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Racial Differences in Mortality and End-Stage Renal Disease

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African Americans in the general population suffer from increased adjusted rates of cardiovascular and noncardiovascular mortality in comparison to whites.^{1,2} By contrast, a paradox exists for individuals with chronic kidney disease (CKD) undergoing long-term dialysis, with African Americans having better survival rates than whites in most studies.^{3–5} The existence of racial/ethnic variations in health outcomes provides unique opportunities for understanding biological, environmental, sociocultural, and healthcare system factors that can lead to new strategies to improving not only CKD care, but the health of the nation.⁶ Several explanations have been posited to contribute to improved outcomes for African Americans on dialysis, such as survival bias,⁷ a “reverse epidemiology” of cardiovascular risk factors (where modest increases in body mass index, elevated lipids, and blood pressure are protective rather than deleterious),⁸ and increased access to health care due to Medicare coverage.^{9,10}

In this issue of the *American Journal of Kidney Diseases*, an analysis of the Cooperative Cardiovascular Project by Newsome and colleagues takes us another step closer to understanding this paradox with a detailed look at progression to end-stage renal disease (ESRD) and pre-ESRD mortality in the same cohort.¹¹ They evaluated data on over 125,000 Medicare beneficiaries aged 65 years or older and admitted to a hospital with acute myocardial infarction and assessed rates of ESRD or mortality over a 10-year period. African Americans made up only 6.5% of the study population, but were 14.9% of the 2,161 patients progressing to ESRD (adjusted hazard ratio, 1.90 [95% confidence interval, 1.78 to 2.03]). Adjusted pre-ESRD mortality rates were similar for African Americans and whites, with African Americans more likely than their white counterparts to die if the baseline glomerular filtration rate (GFR) was greater than 60 mL/min and more likely to survive if the baseline GFR was below 60 mL/min. Newsome and colleagues showed a similar finding with respect to mortality in a previous analysis where African American patients with worse kidney function, when compared with their white counterparts, experienced better survival, although the reasons remain poorly defined.¹² These prior findings support the current report by Newsome et al that racial differences in ESRD rates were not accounted for by lower mortality rates among African Americans, especially those with lower GFR, suggesting other factors are involved.

One limitation to generalizing the results of this study is that it selectively examined a group of Medicare patients with coronary artery disease who were hospitalized for acute myocardial infarction. However, the high rates of cardiovascular disease in CKD patients, the aging of the

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ESRD population, and the national movement toward coordinated care delivery systems for the chronically ill and capitated or single-payor financing systems for such individuals lend added relevance to this study. Suboptimal use of cardiovascular procedures has generally been reported for minorities, but for CKD patients who are minorities, the initiation of dialysis with its transition to Medicare coverage seems to have leveled the playing field with regard to access to cardiovascular care.¹³ The findings of a single-payor, coordinated-care system leading to more uniform CKD care was reinforced by a recent report by Gao and colleagues of over 13,000 beneficiaries receiving care through the Department of Defense (DOD). They found similar rates of provider compliance for evidence-based treatment recommendations for African Americans and whites for stages 3 and 4 CKD targets.¹⁴ The findings of equity in care for CKD patients treated within such standardized/coordinated care delivery and single-payor financing systems, the latter such as through the DOD or Medicare, coupled with similar non-ESRD mortality rates across racial groups as reported in this issue by Newsome et al, lend further support to the premise that the persistently high ESRD rates in older African Americans with Medicare coverage are due to other factors beyond racial differences in pre-ESRD survival or access to care.

The findings of Newsome et al are also consistent with those of Xue and coworkers, who investigated racial differences in developing ESRD or death due to diabetes and hypertension over a 10-year period in over 1.3 million Medicare beneficiaries older than 66 years at the study start.¹⁵ After adjustment for age and sex, African Americans were 2.4 to 2.9 times more likely than whites to develop ESRD, while the mortality rate for African Americans in the overall cohort was 10% higher than their white counterparts, leaving an even smaller pool of African Americans to reach ESRD.

Using pooled analyses of persons with CKD from 4 community-based studies, Weiner and colleagues reported a greater risk of the composite end point of death, nonfatal myocardial infarction, and stroke among African Americans than among whites, due in part to a greater severity of hypertension and/or diabetes in the former.¹⁶ Similar findings of an excess burden of clinical risk factors for CKD progression among African Americans were noted in a birth cohort analysis by Hsu et al using data from over 13,000 adults in the Third National Health and Nutrition Examination Survey (NHANES III) and in the US Renal Data System spanning years 3 to 8 after the midpoint of NHANES III.¹⁷ They found the prevalence of CKD (defined as a GFR of 15 to 59 mL/min) did not differ between African American and white adults, while ESRD incidence was 4.8-fold higher for African Americans. The high rate of ESRD in African Americans with CKD was accompanied by higher systolic (147 versus 136 mm Hg; $P = 0.001$) and diastolic (82 versus 77 mm Hg; $P = 0.02$) blood pressure and greater albuminuria (422 versus 158 $\mu\text{g}/\text{mg}$ urine albumin-creatinine ratio; $P = 0.01$). Additional factors that might explain the excess rates of ESRD include higher rates of diabetes, and sociocultural, environmental, and biologic factors as summarized in Table 1.

With regards to pre-ESRD mortality, Mehrotra et al recently reported a higher all-cause and cardiovascular mortality for African Americans with early stage CKD from a nationally representative sample, a risk modified by age. This disparity remained after accounting for differences in prevalence of cardiovascular risk factors but was attenuated to a nonsignificant level when adjusted for socioeconomic status.¹⁸ The modifying effect of age on the racial differences in outcomes revealed greater health disparities in the younger age groups and may explain in part the lack of racial differences in mortality rates in the older cohort followed by Newsome et al. In addition, the analysis by Mehrotra et al did not explore ESRD progression. While survivor bias (such that only the healthiest African Americans survive into old age) or the benefit of Medicare as a single payor providing improved access to care for participating individuals equally may explain improved survival for African Americans with_[DB3] ESRD, they do not explain the high rates of ESRD.

In conclusion, to echo the reflections of Dr. Neil Powe: “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?”⁷ As we move forward, what are the key issues around CKD risk factors that may guide our understanding? Outlined in Table 1 are a number of areas for exploration. Select biologically based factors may have both racial and nonracial contributions, such as hypovitaminosis D, which is associated with increased rates of CKD initiation factors (ie, hypertension, diabetes)¹⁹ and progression factors (ie, inflammation, fibrosis),²⁰ while vitamin D repletion may improve CKD-related mortality.²¹ Environmental influences modify gene and/or receptor expression (gene-environmental) as supported by genetic linkage studies describing susceptibility genes for CKD.²² Increased rates of overexpression of transforming growth factor β (TGF- β 1) and/or a higher prevalence of specific TGF- β 1 polymorphisms in African Americans may contribute to CKD progression and complications.²³ Sickle cell trait, which can be found in approximately 8% of African Americans and has traditionally been described as causing renal micro-infarction and hyposthenuria,²⁴ but not CKD, may in fact be an important unrecognized factor contributing to intrarenal inflammation/fibrosis and refractory response to antihypertensive and antidiabetic therapy, as well as other CKD-related vascular complications.⁶ Newer approaches to assess disease risk for established conditions, such as the use of 24-hour blood pressure monitoring^[ND4] in patients with hypertensive CKD who are not responding to therapy²⁵ and the use of allostatic load as a more comprehensive indicator of vascular stress,^{26,27} may help to advance CKD care and reduce the burden of ESRD. A rejuvenation of research investments is needed not only for promising basic and clinical renal science, but also in health service delivery and health systems policy. Finally, integrating scientific discovery with increasing public awareness and education regarding CKD represent important strategies for early identification of at risk populations and early intervention for key determinants of health behaviors that directly affect clinical outcomes.^{28,29} In addition, further expansion of creative chronic care coordination approaches, such as reported from the DOD, or currently part of demonstration projects funded by Centers for Medicare and Medicaid Services (CMS), has considerable potential to permit focused attention to the needs of CKD patients, and to do so equally for all ethnic/racial groups. This combined approach will be necessary to help bridge socioeconomic disparities, fully activating our potential to address the CKD epidemic and improve the health of our nation.

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Table 1
Key factors contributing to increased end-stage renal disease rates in African Americans.

Healthcare Systems Level Factors

- Multiple payers and non-uniform provider incentives lead to marked variations in quality of care.
- Paucity of evidence-based data for clinical response to pharmacologic interventions among women and minorities who are under-represented in most trials.

Biologic Factors (Hereditary and/or Environmentally Influenced)

- Increased rates of hypertension and diabetes.
- Accelerated vascular damage (typically characterized by excess rates of albuminuria) due to increased rates of stress, nutritional deficiencies, toxin exposures, and other.
- Racial/ethnic variations in select enzyme activity, gene expressions, receptor densities and/or polymorphisms, for an array of signaling and metabolic pathways that may affect ESRD progression (eg, increased TGF- β , dysregulation of intrarenal renin-angiotensin system).

Societal and Patient Level Factors

- Institutional racism leading to poverty and high rates of unemployment, under- or un-insurance, and mistrust in large institutions, including health systems; contributes to delays in seeking health care.
- Residential segregation: suboptimal educational systems leading to lower rates of literacy, increased poverty, lower community-level healthcare resources, increased exposure to environmental toxins (eg, small particulate matter, lead), and reduced access to healthy foods and safe environments needed to meet lifestyle recommendations.
- Increased stress and/or depression, low self esteem, reduced personal responsibility related to above, often manifests as maladaptive coping behaviors (eg, overeating, drinking, smoking, substance abuse), increased nocturnal blood pressure, sympathetic activity, and oxidative stress.
- Cultural conflicts and linguistic barriers which may be perceived by providers or healthcare systems as patient insolence or ignorance; limits trust and effective communication, reduces adherence, and may influence health recommendations or availability of services.

Note: Adapted with permission from⁶