Editorial

***APOL1* and Mortality in Patients on Dialysis**

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KeywordsAfrican Americans · *APOL1* · Cardiovascular disease · Chronic kidney disease · Survival

Ancestry-based disparities in medical outcomes are widely appreciated. In this issue of *Cardiorenal Medicine*, Lertdumrongluk et al. [1] assess mortality based on ancestry and reported the cause of end-stage kidney disease (ESKD) in patients treated at a large dialysis organization. As expected, African Americans had a significantly lower mortality rate than European Americans; the largest differences in mortality in favor of African Americans were in patients felt likeliest to have apolipoprotein L1 gene (*APOL1*)-associated kidney diseases. These included patients with idiopathic focal segmental glomerulosclerosis, histologically not-examined glomerular diseases presumably attributed to hypertension and/or arterio-nephrosclerosis (e.g., solidified glomerulosclerosis), lupus nephritis, and nephropathy due to illicit drug use. A strength of this work was the large sample size; a weakness that *APOL1* genotyping was not performed. The authors estimated *APOL1* genotype frequencies based upon reported causes of ESKD and these may be inaccurate [2]. Results confirmed those from a prior report where African Americans with *APOL1* high-risk genotypes (G1G1, G2G2 and G1G2) had lower mortality than African Americans with low-risk genotypes and European Americans, a work that included *APOL1* genotyping in a smaller cohort [3].

In the general population, African Americans experience higher mortality rates from cardiovascular disease (CVD), and at younger ages, than European Americans. Unfortunately, this results in a 3.4 years' shorter average life expectancy. In contrast, African Americans with dialysis-dependent ESKD have 45% lower mortality than European Americans, regardless of dialysis modality (in-center hemodialysis, home hemodialysis or peritoneal dialysis) and after adjustment for comorbid illnesses, biochemical factors and health-related quality of life. This "paradoxical" survival advantage in African Americans with ESKD is reproducibly observed despite disparities in income and residential segregation [4]. Lower mortality in African Americans with ESKD, relative to European Americans, could coincide with improved access to healthcare; the Centers for Medicare and Medicaid Services support dialysis costs for many patients in the US. Outcomes in patients with ESKD appear consistent with those at

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Veterans Administration (VAMC) and Kaiser Permanente Medical Centers; these healthcare systems provide equivalent healthcare to all patients. African Americans with diabetes mellitus have significantly lower mortality and 50% lower rates of myocardial infarction than European Americans at the VAMC; reduced rates of myocardial infarction are also observed in African Americans at Kaiser Permanente (reviewed in Freedman et al. [5]).

In addition to differential access to healthcare prior to ESKD, unique metabolic, cardiac and vascular changes occur in patients on hemodialysis. This pathophysiology contributes to survival on dialysis. Demographic- and morbidity-adjusted mortality rates in dialysis patients are 10- to 30-fold higher than in the general population. Arrhythmias, sudden death, heart failure, myocardial infarction, stroke and atherosclerotic heart disease (CVD) represent 55% of all deaths in patients on dialysis; sudden death represents 40% of total mortality. Biologic factors in patients with ESKD that increase risk for CVD and death include higher burdens of myocardial fibrosis, vascular calcification, rapidly shifting electrolyte concentrations, hypervolemia, oxidative stress, and inflammation.

Ancestry-based genetic variation contributes to differences in the concentrations and/or action of ion channels, endogenous inhibitors of calcification, myocardial fibrosis, and vitamin D metabolism. These may plausibly contribute to differences in mortality in dialysis. African Americans have a lower incidence of atrial fibrillation than European Americans and gene-based differences in ion channels have been suggested as underlying ancestry-based differences in risk for arrhythmia in the general population and sudden death in patients on dialysis [6]. It is noteworthy that African Americans have a significantly lower prevalence and burden of calcium deposition in the coronary arteries and other major blood vessels compared to European Americans. This difference in subclinical CVD is present in the general population and in those with risk factors for CVD, including diabetes mellitus (reviewed in Freedman et al. [5]).

Biologic mechanisms for the reduced mortality rate in African Americans on dialysis could relate to the presence of (or enrichment for) gene variants that increase risk for kidney disease and also associate with lower risk for CVD. The two coding renal-risk variants in *APOL1* directly contribute to increased risk for renal-limited kidney disease in people who have recent African ancestry; relationships between *APOL1* and CVD have been assessed [7]. Whether *APOL1* plays a direct role in the risk for CVD remains unclear. Conflicting results have been reported by several cohorts and a large meta-analysis is currently underway. A concern is that the excess frequency of hypertension in individuals with *APOL1* renal-risk genotypes could relate to secondary hypertension from the inherited kidney disease; this could confound *APOL1* associations with CVD.

Additional limitations should also be acknowledged. Enhanced survival on dialysis in African Americans could be a byproduct of unequal rates of kidney transplantation. As European Americans are more likely to receive a kidney transplant, this leaves healthier African Americans on dialysis to be compared with European Americans likely to have more severe comorbid conditions. The survival advantage in African Americans with ESKD is greatest in older patients and those with high levels of systemic inflammation; survival differences were reduced using a competing risk regression model that accounted for differential rates of transplantation [4].

We conclude that the findings reported by Lertdumrongluk et al. [1] have a scientific basis. Recent African ancestry, defined as inheritance of gene variants currently present in populations residing in Africa, associate with the risk for *APOL1*-associated nephropathy and protection from myocardial infarction and subclinical CVD. In the admixed African American population, greater degrees of African ancestry, reflecting less European ancestry, are associated with lower levels of coronary artery calcified atherosclerotic plaque. *APOL1*-associated kidney diseases, which occur in Africans, African Americans, Hispanic blacks, South Amer-

icans and Afro-Caribbeans, are typically renal-limited disorders and affected patients often have minimal systemic vascular involvement. This lowers the mortality seen with ESKD. Fewer kidney transplants in African Americans also lead to a healthier population on dialysis. Investigating the ancestry-based genetic differences that modulate risk for CVD in African Americans remains critical to perform. Finally, reduced access to healthcare, a remediable environmental risk factor, can overwhelm the protective effects of genetic ancestry and contribute to the shorter survival in the general African American population. Efforts to equalize healthcare access for all patients are urgently required, regardless of socioeconomic status or ancestry.

Disclosure Statement

Wake Forest University Health Sciences and Barry Freedman have rights to an issued US patent related to *APOL1* genetic testing (www.apol1genetest.com). Dr. Freedman is a consultant for AstraZeneca Pharmaceuticals and Renalytix AI.

Funding Sources

B.I.F. received NIH grants R01 DK070941 and DK084149.

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