APOL1 Risk Variants and Cardiovascular Disease

Results From the AASK (African American Study of Kidney Disease and Hypertension)

Teresa K. Chen, Lawrence J. Appel, Morgan E. Grams, Adrienne Tin, Michael J. Choi, Michael S. Lipkowitz, Cheryl A. Winkler, Michelle M. Estrella

Objective—Among African Americans, the apolipoprotein L1 (*APOL1*) risk variants have been associated with various types of kidney disease and chronic kidney disease progression. We aimed to determine whether these same risk variants also confer an increased risk for cardiovascular disease.

Approach and Results—In a cohort of African Americans with hypertension-attributed chronic kidney disease followed for up to 12 years, we used Cox proportional hazards models to estimate the relative hazard of a composite cardiovascular disease outcome (cardiovascular death or hospitalization for myocardial infarction, cardiac revascularization procedure, heart failure, or stroke) for the *APOL1* high- (2 risk variants) versus low-risk (0–1 risk variant) genotypes. We adjusted for age, sex, ancestry, smoking, heart disease history, body mass index, cholesterol, randomized treatment groups, and baseline and longitudinal estimated glomerular filtration rate, systolic blood pressure, and proteinuria. Among 693 participants with *APOL1* genotyping available (23% high risk), the high-risk group had lower mean estimated glomerular filtration rate (44.7 versus 50.1 mL/min per 1.73 m^2) and greater proteinuria (median 0.19 versus 0.06) compared with the low-risk group at baseline. There was no significant association between *APOL1* genotypes and the composite cardiovascular disease outcome in both unadjusted (hazard ratio=1.23; 95% confidence interval: 0.83–1.81) and fully adjusted (hazard ratio=1.16; 95% confidence interval: 0.77–1.76) models; however, in using an additive model, *APOL1* high-risk variants were associated with increased cardiovascular mortality.

Conclusions—Among African Americans with hypertension-attributed chronic kidney disease, *APOL1* risk variants were not associated with an overall risk for cardiovascular disease although some signals for cardiovascular mortality were noted.

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Key Words: cardiovascular disease ■ coronary artery disease ■ heart failure ■ hypertension ■ myocardial infarction

Cardiovascular disease (CVD) is the leading cause of death in patients with chronic kidney disease (CKD), with the risk for CVD mortality increasing incrementally as kidney function declines.[1–3] Compared with European Americans, African Americans are at heightened risk for all-cause mortality and CVD associated with CKD.[4] Although racial disparities in traditional risk factors and quality of care exist, genetic susceptibilities may also contribute.[2,4,5]

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Among African Americans, risk variants in the gene encoding apolipoprotein L1 (*APOL1*) have been associated with many types of kidney disease.[6–10] Parsa et al[10] reported in the AASK (African American Study of Kidney Disease and Hypertension) that individuals with 2 copies of the *APOL1* high-risk variants had a ≈2-fold greater risk of CKD progression compared with individuals with 0 or 1 copy. Whether these risk variants also confer an increased risk for CVD is uncertain because results from the few available studies have been conflicting.[11–15] In the JHS (Jackson Heart Study), the WHI (Women's Health Initiative), and the CHS (Cardiovascular Heart Study), the *APOL1* high-risk variants have been associated with an increased risk of adverse cardiovascular events.[11,16] Other studies, however, have suggested no association between the risk variants and CVD.[11,12,15] Importantly, the majority of participants in these cohorts did

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From the Divisions of Nephrology (T.K.C., M.E.G., M.J.C.) and General Internal Medicine (L.J.A.), Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD; Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins Medical Institutions, Baltimore, MD (L.J.A., M.E.G., A.T.); Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (A.T.); Division of Nephrology and Hypertension, Department of Medicine, Georgetown University School of Medicine, Washington, DC (M.S.L.); Basic Research Laboratory, Center for Cancer Research, National Cancer Institute, National Institutes of Health and Leidos Biomedical, Frederick National Laboratory, MD (C.A.W.); and Kidney Health Research Collaborative, Department of Medicine, San Francisco VA Medical Center and University of California (M.M.E.).

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Correspondence to Teresa K. Chen, MD, MHS, Division of Nephrology, Department of Medicine, Johns Hopkins University School of Medicine, 301 Mason F. Lord Dr, Suite 2500, Baltimore, MD 21224-2780. E-mail tchen39@jhmi.edu

Nonstandard Abbreviations and Acronyms

AA-DHS	African American Diabetes Heart Study
AASK	African American Study of Kidney Disease and Hypertension
APOL1	apolipoprotein L1
CHS	Cardiovascular Heart Study
CI	confidence interval
CKD	chronic kidney disease
CVD	cardiovascular disease
ESRD	end-stage renal disease
HR	hazard ratio
JHS	Jackson Heart Study
SPRINT	Systolic Blood Pressure Intervention Trial
WHI	Women's Health Initiative

not have established CKD. Thus, how *APOL1* relates to CVD in the context of reduced kidney function remains unknown.

With up to 12 years of follow-up from the well-characterized population of AASK, we aimed to determine whether the *APOL1* high-risk variants were associated with an increased risk for CVD outcomes in African Americans with hypertension-attributed CKD.

Materials and Methods

Materials and Methods are available in the online-only Data Supplement.

Results

Baseline Characteristics

Among the 693 AASK participants with *APOL1* genotyping available, 33 (21%) individuals with the *APOL1* high-risk genotypes (2 risk variants) and 111 (21%) individuals with the low-risk genotypes (0–1 risk variant) experienced the composite CVD outcome, which consisted of cardiovascular death or hospitalization for nonfatal myocardial infarction, cardiac revascularization procedure, heart failure, or stroke before the onset of end-stage renal disease (ESRD). At baseline, individuals with the *APOL1* high-risk genotypes were younger (mean age: 51.7 versus 54.8 years) and had lower estimated glomerular filtration rates (mean: 44.7 versus 50.1 mL/min per 1.73 m^2) and greater proteinuria (median urine protein-to-creatinine ratio: 0.19 versus 0.06 g/g Cr) compared with those with the low-risk genotypes. History of heart disease was less common in the *APOL1* high-risk group compared with the low-risk group (43% versus 53%, respectively; Table 1).

Association Between *APOL1* Risk Variants and Incident CVD

During a mean follow-up of 7.7 years, the risk of a CVD event was not significantly different in the *APOL1* high-risk group compared with the low-risk group (unadjusted hazard ratio [HR]=1.23; 95% confidence interval [CI]: 0.83–1.81; *P*=0.31; Table 2; Figure). After adjusting for sociodemographic and clinical factors, the association between *APOL1* risk status and CVD event remained null (model 4 adjusted HR=1.16; 95% CI: 0.77–1.76; *P*=0.47; Table 2). Similar results were obtained when analyses were repeated using an additive or dominant genetic model (data not shown).

Table 1. Baseline Characteristics of Study Population by *APOL1* Risk Allele Status

Characteristic	*APOL1* Low Risk (n=533)	*APOL1* High Risk (n=160)	*P* Value
Age at randomization, y	54.8±10.1	51.7±11.8	<0.01
Female	210 (39%)	69 (43%)	0.40
European ancestry, %	17±14	16±12	0.19
Smoking			0.73
Never	224 (42%)	72 (45%)	
Current	150 (28%)	45 (28%)	
Past	159 (30%)	43 (27%)	
History of heart disease	281 (53%)	69 (43%)	0.03
Body mass index, kg/m^2	30.9±6.5	31.7±7.2	0.23
Systolic blood pressure, mm Hg	144±23	141±23	0.24
Total cholesterol, mg/dL	211±44	213±44	0.70
eGFR, mL/min per 1.73 m^2	50.1±14.7	44.7±13.5	<0.01
Urine protein-to-creatinine ratio, g/g Cr	0.06 (0.03–0.22)	0.19 (0.04–0.72)	<0.01
Randomized blood pressure goal			0.99
Low	270 (51%)	81 (51%)	
Usual	263 (49%)	79 (49%)	
Randomized blood pressure drug			0.77
Metoprolol	205 (38%)	66 (41%)	
Ramipril	224 (42%)	66 (41%)	
Amlodipine	104 (20%)	28 (18%)	

Values presented as mean±SD, median (interquartile range), or n (%).

APOL1 high risk defined as having 2 risk variants and low risk defined as having 0 to 1 risk variant. *APOL1* indicates apolipoprotein L1; Cr, creatinine; and eGFR, estimated glomerular filtration rate.

In sensitivity analyses, we found no significant association between *APOL1* risk status and individual components of the composite CVD outcome in fully adjusted recessive genetic models (Table I in the online-only Data Supplement). We did, however, note that increasing numbers of *APOL1* risk variants were associated with increased risk of cardiovascular death when using the additive genetic model (model 4 adjusted HR=1.74; 95% CI: 1.03–2.96; *P*=0.04; Table 3). Other analyses using the additive and dominant genetic models revealed no significant association between *APOL1* risk status and secondary CVD outcomes (*P*>0.05 for each). When considering 2 versus 0 *APOL1* risk variants for the composite CVD outcome (model 4 adjusted HR=1.53; 95% CI: 0.92–2.54; *P*=0.10) or when using an alternative composite outcome of myocardial infarction, revascularization procedure, and stroke (model 4 adjusted HR=1.41; 95% CI: 0.85–2.36; *P*=0.19; recessive genetic model), the HRs were slightly higher but still not statistically significant. Finally, we performed analyses taking into account the competing risks of ESRD and death and found that the results for the composite CVD outcome were similar (adjusted sub-HR=1.16; 95% CI: 0.74–1.80; *P*=0.52).

Table 2. *APOL1* Risk Status and the Relative Hazard of Composite Cardiovascular Outcomes

Model	n	Events	HR *APOL1* High Risk vs Low Risk*	95% CI	*P* Value
Unadjusted	693	144	1.23	0.83–1.81	0.31
Model 1: adjusted for age, sex, % European ancestry, and randomized treatment groups	693	144	1.25	0.84–1.85	0.27
Model 2: additionally adjusted for baseline smoking, body mass index, total cholesterol, systolic blood pressure, and history of heart disease	684	140	1.33	0.89–1.99	0.16
Model 3: additionally adjusted for baseline eGFR and log-transformed proteinuria	682	139	1.23	0.81–1.86	0.34
Model 4: additionally adjusted for longitudinal systolic blood pressure, eGFR, and log-transformed proteinuria as time-varying covariates	682	139	1.16	0.77–1.76	0.47

APOL1 indicates apolipoprotein L1; CI, confidence interval; eGFR, estimated glomerular filtration rate; and HR, hazard ratio.
**APOL1* high risk defined as having 2 risk variants and low risk defined as having 0 to 1 risk variant.

Discussion

Among African Americans with CKD attributed to hypertension, the *APOL1* high-risk genotypes were not associated with an increased risk for CVD events. These results were consistent in crude analysis, analysis adjusted for demographics, traditional risk factors, and kidney function, further adjustment for longitudinal systolic blood pressure, estimated glomerular filtration rate, and log-transformed proteinuria, and when we accounted for the competing risks of ESRD and death. Furthermore, the *APOL1* high-risk genotypes were not associated with any single component of the CVD composite outcome with the exception of cardiovascular death (additive model only). These findings add to the growing body of literature on the *APOL1* risk variants and CVD in the general population.[11,12,15,16] Consistent with our study, the SPRINT (Systolic Blood Pressure Intervention Trial) and Atherosclerosis Risk in Communities study suggested no association between the *APOL1* high-risk variants and prevalent[12] or incident CVD,[15] respectively. However, in the JHS and the WHI, individuals with 2 *APOL1* risk variants compared with those with no risk variant had a 1.8- to 3.2-fold higher risk of experiencing a major adverse cardiovascular event.[11] In the CHS, a cohort of adults aged ≥65 years, the *APOL1* high-risk genotypes were associated with an increased risk for incident myocardial infarction but not stroke or congestive heart failure.[16]

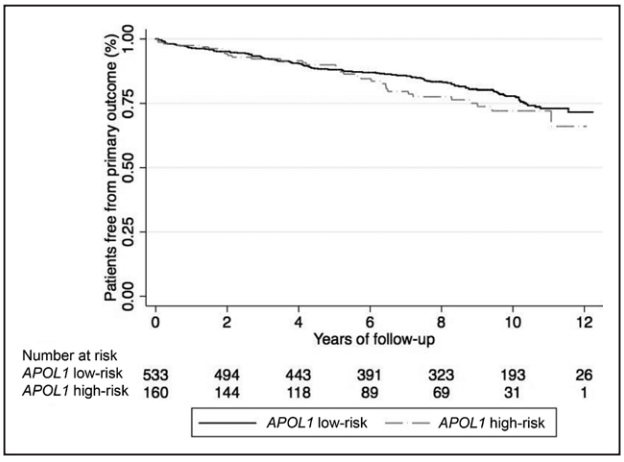

Figure. Kaplan–Meier survival curves for composite cardiovascular events by apolipoprotein L1 (*APOL1*) risk status.

Our study population is unique in that it consisted of individuals with moderate CKD (mean estimated glomerular filtration rate, 45 mL/min per 1.73 m^2 for *APOL1* high-risk and 50 mL/min per 1.73 m^2 for low-risk groups), whereas the other studies included individuals with mild or no CKD (mean estimated glomerular filtration rates from 73 to 112 mL/min per 1.73 m^2).[11,12,15,16] Like SPRINT,[12] another negative study on the association of *APOL1* with CVD, AASK excluded individuals with diabetes mellitus. Perhaps, the association between *APOL1* risk variants and CVD differs in the context of diabetes mellitus. In the 3 cohorts that reported a positive association between the *APOL1* high-risk variants and CVD, approximately one quarter of participants had a history of diabetes mellitus.[11,16] Our study has frequent assessments of kidney function, allowing for the investigation of mediation by change in kidney function; in contrast, the analyses in SPRINT were limited to prevalent, self-reported CVD.[12]

In support of our findings, associations between *APOL1* risk variants with subclinical CVD have been largely negative. Although apolipoprotein L1's role in trafficking of high-density lipoprotein[17] and expression within endothelial and smooth muscle cells could suggest a role in CVD,[18,19] Ito et al[11] reported an association between the *APOL1* risk variants and lower Agatston scores (as a measure of coronary artery calcium) in the JHS. Similarly, the *APOL1* risk variants were associated with less carotid and coronary artery calcified plaques in the AA-DHS (African American Diabetes Heart Study).[13] Freedman et al[14] reported that the *APOL1* risk variants were associated with less white matter lesion volume (a marker of severe cerebral small vessel disease) in the AA-DHS MIND (Memory IN Diabetes).

We did find an association between the number of *APOL1* risk variants and an increased risk for cardiovascular death; however, this was only when using the additive genetic model. These results should be interpreted with caution because they may be spurious in the context of multiple testing and few events (n=31) for this secondary outcome. To our knowledge, only one other study has examined the association between *APOL1* risk variants and cardiovascular mortality. In the CHS, risk for cardiovascular

Table 3. *APOL1* Risk Status and the Relative Hazard of Cardiovascular Death

Model	HR per *APOL1* Risk Variant	95% CI	*P* Value
Additive genetic model			
Unadjusted	1.62	0.99–2.65	0.05
Model 1: adjusted for age, sex, % European ancestry, and randomized treatment groups	1.74	1.05–2.86	0.03
Model 2: additionally adjusted for baseline smoking, body mass index, total cholesterol, systolic blood pressure, and history of heart disease	1.87	1.11–3.14	0.02
Model 3: additionally adjusted for baseline eGFR and log-transformed proteinuria	1.91	1.12–3.25	0.02
Model 4: additionally adjusted for longitudinal systolic blood pressure, eGFR, and log-transformed proteinuria as time-varying covariates	1.74	1.03–2.96	0.04
	HR comparing *APOL1* 1 or 2 risk variants vs no risk variant		
Dominant genetic model			
Unadjusted	2.35	0.97–5.74	0.06
Model 1: adjusted for age, sex, % European ancestry, and randomized treatment groups	2.47	1.01–6.05	0.05
Model 2: additionally adjusted for baseline smoking, body mass index, total cholesterol, systolic blood pressure, and history of heart disease	2.44	0.99–6.01	0.05
Model 3: additionally adjusted for baseline eGFR and log-transformed proteinuria	2.45	0.99–6.03	0.05
Model 4: additionally adjusted for longitudinal systolic blood pressure, eGFR, and log-transformed proteinuria as time-varying covariates	2.35	0.94–5.84	0.07

APOL1 indicates apolipoprotein L1; CI, confidence interval; eGFR, estimated glomerular filtration rate; and HR, hazard ratio.

mortality was not significantly greater among individuals with 2 *APOL1* risk variants compared with individuals with 1 or no variants although a modest increase for total and noncardiovascular mortality was noted.[16] Other studies have reported either improved survival[13,20] or no difference in risk for all-cause mortality[15] associated with the *APOL1* high-risk variants.

Our study has several strengths. First, we used a well-characterized cohort of African Americans in which data were collected prospectively with an active follow-up process. Second, all CVD events were centrally adjudicated by trained clinicians using a common protocol.[21–23] Third, given the known associations between the *APOL1* risk variants and kidney disease, the results of our study are applicable to a large proportion of patients seen in clinical practice who are already at increased risk for CVD because of their underlying CKD. Finally, our findings were robust, with similar conclusions obtained when using additive or dominant genetic models and after accounting for competing risks (ESRD and death).

Limitations include a relatively small number of outcome events, which may have limited our power to detect associations between the *APOL1* risk variants and CVD. With only 144 cases of the composite CVD outcome, we had 80% power to detect a minimum HR of 1.85 for the *APOL1* high-risk compared with the low-risk genotypes (recessive genetic model). Still, this HR is within the range of what was reported in the JHS and WHI.[11] Our sensitivity analyses examining secondary end points were likely underpowered, particularly for cardiovascular death, which had the fewest number of events (minimum detectable HR of 3.74 for 80% power). Furthermore, study participants were not followed for CVD events once they developed ESRD. There may have been additional cases of CVD that were not captured; however, the pathophysiology of CVD events post-ESRD (ie, more sudden cardiac death) likely differs from that of pre-ESRD CVD events.[24]

In conclusion, we did not detect an association of *APOL1* high-risk variants with a composite CVD outcome in African Americans with CKD attributed to hypertension. Sensitivity analyses, however, suggested an increased risk of cardiovascular death associated with increasing number of *APOL1* risk variants. Our results are consistent with some, but not all, prior studies. In view of the common association of CVD with kidney disease, additional research is warranted to better understand whether the *APOL1* risk variants are associated with CVD outcomes, and if so, the pathophysiological basis for an association.

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Disclosures

T.K. Chen previously owned stock in Pfizer Pharmaceuticals. The other authors report no conflicts.

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Highlights

- Prior studies have demonstrated that carrying 2 risk variants in the gene encoding apolipoprotein L1 (*APOL1*) is associated with an increased risk of kidney disease among African Americans. Whether these same risk variants are also associated with an increased risk of cardiovascular disease is less clear.
- In a cohort of African Americans with hypertension-attributed chronic kidney disease, we report that the risk of experiencing a composite cardiovascular outcome (cardiovascular death or hospitalization for myocardial infarction, cardiac revascularization procedure, heart failure, or stroke) did not differ significantly by *APOL1* risk status.
- In sensitivity analyses using an additive model, we found that with each additional number of *APOL1* risk variants, the risk of cardiovascular mortality incrementally increased.

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MATERIALS AND METHODS

Study Population

Details regarding the AASK trial and cohort have previously been published.[1,2] Briefly, AASK was a multi-center, 3-x-2 factorial trial designed to study the effects of three classes of blood pressure medications (metoprolol, ramipril, or amlodipine) and two levels of blood pressure control (mean arterial blood pressure ≤92 mmHg or 102-107 mmHg) on kidney function decline. During enrollment from 1995 to 1998, 1094 African Americans with hypertension-attributed CKD (baseline ^{123}I-iothalamate GFR 20-65 ml/min/1.73 m^2) were randomized to a blood pressure drug and goal.[1] After the trial phase, which ended in 2001, those who did not develop ESRD were recruited to enroll in the AASK cohort. During this phase of the study (2002-2007), all participants received ramipril and targeted a blood pressure goal of <140/90 mmHg, followed by <130/80 mmHg in 2004.[2] Study protocols for both phases of AASK were approved by institutional review boards of each participating center.[1-3] Exclusion criteria included history of diabetes (defined as a fasting glucose ≥140 mg/dL, random glucose >200 mg/dL, or need for drug therapy), urine protein-to-creatinine ratio >2.5 g/g Cr, malignant hypertension in the 6 months prior to enrollment, secondary hypertension, serious systemic disease, or a specific need for or contraindication to a study drug.[1,2] Eight-hundred and thirty-six of the 1094 AASK trial participants consented to genetic research, of whom 693 were genotyped for the *APOL1* G1 and G2 risk variants. These 693 individuals have previously been described in detail[4,5] and were included in our study.

Outcomes and Predictors

Our primary outcome was time to first pre-ESRD CVD event, which was defined as cardiovascular death or hospitalization for nonfatal myocardial infarction, cardiac revascularization procedure, heart failure, or stroke. Secondary outcomes included individual components of the composite CVD outcome. All CVD events were adjudicated by the Cardiovascular Outcomes Committee. Details regarding the classification of CVD events in AASK have previously been published.[3,6,7] Briefly, nonfatal myocardial infarction was defined by a clinical report of myocardial infarction supported by changes in serum cardiac enzymes (creatine kinase, MB fraction, or troponin I) or on electrocardiogram (new pathologic Q-waves, appearance of a R wave in lead V_1, or loss of progression of R waves in leads V_2 to V_5). Cardiac revascularization procedures included coronary artery bypass graft surgery, angioplasty, and percutaneous stent placement. Heart failure was defined as a hospitalization for congestive heart failure with need for inotropic, vasodilator, or angiotensin-receptor inhibitor therapy, escalation of diuretic therapy, ultrafiltration, or dialysis. Stroke was defined as a neurologic deficit persisting beyond 24 hours attributed to stroke and verified by imaging. Probable myocardial infarction and stroke were defined by clinical reports of each but without supporting documentation.[6]

The primary exposure was *APOL1* genotype. The *APOL1* risk variants (G1 [rs73885319 or rs60910145] and G2 [rs71785313]) were determined using ABI Taqman (Applied Biosystems, Foster City, CA).[4] In our main analyses, we used a recessive genetic model in which *APOL1* high-risk status was defined as having two risk variants, and low-risk status was defined as having one or no risk variant. European ancestry was determined using ANCESTRYMAP software and based on 140 ancestry informative markers.[4,8]

Estimated glomerular filtration rate was calculated using the AASK trial equation (eGFR = 329 x [Scr]$^{-1.096}$ x [age]$^{-0.294}$ x [0.736 if female], which has previously been validated, and was measured at baseline and every 6 months thereafter.[9,10] Proteinuria, as estimated by urine protein-to-creatinine ratio, was based on 24-hour urine collections obtained at baseline, every 6 months during the trial phase, and annually during the cohort phase.[1,2] Systolic blood pressure was determined by averaging the latter 2 of 3 consecutive blood pressure readings measured at

rest using a Hawksley random zero sphygmomanometer. [1] For clusters of blood pressure measurements due to the titration of blood pressure regimens (in order to achieve randomized blood pressure goals), we used the first averaged measurement of each visit.

Statistical Analyses

Baseline characteristics were compared by *APOL1* risk status using Student's t-test or Wilcoxon rank-sum test for continuous variables and Chi-squared tests for categorical variables. We then constructed a series of Cox proportional hazards models to assess the association between *APOL1* risk status and time to first cardiovascular event: a) unadjusted model; b) Model 1, which adjusted for age at randomization, gender, percentage of European ancestry, and randomized treatment groups; c) Model 2, which additionally adjusted for traditional CVD risk factors including baseline smoking, body mass index, total cholesterol, systolic blood pressure, and history of heart disease; d) Model 3, which additionally adjusted for markers of kidney function including baseline eGFR and log-transformed proteinuria; and e) Model 4, which adjusted for longitudinal systolic blood pressure, eGFR, and log-transformed proteinuria. Participants were censored at ESRD, death, lost to follow-up, or end of follow-up. Nine individuals had missing data on total cholesterol and two individuals had missing data on baseline proteinuria. Therefore, Model 2 included 684 individuals and Models 3 and 4 included 682 individuals. In additional analyses, we used additive (2 vs. 1 vs. 0 risk variants) and dominant (1-2 vs. 0 risk variants) genetic models. The proportional hazards assumption was checked using Schoenfeld residuals and log-log plots. We then examined each component of the composite CVD outcome individually as secondary outcomes. In additional analyses, we considered 2 vs. 0 *APOL1* risk variants for our composite CVD outcome. Using a recessive genetic model, we also considered an alternative composite outcome, which included myocardial infarction, cardiac revascularization procedure, and stroke. Finally, we performed competing risks analyses, with the outcome of interest being first cardiovascular event and competing risks being ESRD and death. We adjusted for the same covariates as in our primary analyses with the exception of using only baseline values. Data were analyzed using Stata (Version 12, 2011; College Station, TX) statistical software. P-values less than 0.05 were considered to be statistically significant.

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Supplemental Table I: *APOL1* risk status and the relative hazard of individual components of composite cardiovascular outcome.

	Hazard ratio comparing *APOL1* high- vs. low-risk* (95% Confidence Interval)			
	Cardiovascular Death	Coronary Artery Disease	Stroke†	Heart Failure
Number of events	31	48	50	67
Models				
Unadjusted	1.63 (0.73, 3.65)	1.76 (0.94, 3.29)	1.08 (0.55, 2.12)	1.12 (0.62, 2.03)
Model 1: Adjusted for age, gender, % European ancestry, and randomized treatment groups	1.83 (0.81, 4.13)	1.83 (0.97, 3.44)	1.07 (0.54, 2.09)	1.11 (0.61, 2.01)
Model 2: Additionally adjusted for baseline smoking, body mass index, total cholesterol, systolic blood pressure, and history of heart disease	2.20 (0.96, 5.05)	1.94** (1.02, 3.67)	1.15 (0.58, 2.27)	1.36 (0.74, 2.50)
Model 3: Additionally adjusted for baseline eGFR and log-transformed proteinuria.	2.29 (0.98, 5.33)	1.71 (0.86, 3.40)	1.27 (0.63, 2.57)	1.05 (0.55, 2.01)
Model 4: Additionally adjusted for longitudinal systolic blood pressure, eGFR, and log-transformed proteinuria as time-varying covariates	1.88 (0.80, 4.46)	1.72 (0.87, 3.43)	1.25 (0.62, 2.53)	1.03 (0.54, 1.96)

**APOL1* high-risk defined as having 2 risk variants and low-risk defined as having 0-1 risk variants.

**denotes $p<0.05$

†Proportional hazards assumption was violated for *APOL1* risk status variable. Additional analyses were performed using piecewise specifications. Before 7 years of follow-up, *APOL1* high-risk status was associated with a lower relative hazard for stroke compared to low-risk status (Model 4 adjusted HR: 0.85; 95% CI: 0.34 to 2.12). After 7 years of follow-up, *APOL1* high-risk status was associated with a higher relative hazard for stroke compared to low-risk status (Model 4 adjusted HR: 2.58; 95% CI: 0.87 to 7.66). These associations were not statistically significant.

Abbreviations: eGFR=estimated glomerular filtration rate.

Coronary artery disease includes myocardial infarction and cardiac revascularization procedure.