HHS Public Access

Author manuscript

Kidney Int Rep. Author manuscript; available in PMC 2017 July 26.

Published in final edited form as:

Kidney Int Rep. 2017 July ; 2(4): 713–720. doi:10.1016/j.ekir.2017.03.008.

APOL1 renal-risk variants do not associate with incident cardiovascular disease or mortality in the Systolic Blood Pressure Intervention Trial

Barry I. Freedman, MD[1], **Michael V. Rocco, MD**[1], **Jeffrey T. Bates, MD**[2], **Michel Chonchol, MD**[3], **Amret T. Hawfield, MD**[1], **James P. Lash, MD**[4], **Vasilios Papademetriou, MD**[5], **John R. Sedor, MD**[6], **Karen Servilla, MD**[7], **Paul L. Kimmel, MD**[8], **Barry M. Wall, MD**[9], **Nicholas M. Pajewski, PhD**[10], and **for the SPRINT Research Group**

[1]Department of Internal Medicine, Section on Nephrology; Wake Forest School of Medicine, Winston-Salem, NC

[2]Michael E. DeBakey Veterans Administration Medical Center and Baylor College of Medicine, Houston, TX

[3]Department of Medicine, Division of Renal Diseases and Hypertension; University of Colorado Anschutz Medical Campus, Aurora, CO

[4]Department of Medicine, Division of Nephrology; University of Illinois, Chicago, IL

[5]Center for Hypertension, Kidney & Vascular Research; Georgetown University Medical Center, Washington, DC

[6]Department of Medicine; MetroHealth Medical Center and Department of Physiology and Biophysics; Case Western Reserve University, Cleveland, OH

[7]Internal Medicine, Renal Section; New Mexico Veterans Administration Health Care System, Albuquerque, NM

[8]National Institute of Diabetes and Digestive and Kidney Diseases; Bethesda, MD

[9]Department of Nephrology; University of Tennessee Health Science Center and Veterans Affairs Medical Center, Memphis, TN

[10]Department of Biostatistical Sciences, Division of Public Health Sciences; Wake Forest School of Medicine, Winston-Salem, NC

Correspondence: Barry I. Freedman, M.D., Section on Nephrology, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1053, U.S.A., Phone: 336-716-6192, Fax: 336-716-4318, bfreedma@wakehealth.edu.

Disclosures

Wake Forest University Health Sciences and Dr. Freedman have filed for a patent related to *APOL1* genetic testing. Dr. Freedman receives research support from Novartis Pharmaceuticals and is a consultant for AstraZeneca and Ionis Pharmaceuticals. No other author has a relevant disclosure.

ClinicalTrials.gov Identifier NCT0120602

Abstract

Introduction—Relationships between apolipoprotein L1 gene (*APOL1*) renal-risk variants (RRVs) and cardiovascular disease (CVD) remain controversial. To clarify associations between *APOL1* and CVD, 2,568 African American Systolic Blood Pressure Intervention Trial (SPRINT) participants were assessed for the incidence of CVD events (primary composite including non-fatal myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, nonfatal stroke, non-fatal acute decompensated heart failure, and CVD death), renal outcomes, and all-cause mortality.

Methods—Cox proportional hazards regression models were employed adjusting for age, sex, African ancestry proportion, and treatment group (systolic blood pressure target of <120 mm Hg versus <140 mm Hg).

Results—Fourteen percent of participants had two *APOL1* RRVs; these individuals also had lower baseline estimated GFR and higher levels of albuminuria and BMI. After a median follow-up of 39 months, no significant association was observed between *APOL1* RRVs and the primary composite CVD outcome, any of its components, or all-cause mortality (recessive or additive genetic models). *APOL1* demonstrated a trend toward association with sustained 30% reduction in estimated GFR to <60 ml/min/1.73m^2 in those with normal kidney function at baseline (hazard ratio [95% CI] 1.64 [0.85–2.93]; p=0.114, recessive model).

Conclusion—*APOL1* RRVs were not associated with incident CVD in high-risk hypertensive, non-diabetic African American participants in SPRINT.

Keywords

African Americans; albuminuria; APOL1; cardiovascular disease; chronic kidney disease; SPRINT

Introduction

Apolipoprotein L1 gene (*APOL1*) G1 and G2 renal-risk variants (RRVs) are powerfully associated with a spectrum of progressive non-diabetic forms of nephropathy in individuals who possess recent African ancestry.(1,2) These primary kidney diseases reside in the focal segmental glomerulosclerosis (FSGS) spectrum and contribute to approximately 40% of end-stage kidney disease (ESKD) in African Americans.(3,4) *APOL1* is expressed in podocytes, glomerular endothelial cells, and renal tubular cells.(5,6) Several lines of evidence support intrinsic kidney *APOL1* gene expression and not circulating APOL1 protein as underlying the development of kidney disease.(7–11) *APOL1* expression is increased by interferons and other inflammatory mediators;(12) these factors may be the second hits required to cause kidney disease.(13) Postulated mechanisms whereby *APOL1* may cause kidney disease include APOL1 RRV proteins damaging cell membranes with loss of intracellular potassium and secondary activation of stress-activated protein kinases and mitochondrial dysfunction even prior to intracellular potassium depletion.(14,15)

In addition to the kidney, *APOL1* is expressed in the vasculature and its RRVs associate with high density lipoprotein (HDL)-cholesterol particle concentrations.(5,6,16) Therefore,

APOL1 could be involved in susceptibility to (or protection from) cardiovascular disease (CVD). Three studies have detected increased risk for CVD in individuals with two *APOL1* RRVs; however, paradoxically *lower* levels of subclinical CVD (coronary artery calcium) were detected, and these results could have been confounded by *APOL1* association with chronic kidney disease (CKD), a known contributor to CVD.(17,18) In contrast, several studies have reported protective effects of *APOL1* renal-risk variants on subclinical atherosclerosis, cerebrovascular disease, and all-cause mortality and other studies saw no relationship between *APOL1* with CVD or survival.(19–24)

Potential therapeutic targets for preventing nephropathy include the *APOL1* gene and its protein products. Therefore, it is critical to determine whether *APOL1* RRVs protect from CVD, because inhibiting this gene to prevent kidney disease could accelerate atherosclerosis. The present analyses assessed relationships between *APOL1* RRVs with incident CVD outcomes, incident renal outcomes, and mortality in African Americans participating in the Systolic Blood Pressure Intervention Trial (SPRINT).

Methods

Participants and genotyping

SPRINT is a multi-center, randomized clinical trial of blood pressure control in individuals ≥50 years old at increased risk for CVD.(25) The high risk of CVD in SPRINT was based on Framingham Risk Score, prior CVD events, age ≥75 years, or CKD. Details of the intervention and outcomes have previously been reported.(26) Exclusion criteria included participants taking medications for diabetes mellitus at any time in the 12 months prior to baseline, urine albumin levels more than 600 mg/day or urine protein levels more than 1000 mg/day, or an eGFR <25 ml/min/1.73m^2. Participants were randomized to systolic blood pressure control targets of <140 mm Hg (Standard-treatment) versus <120 mm Hg (Intensive-treatment).

Outcomes

The primary study outcome was a composite of CVD events, all were adjudicated and they included myocardial infarctions (MI), non-MI acute coronary syndrome, strokes, heart failure, and CVD deaths. A predefined participant subgroup included CKD, defined as an eGFR <60 ml/min/1.73m^2 based upon the 4-variable Modification of Diet in Renal Disease (MDRD) equation. Secondary outcomes in the CKD subgroup included the rate of development of ESRD and a 50% decline from baseline eGFR. Secondary outcomes in the non-CKD subgroup included the rate of ESRD and a 30% decrease from baseline eGFR with an end-value <60 ml/min/1.73m^2. Due to when SPRINT was designed, note that the CKD subgroup and renal outcomes definitions were based on the MDRD eGFR equation. However, in the present analysis, all eGFRs are based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. (27) Spot urine samples were collected for albumin and creatinine concentration to compute the urine albumin:creatinine ratio (UACR) at specified study visits. Incident albuminuria was defined as a doubling of UACR from <10 mg/g to ≥10 mg/g, confirmed by a subsequent laboratory test ≥90 days later.

Participants were recruited from approximately 100 clinics in the U.S. and each had institutional review board approval. Written informed consent was obtained from all participants. The present analyses were limited to self-reported African American participants; from all 2,802 African American SPRINT participants, 2,568 (91.6%) consented to participation in genetics studies. Genotyping methods for *APOL1*, ancestry informative markers, and results of quality control have been reported.(20)

Statistical Analyses

The incidence of CVD events and all-cause mortality was estimated using standard Kaplan-Meier techniques, with log-rank tests to compare the incidence of these events by *APOL1* genotype within each treatment group. The time to first occurrence of CVD outcomes, all-cause mortality, and renal outcomes were compared by *APOL1* risk genotype using Cox proportional hazards regression models. Follow-up time was censored as of the National Heart, Lung, and Blood Institute Director decision to stop the SPRINT intervention on August 20th, 2015. We considered both an additive (0, 1, or 2 *APOL1* RRVs) and recessive (2 *APOL1* RRVs versus 0 or 1) coding of *APOL1* risk genotype. All models included age, sex, proportion of African ancestry, and treatment group as covariates. Baseline eGFR and log(UACR) were also included as covariates for the CVD outcomes and all-cause mortality. We used multiple imputation (100 datasets) to address the small amount of missing data with baseline eGFR (N=7, 0.3%) and UACR (N=91, 3.5%). The imputation models included age, sex, smoking status, history of cardiovascular disease, systolic and diastolic blood pressure, use of ACE inhibitors, use of angiotensin receptor blockers, body mass index, total cholesterol, HDL cholesterol, and log triglycerides as predictors. In addition, eGFR was included as a predictor in the imputation model for log(UACR).

The power to detect an association between being a carrier of 2 *APOL1* RRVs (recessive model) and incident events was estimated *a priori* assuming an alpha level of 0.05, 3 years of follow-up, and a loss to follow-up rate of 2% per year.(28) Assuming overall annual incidence rates of 0.5%, 1.0%, 1.5%, and 2.0% per year, we estimated that we would have at least 80% power provided that the hazard ratio associated with carrying two *APOL1* RRVs was at least 3.3, 2.3, 2.0, and 1.9 respectively.

Linear mixed-effect models were used to compare longitudinal trajectories for eGFR by *APOL1* risk genotype and treatment group, assuming an unstructured covariance matrix. For each combination of *APOL1* genotype and treatment group, we assumed a two-slope linear model with a change-point at ≤6 months or >6 months post-randomization. The change-point in the slope of eGFR was designed to reflect mean trajectories in the acute phase of the intervention potentially due to hemodynamic effects (≤6 months post-randomization) versus trajectories in the chronic phase (>6 months post-randomization). Slopes for eGFR were compared using Wald tests based on the estimated model coefficients and standard errors. Baseline eGFR, age, sex, history of CVD, and proportion of African ancestry were included in the model as covariates. Finally, because small (but statistically significant) changes in mean eGFR were observed in SPRINT when comparing fasting to non-fasting study visits, we included indicators denoting fasting visits as covariates, assuming separate effects for

each of the 4 combinations of *APOL1* risk genotype and treatment group. All analyses were performed using SAS v9.4 (Cary, NC) or the R Statistical Computing Environment.

Results

A total of 2,568 African American SPRINT participants were included, 360 (14.0%) had two *APOL1* RRVs and 2,208 (86%) had fewer than two RRVs. Table 1 displays baseline demographic and laboratory characteristics of individuals based on *APOL1* high-risk genotype. Participants with two *APOL1* RRVs had significantly higher body mass index, higher UACR and lower eGFR but were otherwise similar to those with fewer than two *APOL1* RRVs. Significant (cross-sectional) association between *APOL1* RRVs with baseline UACR, serum creatinine concentration, and eGFR in SPRINT have previously been reported (recessive model).(20)

Kaplan-Meier curves by treatment group and *APOL1* risk genotype for the primary composite CVD outcome (non-fatal MI, acute coronary syndrome not resulting in MI, stroke, acute decompensated heart failure and death from CVD) and the primary CVD composite plus all-cause mortality are shown in Figure 1 and Figure 2 respectively. Within each treatment group, there were not significant differences by *APOL1* genotype for either outcome (all p-values >0.15). Table 2 displays hazard ratios (HRs) for the composite CVD outcome, its component events, all-cause mortality, and renal outcomes. After a median follow-up of 39.0 months (interquartile range = 33.8 to 45.5 months), there were 22 adjudicated CVD events in the 360 participants with two *APOL1* RRVs versus 106 in the 2,208 participants with fewer than two *APOL1* RRVs (HR [95% CI] 1.20 [0.76–1.92], p=0.435 recessive model; HR [95% CI] 1.10 [0.86–1.41], p=0.458 additive model). The HR for all-cause mortality, MI, and all CVD events comprising the primary SPRINT CVD outcome did not differ based upon *APOL1* RRVs in either additive or recessive models.

In contrast to significant relationships between *APOL1* RRVs and baseline (prevalent) kidney disease,(20) no significant *APOL1* associations were seen with the pre-specified renal outcomes of: (a) 50% reduction in eGFR (measured twice at least 90 days apart), initiation of dialysis, or kidney transplantation, or (b) proteinuria assessed as doubling of UACR from <10 to ≥10 mg/g (measured twice at least 90 days apart in participants with CKD and baseline UACR <10 mg/g) in the CKD sub-group (those with an initial eGFR <60 ml/min/1.73m^2). In the subgroup without CKD at baseline, a non-significant trend was observed for the pre-specified end-point of a 30% reduction in eGFR (measured twice at least 90 days apart) to an eGFR <60 ml/min/1.73m^2, initiation of dialysis, or kidney transplantation (HR [95% CI] 1.64 [0.85–2.93], p=0.114 recessive model), but not for incident proteinuria.

Table 3 displays the slopes for eGFR decline using linear mixed models over the course of follow-up in African American SPRINT participants by treatment group and *APOL1* risk genotypes. Graphical depictions of eGFR group means over time and time estimated slopes from the mixed model analyses are presented in Supplementary Figure 1 (entire cohort), Supplementary Figure 2 (eGFR <60 ml/min/1.73m^2 at randomization), and Supplementary Figure 3 (eGFR ≥60 ml/min/1.73m^2 at randomization). Whether assessing eGFR slope

during the initial 6 months following randomization or after 6 months, *APOL1* risk genotypes did not significantly impact the rate of decline in kidney function in the standard or intensive treatment groups.

Discussion

The present report assessed *APOL1* RRV associations with incident CVD and mortality in 2,568 hypertensive non-diabetic African American SPRINT participants. After a median follow-up of 39 months and 177 total CVD events and deaths, no significant association was observed between *APOL1* RRVs and all-cause mortality, incident non-fatal MI, acute coronary syndrome without MI, stroke, heart failure, or the primary SPRINT composite CVD outcome. There were advantages to performing these analyses in SPRINT. The sample was relatively large and CKD was generally mild. This cohort was also at high risk for CVD based on age and prior CVD events; yet only 14% possessed two *APOL1* RRVs. This is similar to the 13% frequency of two *APOL1* RRVs in the general population and should limit confounding of CKD with CVD.(1) Small numbers of CVD events may have limited study power. As such, meta-analyses including several studies are needed to help clarify the CVD effects of *APOL1*.

SPRINT results are similar to those reported in the Atherosclerosis Risk In Communities (ARIC) and African American Study of Kidney Disease and Hypertension (AASK), where no association between *APOL1* RRVs and survival or CVD events was observed.(23,24) However, SPRINT, AASK and ARIC results contrast with higher rates of CVD with *APOL1* RRVs in the Jackson Heart Study (JHS), Women's Health Initiative (WHI), and Cardiovascular Health Study (CHS).(17,18) *APOL1* RRVs were associated with baseline CKD, incident CKD, CKD progression, or albuminuria in all of these studies, so confounding between CKD and CVD is not likely to fully explain differences in results. Confounding should be least likely in SPRINT and CHS, where mild kidney disease was present and *APOL1* RRVs were only associated with baseline CKD or UACR, not with incident reductions in eGFR.(18) There were relatively few kidney disease events in SPRINT participants, an effect that reduced power to detect associations with renal outcomes. A trend toward sustained 30% reductions in eGFR to <60 ml/min/1.73m^2, need for dialysis or kidney transplantation was seen with *APOL1* (recessive model) in the non-CKD subgroup (Table 2; p=0.11). No association was seen between *APOL1* genotypes and all-cause mortality; 95 deaths occurred during study follow-up. Several other studies reported protective effects of *APOL1* RRVs on related outcomes, including improved survival in non-diabetic patients on hemodialysis and in African American-Diabetes Heart Study (AA-DHS) participants, less calcified atherosclerotic plaque in AA-DHS, and less cerebrovascular disease (larger gray matter and smaller white matter lesion volumes) in AA-DHS MIND and SPRINT MND.(19,21,22)

It remains important to determine whether *APOL1* RRVs are associated with CVD, because targeting *APOL1* G1 and G2 variants to treat CKD could influence CVD outcomes. If *APOL1* RRVs are protective from CVD, there is a risk that atherosclerotic complications might develop from targeting this gene. If *APOL1* RRVs are associated with risk for CVD, targeting them could simultaneously reduce CVD and CKD. *APOL1* relationships with

incident CVD outcomes in SPRINT, AASK, and ARIC suggest that significant associations do not exist.(23,24) In contrast, JHS, WHI and CHS reported positive relationships between *APOL1* RRVs and incident CVD.(17,18) It should be noted that JHS only compared African Americans with two versus zero *APOL1* RRVs; results in those with a single RRV (or in additive models) were not reported.(17) Further, two *APOL1* RRVs in JHS was associated with lower levels of coronary artery calcified plaque (less subclinical CVD).(17) This was a paradoxical observation given the higher reported risk for CVD in this group.(29)

As in prior reports assessing the effects of *APOL1* on CVD, SPRINT has strengths and limitations. Strengths included adjudication of CVD outcomes, renal outcomes, and deaths by an expert panel. Despite the relatively large sample of African Americans in SPRINT, we observed relatively few CVD events and deaths during a median of 39 months of follow-up. We were only adequately powered to detect strong associations between *APOL1* RRVs and incident CVD. As such, our data does not preclude effects of the magnitude reported, for example, in CHS, which had longer follow-up and more events.

In conclusion, results in SPRINT add to the expanding literature assessing relationships between renal-risk variants in the *APOL1* nephropathy gene and incident cardiovascular outcomes. Significant relationships were not observed between *APOL1* RRVs and incident nonfatal MI, stroke, heart failure, non-MI acute coronary syndrome, or CVD-related death in African American SPRINT participants. Significant relationships were also not observed with the composite of these outcomes or with all-cause mortality. Given limitations of the current study, and the existing conflicting reports in the literature, additional research is required in this important area.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors wish to thank study participants and study coordinators in SPRINT. The Systolic Blood Pressure Intervention Trial is funded with Federal funds from the National Institutes of Health (NIH), including the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute on Aging (NIA), and the National Institute of Neurological Disorders and Stroke (NINDS), under Contract Numbers HHSN268200900040C, HHSN268200900046C, HHSN268200900047C, HHSN268200900048C, HHSN268200900049C, and Inter-Agency Agreement Number A-HL-13-002-001. It was also supported in part with resources and use of facilities through the Department of Veterans Affairs. The SPRINT investigators acknowledge the contribution of study medications (azilsartan and azilsartan combined with chlorthalidone) from Takeda Pharmaceuticals International, Inc. All components of the SPRINT study protocol were designed and implemented by the investigators. The investigative team collected, analyzed, and interpreted the data. All aspects of manuscript writing and revision were carried out by the coauthors. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH, the U.S. Department of Veterans Affairs, or the United States Government. For a full list of contributors to SPRINT, please see the supplementary acknowledgement list:

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We also acknowledge the support from the following CTSAs funded by NCATS: CWRU: UL1TR000439, OSU: UL1RR025755, U Penn: UL1RR024134& UL1TR000003, Boston: UL1RR025771, Stanford: UL1TR000093, Tufts: UL1RR025752, UL1TR000073 & UL1TR001064, University of Illinois: UL1TR000050, University of Pittsburgh: UL1TR000005, UT Southwestern: 9U54TR000017-06, University of Utah: UL1TR000105-05, Vanderbilt University: UL1 TR000445, George Washington University: UL1TR000075, University of CA, Davis:

UL1 TR000002, University of Florida: UL1 TR000064, University of Michigan: UL1TR000433, Tulane University: P30GM103337 COBRE Award NIGMS.

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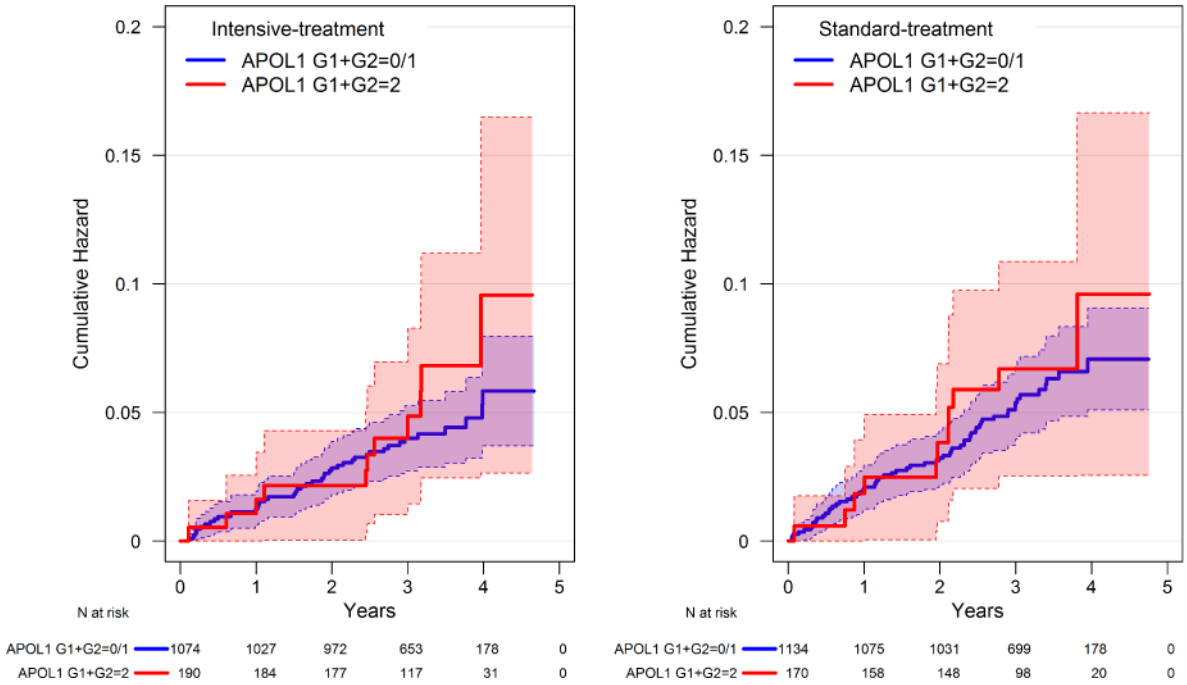

Figure 1.

Kaplan-Meier curves for the primary cardiovascular disease (CVD) outcome in SPRINT for African American participants by treatment group and *APOL1* risk genotype

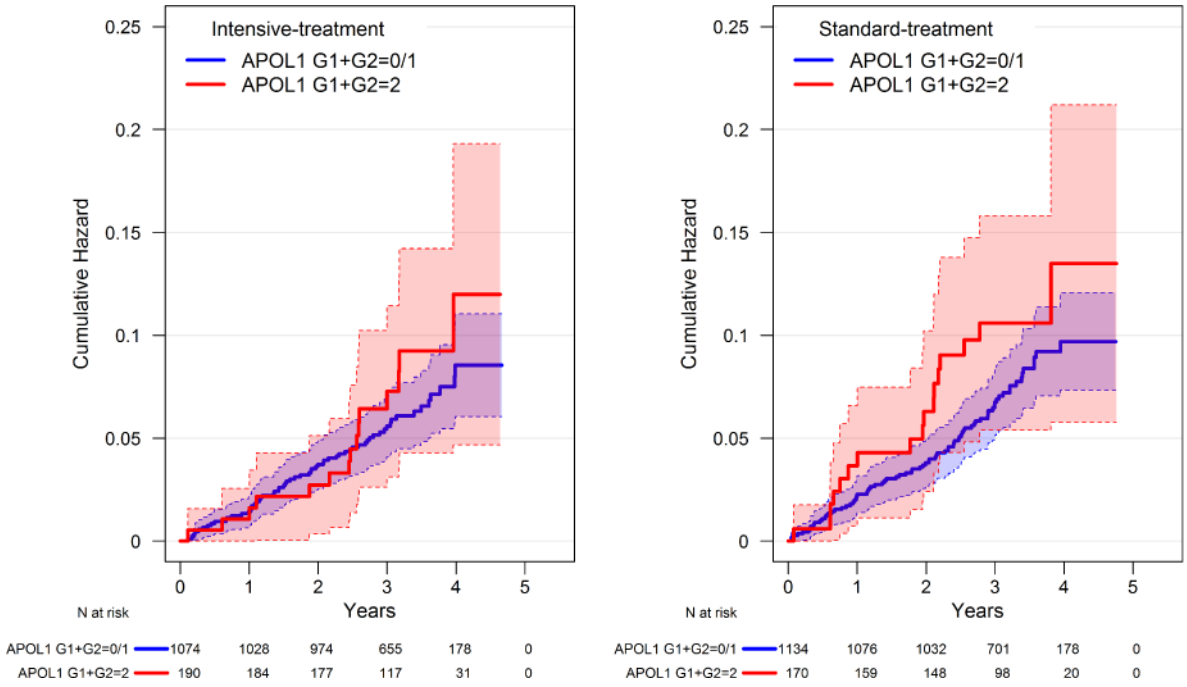

Figure 2.

Kaplan-Meier curves for the primary cardiovascular disease (CVD) outcome plus all-cause mortality in SPRINT for African American participants by treatment group and *APOL1* risk genotype

Table 1

Baseline demographic and laboratory data for African American participants with *APOL1* genotyping in SPRINT

Variable	APOL1 G1+G2 2 risk variants N=360	APOL1 G1+G2 0/1 risk variants N=2,208	p-value
Randomized to intensive-treatment	190 (52.8)	1,074 (48.6)	0.162
Age (years), mean (SD)	63.5 ± 9.0	64.4 ± 9.0	0.053
Female sex	169 (46.9)	997 (45.2)	0.565
Education			0.105
<High School Education	66 (18.3)	320 (14.5)	
High School Education	228 (63.3)	1,372 (62.1)	
College Graduate	46 (12.8)	332 (15.0)	
Graduate Degree	20 (5.6)	183 (8.3)	
Missing	0 (0.0)	1 (0.0)	
Alcohol consumption			0.663
Non-drinker	200 (55.6)	1,203 (54.5)	
Light drinker	72 (20.0)	415 (18.8)	
Moderate drinker	42 (11.7)	308 (13.9)	
Heavy drinker	22 (6.1)	156 (7.1)	
Missing	24 (6.7)	126 (5.7)	
Smoking status			0.167
Never smoker	169 (46.9)	950 (43.1)	
Former smoker	105 (29.2)	754 (34.2)	
Current smoker	86 (23.9)	501 (22.7)	
Pack-years in smokers, mean (SD)	16.1 ± 18.9	16.2 ± 17.5	0.214
Body Mass Index (kg/m^2), mean (SD)	31.5 ± 6.7	30.8 ± 6.3	0.044
History of CVD	60 (16.7)	359 (16.3)	0.907
Systolic BP (mmHg), mean (SD)	139.4 ± 15.8	139.8 ± 16.4	0.653
Diastolic BP (mmHg), mean (SD)	82.3 ± 12.6	81.1 ± 12.4	0.081
eGFR (ml/min/1.73m^2), mean (SD)	73.3 ± 24.6	76.8 ± 22.6	0.008
eGFR<60 ml/min/1.73m^2	102 (28.4)	524 (23.8)	0.069
UACR (mg/g), median (IQR)	12.2 (6.5 to 32.8)	8.7 (5.0 to 21.5)	<0.001
Albuminuria			<0.001
UACR≤30 mg/g	255 (72.9)	1,707 (80.3)	
UACR>30 to ≤300 mg/g	71 (20.3)	354 (16.6)	

Variable	APOL1 G1+G2 2 risk variants N=360	APOL1 G1+G2 0/1 risk variants N=2,208	p-value
UACR>300 mg/g	24 (6.9)	66 (3.1)	
Fasting glucose (mg/dL), mean (SD)	96.8 ± 13.9	97.9 ± 16.0	0.213
Total cholesterol (mg/dL), mean (SD)	195.8 ± 42.3	196.2 ± 40.6	0.837
HDL cholesterol (mg/dL), mean (SD)	54.4 ± 13.8	55.3 ± 15.2	0.280
# of antihypertensive medications, mean (SD)	2.1 ± 1.1	2.0 ± 1.0	0.062
Use of ACEi/ARB	202 (56.1)	1,151 (52.1)	0.178
Use of Statins	123 (34.3)	744 (33.9)	0.944

(SD) Standard Deviation. (IQR) Interquartile Range. (CVD) Cardiovascular Disease. (BP) Blood Pressure. (eGFR) Estimated Glomerular Filtration Rate based on CKD-EPI study equation. (UACR) Urine albumin:creatinine ratio. (ACEi) ACE inhibitor. (ARB) angiotensin receptor blocker

Table 2

Incidence of CVD, renal, and mortality outcomes by *APOL1* renal-risk genotype in African American SPRINT participants

	***APOL1* G1+G2 = 2**		***APOL1* G1+G2 = 0/1**					
	No. With Events	**% with events**	**No. With Events**	**% with events**	**Recessive Model**		**Additive Model**	
	N=360	**per yr (95% CI)**	**N=2,208**	**per yr (95% CI)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
All participants								
CVD Primary Outcome[a]	22	1.97 (1.30, 2.99)	106	1.53 (1.26, 1.85)	1.20 (0.76, 1.92)	0.435	1.10 (0.86, 1.41)	0.458
Myocardial infarction (MI)	6	0.53 (0.24, 1.18)	39	0.56 (0.41, 0.76)	1.02 (0.43, 2.45)	0.961	1.12 (0.73, 1.72)	0.607
ACS not resulting in MI	2	0.18 (0.04, 0.70)	12	0.17 (0.10, 0.30)	1.04 (0.23, 4.79)	0.958	1.02 (0.47, 2.20)	0.957
Stroke	7	0.62 (0.30, 1.30)	23	0.33 (0.22, 0.49)	1.66 (0.70, 3.92)	0.251	1.26 (0.77, 2.08)	0.359
Heart failure	7	0.62 (0.30, 1.30)	39	0.55 (0.41, 0.76)	0.98 (0.43, 2.23)	0.970	0.83 (0.54, 1.28)	0.403
Cardiovascular disease death	4	0.35 (0.13, 0.94)	22	0.31 (0.20, 0.47)	0.94 (0.32, 2.75)	0.905	1.27 (0.74, 2.16)	0.384
Non-fatal MI	6	0.53 (0.24, 1.18)	38	0.54 (0.39, 0.74)	1.07 (0.45, 2.57)	0.879	1.12 (0.72, 1.72)	0.618
Non-fatal stroke	7	0.62 (0.30, 1.30)	22	0.31 (0.21, 0.48)	1.76 (0.74, 4.18)	0.202	1.26 (0.76, 2.09)	0.379
Non-fatal heart failure	7	0.62 (0.30, 1.30)	37	0.53 (0.38, 0.73)	1.05 (0.46, 2.39)	0.905	0.89 (0.58, 1.38)	0.609
All-cause mortality	16	1.40 (0.86, 2.29)	79	1.11 (0.89, 1.39)	1.19 (0.69, 2.05)	0.530	1.10 (0.82, 1.46)	0.529
Primary+all-cause mortality	32	2.85 (2.02, 4.04)	145	2.09 (1.77, 2.46)	1.28 (0.87, 1.89)	0.212	1.10 (0.89, 1.36)	0.361
eGFR<60 ml/min/1.73 m^2								
Primary CKD Outcome[b]	1/102	0.29 (0.04, 2.09)	10/524	0.59 (0.32, 1.09)	0.48 (0.03, 2.51)	0.482	0.56 (0.19, 1.33)	0.228
Incident Albuminuria[c]	0/21	–	23/201	3.87 (2.57, 5.83)	–	–	0.70 (0.35, 1.34)	0.301
eGFR>60 ml/min/1.73 m^2								
Secondary CKD Outcome[d]	13/257	1.66 (0.97, 2.86)	53/1,678	0.99 (0.76, 1.29)	1.64 (0.85, 2.93)	0.114	1.06 (0.73, 1.50)	0.766
Incident Albuminuria[c]	10/128	2.73 (1.47, 5.07)	61/961	2.08 (1.62, 2.67)	1.32 (0.63, 2.50)	0.417	1.41 (1.00, 1.99)	0.051

(ACS) Acute Coronary Syndrome. (CKD) Chronic Kidney Disease. (HR) Hazard Ratio. (eGFR) estimated glomerular filtration rate.

[a] Includes nonfatal MI, ACS not resulting in MI, nonfatal stroke, nonfatal acute decompensated heart failure, and cardiovascular disease death.

[b] Includes a 50% reduction in eGFR (measured twice at least 90 days apart), dialysis, or kidney transplantation.

[c] Only applies to participants with urine albumin:creatinine ratio <10 mg/g at baseline, and required a doubling from <10 mg/g to ≥10 mg/g (measured twice at least 90 days apart).

[d] Includes a 30% reduction in eGFR (measured twice at least 90 days apart) to an eGFR <60 ml/min/1.73m^2, dialysis, or kidney transplantation. HRs for CKD and albuminuria outcomes adjusted for age, sex, African admixture, and treatment group. HRs for CVD outcomes and all-cause mortality additionally adjusted for eGFR and log(urine albumin:creatinine ratio).

Table 3

Slopes from linear mixed model for estimated Glomerular Filtration Rate (eGFR) over the course of follow-up in African-American SPRINT participants by treatment group and *APOL1* risk genotype

Group	Time Period[a]	Group	*APOL1* G1+G2=2 Slope (95% CI)[b]	*APOL1* G1+G2=0/1 Slope (95% CI)[b]	*APOL1* G1+G2: 2 - 0/1 Difference (95% CI)	p-value
All	Acute (≤6M)	Standard	−0.31 (−2.87, 2.26)	0.80 (−0.46, 2.07)	−1.11 (−3.69, 1.47)	0.398
All	Acute (≤6M)	Intensive	−4.18 (−6.57, −1.79)	−3.53 (−4.82, −2.25)	−0.65 (−3.06, 1.77)	0.600
All	Chronic (>6M)	Standard	−1.13 (−2.34, 0.08)	−0.97 (−1.42, −0.52)	−0.16 (−1.45, 1.12)	0.806
All	Chronic (>6M)	Intensive	−1.36 (−2.46, −0.26)	−1.01 (−1.47, −0.54)	−0.35 (−1.54, 0.84)	0.564
CKD (eGFR<60 ml/min/1.73m^2)	Acute (≤6M)	Standard	0.85 (−2.22, 3.91)	2.07 (0.48, 3.67)	−1.23 (−4.46, 2.00)	0.457
CKD (eGFR<60 ml/min/1.73m^2)	Acute (≤6M)	Intensive	0.06 (−2.93, 3.05)	−1.97 (−3.49, −0.45)	2.03 (−1.10, 5.16)	0.204
CKD (eGFR<60 ml/min/1.73m^2)	Chronic (>6M)	Standard	−1.41 (−2.50, −0.32)	−0.60 (−1.13, −0.06)	−0.81 (−2.03, 0.40)	0.190
CKD (eGFR<60 ml/min/1.73m^2)	Chronic (>6M)	Intensive	−0.82 (−1.91, 0.27)	−0.75 (−1.24, −0.26)	−0.07 (−1.26, 1.12)	0.908
Non-CKD (eGFR≥60 ml/min/1.73 m^2)	Acute (≤6M)	Standard	−0.18 (−3.29, 2.93)	0.48 (−0.98, 1.94)	−0.66 (−3.77, 2.45)	0.679
Non-CKD (eGFR≥60 ml/min/1.73 m^2)	Acute (≤6M)	Intensive	−5.44 (−8.27, −2.60)	−3.99 (−5.49, −2.48)	−1.45 (−4.31, 1.42)	0.322
Non-CKD (eGFR≥60 ml/min/1.73 m^2)	Chronic (>6M)	Standard	−1.17 (−2.71, 0.36)	−1.20 (−1.72, −0.69)	0.03 (−1.59, 1.64)	0.975
Non-CKD (eGFR≥60 ml/min/1.73 m^2)	Chronic (>6M)	Intensive	−1.83 (−3.18, −0.49)	−1.20 (−1.75, −0.64)	−0.64 (−2.09, 0.81)	0.388

[a] For acute time period (≤6 months (M) post-randomization), slopes reflect mean change in eGFR (in ml/min/1.73m^2) over 6 months. For chronic time period (>6M post-randomization), slopes reflect mean change in eGFR per one year.

[b] Adjusted for baseline eGFR, age, sex, history of cardiovascular disease, proportion of African admixture, and whether or not measurement occurred at a fasting study visit.