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 m^2/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 pattern[26] 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 ± 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

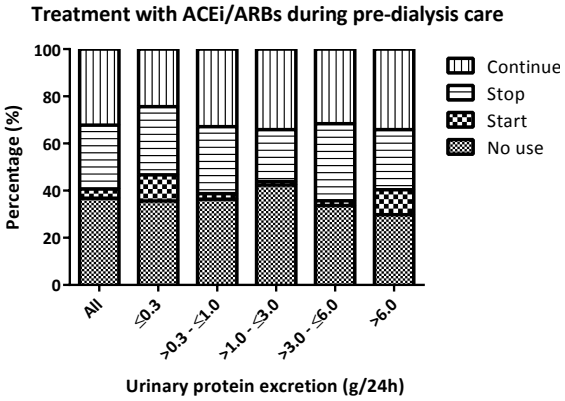
	Total	No proteinuria	Proteinuria			
		≤0.3[1]	>0.3 to ≤1.0	>1.0 to ≤3.0	>3.0 to ≤6.0	>6.0
	n=413	n=45	n=88	n=132	n=101	n=47
Age (years)	63 (50-73)	67 (56-75)	67 (52-75)	66 (48-73)	54 (44-70)	61 (52-70)
Sex (male, %)	58	38	53	62	61	64
Body mass index (kg/m^2)[2]	26 ± 5	26 ± 4	25 ± 5	26 ± 5	26 ± 5	28 ± 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 m^2/month. RFD accelerated with increasing UPE (adjusted additional decline 0.04 [95% confidence interval (CI) 0.01;0.08] ml/min/1.73 m^2/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 m^2/month) compared with patients without proteinuria (≤0.3 g/24h, mean ± SD decline 0.07 ± 0.84 ml/min/1.73 m^2/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)
Amount of urinary protein excretion (g/24h):					
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 m^2 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 m^2/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]
Amount of urinary protein excretion (g/24h):				
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]
ACEi/ARB						
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]
ACEi/ARB						
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 ≥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 ± SD age of 73.3 ± 1.8 years) with relatively high eGFR (16.38 ± SD 1 ml/min/1.73 m^2). 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 patients[15-20], 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 m^2 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 m^2, 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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