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Narrative Review

# *APOL1* Gene Kidney Risk Variants and Cardiovascular Disease: Getting to the Heart of the Matter

*Nicholas O. McLean, MD, Todd W. Robinson, MD, and Barry I. Freedman, MD*

Apolipoprotein L1 gene (*APOL1*) renal risk variants exhibit strong genetic associations with a spectrum of nondiabetic kidney diseases in individuals with recent African ancestry. Relationships between *APOL1* kidney risk variants and cardiovascular disease (CVD) susceptibility and CVD-related death remain controversial. Some studies detected an increased risk for CVD, whereas others support protection from death and subclinical CVD and cerebrovascular disease. Because treatments for nondiabetic kidney disease may target this gene and its protein products, it remains critical to clarify the potential extrarenal effects of *APOL1* kidney risk variants. This review addresses the current literature on *APOL1* associations with CVD, cerebrovascular disease, and death. Potential causes of disparate results between studies are discussed.
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***INDEX WORDS:*** African Americans; apolipoprotein L1 (*APOL1*); cardiovascular disease (CVD); kidney risk variants; genetic risk; atherosclerosis; nonmodifiable risk factor; racial disparities; chronic kidney disease (CKD); death; mortality; cerebrovascular disease; coronary artery calcification (CAC); review.

The apolipoprotein L1 gene (*APOL1*) association with a spectrum of nondiabetic kidney diseases is among the strongest genetic causes of complex disease.[1-3] Identification of *APOL1* has dramatically altered our understanding of susceptibility to glomerulosclerosis in populations with recent African ancestry.[4] In contrast, associations of *APOL1* kidney risk variants with cardiovascular disease (CVD) and death have been inconsistent; several studies suggest enhanced risk, whereas a growing body of evidence supports protection.[5-8] *APOL1* is expressed in the renal and systemic vasculature,[9,10] and its kidney risk variants are associated with increased plasma small high-density lipoprotein cholesterol particle concentrations.[11] These findings support the potential for vascular involvement. Because therapies for *APOL1*-associated kidney disease will likely target the gene and its protein products, it is critical to fully understand extrarenal effects, including those involving blood vessels (Fig 1). It remains important to halt the development and progression of *APOL1*-associated chronic kidney disease (CKD) without increasing the potential risk for atherosclerotic complications.

## STUDIES FINDING AN ASSOCIATION OF *APOL1* AND INCREASED RISK FOR CVD AND MORTALITY

To assess effects of *APOL1* on CVD, Ito et al[12] examined 2 study cohorts containing African American participants. First, they looked at 1,959 participants in the Jackson Heart Study (JHS), which followed up a general African American population for 5 years. Of participants aged 35 to 84 years, 284, 892, and 783, respectively, had 2, 1, and 0 *APOL1* kidney risk variants. Baseline clinical CVD risk factors were similar among the 3 genotypic groups. JHS participants with 2 *APOL1* kidney risk variants had a significant increase in the composite outcome of myocardial infarction (MI), stroke, and therapeutic surgical or endovascular interventions relative to those with 0 kidney risk variants (odds ratio [OR], 2.17; $P = 9.4 \times 10^{-4}$). The increased risk for CVD remained significant in a Cox proportional hazard model that adjusted for age, sex, body mass index, diabetes, hypertension, smoking, lipid levels, and CKD ($P = 0.029$). The expected *APOL1* associations with CKD, dialysis, and earlier age at onset of kidney disease were present in this population-based report.

In addition, an undisclosed number of JHS participants underwent computed tomography (CT) to measure coronary artery calcified atherosclerotic plaque (coronary artery calcification [CAC]). Surprisingly, despite its association with the composite of MI and stroke, those with 2 *APOL1* kidney risk variants (vs 0 kidney risk variants) had lower CAC; however, CT methods, CAC scores, and analysis results were not provided. Effects on CAC reportedly remained significant when participants with CKD were excluded. Although lower CAC is protective from CVD events and mortality in all populations,[13,14] it has not been associated with an increased risk for CVD as in the JHS. Finally,

*From the Section on Nephrology, Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC.*
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*Address correspondence to Barry I. Freedman, MD, Section on Nephrology, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157-1053. E-mail: bfreedma@wakehealth.edu*

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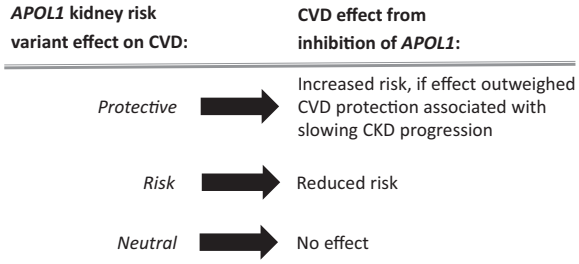


**Figure 1.** Postulated effects of *APOL1* inhibition on cardiovascular disease (CVD). Abbreviation: CKD, chronic kidney disease.

analyses assessing JHS participants with 1 *APOL1* kidney risk variant in additive (0 vs 1 vs 2 kidney risk variants) or recessive (0/1 vs 2 kidney risk variants) models were not provided.

Ito et al[12] also evaluated 749 African American women aged 50 to 79 years from the Women's Health Initiative (WHI), a multicenter randomized controlled trial of postmenopausal hormone replacement therapy. Women with advanced CKD were excluded. WHI participants with 2 (n = 103) and 0 (n = 302) *APOL1* kidney risk variants were compared for rates of incident CVD and baseline estimated glomerular filtration rates (eGFRs) after a mean follow-up of 2.5 years. Those with 2 *APOL1* kidney risk variants had significantly lower eGFRs at baseline; they also had higher risk for incident CVD (OR, 1.98) during follow-up.

Mukamal et al[15] examined 798 older African Americans in the Cardiovascular Health Study (CHS), a prospective cohort including 5,888 African American and European American participants 65 years or older from 4 US centers; more than 10-year follow-up was available. African American participants with 2 *APOL1* kidney risk variants (n = 91) had significantly higher baseline albuminuria than the 707 participants with 0 or 1 kidney risk variant ($P<0.001$), without statistically significant differences in baseline eGFRs or CVD. Changes in eGFRs over time did not differ significantly between *APOL1* genotype groups; this may have been a result of the advanced age of this cohort. African Americans developing *APOL1*-related CKD typically do so at earlier ages; the CHS may contain a sample at lower risk for accelerated declines in eGFRs, perhaps due to the absence of requisite second hits necessary to initiate progressive kidney disease.[16] Compared to the group with 0 or 1 *APOL1* kidney risk variant, the CHS group with 2 kidney risk variants had significantly higher all-cause mortality (hazard ratio [HR], 1.3; $P = 0.05$), noncardiovascular mortality (HR, 1.4; $P = 0.05$), and MI (HR, 1.8; $P = 0.02$). In contrast, there were no statistically significant differences in cardiovascular mortality (HR, 1.3; $P = 0.31$), stroke (HR, 1.2; $P = 0.80$), or congestive heart failure (HR, 1.0; $P = 0.98$). End points were generally similar between African Americans with fewer than 2 *APOL1* kidney risk variants and European American CHS participants. Table 1 summarizes the major findings from the JHS, WHI, and CHS. None of these studies adjusted for the overall proportion of African ancestry in their cohorts.

## STUDIES NOT FINDING AN ASSOCIATION OF *APOL1* AND INCREASED RISK FOR CVD AND MORTALITY

Prior to direct analysis of potential *APOL1* effects on CVD, the African American Study of Kidney Disease and Hypertension (AASK) detected a far higher frequency of kidney end points relative to deaths after 10-year follow-up of treated hypertension in nondiabetic African Americans with CKD attributed to high blood pressure.[17,18] The composite AASK primary end point included death, doubling of serum creatinine concentration, or initiation of dialysis therapy. The AASK investigators reported higher frequencies of doubling of serum creatinine levels and dialysis therapy relative to death. Subsequently, *APOL1* kidney risk variants were strongly associated with AASK kidney outcomes, increasing serum creatinine concentrations, and albuminuria, whereas the blood pressure treatment arm (standard vs intensive control) and class of antihypertensive medications were not.[19,20] Kidney function declined relatively steadily among AASK participants with 2 *APOL1* kidney risk variants, supporting the presence of an intrinsic kidney disease process, such as primary forms of glomerulosclerosis.[21] A recent AASK analysis failed to detect a significant effect of *APOL1* kidney risk variants on survival.[22] Results suggested that participants in the intensive blood pressure control arm with 2 *APOL1* kidney risk variants might have improved long-term survival; this effect was not seen in those in the less intensive blood pressure control arm.[22]

Results from 4 studies detecting protective or neutral effects of *APOL1* kidney risk variants on CVD and mortality are summarized in Table 2. The African American−Diabetes Heart Study (AA-DHS) evaluated 717 participants: 91 with 2, 350 with 1, and 276 with 0 *APOL1* kidney risk variants.[23] The AA-DHS included only type 2 diabetes−affected individuals, and *APOL1* kidney risk variants do not associate with classic diabetic kidney disease. Hence, unlike the JHS, WHI, and CHS, in which *APOL1* kidney risk variants were associated with kidney disease and/or albuminuria at baseline, confounding of *APOL1* kidney disease risk on CVD and mortality outcomes were absent.[12,15] *APOL1* kidney risk variants showed a significant negative association with CT-derived