

Reverse Race and Ethnic Disparities in Survival Increase with Severity of Chronic Kidney Disease: What Does This Mean?

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End-stage renal disease (ESRD) is more prevalent among black Americans (1). Early studies suggested that this was due to a higher incidence of renal disease progression, but evidence was lacking about rates of disease initiation or prevalence of early stages of chronic disease (2–3). More recently a higher prevalence of milder stages of kidney disease in blacks *versus* whites has been ruled out, suggesting that initiation of disease is not more common among blacks (4–6). Even more strongly, this evidence suggests that accelerated rates of renal disease progression at later stages are responsible for the higher incidence of ESRD among blacks. In this issue of *CJASN*, Newsome *et al.* provide intriguing evidence from the Cooperative Cardiovascular Project that there is a survival advantage for black chronic kidney disease patients and, most importantly, that it begins well before patients develop ESRD (7). From this large-scale quality improvement project begun in 1992 (8), Newsome *et al.* designed a retrospective cohort study of nearly 60,000 persons age ≥ 65 yr who were admitted for a first episode of acute myocardial infarction and followed passively for death over 3 yr using government records. The authors found that the magnitude of the survival advantage for blacks increases as GFR, estimated from the Modification of Diet in Renal Disease equation, decreases.

The study has many strengths characteristic of outstanding effectiveness and outcomes research, including its national scope with relatively unselected patients, good validity of race designation and Medicare death ascertainment, and adjustment for prognostic factors that might influence differences in survival between blacks and whites. Newsome *et al.* infer that the longer survival, and therefore longer duration in advanced stages of chronic kidney disease, for blacks *versus* whites may explain prior observations of blacks' lower prevalence of kidney dysfunction at mild or moderate levels, but a greater inci-

dence at the most severe level (stage 5) of chronic kidney disease (7).

Among ethnic groups in the US population, blacks score worst on many indices of health status (9). However, blacks experience better survival when they develop ESRD, a fact we have known for decades (10). Despite blacks in the US less often receiving intensive medical and surgical treatment (11–12), the survival advantage in ESRD is not due to blacks with more severe illness receiving less renal replacement therapy (13). The study by Newsome *et al.* of patients with a history of acute myocardial infarction, along with an earlier study of heart failure patients (14), is consistent with this because it documents that the survival advantage starts at earlier stages of chronic kidney disease, rather than after renal replacement therapy with dialysis. This study has a number of limitations, including the lack of calibration of serum creatinine for GFR estimation, its limitation to patients with a comorbid heart disease and older adults, and the lack of measurement of socioeconomic status. However, it is a very important contribution to the literature on disparities in renal disease because it sheds light on the determinants of higher ESRD rates among blacks.

But the intriguing scientific question still exists as to why blacks in the general population live shorter lives than whites, but when they are unfortunate enough to develop chronic kidney disease they live longer. This reversal in the direction of a race and ethnic disparity could arise from blacks having a different genetic makeup (*e.g.*, variations leading to adaptations of the renin-angiotensin system, sympathetic nervous systems, or other regulatory systems) that imparts this superiority in survival, much as patients with sickle cell trait, who have one gene for hemoglobin S and one gene for hemoglobin A, have a greater chance of surviving malaria while not suffering the adverse consequences of homozygous sickle cell disease. The consequence of such genetic variation, which impairs processes involved in pathogenesis (*e.g.*, malaria growth and development with sickle hemoglobin), is a hypothesis that should be investigated in chronic kidney disease. Susceptibility to subsequent cardiac ischemia or inflammation might be altered in blacks compared with whites in the presence of renal injury, thereby conferring a survival advantage. For example, it has

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been shown that ischemic reperfusion injury in the kidney is under genetic regulation (15). A better understanding of what drives these reverse disparities could open up possible pathways for therapeutic intervention.

So if blacks with chronic kidney disease live long enough to develop ESRD but fewer whites do, how does this information inform science and ultimately treatment of patients? Does this mean that the risk factors for kidney disease progression are really common across ethnic groups and, given long enough survival, whites would develop as much ESRD as blacks? That is, this longer chronic kidney disease duration would explain all of the racial difference in incidence of ESRD rather than a contribution of racial differences in the prevalence or potency of risk factors (including possible genetic makeup) to kidney disease progression. It is likely that a complex biology and social milieu produces observed racial disparities in progression of chronic kidney disease as well as the competing risks for death and chronic kidney progression described by Newsome *et al.* Much progress has been made in identifying many of the modifiable and currently nonmodifiable risk factors for renal disease initiation and progression in different racial and ethnic groups (diabetes, hypertension, and their lack of detection and early treatment; dietary protein consumption; family history and possible genetic predisposition; smoking, nephrotoxin exposure; poverty and access to health care) and we now have therapeutics (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) that slow progression. However, we lack universally effective means for completely arresting progression of chronic kidney disease in all race and ethnic groups. This is due in part to an incomplete understanding of the renal biology and pathophysiology that explain known risk factors. Lack of robust funding for translational efforts to identify more powerful and effective therapies or prevention also contributes. We should be making strong investments to accelerate the progress in renal science and prevention of the progression of chronic kidney disease. Continuing research investments in promising basic and clinical renal science have great potential for improving health and well-being as well as averting the expense of more intensive treatments for ESRD.

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Please see the related article, “Survival Advantage of Black Patients with Kidney Disease after Acute Myocardial Infarction,” on pages 993–999.