for or stratification by the presence of left ventricular hypertrophy, angina pectoris, myocardial infarction, coronary disease, or congestive heart failure, the U-shaped association remained present in our cohort. However, congestive heart failure and a low BP often coincide, and therefore we cannot exclude the possibility that symptoms associated with congestive heart failure influence the clinical decision to start with RRT. Fifth, chronic hypoperfusion could be the cause of a higher rate of starting RRT in patients with low DBP. It

is possible that in elderly pre-dialysis patients low DBP, leading to hypoperfusion, may introduce overhydration and thereby lead to an earlier start of RRT. However, adjustment for overhydration did not change the results.

Our data showed that SBP and DBP at the start of pre-dialysis care are differently associated with the start of RRT in elderly compared with young pre-dialysis patients and this could have clinical implications. In young pre-dialysis patients, it seems important to keep SBP and DBP as low as possible. Therefore, the current BP treatment target of $<130/80$ mmHg^{26;40} in CKD patients, irrespective of age, seems correct for young pre-dialysis patients. However, the very low percentage of patients on pre-dialysis care achieving this treatment target level may suggest that it is very difficult to bring SBP and DBP into the range proposed in the guidelines. In elderly patients, only very high SBP and DBP were associated with the start of RRT. Therefore, targeting a blood pressure level of 130/80 mmHg may not be necessary in elderly pre-dialysis patients. This is of interest because anti-hypertensive drugs can cause a lot of side effects in elderly patients. Furthermore, elderly patients with extreme low DBP should be monitored carefully because they started RRT earlier than patients with moderate DBP levels. Our data are consistent with these clinical implications, but do not provide enough evidence to change clinical practice due to the observational character of our study. Therefore, further studies are necessary to investigate whether a less stringent BP treatment target for elderly pre-dialysis patients is just as beneficial or better as the current target, to postpone the start of RRT.

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Chapter 4 |

Proteinuria as a risk marker for the progression of chronic kidney disease in patients on pre-dialysis care and the role of angiotensin-converting enzyme inhibitor/ angiotensin-II receptor blocker treatment

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Abstract

Background: Proteinuria is a risk marker for progression of chronic kidney disease (CKD) and treatment with an angiotensin-converting enzyme inhibitor and/or angiotensin-II receptor blocker (ACEi/ARB) is beneficial in these patients. However, little is known about proteinuria and ACEi/ARB treatment in patients on specialized pre-dialysis care. Therefore, we investigated the association of urinary protein excretion (UPE) and ACEi/ARB treatment with renal function decline (RFD) and/or the start of renal replacement therapy (RRT) in patients on pre-dialysis care.

Methods: In the PRE-dialysis PATient REcord-1 (PREPARE-1) cohort, 547 incident pre-dialysis patients (CKD stages 4-5), referred as part of the usual care to outpatient clinics of eight Dutch hospitals, were included (1999-2001) and followed until the start of RRT, mortality, or January 1, 2008. The main outcomes were rate of RFD, estimated as the slope of available estimated glomerular filtration rate (eGFR) measurements, and the start of RRT.

Results: Patients with mild proteinuria (>0.3 to ≤ 1.0 g/24h) had an adjusted additional RFD of 0.35 [95% confidence interval (CI) 0.01;0.68] ml/min/1.73 m²/month and a higher rate of starting RRT (adjusted hazard ratio (HR) 1.70 [95% CI 1.05;2.77]) compared with patients without proteinuria (≤ 0.3 g/24h). With every consecutive UPE category (>1.0 to ≤ 3.0 , >3.0 to ≤ 6.0 , and >6.0 g/24h), RFD accelerated and the start of RRT was earlier. Furthermore, patients starting (n=16) or continuing (n=133) treatment with ACEi/ARBs during pre-dialysis care had a lower rate of starting RRT compared with patients not using treatment (n=152, adjusted HR 0.56 [95% CI 0.29;1.08] and 0.90 [95% CI 0.68;1.20], respectively).

Conclusion: In patients on pre-dialysis care, we confirmed that proteinuria is a risk marker for the progression of CKD. Furthermore, no evidence was present that the use of ACEi/ARBs is deleterious.

Introduction

Proteinuria is an important risk marker for renal function decline (RFD)¹⁻³ and progression to chronic kidney disease (CKD)⁴⁻⁷ in the general 'healthy' population. In patients with CKD (mainly stages 1-4) proteinuria, defined by a specific cutoff value, remains a risk marker for CKD progression.^{4;8-14} Proteinuria deserves much attention because it is a 'modifiable' risk marker that can be treated with anti-hypertensive medication such as an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin-II receptor blocker (ARB).

Several trials have shown that treatment with ACEi/ARBs can delay the progression to end-stage renal disease and lower the risk of mortality in patients with CKD.¹⁵⁻²⁰ Brenner *et al.*¹⁵ showed that treatment with an ARB results in a 28% risk reduction of progression to end-stage renal disease and 25% risk reduction of doubling of serum creatinine. For an ACEi the results vary from risk reductions of approximately 22 to 56%.¹⁶⁻²⁰ Based on this evidence, the current guidelines recommend to start treatment with ACEi/ARBs, independent of the exact stage of CKD, when the protein-to-creatinine ratio is ≥ 500 -1,000 mg/g (equivalent to ≥ 0.5 -1.0 g/24h).²¹ However, for the specific population of patients with CKD stages 4-5 on specialized pre-dialysis care, little evidence is available about whether proteinuria is still a risk marker for disease progression and whether a higher proteinuria level strengthens this effect (dose-response relation). Furthermore, it is unknown whether treatment with ACEi/ARBs might delay the need for renal replacement therapy (RRT) in this specific patient group on pre-dialysis care.

Indeed, the evidence for the effect of ACEi/ARBs on CKD progression is contradictory in patients on pre-dialysis care who are in the transition phase between advanced CKD and dialysis. In clinical practice, not prescribing ACEi/ARBs or discontinuing ACEi/ARBs during pre-dialysis care is common practice, especially in the elderly and patients with acute renal failure. This practice was recently supported by a study that showed a delayed onset of RRT after the discontinuation of ACEi/ARBs in advanced CKD patients (stages 4-5).²² Furthermore, a debate is ongoing concerning the general applicability of the many trials showing a delayed progression to end-stage renal disease when treated with ACEi/ARBs in patients with mainly CKD stages 1-4.²³

Taking all these considerations into account, the first aim of this study was to investigate whether and from what level urinary protein excretion (UPE) is an independent risk marker for the progression of CKD, assessed as RFD and the start of RRT, in the specific population of patients on pre-dialysis care (advanced CKD stages 4-5). Our second aim was to investigate what the frequency is of different prescription choices of ACEi/ARB treatment at the start of pre-dialysis care (yes or no treatment) and during pre-dialysis care (no use, start, stop, or continue treatment) within the population of patients on pre-dialysis care and whether treatment with ACEi/ARBs at the start and during pre-dialysis care were associated with the progression to RRT.

Methods

Study design and participants

The PRE-dialysis PATient REcord-1 (PREPARE-1) study is a follow-up study in which consecutive incident adult patients with advanced CKD were included from outpatient clinics of eight Dutch hospitals when referred for pre-dialysis care between 1999 and 2001. Referral to these outpatient clinics was indicated if patients were expected to need RRT within one year and if their estimated creatinine clearance was below 20 ml/min. Patients who spent less than one month on pre-dialysis care or patients with prior RRT were excluded. The clinical course of pre-dialysis patients was followed through the medical charts until the start of dialysis, transplantation, death, lost to follow-up, or January 1, 2008, whichever was earliest. Predefined data on demography, anthropometry, and clinical symptoms were extracted from medical charts at the start and end of follow-up. All available data concerning laboratory measurements during pre-dialysis care were extracted from the hospital information systems. The use of medication and laboratory measurements during pre-dialysis care were extracted until January 1, 2003. The study was approved by the Institutional Review Boards of the participating hospitals.

Measurements and definitions

A 24 hour urine sample was collected routinely at the first pre-dialysis visit, and the amount of excreted protein (g) in this sample was measured according to the standard procedure applied in each outpatient clinic. Data on treatment with ACEi/ARBs was collected at the first pre-dialysis visit and at the end of follow-up. All other variables used for the adjustment in multivariable analyses were routinely assessed at the first pre-dialysis visit and measured according to the standard procedure applied in each outpatient clinic. The presence of proteinuria was defined as excreting more than 0.3 g/24h protein in the urine, according to the guidelines.²⁴ Glomerular filtration rate (GFR) was estimated using the four-variable Modification of Diet in Renal Disease formula, taking into account age, sex, race, and serum creatinine.²⁵ Baseline serum creatinine, hemoglobin, and proteinuria measurements were defined as the measurement closest to the start of pre-dialysis care, within 90 days before and 14-30 days after the start of pre-dialysis care.

Outcome

The study outcomes were RFD and the start of RRT during complete follow-up (until January 1, 2008). For the patients who were still in the study after January 1, 2003 (n=75) no complete follow-up data on eGFR and medication use was available. To prevent loss of power, we also included these patients and made the assumption that RFD followed a linear pattern²⁶ and medication use remained stable after this date. It is plausible to assume that these 75 patients are 'stable' patients because none of them started dialysis within the first two years of pre-dialysis care. In each individual patient, the rate of RFD was estimated as the slope of a linear regression model including all available eGFR measurements. eGFR measurements

between one month prior to inclusion and two weeks before reaching an endpoint were used and at least two measurements had to be available to estimate the rate of RFD. Furthermore, the start of RRT was defined as starting dialysis or being transplanted during pre-dialysis care.

Statistical analyses

Continuous data were expressed as mean $\pm$ standard deviation (SD) and skewed data as median (boundaries of interquartile range, IQR). UPE was divided into five categories; ≤ 0.3 (no proteinuria, reference group), >0.3 to ≤ 1.0 , >1.0 to ≤ 3.0 , >3.0 to ≤ 6.0 , and >6.0 g/24h. This classification is based on the definition of proteinuria (>0.3 g/24h) and the upper limit of the treatment target of proteinuria (≤ 1.0 g/24h) below which UPE at least should be reduced. Furthermore, to investigate the frequency of different ACEi/ARB prescription choices and the association of ACEi/ARB treatment with the start of RRT, we performed an analysis with ACEi/ARB treatment at the start of pre-dialysis care (yes or no treatment) and the change of ACEi/ARB treatment during pre-dialysis care (no use, start, stop, or continue treatment) as determinants. We also chose to investigate the change of ACEi/ARB treatment during pre-dialysis care because it is known from clinical practice that in certain patients on pre-dialysis care, often with the worst prognosis, treatment is not started or discontinued to preserve renal function. For the change of treatment during pre-dialysis care, four categories were defined based on the prescription of ACEi/ARBs at the start of pre-dialysis care and at the end of follow-up. The categories were coded as follows: (1) no use of treatment (reference group); 'no' at the start and 'no' at the end of follow-up; (2) start treatment; 'no' at the start and 'yes' at the end of follow-up; (3) stop treatment; 'yes' at the start and 'no' at the end of follow-up, and (4) continue treatment; 'yes' at the start and 'yes' at the end of follow-up. The baseline and treatment characteristics were presented for the total study population and for the population stratified by the five UPE categories.

A linear regression analysis was used to investigate the association of UPE, both continuously and in the defined five categories, with RFD. Multivariable analyses were used to adjust for the possible confounders age, sex, primary kidney disease, baseline eGFR, systolic blood pressure, hemoglobin level, presence of cardiovascular disease (angina pectoris, coronary disease, and/or myocardial infarction), and presence of diabetes mellitus. Systolic blood pressure and/or hemoglobin level were missing for nine patients.

Cox proportional hazard regression analysis was used to assess the association of: (1) UPE, continuously and in the five defined categories, and (2) ACEi/ARB treatment, at the start (yes, no), and changes during pre-dialysis care (no use, start, stop, continue), with the start of RRT. The hazard ratio of starting RRT was adjusted for the same confounders as used in the multivariable linear regression analysis described earlier. The time from the first pre-dialysis visit until the start of RRT was used as follow-up time in the Cox proportional hazard regression model. Both 'mortality' and 'lost to follow-up' were censored events. Finally, we also investigated whether the association of ACEi/ARB treatment at the start or during pre-

dialysis care with the start of RRT is dependent on the level of proteinuria, by performing analyses stratified by the five UPE categories.

Multiple sensitivity analyses were performed. First, we investigated whether the association of UPE with the progression of CKD is different after stratifying by treatment with ACEi/ARBs at the start of pre-dialysis care. Second, all analyses with the start of RRT as outcome were repeated with follow-up time until January 1, 2003 instead of January 1, 2008. Third, a linear mixed model was used to validate our chosen method for estimating the rate of RFD. Fourth, systolic blood pressure, hemoglobin, UPE and RFD were imputed (using five repetitions) in patients who had no prior RRT and received at least one month of pre-dialysis care (n=525) with a missing value at baseline (n=17, n=68, n=112, and n=53 respectively). Multiple imputation is a recommended technique where missing data for a patient are imputed by a value that is predicted by other known characteristics of this patient (i.e. demographic, anthropometric, and clinical characteristics, as well as the outcome).^{27;28} Multiple imputation may increase statistical power because all patients are included in the analysis. At the same time, it may reduce selection bias as patients with missing values often have poor prognosis and are therefore more prone to have poor outcomes. Data were analyzed with PASW/SPSS version 17.

Results

Baseline characteristics

In our pre-dialysis cohort, 547 patients were included, of whom 525 patients had no prior RRT and received at least one month of pre-dialysis care. At baseline, UPE was available for 413 patients and these patients were included in our statistical analyses. These 413 patients were slightly younger, had a higher systolic blood pressure, lower eGFR, and higher prevalence of cardiovascular disease and diabetes mellitus compared with patients without an available UPE at baseline (n=112). At the start of pre-dialysis care, 368 of the 413 patients (89%) had proteinuria (>0.3 g/24h, Table 1). Patients with proteinuria were younger, more often male, had a higher prevalence of diabetes mellitus, a lower eGFR, and higher systolic blood pressure. These differences became more pronounced with increasing UPE.

Table 1: Baseline characteristics of the total population and stratified by urinary protein excretion categories

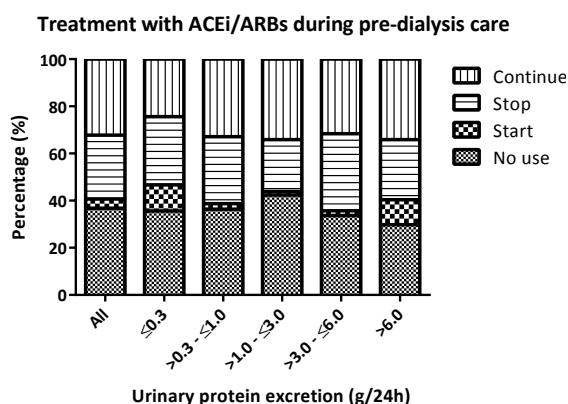
	Total n=413	No proteinuria		Proteinuria		
		≤0.3 ¹ n=45	>0.3 to ≤1.0 n=88	>1.0 to ≤3.0 n=132	>3.0 to ≤6.0 n=101	>6.0 n=47
Age (years)	63 (50-73)	67 (56-75)	67 (52-75)	66 (48-73)	54 (44-70)	61 (52-70)
Sex (male, %)	58	38	53	62	61	64
Body mass index (kg/m ²) ²	26 ± 5	26 ± 4	25 ± 5	26 ± 5	26 ± 5	28 ± 5
Smokers / quitters (%)	56	49	64	59	53	49
Primary kidney disease (%)						
Diabetes mellitus	18	4	8	15	22	49
Glomerulonephritis	10	4	3	9	17	19
Polycystic kidney disease	13	18	30	11	6	0
Renal vascular disease	22	38	22	21	21	15
Other	37	36	37	44	34	17
eGFR (ml/min/1.73 m ²) ³	13.1 ± 5.6	17.1 ± 9.2	13.6 ± 4.6	13.1 ± 5.6	11.6 ± 4.2	11.2 ± 3.6
Urinary protein excretion (g/24h)	2.0 (0.7-3.8)	0.2 (0.1-0.3)	0.6 (0.4-0.8)	1.9 (1.4-2.5)	4.0 (3.5-4.4)	7.6 (6.9-10.1)
Systolic blood pressure (mmHg) ⁴	153 ± 28	150 ± 27	144 ± 25	152 ± 26	160 ± 29	161 ± 30
Diastolic blood pressure (mmHg) ⁴	84 ± 14	83 ± 13	81 ± 11	83 ± 14	86 ± 14	85 ± 17
Hemoglobin (g/dl) ⁵	11.3 ± 1.6	11.3 ± 1.4	11.6 ± 1.6	11.4 ± 1.8	10.9 ± 1.6	11.4 ± 1.3
Co-morbidities (%)						
Cardiovascular disease ⁶	37	42	35	43	29	38
Diabetes mellitus ⁷	28	18	15	26	31	62

Median (boundaries of interquartile range) is given for age and proteinuria and for the other continuous variables mean ± standard deviation is given. ¹ Urinary protein excretion (UPE) is given in g/24h. ² Available for 386 patients. ³ Estimated glomerular filtration rate (eGFR) calculated with the four-variable Modification of Diet in Renal Disease formula. ⁴ Available for 405 patients. ⁵ Available for 412 patients. ⁶ Defined as the presence of angina pectoris, coronary disease, and/or myocardial infarction. ⁷ Including patients with diabetes mellitus as primary kidney disease.

Treatment characteristics

At the start of pre-dialysis care, 41% (n=168) of the 413 patients were not treated and 59% (n=245) were treated with ACEi/ARBs (Figure 1). Furthermore, of all patients, 4% (n=16) started treatment and 27% (n=112) stopped treatment with ACEi/ARBs during pre-dialysis care. This means that 10% (16 of the 168) of the patients not treated at the start of pre-dialysis care started treatment, and 46% (112 of the 245) of the patients treated at the start of pre-dialysis care stopped ACEi/ARB treatment. The treatment characteristics did not differ much between the UPE categories (Figure 1). The frequency of patients starting ACEi/ARB treatment was somewhat lower in patients with proteinuria (>0.3 to ≤6.0 g/24h) compared with patients without proteinuria. Furthermore, the frequency of patients continuing treatment was somewhat higher in patients with proteinuria.

Figure 1: Treatment with ACEi/ARBs during pre-dialysis care



Treatment characteristics of the total population and stratified by urinary protein excretion (UPE) categories. On the y-axis the percentage (%) of patients in each of the four ACEi/ARB treatment categories during pre-dialysis care (legend) is presented. The four treatment categories with ACEi/ARBs were based on the use or no use of ACEi/ARBs at the start of pre-dialysis care and at the end of follow-up (no use, start, stop, and continue). The results are given for the total population (all, x-axis) and stratified by UPE categories (≤0.3, >0.3 to ≤1.0, >1.0 to ≤3.0, >3.0 to ≤6.0, and >6.0 g/24 h, x-axis).

Association of UPE with the progression of CKD

Two or more eGFR measurements to estimate the rate of RFD, were available for 408 patients. In these patients, the median (IQR) number of available eGFR measurements was 13 (7-19) and the mean ± SD RFD was 0.43 ± 0.87 ml/min/1.73 m²/month. RFD accelerated with increasing UPE (adjusted additional decline 0.04 [95% confidence interval (CI) $0.01;0.08$] ml/min/1.73 m²/month per g/24h increase, Table 2). The same trend was present when UPE was analyzed in categories. Even patients with mild proteinuria (>0.3 to ≤1.0 g/24h) already had an accelerated RFD (adjusted additional decline 0.35 [95% CI $0.01;0.68$] ml/min/1.73 m²/month) compared with patients without proteinuria (≤0.3 g/24h, mean ± SD decline 0.07 ± 0.84 ml/min/1.73 m²/month). Every consecutive higher UPE category showed an increasing additional decline compared with the reference category (patients without proteinuria, ≤0.3 g/24h).

At the end of follow-up (January 1, 2008), 43% started hemodialysis and 37% peritoneal dialysis, 4% were transplanted, 11% died, and 5% were lost to follow-up. The median (IQR) follow-up time was 11.6 (4.7-22.4) months. For the consecutive UPE categories the follow-up time was 23.0 (10.9-42.5), 16.4 (6.0-29.2), 14.1 (4.8-24.1), 7.0 (4.2-15.0), and 6.9 months (3.2-17.7). The association of increasing UPE with the start of RRT showed a similar pattern as increasing UPE with RFD (adjusted hazard ratio (HR) 1.06 [95% CI 1.02;1.10] per g/24h increase, Table 3). Patients with mild proteinuria (>0.3 to ≤1.0 g/24h) had a higher rate of starting RRT compared with patients without proteinuria (adjusted HR 1.70 [95% CI 1.05;2.77]). Every consecutive higher UPE category showed an even higher rate compared with the reference category.

Table 2: Association of urinary protein excretion with renal function decline

	n	Baseline eGFR ¹	Crude additional decline [95% CI] (ml/min/1.73 m ² /month)	Adjusted additional decline ² [95% CI] (ml/min/1.73 m ² /month)	Adjusted additional decline ³ [95% CI] (ml/min/1.73 m ² /month)
<u>Amount of urinary protein excretion (g/24h):</u>					
Steps of 1	408	13.1 ± 5.6	0.05 [0.02;0.09]	0.05 [0.02;0.08]	0.04 [0.01;0.08]
≤0.3	45	17.1 ± 9.2	0 ⁴	0	0
>0.3 - ≤1.0	86	13.6 ± 4.5	0.26 [-0.05;0.57]	0.24 [-0.07;0.55]	0.35 [0.01;0.68]
>1.0 - ≤3.0	132	13.1 ± 5.6	0.31 [0.02;0.60]	0.28 [-0.02;0.57]	0.34 [0.01;0.66]
>3.0 - ≤6.0	98	11.6 ± 4.2	0.56 [0.25;0.86]	0.50 [0.19;0.81]	0.53 [0.18;0.89]
>6.0	47	11.2 ± 3.6	0.62 [0.27;0.97]	0.59 [0.23;0.94]	0.64 [0.22;1.06]

The decline [95% confidence interval (CI)] for steps of 1 indicates the additional renal function decline (RFD) with every 1 g/24h increase in urinary protein excretion (UPE). The decline [95% CI] presented for each UPE category indicates the additional RFD compared with the reference category (no proteinuria, ≤0.3 g/24h). A positive decline is equivalent to a faster RFD. ¹ Mean estimated glomerular filtration rate (eGFR) in ml/min/1.73 m² at baseline. ² Adjusted for sex and age. ³ Adjusted for sex, age, primary kidney disease, systolic blood pressure, hemoglobin level, baseline eGFR, and the co-morbidities cardiovascular disease and diabetes mellitus and complete data available for 399 patients. ⁴ The mean ± standard deviation crude RFD is 0.07 ± 0.84 ml/min/1.73 m²/month for the reference group.

Table 3: Association of urinary protein excretion with the start of renal replacement therapy

	Events/n	Crude HR [95% CI]	Adjusted HR ¹ [95% CI]	Adjusted HR ² [95% CI]
<u>Amount of urinary protein excretion (g/24h):</u>				
Steps of 1	344/413	1.09 [1.06;1.13]	1.09 [1.06;1.12]	1.06 [1.02;1.10]
≤0.3	27/45	1	1	1
>0.3 - ≤1.0	72/88	1.95 [1.24;3.06]	1.86 [1.18;2.94]	1.70 [1.05;2.77]
>1.0 - ≤3.0	109/132	2.19 [1.43;3.37]	1.98 [1.28;3.08]	1.87 [1.17;3.00]
>3.0 - ≤6.0	92/101	4.03 [2.58;6.29]	3.68 [2.34;5.81]	2.62 [1.59;4.33]
>6.0	44/47	3.67 [2.25;5.99]	3.44 [2.10;5.63]	2.52 [1.45;4.39]

The hazard ratio (HR) [95% confidence interval (CI)] for steps of 1 indicates the increased rate of starting renal replacement therapy (RRT) with every 1 g/24h increase in urinary protein excretion (UPE). The HR [95% CI] presented for each UPE category indicates the increased rate of starting RRT compared with the reference category (no proteinuria, ≤0.3 g/24h). ¹ Adjusted for sex and age. ² Adjusted for sex, age, primary kidney disease, systolic blood pressure, hemoglobin level, baseline eGFR, and the co-morbidities cardiovascular disease and diabetes mellitus and complete data available for 404 patients.

Association of treatment with ACEi/ARBs with the start of RRT

The median (IQR) follow-up time was 11.4 months (4.8-22.1) for patients treated and 12.5 months (4.2-23.2) for patients not treated with ACEi/ARBs at the start of pre-dialysis care. The Cox proportional hazard regression model also showed that patients treated with ACEi/ARBs at the start of pre-dialysis care had a somewhat higher rate of starting RRT compared with patients not treated with ACEi/ARBs (adjusted HR 1.13 [95% CI 0.89;1.44], Table 4). For patients not using, starting, stopping, or continuing treatment during pre-dialysis care, the median (IQR) follow-up time was 11.7 (4.1-21.7), 16.0 (4.6-34.7), 8.2 (4.5-20.6), and 11.8 (6.7-24.9) months, respectively. Patients starting treatment with ACEi/ARBs during pre-dialysis care had a lower rate of starting RRT compared with patients not using treatment with ACEi/ARBs, which was not significant (adjusted HR 0.56 [95% CI 0.29;1.08], Table 4). Patients continuing treatment with ACEi/ARBs during pre-dialysis care also had a slightly lower rate of starting RRT compared with the patients not using treatment (adjusted HR 0.90 [95% CI 0.68;1.20]). Compared with the reference group, patients discontinuing the use of ACEi/ARBs during pre-dialysis care had a higher rate of starting RRT. However, this difference was not significant (adjusted HR 1.27 [95% CI 0.95;1.70]). Furthermore, the association of ACEi/ARB treatment at the start or during pre-dialysis care with the start of RRT varied through the UPE categories; however, no clear pattern was detected.

Table 4: Association of treatment with ACEi/ARBs with the start of renal replacement therapy

	Start ¹	End ¹	Events/n	Crude HR [95% CI]	Adjusted HR ² [95% CI]	Adjusted HR ³ [95% CI]
<u>ACEi/ARB</u>						
Not treated	No	-	133/168	1	1	1
Treated	Yes	-	211/245	1.08 [0.87;1.35]	1.05 [0.84;1.31]	1.13 [0.89;1.44]
<u>ACEi/ARB</u>						
No use	No	No	122/152	1	1	1
Start	No	Yes	11/16	0.67 [0.36;1.24]	0.63 [0.34;1.17]	0.56 [0.29;1.08]
Stop	Yes	No	95/112	1.18 [0.90;1.55]	1.17 [0.89;1.53]	1.27 [0.95;1.70]
Continue	Yes	Yes	116/133	0.95 [0.73;1.22]	0.89 [0.69;1.15]	0.90 [0.68;1.20]

The hazard ratio (HR) [95% confidence interval (CI)] presented for each treatment category (the use of ACEi/ARBs at the start of pre-dialysis care, or the use of ACEi/ARBs during pre-dialysis care) indicates the increased rate of starting renal replacement therapy (RRT) compared with the reference category (no use at the start or during pre-dialysis care). ¹ Defined as the use of ACEi/ARBs at the start of pre-dialysis care and at the end of follow-up (RRT, mortality, lost to follow-up, or January 1, 2003). ² Adjusted for sex and age. ³ Adjusted for sex, age, primary kidney disease, systolic blood pressure, hemoglobin level, baseline eGFR, and the co-morbidities cardiovascular disease and diabetes mellitus and complete data available for 404 patients.

Sensitivity analyses

The point estimates for the association of UPE with RFD and the start of RRT were higher in patients treated than in patients not treated with ACEi/ARBs at the start of pre-dialysis care. The point estimates for the association of UPE and the use of ACEi/ARBs with the start of RRT remained similar when using follow-up until January 1, 2003 for all patients. Only the confidence intervals for the hazard ratios became somewhat larger, probably because 75

patients have not reached an endpoint on this date yet. Using linear mixed models resulted in similar significant results for the association of UPE with RFD, with lower point estimates and smaller confidence intervals. Finally, multiple imputation resulted in similar results for the continuous and categorical association of UPE with RFD and the start of RRT.

Discussion

In our cohort of patients on specialized pre-dialysis care, 89% of the patients had proteinuria (>0.3 g/24h) and almost half of the patients, irrespective of proteinuria, were not treated with ACEi/ARBs. Of all 413 patients, only 10% of the patients not treated with ACEi/ARBs at the start of pre-dialysis care started the treatment, and 46% of the patients treated with ACEi/ARBs at the start of pre-dialysis care discontinued the treatment during pre-dialysis care. Increased UPE was associated with a faster progression of CKD, assessed as an accelerated RFD and an earlier start of RRT. Even patients with mild proteinuria (>0.3 to ≤ 1.0 g/24h) already experienced a faster progression of CKD compared with patients without proteinuria (≤ 0.3 g/24h) and every consecutive higher UPE category resulted in an even faster progression of CKD. Patients treated with ACEi/ARBs at the start of pre-dialysis care started RRT somewhat earlier. In contrast, according to ACEi/ARB treatment during pre-dialysis care, patients continuing or starting treatment with ACEi/ARBs during pre-dialysis care, had a somewhat later start of RRT compared with patients not using ACEi/ARB treatment. Furthermore, patients discontinuing treatment had a considerable faster rate of starting RRT compared with patients not using ACEi/ARB treatment during pre-dialysis care. Therefore, the small increased rate in all patients on ACEi/ARB treatment at the start of pre-dialysis care can be explained by the increased rate of starting RRT and shorter median follow-up time in patients discontinuing treatment with ACEi/ARBs during pre-dialysis care as seen in our analyses. These results may indicate that in the clinic, treatment with ACEi/ARBs is especially discontinued in patients with a bad prognosis.

Our findings of a dose-response relation between increasing UPE and a faster progression of CKD, assessed as RFD and the start of RRT, has not been shown previously in patients with advanced CKD (stages 4-5). A faster progression was already present in patients with mild proteinuria (>0.3 to ≤ 1.0 g/24h). Other observational studies have investigated proteinuria as a risk marker for CKD progression.^{4;8;10-14} However, these studies included patients in all stages of CKD and/or proteinuria was defined only as a dichotomous variable. The study of Obi *et al.*¹⁰ resembles our study the most, as this study was performed in a cohort of patients with CKD stages 3-5 referred to nephrologists. They showed that patients with overt proteinuria, defined as a urinary protein/creatinine ratio ≥ 1 g protein/g creatinine or a urine dipstick $\geq 2+$ (both equivalent to ≥ 1.0 g/24h), started RRT earlier compared with patients without overt proteinuria (adjusted HR 4.97 [95% CI 2.23;11.1]). Besides these observational studies, a meta-analysis by Jafar *et al.*¹⁷ showed that the beneficial effect of ACEi/ARBs on the progression of CKD, defined as the doubling of serum creatinine or progression to end-stage renal disease, acts in part via the lowering of proteinuria. This finding may indicate that

lowering proteinuria slows down the progression of CKD which is consistent with the dose-response relation we found between increasing UPE and a faster progression of CKD.

In our cohort, 59% of the patients (245 of the 413 patients) were treated with ACEi/ARBs (most of them used an ACEi) and this finding is in line with other studies.^{29;30} Furthermore, we found that 112 of the 245 patients (46%) who were treated with ACEi/ARBs at the start of pre-dialysis care discontinued the use of ACEi/ARBs during pre-dialysis care. For the 168 patients not treated with ACEi/ARBs at the start of pre-dialysis care, only 16 patients (10%) started treatment. These findings are in line with the clinical practice because in many pre-dialysis patients treatment with ACEi/ARBs is not started or discontinued to preserve the patients' renal function or because of hyperkalemia. Recently, this practice became more evidence-based, as Ahmed *et al.*²² showed that discontinuing the use of ACEi/ARBs delayed the onset of RRT in patients with CKD stages 4-5. However, their patient population was very specific, consisting of elderly patients (mean $\pm$ SD age of 73.3 ± 1.8 years) with relatively high eGFR (16.38 ± 1 ml/min/1.73 m²). Unfortunately, in our cohort we could not investigate whether kidney function improves after discontinuation of ACEi/ARB treatment because we do not know the exact date of discontinuation. Therefore, future studies should focus on this possible beneficial effect of not prescribing ACEi/ARB treatment in patients on pre-dialysis care.

Our study furthermore showed that ACEi/ARB treatment at the start of pre-dialysis care was associated with a somewhat faster progression to RRT (adjusted HR 1.13 [95% CI 0.89;1.44]). This finding is in line with the study of Ahmed *et al.*²², who showed that treatment with ACEi/ARBs in pre-dialysis patients is detrimental. However, this possible detrimental effect of ACEi/ARBs disappeared when we performed an analysis taking into account the treatment of ACEi/ARBs during pre-dialysis care (no use, start, stop, or continue treatment). Patients who discontinue ACEi/ARB treatment during pre-dialysis care started RRT earlier than patients not using treatment, which explained the detrimental effect found at baseline. However, patients continuing or starting treatment with ACEi/ARBs during pre-dialysis care have a somewhat slower progression to RRT compared with patients not using treatment with ACEi/ARBs. This finding is in line with several trials performed in CKD patients¹⁵⁻²⁰, but in contrast to the study of Ahmed *et al.*²². An explanation for this contradictory finding could be that in the study of Ahmed *et al.*, all included patients discontinued ACEi/ARB treatment and in our study, ACEi/ARB treatment was only discontinued in patients with clinical indications to stop, such as hyperkalemia, renal dysfunction, and/or angioedema.³¹

Our results representing the association of ACEi/ARB treatment with the start of RRT are therefore contradictory. We found a very small detrimental effect of ACEi/ARB treatment, but this effect became somewhat beneficial when we excluded patients that discontinue the treatment. Because of this current clinical practice to stop or not start ACEi/ARB treatment in some pre-dialysis patients to preserve renal function, we could get problems with confounding by indication. Therefore, it is difficult to prove whether our findings of a somewhat beneficial effect of treatment with ACEi/ARBs during pre-dialysis care is due to the

absence of clinical indications to stop the treatment, often related to a better prognosis, or due to a real beneficial effect of ACEi/ARBs. The combination of our observational results showing that the clinical practice is to discontinue ACEi/ARB treatment in specific pre-dialysis patients and the fact that the patients in the study of Ahmed *et al.*²² were mainly elderly patients with a relatively high eGFR may support the thought that ACEi/ARB treatment is not beneficial for a specific subgroup of pre-dialysis patients. However, future studies in pre-dialysis patients should elaborate whether discontinuation of ACEi/ARBs is indeed beneficial, and if so, for which specific subgroups.

Our study has some potential limitations. First, in the general population, 36-65% of the patients with an eGFR below 15 ml/min/1.73 m² are not treated by a nephrologist.³² Therefore, our results may not be generalizable to all patients with an eGFR below 15 ml/min/1.73 m², but only to those who receive specialized pre-dialysis care. However, for clinical practice our cohort is a highly representative and relevant population because this is the patient population seen and treated by nephrologists. Second, for estimating the rate of RFD with available eGFR measurements, we assumed that RFD follows a linear pattern in the advanced stages of CKD. It has been shown previously that linearity of the course in eGFR is a reliable assumption, although on theoretical grounds an exponential decline could be present over a longer period of time.²⁶ Third, our finding that treatment with ACEi/ARBs during pre-dialysis care resulted in a slower progression of CKD should be interpreted with caution due to the observational character of our study and thereby possible confounding by indication. To draw confirmative conclusions about the effect of a treatment, a randomized controlled trial is the most optimal study design to ensure an equal prognosis between the two treatment groups. However, the results in our study did not change essentially after the adjustment for clinical indications (high blood pressure and proteinuria) and contraindications (hyperkalemia and edema; data not shown) considered in the decision to prescribe anti-hypertensive medication. Unfortunately, we cannot adjust for RFD before the start of pre-dialysis care, the third main indication. No RFD could be estimated because the number of available creatinine levels prior to one month before the start of pre-dialysis care was too scarce in our cohort. However, if patients treated with ACEi/ARBs indeed had a faster RFD before the start of pre-dialysis care, our observed associations might even be stronger. Fourth, the prescription of ACEi/ARBs was only assessed at the start of pre-dialysis care and at the end of follow-up. The treatment regimen in the intervening time and the actual compliance to the medication is unknown and could not be accounted for. However, it is unlikely that patients stop and restart treatment with ACEi/ARBs during pre-dialysis care. Besides this, we do not know the exact date of discontinuation of ACEi/ARBs, which could be just before the start of dialysis. Furthermore, we were not able to perform an analysis in which the single treatment with ACEis or ARBs and the combined treatment with ACEis and ARBs was investigated due to the low frequency of patients using an ARB.

Our results indicate that during specialized pre-dialysis care, proteinuria can be used as a risk marker, independent of other risk factors, for the progression of CKD. High-risk pre-dialysis

patients can be identified, treated more strictly, and timely preparation for dialysis can be assured. Furthermore, in our pre-dialysis cohort, a large part of the patients were not treated with ACEi/ARBs to lower proteinuria and slow down the progression of CKD. More studies are necessary to elaborate on the clinical indications for discontinuation of ACEi/ARB treatment and the clinical course after discontinuation. Moreover, patients starting or continuing treatment with ACEi/ARBs during pre-dialysis care started RRT somewhat later, indicating no deleterious effect of ACEi/ARB treatment. In conclusion, the results from this study provide evidence for using the proteinuria level as a strong and independent risk marker for the progression of CKD in patients on specialized pre-dialysis care.

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Chapter 5 |

Lipid levels and renal function decline in pre-dialysis patients

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Abstract

Background: Little is known about the effect of low-density lipoprotein (LDL) cholesterol, triglyceride (TG), and high-density lipoprotein (HDL) cholesterol levels on renal function decline in patients receiving specialized pre-dialysis care.

Methods: In the prospective PRE-dialysis PATient REcord-2 (PREPARE-2) study, incident patients starting pre-dialysis care were included when referred to one of 25 Dutch specialized pre-dialysis outpatient clinics (2004-2011). Clinical and laboratory data were collected every six-month interval. A linear mixed model was used to compare renal function decline between patients with LDL cholesterol, TG, or HDL cholesterol levels above and below the treatment target (LDL cholesterol: <2.50 mmol/l, TG: <2.25 mmol/l, and HDL cholesterol: ≥ 1.00 mmol/l). Additionally the HDL/LDL cholesterol ratio was investigated (≥ 0.4).

Results: In our study population (n=306), the median age was 69 years, and 70% were male. Patients with LDL cholesterol levels above the target of 2.50 mmol/l experienced an accelerated renal function decline compared with patients with levels below the target (crude additional decline 0.10 [95% confidence interval (CI) 0.00;0.20] ml/min/1.73 m²/month, $p < 0.05$). A similar trend was found for TG levels above the target of 2.25 mmol/l (0.05 [95% CI -0.06;0.16] ml/min/1.73 m²/month) and for a HDL/LDL cholesterol ratio below 0.4 (0.06 [95% CI -0.05;0.18] ml/min/1.73 m²/month). Adjustment for potential confounders resulted in similar results and exclusion of patients whom were prescribed lipid-lowering medication (statin, fibrate, or cholesterol absorption inhibitor) resulted in a larger estimated effect.

Conclusion: Especially high levels of LDL cholesterol were associated with an accelerated renal function decline, independent of the prescription of lipid-lowering medication.

Introduction

In the general population it is known that abnormal lipid levels (i.e. high low-density lipoprotein (LDL) cholesterol, high triglycerides (TG), and low high-density lipoprotein (HDL) cholesterol) are associated with higher cardiovascular mortality.¹⁻³ For patients on dialysis treatment, the association of abnormal lipid levels with all-cause and cardiovascular mortality is different compared with the general population. In this phase, having abnormal lipid levels (especially high total cholesterol) seems to have a beneficial effect, associated with lower risks of mortality.⁴⁻⁶ Studies investigating the association of abnormal lipid levels with all-cause and cardiovascular mortality in chronic kidney disease (CKD) patients not on dialysis⁷⁻⁹, showed no or a slightly reversed association. However, this reversed association was again mainly observed for total cholesterol levels, which is a combination of 'good' and 'bad' lipids. Furthermore, low cholesterol levels may be a consequence of inflammatory processes.^{10;11} Besides this, a subgroup analysis of a recently published large trial showed that a lipid-lowering combination therapy of a statin plus cholesterol absorption inhibitor, both LDL cholesterol-lowering drugs, decreased the risk of major cardiovascular events, including cardiovascular mortality, in pre-dialysis patients.¹² Primarily based on the results from this trial, lipid-lowering medication is recommended to pre-dialysis patients for preventing cardiovascular complications. Is there also enough evidence available for renal function decline, another important clinical outcome?

In the general population, several studies found a possible association of abnormal lipid levels with an accelerated renal function decline.¹³⁻¹⁶ This association seems comparable in patients with CKD, in whom abnormal lipid levels are associated with a faster progression.¹⁷⁻²¹ However, these studies mainly focused on total cholesterol levels in early-stage CKD patients (stages 1-3). Data are lacking on the association of high LDL cholesterol, high TG, and low HDL cholesterol levels with progression of CKD in pre-dialysis patients (stages 4-5). Furthermore, trials investigating the effect of statins on disease progression, either defined by increasing proteinuria levels or renal function decline, are scarce and show contradictory results in pre-dialysis patients.^{12;22} Therefore, we investigated the association of abnormal lipid levels (high LDL cholesterol, high TG, and low HDL cholesterol) with renal function decline in incident patients receiving specialized pre-dialysis care (CKD stages 4-5).

Methods

Study design

The PRE-dialysis PATient REcord-2 (PREPARE-2) study is an ongoing, prospective follow-up study of incident pre-dialysis patients treated in one of the 25 participating nephrology outpatient clinics in The Netherlands. Patients were included between July 2004 and June 2011, at the start of specialized pre-dialysis care. They were treated by their nephrologists in their regular scheme according to the treatment guidelines of the Dutch Federation of Nephrology²³, a guideline partly based on the K/DOQI and KDIGO guidelines^{24;25}. At the start

of specialized pre-dialysis care and in subsequent six-month intervals clinical data were collected. Patients were followed until the start of dialysis, receiving a kidney transplant, death, or censoring. Censoring was defined as: moving to an outpatient clinic not participating in the PREPARE-2 study, recovery of kidney function, refusal of further study participation, lost to follow-up, or August 1, 2012 (end of follow-up), whichever came first. The study was approved by the Medical Ethics Committee or Institutional Review Board (as appropriate) of all participating centers.

Patients

To be eligible for inclusion in the PREPARE-2 study, patients had to be at least eighteen years of age and the inclusion should take place at the moment of referral to a specialized pre-dialysis outpatient clinic. In practice, this refers to incident pre-dialysis patients with an estimated glomerular filtration rate (eGFR) of less than 20-30 ml/min/1.73 m², in whom renal function loss is progressive. Patients with a failing kidney transplant were also included in the study if the transplantation was at least one year ago. All participants gave their written informed consent prior to study inclusion.

Data collection

Data on demography, biometry, primary kidney disease, co-morbidities, medication use, and health-related quality of life were collected at the start of specialized pre-dialysis care and in subsequent six-month intervals. Corresponding laboratory data were extracted from the electronic hospital information systems or medical records. Primary kidney disease was classified according to the codes of the European Renal Association-European Dialysis and Transplantation Association.²⁶

Measurements and definitions

GFR was estimated using the four-variable Modification of Diet in Renal Disease (MDRD) formula.²⁷ TG and HDL cholesterol levels (given in mmol/l) were directly measured according to the standard procedure in each participating outpatient clinic. LDL cholesterol (given in mmol/l) was either directly measured or estimated with the Friedewald equation; total cholesterol – HDL cholesterol – TG/2.2²⁸.

Outcome

The primary outcome of our study was renal function decline. To assess this decline, all individual eGFR measurements during the first two years of pre-dialysis care were used. Complete follow-up was not used because the healthy and stable patients, whom are still on pre-dialysis care after two years, will then have a relatively large contribution to the overall renal function decline, possibly leading to a dilution of the estimated decline.

Statistical analyses

For our statistical analyses we only included the patients with at least one LDL cholesterol, TG, HDL cholesterol, and eGFR measurement during the first two years of pre-dialysis care (n=306). Baseline characteristics were presented as mean $\pm$ standard deviation (SD) for normally distributed variables and as median (boundaries of interquartile range, IQR) for skewed variables. LDL cholesterol, TG, and HDL cholesterol levels were used as determinants. All determinants were analyzed in categories based on the treatment targets recommended by the Dutch²³ and international^{24;29} pre-dialysis guidelines. The targets were <2.50 mmol/l for LDL cholesterol, <2.25 mmol/l for TG, and ≥ 1.00 mmol/l for HDL cholesterol. Two additional analyses were performed: HDL cholesterol relative to LDL cholesterol (ratio: $1 \text{ mmol/l} / 2.50 \text{ mmol/l} = 0.4$; target: ≥ 0.4) because HDL cholesterol levels can be influenced by LDL cholesterol levels, and the number of targets that are not reached (ranging from 1, not reaching one of the three targets, to 3, reaching none of the targets), to estimate the combined effect of lipid levels.

To associate these lipid levels with renal function decline we used a linear mixed model. This model takes into account a correlation between individual repeated eGFR measurements and the deviation of the individual slopes from the mean slope.³⁰ All lipid levels and eGFR measurements during the first two years of pre-dialysis care were included in the model. The covariates included in the model were time (random), lipid levels, and time*lipid levels (interaction term; to assess the difference in renal function decline between the lipid level categories). All analyses were adjusted for the potential baseline confounders age, sex, primary kidney disease, smoking status, cardiovascular disease, diabetes mellitus, body mass index, systolic blood pressure, and proteinuria. In an additional model we further adjusted for available malnutrition-inflammation complex system related factors (albumin, c-reactive protein, and subjective global assessment). To maintain power and avoid bias, missing baseline confounder values were imputed (using ten repetitions) with the method of multiple imputation in PASW/SPSS version 20.0. This is a recommended technique where missing data for a patient are imputed by a value that is predicted by other known characteristics of this patient.^{31;32} All characteristics in Table 1 and 2, follow-up time, and the outcome (dialysis, transplantation, death, or censoring) were included in the imputation model because missing baseline characteristics are often related to the outcome.³³ For each baseline characteristic, the number of patients with an available value is given in Table 1 and 2. Skewed distributed continuous variables, including follow-up time, were logarithmically transformed.

We performed several additional analyses. First, we excluded patients who were prescribed lipid-lowering medication, defined as either a statin, a fibrate, or a cholesterol absorption inhibitor. Second, we analyzed the abnormal lipid levels continuously to investigate whether there was a similar association throughout the entire range of lipid levels. Third, we compared the effect of LDL cholesterol levels on renal function decline between the centers who estimated LDL cholesterol levels with the Friedewald equation and the centers who directly measured LDL cholesterol. Fourth, we excluded eGFR values measured in the two weeks

before starting dialysis, receiving a kidney transplant, death, or censoring because there can be a large variation between eGFR measurements during this period. Finally, we repeated all analyses after excluding the patients with only one eGFR measurement, to check whether the results from our linear mixed model were robust. P-values <0.05 were considered statistically significant and data were analyzed with PASW/SPSS version 20.0.

Results

Baseline characteristics

Of the 502 patients, 306 patients had at least one LDL cholesterol, TG, HDL cholesterol, and eGFR measurement during the first two years of follow-up. These 306 patients were included in our statistical analyses and the known baseline characteristics of these patients (Table 1) were very similar to the baseline characteristics of the 196 patients excluded. The median age of the population was 69 (IQR 56-76) years of whom 70% were male. Mean eGFR was $16.7 \pm \text{SD } 6.1$ ml/min/1.73 m² and median proteinuria was 1.1 (IQR 0.3-2.2) g/24h. Stratification by the LDL cholesterol treatment target (<2.50 mmol/l) revealed that patients above the target were slightly younger, less often male, had a slightly higher eGFR, higher systolic blood pressure, and had less often diabetes mellitus and cardiovascular disease (as primary kidney disease or co-morbidity) than patients below the target.

Table 1: Baseline patient characteristics for the total population and stratified by the LDL cholesterol target

	Total n=306	LDL cholesterol ¹ Below target (<2.50 mmol/l) n=100	LDL cholesterol ¹ Above target (≥2.50 mmol/l) n=97
Age (years)	69 (56-76)	70 (60-78)	67 (55-75)
Sex (male, %)	70	73	62
Smokers / quitters <1 year before inclusion (%)	26	26	27
Primary kidney disease (%)			
Diabetes mellitus	15	18	10
Glomerulonephritis	12	11	10
Renal vascular disease	32	36	27
Other	41	35	45
eGFR (ml/min/1.73 m ²) ²	16.7 ± 6.1	15.9 ± 6.1	16.5 ± 5.8
Proteinuria (g/24h) ³	1.1 (0.3-2.2)	1.2 (0.4-2.3)	1.0 (0.3-2.2)
Systolic blood pressure (mmHg) ⁴	143 ± 22	142 ± 20	146 ± 23
Hemoglobin (g/dl) ⁵	12.3 ± 1.4	12.3 ± 1.4	12.3 ± 1.4
Cardiovascular disease (%) ⁶	43	46	37
Diabetes mellitus (%) ⁷	27	37	17

Median (boundaries of interquartile range) is given for age and proteinuria and mean $\pm$ standard deviation is given for all other normally distributed continuous variables. ¹ Before multiple imputation, low density lipoprotein (LDL) cholesterol levels were available for 197 patients. ² Estimated glomerular filtration rate (eGFR) is calculated with the four-variable Modification of Diet in Renal Disease formula and available for 286 patients. ³ Available for 178 patients. ⁴ Available for 304 patients. ⁵ Available for 288 patients. ⁶ Defined as the presence of a cerebrovascular accident, vascular problems, angina pectoris, myocardial infarction, or decompensatio cordis. ⁷ Present as primary kidney disease or co-morbidity.

At the start of pre-dialysis care 17% of all 306 patients were treated with lipid-lowering medication (including statins, fibrates, and cholesterol absorption inhibitors, Table 2). Of the patients with LDL cholesterol levels above the treatment target (≥ 2.50 mmol/l) only 19% were prescribed lipid-lowering medication. For patients with TG levels above the treatment target (≥ 2.25 mmol/l) this percentage was 23%. After six months of follow-up, these percentages slightly increased to 21% and 26% respectively. After stratification by the LDL cholesterol treatment target (< 2.50 mmol/l), malnutrition/inflammation markers – such as serum albumin and c-reactive protein – were similar between patients below and above the target.

Table 2: Baseline lipid, treatment, and malnutrition-inflammation characteristics for the total population and stratified by the LDL cholesterol target

	Total n=306	LDL cholesterol ¹ Below target (< 2.50 mmol/l) n=100	LDL cholesterol ¹ Above target (≥ 2.50 mmol/l) n=97
LDL cholesterol (mmol/l) ¹	2.5 $\pm$ 0.9	1.8 $\pm$ 0.5	3.2 $\pm$ 0.7
TG (mmol/l) ²	1.8 $\pm$ 1.1	1.7 $\pm$ 0.9	1.9 $\pm$ 0.8
HDL cholesterol (mmol/l) ²	1.3 $\pm$ 0.4	1.2 $\pm$ 0.4	1.4 $\pm$ 0.5
Lipid-lowering medication (%) ³	17	17	19
Body mass index (kg/m ²) ⁴	26.4 $\pm$ 4.8	26.9 $\pm$ 5.1	25.9 $\pm$ 4.7
Albumin (mmol/l) ⁵	41.0 $\pm$ 4.5	40.6 $\pm$ 4.7	42.0 $\pm$ 4.0
C-reactive protein (mg/l) ⁶	4.2 (3.0-10.0)	4.5 (1.9-13.3)	4.0 (3.0-8.0)
Subjective global assessment (%) ⁷			
Well nourished	88	89	90
Moderately malnourished	12	11	10
Severely malnourished	0	0	0

Median (boundaries of interquartile range) is given for C-reactive protein and mean $\pm$ standard deviation is given for all other normally distributed continuous variables. ¹ Before multiple imputation, low density lipoprotein (LDL) cholesterol levels were available for 197 patients. ² Triglyceride (TG) and high density lipoprotein (HDL) cholesterol levels were available for 206 and 203 patients. ³ Defined as the prescription of statins, fibrates, and cholesterol absorption inhibitors and available for 270 patients. ⁴ Available for 303 patients. ⁵ Available for 270 patients. ⁶ Available for 178 patients. ⁷ Defined as well nourished (subjective global assessment (SGA) 6-7), moderately malnourished (SGA 3-5), and severely malnourished (SGA 1-2) and available for 232 patients.

Renal function decline

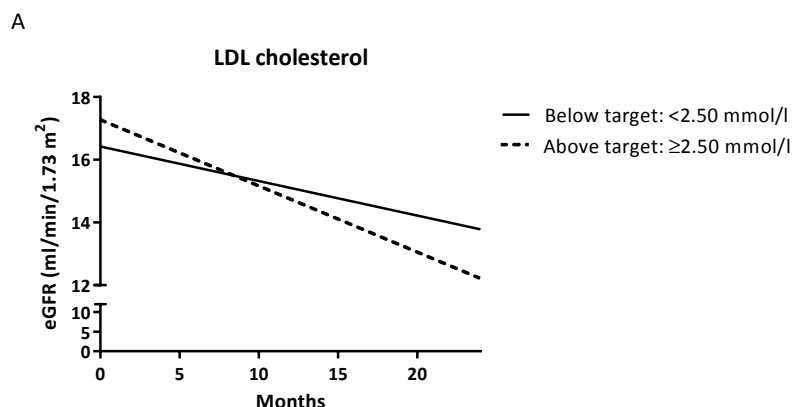
The overall renal function decline for all 306 patients was 0.19 [95% confidence interval (CI) 0.14;0.23] ml/min/1.73 m²/month. The median number of eGFR measurements during the first two years of follow-up was 3 (IQR 2-4) and 8%, 33%, and 59% of these patients had one, two, and three or more measurements respectively. Patients with LDL cholesterol levels above the treatment target of 2.50 mmol/l experienced an additional renal function decline (crude 0.10 [95% CI 0.00;0.20] ml/min/1.73 m²/month, $p < 0.05$) compared with patients with levels below the target (mean decline of 0.11 ml/min/1.73 m²/month, Table 3 and Figure 1A). A similar trend (crude 0.05 [95% CI -0.06;0.16] ml/min/1.73 m²/month) was found for patients with TG levels above the treatment target of 2.25 mmol/l (mean decline of 0.15 ml/min/1.73 m²/month in patients with levels below the target, Table 3 and Figure 1B). For HDL cholesterol the association was reversed, meaning that patients with HDL cholesterol levels

below the treatment target of 1.00 mmol/l experienced a slower renal function decline (crude -0.06 [95% CI -0.17;0.04] ml/min/1.73 m²/month) compared with patients with levels above the target (mean decline of 0.17 ml/min/1.73 m²/month, Table 3 and Figure 1C). However, when we analyzed HDL cholesterol levels as a ratio of LDL cholesterol levels (1.00 mmol/l / 2.50 mmol/l = 0.4), we again found a trend towards a faster renal function decline in patients with a ratio below 0.4 (crude 0.06 [95% CI -0.05;0.18] ml/min/1.73 m²/month) compared with patients above this ratio (mean decline of 0.14 ml/min/1.73 m²/month, Table 3 and Figure 1D). Adjustment for potential confounders did not change the results substantially (Table 3). Analyzing the number of targets not reached (including LDL cholesterol, TG, and HDL/LDL cholesterol ratio (range 1-3)) showed no additional decline when two or more targets, instead of only one target, were not reached.

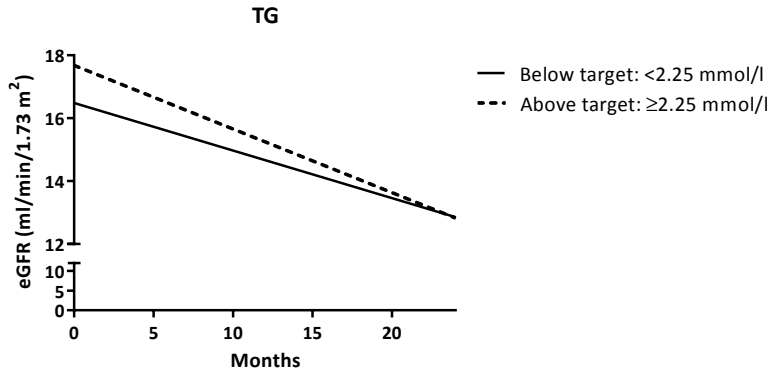
Additional analyses

LDL cholesterol levels above the treatment target of 2.50 mmol/l remained associated with an accelerated renal function decline after excluding patients whom were prescribed lipid-lowering medication, at any moment during follow-up (n=224 included in analysis, additional decline of 0.14 [95% CI 0.03;0.24] ml/min/1.73 m²/month, model 3 adjusted). The association of LDL cholesterol levels with renal function decline was comparable between centers that estimated (n=91) and directly measured (n=215) LDL cholesterol (additional decline of 0.12 [95% CI -0.04;0.27] ml/min/1.73 m²/month, model 3 adjusted, and 0.07 [95% CI -0.05;0.19] ml/min/1.73 m²/month, model 3 adjusted, respectively). Analyzing LDL cholesterol levels continuously resulted in an adjusted additional renal function decline of 0.06 ml/min/1.73 m²/month ([95% CI 0.01;0.11], model 3 adjusted) per each 1 mmol/l increase. For TG levels and the HDL/LDL ratio the trend remained present but did not reach statistical significance. Excluding eGFR values measured in the two weeks before reaching an endpoint (starting dialysis, receiving a kidney transplant, death, censoring) or excluding patients with only one eGFR measurement (n=281 included in analysis) resulted in very similar results.

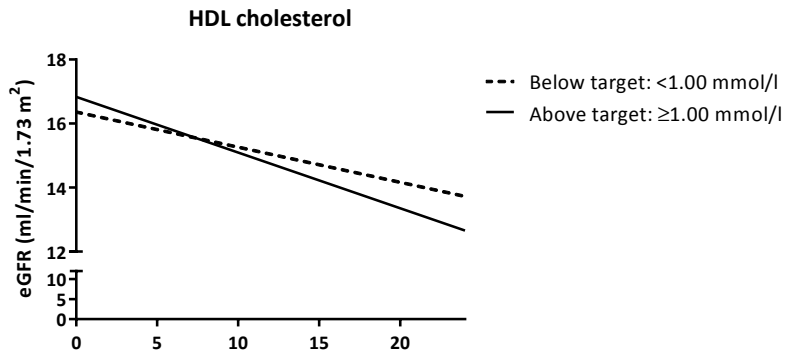
Figure 1: Association of lipid levels with renal function decline



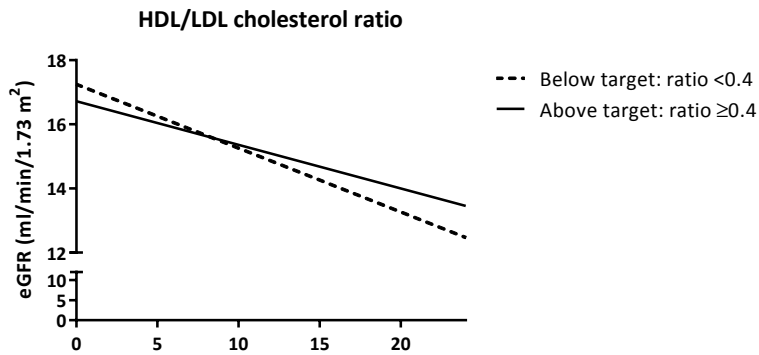
B



C



D



The lines represent the crude renal function decline for patients below and above the recommended treatment target for low density lipoprotein (LDL) cholesterol levels (A), triglyceride (TG) levels (B), high density lipoprotein (HDL) cholesterol levels (C), and the HDL/LDL cholesterol ratio (D). These intercepts and slopes were estimated with a linear mixed model.

Table 3: Association of lipid levels with renal function decline

	% of measure-ments	Crude additional decline [95% CI] (ml/min/1.73 m ²)	Adjusted additional decline ² [95% CI] (ml/min/1.73 m ²)	Adjusted additional decline ³ [95% CI] (ml/min/1.73 m ²)	Adjusted additional decline ⁴ [95% CI] (ml/min/1.73 m ²)
LDL cholesterol (mmol/l)					
<2.50	60	0 ⁵	0	0	0
≥2.50	40	0.10 [0.00;0.20] ⁶	0.11 [0.01;0.21] ⁶	0.11 [0.01;0.21] ⁶	0.11 [0.01;0.21] ⁶
TG (mmol/l)					
<2.25	74	0 ⁵	0	0	0
≥2.25	27	0.05 [-0.06;0.16]	0.06 [-0.05;0.17]	0.06 [-0.05;0.17]	0.06 [-0.05;0.17]
HDL cholesterol (mmol/l)					
<1.00	71	-0.06 [-0.17;0.04]	-0.07 [-0.17;0.03]	-0.07 [-0.18;0.03]	-0.07 [-0.18;0.03]
≥1.00	29	0 ⁵	0	0	0
HDL/LDL cholesterol ratio					
<0.40	27	0.06 [-0.18;0.05]	0.07 [-0.18;0.05]	0.07 [-0.18;0.04]	0.07 [-0.18;0.04]
≥0.40	73	0 ⁵	0	0	0
Targets not reached ¹					
1	74	0 ⁵	0	0	0
2	18	-0.01 [-0.15;0.13]	0.00 [-0.14;0.14]	0.00 [-0.14;0.14]	0.00 [-0.14;0.14]
3	8	0.04 [-0.15;0.23]	0.04 [-0.15;0.23]	0.04 [-0.15;0.23]	0.04 [-0.15;0.23]

The additional decline in renal function [95% confidence interval (CI)] is given for the lipid level category reaching the recommended treatment target (low density lipoprotein (LDL) cholesterol: ≥2.50 mmol/l; triglycerides (TG): ≥2.25 mmol/l; high density lipoprotein (HDL) cholesterol: <1.00 mmol/l) compared with the reference category (not reaching the recommended treatment target). The decline was assessed with a linear mixed model and a positive number indicates an additional decline in renal function. ¹ Including the targets for LDL cholesterol, TG, and HDL/LDL cholesterol ratio. ² Adjusted for sex and age. ³ Additionally adjusted for primary kidney disease, smoking, cardiovascular disease, diabetes mellitus, body mass index, systolic blood pressure, and proteinuria. ⁴ Additionally adjusted for albumin, c-reactive protein, and subjective global assessment. ⁵ The crude mean [95% CI] renal function decline in patients reaching the recommended treatment targets, were 0.11 [95% CI 0.04;0.18] ml/min/1.73 m²/month for LDL cholesterol, 0.15 [95% CI 0.09;0.22] ml/min/1.73 m²/month for TG, 0.17 [95% CI 0.11;0.24] ml/min/1.73 m²/month for HDL cholesterol, 0.14 [95% CI 0.07;0.20] ml/min/1.73 m²/month for HDL/LDL cholesterol ratio, and 0.15 [95% CI -0.08;0.22] ml/min/1.73 m²/month for reaching only one of the targets. ⁶ p<0.05.

Discussion

In our cohort of incident patients receiving pre-dialysis care, an accelerated renal function decline was present in patients with LDL cholesterol levels above compared with below the treatment target (<2.50 mmol/l), independent of the prescription of lipid-lowering medication. For TG levels above the treatment target (≥ 2.25 mmol/l) and a HDL/LDL cholesterol ratio below 0.4 a trend was present, which did not reach statistical significance. Furthermore, at the start of pre-dialysis care lipid-lowering medication was only prescribed to 19% of the patients with LDL cholesterol levels above the treatment target and 23% of the patients with TG levels above the treatment target.

Our observation that abnormal lipid levels were associated with an accelerated renal function decline is in line with studies performed in patients with early to moderate stages of CKD (stages 1-4).¹⁷⁻²¹ Our findings are not in line with studies performed in patients receiving dialysis, in whom abnormal lipid levels seem to be beneficial.⁴⁻⁶ In terms of risk profiles, pre-dialysis patients resemble early-stage CKD patients more than patients receiving dialysis. This could explain why we did not find a similar reversed association as seen in dialysis patients. Moreover, we found that especially high LDL cholesterol levels were associated with an accelerated renal function decline. Our results may therefore suggest that statins (possibly combined with cholesterol absorption inhibitors), which mainly lowers LDL cholesterol, can slow down renal function decline. However, statin trials showed contradictory effects on renal function decline in pre-dialysis patients^{22;34;35}, but we have to keep in mind that these trials rarely included patients with advanced stages of CKD (4-5). Only in the recently published SHARP trial¹² more than half of the included pre-dialysis patients had CKD stages 4-5 (3,786 out of 6,247). This trial showed no effect on the combined endpoint of reaching end-stage renal disease, defined as starting dialysis or receiving a kidney transplant, or the doubling of serum creatinine. This is in line with our findings, revealing that the effect of abnormal lipid levels on renal function decline was independent of the prescription of lipid-lowering medication. Unfortunately, our study was underpowered to investigate the course of renal function decline in patients who were prescribed these medications (n=52).

Furthermore, we found a low percentage of patients whom were prescribed lipid-lowering medication (17%), which is in line with other studies performed in pre-dialysis patients³⁶ and in patients receiving hemodialysis³⁷. In addition, a striking finding in our cohort is that only 19% of the patients with LDL cholesterol levels above the treatment target (≥ 2.50 mmol/l) and 23% of the patients with TG levels above the treatment target (≥ 2.25 mmol/l) were actually prescribed lipid-lowering medication at baseline. These percentages increased to 21% and 26% respectively after six months of pre-dialysis care, but were still quite low. These findings are in line with the study of Mason *et al.*³⁷, showing that only 20.8% of the patients on hemodialysis with a total cholesterol level ≥ 5.17 mmol/l, resembling patients with LDL cholesterol and/or TG levels above the treatment target, were actually treated with statins. An explanation for this low percentage in patients receiving pre-dialysis care and dialysis treatment could be that physicians are not convinced that the prescription of lipid-lowering

medication is beneficial in these patients. For example, it may have been unclear for physicians whether patients with abnormal lipid levels, but without an additional cardiovascular risk factor (e.g. history of diabetes mellitus or cardiovascular disease), should be treated with lipid-lowering medication. Our findings indeed showed a low prevalence of these co-morbidities in patients with LDL cholesterol levels above the treatment target of 2.50 mmol/l. Furthermore, a subgroup analysis in the SHARP trial suggests that lipid-lowering medication is beneficial for patients without diabetes mellitus or cardiovascular disease, leading to less major cardiovascular events. This evidence may have convinced physicians to only prescribe lipid-lowering medication to these patients. However, the effect of lipid-lowering medication on renal function decline has not been elucidated yet. More trials in pre-dialysis patients that investigate this effect are needed but may not be justified to perform. The effect of lipid-lowering medication on the reduction of major cardiovascular events is substantial and this evidence may be sufficient to prescribe these medications to pre-dialysis patients. Therefore, post-hoc subgroup analyses of published trials, meta-analyses, and new prospective follow-up data should gain more information about the possible renoprotective effect of lipid-lowering medication.

The great strength of our study is the longitudinal character in incident patients. In this way we could take into account lipid level variability and changes during pre-dialysis care. Furthermore, we could assess renal function decline, which is a more detailed outcome measure as compared with the robust measures used in for example the SHARP trial (starting end-stage renal disease or doubling of serum creatinine). A disadvantage of our study is the presence of missing data. Lipid levels were not routinely measured at each pre-dialysis care visit. These missing data resulted in exclusion of 39% (196 out of 502) of the patients. Fortunately, baseline characteristics were very similar between the 306 patients included and 196 patients excluded from our statistical analyses. Therefore, we could reasonably assume that the exclusion of patients with missing lipid levels did not bias our results. The last thing we have to keep in mind is that our study only includes patients with an eGFR <20-30 ml/min/1.73 m² who are referred to an outpatient clinic for pre-dialysis care. Therefore, these results are not generalizable to all patients with CKD stages 4-5.

In conclusion, high levels of LDL cholesterol are associated with an accelerated renal function decline. These findings make the recommendation to prescribe lipid-lowering medication to pre-dialysis patients even stronger. However, further research in the specific population of pre-dialysis patients is necessary to investigate whether lipid-lowering medication can indeed slow down renal function decline.

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Chapter 6 |

Course of uremic symptoms and health-related quality of life during specialized pre-dialysis care

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Abstract

Background: Concerns are present on the limited value of renal function alone in defining the optimal moment to start with dialysis. Uremic symptoms and health-related quality of life (HRQOL) may have additional clinical value in defining this moment, but no prospective data are available. The aims of our study were to describe the course of uremic symptoms and HRQOL during pre-dialysis care and to investigate their association with the start of dialysis.

Methods: In the prospective PRE-dialysis PATient REcord-2 (PREPARE-2) cohort study, incident patients starting specialized pre-dialysis care were included when referred to one of the 25 Dutch participating outpatient clinics (2004-2011). In the present analysis, 436 patients were included because of available information on uremic symptoms and HRQOL. Clinical data, uremic symptoms (revised illness perception questionnaire), and HRQOL (short form-36 questionnaire; physical and mental summary score) were collected every six-month interval. A time-dependent Cox proportional hazards model was used to associate uremic symptoms and physical/mental HRQOL with the start of dialysis.

Results: All symptoms increased, especially fatigue and loss of strength, and both the physical and mental summary score decreased over time, with the most pronounced change during the last 6-12 months. Furthermore, each additional symptom (adjusted hazard ratio (HR) 1.05 [95% confidence interval (CI) 1.00;1.10]) and each 3-point lower physical and mental summary score (adjusted HR 1.04 [95% CI 1.02;1.06] and 1.04 [95% CI 1.02;1.07] respectively) were associated with a higher risk of starting dialysis within the subsequent six months.

Conclusion: The number of uremic symptoms increased and both the physical and mental HRQOL score decreased during pre-dialysis care and these changes were associated with the start of dialysis. These results may indicate that symptoms and HRQOL are good markers for the medical condition and disease stage of pre-dialysis patients, and are therefore good candidates to be used in defining the optimal moment to start with dialysis.

Introduction

A large debate is ongoing about the optimal moment to start with dialysis.¹⁻⁵ The last decades there has been a trend towards starting dialysis at higher levels of renal function.⁶⁻⁹ However, many observational studies⁹⁻¹⁸ and the first randomized controlled trial, the Initiating Dialysis Early and Late (IDEAL) study¹⁹, showed no difference in patient survival between early and late initiation of dialysis. In addition, consensus has been reached within the European Renal Best Practice guidelines on the limited value of renal function alone in the decision to start with dialysis.⁴ Uremic signs and symptoms (throughout text indicated as symptoms) and a low health-related quality of life (HRQOL), are highly present in pre-dialysis patients and therefore may have an added clinical value on top of renal function in this difficult decision.

Symptoms can start appearing when renal function decreases to half of the normal function and continue to rise when renal function further decreases.²⁰ Furthermore, several cross-sectional studies showed that a low renal function is associated with a low HRQOL²¹⁻²³ and that HRQOL is a good predictor for mortality and progression to end-stage renal disease in chronic kidney disease (CKD) patients²⁴. However, knowledge is lacking on the specific development of symptoms and HRQOL during pre-dialysis care. Several guidelines indicating when to start dialysis already take into account the presence of symptoms.^{25;26} However, the incorporation of these symptoms into the guidelines are not consistent and specific. Furthermore, both the IDEAL study and some observational studies showed that for the decision to start with dialysis, symptoms were at least as important as renal function.^{3;4;19;27} In the late-start group of the IDEAL study, many patients (75.9%) started dialysis earlier than intentioned because of these symptoms. However, no prospective data is present about which symptoms and what level of HRQOL are important for nephrologists and patients in this decision.

To get a better understanding of whether, when, and how the presence of symptoms and the level of HRQOL could be used in clinical practice in defining the optimal moment to start with dialysis, knowledge on the precise course of multiple symptoms and HRQOL, both physical and mental, in pre-dialysis patients is necessary. Therefore, our aims were to describe the course of symptoms and HRQOL during pre-dialysis care (CKD stages 4-5) and their associations with the risk of starting dialysis.

Methods

Study design

The PRE-dialysis PATient REcord-2 (PREPARE-2) study is a follow-up study of incident pre-dialysis patients treated in 25 Dutch nephrology outpatient clinics in The Netherlands. Of these participating outpatient clinics 4 were academic and 21 were peripheral, and all were publicly funded. Patients were included between July 2004 and June 2011, at the start of specialized pre-dialysis care. Patients were treated by their nephrologists in a regular scheme

according to the treatment guidelines of the Dutch Federation of Nephrology²⁸, a Dutch guideline partly based on the K/DOQI²⁶ and KDIGO guidelines²⁹. Patients were followed until the start of dialysis, receiving a kidney transplant, death, or censoring. Censoring was defined as: moving to an outpatient clinic not participating in the PREPARE-2 study, recovery of kidney function, refusal of further study participation, lost to follow-up or August 1, 2012, whichever came first. The study was approved by the Medical Ethics Committee or Institutional Review Board (as appropriate) of all participating centers.

Patients

To be eligible for inclusion, patients had to be at least eighteen years of age and the inclusion should take place at the moment of referral to a specialized pre-dialysis outpatient clinic. In practice, this refers to incident pre-dialysis patients with an estimated glomerular filtration rate (eGFR) of less than 20-30 ml/min/1.73 m², and most of them have a progressive renal function loss. Patients with a failing kidney transplant were also included in the study if the transplantation was at least one year ago. All participants gave their written informed consent prior to study inclusion.

Data collection

Data on demography, biometry, primary kidney disease, co-morbidities, medication use, and HRQOL were collected at the start of specialized pre-dialysis care, at the moment of reaching one of the study endpoints (throughout text indicated as endpoint) as described above, and in intermediate six-month intervals. Laboratory data were extracted from the electronic hospital information systems or medical records. Primary kidney disease was classified according to the codes of the European Renal Association-European Dialysis and Transplantation Association.³⁰

Measurements and definitions

The revised illness perception questionnaire (IPQ-R)³¹ was used to assess the onset of symptoms. This questionnaire has been validated^{32,33} and is widely used in the field of nephrology³⁴⁻³⁶. The following symptoms from the IPQ-R (12 out of 14 symptoms) can be considered as uremia- or disease-related and were included in our analyses; pain, nausea, breathlessness, weight loss, fatigue, stiff joints, wheeziness, headaches, upset stomach, sleep difficulties, dizziness, and loss of strength. The onset of these symptoms during pre-dialysis care was defined as answering 'yes' for the first time on the question 'I have experienced this complaint since the beginning of my kidney disease'. HRQOL was assessed with the short form-36 (SF-36) questionnaire³⁷, a generic validated questionnaire consisting of 36 items that can be divided into eight subscales. The scores on the individual items within a subscale were summed and transformed to a 0-100 scale, with higher scores indicating a better HRQOL. The eight subscales can further be divided into two summary measures; physical summary score (consisting of the four subscales physical functioning, role-physical, bodily pain, and general health) and mental summary score (consisting of the four subscales vitality, social functioning,

role-emotional, and mental health). Only the two summary measures (unstandardized) were used in our analyses. Estimated GFR and creatinine clearance (CrCl) were used as indicators for renal function. GFR was estimated using the four-variable Modification of Diet in Renal Disease (MDRD) formula.³⁸ CrCl was estimated with the following formula: creatinine in urine (mmol/24h) * 700 / serum creatinine (μmol/l), and normalized per 1.73 m² of body surface area using the formula of Du Bois and Du Bois³⁹. The measurement at the moment of reaching an endpoint was defined as follows; the measurement closest to the moment of reaching an endpoint and not measured more than six months before this moment.

Outcome

The outcomes for our first aim were the frequencies of all symptoms and the mean physical and mental summary score over time before reaching one of the endpoints. The outcome for our second aim was the start of dialysis during follow-up.

Statistical analyses

The patients who filled in at least one HRQOL questionnaire, including the IPQ-R and the SF-36, during pre-dialysis care (n=436) were included. Baseline characteristics were presented as mean ± standard deviation (SD) for normally distributed variables and as median (boundaries of interquartile range, IQR) for skewed variables. Missing values at baseline and at the moment of reaching an endpoint were imputed (using twenty repetitions) with the method of multiple imputation in PASW/SPSS version 20.0. This is a recommended technique when data is missing at random, in which missing data for a patient are imputed by a value that is predicted by other known characteristics of this patient.^{40;41} All characteristics in Table 1, all symptoms, and the physical and mental summary score (at baseline and at the moment of reaching an endpoint), follow-up time, and the type of endpoint reached (starting dialysis, receiving a kidney transplant, death, end of follow-up (August 1, 2012), or other endpoint; moving to an outpatient clinic not participating in the PREPARE-2 study, recovery of kidney function, refusal of further study participation, or lost to follow-up) were included in the model. Skewed distributed continuous variables and the follow-up time were logarithmically transformed. At baseline, 100% of the patients filled in a questionnaire completely or partly and this was 66% at the moment of reaching an endpoint.

To describe the course of symptoms and HRQOL during pre-dialysis care, the frequency of all twelve separate symptoms, the mean (standard error of the mean [SEM]) total number of symptoms, the mean [SEM] physical summary score, and the mean [SEM] mental summary score at the start of pre-dialysis care and at the moment of reaching an endpoint were calculated. A linear mixed model was used to investigate the statistical difference between these two time points, adjusted for eGFR. This model takes into account correlations between repeated measurements within the same individual. Second, the mean [SEM] total number of symptoms, physical summary score, mental summary score, eGFR, and CrCl at the moment of reaching an endpoint and the preceding three time points were estimated with a linear mixed

model. Moreover, on each time point a Pearson's correlation was calculated between eGFR or CrCl and the total number of symptoms, the physical summary score, and the mental summary score. Furthermore, we repeated all analyses in the subgroup of patients that started dialysis and in the subgroup of patients that did not start with dialysis but reached one of the other type of endpoints.

A time-dependent Cox proportional hazards model was used to investigate the risk of starting dialysis within six months. Symptoms were analyzed separate and as a total number. The physical and mental summary score were analyzed in steps of 3 score points (is considered to be clinically relevant⁴²). The analyses were adjusted for the potential confounders age, sex, diabetes mellitus, cardiovascular disease, and time-dependent eGFR.

To test the robustness of our analyses, four sensitivity analyses were performed. First, we repeated our analyses subdividing the group of patients who did not start with dialysis into more categories: receiving a kidney transplant, death, end of follow-up, and other endpoint. Second, we repeated our imputation procedure and analyses after defining our measurement at the moment of reaching an endpoint as really measured at that moment, and not in the preceding six months. Third, we performed a time-dependent Cox proportional hazards model with starting dialysis, receiving a kidney transplant, and death as a combined outcome. Fourth, we used other available measurements to define weight loss and fatigue at the moment of reaching an endpoint. Weight loss was redefined as >5% of weight lost. Fatigue was redefined as scoring below the Dutch mean normal score on the vitality subscale of the SF-36 questionnaire ($68.6 \approx 70$ ⁴³).

Results

Baseline characteristics

In total, 502 incident pre-dialysis patients were included in the PREPARE-2 study of whom 436 patients were available for our analysis. Table 1 shows that the median (IQR) age of these patients was 69 (56-76) years, 66% were male and the mean $\pm$ SD eGFR was 16.9 ± 6.1 ml/min/1.73 m². The 66 patients excluded from our analyses were younger, had a lower eGFR and CrCl, experienced more proteinuria, and had a higher prevalence of diabetes mellitus.

Table 1: Baseline characteristics for total population and stratified by type of endpoint

	Total n=436	Started dialysis n=225	Other endpoint n=211
Age (years)	69 (56-76)	68 (56-75)	71 (56-78)
Sex (male, %)	66	68	64
Caucasian (%)	92	92	93
Body mass index (kg/m ²) ¹	26.7 ± 5.1	27.1 ± 5.0	26.2 ± 5.2
Smokers / quitters <1 year before inclusion (%)	25	24	25
Primary kidney disease (%)			
Diabetes mellitus	13	12	15
Glomerulonephritis	14	14	13
Renal vascular disease	31	31	30
Other	42	43	42
eGFR (ml/min/1.73 m ²) ²	16.9 ± 6.1	14.5 ± 5.3	19.4 ± 5.8
Proteinuria (g/24h) ³	1.0 (0.3-2.2)	1.4 (0.4-2.6)	0.7 (0.2-1.4)
Urea (mmol/l) ⁴	22.2 ± 7.0	23.7 ± 7.1	20.5 ± 6.6
Creatinine clearance (ml/min/1.73 m ²) ⁵	19.2 ± 7.9	16.6 ± 7.0	22.6 ± 7.7
Systolic blood pressure (mmHg) ⁶	142 ± 22	143 ± 22	140 ± 23
Hemoglobin (g/dl) ⁷	12.3 ± 1.5	12.2 ± 1.4	12.4 ± 1.6
Potassium (mmol/l) ⁸	4.7 ± 0.6	4.7 ± 0.7	4.7 ± 0.6
Bicarbonate (mmol/l) ⁹	23.0 ± 4.0	22.1 ± 3.7	24.0 ± 4.0
Co-morbidities (%)			
Cardiovascular disease ¹⁰	42	42	43
Diabetes Mellitus ¹¹	26	25	27

Median (boundaries of interquartile range) is given for age and proteinuria and mean ± standard deviation is given for all other normally distributed continuous variables. ¹ Available for 428 patients. ² Estimated glomerular filtration rate (eGFR) is calculated with the four-variable Modification of Diet in Renal Disease formula and available for 379 patients. ³ Available for 225 patients. ⁴ Available for 365 patients. ⁵ Creatinine clearance is estimated with the formula creatinine in urine (mmol/24h) * 700 / serum creatinine (μmol/l) and available for 242 patients. ⁶ Available for 432 patients. ⁷ Available for 378 patients. ⁸ Available for 377 patients. ⁹ Available for 223 patients. ¹⁰ Defined as presence of a cerebrovascular accident, vascular problems, angina pectoris, myocardial infarction, or decompensatio cordis. ¹¹ Present as primary kidney disease or co-morbidity.

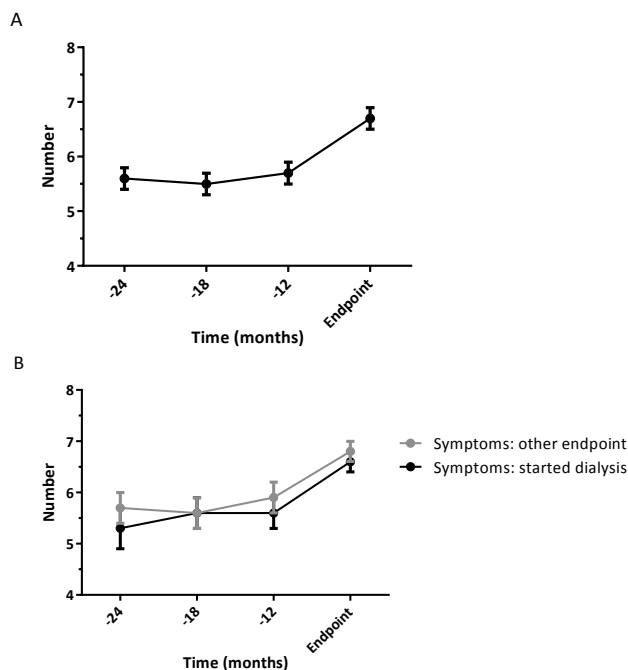
Description of the course of symptoms, HRQOL, and renal function

In total, 225 of the 436 patients (52%) started dialysis (median follow-up 12.2 (IQR 5.3-21.4) months). Of the 211 patients that reached another endpoint (median follow-up 22.5 (IQR 11.9-40.8) months), 15% were transplanted, 13% died, 24% refused further participation, 8% had a recovered kidney function, 4% moved to another center, and 36% were still in the study. The overall eGFR and CrCl decline (n=436) were 0.16 [95% CI 0.11;0.21] and 0.21 [95% CI 0.10;0.32] ml/min/1.73 m²/month respectively. The median number of filled in HRQOL questionnaires was 3 (IQR 2-4) and respectively 19%, 26%, and 55% filled in one, two, and three or more questionnaires during pre-dialysis care. Only the minority were filled in with the help of medical staff (1%). Furthermore, 21% were filled in with the help of a friend or family member and 78% were filled in with no help. After imputation all patients had at least two complete questionnaires.

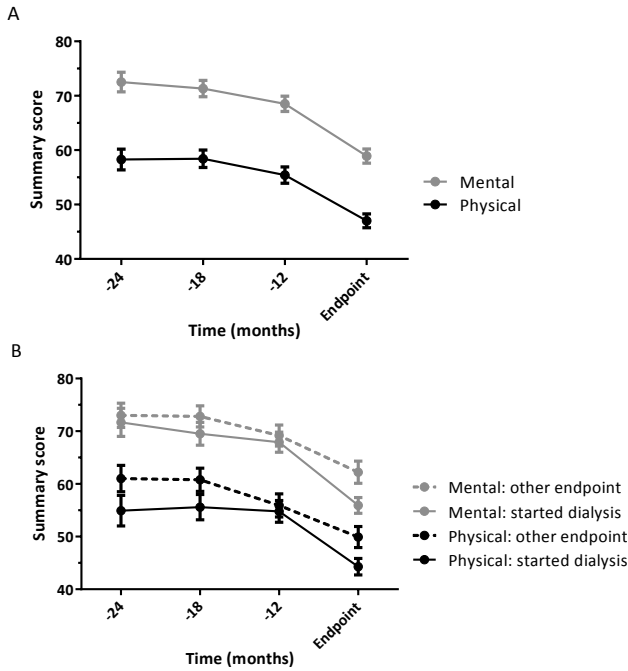
At the start of pre-dialysis care, most of the symptoms were already experienced by 20 to 50% of the patients (Table 2). Only the symptoms fatigue, stiff joints, and loss of strength were experienced by more than 50% of the patients. The onset of fatigue and loss of strength were the strongest during pre-dialysis care and of wheeziness, headaches, and upset stomach the lowest. The onset of all symptoms was comparable between patients who started dialysis and patients reaching another endpoint. The mean [SEM] total number of symptoms was 4.8 [0.1] at the start of pre-dialysis care and 6.7 [0.2] at the moment of reaching an endpoint. Figure 1A depicts the course of the total number of symptoms during the last two years of pre-dialysis care. The onset of symptoms was most frequent during the last six to twelve months before reaching an endpoint, which was comparable between patients who started dialysis and patients reaching another endpoint (Figure 1B). On all four time points, symptoms were not correlated with eGFR or CrCl.

The physical summary score decreased from 54.4 [SEM 1.1] at the start of pre-dialysis care to 47.0 [SEM 1.3] at the moment of reaching an endpoint (Table 2). The mental summary score decreased from 67.8 [SEM 1.0] to 58.9 [SEM 1.4]. The sharpest decrease was observed in the six to twelve months before reaching an endpoint (Figure 2A). After stratification by the type of endpoint reached, patients who started dialysis showed a slightly stronger decrease of both the physical and mental summary score (Figure 2B). On all four time points, no correlation was present with eGFR or CrCl. Figure 3A confirms the gradual decrease of eGFR and CrCl during pre-dialysis care, which was stronger in patients who started dialysis (Figure 3B).

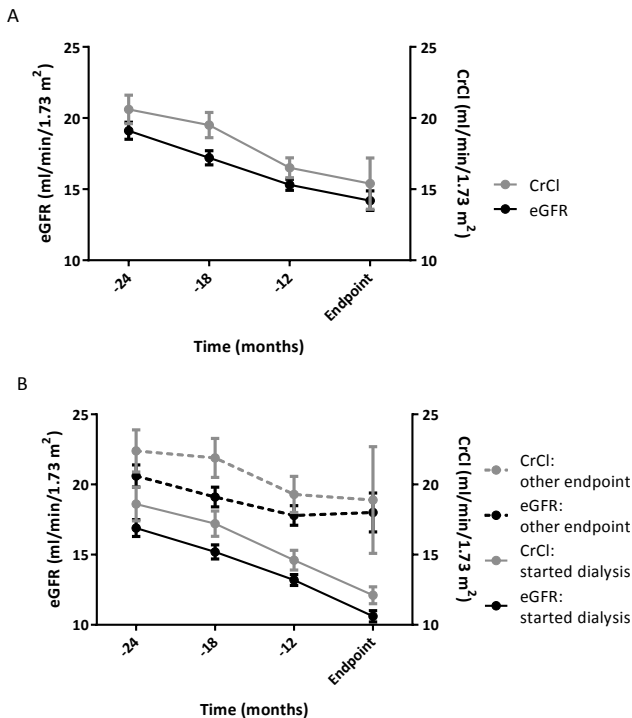
Figure 1: Course of symptoms during pre-dialysis care



The course of the total number of symptoms is presented for the total population (A) and stratified by the type of endpoint reached (dialysis or other endpoint, B). The black and grey dots indicate the mean and the error bars indicate the standard error of the mean [SEM]. The time in months before reaching an endpoint is presented on the x-axis (-12 means that the measurement was 7-12 months before reaching an endpoint, -18 means 13-18 months etc). On the y-axis, the mean [SEM] total number of symptoms is presented, which can range from 0 to 12.

Figure 2: Course of health-related quality of life during pre-dialysis care

The course of the physical and mental summary score are presented for the total population (A) and stratified by the type of endpoint reached (dialysis or other endpoint, B). The black and grey dots indicate the mean and the error bars indicate the standard error of the mean [SEM]. The time in months before reaching an endpoint is presented on the x-axis (-12 means that the measurement was 7-12 months before the moment of reaching an endpoint, -18 means 13-18 months etc). On the y-axis, the mean [SEM] score from the short form-36 questionnaire is presented (separately for the physical and mental summary measure), which can range from 0 to 100.

Figure 3: Course of renal function during pre-dialysis care

The course of estimated glomerular filtration rate (eGFR) and creatinine clearance (CrCl) are presented for the total population (A) and stratified by the type of endpoint reached (dialysis or other endpoint, B). The black and grey dots indicate the mean and the error bars indicate the standard error of the mean [SEM]. The time in months before reaching an endpoint is presented on the x-axis (-12 means that the measurement was 7-12 months before the moment of reaching an endpoint, -18 means 13-18 months etc). On the left y-axis, the mean [SEM] eGFR (ml/min/1.73 m²) is presented, and on the right y-axis the mean [SEM] CrCl (ml/min/1.73 m²).

Table 2: Comparison of the presence of symptoms and health-related quality of life at the start of pre-dialysis care and the moment of reaching an endpoint

	All n=436			Started dialysis n=225			Other endpoint n=211		
	Start	Endpoint	% onset ¹	Start	Endpoint	% onset ¹	Start	Endpoint	% onset ¹
<i>Symptoms</i>									
Pain	34.0	52.4	27.9	32.1	50.9	27.7	36.0	53.9	28.0
Nausea	29.0	46.8	25.1	30.8	45.0	20.5	27.0	48.7	29.7
Breathlessness	30.6	50.3	28.4	34.2	51.4	26.1	26.7	49.2	30.7
Weight loss	38.7	54.5	25.8	37.2	54.7	27.9	40.4	54.3	23.3
Fatigue	82.5	94.0	65.7	83.4	93.1	58.4	81.5	94.9	72.4
Stiff joints	51.3	67.9	34.1	51.0	64.7	28.0	51.6	71.4	40.9
Wheeziness	25.2	34.8	12.8	26.1	33.6	10.1	24.4	36.1	15.5
Headaches	23.0	37.1	18.3	20.4	33.4	16.3	25.7	41.1	20.7
Upset stomach	30.2	42.9	18.2	30.4	43.0	18.1	30.0	42.7	18.1
Sleep difficulties	37.9	55.3	28.0	41.1	57.7	28.2	34.5	52.8	27.9
Dizziness	33.7	50.3	25.0	34.6	48.0	20.5	32.8	52.8	29.8
Loss of strength	61.1	82.8	55.8	61.6	81.5	51.8	60.6	84.1	59.6
Number (total is 12)	4.8 [0.1]	6.7 [0.2] ⁴	-	4.8 [0.2]	6.6 [0.2] ⁴	-	4.7 [0.2]	6.8 [0.2] ⁴	-
<i>HRQOL</i>									
Physical ²	54.4 [1.1]	47.0 [1.3] ⁴	-	53.6 [1.5]	44.3 [1.6] ⁴	-	55.2 [1.6]	49.9 [2.0] ³	-
Mental ²	67.8 [1.0]	58.9 [1.4] ⁴	-	67.0 [1.4]	55.9 [1.7] ⁴	-	68.7 [1.4]	62.2 [2.2] ³	-

Symptoms are presented as frequencies (%) and the number of symptoms and health-related quality of life (HRQOL) as mean [standard error of the mean]. ¹ The onset of symptoms (%) was calculated as follows: (% endpoint - % start)/(100% - % start). ² The mean physical and mental summary scores in the general Dutch population are 76.3 and 77.9 respectively. ³ p < 0.05, adjusted for eGFR; ⁴ p < 0.005, adjusted for eGFR, difference between baseline and the moment of reaching an endpoint, obtained with a linear mixed model.

Association of symptoms and HRQOL with the start of dialysis

The symptoms breathlessness, weight loss, fatigue, and wheeziness showed the strongest association with the start of dialysis within the subsequent six months (Table 3, adjusted column). Each additional symptom resulted in a crude 1.02 fold [95% confidence interval (CI) 0.97;1.07] increased risk. Adjustment for potential confounders increased this hazard ratio (HR) to 1.05 [95% CI 1.00;1.10]. For HRQOL, every 3-point lower physical and mental summary score were associated with a higher risk of starting dialysis within the subsequent six months (crude HR 1.03 [95% CI 1.01;1.05] and HR 1.04 [95% CI 1.02;1.06], respectively). The results slightly increased after adjustment for potential confounders (Table 3).

Sensitivity analyses

All sensitivity analyses - 1.) extensive stratification of the subgroup of patients that did not start with dialysis but reached one of the other type of endpoints, 2.) defining the measurement at the moment of reaching an endpoint as really measured at that moment (not in the preceding six months), 3.) using a combined outcome including the start of dialysis, receiving a kidney transplant, and death, and 4.) redefining fatigue and weight loss - resulted in comparable courses of symptoms and HRQOL over time and similar risk estimates, implying robust results.

Table 3: Association of symptoms and a low health-related quality of life with the risk of starting dialysis within the subsequent six months based on separate time-dependent Cox proportional hazards model

	Crude HR [95% CI] (events/n = 225/436)	Adjusted HR ¹ [95% CI] (events/n = 225/436)
<i>Symptoms</i>		
Pain	1.02 [0.77;1.35]	1.04 [0.78;1.39]
Nausea	1.13 [0.85;1.49]	1.10 [0.81;1.49]
Breathlessness	1.29 [0.98;1.69]	1.28 [0.96;1.71]
Weight loss	1.00 [0.75;1.32]	1.33 [0.99;1.77]
Fatigue	1.25 [0.81;1.94]	1.48 [0.94;2.31]
Stiff joints	0.95 [0.72;1.26]	1.07 [0.80;1.44]
Wheeziness	1.06 [0.79;1.42]	1.29 [0.94;1.78]
Headaches	0.86 [0.63;1.18]	1.08 [0.76;1.53]
Upset stomach	1.08 [0.82;1.43]	0.90 [0.67;1.22]
Sleep difficulties	1.22 [0.92;1.60]	1.17 [0.89;1.55]
Dizziness	0.95 [0.72;1.26]	1.13 [0.86;1.49]
Loss of strength	1.00 [0.74;1.34]	1.20 [0.89;1.64]
Number (per 1 complaint)	1.02 [0.97;1.07]	1.05 [1.00;1.10]
<i>HRQOL</i>		
Physical (per 3 score points)	1.03 [1.01;1.05] ³	1.04 [1.02;1.06] ³
Mental (per 3 score points)	1.04 [1.02;1.06] ³	1.04 [1.02;1.07] ³

HRQOL; health-related quality of life. The hazard ratio (HR) [95% confidence interval (CI)] represents the increased risk of starting dialysis within the subsequent six months in patients with the symptom compared with patients without the symptom present, the increased risk with each additional symptom, and the increased risk with every 3-point lower physical and mental summary score. ¹ Adjusted for age, sex, diabetes mellitus, cardiovascular disease, and time dependent eGFR. ² $p < 0.05$; ³ $p < 0.005$.

Discussion

In our cohort of incident patients on pre-dialysis care, many patients had already experienced symptoms at the start of pre-dialysis care. In addition, the presence of all reported symptoms increased during pre-dialysis care, especially fatigue and loss of strength. HRQOL, defined as physical and mental summary score, decreased during pre-dialysis care. The sharpest increase of symptoms and decrease of HRQOL was observed during the last six to twelve months of pre-dialysis care. These results were supported by the observation that patients who reported a high number of symptoms or a low HRQOL started dialysis earlier than patients who reported a low number of symptoms or a high HRQOL.

To our knowledge, this is the first study to report the onset of symptoms over time in patients on specialized pre-dialysis care. Our finding that HRQOL, both physical and mental, decreased during pre-dialysis care is in line with other studies.²¹⁻²³ These cross-sectional studies demonstrated that HRQOL was highest in the 'healthy' general population, lowest in patients on dialysis, and in between in patients with CKD not on dialysis. However, the results of these studies were not CKD-stage specific and because of the cross-sectional character, the change of HRQOL over time could not be described or associated with the start of dialysis.

Therefore, the major strength of our study is the follow-up character, instead of a cross-sectional design. This gave us the opportunity to report the course of symptoms and HRQOL over the last years of pre-dialysis care. However, an issue that deserves further attention is that not all consecutive patients starting pre-dialysis care were included in the PREPARE-2 study, only those who were asked and willing to participate, which could have led to selection bias. Unfortunately, it is very difficult to ascertain the direction of this bias. Besides this important issue, some patients reached another endpoint than dialysis, leading to a large diversity of patients at the moment of reaching an endpoint. However, results were comparable between all type of endpoints reached. Another issue that deserves attention is that symptoms were obtained from the IPQ-R. This questionnaire is not primarily designed to assess the longitudinal presence of symptoms and does not include questions about severity. This means that the 'yes' category of the IPQ-R consists of patients having experienced the onset of that symptom a few years ago or just recently. This mixture of onset times in our study could have led to an underestimation of the real risks of starting dialysis. Besides this, symptom burden is a reliable measure because it shows similar correlations with HRQOL and illness perceptions as symptom severity.^{44,45} Moreover, in answering symptom questions in the IPQ-R, patients' perceptions of illness play a major role.⁴⁶ The formulation of the question may also influence the response of patients. However, more objective measures of weight loss and fatigue resulted in similar frequencies. Finally, a completely filled in IPQ-R and SF-36 questionnaire were not available for 66 patients. Therefore, our choice to only analyze patients with at least one filled in questionnaire could have led to selection bias.⁴¹ However, the 66 excluded patients had a slightly worse prognosis than the 436 included patients, so our results may be an underestimation.

Uremia is defined as all the signs and symptoms accompanying advanced kidney failure that cannot be attributed to co-morbid disease. The onset of uremia-related signs and symptoms can become present when renal function decreases to half of the normal function (normal eGFR is 100-120 ml/min/1.73 m² on the age of 30) and continue to rise when renal function further decreases.²⁰ This means that uremia-related symptoms mainly become present in patients with CKD stages 4-5. Therefore, the results from our pre-dialysis cohort, showing an increase in symptoms over time and as a consequence a decrease in perceived physical and mental HRQOL, are biologically plausible. Breathlessness, weight loss, fatigue, and wheeziness were the symptoms most strongly associated with the start of dialysis. This finding could indicate that these symptoms were considered the most by nephrologists and patients in the decision to start with dialysis. However, in our cohort data is lacking on whether the decision to start was indeed based on these symptoms. The possible role of breathlessness and wheeziness in the decision to start with dialysis could be explained by the presence of fluid overload. Fluid overload is a main indication to start with dialysis, as is stated in several guidelines^{25;26}, and breathlessness and wheeziness can be consequences of pulmonary edema.

In conclusion, the presence of all symptoms increases and both physical and mental HRQOL decreases during pre-dialysis care with the sharpest change in the last six to twelve months before reaching an endpoint. This may indicate that symptoms and both physical and mental HRQOL are good markers for the medical condition and disease stage of pre-dialysis patients, and are therefore good candidates to be used in defining the optimal moment to start with dialysis. Indeed, we found that several symptoms and a lower level of HRQOL were already associated with the start of dialysis, which may indicate that these symptoms were already considered by nephrologists and patients in this decision. However, for each individual we need to know the exact reason for starting dialysis and the survival time on dialysis, to investigate on which specific symptoms and what level of HRQOL this decision should be based. Therefore, in the future, more research should focus on finding clinical signs and symptoms that can help to plan when to start dialysis to increase survival and HRQOL on dialysis. The European EQUAL study⁴⁷ will focus on this specific question. Eventually, a clinical decision rule based on all known factors may be a good and helpful tool for nephrologists and patients to make a more evidence-based choice when a patient needs to start with dialysis.

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Chapter 7 |

Hemoglobin levels and health-related quality of life in young and elderly patients on specialized pre-dialysis care

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Abstract

Background: In pre-dialysis patients, the optimal treatment choices for controlling hemoglobin (Hb) are unknown because targeting high Hb levels has negative effects – poorer survival – but possible positive effects as well – better health-related quality of life (HRQOL). Moreover, these negative and positive effects may be different in specific subgroups, for example young versus elderly patients.

Methods: In the prospective PRE-dialysis Patient REcord-2 (PREPARE-2) follow-up study, incident patients starting pre-dialysis care were included between 2004 and 2011 when referred to one of the 25 participating Dutch outpatient clinics. HRQOL was assessed each six-month interval with the short form-36 questionnaire (physical/mental summary measure and eight subscales (range 0-100)). A linear mixed model was used to associate Hb (<11, 11-12 (reference), 12-13, ≥ 13 g/dl) with HRQOL, stratified by anemia-medication (erythropoiesis stimulating agent and/or iron supplement, ESA/iron) and age (young: <65 years, elderly: ≥ 65 years).

Results: In elderly patients (n=214) only, a natural high Hb (≥ 13 g/dl versus 11-12 g/dl) was associated with a statistically significant ($p < 0.05$) and/or clinically relevant (> 3 -5 points) higher physical (11.9 [95% confidence interval (CI) 1.7;22.2]) and mental (6.4 [95% CI -1.7;14.6]) summary score. An ESA/iron induced high Hb did not result in a higher HRQOL in elderly patients. However, in young patients (n=157), only an ESA/iron induced high Hb (≥ 13 versus 11-12 g/dl) showed an association with a higher physical (8.9 [95% CI 2.1;15.8]) and mental (6.2 [95% CI -0.4;12.8]) summary score. This effect was present on all physical and mental subscales, with the exception of mental health.

Conclusion: The association of Hb levels with HRQOL is different between young and elderly patients with or without prescribed ESA/iron on specialized pre-dialysis care. Therefore, medical care should aim for shared-decision making regarding the appropriate Hb target for each patient leading to a more individualized care.

Introduction

Anemia is a common complication in patients with chronic kidney disease (CKD)¹, and associated with increased mortality and morbidity, lower health-related quality of life (HRQOL), and faster progression to end-stage renal disease²⁻⁹. Therefore, treatment of anemia with erythropoiesis stimulating agents (ESA), iron supplements, or a combination of the two is important, and several studies have shown that treatment with ESA has a beneficial effect on various health outcomes.¹⁰⁻¹⁴

However, the optimal hemoglobin (Hb) treatment target level for anemic patients with CKD is still unknown. A meta-analysis¹⁵ showed that targeting high Hb levels (≥ 12 g/dl) with ESA in anemic CKD patients increases their HRQOL. Positive effects were predominantly found on the physical summary measure of the short form-36 (SF-36) questionnaire.¹⁶ These effects are biologically plausible because common symptoms like low energy, fatigue, and weakness can be ameliorated by treating anemic patients with ESA.¹¹ Moreover, increasing HRQOL may have additional positive effects independently of other factors because it has been shown that starting dialysis with a high HRQOL increases survival.^{17;18}

Besides the positive effects on HRQOL, high Hb targets (≥ 12 g/dl) in CKD patients can also have negative effects, such as an increased risk of mortality and cardiovascular events, and an accelerated progression to end-stage renal disease.¹⁹ These contradictory results on different health outcomes indicate that it is important to make a well-considered treatment decision, taking personal preferences of CKD patients into account. Good clinical practice would be that each patient discusses the possible positive effects on HRQOL and possible negative effects on other clinical outcomes together with their physician to make an informed decision about the appropriate Hb treatment target.

Unfortunately, there is still insufficient evidence regarding the effect of targeting high Hb levels with anemia-medication on HRQOL to make such a well-considered decision. The studies that are available do not report all HRQOL subscales, do not show clinically relevant effects, and only report results about a heterogeneous population, instead of different subgroups of CKD patients. For example, positive effects on HRQOL may vary with age and CKD stage. Elderly patients and late-stage CKD patients experience more morbidities and have a lower HRQOL compared with young²⁰ and early-stage²¹ CKD patients. A lower HRQOL can lead to a larger possible improvement. Or the opposite may take place, in which treatment ameliorates anemia-related symptoms whereas other morbidity-related symptoms among older patients in late CKD stages remain present, and consequently lead to a less increased HRQOL.

The aim of the current study was to gain more knowledge about the combined association of Hb levels and the prescription of anemia-medication on all HRQOL subscales, in elderly compared with young CKD patients starting specialized pre-dialysis care.

Methods

Study design

The PRE-dialysis PATient REcord-2 (PREPARE-2) study is an ongoing, prospective follow-up study of incident pre-dialysis patients treated in 25 nephrology outpatient clinics in The Netherlands. Patients were included between July 2004 and June 2011, at the start of specialized pre-dialysis care. They were treated by their nephrologist in their regular scheme according to the treatment guideline of the Dutch Federation of Nephrology²², a guideline partly based on the K/DOQI²³ and KDIGO²⁴ guidelines. Patients were followed until the start of dialysis, receiving a kidney transplant, death, or censoring. Censoring was defined as: moving to an outpatient clinic not participating in the PREPARE-2 study, recovery of kidney function, refusal of further study participation, lost to follow-up, or August 1, 2012 (end of follow-up), whichever came first. The study was approved by the Medical Ethics Committee or the Institutional Review Board (as appropriate) of all participating centers.

Patients

To be eligible for inclusion, patients had to be at least eighteen years of age and the inclusion should take place at the moment of referral to a specialized pre-dialysis outpatient clinic. In practice, this refers to incident pre-dialysis patients with an estimated glomerular filtration rate (eGFR) of less than 20-30 ml/min/1.73 m², in whom renal function loss is progressive. Patients with a failing kidney transplant were also included in the study, if the transplantation was at least one year ago. All participants gave their written informed consent prior to study inclusion.

Data collection

Data on demography, biometry, primary kidney disease, co-morbidities, medication prescriptions, and HRQOL were collected at the start of specialized pre-dialysis care and in subsequent six-month intervals. Corresponding laboratory data were extracted from the electronic hospital information systems or medical records. Primary kidney disease was classified according to the codes of the European Renal Association-European Dialysis and Transplantation Association.²⁵

Measurements and definitions

HRQOL was assessed with the generic validated SF-36 questionnaire¹⁶, which consists of 36 items that can be divided into eight subscales. The scores on the items within each subscale are summed and transformed to a 0-100 scale, with higher scores indicating a better HRQOL. Two summary measures can be composed of the eight subscales: physical summary score (consisting of the four subscales physical functioning, role-physical, bodily pain, and general health) and mental summary score (consisting of the four subscales vitality, social functioning, role-emotional, and mental health). GFR was estimated using the four-variable Modification

of Diet in Renal Disease (MDRD) formula²⁶. The Hb levels (mmol/l) were measured according to the standard procedure in each participating outpatient clinic. We converted the Hb level in mmol/l to g/dl with the conversion factor 1.6113 and categorized it into four groups (<11, ≥11-<12, ≥12-<13, and ≥13 g/dl). The chosen categories were based on the current treatment guideline for anemic CKD patients (target is ≥11-<12 g/dl, and ≥13 g/dl should not be targeted²⁷).

Statistical analyses

Continuous baseline characteristics were presented as mean ± standard deviation (SD) or median (boundaries of interquartile range, IQR) and dichotomous baseline characteristics were presented as percentages. A linear mixed model was used to associate the Hb categories (11-12 g/dl as reference) with HRQOL during the first two years of pre-dialysis care. We chose to restrict the time of follow-up until two years to prevent selection bias, as the healthy and stable patients, whom are still on pre-dialysis care after two years, would have a relatively large contribution to the overall association. In the model we included the four Hb categories as a fixed independent variable and the continuous HRQOL as a dependent variable, both updated each six months, and the variable time as a random variable. The results from this model indicate the difference in HRQOL score between the different Hb categories (compared with the reference category ≥11-<12 g/dl) on each time point during the first two years of pre-dialysis care. In other words, the results indicate the 'average' HRQOL difference between Hb categories. This linear mixed model was also performed after stratification by (1) the prescription of anemia-medication (erythropoiesis stimulating agent and/or iron supplement, ESA/iron) at the start of pre-dialysis care (yes/no) and (2) age (young: <65 years, and elderly: ≥65 years). To avoid power problems we also performed a continuous (per 1 g/dl increase) analysis in patients with Hb levels ≥11 g/dl (i.e. patients with optimal and high Hb levels). Patients with Hb levels <11 g/dl were excluded because categorical analyses before stratification showed a different effect size on HRQOL in these patients. We adjusted for the potential baseline confounders age, sex, primary kidney disease, cardiovascular disease, diabetes mellitus, eGFR, proteinuria, albumin, and systolic blood pressure. Associations of Hb with HRQOL were interpreted both statistically ($p < 0.05$) and clinically (categorical analyses: >3-5 points²⁸, and for the continuous analyses: >1.5-2.5 points per each 1 g/dl increase). When information on stratification variables – age and ESA/iron prescription - or confounders were missing at the start of pre-dialysis care, data were imputed with the method of multiple imputation in PASW/SPSS (using ten repetitions). Multiple imputation is a technique where missing data for a patient are imputed by a value that is predicted by other known characteristics of this patient.^{29;30} The imputation model included all characteristics described in Table 1, plus the outcome reached and follow-up time because missing baseline characteristics are often related to the outcome.³¹ Skewed distributed continuous variables, including follow-up time, were logarithmically transformed before entering into the model. All statistical analyses were performed with PASW/SPSS version 20.0.

Sensitivity analyses

We performed five sensitivity analyses to test the robustness of our results. First, we repeated all analyses after imputation of the missing baseline characteristics of all 502 included patients. Second, after defining young patients as <70 years and elderly patients as ≥70 years, analyses were repeated. Third, we repeated all linear mixed model analyses with an additional interaction term in the model: Hb categories*time. By including this term we investigated whether the association between Hb and HRQOL is different over time. In other words, whether the pattern of HRQOL over time differs between the Hb categories. Fourth, during pre-dialysis care some patients discontinue and others start using ESA/iron and patients can switch from the category <65 to ≥65 years. Therefore, we included the time-dependent variables ESA/iron prescription and age (young: <65 years, elderly: ≥65 years), updated each six months, in the linear mixed model instead of stratifying the analyses by ESA/iron prescription and age at the start of pre-dialysis care. Thereafter, we performed an additional analysis with the potential confounders systolic blood pressure, eGFR, proteinuria, and albumin also included as time-dependent variables.

Results

Baseline characteristics

Of the 502 patients included in the PREPARE-2 study, 371 patients were included in our primary statistical analyses. Patients were excluded if a Hb measurement and physical or mental summary score in the same six-month interval during the first two years of pre-dialysis care were not available. Table 1 shows the baseline clinical characteristics of these patients. Respectively 19%, 30%, and 51% had Hb levels below, on, or above the current treatment target (11-12 g/dl, Table 1). The majority had renal vascular disease as primary kidney disease and often diabetes mellitus as co-morbidity. Patients with Hb levels ≥13 g/dl had a higher eGFR, lower body mass index, less often diabetes mellitus, and more often cardiovascular disease compared with patients on target (≥11-<12 g/dl). Moreover, the higher prevalence of cardiovascular disease was present in elderly patients (≥65 years; 62% for ≥13 g/dl and 45% for 11-12 g/dl) and not in young patients (<65 years; 32% and 28%, respectively). Information regarding prescription of medication at the start of pre-dialysis care was only available for 323 (87%) patients. Of these, 54% were prescribed ESA/iron therapy, which was similar across all Hb levels. Darbepoetin and iron supplements were prescribed more often than epoetin, especially in patients with high Hb levels (≥12 g/dl).

Association of Hb levels with HRQOL

Patients with high Hb levels (≥13 g/dl) had a statistically ($p<0.05$) and clinically (>3-5 points) higher physical summary score (56.7 versus 51.8, Table 2) compared with patients on target (11-12 g/dl). Adjustment for confounders did not essentially change the results. On all physical subscales, with the exception of bodily pain, this difference was clinically relevant. Furthermore, patients with low Hb levels (<11 g/dl) had a lower mental summary score

compared with patients on target (60.4 versus 66.1, $p < 0.05$). On all subscales of the mental summary measure, with the exception of mental health, this difference was clinically relevant.

Table 1: Baseline clinical characteristics of the total study population and stratified by categories of hemoglobin levels

	Total n=371	<11 ¹ n=68	≥11-<12 ¹ n=104	≥12-<13 ¹ n=75	≥13 ¹ n=106
Age (years)	69 (55-76)	70 (51-78)	69 (57-75)	69 (57-76)	65 (53-76)
Sex (% male)	67	60	67	65	73
Body mass index (kg/m ²) ²	26.4 ± 4.9	27.0 ± 5.4	26.3 ± 5.0	26.4 ± 4.6	26.1 ± 4.8
Smokers / quitters <1 year before inclusion (%)	24	18	24	24	27
Primary kidney disease (%)					
Diabetes mellitus	13	18	11	12	13
Glomerulonephritis	14	10	14	17	12
Renal vascular disease	30	41	28	29	29
Other	43	31	47	42	46
eGFR (ml/min/1.73 m ²) ³	16.9 ± 6.0	15.5 ± 4.9	15.9 ± 5.9	17.6 ± 5.2	18.4 ± 6.8
Urinary protein excretion (g/24h) ⁴	1.0 (0.3-2.1)	1.1 (0.3-2.0)	1.0 (0.4-2.4)	0.7 (0.2-2.0)	1.1 (0.4-2.2)
Urea (mmol/l) ⁵	22.1 ± 7.0	23.7 ± 7.1	22.6 ± 6.9	21.1 ± 6.4	21.4 ± 7.5
Albumin (g/l) ⁶	40.7 ± 4.6	39.1 ± 5.0	40.5 ± 4.4	41.3 ± 4.7	41.5 ± 4.5
Systolic blood pressure (mmHg) ⁷	142 ± 22	142 ± 23	144 ± 24	139 ± 19	141 ± 23
Hemoglobin (g/dl) ¹	12.3 ± 1.5	10.3 ± 0.5	11.6 ± 0.3	12.5 ± 0.3	14.0 ± 0.9
Diabetes mellitus (%) ⁸	26	38	25	21	22
Cardiovascular disease (%) ⁹	43	40	39	41	47

Continuous variables are presented as mean ± standard deviation for normally distributed variables and as median (boundaries of interquartile range) for skewed variables. ¹ Hemoglobin level is given in g/dl and available for 353 patients. Available for: ² 366, ⁴ 210, ⁵ 338, ⁶ 324, ⁷ 368 patients. ³ Estimated glomerular filtration rate (eGFR) is calculated with the four-variable Modification of Diet in Renal Disease formula and available for 351 patients. ⁸ Defined as the presence of a cerebrovascular accident, vascular problems, angina pectoris, myocardial infarction, or decompensatio cordis. ⁹ Present as primary kidney disease or co-morbidity.

Table 2: Association of hemoglobin levels with health-related quality of life during pre-dialysis care

	<11 Mean [95% CI]	≥11-<12 Mean [95% CI]	≥12-<13 Mean [95% CI]	≥13 Mean [95% CI]
Physical functioning	54.3 [50.6;58.0]	56.5 [53.1;59.9]	59.6 [56.3;63.0] ¹	60.7 [57.2;64.2] ^{1,2}
Role-physical	39.7 [32.9;46.6]	43.0 [37.1;48.9]	43.1 [37.2;49.1]	50.3 [44.2;56.4]
Bodily pain	65.1 [61.1;69.2] ^{1,2}	70.8 [67.3;74.3]	71.6 [68.1;75.1]	73.6 [70.0;77.1]
General health	38.5 [35.8;41.1]	38.7 [36.4;41.0]	40.0 [37.7;42.3]	41.8 [39.4;44.1] ^{1,2}
<u>Physical summary</u>	49.9 [46.5;53.2]	51.8 [48.9;54.8]	53.9 [50.9;56.9]	56.7 [53.6;59.8] ^{1,2}
Vitality	47.9 [44.9;50.9] ^{1,2}	52.8 [50.2;55.5]	52.6 [49.9;55.2]	52.9 [50.2;55.7]
Social functioning	65.3 [61.5;69.1] ^{1,2}	73.0 [69.7;76.3]	71.7 [68.3;75.0]	75.3 [71.9;78.7]
Role-emotional	62.1 [55.4;68.7]	68.6 [63.1;74.1]	69.1 [63.4;74.7]	71.9 [66.6;77.2]
Mental health	70.1 [67.3;72.8]	72.8 [70.4;75.2]	73.4 [71.0;75.8]	73.5 [71.0;75.9]
<u>Mental summary</u>	60.4 [57.2;63.7] ^{1,2}	66.1 [63.3;68.9]	66.4 [63.6;69.3]	67.7 [64.8;70.6]

For each hemoglobin (Hb, g/dl) category the mean [95% confidence interval (CI)] score on the two summary measures and eight subscales is given. The p-values are from a linear mixed model investigating whether the scores were significantly different compared with the reference category (Hb level of ≥11-<12 g/dl). ¹ Crude $p < 0.05$.

² Adjusted $p < 0.05$: sex, age, primary kidney disease, estimated glomerular filtration rate, proteinuria, albumin, systolic blood pressure, cardiovascular disease, and diabetes mellitus.

Association of Hb levels with HRQOL, stratified by ESA/iron prescription and age

In young patients (<65 years) not prescribed ESA/iron at the start of pre-dialysis care, the physical and mental summary scores were similar across all Hb levels (Tables 3 and 4). When young patients were prescribed ESA/iron, high Hb levels (≥ 13 g/dl) resulted in a statistically significant and clinically relevant higher physical (8.9 [95% confidence interval (CI) 2.1;15.8]) and clinically relevant mental summary score (6.2 [95% CI -0.4;12.8]) compared with young patients on target (≥ 11 -<12 g/dl, Table 3). Comparable results were found when analyzing Hb levels continuously; per 1 g/dl increase of Hb, the physical summary score increased with 4.0 [95% CI 1.2;6.7] and the mental summary score with 2.4 [95% CI -0.1;4.9] points in patients with Hb levels ≥ 11 g/dl (Table 4). On all physical and mental subscales, with the exception of mental health, this difference was clinically relevant (>1.5-2.5 points increase with each 1 g/dl Hb increase, Figures 1A and 1B).

In elderly patients (≥ 65 years) not prescribed ESA/iron at the start of pre-dialysis care, natural high Hb levels were associated with a statistically significant and clinically relevant higher physical and clinically relevant mental summary score compared with elderly patients with natural Hb levels ≥ 11 and <12 g/dl (11.9 [95% CI 1.7;22.2] and 6.4 [95% CI -1.7;14.6], respectively, Table 3). Continuous analyses showed similar results; per 1 g/dl increase of Hb, the physical summary score increases with 3.6 [95% CI -0.1;7.2] and the mental summary score with 2.5 [95% CI -0.6;5.6] points in patients with a Hb level ≥ 11 g/dl (Table 4). On all physical subscales and the mental subscales role emotional and mental health, this difference was clinically relevant (Figures 1C and 1D).

In contrast, in elderly patients who were prescribed ESA/iron higher Hb levels were not associated with HRQOL. However, low Hb levels (<11 g/dl) were associated with a lower physical (-7.4 [95% CI -13.7;-1.0]) and mental summary score (-14.2 [95% CI -20.7;-7.6]) compared with target Hb levels (Table 3). Adjustment for confounders did not essentially change the results (Table 3).

Sensitivity analyses

Our first sensitivity analysis showed that results were essentially the same when repeating analyses after imputation or after defining young patients as <70 instead of <65 years. None of the linear mixed models showed a significant interaction term between Hb categories and time, indicating that the association of Hb with HRQOL did not change during pre-dialysis care. Using time-dependent variables of ESA/iron prescription, age, and the potential confounders during pre-dialysis care also did not change the results.

Table 3: Association of categorical hemoglobin levels with the physical and mental summary score on each time point during pre-dialysis care, stratified by ESA/iron prescription and age

	n at baseline	<11 Crude Δ score [95% CI]	≥ 11 -<12	≥ 12 -<13 Crude Δ score [95% CI]	≥ 13 Crude Δ score [95% CI]
<u>Physical summary</u>					
Young – No ESA/iron	79	-1.1 [-9.4;7.1]	0	-3.1 [-9.5;3.2]	-0.9 [-8.2;6.4]
Elderly – No ESA/iron	88	1.5 [-7.0;10.1]	0	4.1 [-4.4;12.6]	11.9 [1.7;22.2] ^{1,2}
Young – ESA/iron	78	1.7 [-6.1;9.4]	0	2.2 [-4.5;8.9]	8.9 [2.1;15.8] ^{1,2}
Elderly – ESA/iron	126	-7.4 [-13.7;-1.0] ¹	0	3.7 [-1.7;9.0]	1.1 [-5.0;7.2]
<u>Mental summary</u>					
Young – No ESA/iron	79	1.8 [-6.5;10.1]	0	0.4 [-6.1;6.9]	0.0 [-7.4;7.3]
Elderly – No ESA/iron	88	-3.0 [-10.0;3.9]	0	1.1 [-5.7;7.9]	6.4 [-1.7;14.6] ²
Young – ESA/iron	78	-1.5 [-8.5;5.6]	0	2.7 [-3.7;9.2]	6.2 [-0.4;12.8]
Elderly – ESA/iron	126	-14.2 [-20.7;-7.6] ^{1,2}	0	-1.2 [-6.7;4.3]	-2.6 [-8.8;3.6]

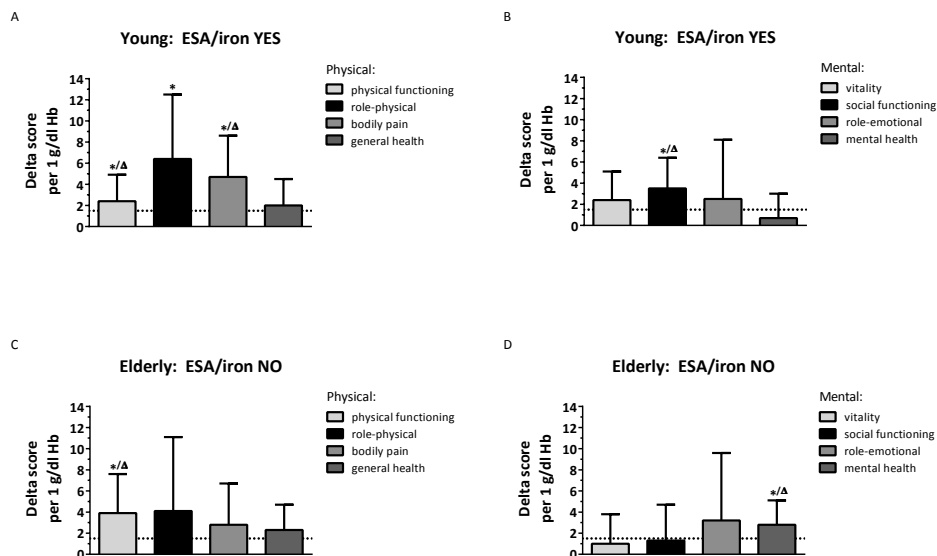
For each hemoglobin (Hb, g/dl) category the difference (Δ score) [95% confidence interval (CI)] in the physical and mental summary score is given, compared with the reference category (Hb level of ≥ 11 -<12 g/dl). All analyses were stratified by ESA/iron prescription at the start of pre-dialysis care and age (<65 years, young, and ≥ 65 years, elderly). The p-values are from a linear mixed model investigating whether the scores were significantly different between the Hb categories. ¹ Crude $p < 0.05$. ² Adjusted $p < 0.05$: adjusted for sex, age, primary kidney disease, estimated glomerular filtration rate, proteinuria, albumin, systolic blood pressure, cardiovascular disease, and diabetes mellitus.

Table 4: Association of continuous hemoglobin levels with the physical and mental summary score on each time point during pre-dialysis care, stratified by ESA/iron prescription and age

	n at baseline	Hb ≥ 11 : optimal and high Per 1 g/dl increase Crude Δ score [95% CI]
<u>Physical summary</u>		
Young – No ESA/iron	79	1.0 [-1.5;3.6]
Elderly – No ESA/iron	88	3.6 [-0.1;7.2] ²
Young – ESA/iron	78	4.0 [1.2;6.7] ^{1,2}
Elderly – ESA/iron	126	1.0 [-1.6;3.6]
<u>Mental summary</u>		
Young – No ESA/iron	79	0.9 [-1.7;3.4]
Elderly – No ESA/iron	88	2.5 [-0.6;5.6] ²
Young – ESA/iron	78	2.4 [-0.1;4.9]
Elderly – ESA/iron	126	-0.4 [-2.8;2.0]

For each 1 g/dl increase in hemoglobin (Hb) level the difference (Δ score) [95% confidence interval (CI)] in the physical and mental summary score is given. All analyses were stratified by ESA/iron prescription at the start of pre-dialysis care and age (<65 years, young, and ≥ 65 years, elderly). The p-values are from a linear mixed model investigating whether the scores significantly changed with each g/dl Hb increase. ¹ Crude $p < 0.05$. ² Adjusted $p < 0.05$: adjusted for sex, age, primary kidney disease, estimated glomerular filtration rate, proteinuria, albumin, systolic blood pressure, cardiovascular disease, and diabetes mellitus.

Figure 1: Association of hemoglobin levels with all physical and mental subscales during pre-dialysis care in patients with a hemoglobin level ≥ 11 g/dl, stratified by ESA/iron prescription and age



The bars indicate the change and the error bars the 95% confidence interval of the subscale scores (y-axis), with each 1 g/dl increase in hemoglobin (Hb) level. Analyses were stratified by ESA/iron prescription at the start of pre-dialysis care and for age (young: <65 years, and elderly: ≥ 65 years). A linear mixed model was used to investigate whether the subscale scores changed significantly. The dashed horizontal lines represent an increase in the subscale score of 1.5-2.5 points with each 1 g/dl increase in Hb, which is considered clinically relevant. * Crude $p < 0.05$. ^a Adjusted $p < 0.05$: adjusted for sex, age, primary kidney disease, estimated glomerular filtration rate, proteinuria, albumin, systolic blood pressure, cardiovascular disease, and diabetes mellitus.

Discussion

This study in patients on specialized pre-dialysis care found several significant improvements in HRQOL throughout different ranges of Hb levels. The most pronounced difference in HRQOL was present in patients with Hb levels below compared with on target (11-12 g/dl) and this difference was clinically relevant for the mental summary measure and five subscales; role-physical, bodily pain, vitality, social functioning, and role-emotional. In patients with high Hb levels (≥ 13 g/dl), additional increases of HRQOL were present, which were clinically relevant for the physical summary measure and four subscales; physical functioning, role-physical, general health and role-emotional. These findings are in line with the literature³, although the study of Finkelstein *et al.* found a stronger effect on the vitality subscale in the upper Hb ranges.

Although these results in the overall heterogeneous pre-dialysis population are interesting, we should focus on specific subgroups because after stratifying by the prescription of ESA/iron and age (young, <65 years, and elderly, ≥ 65 years), various associations of Hb levels

with HRQOL were found. In elderly patients without ESA/iron prescription, high Hb levels (≥ 13 g/dl) were associated with a clinically relevant higher physical and mental summary score, except on the subscales vitality and social functioning. No association was found in young patients without ESA/iron prescription. Possibly, elderly patients with high 'natural' Hb levels (≥ 13 g/dl) are very vital (score on the subscale vitality in our data; 51.6) and have less severe co-morbidities, and thereby experience a high HRQOL. Furthermore, the absent association of low Hb levels (< 11 g/dl) with HRQOL in both young and elderly patients without ESA/iron prescription may be explained by the presence of clinical indications to not prescribe ESA/iron despite low Hb levels, for instance the absence of anemia-related symptoms.

Besides this, young patients with high Hb levels (≥ 13 g/dl) compared with patients on target (11-12 g/dl) who are prescribed ESA/iron experienced a clinically relevant higher physical and mental summary score, except for the subscale mental health, and this difference was most pronounced for the physical summary measure. In contrast, in elderly patients who are prescribed ESA/iron no association was found between high Hb levels and better HRQOL. Only elderly patients with low Hb levels (< 11 g/dl) had a lower physical and mental summary score, and this difference was most pronounced on the mental summary measure.

Our finding that in young anemic patients high Hb levels were independently associated with a higher physical summary score is in line with the pre-dialysis trials included in the meta-analysis of Clement *et al.*³²⁻³⁶ However, the effects found in these trials were on average smaller than in our study. This discrepancy can be explained by age (our cohort is younger) and a different classification of Hb categories.^{32;34;36} Our finding that high Hb levels in young patients who are prescribed ESA/iron were also independently associated with a higher mental summary score is in line with two trials included in the meta-analysis.^{32;33} An explanation for finding an increased HRQOL with higher Hb levels in young and not in elderly patients who are prescribed ESA/iron could be the following. Besides anemia, elderly patients often experience many co-morbidities. By prescribing ESA/iron, elderly patients are only relieved of their anemia-related symptoms and this may lead to a smaller improvement of HRQOL than in young patients. Another explanation could be that, compared with young patients, elderly patients experience less demanding daily activities, such as occupational activities.³⁷ The effects in young patients were mainly found on the physical subscale role-physical and on the mental subscale social functioning. This finding could be explained by the fact that, generally speaking, daily activities are restored when Hb is targeted to 11-12 g/dl, but that in young patients a higher Hb level may be necessary to perform all daily activities.

Our study furthermore showed that for 68 patients who were prescribed ESA/iron Hb levels were still below target (< 11 g/dl). Possible explanations for this low Hb level are ESA resistance (non-responders)³⁸ and ESA/iron non-compliance. Non-compliance to medication is extremely high (30-60%) in patients with chronic illnesses³⁹, including CKD patients⁴⁰. In this study, we found that solely in elderly patients low Hb levels, despite ESA/iron prescription, were associated with a lower HRQOL, especially regarding the mental summary measure. A possible explanation for this discrepancy could be that elderly patients often are prescribed

more medications and lifestyle restrictions than young patients. Being non-compliant can thereby affect various aspects of their health and can consequently lead to a lower HRQOL. The stronger effect on the mental summary measure could be explained by the fact that normalization of Hb levels with ESA/iron has the strongest effect on the mental subscale vitality²⁸ and that non-compliance is often associated with depressive symptoms and poor well-being^{41,42}.

In contrast to the beneficial effect on HRQOL, targeting high Hb levels may have serious disadvantages as well. Consistent with the studies showing a higher risk of cardiovascular events when targeting high Hb levels¹⁹, we found a higher prevalence of cardiovascular disease in patients with Hb levels ≥ 13 g/dl compared with 11-12 g/dl (47% versus 39%). Moreover, this higher prevalence of cardiovascular disease was more pronounced in elderly compared with young patients. This finding may implicate that in elderly patients prescribed with ESA/iron, high Hb levels do lead to negative effects but not give rise to positive effects. This may even more advocate the development of age-specific anemia treatment guidelines for patients on pre-dialysis care. Unfortunately, we could not investigate whether the mortality risk increases with increasing Hb levels due to the low event rate before the start of dialysis.

A great strength of the PREPARE-2 study is the longitudinal instead of cross-sectional character, resulting in Hb levels and HRQOL measurements for every six-month interval during pre-dialysis care. Because of these repeated measurements, changes over time, for example HRQOL, can be investigated. Furthermore, our results can be generalized to the complete period of pre-dialysis care in patients with an eGFR below 30 ml/min/1.73 m² who are starting specialized pre-dialysis care. A disadvantage of our study is that we have missing data because not all patients visited a pre-dialysis outpatient clinic each six months and most data was routinely collected. Due to the missing data, we could only include 371 of the 502 patients in our statistical analyses, which may lead to selection bias. However, baseline characteristics were similar between the 371 included and 131 excluded patients. Furthermore, results remained similar after imputing missing values at the start of pre-dialysis care for all 502 patients included in the study, which makes it less likely that our analyses suffered from selection bias. In addition, we stratified by ESA/iron therapy solely based on the prescription of these medications at the start of pre-dialysis care. In practice, the prescription of ESA/iron can change over time. However, results did not change when the prescription of these medications was updated over time. Furthermore, we only know whether ESA/iron was prescribed and we do not know what the medication compliance rates are.

Although trials are needed to confirm our findings, our results indicate that targeting high Hb levels in young, and not in elderly, patients on specialized pre-dialysis care increases their HRQOL. Furthermore, more studies are needed to investigate whether the negative effects of targeting high Hb levels on clinical outcomes are more present in elderly compared with young patients. We believe that future research should investigate negative (mortality and morbidity) and positive (better HRQOL and survival on dialysis) effects in subgroups of specific

patients. This scientific evidence is needed to better inform physicians and patients for making an individualized treatment decision regarding the appropriate Hb target, also based on patients' preferences.

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Chapter 8 |

Differences in progression to end-stage renal disease between black and white patients receiving pre-dialysis care in a universal healthcare system

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Abstract

Background: Studies performed in the United States showed that blacks progress from chronic kidney disease (CKD) to end-stage renal disease faster than do whites. Possible explanations are differences in healthcare system factors. This study investigated whether progression is also faster in a universal healthcare system, where all patients receive comparable care.

Methods: Data from the PRE-dialysis PATient REcord (PREPARE) study, a multicenter follow-up study of patients with CKD who started pre-dialysis care in The Netherlands between 1999 and 2011 were analyzed. Time-dependent Cox proportional hazards models were used to estimate the hazard ratio (HR) for starting renal replacement therapy (RRT) and linear mixed models were used to compare renal function decline (RFD) between blacks and whites. To explore possible mechanisms, analyses were adjusted for patient characteristics.

Results: At initiation of pre-dialysis care, blacks (n=49) were younger, had more diabetes mellitus, higher proteinuria levels, and a higher estimated glomerular filtration rate than whites (n=946). Median follow-up time in months was similar (blacks: 13.9 (boundaries of interquartile range (IQR) 5.3-19.5); whites 13.1 (IQR 5.1-24.0)). For blacks compared with whites, the crude HR for starting RRT within the first 15 months was 0.86 [95% confidence interval (CI) 0.55;1.34] and from 15 months onward 2.26 [95% CI 1.03;4.95], which increased after adjustment. RFD was faster by 0.18 [95% CI 0.05;0.32] ml/min/1.73 m²/month in blacks compared with whites.

Conclusion: Blacks receiving pre-dialysis care in a universal healthcare system have faster disease progression than whites, suggesting that healthcare system factors have a less influential role than had been thought in explaining black-white differences.

Introduction

Black Americans have a threefold higher incidence of end-stage renal disease (ESRD) compared with white Americans.¹ This has been largely attributed to faster rates of progression from chronic kidney disease (CKD) to ESRD in blacks.²⁻⁴ Explanations are likely to involve a complex interaction of biologic, societal, and healthcare system factors.^{5,6} Biologic factors may relate to genetic differences.⁷⁻⁹ Societal factors may relate to a lower socioeconomic status among blacks and possible cultural conflicts for blacks that lead to reduced adherence of health recommendations.⁵ Healthcare system factors may relate to differences in access to healthcare and decreased quality of care for blacks.⁵

Most studies regarding black-white differences in progression to ESRD derive from the United States.¹⁰ In the United States, blacks have less access to healthcare and studies suggest that blacks receive lower quality of care.^{11,12} To investigate the role of healthcare differences in the faster progression to ESRD in blacks, several studies have tried to control for it by studying cohorts of patients who are insured in the healthcare system of the United States, for example by Medicare^{13,14} or the department of Veterans Affairs^{2,15}. However, these studies included only subsets of patients and therefore have limited generalizability.¹⁰

To get further insight into the role of healthcare system factors, studies are needed in a setting where all patients have equal access to healthcare and receive similar highly standardized care, irrespective of age or socioeconomic status. The pre-dialysis care setting in The Netherlands is such a setting.¹⁶ Patients with CKD stages 4-5 are referred to specialized pre-dialysis care to adequately prepare for renal replacement therapy (RRT) and to improve therapeutic options. During this care, patients are monitored closely by nephrologists, dietitians, and social workers and are treated according to strict guidelines.^{17,18}

We sought to determine whether black and white patients with CKD starting specialized pre-dialysis care in the universal healthcare system of The Netherlands have differences in time until the start of RRT and rate of renal function decline.

Methods

Study design

Data from the PRE-dialysis PATient REcord (PREPARE) study were used. PREPARE is a multicenter follow-up study of incident patients starting specialized pre-dialysis care (eighteen years or older) in The Netherlands. In practice, patients are referred to a pre-dialysis nephrology outpatient clinic if they have an estimated glomerular filtration rate (eGFR) below 20-30 ml/min/1.73 m² (CKD stages 4-5) and a progressive loss of renal function. The PREPARE study consists of a retrospective and a prospective cohort. In the retrospective cohort (PREPARE-I), incident 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 patients who started pre-dialysis care in one of 25 participating outpatient clinics

between 2004 and 2011, were willing to participate in the study, and understood the Dutch language were included. Patients were followed until the start of RRT (defined as dialysis or renal transplantation), death, lost 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 August 2012 for PREPARE-II), whichever came first. 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 less than one 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.

Race

Information on race was reported by medical staff during a patient's visit to the pre-dialysis outpatient clinic. Whites were observed as patients originating from European countries, Turkey, and Morocco. Blacks were observed as patients with a sub-Saharan African origin, including Surinamese creoles. For the present analyses, patients with missing race data were considered as whites because we assumed that non-white race would have been noted (the population in The Netherlands is predominantly white¹⁹).

Baseline data

Baseline was defined as the date of the first visit at the pre-dialysis outpatient clinic. Baseline data were collected from medical records and extracted from the hospital information systems. Primary kidney disease was classified according to the codes of the European Renal Association-European Dialysis and Transplantation Association.²⁰ Cardiovascular disease was defined as the presence of angina pectoris, coronary artery disease, and/or myocardial infarction. The eGFR was calculated by using the Modification of Diet in Renal Disease (MDRD) formula, taking into account age, sex, black race, and serum creatinine.²¹

Follow-up data

Follow-up time was restricted to two years because after two years the number of patients at risk became too small.²² Follow-up time was defined as the time between the first visit and the start of RRT or censoring (i.e. death, lost to-follow-up, refusal to further participate in the study (PREPARE-II), recovery of renal function, or reaching the end of the study period within two years of follow-up). Recovery of renal function was defined as a substantial improvement in renal function and was based on the clinical impression of the nephrologist. Information on the date of starting RRT was collected from medical records. The rate of renal function decline was calculated by using all available eGFR measurements during the first two years of follow-up.

Statistical analyses

Descriptive statistics are presented as mean $\pm$ standard deviation (SD) or in case of a skewed distribution as median with boundaries of the interquartile range (IQR), stratified in white and black patients. Competing risk analysis was applied to calculate cumulative incidence curves for starting RRT for white and black patients, with death as a competing endpoint.²³ Because the cumulative incidence curves for black and white patients crossed, a time-dependent Cox proportional hazards analysis was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for starting RRT. This time-dependent model included an interaction term between race and time period (before and after time point of crossing curves) resulting in two separate HRs for each time period. A linear mixed model, including the intercept and slope as a random term, was used to estimate renal function decline for black versus white patients. This model takes into account a correlation between individual repeated eGFR measurements and the deviation of the individual slopes from the mean slope.²⁴ Both the HRs and the slopes were gradually adjusted for more variables to explore underlying mechanisms.

To maintain power and to avoid bias, missing data for baseline variables were imputed with standard multiple imputation techniques in PASW/SPSS (using ten repetitions). Missing values were predicted under the assumption of missing 'at random' using the patient's available characteristics.²⁵⁻²⁷ The imputation model included the characteristics described in Table 1 except race because this is the determinant of interest. In addition, data on starting RRT (yes/no) and follow-up time were included because missing baseline characteristics are often related to the outcome.²⁸ Skewed distributed continuous variables (i.e. age, parathyroid hormone, proteinuria, and the time until the start of RRT) were logarithmically transformed before entering into the model. Significance levels were determined at $p < 0.05$. Analyses were carried out with PASW/SPSS version 20.0 for Windows.

Subgroup and sensitivity analyses

Two subgroup analyses were performed regarding renal function decline, in which the results were stratified by the presence of diabetes mellitus and by proteinuria levels (above and below 1.5 g/24h, median value). These analyses were selected based on the high prevalence of diabetes mellitus and proteinuria in black patients with CKD.^{1,29}

To test the robustness of the results, several sensitivity analyses were performed. Analyses were repeated (1) with exclusion of patients with missing data on race; (2) with use of unrestricted follow-up time; (3) with stratification by PREPARE-I and PREPARE-II; (4) with additional adjustment for education level as proxy for socioeconomic status (available only in PREPARE-II) and in a separate model for pre-dialysis center as proxy for deprivation area (available in PREPARE-I and PREPARE-II); and (5) with use of the CKD-Epidemiology Collaboration (CKD-EPI) equation³⁰ instead of the MDRD formula.

Results

Patient characteristics

In total, 1049 patients were included, of whom 663 were white, 49 were black, 54 were grouped as other, and 283 had missing data on race. Patients grouped as 'other' were excluded and patients with missing race data were observed as being white. Of these 946 white and 49 black patients, 51% and 41% respectively, were from the PREPARE-I study. Of all patients, 75% were referred by a nephrologist and 14% by a specialist of internal medicine, which was similar between blacks and whites (data based on PREPARE-I). Compared with whites, black patients were ten years younger and more likely to have diabetes mellitus or glomerulonephritis as primary kidney disease. Furthermore, blacks had a higher eGFR at initiation of pre-dialysis care and higher levels of proteinuria (Table 1).

Follow-up and outcomes

With follow-up time censored at two years, Table 2 shows the median follow-up time and frequencies of outcomes. Follow-up time and outcome frequencies were approximately the same for blacks and whites. Figure 1 demonstrates that during the first 15 months of pre-dialysis care, blacks experienced a slightly lower probability of starting RRT compared with whites, whereas from 15 months onward blacks had a higher probability. For blacks compared with whites, the crude HR for starting RRT within the first 15 months was 0.86 [95% CI 0.55;1.34] and from 15 months onward 1.93 [95% CI 1.02;3.68], which remained approximately the same after adjustment for demographic characteristics, comorbidities/lifestyle, and prescribed medication. After additional adjustment for eGFR and proteinuria at baseline, these HRs increased to 1.16 [95% CI 0.73;1.85] and 3.61 [95% CI 1.87;7.00], respectively. After further adjustment for other laboratory measurements, these HRs attenuated to 1.09 [95% CI 0.67;1.75] and 3.12 [95% CI 1.56;6.23], respectively (Table 3).

Decline in renal function

Among whites, 6%, 19%, and 75% had one, two, and three or more available eGFR measurements in the first two years of follow-up, respectively. Among blacks, these percentages were 11%, 11%, and 78%. The median number of eGFR measurements (boundaries of IQR) was 4 (3-12) in whites and 4 (3-11) in blacks. In whites, the mean rate of renal function decline was 0.23 [95% CI 0.20;0.26] ml/min/1.73 m²/month and in blacks it was 0.41 [95% CI 0.28;0.54] ml/min/1.73 m²/month. Table 4 shows that the faster decline in renal function of 0.18 [95% CI 0.05;0.32] ml/min/1.73 m²/month in blacks remained present after adjustment. Results were essentially similar when analyses were repeated with inclusion of imputed baseline eGFR values and somewhat stronger when we limited the analyses to patients with at least three measurements of eGFR (0.22 [95% CI 0.06;0.38] ml/min/1.73 m²/month, adjustment model 6).

Table 1: Demographic and clinical characteristics at the start of pre-dialysis care for black and white patients

	Whites n=946	Blacks n=49
Age (years)	67 (52-75)	57 (42-67)
Sex (% male)	63	49
Body mass index (kg/m ²) ¹	26 ± 5	27 ± 6
Blood pressure (mmHg) ²		
Systolic	147 ± 26	150 ± 24
Diastolic	80 ± 13	84 ± 13
Smoking (%) ³	27	20
Primary kidney disease (%)		
Diabetic nephropathy	15	33
Glomerulonephritis	11	16
Renal vascular disease	24	14
Hypertension	12	12
Other cause	12	2
Co-morbidity (%)		
Diabetes mellitus ⁴	24	47
Cardiovascular disease ⁵	33	27
Medication (%) ⁶		
ACEi/ARB	66	79
ESA	37	33
Laboratory measurements ⁷		
eGFR (ml/min/1.73 m ²) ⁸	14.7 ± 6.2	18.4 ± 8.4
Proteinuria (g/24h)	1.5 (0.5-3.3)	2.5 (1.1-4.2)
Hemoglobin (g/dl)	11.8 ± 1.7	11.7 ± 1.9
Albumin (g/l)	39.9 ± 5.0	37.6 ± 6.1
Calcium (mmol/l) ⁹	2.3 ± 0.2	2.3 ± 0.2
Phosphorus (mmol/l)	1.5 ± 0.4	1.4 ± 0.3
PTH (pmol/l)	16.3 (9.2-28.8)	21.9 (9.0-37.0)

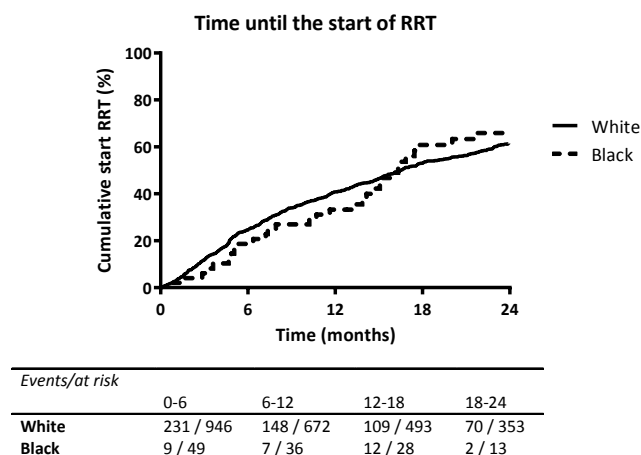
Values are presented as mean ± standard deviation or median (boundaries of interquartile range) or percentage. ACEi/ARB = angiotensin-converting enzyme inhibitor and/or angiotensin-II receptor blocker; ESA = erythropoiesis stimulating agents; eGFR = estimated glomerular filtration rate; PTH = parathyroid hormone. ¹ Available for 940 patients. ² Available for 973 patients. ³ Defined as smoking or quit smoking <1 year before the start of pre-dialysis care. ⁴ Defined as primary kidney disease and/or as co-morbidity. ⁵ Defined as the presence of angina pectoris, coronary artery disease, and/or myocardial infarction. ⁶ Available for 933 patients. ⁷ eGFR, proteinuria, hemoglobin, albumin, calcium, phosphorus, and PTH available for 859, 642, 863, 822, 820, 839, and 496 patients, respectively. ⁸ GFR estimated with the four-variable Modification of Diet in Renal Disease formula. ⁹ Corrected for albumin concentration.

Table 2: Median follow-up time and outcomes of incident black and white patients receiving pre-dialysis care during the first two years of pre-dialysis care

	Whites n=946	Blacks n=49
<u>Median follow-up time in months (boundaries of IQR)</u>		
All patients	13.1 (5.1-24.0)	13.9 (5.3-19.5)
Patients starting RRT	7.6 (3.8-14.6)	11.2 (5.0-15.9)
Censored patients ¹	10.9 (5.3-16.7)	12.0 (4.0-14.7)
<u>Outcomes, number (%)</u>		
Start RRT	558 (59)	30 (61)
Dialysis	517 (55)	29 (59)
Renal transplantation	41 (4)	1 (2)
Death	67 (7)	4 (8)
Other ²	321 (34)	15 (31)

IQR = interquartile range; RRT = renal replacement therapy (dialysis or renal transplantation). ¹ Patients who refused further study participation, were lost to-follow-up, had a recovery of renal function, died while receiving pre-dialysis care, or reached the end of the study period within two years of follow-up. Excluding patients still receiving pre-dialysis care after two years of follow-up. ² Refused further study participation, lost to-follow-up, recovery of renal function, reached end the of the study period within two years of follow-up, or reached end of two years follow-up.

Figure 1: Time until the start of renal replacement therapy separate for black and white patients



The cumulative incidence curves for starting renal replacement therapy (RRT), with death as competing endpoint, show the percentages of black and white incident patients starting RRT over time, with follow-up censored at two years.

Table 3: Hazard ratios for the start of renal replacement therapy for incident black versus white patients receiving pre-dialysis care, adjusted using gradually more complex multivariable models

Model		Blacks (n=49) versus Whites (n=946) (0-15 months)	Blacks (n=22) versus Whites (n=422) (15-24 months) ¹	Variables included in the model
		HR [95% CI]	HR [95% CI]	
1.	Unadjusted	0.86 [0.55;1.34]	1.93 [1.02;3.68]	Race
2.	Demographic	0.80 [0.51;1.25]	1.82 [0.95;3.46]	Model 1 <i>plus</i> age, sex
3.	Co-morbidities/ lifestyle	0.76 [0.48;1.20]	1.81 [0.95;3.46]	Model 2 <i>plus</i> PKD, systolic BP, BMI, DM, CVD, smoking status
4.	Medication	0.79 [0.50;1.25]	1.75 [0.91;3.35]	Model 3 <i>plus</i> ACEi/ARB, ESA
5.	Renal function/ damage	1.16 [0.73;1.85]	3.61 [1.87;7.00]	Model 4 <i>plus</i> eGFR at start of pre- dialysis care, proteinuria
6.	Laboratory	1.09 [0.67;1.75]	3.12 [1.56;6.23]	Model 5 <i>plus</i> Hb, calcium ² , phosphorus, PTH, albumin

HR = hazard ratio; CI = confidence interval; PKD = primary kidney disease; BP = blood pressure; BMI = body mass index; DM = diabetes mellitus; CVD = cardiovascular disease; ACEi/ARB = angiotensin-converting enzyme inhibitor and/or angiotensin-II receptor blocker; ESA = erythropoiesis stimulating agents; eGFR = estimated glomerular filtration rate calculated with the four-variable Modification of Diet in Renal Disease formula; Hb = hemoglobin; PTH = parathyroid hormone. ¹ In all six models, the HR for the time period 15-24 months is significantly different from the HR for the time period 0-15 months (interaction term between race and time period). ² Corrected for albumin concentration.

Table 4: Additional decline in renal function (ml/min/1.73 m²/month) for incident black versus white patients receiving pre-dialysis care, adjusted using gradually more complex multivariable models and with follow-up censored at two years

Model		Blacks versus Whites ¹ Additional decline ² [95% CI]	Variables included in the model
1.	Unadjusted	0.18 [0.05;0.32]	Race
2.	Demographic	0.18 [0.05;0.31]	Model 1 <i>plus</i> age, sex
3.	Co-morbidities/ lifestyle	0.18 [0.05;0.31]	Model 2 <i>plus</i> PKD, systolic BP, BMI, DM, CVD, smoking status
4.	Medication	0.18 [0.04;0.32]	Model 3 <i>plus</i> ACEi/ARB, ESA
5.	Renal function/ damage	0.16 [0.02;0.31]	Model 4 <i>plus</i> eGFR at start of pre-dialysis care, proteinuria
6.	Laboratory	0.16 [0.02;0.31]	Model 5 <i>plus</i> Hb, calcium ³ , phosphorus, PTH, albumin

CI = confidence interval; PKD = primary kidney disease; BP = blood pressure; BMI = body mass index; DM = diabetes mellitus; CVD = cardiovascular disease; ACEi/ARB = angiotensin-converting enzyme inhibitor and/or angiotensin-II receptor blocker; ESA = erythropoiesis stimulating agents; eGFR = estimated glomerular filtration rate calculated with the four-variable Modification of Diet in Renal Disease formula; Hb = hemoglobin; PTH = parathyroid hormone.

¹ Patients included with one or more eGFR measurements (850 whites and 46 blacks). ² An additional decline of 0.18 represents a faster decline in renal function of 0.18 ml/min/1.73 m²/month in blacks compared with whites.

³ Corrected for albumin concentration.

Subgroup analyses

Black patients with diabetes mellitus experienced a 0.43 ml/min/1.73 m²/month ([95% CI 0.09;0.76], adjustment model 6) faster renal function decline than white patients with diabetes mellitus (0.61 versus 0.18 ml/min/1.73 m²/month). Furthermore, black patients with high proteinuria levels (≥1.5 g/24h) experienced a 0.27 ml/min/1.73 m²/month ([95% CI -0.04;0.58], adjustment model 6) faster renal function decline than white patients with high proteinuria levels (0.60 versus 0.33 ml/min/1.73 m²/month). In black versus white patients without diabetes mellitus and in black versus white patients with low proteinuria levels, renal function decline did not differ. The interaction term p-value was 0.002 for diabetes with race and 0.274 for proteinuria with race.

Sensitivity analyses

Several sensitivity analyses were performed. First, excluding patients with missing data on race showed similar results. Second, the crude HR with use of unrestricted follow-up from 15 months onward was lower (HR 1.07 [95% CI 0.59;1.96]) compared with the main analyses, but after adjustment for the variables in model 6 blacks had a 2.21 fold higher hazard. Results related to renal function decline did not materially change. Third, patients in PREPARE-I had a lower baseline eGFR and a higher level of proteinuria than patients in PREPARE-II, but in both studies blacks had a higher eGFR and more proteinuria at baseline than white patients. In line with this, the median follow-up time was 4.6 months shorter in PREPARE-I. The fully adjusted HR from 15 months onward was higher in PREPARE-II (PREPARE-I: 1.82 [95% CI 0.62;5.32]); PREPARE-II: 7.93 [95% CI 2.97;21.22]). In both studies, renal function decline was faster in blacks than in whites. In PREPARE-I, renal function decline in whites was 55% of that of blacks (0.28 and 0.51 ml/min/1.73 m²/month, respectively) and in PREPARE-II 50% (0.17 and 0.34 ml/min/1.73 m²/month, respectively). Fourth, additional adjustment for education level (available for 86% of the patients in PREPARE-II (n=425)), did not change our point estimates. In a separate model, additional adjustment for pre-dialysis center (available for all patients) also did not change our point estimates. Finally, results remained similar when the CKD-EPI formula was used.

Discussion

This study found no difference in time until the start of RRT within the first 15 months of pre-dialysis care between black and white incident patients starting pre-dialysis care in a universal healthcare system. However, black patients initiated pre-dialysis care with a higher eGFR than whites. From 15 months onward, blacks had a 1.93 fold higher hazard of starting RRT compared with whites. Adjustment for differences in demographic characteristics, comorbidities/lifestyle, prescribed medication, proteinuria, eGFR, and laboratory measurements at baseline increased this HR to 2.87. Renal function decline was 0.18 ml/min/1.73 m²/month faster in black than in white patients and remained faster after adjustment.

Our finding that blacks have a faster progression to ESRD than whites is in line with the results of studies examining cohorts of patients who are insured in the healthcare system of the United States.^{2,31} However, these studies have limited generalizability because of the selected study population. Our study presents several new findings. First, except for a small study from the United Kingdom showing no difference in progression to ESRD between white (n=24) and African-Caribbean (n=11) patients with diabetic nephropathy³², differences in progression to ESRD between blacks and whites have not been previously investigated in a European universal healthcare system. Second, to our knowledge, a faster progression to ESRD in blacks compared with whites has not been described before in patients starting pre-dialysis care. A study from the United States, found that among patients with GFRs ranging from 13 to 24 ml/min/1.73 m² blacks had a 2.87 ml/min/1.73 m²/year faster renal function decline compared with non-blacks, but these were not incident patients starting pre-dialysis care.³³ Another study in the United States found a faster decline of only 0.3 ml/min/1.73 m²/year in blacks compared with whites who were referred to a nephrology clinic (median follow-up 2.8 years). However, this study included patients with CKD stages 1-5 (mean eGFR 37.4 ml/min/1.73 m²) and thus results are not comparable to those of our study.³⁴ A third study in the United States demonstrated that black patients with eGFR <15 ml/min/1.73 m² and with eGFR between 15 and 29 ml/min/1.73 m² had 1.4 and 1.8 fold higher risks of progression to ESRD, respectively, compared with whites. However, these results were based on patients admitted to the hospital with acute myocardial infarction and no eGFR measurements were available during follow-up. Furthermore, it was unclear whether these patients received specialized pre-dialysis care.³⁵ Third, to our knowledge, no previous studies have shown that blacks are referred to pre-dialysis care with higher eGFR compared with whites.

Strengths of our study include the presence of a well defined population receiving standardized care in a universal healthcare system, the longitudinal design, and the multiple eGFR measurements during follow-up. Some limitations need to be mentioned. First, the retrospective and the prospective cohorts of the PREPARE study were pooled, whereas the prospective cohort included only patients who were willing to participate in the study. This may have resulted in the selection of 'healthier' patients, as indicated by the higher eGFR at baseline and the slower decline in renal function in PREPARE-II versus PREPARE-I. However, we feel that pooling PREPARE-I and PREPARE-II is justified because both studies included incident patients starting pre-dialysis care in The Netherlands. The absence of a difference in time until the start of RRT between whites and blacks in PREPARE-I could be explained by the lower baseline eGFR compared with PREPARE-II (in PREPARE-I there was a shorter period to develop a difference). Second, patients with missing race data were considered as whites and race was assessed by medical staff. This may have resulted in misclassification of race. Nevertheless, in our opinion this has not influenced the results substantially because similar results were found after exclusion of patients with missing race data. Furthermore, although not optimal, the assessment of race/ethnicity by medical staff is considered to be suitable for assessing race/ethnicity.³⁶ Third, data on area deprivation were lacking. Differences in area

deprivation could have biased our results if deprivation is associated with both race and progression to ESRD. However, a great strength of the universal healthcare system in The Netherlands is the equal access to healthcare and highly standardized care for each individual, minimizing area differences in CKD progression and thereby minimizing bias. Furthermore, adjustment for pre-dialysis center, some in a more deprived area than others, did not change our effect estimate. Fourth, we do not have data on the magnitude and the characteristics of the patient group not referred to pre-dialysis care. However, the purpose of this study was not to investigate progression to ESRD in patients who could have been referred to pre-dialysis care but rather in patients who actually received specialized pre-dialysis care.

Our finding that black-white differences in progression to ESRD exist among patients receiving pre-dialysis care in a universal healthcare system suggests that previously reported differences could less likely be completely explained by healthcare related factors.²⁻⁴ Our finding that the faster decline in renal function for black compared with white patients is predominantly present in patients with diabetes mellitus and in patients with high proteinuria levels, may suggest that in blacks diabetes mellitus leads to more extensive damage of the kidneys causing a faster decline in renal function. In addition, it is reported that other factors, such as genetic differences⁷⁻⁹, decreased production of vitamin D in blacks³⁷⁻³⁹, and a greater incidence of low birth weight in blacks⁴⁰ may also explain the different disease progression.

Several explanations for the higher level of renal function at the start of pre-dialysis care for blacks compared with whites could be postulated. Guidelines suggest that patients need to be referred to pre-dialysis care at least one year before the start of RRT.⁴¹ If healthcare workers are aware of the faster renal function decline among blacks, they may refer such patients earlier to pre-dialysis care. Furthermore, healthcare professionals may refer blacks earlier because of their high prevalence of diabetes mellitus as underlying kidney disease or comorbidity.^{42;43} Additionally, it is possible that healthcare workers do not take into account that blacks have a higher creatinine production than whites due to differences in muscle mass, metabolism, and tubular handling of creatinine.⁴⁴⁻⁴⁶ The different association of creatinine and eGFR in blacks and whites is reflected in the MDRD equation by the multiplicative 1.212 term.²¹ Not applying this manual correction in our black population yields an eGFR that is only slightly higher than the eGFR among whites (15.2 and 14.7 ml/min/1.73 m², respectively).

In conclusion, although the number of black patients was relatively small, this study demonstrated that black patients receiving pre-dialysis care in a universal healthcare system had a faster progression to ESRD than whites, suggesting that healthcare system factors have a less influential role in explaining this black-white difference. Our results may suggest that black patients with CKD should be referred to pre-dialysis care earlier than white patients to assure timely preparation for RRT. Fortunately, in The Netherlands this is already the case because our data showed that black patients had a higher eGFR at the start of pre-dialysis care than white patients. Further investigation is needed to understand the mechanisms underlying the faster progression to ESRD in blacks.

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Chapter 9 |

Renal function in familial longevity: the Leiden Longevity Study

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Abstract

Background: Studying renal function in subjects with a familial propensity for longevity may provide insight in (un)known mechanisms that determine the age-related decline in renal function of normal subjects.

Methods: In the Leiden Longevity Study, middle-aged offspring of non-agenarian siblings and their partners as environmentally matched controls were included. Information was collected on lifestyle, medical history, medication use, and a non-fasting blood sample was drawn. Renal function (estimated glomerular filtration rate, eGFR) was assessed with the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula. Linear mixed models were used to account for familial dependencies within the offspring and all analyses were stratified by sex.

Results: eGFR was similar between female offspring and female controls (0.44 ml/min/1.73 m² [standard error (SE) 0.72] difference, p=0.54, age-adjusted). Male offspring had a higher eGFR compared with male controls (1.78 ml/min/1.73 m² [SE 0.78] difference, p=0.022, age-adjusted), and further adjustments for various characteristics did not materially change this difference. Among men with a history of hypertension, or myocardial infarction and/or stroke, offspring had a higher eGFR compared with controls (4.74 ml/min/1.73 m² [SE 1.53] difference, p=0.002, age-adjusted, and 6.21 ml/min/1.73 m² [SE 2.85], p=0.033, age-adjusted, respectively).

Conclusion: Middle-aged men, but not women, with a propensity for longevity have better renal function compared with environmentally matched controls, especially among those with a history of, or at risk of cardiovascular disease.

Introduction

Longevity is a complex phenotype that results from genetic factors, environment (including lifestyle), chance, and the interaction between these factors. Studies designed to identify genetic determinants for familial longevity have shown that centenarians¹ and their offspring^{2,3}, and offspring of familial non-agenarians⁴ have a lower prevalence of diabetes mellitus, hypertension, and cardiovascular disease, including myocardial infarction. Furthermore, insulin sensitivity is preserved in centenarians⁵ and offspring of non-agenarians have better glucose tolerance⁶ and better peripheral insulin sensitivity⁷ than environmentally matched controls. These observations indicate that offspring of long-lived subjects have a better metabolic profile. Moreover, most parameters associated with longevity differ between men and women.

Studying renal function in subjects with a familial propensity for longevity may provide insight in (un)known mechanisms that influence the decline in renal function of normal subjects. With increasing age, renal function decreases with approximately 0.4 ml/min/1.73 m²/year from the age of eighteen years onwards.⁸ This age-related decline is higher in patients with cardiovascular disease and diabetes mellitus, which are two important risk factors for the decline in renal function.⁹ Risk factors for these co-morbidities, such as body mass index (BMI), blood pressure, inflammation, glucose metabolism, and lipid metabolism, also independently accelerate renal function decline.^{9,10} Treatment of patients with renal insufficiency mainly focuses on these modifiable renal risk factors.¹¹

The Leiden Longevity Study was designed to identify genetic determinants of familial longevity.^{4,12} In this study, non-agenarian siblings and their offspring, who are genetically enriched for longevity, were included. The offspring and the controls, partners of the offspring who are environmentally matched, were used to assess whether at middle-age familial factors related to longevity (genetic or early environmental) influence renal function.

Methods

Study design and participants

In the Leiden Longevity Study 421 families were included, with at least two alive long-lived siblings of 89 years or older for men and 91 years or older for women and with identical Dutch parents. A more detailed description of the study design has been provided elsewhere.^{4,12} For 1671 of the offspring of these families and 744 partners of these offspring, all Caucasian, non-fasting blood serum samples were drawn at baseline. Additional information was collected on self-reported lifestyle, information on medical history from the participants' general practitioners and information on medication use from the participants' pharmacies. The Medical Ethics Committee of the Leiden University Medical Center approved the study and written informed consent was obtained from all subjects.

Renal function

Glomerular filtration rate (GFR) was estimated with the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula¹³, the Modification of Diet in Renal Disease (MDRD) formula¹⁴, and creatinine clearance (ml/min) was estimated with the Cockcroft Gault (CG) formula¹⁵. The CKD-EPI and MDRD formula use sex, age, black race, and serum creatinine to estimate GFR (eGFR, ml/min/1.73 m²). Compared with these formulas, the CG formula includes body weight and excludes black race. To compare the CG estimate with the other two estimates, we normalized it per 1.73 m² of body surface area (BSA) using the formula of Du Bois and Du Bois¹⁶.

Blood parameters

Creatinine levels were measured in a non-fasting blood sample by Kinetic Alkaline Picrate methodology. Glucose, high sensitivity C-reactive protein (hsCRP), high density lipoprotein (HDL) cholesterol, and triglyceride levels were measured on a Hitachi Modular P 800 (Roche, Almere, The Netherlands).

Statistical analyses

Continuous data are given as mean $\pm$ standard deviation (SD) and dichotomous data are given as percentages (%). hsCRP and triglyceride levels were logarithmically transformed prior to analyses and geometric means with their SD are reported for these transformed variables. Independent t-tests were used to assess differences in continuous data between offspring and controls and for dichotomous data chi-square tests were used.

As primary outcome we used the eGFR calculated with the CKD-EPI formula. This formula has the highest accuracy in patients with an eGFR above 60 ml/min/1.73 m².¹⁷ Because renal function declines with increasing age¹⁸ and effects related to longevity often differ between women and men, first the mean [standard error (SE)] eGFR was calculated, stratified by sex, offspring/control status, and age group (<55, 55-59, 60-64, and $\geq$ 65 years). Second, differences in eGFR between offspring and controls (Δ eGFR), stratified by sex, were assessed with linear mixed models to adjust for correlation of sibling relationship. Furthermore, an interaction term between age continuously and offspring/control status was included in the model to assess whether the difference in eGFR between offspring and controls changes with increasing age. Thereafter, Δ eGFR was further adjusted for age, history of hypertension, cardiovascular disease (myocardial infarction and stroke), diabetes mellitus, anti-hypertensive medication, glucose-lowering medication, glucose, hsCRP, HDL cholesterol, and triglyceride levels, smoking (current smoker), and BMI. We made separate models instead of gradually more complex models during adjustment, as otherwise many patients would be excluded from the final model because of missing values for one or more of the variables. Finally, we stratified the analyses by the presence of hypertension and by the presence of myocardial infarction or stroke.

GFR was also estimated with the MDRD and CG formula and as a sensitivity analysis we repeated all analyses with these two measurements. Furthermore, we investigated whether associations remained when analyses were repeated in patients without evidence of renal insufficiency as indicated by an eGFR >60 ml/min/1.73 m². As a final sensitivity analysis we imputed all missing values with multiple imputation (using five repetitions). This is a recommended technique where missing data for a subject are imputed by a value that is predicted by other known characteristics of this subject (e.g. demographic, anthropometric, and clinical characteristics).^{19,20} All characteristics illustrated in Table 1 were included in the model. Statistical analyses were done with PASW/SPSS version 20. P-values smaller than 0.05 were considered statistically significant.

Results

Of the 1671 included offspring and 744 included controls, 1300 offspring and 596 controls had a creatinine measurement as well as information on medical history and medication use. The population characteristics in Table 1 show that 695 (53%) of the offspring were female and 342 (57%) of the controls were female. The female offspring were older than the female controls (mean ± SD; 59.3 ± 6.5 versus 56.9 ± 6.9 years, $p < 0.001$). The age difference between male offspring and male controls was smaller (mean ± SD; 59.3 ± 6.5 versus 60.9 ± 6.9 years, $p = 0.001$). Despite the generally older age, offspring were less likely to have hypertension, myocardial infarction, and diabetes mellitus compared with controls. A difference in the prevalence of myocardial infarction was only present in men, 8% versus 4% ($p = 0.024$), and the difference in prevalence of diabetes mellitus was most pronounced in men, 11% versus 5% ($p = 0.005$). In both males and females, glucose and triglyceride levels were lower in offspring compared with controls.

Table 2 and Figure 1A and 1B show the mean eGFR for female and male offspring and controls, stratified by age. Estimated GFR was similar between female offspring and female controls (75.5 ml/min/1.73 m² [SE 0.52] versus 76.8 ml/min/1.73 m² [SE 0.69], $p = 0.090$) but higher in male offspring (82.7 ml/min/1.73 m² [SE 0.53]) than in male controls (79.6 ml/min/1.73 m² [SE 0.77]) ($p < 0.001$). In female offspring, with increasing age eGFR decreased 0.78 ml/min/1.73 m²/year ([SE 0.06], $p < 0.001$) and in female controls this was 0.73 ml/min/1.73 m²/year ([SE 0.08], $p < 0.001$) (p -value for interaction=0.63). In male offspring, with increasing age eGFR decreased 0.79 ml/min/1.73 m²/year ([SE 0.07], $p < 0.001$) and in male controls this was 0.86 ml/min/1.73 m²/year ([SE 0.09], $p < 0.001$) (p -value for interaction=0.53). These results and the results in Table 2 and Figure 1A and 1B indicate that at any age the eGFR difference between offspring and controls, in both women and men, was similar.

Table 1: Characteristics for the total study population, stratified by sex

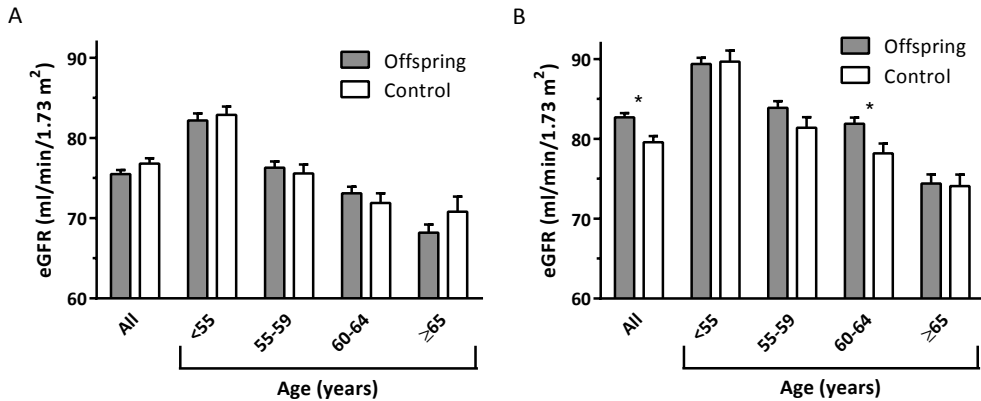
	Women		p-value	Men		p-value
	Offspring n=695	Control n=342		Offspring n=605	Control n=254	
Age (years)	59.3 ± 6.5	56.9 ± 6.9	<0.001	59.3 ± 6.5	60.9 ± 6.9	0.001
Smoking, n (%) ¹	75 (12)	45 (15)	0.26	76 (15)	37 (16)	0.68
Body mass index (kg/m ²) ¹	25.1 ± 4.0	25.3 ± 3.7	0.37	25.7 ± 2.9	25.9 ± 3.3	0.54
Hypertension, n (%) ²	158 (23)	93 (28)	0.094	136 (23)	68 (27)	0.20
Anti-hypertensive, n (%) ³	118 (17)	78 (23)	0.024	96 (16)	58 (23)	0.015
Myocardial infarction, n (%) ²	6 (1)	4 (1)	0.62	23 (4)	19 (8)	0.024
Stroke, n (%) ²	12 (2)	9 (3)	0.32	32 (5)	7 (3)	0.10
Diabetes mellitus, n (%) ²	26 (4)	19 (6)	0.16	31 (5)	26 (11)	0.005
Glucose-lowering, n (%) ⁴	10 (1)	9 (3)	0.17	12 (2)	13 (5)	0.013
Glucose (mmol/l) ⁵	5.7 ± 1.2	6.0 ± 1.5	0.003	5.9 ± 1.4	6.3 ± 2.0	0.008
hsCRP (mg/l) ⁵	1.41 ± 2.95	1.52 ± 3.01	0.31	1.34 ± 2.85	1.32 ± 2.82	0.79
HDL cholesterol (mmol/l) ⁵	1.59 ± 0.45	1.56 ± 0.48	0.27	1.27 ± 0.36	1.22 ± 0.36	0.050
Triglycerides (mmol/l) ⁵	1.39 ± 1.66	1.49 ± 1.72	0.048	1.72 ± 1.71	1.83 ± 1.71	0.11

Continuous variables are illustrated as mean ± standard deviation (SD) and as geometric mean ± SD for the logarithmically transformed variables high sensitive C-reactive protein (hsCRP) and triglyceride levels. ¹ Smoking and body mass index were available for 1654 and 1657 subjects respectively. ² Percentage of subjects with this co-morbidity present in their medical history; hypertension, myocardial infarction, stroke, and diabetes mellitus were available for 1856, 1886, 1890, and 1864 subjects respectively. ³ All types of anti-hypertensive medication. ⁴ Insulin and other blood glucose-lowering medication. ⁵ Glucose, hsCRP, high density lipoprotein (HDL) cholesterol, and triglyceride levels were available for 1884, 1889, 1895, and 1895 subjects respectively. The p-value was obtained with an independent t-test, for continuous variables, or with a chi-square test.

Table 2: Mean estimated glomerular filtration rate for offspring and controls, stratified by age and sex

	Women				p-value	Men				p-value
	Offspring		Control			Offspring		Control		
	n	Mean [SE]	n	Mean [SE]		n	Mean [SE]	n	Mean [SE]	
Total	695	75.5 [0.52]	342	76.8 [0.69]	0.090 ¹	605	82.7 [0.53]	254	79.6 [0.77]	<0.001 ¹
<55 years	176	82.2 [0.89]	126	82.9 [1.04]	0.59	155	89.4 [0.78]	49	89.7 [1.39]	0.83
55-59 years	215	76.3 [0.79]	103	75.6 [1.10]	0.59	170	83.9 [0.83]	62	81.4 [1.34]	0.10
60-64 years	164	73.1 [0.84]	77	71.9 [1.21]	0.42	168	81.9 [0.78]	68	78.2 [1.22]	0.011
≥65 years	140	68.2 [1.02]	36	70.8 [1.91]	0.20	112	74.4 [1.17]	75	74.1 [1.43]	0.85

For each category based on sex and age, the crude mean [standard error (SE)] estimated glomerular filtration rate (eGFR) calculated with the Chronic Kidney Disease-Epidemiology Collaboration formula is presented. P-values were obtained from linear mixed models adjusted for sibling relationship. ¹ P-values for the interaction term between age and offspring/control status were 0.63 for women and 0.53 for men. This indicates that the eGFR difference between offspring and controls remained similar with increasing age.

Figure 1: Mean estimated glomerular filtration rate for offspring and controls, stratified by sex and age

For each age category (x-axis) in women (A) and men (B) the crude mean (bar) and standard error (error bar) of the glomerular filtration rate (GFR) estimated with the Chronic Kidney Disease-Epidemiology Collaboration formula (y-axis) is presented for both offspring and controls (legend). * P-value for eGFR difference between offspring and controls is <0.05 and obtained from linear mixed models adjusted for sibling relationship.

Table 3 shows the difference in eGFR between offspring and controls, stratified by sex and adjusted for various characteristics. Female offspring had a similar eGFR compared with female controls (-1.32 ml/min/1.73 m² [SE 0.78], $p=0.090$). After adjustment for age, hypertension, myocardial infarction, stroke, and diabetes mellitus the difference remained unaltered (0.13 ml/min/1.73 m² [SE 0.75], $p=0.86$). Male offspring had a significant higher crude eGFR compared with male controls (3.05 ml/min/1.73 m² [SE 0.87], $p<0.001$). After adjustment for age, the point estimate in men changed to 1.78 ml/min/1.73 m² [SE 0.78], $p=0.022$). Further adjustment for hypertension, myocardial infarction, stroke, and diabetes mellitus did not affect the observed difference in men (1.83 ml/min/1.73 m² [SE 0.80], $p=0.022$). Adjustment for medication use, blood parameters or lifestyle factors slightly attenuated the difference in men (1.63 [SE 0.77], $p=0.035$; 1.54 [SE 0.78], $p=0.048$; and 1.73 [SE 0.83], $p=0.036$, respectively).

Table 4 shows the age-adjusted difference in eGFR between offspring and controls stratified by sex and additionally stratified by the presence of hypertension and the presence of myocardial infarction or stroke. In women there was no difference between offspring and controls in any of the strata. In men with hypertension, offspring had a higher eGFR compared with controls (4.74 ml/min/1.73 m² [SE 1.53], $p=0.002$, age-adjusted). Moreover, in men with a previous history of myocardial infarction or stroke, offspring had a higher eGFR compared with controls (6.21 ml/min/1.73 m² [SE 2.85], $p=0.033$, age-adjusted).

Table 3: Difference in estimated glomerular filtration rate between offspring and controls, stratified by sex

	Women ¹			Men ²		
	n	ΔeGFR [SE]	p-value	n	ΔeGFR [SE]	p-value
Crude	1037	-1.32 [0.78]	0.090	859	3.05 [0.87]	<0.001
+ age	1037	0.44 [0.72]	0.54	859	1.78 [0.78]	0.022
+ age, HT, MI, stroke, diabetes mellitus	998	0.13 [0.75]	0.86	822	1.83 [0.80]	0.022
+ age, anti-hypertensive medication, glucose-lowering medication	1037	0.23 [0.72]	0.74	859	1.63 [0.77]	0.035
+ age, glucose, hsCRP, triglycerides, HDL cholesterol	1026	0.11 [0.73]	0.87	851	1.54 [0.78]	0.048
+ age, smoking, BMI	898	0.36 [0.77]	0.64	747	1.73 [0.83]	0.036

Δ estimated glomerular filtration rate (eGFR) is the difference in eGFR, calculated with the Chronic Kidney Disease-Epidemiology Collaboration formula, between offspring and controls assessed with a linear mixed model. A positive number means that eGFR is higher in offspring compared with controls. The crude ΔeGFR was adjusted for sibling relationship. We additionally adjusted for age and the main risk factors for decline in renal function: hypertension (HT), myocardial infarction (MI), stroke, diabetes mellitus (DM), anti-hypertensive medication, glucose-lowering medication, glucose, high sensitivity C-reactive protein (hsCRP), high density lipoprotein (HDL) cholesterol, triglyceride levels, smoking and body mass index (BMI). hsCRP and triglyceride levels were logarithmically transformed. ¹ Offspring n=695 and control n=342. ² Offspring n=605 and control n=254.

Table 4: Difference in age-adjusted estimated glomerular filtration rate between offspring and controls, stratified by sex and presence of hypertension or cardiovascular disease

	Women ¹			Men ²		
	n	ΔeGFR [SE]	p-value	n	ΔeGFR [SE]	p-value
Hypertension ³						
No	725	0.27 [0.86]	0.75	589	0.35 [0.88]	0.69
Yes	296	0.22 [1.41]	0.87	248	4.74 [1.53]	0.002
Myocardial infarction / stroke						
No	1001	0.00 [0.73]	0.99	781	1.30 [0.80]	0.10
Yes	28	6.98 [5.46]	0.21	74	6.21 [2.85]	0.033

Δ estimated glomerular filtration rate (eGFR) is the difference in eGFR, calculated with the Chronic Kidney Disease-Epidemiology Collaboration formula, between offspring and controls assessed with a linear mixed model. A positive number means that eGFR is higher in offspring compared with controls. We adjusted for sibling relationship and age.

¹ Offspring n=695 and control n=342. ² Offspring n=605 and control n=254. ³ Defined as either having hypertension and/or using anti-hypertensive medication.

The sensitivity analysis with GFR estimated with the MDRD or CG formula as outcome showed similar crude and adjusted results. Repeating the analyses in subjects with eGFR >60 ml/min/1.73 m² (offspring n=1220, controls n=556) resulted in similar differences in eGFR in female offspring compared with female controls (0.10 ml/min/1.73 m² [SE 0.66], p=0.87, age-adjusted), and in male offspring compared with male controls (1.59 ml/min/1.73 m² [SE 0.71], p=0.026, age-adjusted). Multiple imputation of missing data resulted in a similar eGFR in female offspring compared with female controls (-0.01 ml/min/1.73 m² [SE 0.72], p=0.99) and a non-significant higher eGFR in male offspring compared with male controls (1.39 ml/min/1.73 m² [SE 0.78], p=0.073).

Discussion

Our aim was to investigate whether subjects with a familial propensity for longevity have better renal function compared with control subjects. We found that in the male but not in the female sex, middle-aged individuals with a propensity for longevity had a better renal function compared with environmentally matched controls. This renal function difference in men was predominately present in subjects with hypertension or cardiovascular disease.

In our study three findings dependent on sex were present. First, we found that at middle-age, women had a lower renal function compared with men. This is in line with several other studies^{8;10;21}, showing a lower eGFR in women throughout life, and in line with the correction factor for women used in the CKD-EPI¹³, MDRD¹⁴, and CG formula¹⁵. Second, in men the age-associated decrease in eGFR was slightly stronger than in women. This difference may suggest that men are biologically older than women at a similar calendar age, which is in line with the evidence that men live five to ten years shorter than women.²² Third, women had less cardiovascular disease and diabetes mellitus than men. This is in line with the fact that men develop co-morbidities, such as cardiovascular disease²³ or diabetes mellitus²⁴, at an earlier age in life than women.

In men, a difference in renal function between longevity-prone subjects and environmentally matched controls was observed. This difference may be explained by the lower prevalence of (sub)clinical hypertension and cardiovascular disease in men from long-lived families, which probably reflects a lower degree of atherosclerosis. Atherosclerosis is an inflammatory process in which inflammation has an important role in each phase of the process. Inflammation is involved in fat accumulation in the vessel wall, maturation of the vascular lesion, and eventually ruptures of the atherosclerotic plaque leading to myocardial infarction or stroke.^{25;26} Longevity-prone men may better handle inflammatory stress and thereby have less atherosclerosis and a later onset of inflammatory diseases, such as myocardial infarction and stroke. This better handling of inflammatory stress may furthermore reduce the negative consequences of inflammatory diseases, such as fibrosis of renal tissue.²⁷ Our finding of a larger eGFR difference in male offspring compared with male controls with a previous history of myocardial infarction or stroke compared with male subjects without such a history may support this. However, our data showed that hsCRP levels were similar between male offspring and controls, but hsCRP may not be a good indicator for these inflammatory processes.

In women we observed no difference in renal function between offspring and controls. There are two possible reasons to explain the absence of a difference. First, the prevalence of atherosclerotic disease in women aged 60-70 years is much lower than in men in the same age category. Moreover, the difference between male offspring and male controls was mainly observed in men with hypertension or cardiovascular disease. Although, we found no statistical significant difference in women, we did find a trend in women with a myocardial infarction or stroke in their history (eGFR difference of 6.98 ml/min/1.73 m² [SE 5.46],

$p=0.21$). Second, the absence of a difference in renal function between women from long-lived families and controls might be explained by the effect of sex hormones. Sex hormones have immuno-modulating actions often resulting in a more anti-inflammatory state.²⁸ The genes involved in longevity leading to a better handling of inflammatory stress and less atherosclerosis may then play a less important role. Furthermore, our findings might suggest that the anti-inflammatory effects of sex hormones are less effective once myocardial infarction or stroke has developed. However, the exact pro- and anti-inflammatory actions of sex hormones need to be elucidated.

There are some limitations to our study. First, baseline information on medical history and medication use were not available for all offspring and controls. However, it is unlikely that this selection of subjects has led to biased results because these data were only missing when the subjects' general practitioner or pharmacy did not respond, which was a random process. Second, for our main analyses the GFR was estimated with the CKD-EPI formula. A problem with the CKD-EPI formula is that it sometimes overestimates the real GFR in patients with low renal function (<60 ml/min/1.73 m²) and patients with a low BMI (<18.5 kg/m²).^{17;29} However, only a small proportion of subjects fell in these categories and with the other two formulas, the MDRD and CG formula, we found similar results. Besides this, for each subject only one eGFR measurement was available, making it not possible to relate longevity to renal function decline. Third, we could not adjust for all established risk factors for decline in renal function, such as hemoglobin and calcium/phosphate levels because this information was lacking.

We conclude that renal function was higher in middle-aged men with a propensity for longevity compared with environmentally matched controls. A possible explanation for the observed effect is the presence of a different strategy for inflammation and atherosclerosis in subjects with a familial propensity for longevity.

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Chapter 10 |

Commentary; Audit-based education: a potentially effective program for improving guideline achievement in chronic kidney disease patients

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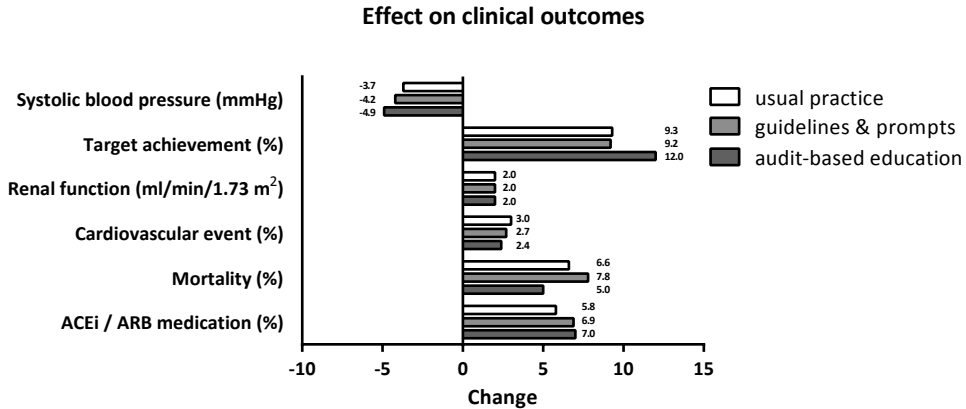
Abstract

The achievement of treatment guidelines in patients with chronic kidney disease is poor and more efforts are needed to improve this. Audit-based education is a program that may contribute to this improvement. Therefore, de Lusignana *et al* investigated whether audit-based education is effective in lowering systolic blood pressure in a primary care setting. Although the program is inventive and promising, several adjustments are needed before it can be applied as an effective strategy.

Hypertension is an important independent risk factor of cardiovascular events, mortality and renal function decline in patients with chronic kidney disease (CKD). Therefore, current international treatment guidelines for CKD patients recommend lowering blood pressure in this specific population (target: 140/90 mmHg and 130/80 mmHg for patients with >30 mg albuminuria/day).^{1,2} The primary recommended pharmacological therapy is the prescription of an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin-II receptor blocker (ARB). Indeed, in addition to blood pressure lowering effects, these drugs have direct renoprotective effects.³ This therapy can be combined with other anti-hypertensive drugs and lifestyle changes such as sodium restriction and increasing physical activity. Despite these treatment guidelines, guideline achievement for controlling blood pressure in patients with CKD is poor.⁴ A possible explanation for this could be that physicians are reluctant in prescribing ACEi/ARBs because of contra-indications or side effects. In addition, physicians might be unaware of the current treatment guidelines thereby resulting in suboptimal treatment of patients. Therefore, more guidance and education of physicians on the treatment of hypertension is necessary. Several programs to achieve this have been suggested but the effectiveness of these programs has not been evaluated extensively. The trial of de Lusignana *et al.*⁵ in this issue of *Kidney International* is one of the first, in which an audit-based education program was investigated.

Audit-based education is a quality improvement intervention that provides feedback, education and guidance, and documents the gap between achievement and guidelines.^{6,7} For the auditing step, anonymised data needs to be extracted from participating practices and processed. After data processing several important outcome measures, such as the percentage of patients not reaching the recommended treatment target, are documented and compared between practices. Based on these results, feedback is provided for each practice, preferably with an accompanied target or action plan. Furthermore, local queries are performed to provide each physician with a list of individuals that need adjustment of their treatment in order to reach the targets of the current guidelines. Theoretically, audit-based education could be applied to improve the achievement of all recommended treatment targets throughout all stages of CKD, thereby including primary care practices but also nephrology outpatient clinics. De Lusignana *et al.* specifically focused on the effectiveness of audit-based education on systolic blood pressure lowering in a primary care setting in the United Kingdom. The rationale of this study was that primary care physicians feel they lack knowledge about and confidence in managing CKD. Therefore, the authors hypothesized that an audit-based education program could have a large effect on quality of care in this specific setting. From the 565,016 adult people that were registered in the 93 primary practices participating in the study, 41,183 patients were diagnosed with CKD stages 3-5 (7.3%). Of these CKD patients, 36,288 were not lost to follow-up. These patients were included in the analyses. Block randomization was used to randomize the 93 participating practices into one of the following arms; audit-based education (n=30), guidelines & prompts (n=32), and usual practice (n=31).

This study revealed that patients treated according to the audit-based education program experienced a crude additional 1.2 mmHg decrease in systolic blood pressure compared with patients treated according to usual practice (4.9 versus 3.7 mmHg, Figure 1). In addition, in the audit-based education arm 2.7% more patients reached the target of 140/90 mmHg compared with the usual practice arm (12.0 versus 9.3%, Figure 1). Unfortunately, it remains unclear why the authors chose this target and not the target of 130/80 mmHg for patients with albuminuria (unclear which percentage of patients has albuminuria, but this is approximately 70% according to the USRDS⁸). The question arises if such a reduction in systolic blood pressure is relevant for CKD patients in terms of clinical outcomes. In this respect, a reduction of 5 mmHg indeed has beneficial effects on several clinical outcomes in the general population.⁹ However, these study populations consisted of relatively young and healthy individuals, which is in contrast with the elderly CKD patients (mean age 75 years) in the trial by de Lusignana *et al.*, in whom blood pressure lowering may have a different effect. In line with this, the effect on other clinically important outcomes in the trial of de Lusignana *et al.*, such as stabilization of renal function and prevention of cardiovascular events and death, was less pronounced (Figure 1). Patients following the audit-based education program experienced a similar change in estimated glomerular filtration rate compared with patients following usual practice (increase of 2.0 ml/min/1.73 m² during a follow-up period of approximately two to two-and-a-half years). Furthermore, the incidence of cardiovascular events and mortality was 2.4% and 5.0% respectively in the audit-based education program and 3.0% and 6.6% respectively during usual practice. The latter implies that approximately 167 and 63 patients need to be treated for two to two-and-a-half years according to the audit-based education program in order to prevent one cardiovascular event and death respectively (number needed to treat = 1 / risk difference). These numbers indicate that the positive effect of the audit-based education program on cardiovascular events is quite small but that it is substantial on mortality. The effect on mortality could not be entirely explained by a greater switch to ACEi/ARB medication, as suggested by de Lusignana *et al.* Indeed, the percentage of patients starting with an ACEi/ARB is similar between the audit-based education and guidelines & prompts arm (7.0 versus 6.9%) in contrast to the incidence of mortality which was different (5.0 versus 7.8%, Figure 1). Therefore, it needs to be explored which element of the audit-based education program is actually causing the lower mortality. With respect to renal function stabilization and cardiovascular events, we have to keep in mind that the follow-up time in the trial of de Lusignana *et al.* may be too short to detect large effects on these outcomes. The above-mentioned results raised the question whether the clinical effects of the audit-based education program were worth the accompanying time, efforts, and costs.

Figure 1: Overview of the effect of audit-based education on clinical outcomes

The audit-based education program consists of several steps that can be experienced as burdensome, time-consuming, and costly. The step of data extraction and processing is time-consuming for the executive authorities. Following this audit, an individualized action plan needs to be developed and explained to all treating physicians. To achieve this feedback and education, physicians need to attend workshops or meetings that can be experienced as burdensome. In this respect, de Lusignana *et al.* encountered a suboptimal attendance of physicians to the feedback workshops in the study. Since the adherence to treatment guidelines outside a clinical trial is expected to be even lower, the application of the audit-based education program to all primary practices may lead to a lower attendance and thereby a smaller effect on blood pressure and cardiovascular burden. Furthermore, in the trial of de Lusignana *et al.* the local queries were excluded from the trial due to practical reasons (i.e. concerns about ethics and recruitment of practices). Theoretically, local queries could have significantly increased the effect on blood pressure because it provides a list of individuals that need to be targeted. However, if concerns are present about feasibility in a highly standardized trial, it will definitely not be feasible in real clinical practice. Altogether, the audit-based education program may be seen as a time-consuming and costly program, which is only justified when the accompanying clinical effect is substantial.

It is indisputable that the strict implementation of treatment guidelines is necessary to improve quality of care, thereby leading to better clinical outcomes. The trial of de Lusignana *et al.* showed that an education-based program slightly improves the implementation of one treatment target guideline, namely blood pressure control. Unfortunately, it was not assessed whether the intervention was cost-effective and further research should therefore focus on this aspect. Despite the small clinical effect, the audit-based education program can still be a valuable tool in improving guideline achievement and thereby quality of care. By identifying the parts of the program that are most effective, the ineffective parts can be excluded, thereby reducing efforts and costs. In addition, blood pressure is not the only risk factor

poorly controlled in CKD patients. Treatment guidelines focusing on other important risk factors, such as lipid levels, proteinuria, potassium/sodium levels and calcium/phosphate levels, are also poorly achieved. Therefore, expanding the program with other risk factors may increase the effect on clinical outcomes (e.g. less cardiovascular events, lower mortality, and a slower renal function decline). In addition, improving other medical issues in CKD patients, such as low treatment compliance and detrimental lifestyle, can even lead to a greater effect. Future research focusing on these aspects can improve the program and may lead to a cost-effective strategy for improving guideline achievement and quality of care in CKD patients.

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Chapter 11 |

Multiple imputation: dealing with missing data

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Abstract

In many fields, including the field of nephrology, missing data are unfortunately an unavoidable problem in clinical/epidemiological research. The most common methods for dealing with missing data are complete case analysis – excluding patients with missing data –, mean substitution – replacing missing values of a variable with the average of known values for that variable –, and last observation carried forward. However, these methods have severe drawbacks potentially resulting in biased estimates and/or standard errors. In recent years, a new method has arisen for dealing with missing data called multiple imputation. This method predicts missing values based on other data present in the same patient. This procedure is repeated several times, resulting in multiple imputed datasets. Thereafter, estimates and standard errors are calculated in each imputation set and pooled into one overall estimate and standard error. The main advantage of this method is that missing data uncertainty is taken into account. Another advantage is that the method of multiple imputation gives unbiased results when data are missing at random, which is the most common type of missing data in clinical practice, whereas conventional methods do not. However, the method of multiple imputation has scarcely been used in medical literature. We therefore encourage authors to do so in the future when possible.

Introduction

Missing data are a problem that is often encountered when performing clinical studies. In any study design, such as a randomized controlled trial, a cohort study, and a case-control study, missing data can occur. Especially, in studies with routinely collected data, missing values are unfortunately unavoidable. Even after the introduction of statistical software allowing more sophisticated procedures, the methods most often used to deal with missing data are complete case analysis, mean substitution, and last observation carried forward (LOCF).

In a complete case analysis, patients with missing data are excluded from the statistical analyses. Consequently, only patients with complete data will contribute to the results. Mean substitution is a method in which missing observations for a certain variable are replaced by the average of observed data for that variable in other patients. However, both these methods have severe drawbacks. Performing a complete case analysis not only leads to a smaller sample size and therefore may reduce statistical power but can also lead to biased results. These biased results can occur when the patients excluded from the analysis have different patient characteristics compared with those who were included. Mean substitution will maintain the original sample size, but can still lead to biased results when the patients with missing data have different patient characteristics compared with those with available data. Furthermore, the variances obtained with mean substitution are biased downwards because the substituted values are treated as 'real' observed values although they are all centered on the mean, resulting in a narrower distribution of values. LOCF is a method frequently used with missing longitudinal data, such as trials and cohort studies. This method replaces missing values with the last observation measured before the one that is missing. In this way data are kept constant over time and the method will lead to biased results when in reality data change over time.

In recent years, a new method for dealing with missing data called multiple imputation has arisen. However, in medical literature the application of this method is quite uncommon but has been rising during the last few years.^{1,2} In this educational article we provide a brief introduction to the method. We will not go into details of the technical or practical aspects of the multiple imputation method. For those details we refer to other literature.³⁻⁶ Our goal is to describe the different types of missing data, for what types of missing data the multiple imputation method can be used, and explain why this new method is preferred over other conventional methods for dealing with missing data.

Types of missing data

Missing data can roughly be classified into three types: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR) (Box 1). With MCAR, the underlying reasons for data being missing are independent of known and unknown patient characteristics. In other words, subjects with missing values are a completely random subset of the study population and patient characteristics will therefore be similar between

subjects with and without missing data. An example of data being MCAR is when a tray with blood samples is accidentally broken resulting in missing laboratory values.

Box 1: Types of missing data

- Missing completely at random (MCAR) – The underlying reasons for data being missing are independent of known and unknown patient characteristics. An example is when a tray with blood samples is accidentally broken, resulting in missing laboratory values.
- Missing at random (MAR) – The underlying reasons for data being missing are related to known patient characteristics. An example is the higher probability that a blood sample could not be drawn before the start of dialysis in patients who started acutely.
- Missing not at random (MNAR) – The underlying reasons for data being missing are related to unknown patient characteristics. An example is that subjects with a low education are more likely to skip a question about their level of education in a questionnaire.

The underlying reasons for data being missing in clinical research, however, are often related to several known patient characteristics. This type of missing data is called MAR, as conditional on the known patient characteristics data are missing randomly. An example of this type of missing data is the higher probability that a blood sample could not be drawn before the start of dialysis in patients who started dialysis acutely. It is highly likely that patient characteristics of subjects starting dialysis acutely are different compared with subjects not starting acutely. In that case, patients with missing blood samples are not a random subset of the study population, and their true laboratory values are probably different from those for whom a blood sample was available. However, it could be possible to predict from the available data which patients are acute starters and therefore have missing blood samples. Conditional on these prediction characteristics, meaning within the different strata, subjects with a missing blood sample do constitute a random subset, and therefore this type of missing data is called MAR.

The third type of missing data, MNAR, is the most complicated type of missing data, as here the underlying reasons for data being missing are related to unknown patient characteristics. For example, subjects with a low education are more likely to skip a question about their level of education in a questionnaire. The level of education depends on many characteristics, which may not all be measured. Neither conventional methods nor the multiple imputation method are suitable when missing data are MNAR. There are some other methods available, but these methods are very complex and subject to many assumptions, and are therefore outside the scope of this article.⁷ It is common in clinical practice that the missing data type MNAR coexists with the other two types (MCAR and MAR). For example, when quality of life data are missing, some patients have not filled in the questionnaire because their pencil broke (MCAR), some because of clinical characteristics – like age – which are measured (MAR), and some patients because they have a low quality of life for reasons unrelated to

measured patient characteristics (MNAR). When the MNAR type is rare in this mixture of different missing data types, multiple imputation can be used.

In the next section we will describe the conventional methods of complete case analysis, mean substitution, and LOCF and indicate for which types of missing data, MCAR and MAR, these methods give unbiased results.

Conventional methods: when to use them?

To illustrate when a complete case analysis, mean substitution, and LOCF can be used, we simulated a situation where data were missing. In this example, the mean [standard error] serum urea level at the start and end of pre-dialysis care, and the change [standard error] of urea, were measured in 1500 incident patients starting pre-dialysis care. Standard compute commands in PASW/SPSS version 20 were used for data simulation. The first urea measurement at the start of pre-dialysis care (U1) was simulated by taking a random subset of 1500 patients from a normal distribution (mean 20 mmol/l, standard deviation 6, computed with the random variable function `rv.normal`). The second urea measurement at the end of pre-dialysis care (U2) had a mean of 24 and a standard deviation of 6. The correlation between U1 and U2 was specified at 0.75. Table 1 shows the mean [standard error] U1, U2, and change of urea (U2-U1) for these 1500 patients from the main analysis of our simulation. The increase in urea (U2-U1) during pre-dialysis care was 4.0 [0.11] mmol/l, with a urea level of 20.0 [0.15] mmol/l at the start of pre-dialysis care and 24.0 [0.15] mmol/l at the end.

Table 1: Simulation study: results of conventional and multiple imputation method when data is missing completely at random (MCAR)

	Main analysis n=1500	Complete case n=1218	Mean substitution n=1500	LOCF n=1500	Multiple imputation n=1500
Mean [SE] U1	20.0 [0.15]	20.0 [0.17]	20.0 [0.15]	20.0 [0.15]	20.0 [0.15]
Mean [SE] U2	24.0 [0.15]	24.0 [0.17]	24.0 [0.14]	23.3 [0.16]	24.0 [0.15]
Mean [SE] U2-U1	4.0 [0.11]	4.0 [0.12]	4.0 [0.12]	3.3 [0.11]	4.0 [0.11]

U2 was made MCAR for ~20% of the subjects, computed with the random number function `uniform(n)`, resulting in the missing data type MCAR. Now, for only 1218 patients both U1 and U2 were measured. A complete case analysis in these 1218 patients resulted in an increase in urea of 4.0 [0.12] mmol/l, U1: 20.0 [0.17] mmol/l and U2: 24.0 [0.17] mmol/l. All values were similar to the values from the main analysis. The standard errors were somewhat higher due to the lower sample size (n=1218). When performing the mean substitution method we found an increase in urea of 4.0 [0.12] mmol/l, U1: 20.0 [0.15] mmol/l and U2: 24.0 [0.14] mmol/l. Again all values were similar to the values from the main analysis. However, the standard error of U2 is biased downwards because all substituted data had the same value, resulting in less variance. Although the method of LOCF is not justified when only two data points are

present in a study we applied this method to our simulated situation for illustrative purposes. Using LOCF when data were MCAR resulted in an increase in urea of 3.3 [0.11] mmol/l, U1: 20.0 [0.15] mmol/l and U2: 23.3 [0.16] mmol/l. The mean value for U2 and thereby the increase in urea were biased downwards.

What results would the conventional methods give if data were MAR? We therefore simulated U2, using the uniform(n) function, with a 1% higher chance of being missing for each mmol/l higher U1. In Table 2, the results of the conventional methods are presented. In the complete case analysis the values U1 (19.6 [0.17] mmol/l) and U2 (23.7 [0.17] mmol/l) were biased downwards. This finding can be explained by the fact that subjects with a high mean U1 have a higher chance of having missing data for U2. In a complete case analysis, these subjects are excluded from the analysis, resulting in a lower mean U1. The mean U2 is also lower because a high correlation was specified between U1 and U2 (0.75). Had this correlation been lower, the resulting value of U2-U1 would have been even more biased, as the mean U2 would move towards the mean of the main analysis. In the mean substitution analysis the values of U2 (23.7 [0.13] mmol/l) and thereby also U2-U1 (3.7 [0.12] mmol/l) were biased downwards. Again this is explained by the fact that subjects with a high U2 have a higher chance of having missing data. Therefore, substitution of the mean U2 will result in an underestimation. LOCF again resulted in biased values for U2 and U2-U1, 23.2 [0.15] mmol/l and 3.2 [0.11] mmol/l, respectively.

Table 2: Simulation study: results of conventional and multiple imputation method when data is missing at random (MAR)

	Main analysis n=1500	Complete case n=1173	Mean substitution n=1500	LOCF n=1500	Multiple imputation n=1500
Mean [SE] U1	20.0 [0.15]	19.6 [0.17]	20.0 [0.15]	20.0 [0.15]	20.0 [0.15]
Mean [SE] U2	24.0 [0.15]	23.7 [0.17]	23.7 [0.13]	23.2 [0.15]	24.0 [0.15]
Mean [SE] U2-U1	4.0 [0.11]	4.1 [0.12]	3.7 [0.12]	3.2 [0.11]	4.0 [0.11]

The simulation studies presented above clearly demonstrate that the conventional method of complete case analysis gives unbiased estimates and standard errors – only slightly higher due to a smaller sample size and thereby loss of power – when data are MCAR, but not when data are MAR. With mean substitution the standard errors are biased downwards in both types of missing data due to a higher number of values centered on the mean. Loss of statistical power and/or biased results makes neither method the method of choice. Furthermore, it is likely that in clinical research the two types of missing data are mixed and it is very difficult to assess which type is (most) present. When using the method of LOCF, urea levels were kept constant between the start and end of pre-dialysis care. The analysis thereby resulted in a too small increase in urea in both types of missing data and is also not the preferred method. This dilution would be less prominent when more data points were available, so that missing urea values at the end of pre-dialysis care can be replaced by a value

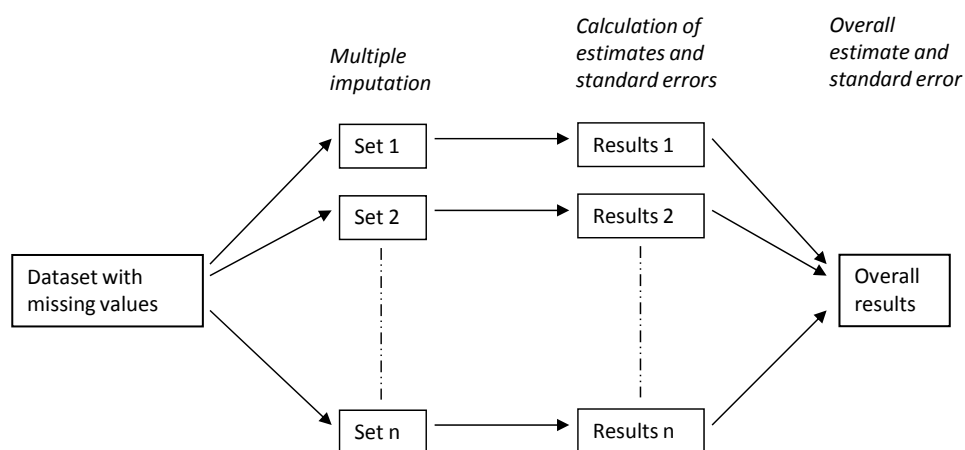
measured at a closer data point. It can be concluded that all three conventional methods have limitations and are not preferred for handling missing data. In the next sections, we discuss the method of multiple imputation and when this method can be used.

Multiple imputation: explanation of the method

Multiple imputation is a method in which missing data are predicted based on known data and on the pattern of missing data.⁸ In our view, this method builds on and improves the idea of mean substitution. When using mean substitution, missing values are replaced with the overall mean and imputed values are treated as ‘real’ observed values. Obviously, this approach is too simplistic and generally leads to biased results as in reality some patients have higher values than the mean and other patients have lower values. The overall mean is therefore not the best estimate for all of them. An improvement on simple mean substitution could be made by stratifying by age, for example, and substituting the mean among young patients for missing values among young patients and that among old patients for missing values among old patients. This line of reasoning can be followed further, by stratifying by more relevant variables, and substituting a variety of mean values in a multitude of subgroups. In principle, the method of multiple imputation thus makes strata based on the variables known by creating a prediction model for the missing variable. Each patient falls within a stratum based on his or her known characteristics. A patient’s missing value is then replaced by the mean of that stratum. However, in reality there is variation around the mean, even in small strata. If you impute the same value for all patients within a stratum, the variation will be too low. Therefore, a random error component should be added to the imputed mean value. This error component should be randomly drawn from the error distribution (i.e. from the residuals) from the prediction model. In the above example, in patients on pre-dialysis care with missing U2, their missing U2 would be replaced by a predicted value of U2 based on the available U1. Usually, it is possible to predict the missing U2 values based on more variables, such as age and sex. If the patients with missing U2 are also old and male, it makes sense to replace their missing value with a value similar to that of old male patients. It is very important to think about the known variables you want to include in the model to predict the missing value of interest. There are several strategies you can follow in this respect⁶, but generally all variables (continuous or categorical) used for your final analyses should be included. Inclusion of the outcome is also necessary because reasons for missing data are usually related to the outcome status.⁹ It is important to keep in mind that depending on the statistical software used, difficulties can arise when continuous variables are not normally distributed – which can be solved with transformation – or when categorical variables need to be imputed. Another important thing to keep in mind is that the imputation model will not always perform better and may even lead to biased results when including large numbers of variables, especially, when these variables have many missing values themselves. For a more in-depth description of these two important computational issues we refer to other literature.^{10;11}

Performing the imputation procedure only once is not to be recommended. With single imputation, imputed values are treated as 'real' observed values and, as mentioned earlier, the standard error will be underestimated. Single imputation resembles mean substitution conditional on other known data, and therefore will have the same problem with underestimating standard errors. The imputation procedure should be repeated several times resulting in multiple imputation data sets. Each imputation takes a random draw from the error distribution, and adds this to the predicted mean value. How many times this procedure should be repeated depends on the rates of missing data. It has been claimed that 3-10 imputations are sufficient to obtain an adequate efficiency.^{12;13} Only when the percentage of missing data is very high (>30%) more imputations are recommended. After performing multiple imputations, the analyses of interest are performed within each individual imputation set. The obtained estimates and standard errors of each imputation set are then pooled together into one overall estimate and standard error. For the overall estimate the average is taken of all separate estimates. The overall standard error consists of the within- and between-imputation variance, based on Rubin's rules.¹² With multiple imputation, the uncertainty of the separate imputations is taken into account by incorporating the between-imputation variance, which when compared with mean substitution or single imputation results in a less biased standard error. The combination of predicting missing values, based on other known information, and taking into account imputation uncertainty does not support the term 'data creation' introduced by critics of the method. Figure 1 presents a more graphical representation of the method of multiple imputation.

Figure 1: Graphical representation of the multiple imputation procedure



Multiple imputation: when to use?

In this section, we demonstrate how multiple imputation affects the results when data is either MCAR or MAR. We used the same example of urea levels during pre-dialysis care (U1 and U2) as described before. In this example missing U2 values were imputed based on known U1 values (n=1500). We performed five imputations because U2 data were only missing for ~20% of the patients. Tables 1 and 2 show that multiple imputation resulted in the same values and standard errors when compared with the main analysis, for both MCAR and MAR. Our simulation results show that multiple imputation performs well in both types of missing data, and is therefore the preferred method in clinical practice where mixtures of missing data types are common.

Multiple imputation in the field of nephrology

Studies performed in the field of nephrology often aim to estimate the association of a determinant with an outcome, such as the start of dialysis or mortality. Unfortunately, quite often the outcome cannot be established for all patients due to study drop-out or reaching the end of the study period. A complete case analysis is not the preferred method because of power problems and possible biases. Time-to-event analysis estimates an incidence rate and can handle these missing outcomes through censoring.¹⁴ All patients can be included in this analysis because follow-up time until the event of interest or the moment of censoring is taken into account. If time-to-event data are not available, or the assumption of non-informative censoring is violated, multiple imputation could be used to impute these missing outcomes. Deo *et al.*¹⁵ investigated how many trials performed in patients on renal replacement therapy without time-to-event data available, reported a method to impute missing outcome data, which they found were only 5 of the 110 trials (5%). However, none of these studies used the technique of multiple imputation.

Furthermore, when routinely collected data are used, which is often the case in the field of nephrology, the determinant of interest or the confounders you want to adjust for can have missing values. The reason for these missing data is often based on other known patient characteristics. For example, when data from a national registry of patients on dialysis are used to develop a prediction model for the risk of mortality, it is not surprising that many patients have missing data on co-morbidities and laboratory values. Wagner *et al.*¹⁶ found that patients with missing data (~50%) have a higher risk of mortality, were older, more likely to be white, and had more often an uncertain diagnosis of primary kidney disease, resulting in missing data type MAR. Excluding these patients from the analyses can lead to biased results. Therefore, the authors of this article performed multiple imputation as a sensitivity analysis. Another article, by Collier *et al.*¹⁷, also used the technique of multiple imputation as a sensitivity analysis to check the robustness of their main complete case analysis. They investigated the association of co-morbidities with survival in patients on renal replacement therapy. The association found when using the method of multiple imputation was less strong compared with the association found when using a complete case analysis. This dilution is

probably due to the fact that patients excluded from the main complete case analysis had more co-morbidities.

In summary, only a few years ago the multiple imputation method was scarcely used in the field of nephrology as shown by Deo *et al.* Currently, a full text search of ‘multiple imputation’ on the website of Nephrology Dialysis Transplantation resulted in seven hits between 2006 and 2008. However, this number has been rising during the last few years as there were eighteen hits between 2009 and 2011. And although it has been applied as a sensitivity analysis in the study of Wagner *et al.* and Collier *et al.*, hardly any study uses it in its main analyses with full attention to the imputed results. We recommend to present results the other way around, so multiple imputation results as main analysis and complete case results as a sensitivity analysis. This and other important recommendations on how to report analyses using the method of multiple imputation can be found in the article of Sterne *et al.*¹⁸

Conclusion

We can conclude that the multiple imputation method gives unbiased estimates and standard errors provided that data are either MCAR or MAR, and the prediction model specification is adequate, which may require the help of a statistician. The conventional method complete case analysis only gives unbiased results – and a somewhat higher standard error due to the loss of power - when data are MCAR. In both types of missing data, mean substitution and LOCF give biased results. In clinical practice, combinations of missing data types are most common and it is difficult to assess which type(s) is present for which patient. We can only theoretically imagine which types are present. However, overall multiple imputation performs better than the conventional methods and is therefore the method of choice. In the field of nephrology, multiple imputation is not used very often, and we encourage authors to do so in the future. Especially, because the method is relatively easy to perform in many statistical packages, such as recent versions of PASW/SPSS, STATA, and SAS. One problem about multiple imputation is that some people feel that the method is making up data, which is not scientifically ethical. With this educational article, we hope to have demonstrated that the multiple imputation method predicts data based on known variables with the incorporation of missing-data uncertainty, which will lead to estimates closest to the truth.

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Chapter 12 |

Letter to the editor; Body mass index and progression of chronic kidney disease

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http://ndt.oxfordjournals.org/content/27/7/2776.abstract/reply#ndt_el_99

Dear Editor,

In the article of Brown *et al.*¹ a clinically relevant question was addressed. They investigated whether in non-diabetic chronic kidney disease (CKD) patients (stages 3-5) obesity is related to the rate of progression of CKD, defined as the start of renal replacement therapy (RRT) and estimated glomerular filtration rate (eGFR) decline. The authors concluded that a high body mass index (BMI), either analyzed as a continuous or dichotomous variable, was not associated with the progression of CKD. However, we believe that the used statistical analyses are insufficient to draw a reliable conclusion.

First, it can be questioned whether comparing obese patients (BMI ≥ 30 kg/m²) to a broad reference group (BMI < 30 kg/m²) is correct. Previous studies performed in the general population and in dialysis patients showed that subjects with a low BMI (< 20 kg/m²) have a higher risk of mortality^{2,3} compared with those with a BMI between 20 and 25 kg/m². Therefore, a reference group excluding patients with a low BMI would be more appropriate, to prevent underestimation of the effect of obesity. Second, Table 2 shows a higher eGFR decline in non-obese patients, except for stage 5 where the decline is lower in non-obese patients. Therefore, we believe it is not justified to combine all stages of CKD in the subsequent analyses. Third, not controlling for important confounders, such as smoking, age, and co-morbidities, and inappropriate control for biological effects of obesity, such as hypertension, may result in bias. In line with this, the association of BMI with the rate of starting RRT should be investigated with a multivariable Cox Regression model. With this model, crude incidence rate ratios can be statistically tested and adjusted for confounders. For the eGFR decline a linear mixed model would be an appropriate method.⁴ This type of model calculates individual slopes and takes its deviation from the mean slope into account. This is useful when limited measurements per individual are available as is the case in this study. Fourth, the stratified analysis presented in Table 5 may introduce bias. The eGFR decline is compared between obese and non-obese patients who started RRT, died, or reached end of study. Obesity and eGFR decline are competing risk factors for mortality. Therefore, if a patient dies it may be either because of obesity, or because of eGFR decline. Consequently, the results of Table 5 improperly suggest that non-obese patients who died have a faster eGFR decline than obese patients who died.⁵

In conclusion, we invite the authors to perform further analyses to give a reliable insight into the effect of obesity on progression of CKD in non-diabetic patients with CKD stages 3-5.

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Chapter 13 |

Summary and general discussion

Introduction

Chronic kidney disease (CKD) has become a major public health problem worldwide.¹⁻⁴ The increasing prevalence of patients with CKD^{1;5;6} can be explained by the growing elderly population and lifestyle changes. Renal function has an age-related natural decline⁷, leading to a moderately reduced renal function at older age⁵. Lifestyle changes, such as high-fat diets and low physical activity, have led to an increasing prevalence of hypertension⁸ and type 2 diabetes mellitus⁹. These morbidities are known to accelerate renal function decline, thereby increasing the risk of developing CKD. CKD is defined by a progressive loss of renal function which may eventually lead to the need for renal replacement therapy (RRT, starting dialysis or receiving a kidney transplant; also defined as end-stage renal disease, ESRD).¹⁰ Ideally, progression towards the start of RRT is slowed down in early stages of the disease process, in which renal function is normal or mildly reduced and albuminuria/proteinuria is present (CKD stages 1 and 2). However, in most patients CKD only becomes symptomatic when renal function deteriorates and drops below 30-60 ml/min/1.73 m² (CKD stages 3-5).¹¹ Screening strategies based on albuminuria/proteinuria to identify patients in earlier stages of the disease process are unfortunately not optimal yet. At this moment, no consensus has been reached regarding the appropriate type of test, which thresholds to use, which patient populations to screen and whether a screening strategy is cost-effective.^{4;12-14} Therefore, treatment to slow down the disease progression is mainly performed in more advanced CKD stages and guidelines for this population are important. In The Netherlands young patients (<65 years) with a renal function below 60 ml/min/1.73 m² (CKD stages 3-5) should be referred to a nephrologist and treated according to guidelines.^{10;15} Elderly patients should only be referred when this moderately reduced renal function coincides with the presence of proteinuria (>1 g/24h) or a progressive loss of renal function (>3 ml/min/1.73 m²/year). When renal function deteriorates even further (<30 ml/min/1.73 m², CKD stages 4-5), both young and elderly patients are referred to an outpatient clinic for multidisciplinary pre-dialysis care. Treatment guidelines for this specific population have been developed in The Netherlands.¹⁶ However, these guidelines are mainly based on studies performed in early- to middle-stage CKD patients and mainly focus on the objectively assessed outcome renal function decline. Studies in the pre-dialysis population are therefore needed to make these guidelines more evidence-based. Therefore, the main goal of this thesis was to investigate the effect of several risk factors on objectively assessed disease progression, defined as renal function decline and time until the start of RRT, and subjectively assessed disease progression, defined as disease-related symptoms and health-related quality of life, in patients on specialized pre-dialysis care. We furthermore tried to explore (un)known mechanisms that determine renal function decline in pre-dialysis patients. For both aims data were used from the PRE-dialysis PATient REcord (PREPARE) study. We also explored (un)known mechanisms of the age-related renal function decline in the general population and for this aim the Leiden Longevity Study was used. This study consists of subjects with a propensity for longevity and environmentally matched controls without this propensity.^{17;18} The exploration of (unknown) mechanisms may

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

Summary of main findings

Outcome: renal function decline

In **chapters 2, 4, and 5** we used renal function decline as outcome. Renal function was expressed as glomerular filtration rate (GFR) and we used serum creatinine-based formulas to estimate the GFR (eGFR). These chapters provide evidence that current treatment targets for controlling blood pressure (systolic below 130 mmHg and diastolic below 80 mmHg, when proteinuria is present), proteinuria (below 0.3 to 1.0 g/24h) and lipid levels (low density lipoprotein (LDL) cholesterol levels below 2.5 mmol/l and triglyceride levels below 2.25 mmol/l¹⁶) are clinically well defined regarding the outcome renal function decline. Patients on pre-dialysis care with levels below these targets experience a slower renal function decline compared with patients having levels above the treatment target. For all three important risk factors a dose-response relation was found, indicating that higher levels were associated with a faster renal function decline. Clinically relevant increases of these risk factors (10 mmHg increase in systolic and diastolic blood pressure, 1 g/24h increase in proteinuria, and 1 mmol/l increase in LDL cholesterol and triglyceride levels) resulted in a 0.04 to 0.06 ml/min/1.73 m²/month faster renal function decline. On a yearly basis this represents a 0.48 to 0.72 ml/min/1.73 m² faster decline in renal function. This additional decline is quite large considering the relatively low renal function at the start of pre-dialysis care (~15 ml/min/1.73 m²). To illustrate the clinical impact of these findings, 17% of all pre-dialysis patients have a systolic blood pressure above 180 mmHg, resulting in a 2.4 ml/min/1.73 m²/year faster renal function decline compared with patients with their blood pressure on target. For proteinuria, 25% of the patients have levels above 3.8 g/24h, leading to a 1.7 ml/min/1.73 m²/year faster renal function decline compared with patients with a level of 0.3 g/24h, which is the lower target boundary. Lowering blood pressure, proteinuria, and lipid levels may therefore slow down the rate of renal function decline. Several large randomized controlled trials indeed showed a slower renal function decline when blood pressure and proteinuria were lowered with an angiotensin-converting enzyme inhibitor (ACEi) and/or an angiotensin-II receptor blocker (ARB).^{19;20} Lowering lipid levels with statins showed an absent or very small effect on renal function decline.²¹⁻²⁴ However, we have to keep in mind that these randomized controlled trials mainly included patients with moderate CKD (stage 3) instead of patients with advanced CKD (stages 4-5) or used renal endpoints that are very robust (e.g. start of RRT and doubling of serum creatinine).

Outcome: start of renal replacement therapy

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

159 mmHg) and diastolic (≥ 100 versus 80-89 mmHg) blood pressure in young (< 65 years) pre-dialysis patients (1.9 and 1.7 fold higher rate, respectively, **chapter 3**). However, **chapter 3** showed contradictory findings with respect to renal function decline in elderly (≥ 65 years) patients. Low systolic (< 120 versus 140-159 mmHg) and diastolic (< 70 versus 80-89 mmHg) blood pressure were associated with an earlier start of RRT in elderly patients (2.8 and 1.6 fold higher rate). This finding may indicate that in clinical practice indications are present to start RRT, that do not influence renal function decline. Congestive heart failure is a complication often seen in CKD patients²⁵ and leads to a reduction in cardiac output. This disease, especially in CKD patients, is often accompanied by volume overload. Fluid overload is one of the most important indications to start RRT. Moreover, a reduced cardiac output will also result in hypo-perfusion of the kidneys and thereby a lower renal function. The loop between cardiac dysfunction and progressive loss of renal function is also called the cardio-renal syndrome.²⁶ The presence of the renal part of this syndrome is not supported by the results presented in **chapter 3**, showing a similar renal function decline in elderly patients with low compared with normal blood pressure. However, it could be that congestive heart failure leads to a sudden drop of renal function followed by an immediate start of RRT. Such a drop may not be detected when calculating renal function decline with multiple measurements over time.

Outcome: symptoms and health-related quality of life

Chapters 6 and 7 focused on disease-related symptoms and/or health-related quality of life, which are considered subjectively assessed outcome measures. As compared with other medical fields, such as the field of cardiovascular disease²⁷, in the field of nephrology these outcome measures are not clearly incorporated into clinical guidelines¹⁶. This is probably caused by the lack of consensus between investigators and clinicians on the meaning, importance, assessment, and interpretation of health-related quality of life²⁸ and symptoms, implicating the need for more research. During the last years more research has been performed on health-related quality of life in CKD patients. Several studies showed that health-related quality of life deteriorates when renal function declines.²⁹⁻³¹ This could be explained by the fact that disease-related symptoms become more present when kidney function decreases. Together with treatment choices that have to be made, the mental and physical well-being of an individual can be affected. Furthermore, health-related quality of life is a good predictor for mortality and progression to ESRD throughout all stages of CKD.³² These findings have changed the thought about health-related quality of life and more studies are now focusing on this outcome. Results from **chapter 6** provide further support for the importance of subjectively assessed outcome measures, by showing an increase in symptoms and a decline in health-related quality of life during pre-dialysis care with the sharpest change in the last 6-12 months before starting dialysis. Furthermore, each additional symptom and each 3-point lower physical and mental health-related quality of life score were associated with a respectively 7%, 2%, and 3% higher risk of starting dialysis within the subsequent six months. Besides these changes during pre-dialysis care, it has been shown that in anemic CKD

patients, targeting hemoglobin levels of 11-12 g/dl (recommended target) improves health-related quality of life.³³ However, a debate is ongoing whether targeting higher (≥ 13 g/dl) hemoglobin levels has more beneficial effects. Evidence supporting this idea is lacking, especially in the specific population of patients on pre-dialysis care. **Chapter 7** showed that only in young (< 65 years) patients treated with anemia-medication (an erythropoiesis stimulating agent and/or an iron supplement), high compared with recommended hemoglobin levels (11-12 g/dl) were associated with a better physical and mental health-related quality of life (8.5 and 6 points respectively, 3-5 points are considered clinically relevant³⁴). In elderly (≥ 65 years) patients treated with anemia-medication, no effect of higher hemoglobin levels on health-related quality of life was present.

Risk factors: explore (un)known mechanisms

To identify new treatment strategies for slowing down renal function decline, exploration of (un)known mechanisms that determine renal function decline should be performed. Several studies have shown that black CKD patients who are not dialysis-dependent, experience a faster renal function decline³⁵ and progression to ESRD^{36;37} than whites. The results described in **chapter 8** are in line with this. In this chapter we tried to explore which underlying mechanism(s) is (are) responsible for the faster decline in blacks (additional decline of 0.16 ml/min/1.73 m²/month). In The Netherlands, a universal healthcare system is present, leading to equal access and comparable quality of care for all patients. Healthcare system related factors could therefore not be the complete explanation for the faster decline found in blacks. Furthermore, results did not change after adjustment for demographic characteristics, comorbidities/lifestyle, medication, renal damage, renal function, and laboratory values. Therefore, these factors could also not explain the difference in renal function decline between blacks and whites. However, the faster decline in renal function in blacks when compared with whites was only present in patients with diabetes mellitus or proteinuria. This finding could indicate that diabetes mellitus in black patients has more severe consequences for the kidneys than in white patients. **Chapter 9** indicated that at middle-age renal function is higher in men with a propensity for longevity compared with men without such a propensity (eGFR difference of 1.78 ml/min/1.73 m²). This finding may implicate that subjects from longevity families are less susceptible to risk factors, such as hypertension and cardiovascular events, that further accelerate the age-related natural renal function decline (0.4 ml/min/1.73 m²/year from the age of eighteen years⁷). An even stronger renal function difference was found in men with a history of hypertension or myocardial infarction/stroke (6.98 and 6.21 ml/min/1.73 m², respectively), which may implicate a better handling of systemic inflammation in male longevity subjects. Further research should focus on finding the specific underlying mechanism causing a faster renal function decline in blacks and a lower renal function in middle-aged subjects with a propensity for longevity. By identifying the genetic pathways responsible, our understanding of how the kidneys work increases and new treatments can be identified.³⁸

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

Progression factor / complication	Target	Outcome	Associations present in PREPARE study
<i>Hypertension</i>	Blood pressure <130/80 mmHg	Renal function decline, start of RRT	Below target, <65 years: - Slower renal function decline - Later start RRT Below target, ≥65 years: - Earlier start RRT
<i>Proteinuria</i>	Urinary protein excretion <1 g/24h	Renal function decline, start of RRT	Below target: - Slower renal function decline - Later start RRT
<i>Hyperglycemia</i>	HbA1c <7%		
<i>Anemia</i>	Hemoglobin 6.8-7.4 mmol/l, avoid ≥8.0 mmol/l, serum ferritin 100-500 µg/l	Health-related quality of life	Above target, <65 years: - Better physical and mental health-related quality of life
<i>Mineral bone disorders</i>	Calcium 2.1-2.37 mmol/l, phosphate 0.7-1.3 mmol/l, PTH ~2-7 pmol/l		
<i>Metabolic acidosis</i>	Serum HCO ₃ 20-22 mmol/l		
<i>Hyperkalemia</i>	Potassium <5.5 mmol/l		
<i>Hyperlipidemia</i>	LDL <2.5 mmol/l, non-HDL <3.4 mmol/l, HDL >1 mmol/l, triglycerides 2.25-4.5 mmol/l	Renal function decline	Below target, LDL: - Slower renal function decline
<i>Lifestyle factors</i>	Stop smoking, balancing nutrition and physical activity		

RRT: renal replacement therapy; HbA1c: hemoglobin A1c; PTH: parathyroid hormone; HCO₃: bicarbonate; LDL: low density lipoprotein; HDL: high density lipoprotein.

Strengths and limitations of the PREPARE study

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

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

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

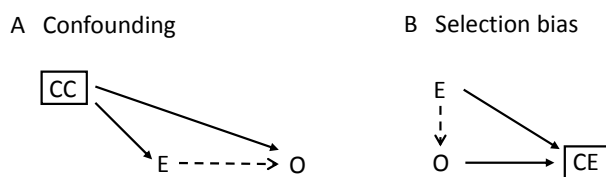
Besides the above mentioned strengths, the PREPARE-1 and PREPARE-2 study have three important methodological limitations, which are discussed in the following three paragraphs.

Confounding

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

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

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



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

Selection of patients

Patients with CKD often die of (cardiovascular) complications before reaching pre-dialysis care or ESRD.⁴¹ Therefore, patients who reach the start of pre-dialysis care are a selection of survivors. By conditioning on the start of pre-dialysis care, independent indications to start are then artificially associated with each other. In our study for example, low health-related quality of life and the presence of hypertension are independent indications to start pre-dialysis care. If a physician refers a patient with low blood pressure to an outpatient clinic for specialized pre-dialysis care, the chance that this patient has a low health-related quality of life – another indication for referral – will be greater. We indeed found this association in the PREPARE-2 study (data not shown in thesis), which could be explained by this form of selection bias⁴², sometimes called index-event bias. Conditioning on a common effect of exposure and outcome is often encountered in scientific literature (**chapter 11**) and the causal structure of this selection bias is represented in Figure 1B. We cannot account for this problem in our statistical analyses, but we have to keep this in mind when interpreting results. However, many of the chapters in this thesis did not investigate an association between two indications for referral. Only the results in **chapter 7** – investigating the

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

Missing data

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

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

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

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

Objective versus subjective outcome measures

In this thesis we aimed to find factors that influence the disease progression of patients on specialized pre-dialysis care. But how can we define disease progression in these patients? The most objective manner agreed upon to define progression is by assessing decline in renal function (eGFR) in each individual patient. Renal function is important for defining CKD stages 3-5¹⁰ and is used as a parameter in the decision when to start with dialysis¹⁶. So, the decline of this parameter reflects progression quite well. But how can we measure renal function? The gold standard for measuring renal function is based on injecting a substance in the blood stream which is freely filtered by the glomerulus and neither secreted nor reabsorbed by the distal tubules, for example inulin⁴⁶ or iothexol⁴⁷. After injection, renal function (in ml/min) is determined by measuring the substance concentration in blood and urine at certain time points. Unfortunately, this is an invasive, time-consuming, and expensive procedure. Therefore, several formulas have been developed to estimate renal function based on serum creatinine levels, such as the MDRD⁴⁸, CKD-EPI⁴⁹, and Cockcroft Gault formula⁵⁰. These formulas experience much inter-variability within and intra-variability between populations⁵¹⁻⁵³, for example between age categories and CKD stages. This variability may be explained by

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

Another outcome used in this thesis is the start of RRT. This outcome is more subjective than the outcome renal function decline. Besides renal function, other factors – such as comorbidities or other clinical parameters (e.g. hyperkalemia, fluid overload), physicians' or patients' preference, patients' physical or mental status – influence the decision when to start RRT.⁵⁶ The actual time until the start of RRT is therefore very subjective to variation. Imagine two patients with a similar renal function at the start of pre-dialysis care ($20 \text{ ml/min/1.73 m}^2$), a similar time until the start of RRT (1 year), but a different renal function when starting RRT (10 versus $5 \text{ ml/min/1.73 m}^2$). With regard to the outcome RRT, disease progression is similar, namely one year. However, in the patient with a renal function of $10 \text{ ml/min/1.73 m}^2$ at the start of RRT, renal function decline is slower (10 versus $15 \text{ ml/min/1.73 m}^2/\text{year}$). The decision to start at a higher renal function is probably based on other reasons, such as those mentioned before. However, time until the start of RRT is clinically very important because the goal of specialized pre-dialysis care is to postpone the start. According to known factors that accelerate RRT initiation⁵⁶, postponement of the start of RRT can be achieved either by the application of therapies that slow down the rate of renal function decline, by regulating clinical parameters/complications, or by improving patients' physical and mental status. For clinical purposes and guideline development, the outcome start of RRT is therefore just as objective as the outcome renal function decline. Research focusing on disease progression should therefore investigate both outcome measures if possible.

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

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

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

Elderly patients

Over the last decades the prevalence and incidence of elderly patients (≥ 65 years) with CKD or ESRD have increased and these numbers will continue to increase over the coming years.⁵ Due to this increasing elderly population, research in the field of healthy ageing becomes more important. Several studies in the field of geriatrics have shown that known risk factors for renal function decline – such as blood pressure, cholesterol, and body mass index – behave differently in the geriatric population.⁶⁰⁻⁶² In the general population it is known that these risk factors increase the risk for mortality and accelerate renal function decline. However, in the geriatric population a protective effect has been found. It could be hypothesized that decreasing body weight, cholesterol, and blood pressure levels are indicators for a declining cardiovascular and cognitive health (e.g. declining nutritional status or increasing prevalence of congestive heart failure). Such a different association may also be present in elderly CKD patients because the prevalence of malnutrition and congestive heart failure is high in this population. Nowadays, pre-dialysis treatment guidelines¹⁶ are based on studies performed throughout the entire range of age. Therefore, we advocate obtaining more evidence for this specific growing elderly population on pre-dialysis care.

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

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

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

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

Conclusions

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

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

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

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

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

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

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

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

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

Clinical implications and future research

Chapters 2-4 showed that high baseline blood pressure levels (especially in young (<65 years) patients), proteinuria, and high lipid levels can be useful in predicting the disease progression of patients starting pre-dialysis care. Furthermore, these results indicate that timely referral and well-controlled blood pressure, proteinuria, and lipid levels at the start of pre-dialysis care are important. So, multidisciplinary guidelines and treatment in the phase before pre-dialysis care is just as important. Unfortunately, patients with earlier stages of CKD are difficult to identify due to the absence of clinical symptoms¹¹ and the lack of appropriate cost-effective screening strategies^{4;12}. Randomized controlled trials performed in the specific population of patients on pre-dialysis care are needed to proof whether the lowering of blood pressure, proteinuria, or lipid levels is causally related to a slower disease progression.

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

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

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

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

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

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

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Nederlandse samenvatting |

Het aantal patiënten met chronische nierinsufficiëntie is de afgelopen jaren sterk toegenomen en verwacht wordt dat dit aantal zal blijven stijgen. Redenen voor deze toename zijn de vergrijzing en het vaker voorkomen van de belangrijke risicofactoren hypertensie en diabetes door met name veranderingen in onze leefstijl. Chronische nierinsufficiëntie wordt gedefinieerd als progressief verlies van de nierfunctie. Als de nieren hun functie hebben verloren zullen patiënten moeten starten met dialyse of een niertransplantatie moeten ondergaan. Om de start van deze nierfunctie vervangende therapieën zo lang mogelijk uit te stellen, maar ook om patiënten voor te bereiden op deze naderende start zijn pre-dialyse poliklinieken ingericht. Patiënten met een sterk verminderde nierfunctie en een progressief verlies worden verwezen naar deze poliklinieken. Door een multidisciplinair team van artsen, verpleegkundigen, diëtisten en maatschappelijk werkers wordt zorg verleend aan deze specifieke groep.

Meer dan 1000 patiënten die starten met gespecialiseerde pre-dialyse zorg zijn geïnccludeerd in de 'PRE-dialysis PATient REcord', PREPARE, studie en van deze patiënten is informatie verzameld tot aan de start van nierfunctie vervangende therapie. De PREPARE studie bestaat uit twee cohorten: PREPARE-1 (547 patiënten, inclusie 1999-2001, informatie terug gezocht in medische dossiers) en PREPARE-2 (502 patiënten, inclusie 2004-2011, patiënten gevolgd over de tijd). Tijdens het gehele pre-dialyse traject zijn van deze patiënten klinische en demografische gegevens, maar ook labwaarden en kwaliteit van leven scores verzameld. Deze gegevens zijn gebruikt voor bijna alle onderzoeken beschreven in dit proefschrift.

Uit dit onderzoek is gebleken dat pre-dialyse patiënten met bloeddruk, lipiden waarden in bloed en eiwit waarden in urine, die voldoen aan de huidige behandeldoelen een langzamere nierfunctie achteruitgang hebben dan patiënten waarbij deze waarden niet voldoen aan de behandeldoelen. Echter, in contrast met deze bevindingen starten oudere pre-dialyse patiënten (65 jaar of ouder) met een lage bloeddruk juist eerder met nierfunctie vervangende therapie. Misschien is deze lage bloeddruk een marker van een ziekteproces dat nierfunctie achteruitgang niet versnelt maar wel een indicatie is om te starten met nierfunctie vervangende therapie (bijvoorbeeld hartfalen). Bovenstaande resultaten impliceren dat het verlagen van bloeddruk, lipiden waarden in bloed en eiwit waarden in urine (bijvoorbeeld door middel van medicatie en/of specifieke dieetvoorschriften) voor en tijdens pre-dialyse zorg belangrijk is om de ziekteprogressie te vertragen. Verder onderzoek is nodig om uit te zoeken of het tegenstrijdige resultaat gevonden in ouderen causaal is. Met andere woorden, leidt een lage bloeddruk in ouderen tot een eerdere start van dialyse of wordt de eerdere start verklaard door een onderliggend ziekteproces?

Verder kwam uit dit onderzoek naar voren dat tijdens pre-dialyse zorg de kwaliteit van leven van deze patiënten afneemt, zowel fysiek als mentaal, en dat de aanwezigheid van ziektegerelateerde klachten toeneemt. De sterkste verandering vindt plaats tijdens de laatste zes maanden van pre-dialyse zorg en is geassocieerd met een eerdere start van dialyse. Beide determinanten kunnen dus mede gebruikt worden om het juiste moment voor de start van dialyse te definiëren. Ook is aangetoond dat hemoglobine waarden in bloed sterk

geassocieerd zijn met de kwaliteit van leven. Bij patiënten jonger dan 65 jaar met bloedarmoede die behandeld worden met medicatie werd een associatie gevonden tussen hoge hemoglobine waarden en een betere kwaliteit van leven. Bij oudere patiënten (65 jaar of ouder) werd deze associatie niet gevonden. In de klinische praktijk is het daarom belangrijk om leeftijd mee te nemen bij de keuze tussen het nastreven van een normale of hoge hemoglobine waarde. Voor deze keuze moet bij ieder individu de negatieve effecten – verhoogde kans op overlijden en ziekte – en positieve effecten – verbeterde kwaliteit van leven – van het verhogen van hemoglobine waarden worden afgewogen.

De verschillende analyses in dit proefschrift ondersteunen of kunnen bijdragen aan het aanscherpen/aanpassen van de huidige behandelrichtlijnen voor patiënten op pre-dialyse zorg. In de toekomst is het bijna onvermijdelijk om in analyses en richtlijnen geen onderscheid te maken tussen oude en jonge patiënten. Dit omdat verscheidene analyses hebben aangetoond dat een aantal risicofactoren niet hetzelfde effect hebben in deze groepen. Het streven zou dan ook moeten zijn om in de toekomst meer naar de geïndividualiseerde zorg toe te gaan omdat de pre-dialyse populatie erg heterogeen is. Verder zullen er meer gerandomiseerde onderzoeken uitgevoerd moeten worden om huidige behandelstrategieën te onderbouwen en waar nodig te veranderen. Daarnaast moet er ook meer focus komen te liggen op het exploreren van (on)bekende biologische processen om zo nieuwe behandelstrategieën te ontdekken. Hier is al een begin voor gemaakt in twee onderzoeken in dit proefschrift. Zo hebben we mogelijke aanwijzingen gevonden voor biologische mechanismen die kunnen verklaren waarom de nierfunctie achteruitgang sneller is in negroïde versus kaukasische patiënten en waarom de nierfunctie hoger is in langlevende versus niet langlevende families. Er kan geconcludeerd worden dat voor het verbeteren van de zorg voor pre-dialyse patiënten nog veel onderzoek moet worden verricht, waaraan dit proefschrift een bijdrage heeft geleverd.

Dankwoord |

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Publicatielijst |

Dit proefschrift

Commentary; Audit-based education: a potentially effective program for improving guideline achievement in chronic kidney disease patients. **de Goeij MC**, Rotmans JI. *Kidney Int.* 2013 Aug [accepted for publication]

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Curriculum Vitae |

Moniek Cornelia Maria de Goeij werd op 14 april 1987 geboren te Vlist. In 2005 behaalde zij haar VWO diploma, profiel natuur en gezondheid, aan het Sint Antonius College te Gouda. Hierna is zij aan de universitaire opleiding Biomedische Wetenschappen in het LUMC te Leiden begonnen. Tijdens haar Research Master heeft zij als eerste de epidemiologie track gevolgd en is in 2010 *cum laude* afgestudeerd.

Tijdens haar afstudeerstage op de afdeling Klinische Epidemiologie in het LUMC, onder begeleiding van prof. dr. Friedo Dekker, dr. Nynke Halbesma en dr. Diana Grootendorst, heeft zij onderzoek uitgevoerd naar het effect van bloeddruk op ziekteprogressie in pre-dialyse patiënten (PREPARE studie). In 2010 heeft dit onderzoek een prijs gewonnen voor 'beste abstracts gepresenteerd door jonge onderzoekers' op het congres van de 'European Registration Association/European Dialysis Transplantation Association'. Tijdens deze stage heeft zij een subsidievoorstel geschreven voor het PhD traject binnen het LUMC die ook daadwerkelijk gehonoreerd is. Deze subsidie heeft er voor gezorgd dat zij het onderzoek binnen de PREPARE studie kon uitbreiden in het kader van een tweejarig promotietraject, onder begeleiding van prof. dr. Friedo Dekker, dr. Nynke Halbesma en dr. Joris Rotmans, wat heeft geleid tot dit proefschrift.

Vanaf 1 april 2013 werkt ze als postdoctoraal onderzoeker bij de afdeling Sociale Geneeskunde in het AMC te Amsterdam.

