Ethnic differences in survival on dialysis in Europe

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9

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

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ABSTRACT

Background Blacks have faster rates of progression to end-stage renal disease (ESRD) compared with whites. It is unknown whether this difference also exists among patients in a universal healthcare system. This study examined whether black and white incident patients starting pre-dialysis care in a universal healthcare system differ in time until the start of renal replacement therapy (RRT) and in rate of renal function decline.

Methods We analyzed data of the PREdialysis PAtient REcord (PREPARE) study. PREPARE is a multicenter follow-up study of patients with chronic kidney disease starting pre-dialysis care in the Netherlands. We used Cox proportional hazards models to estimate the Hazard Ratio (HR) for starting RRT and linear mixed models to compare the rate of renal function decline for blacks versus whites. To explore possible mechanisms, adjustments were made for patient characteristics.

Results 946 patients were white and 49 patients were black. At initiation of pre-dialysis care, blacks were younger, had more diabetes mellitus, higher levels of proteinuria, and a higher estimated glomerular filtration rate (eGFR) compared with whites. The crude HR for starting RRT was 1.05 (95% confidence interval (CI) 0.73–1.52) for blacks compared with whites. This HR increased to 1.51 (95% CI 1.03–2.21) after adjustment for differences in demography, comorbidities/life-style, prescribed medication, proteinuria, and eGFR at baseline. Blacks had a 0.18 mL/min/1.73m^2/month (95% CI 0.05–0.32) faster renal function decline compared with whites, which did not materially change after adjustment for differences in patient characteristics.

Conclusion Blacks on pre-dialysis care in a universal healthcare system have a faster progression to ESRD compared with whites, suggesting that healthcare system factors have a less influential role in explaining black-white differences in the progression to ESRD.

INTRODUCTION

Black Americans have a 3-fold higher incidence of end-stage renal disease (ESRD) compared with white Americans.[1] The higher incidence of ESRD in blacks has been largely attributed to faster rates of progression from chronic kidney disease (CKD) to ESRD in blacks compared with whites.[2-4] Explanations for the faster progression to ESRD in blacks are likely to involve a complex interaction of biologic, societal, and healthcare system factors.[5;6] Biologic factors may relate to genetic differences between blacks and whites.[7-9] Societal factors may relate to a lower socioeconomic status among blacks and possible cultural conflicts for blacks leading 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 compared with whites.[5]

The majority of studies regarding black-white differences in progression to ESRD derive from the United States (US).[10] In the US, blacks have less access to healthcare and studies suggest that blacks receive lower quality of care compared with whites.[11;12] To investigate the role of these healthcare differences in the faster progression to ESRD in blacks compared with whites, several studies have tried to control for these healthcare differences by studying cohorts of patients who are insured in the American health care system, for example in Medicare[13;14] or the Veterans Affairs healthcare system.[2;15] However, these studies included only subsets of patients and have therefore limited generalizability.[10]

To get further insight in the role of healthcare system factors in the faster progression to ESRD in blacks, 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 the therapeutic options to slow down renal function decline. During this specialized pre-dialysis care, patients are monitored closely by nephrologists, dietitians, and social workers and are treated according to strict guidelines, leading to rather standardized pre-dialysis care.[17;18]

In the present study, we determined whether black and white incident patients starting specialized pre-dialysis care in the universal health care 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 PREdialysis PAtient REcord (PREPARE) study were used. PREPARE is a multicenter follow-up study in the Netherlands of incident patients starting specialized pre-dialysis care aged 18 years or above. In practice, patients are referred to a nephrology outpatient clinic for specialized pre-dialysis care if they have an estimated glomerular filtration rate (eGFR) below 20-30 mL/min/1.73m² (CKD stages 4-5) and an expected need for RRT within one year. The PREPARE study consists of a retrospective and a prospective cohort. In the retrospective cohort (PREPARE-I), incident patients who started pre-dialysis care in one of eight participating nephrology outpatient clinics between 1999 and 2001 were included. In the prospective cohort (PREPARE-II), incident patients who started pre-dialysis care in one of 25 participating nephrology 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 of further study participation (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 which was received less than one year prior to the start of pre-dialysis care were excluded. The study was approved by the Medical Ethics Committee or the Institutional Review Board of the participating centres. Patients included in PREPARE-II gave written informed consent prior to study inclusion.

Ethnicity

Information on ethnicity was reported by medical staff based on perceived ethnicity. This information was collected from medical records (PREPARE-I) or directly assessed during data collection (PREPARE-II). Ethnicity was classified into the categories white, black, and other. 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. All other patients were grouped as other. For the present analyses, patients with missing ethnicity data were considered as whites, since we assumed that non-white ethnicity would have been noted (the population in the Netherlands is predominantly white[19]). Data analysis was restricted to patients with either white or black ethnicity.

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. The following characteristics were used: age, sex, body mass index, blood pressure, smoking status, primary kidney disease (PKD), the presence of diabetes mellitus and cardiovascular disease, prescribed medication, eGFR, proteinuria, hemoglobin, albumin, calcium, phosphate, and parathyroid hormone. PKD 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, and/or coronary artery disease, and/or myocardial infarction. The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula, taking into account age, sex, black ethnicity, and serum creatinine.[21]

Follow-up data

Patients' clinical course was followed through medical records and Hospital Information Systems. For the present analyses, follow-up time was restricted to two years and defined as the time between the first visit at the pre-dialysis outpatient clinic and the start of RRT or censoring (i.e. death, lost-to-follow-up, refusal further study participation (PREPARE-II), recovery of renal function, reaching end of study period within two years of follow-up, or reaching end of two years follow-up). The rate of renal function decline was estimated using all available eGFR measurements (PREPARE-I) or eGFR measurements collected at every subsequent 6 months interval (PREPARE-II) during the first two years of follow-up.

Statistical analyses

Descriptive statistics are presented as mean ± standard deviation or in case of a skewed distribution as median (interquartile range (IQR)), stratified for white and black patients. The Kaplan-Meier method with the log-rank test was applied to compare time until the start of RRT between white and black patients. The univariable Cox proportional hazards analysis was used to estimate the hazard ratio (HR) and accompanying 95% confidence interval (CI) for starting RRT for black versus white patients. This HR was gradually adjusted for more variables using multivariable Cox proportional hazards analyses in order to explore underlying mechanisms.

A linear mixed model (LMM) was used to estimate the decline in renal function for black versus white patients. A LMM takes into account a correlation between individual repeated eGFR measurements and the deviation of the individual slopes from the mean slope.[22] To explore mechanisms, adjustments were made for the same variables as used in the multivariable Cox proportional hazards analyses.

To maintain power and to avoid bias in multivariable Cox proportional hazards analyses and LMM analyses, missing data for baseline variables we want to adjust for were imputed with standard multiple imputation techniques in SPSS (using 10 repetitions). Missing values were predicted under the assumption of missing 'at random' using the patient's available characteristics.[23] The imputation model included the characteristics described in Table 1, plus starting RRT (yes/no) and follow-up time, because missing baseline characteristics are often related to the outcome.[24] Skewed distributed continuous variables were square root transformed and the time until the start of RRT was log- transformed before entering into the multiple imputation model. Significance levels were determined at P value ≤0.05. Analyses were carried out with SPSS 20.0 for Windows statistical software.

Sensitivity analyses

To test the robustness of the results, several sensitivity analyses were performed. Analyses were repeated (1) excluding patients with missing data on ethnicity; (2) using unrestricted follow-up time instead of restriction to two years; (3) stratified for PREPARE-I and PREPARE-II; (4) with additional adjustment for education level as proxy for socioeconomic status (only available in PREPARE-II) and in a separate model with additional adjustment for pre-dialysis centre (available in PREPARE-I en -II); and (5) using a composite endpoint including start of RRT and death.

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

Characteristic	Whites (n = 946)		Blacks (n = 49)	
Demographic				
Age *years* ^^^	67	52-75	57	42-67
Sex *% men* ^	63		49	
Clinical				
Body mass index *kg/m²* *	26	5	27	6
Blood pressure *mmHg* †				
Systolic	147	26	150	24
Diastolic ^	80	13	84	13
Smoking *%* ‡	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 § ^^^	24		47	
Cardiovascular disease ‖	33		27	
Medication *%* ¶				
ACE-I/ARB	66		79	
ESA	37		33	
Laboratory measurements #				
eGFR *mL/min/1.73m²* ** ^^	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* ††	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 (SD) or median (interquartile range) or percentage.

^ = *P* value > 0.01, ≤ 0.05, ^^ = *P* value > 0.001, ≤ 0.01, ^^^ = *P* value ≤ 0.001.

Abbreviations: ACE-I/ARB = angiotensin-converting enzyme inhibitor and/or AII receptor blocker; ESA = erythropoiesis stimulating agents; eGFR = estimated glomerular filtration rate; PTH = parathyroid hormone.

* Available for 940 patients.

† Available for 973 patients.

‡ Defined as smoking or quit smoking <1 year before the start of pre-dialysis care.

§ Defined as primary kidney disease and/or as comorbidity.

‖ Defined as the presence of angina pectoris, coronary artery disease and/or myocardial infarction.

¶ Available for 933 patients.

eGFR, proteinuria, hemoglobin, albumin, calcium, phosphorus, and PTH available for 859, 642, 863, 822, 820, 839, and 496 patients, respectively.

** eGFR estimated with the 4-variable Modification of Diet in Renal Disease formula.

†† Corrected for albumin concentration.

RESULTS

Patient characteristics

In total, 1049 patients were included in the PREPARE study. From this cohort, 663 patients were white, 49 were black, 54 were grouped as other, and 283 had missing data on ethnicity. Patients grouped as other were excluded from the analyses and patients with missing ethnicity data were observed as being white. This resulted in the inclusion of 946 white and 49 black patients. Of these patients, respectively 51 and 41% were from the PREPARE-I study. Baseline characteristics of white and black patients are listed in Table 1. Compared with whites, black patients were 10 years younger and more likely to have diabetes mellitus or glomerulonephritis as PKD. Whites, however, were more likely to have renal vascular disease as PKD. Blacks had a higher eGFR at initiation of pre-dialysis care (mean eGFR 18.4 and 14.7 ml/min/1.73m² for blacks and whites, respectively) and higher levels of proteinuria (median proteinuria 2.5 and 1.5 g/24 hour for blacks and whites, respectively).

Follow-up and outcomes

With follow-up censored at 2 years, Table 2 shows the median follow-up time and frequencies of outcomes. The follow-up time was approximately the same for blacks and whites (median follow-up time 13.1 months for whites and 13.9 months for blacks). Five hundred-fifty eight whites (59%) and 30 blacks (61%) started RRT within the first 2 years of follow-up. Only 4% of whites and 2% of blacks underwent a renal transplantation as initial RRT. No difference was found in the percentage of deaths prior to the start of RRT (7% among whites and 8% among blacks). Figure 1 demonstrates the Kaplan-Meier curves showing the percentages of black and white patients on pre-dialysis care over time. During the first 15 months of pre-dialysis care, blacks experienced a slightly lower probability of starting RRT compared with whites, while from 15 months onwards blacks had a higher probability of starting RRT. The crude Cox regression analysis resulted in a HR for starting RRT of 1.05 (95% CI 0.73 – 1.52) for blacks compared with whites, which remained approximately the same after adjustment for demographic characteristics, comorbidities/life-style, and prescribed medication. After additional adjustment for eGFR and proteinuria at baseline, the HR increased to 1.51 (95% CI 1.03 – 2.21). After further adjustment for other laboratory measurements, the HR slightly attenuated to 1.39 (95% CI 0.94 – 2.07) (Table 3).

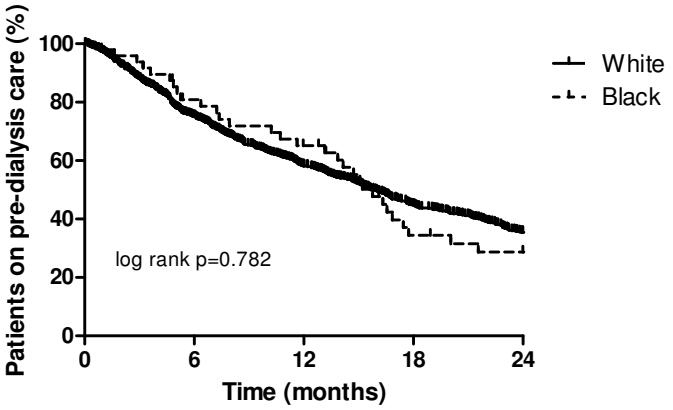
Table 2. Median follow-up time and outcomes of incident black and white patients on pre-dialysis care during the first two years of pre-dialysis care.

	Whites (n = 946)		**Blacks (n = 49)**	
Median follow-up time *months* (IQR)				
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 *	10.9	(5.3-16.7)	12.0	(4.0-14.7)
Outcomes *number* (%)				
Start RRT	558	(59)	30	(61)
Dialysis	517	(55)	29	(59)
Renal transplantation	41	(4)	1	(2)
Death	67	(7)	4	(8)
Other †	321	(34)	15	(31)

Abbreviations: IQR = interquartile range; RRT = renal replacement therapy (dialysis or renal transplantation).

* Patients who refused further study participation, were lost-to-follow-up, had a recovery of renal function, died while on pre-dialysis care, or reached the end of the study period within two years of follow-up. Excluding patients still on pre-dialysis care after two years of follow-up.

† Refused further study participation, lost-to-follow-up, recovery of renal function, reached end of study period within two years of follow-up, or reached end of two years follow-up.



Events/at risk	0-6	6-12	12-18	18-24
White	231 / 946	148 / 672	109 / 493	70 / 353
Black	9 / 49	7 / 36	12 / 28	2 / 13

Figure 1. Kaplan-Meier curves showing the percentages of black and white incident patients on pre-dialysis care over time.

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

Model		Blacks vs. Whites		Variables included in the model
		HR	CI (95%)	
1.	Unadjusted	1.05	0.73-1.52	Ethnicity
2.	Demographic	0.98	0.68-1.42	Model 1 *plus* age, sex
3.	Comorbidities/ life-style	0.95	0.65-1.38	Model 2 *plus* PKD, systolic BP, BMI, DM, CVD, smoking status
4.	Medication	0.97	0.67-1.41	Model 3 *plus* ACE-I/ARB, ESA
5.	Renal function/ damage	1.51	1.03-2.21	Model 4 *plus* eGFR at start of pre-dialysis care, proteinuria
6.	Laboratory	1.39	0.94-2.07	Model 5 *plus* Hb, calcium *, phosphorus, PTH, albumin

Abbreviations: HR = hazard ratio; CI = confidence interval; PKD = primary kidney disease; BP = blood pressure; BMI = body mass index; DM = diabetes mellitus; CVD = chronic vascular disease; ACE-I/ARB = angiotensin-converting enzyme inhibitor and/or Angiotensin II receptor blocker; ESA = erythropoiesis stimulating agents; eGFR = estimated glomerular filtration rate determined with 4-variable formula from the 'Modification of Diet in Renal Disease study'; Hb = hemoglobin; PTH = parathyroid hormone.

* Corrected for albumin concentration.

Decline in renal function

Ninety percent of whites and 94% of blacks had at least one available eGFR measurement in the first two years of follow-up and thus contributed to the analyses of eGFR decline. Of these patients, respectively 94% and 89% had two or more available eGFR measurements (median number of eGFR measurements (IQR) in whites 4 (3-12) and in blacks 4 (3-11)). Figure 2 shows the decline in renal function for white and black patients during the first two years of pre-dialysis care. In whites, the mean rate of renal function decline was 0.23 mL/min/1.73m^2/month (95% CI 0.20 – 0.26) and in blacks 0.41 mL/min/1.73m^2/month (95% CI 0.28 – 0.54). Table 4 shows that the faster decline in renal function of 0.18 mL/min/1.73m^2/month (95% CI 0.05 – 0.32) for blacks compared with whites did not materially change after adjustment for differences in patient characteristics between blacks and whites. Results of the LMM were essentially similar when analyses were repeated including imputed baseline eGFR values.

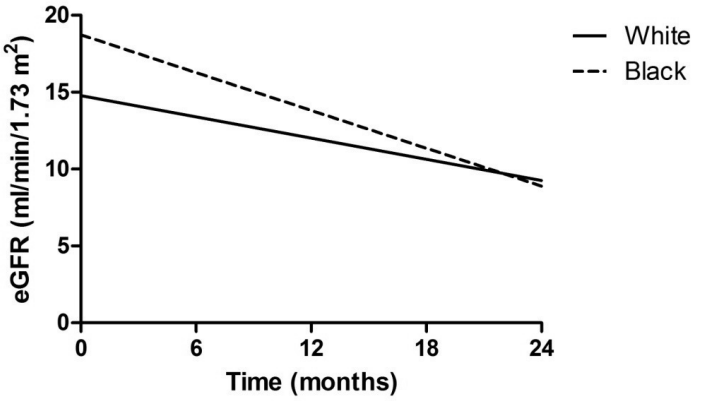


Figure 2. Decline in renal function over time for incident black versus white patients on pre-dialysis care, with follow-up censored at 2 years. Decline in renal function is estimated with linear mixed models resulting in mean betas.

Table 4. Additional decline in renal function (mL/min/1.73m^2/month) for black versus white patients on pre-dialysis care, adjusted using gradually more complex multivariable models and with follow-up maximized at 2 years.

Model		Blacks vs. Whites *		Variables included in the model
		Beta	CI (95%)	
1.	Unadjusted	0.18	0.05-0.32	Ethnicity
2.	Demographic	0.18	0.05-0.31	Model 1 *plus* age, sex
3.	Comorbidities/ life-style	0.18	0.05-0.31	Model 2 *plus* PKD, systolic BP, BMI, DM, CVD, smoking status
4.	Medication	0.18	0.05-0.31	Model 3 *plus* ACE-I/ARB, ESA
5.	Renal function/ damage	0.16	0.02-0.30	Model 4 *plus* eGFR at start of pre-dialysis care, proteinuria
6.	Laboratory	0.16	0.02-0.31	Model 5 *plus* Hb, calcium †, phosphorus, PTH, albumin

Abbreviations: CI = confidence interval; PKD = primary kidney disease; BP = blood pressure; BMI = body mass index; DM = diabetes mellitus; CVD = chronic vascular disease; ACE-I/ARB = angiotensin-converting enzyme inhibitor and/or Angiotensin II receptor blocker; ESA = erythropoiesis stimulating agents; eGFR = estimated glomerular filtration rate determined with 4-variable formula from the 'Modification of Diet in Renal Disease study'; Hb = hemoglobin; PTH = parathyroid hormone.

* Patients included with one or more eGFR measurements (850 whites and 46 blacks).

† Corrected for albumin concentration.

Sensitivity analyses

Several sensitivity analyses were performed. First, the analyses were repeated excluding patients with missing data on ethnicity. Results were essentially similar to the main analyses. Second, the analyses were repeated using unrestricted follow-up time. The crude HR for start of RRT for blacks versus whites was slightly lower (HR 0.92 (95% CI 0.64-1.32)) compared with the main analyses, but after adjustment for the variables in model 5 blacks had a 1.45-fold (95% CI 0.98-2.09) higher rate of starting RRT compared with whites. Results related to decline in renal function did not materially change. Third, the analyses were stratified for PREPARE-I and PREPARE-II. Overall, patients in PREPARE-I had a lower 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 in PREPARE-I was 4.6 months shorter than in PREPARE-II. The fully adjusted HR for starting RRT for blacks versus whites was different (PREPARE-I: HR 1.07 (95% CI 0.61 – 1.89); PREPARE-II: HR 2.01 (95% CI 1.10 – 3.69)). In both studies, renal function decline was faster in blacks than in whites. In PREPARE-I, the rate of renal function decline in whites was 55% of that of blacks and in PREPARE-II 50% (PREPARE-I: 0.51 and 0.28 ml/min/1.73m^2/month in blacks and whites, respectively; PREPARE-II: 0.34 and 0.17 ml/min/1.73m^2/month in blacks and whites, respectively). Fourth, we additionally adjusted for education level as proxy for socioeconomic status (in patients with available data on education level, *i.e.* in 86% of PREPARE-II patients (n=425)), which did not change our point estimates. In a separate model, additional adjustment for pre-dialysis centre (available for all patients) increased the HR to 1.62 (95% CI 1.07-2.46) compared with model 6 (HR 1.39 (95% CI 0.94-2.07)) from the main analyses. Finally, analyses were repeated using a composite endpoint including start of RRT and death. These analyses revealed similar HRs compared with the main analyses.

DISCUSSION

This study, among 995 incident patients starting specialized pre-dialysis care in the Dutch universal healthcare system, compared time until the start of RRT and rate of renal function decline between black and white patients. The crude analyses showed no difference in time until the start of RRT between blacks and whites, but black patients initiated pre-dialysis care with a higher eGFR than whites. After adjustment for differences in demography, comorbidities/life-style, prescribed medication, proteinuria, and eGFR at baseline, blacks had a 1.51-fold higher rate of starting RRT compared with whites. Further adjustment for laboratory measurements slightly decreased this HR to 1.39. The decline in renal function was 0.18 mL/min/1.73m^2 per month faster in black than in white patients. After adjustment for differences in patient characteristics, blacks remained to have a faster decline in renal function.

Our study presents several new findings. First, to our knowledge, a faster progression to ESRD in blacks compared with whites has not been previously described in a universal healthcare system. A small study from the United Kingdom explored rates of progression of renal disease in African-Caribbean (n=11) and white (n=24) patients with diabetic nephropathy, but demonstrated no difference between both groups.[25] 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 US by the MDRD study group, found that among patients with GFRs ranging from 13 to 24 mL/min/1.73m² blacks had a 2.87 mL/min/1.73m² per year faster renal function decline compared with non-blacks. In the final prediction model, black race was one of the six independent predictors of renal function decline.[26] Another US study found a faster decline of only 0.3 mL/min/1.73m² per 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/1.73m²) and thus results were not comparable with our study.[27] Another US study demonstrated that black patients with eGFRs <15 and with eGFRs between 15 and 29 mL/min/1.73m² had respectively 1.4 and 1.8-fold higher risks of progression to ESRD 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.[28] Third, to our knowledge, it has not been previously demonstrated that blacks are referred to pre-dialysis care with higher eGFR compared with whites. A US study showed

that blacks were referred to a nephrology clinic with lower eGFR than whites (mean eGFR in blacks and whites 34.9 and 38.2 mL/min/1.73m², respectively), but referral to a nephrology clinic does not implicate that specialized pre-dialysis care is initiated.[27]

Strengths of our study include the presence of a well defined population receiving standardized care in a universal health care system, the longitudinal design, and the multiple eGFR measurements during follow-up. There are also some possible limitations, which need to be considered in the interpretation of the results.

First, we considered patients with missing ethnicity data as whites since we assumed that non-white ethnicity would have been noted (the population in the Netherlands is predominantly white[19]). This assumption may have resulted in misclassification of ethnicity. Nevertheless, in our opinion this has not influenced the results substantially, as comparable results were found when we repeated our analyses after excluding patients with missing ethnicity data.

Second, the retrospective and the prospective cohort of the PREPARE study were pooled, while in the prospective cohort only patients were included 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 as 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 eGFR at baseline in PREPARE-I compared with PREPARE-II (in PREPARE-I there was a shorter period to develop a difference in time until the start of RRT between whites and blacks).

Third, data on area deprivation were lacking (e.g. a deprivation score - based on unemployment rate, average income, population density, and ethnic variation). Differences in area deprivation could have biased our results if deprivation is both associated with ethnicity 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 differences in health care and CKD progression between area's and thereby minimizing bias. Furthermore, adjustment for pre-dialysis centre, some in a

more deprived area than others, even slightly increased our effect estimate as seen in our sensitivity analysis.

Fourth, we do not have data on the magnitude and the characteristics of the patient group that was 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 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 is of great interest. It suggests that previously reported differences in the progression to ESRD between blacks and whites could not be explained by healthcare related factors.[2-4] The finding that after adjustment for known risk factors for renal function decline blacks remain to have a faster decline in renal function, suggests that conventional clinical factors do not substantially explain the difference in renal function decline. Thus, other factors are involved. Genetic differences between blacks and whites may relate to differences in progression of renal disease.[7-9] Furthermore, increased skin pigmentation for blacks could explain their faster renal function decline. Increased skin pigmentation results in reduced cutaneous synthesis of 25-hydroxyvitamin D, which is related to factors associated with decline in renal function (e.g. fibrosis and inflammation).[29-31] Moreover, a greater incidence of low birth weight in blacks versus whites may explain in part the more rapid renal function decline, since lower birth weight is associated with impaired renal development and lower numbers of nephrons.[32]

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.[33] If healthcare workers are aware of the faster progression of renal function among blacks, they may refer black patients earlier to pre-dialysis care. Furthermore, healthcare professionals may take comorbidities and underlying kidney disease into account when referring to pre-dialysis care. We found a higher prevalence of diabetes mellitus among blacks and diabetes mellitus is associated with earlier referral to nephrologists.[34;35] 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.[36-38] 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 mL/min/1.73m² in blacks versus 14.7 mL/min/1.73m² in whites).

CONCLUSION

Blacks on pre-dialysis care in a universal healthcare system have a faster progression to ESRD compared with whites, suggesting that healthcare system factors have a less influential role in explaining black-white differences in the progression to ESRD. Our results may implicate 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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