Differences in Progression to ESRD between Black and White Patients Receiving Predialysis Care in a Universal Health Care System

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Summary

Background and objectives Studies performed in the United States showed that blacks progress from CKD to ESRD faster than do whites. Possible explanations are differences in health care system factors. This study investigated whether progression is also faster in a universal health care system, where all patients receive comparable care.

Design, setting, participants, & measurements Data from the PREdialysis PATient REcord study, a multicenter follow-up study of patients with CKD who started predialysis care in The Netherlands (1999–2011), 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 predialysis care, blacks (n=49) were younger and had more diabetes mellitus, higher proteinuria levels, and a higher estimated GFR than whites (n=946). Median follow-up time in months was similar (blacks: 13.9 [boundaries of interquartile range (IQR), 5.3 to 19.5]; whites: 13.1 [IQR, 5.1 to 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 to 1.34) and from 15 months onward, 1.93 (95% CI, 1.02 to 3.68), which increased after adjustment. RFD was faster by 0.18 (95% CI, 0.05 to 0.32) ml/min per 1.73 m² per month in blacks compared with whites.

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

Black Americans have a three-fold higher incidence of ESRD compared with white Americans (1). This has been largely attributed to faster rates of progression from CKD to ESRD in blacks (2–4). Explanations are likely to involve a complex interaction of biologic, societal, and health care 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). Health care system factors may relate to differences in access to health care 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 health care, and studies suggest that blacks receive lower quality of care (11,12). To investigate the role of health care 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 health care 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 health care system factors, studies are needed in a setting where all patients have equal access to health care and receive similar highly standardized care, irrespective of age or socioeconomic status. The predialysis care setting in The Netherlands is such a setting (16). Patients with CKD stages 4–5 are referred to specialized predialysis 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 predialysis care...
in the universal health care system of The Netherlands have differences in time to start of RRT and rate of renal function decline (RFD).

Materials and Methods
Study Design
Data from the PREdialysis PAtient REcord (PREPARE) study were used. PREPARE is a multicenter follow-up study of incident patients starting specialized predialysis care (age ≥18 years) in The Netherlands. In practice, patients are referred to a predialysis outpatient clinic if they have an estimated GFR (eGFR) < 20–30 ml/min per 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 predialysis visit between 1999 and 2001 were included from eight outpatient clinics. In the prospective cohort (PREPARE-II), incident patients who started predialysis care in 1 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, loss to follow-up, refusal to further participate in the study (PREPARE-II), recovery of renal function, or reaching end of the study period within 2 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 RFD was estimated by using all available eGFR measurements during the first 2 years of follow-up.

Follow-up Data
Follow-up time was restricted to 2 years because after 2 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, loss to follow-up, refusal to further participate in the study [PREPARE-II], recovery of renal function, or reaching end of the study period within 2 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 RFD was estimated by using all available eGFR measurements during the first 2 years of follow-up.

Statistical Analyses
Descriptive statistics are presented as mean ± SD or, in case of a skewed distribution, as median with boundaries of the interquartile range, stratified for 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 end point (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 RFD 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 SPSS software (using 10 repetitions) (SPSS, Inc., Chicago, IL). 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 SPSS software 20.0 for Windows.

Subgroup and Sensitivity Analyses
Two subgroup analyses were performed regarding RFD, in which the results were stratified by the presence of diabetes mellitus and by proteinuria levels (above and below 1.5 g/24 hours, median value). These analyses were selected according to 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 predialysis center as proxy for deprivation area (available in PREPARE-I and PREPARE-II), and (5) with use of the CKD-Epidemiology Collaboration (CKD-EPI) equation (30) 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 10 years younger and more likely to have diabetes mellitus or GN as primary kidney disease. Furthermore, blacks had a higher eGFR at initiation of predialysis care and higher levels of proteinuria (Table 1).

**Follow-up and Outcomes**

With follow-up time censored at 2 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 predialysis 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 to 1.34) and from 15 months onward, 1.93 (95% CI, 1.02 to 3.68), which remained approximately the same after adjustment for demographic characteristics, comorbid conditions and lifestyle, and prescribed medication. After additional adjustment for eGFR and proteinuria at baseline, these HRs increased to 1.16 (95% CI, 0.73 to 1.85) and 3.61 (95% CI, 1.87 to 7.00), respectively. After further adjustment for other laboratory measurements, these HRs attenuated to 1.09 (95% CI, 0.67 to 1.75) and 3.12 (95% CI, 1.56 to 6.23), respectively (Table 3).

**RFD**

Among whites, 6%, 19%, and 75% had one, two, and three or more available eGFR measurements in the first 2 years of follow-up, respectively. Among blacks, these percentages were 11%, 11%, and 78%. The median numbers of eGFR measurements (boundaries of interquartile range) were 4 (3–12) in whites and 4 (3–11) in blacks. In whites, RFD was 0.23 ml/min per 1.73 m² per month (95% CI, 0.20 to 0.26); in blacks, it was 0.41 ml/min per 1.73 m² per month (95% CI, 0.28 to 0.58). Table 4 shows that the faster RFD of 0.18 ml/min per 1.73 m² per month (95% CI, 0.05 to 0.32) 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 to 0.38] ml/min per 1.73 m² per month, adjustment model 6).

**Subgroup Analyses**

Black patients with diabetes mellitus experienced a 0.43 (95% CI, 0.09 to 0.76) ml/min per 1.73 m² per month (adjustment model 6) faster RFD than white patients with diabetes mellitus (0.61 versus 0.18 ml/min per 1.73 m² per month). Furthermore, black patients with high proteinuria levels (>1.5 g/24 hours) experienced a 0.27 (95% CI, −0.04 to 0.58) ml/min per 1.73 m² per month (adjustment model 6) faster RFD than white patients with high proteinuria levels (0.60 versus 0.33 ml/min per 1.73 m² per month). In black versus white patients without diabetes mellitus and in black versus white patients with low proteinuria levels, RFD did not differ. The interaction term P values were 0.002 for diabetes mellitus with race and 0.27 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 to 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 RFD 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

**Table 2. Median follow-up time and outcomes of incident black and white patients receiving predialysis care during the first 2 years of predialysis care.**

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

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 receiving predialysis care, or reached end of study period within 2 years of follow-up. Excluding patients still receiving predialysis care after 2 years of follow-up.

**Figure 1.** Time until the start of renal replacement therapy (RRT) separate for black and white patients. The cumulative incidence curves for starting RRT, with death as competing end point, show the percentages of black and white incident patients starting RRT over time, with follow-up censored at 2 years.
15 months onward was higher in PREPARE-II (PREPARE-I: 1.82 [95% CI, 0.62 to 5.32]; PREPARE-II: 7.93 [95% CI, 2.97 to 21.22]). In both studies, RFD was faster in blacks than in whites. In PREPARE-I, RFD in whites was 55% of that of blacks (0.28 and 0.51 ml/min per 1.73 m² per month, respectively) and in PREPARE-II, 50% (0.17 and 0.34 ml/min per 1.73 m² per 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 predialysis center (available for all patients) also did not change our point estimates. Finally, results remained similar when the CKD-EPI formula was used.

**Table 3. Hazard ratios for start of renal replacement therapy in incident black versus white patients receiving predialysis care, adjusted using gradually more complex multivariable models**

<table>
<thead>
<tr>
<th>Model</th>
<th>HR (95% CI)</th>
<th>Variables Included in the Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blacks (n=49) versus Whites (n=946) (0–15 mo)*</td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.86 (0.55 to 1.34)</td>
<td>Race</td>
</tr>
<tr>
<td>Demographic</td>
<td>0.80 (0.51 to 1.25)</td>
<td>Model 1 plus age, sex</td>
</tr>
<tr>
<td>Comorbid conditions/lifestyle</td>
<td>0.76 (0.48 to 1.20)</td>
<td>Model 2 plus primary kidney disease, systolic BP, BMI, DM, CVD, smoking status</td>
</tr>
<tr>
<td>Medication</td>
<td>0.79 (0.50 to 1.25)</td>
<td>Model 3 plus ACE inhibitors/ARB, ESA</td>
</tr>
<tr>
<td>Renal function/damage</td>
<td>1.16 (0.73 to 1.85)</td>
<td>Model 4 plus eGFR at start of predialysis care, proteinuria</td>
</tr>
<tr>
<td>Laboratory measurements</td>
<td>1.09 (0.67 to 1.75)</td>
<td>Model 5 plus hemoglobin, calcium, phosphorus, PTH, albumin</td>
</tr>
<tr>
<td>Blacks (n=22) versus Whites (n=422) (15–24 mo)*</td>
<td>1.93 (1.02 to 3.68)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4. Additional renal function decline for incident black versus white patients receiving predialysis care, adjusted using gradually more complex multivariable models and with follow-up censored at 2 years**

<table>
<thead>
<tr>
<th>Model</th>
<th>Blacks versus Whites: Additional Decline (95% CI) (ml/min per 1.73 m² per month)</th>
<th>Variables Included in the Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>0.18 (0.05 to 0.32)</td>
<td>Race</td>
</tr>
<tr>
<td>Demographic</td>
<td>0.18 (0.05 to 0.31)</td>
<td>Model 1 plus age, sex</td>
</tr>
<tr>
<td>Comorbid conditions/lifestyle</td>
<td>0.18 (0.05 to 0.31)</td>
<td>Model 2 plus primary kidney disease, systolic BP, BMI, DM, CVD, smoking status</td>
</tr>
<tr>
<td>Medication</td>
<td>0.18 (0.04 to 0.32)</td>
<td>Model 3 plus ACE inhibitors/ARB, ESA</td>
</tr>
<tr>
<td>Renal function/damage</td>
<td>0.16 (0.02 to 0.31)</td>
<td>Model 4 plus eGFR at start of predialysis care, proteinuria</td>
</tr>
<tr>
<td>Laboratory measurements</td>
<td>0.16 (0.02 to 0.31)</td>
<td>Model 5 plus hemoglobin, calcium, phosphorus, PTH, albumin</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval; BMI, body mass index; DM, diabetes mellitus; CVD, cardiovascular disease; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ESA, erythropoiesis-stimulating agents; eGFR, estimated GFR calculated with the four-variable Modification of Diet in Renal Disease formula; PTH, parathyroid hormone.

* 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).

*Corrected for albumin concentration.

**Discussion**

This study found no difference in time to the start of RRT within the first 15 months of predialysis care between black
and white incident patients starting predialysis care in a universal health care system. However, black patients initiated predialysis 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, comorbid conditions and lifestyle, prescribed medication, proteinuria, eGFR, and laboratory measurements at baseline increased this HR to 3.12. RFD was 0.18 ml/min per 1.73 m² per 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 health care 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 nephropathy (32), differences in progression to ESRD between blacks and whites have not been previously investigated in a European universal health care system.

Second, to our knowledge, a faster progression to ESRD in blacks compared with whites has not been described before in patients starting predialysis care. A study from the United States found that among patients with GFRs ranging from 13 to 24 ml/min per 1.73 m² blacks had a 2.87 ml/min per 1.73 m² per year faster RFD compared with nonblacks, but these were not incident patients starting predialysis care (33). Another study in the United States found a faster decline of only 0.3 ml/min per 1.73 m² 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 per 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 per 1.73 m² and between 15 and 29 ml/min per 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 predialysis care (35).

Third, to our knowledge, no previous studies have shown that blacks are referred to predialysis 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 health care 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 RFD 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 predialysis 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 health care system in The Netherlands is the equal access to health care and highly standardized care for each individual, minimizing area differences in CKD progression and thereby minimizing bias. Furthermore, adjustment for predialysis 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 predialysis care. However, the purpose of this study was not to investigate progression to ESRD in patients who could have been referred to predialysis care but rather in patients who actually received specialized predialysis care.

Our finding that black-white differences in progression to ESRD exist among patients receiving predialysis care in a universal health care system suggests that previously reported differences could less likely be completely explained by health care–related factors (2–4). Our finding that the faster RFD 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 RFD. In addition, it is reported that other factors, such as genetic differences (7–9), decreased production of vitamin D in blacks (37–39), and a greater incidence of low birthweight in blacks (40), may also explain the different disease progression.

Several explanations for the higher level of renal function at the start of predialysis care for blacks compared with whites could be postulated. Guidelines suggest that patients need to be referred to predialysis care at least 1 year before the start of RRT (41). If health care workers are aware of the faster RFD among blacks, they may refer such patients earlier to predialysis care. Furthermore, health care 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 health care 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 per 1.73 m², respectively).

In conclusion, although the number of black patients was relatively small, this study demonstrated that black patients receiving predialysis care in a universal health care system had a faster progression to ESRD than whites, suggesting that health care 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 predialysis 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 predialysis care than white patients. Further investigation is needed to understand the mechanisms underlying the faster progression to ESRD in blacks.

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Disclosure

The authors have had no involvements that might raise the question of bias in the work reported or in the conclusions, implications, or opinions stated. None of the sponsors were involved in study design, collection of data, statistical analyses, interpretation of data, writing of the manuscript, or decision to submit the paper for publication. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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