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Strict blood pressure control associates with decreased mortality risk by APOL1 genotype

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Abstract

Although *APOL1* high-risk genotype partially accounts for the increased susceptibility of blacks to chronic kidney disease (CKD), whether *APOL1* associates differentially with mortality risk remains controversial. Here we evaluate the association between *APOL1* genotype and risk of death, and determine whether *APOL1* status modifies the association between strict versus usual blood pressure control and mortality risk. We performed a retrospective analysis of the African American Study of Kidney Disease and Hypertension trial which randomized black participants with CKD to strict versus usual blood pressure control from 1995 to 2001. This included 682 participants with known *APOL1* genotype (157 with high-risk genotype) previously assigned to either strict (mean arterial pressure [MAP] 92 mm Hg or less) versus usual blood pressure control (MAP 102-107 mm Hg) during the trial. During a median follow-up of 14.5 years, risk of death did not differ between individuals with high- versus low-risk *APOL1* genotypes (unadjusted

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hazard ratio 1.00 [95% confidence interval 0.76-1.33]). However, a significant interaction was detected between *APOL1* risk group and blood pressure control strategy. In the *APOL1* high-risk group, risk of death was 42% lower comparing strict versus usual blood pressure control (0.58 [0.35-0.97]). In the *APOL1* low-risk group, risk of death comparing strict versus usual blood pressure control was not significantly different (1.09 [0.84-1.43]). Thus, strict blood pressure control during CKD associates with a lower risk of death in blacks with the high-risk CKD *APOL1* genotype. Knowledge of *APOL1* status could inform selection of blood pressure treatment targets in black CKD patients.

Keywords

APOL1 genotype; mortality; CKD

Introduction

Blacks are known to have a significantly higher risk of developing end-stage renal disease (ESRD) compared to other races, even after accounting for racial disparities in the control of traditional risk factors for kidney disease.[1-4] The disproportionate burden of renal disease in blacks has been attributed, in part, to a higher prevalence of the high-risk *APOL1* genetic variant,[5-10] which increases the risk of accelerated renal function decline, but also confers resistance against lethal African sleeping sickness.[5, 6, 11-13] *APOL1* has been associated with an increased risk of a variety of renal diseases, including focal segmental glomerulosclerosis,[14] HIV associated nephropathy,[14, 15] hypertension-attributed chronic kidney disease,[6] lupus nephritis,[16] and accelerates the progression of diabetic kidney disease.[7] However, routine screening for *APOL1* risk variants in black patients with CKD is not currently recommended, given the absence of known therapies that improve outcomes in this high-risk population.[17]

Although significant advances have been made in our understanding of the contribution of *APOL1* to adverse renal outcomes, less is known about the mortality risk of individuals with high-risk *APOL1* variants. APOL1 has been localized to the arteriolar endothelium of the kidney[18] and circulates in the plasma,[19] leading some to postulate a potential link between *APOL1* status and cardiovascular disease.[20, 21] Some studies have found a higher risk of atherosclerotic disease in individuals with *APOL1* high-risk genotype, although this finding has not been consistent across all studies.[21-23] Since cardiovascular disease is the leading cause of mortality in patients with CKD, it is plausible that *APOL1* status may associate with a differential risk of death. For example, one recent study demonstrated a 30% excess mortality risk in older blacks with the high- versus low-risk *APOL1* genotype.[21] However, other studies have observed a reduced risk of death in black individuals with the high-risk genotype, so the exact association between *APOL1* and mortality remains a subject of controversy.[22-24]

The primary objectives of this study were to determine 1) whether there is a difference in long-term risk of death by *APOL1* risk group and 2) whether prior assignment to strict BP control associates with mortality benefit in blacks with the high-risk *APOL1* genotype. We

hypothesized that individuals with *APOL1* high-risk genotypes would have a higher risk of death. We also hypothesized that the high-risk *APOL1* group who received strict BP control would have lower risk of death compared to those who received usual BP control, potentially due to cardiovascular benefits associated with exposure to a lower BP. To perform this study, we extended follow-up of participants previously enrolled in African American Study of Kidney Disease (AASK) trial via linkage to the United States Renal Data System and Social Security Death Index for ascertainment of ESRD and vital status.

Results

APOL1 and risk of death

Baseline characteristics of the 682 AASK participants included for analysis by *APOL1* status are shown in Table 1. In general, *APOL1* high-risk individuals were younger, had higher baseline proteinuria, lower GFR, lower BPs, and lower prevalence of heart disease at enrollment. Comparison of AASK participants included and excluded for analysis (due to missing or inadequate genotype or missing patient health identifiers) are shown in Supplementary Table 1. Participants included for analysis had a slightly higher BMI and GFR at baseline entry compared to participants who were excluded from analyses.

Median follow-up duration starting from time of randomization to death was 14.5 [interquartile range (IQR) 11.4-15.9] years. A total of 276 deaths occurred, including 214 in the low-risk *APOL1* group (3.0 per 100 person-years) and 62 (3.0 per 100 person-years) in the high-risk *APOL1* group. The risk of death in unadjusted (HR= 1.00 [95% CI 0.76-1.33]) and adjusted Cox models (HR= 0.90 [95% CI 0.68-1.21]) was not statistically significantly different when comparing *APOL1* high- versus low-risk genotypes (Figure 2A).

Next, we sought to determine whether *APOL1* status modified the association between BP goal assignment and mortality risk. Baseline characteristics of participants randomized to strict versus usual BP control were generally balanced within *APOL1* strata (Table 2). Overall, there was no difference in risk of death by BP arm assignment (Figure 2B). However, there was a statistically significant interaction between *APOL1* status and BP goal assignment (p=0.03). Thus, we analyzed the risk of death by BP goal assignment separately for *APOL1* low- and high-risk groups. We found a statistically significantly lower risk of death in participants previously assigned to strict (versus usual) BP control (unadjusted HR 0.58 [95% CI 0.35-0.97]) in the high-risk *APOL1* group (Figure 3 and Table 3). In contrast, there did not seem to be a difference in risk of death by BP arm assignment amongst those with the low-risk *APOL1* group (unadjusted HR 1.09 [95% CI 0.84-1.43]) (Figure 3 and Table 3). The beneficial association between strict BP control and lower mortality risk was apparent only after five years post-randomization (Figure 3).

BP arm assignment, CV outcomes, and achieved blood pressures

In analysis aimed at exploring reasons for the differential mortality risk of those who received strict versus usual BP control by *APOL1* status, we examined the risk of cardiovascular outcomes during AASK trial and cohort studies. There were a total of 144 cardiovascular outcomes during median follow-up of 9.2 years. *APOL1* high-risk

participants assigned to strict BP control tended towards a lower risk of cardiovascular events (unadjusted HR 0.86 [95% CI 0.43-1.72]) compared to participants assigned to usual BP control, but this difference was not statistically significant (Table 3).

We next explored whether the lower risk of death in the high-risk *APOL1* group was related to differences in achieved clinic-based mean arterial pressures during the trial. Using linear mixed models with achieved clinic-based mean arterial pressures during the trial as the outcome of interest, we did not find any evidence of interaction between *APOL1* genotype and randomized BP assignment in either unadjusted analysis or adjusted analysis (all p >0.10).

In the subset of participants who had *APOL1* genotype and 24 hour ABPM performed at the start of AASK cohort (N=488, 72%), we did find that in the strict BP arm, the high-risk *APOL1* group had an approximately 6 mm Hg lower mean 24 hour systolic BP compared to those in the low-risk *APOL1* group (130.2 vs. 136.0 mmHg) (Supplementary Table 2) despite assignment to the same clinic-based BP targets during the trial. At the start of the AASK cohort, there was a 10 mm Hg lower ambulatory SBP in the strict versus usual BP group in participants with high-risk *APOL1* genotype (130.2 vs. 140.6 mmHg) (p=0.005), compared to a 4 mm Hg SBP difference in participants with low-risk *APOL1* genotype (136.0 vs. 140.3 mmHg) (p=0.01) (Supplementary Table 2). Similarly, by clinic-measured BPs, the high-risk *APOL1* group had over a 10 mm Hg difference in SBP (127.3 versus 141.8 mm Hg) between the two BP target arms, whereas the low-risk *APOL1* group only had a 5 mm Hg difference in their SBPs (132.5 versus 137.0), which was similar to ABPM-based data.

Discussion

In this study, we extended follow-up of former AASK enrollees with available *APOL1* genotyping to determine long-term mortality risk by *APOL1* status. The rationale for our study was based on prior literature that suggested a higher risk of cardiovascular disease and mortality amongst those with *APOL1* high-risk genotypes, although the association between *APOL1* genotype and mortality risk has not been consistent.[20-23]

In our study, there was no evidence of an association between risk of death and *APOL1* status during long-term follow-up in AASK, although our wide confidence intervals cannot definitively rule out the potential presence of a modest difference in mortality risk. However, our results are consistent with the report from Parsa and colleagues who examined mortality risk prior to ESRD onset in AASK by *APOL1* status.[7] Our study extends this observation by comparing mortality risk between *APOL1* risk groups during long-term follow-up and is strengthened by enhanced power (with a six-fold increase in the number of deaths included for analysis) afforded by our linkage to external databases. Our study results also contrast with the lower risk of mortality seen in patients with high-risk *APOL1* genotype in other recent studies, such as patients treated with dialysis or patients with diabetes.[22, 23]

We did find that, depending on *APOL1* risk status, prior exposure to different BP treatment strategies affected mortality risk differently. In *APOL1* high-risk individuals assigned to

strict BP control, risk of death was 42% lower compared to those assigned to usual BP control. In contrast, BP goal assignment was not associated with a statistically significantly different risk of death in *APOL1* low-risk individuals. We believe our finding of an interaction between BP goal assignment and *APOL1* status as it pertains to mortality risk to be novel and important. Our findings of an association between BP goal assignment and mortality also contrasts with the lack of benefit of strict BP control on renal outcomes previously reported by Parsa and colleagues,[7] and suggest that mortality may be more sensitive than renal outcomes to BP interventions.[25]

The reasons for the protective effect of strict BP control in the *APOL1* high-risk group are unclear. We did note a trend towards a lower risk of CV events in the *APOL1* high-risk group assigned to strict BP control, although this did not achieve statistical significance (p=0.68, Table 3). However, this analysis may have limited power, given the small number of CV events during the trial and cohort phase, and our point estimates have wider confidence intervals. We also explored but did not find any evidence of interaction between *APOL1* genotype and BP goal assignment for achieved clinic BPs during AASK trial. Finally, we examined whether there were any sustained differences in achieved BPs after the end of the trial that could potentially contribute to the differential risk of death in the high-risk *APOL1* group who received strict BP control. During AASK cohort phase of study, we found a 10 mm Hg lower SBP in the high-risk *APOL1* participants assigned to strict compared to usual BP control, versus a 4-5 mm Hg lower SBP in the strict versus usual BP arm in low-risk *APOL1* participants by both clinic and ABPM-measured BPs. Since ABPMs were performed at the start of AASK cohort (8 to 20 months after end of trial intervention), the sustained lower BP levels in the high-risk *APOL1* group targeted previously to strict BP control suggests that this group may have benefited more from a “legacy effect” even after end of the randomized intervention in AASK. This may also provide an explanation for the time lag in the appearance of a beneficial association between BP control and mortality risk in this study (Figure 3). The long-term impact of trial interventions has been demonstrated in other contexts such as tight glycemic control.[27-29]

Overall, our results suggest that *APOL1* risk genotype did not increase risk of death in AASK patients with CKD. Furthermore, BP lowering may be associated with significant mortality benefit in the black CKD population with high-risk *APOL1* genotypes, but not in blacks with the low-risk *APOL1* genotypes during long-term follow-up. We note that the risk of death in participants with the high-risk *APOL1* group assigned to usual BP control was higher than that of participants with low-risk *APOL1* group, regardless of their BP control strategy (Figure 3). This observation would support the importance of BP control in the high-risk *APOL1* group.

We believe AASK to be one of the few trials to date that have delivered and tested a targeted intervention in a large number of participants with *APOL1* genotyping for which there is long-term follow-up. The strength of our study lies in the availability of long-term ascertainment of hard outcomes in original AASK enrollees, including a large number of deaths. Our study is also innovative in its span of follow-up from CKD through ESRD. Few studies have followed persons from CKD through ESRD and assessed the impact of medical interventions during CKD on outcomes after ESRD onset.

Limitations to our study include the availability of genotyping and long-term follow-up data in only 62% of original AASK enrollees. In addition, since consent for DNA testing was obtained after start of the trial, bias may be present, given that participants who dropped out or died prior to the consent process would have been excluded for study. We do not have detailed data on use of medications such as statins which can have large effects on CVD events and survival. We do not have long-term follow-up data beyond the cohort phase on cardiovascular outcomes or cause of death after cohort closure. Our results may not generalize to all of the black CKD population, given that trial participants may not be representative of the general population. Finally, it would be important to validate our findings in other cohorts, as we are unable to replicate our findings in a separate validation cohort, and our results could represent a chance finding.

In conclusion, there was no evidence of an association between *APOL1* genotype with death or CVD in AASK. However, strict BP control appears to associate with lower mortality in black CKD trial participants with high-risk *APOL1* genotype during long-term follow-up. Further studies are needed to confirm and understand this association, and to determine whether there is utility in routine genetic screening for *APOL1* status to provide individualized assessments of the potential risks and benefits of intensive BP lowering.

Methods

African American Study of Kidney Disease (AASK)

AASK was a large 2×3 factorial randomized controlled trial that assessed the effect of strict versus usual BP control and anti-hypertensive agents on the progression of CKD in blacks. Details of the trial design and results have been previously published.[30-32] Between June 1995 and September 2001, 1094 participants between 18-70 years of age with GFR 20-65 mL/min/1.73 m^2 were randomized to either strict (mean arterial pressure (MAP) ≤92 mm Hg) versus usual (MAP<102-107 mm Hg) BP control based on clinic BPs. Participants were also simultaneously randomized to an angiotensin-converting enzyme inhibitor (ramipril), sustained release beta blocker (metoprolol), or calcium channel blocker (amlodipine) in 2:2:1 assignment, respectively.

At trial closure, 691 participants (87% of eligible participants) who had not developed ESRD or died consented to continue in the cohort phase of the study, which began in April 2002 and ended June 2007 (Figure 1).[33-35] All AASK cohort participants were switched as first-line therapy to an ACE inhibitor or angiotensin receptor blocker if ACE inhibitor could not be tolerated. During AASK cohort, all participants received a BP target of <140/90 mm Hg based on results of the AASK trial. The target was subsequently changed in 2004 to < 130/80 mm Hg due to an update in the Joint National Committee guidelines.[34, 36]

Long-term ESRD and death ascertainment

To extend ascertainment of ESRD and vital status through June 30, 2012, we performed linkage of all former AASK trial participants with the United States Renal Data System (USRDS), the national ESRD registry (Figure 1). Institutional review board approval was

obtained for data linkage at all 21 original AASK clinic centers, Cleveland Clinic Data Coordinating Center, and University of California San Francisco.

To ensure uniform ascertainment over the study duration, we defined ESRD as receipt of chronic dialysis or kidney transplant according to the USRDS database. For participants who developed ESRD, death dates after ESRD were obtained from the USRDS database. For patients who did not develop ESRD, death dates were ascertained using AASK trial and cohort data if these deaths occurred prior to June 30, 2007. For AASK trial and cohort participants who were not known to have died or developed ESRD, a search of the Social Security Death Index (SSDI) was undertaken to ascertain deaths. Patients were administratively censored if they were alive as of June 30, 2012, the most recent year of USRDS data available at the time of study performance. The USRDS and SSDI have been validated previously as accurate data sources for ESRD onset and death dates, respectively, and have been used in other studies.[37-42] A total of 98% of former AASK participants (1067 out of total 1094) had patient health identifiers that facilitated linkage to external data sources (USRDS and SSDI) for long-term follow-up.

APOL1 genotyping

During the trial and cohort phase, 836 of the original 1094 participants consented for DNA collection. Of these, 693 participants had adequate quality DNA genotyping for *APOL1* risk variant,[6, 7] of whom 682 had patient health identifiers available for long-term follow-up and are included in the current study (Figure 1). Two mutually exclusive coding variants of the *APOL1* gene, G1 and G2, are known to contribute to renal risk.[5] For this study, individuals with zero or one risk alleles (G1 or G2) were considered low-risk, and individuals with two risk alleles (G1/G1, G2/G2, or G1/G2) were considered high-risk in a recessive model. Details regarding genotyping in AASK participants have been previously described.[7] No differences in individuals who had successful versus failed genotyping were previously noted.[43]

Statistical analysis

Primary analysis – all-cause mortality

We tested for differences between baseline characteristics at time of AASK enrollment in the low- and high-risk *APOL1* groups using Student's t-test, χ^2, or Kruskal-Wallis test as indicated. We assessed the primary outcome of interest, all-cause mortality (including deaths before and after ESRD), using *APOL1* status as the primary predictor in unadjusted Cox models. We subsequently adjusted this model for age at enrollment, sex, glomerular filtration rate (GFR), proteinuria (on logarithmic scale), smoking, and heart disease (based on self-report, chart review, or baseline electrocardiogram reading), all determined at time of randomization.

We then tested formally for the presence of interaction between BP goal assignment and APOL1 status. Because of the presence of an interaction, we determined whether there was a difference in risk of death using BP goal assignment as the primary predictor in separate unadjusted Cox models for low-and high-risk *APOL1* risk group. To preserve the original

randomization scheme, our analyses were conducted in an intention-to-treat fashion amongst the subset of participants included for analysis. This unadjusted Cox model served as our primary analysis. In sensitivity analysis, we adjusted these models for the same baseline factors as described above.

Exploratory analyses

In order to further explore potential reasons for the differential mortality risk by *APOL1* status, we performed multiple additional analyses. First, we examined risk for a composite outcome of first cardiovascular hospitalization (for myocardial infarction, stroke, congestive heart failure, or revascularization event) and cardiovascular death using BP goal assignment as the primary predictor in separate models for *APOL1* low- and high-risk groups. Cardiovascular outcomes were adjudicated during AASK trial and cohort studies, and have been previously described.[33, 44, 45] This analysis was restricted to the trial and cohort phases of AASK study due to the lack of ascertainment of cardiovascular outcomes after end of the cohort (Figure 1), and censors participants at time of ESRD onset (since CVD events and causes of death after ESRD were not captured during AASK trial or cohort studies). We repeated our Cox models to determine the risk of a CV composite outcome in unadjusted and adjusted models, adjusted for the same baseline covariates as described above in our primary analyses.

Second, to explore whether the lower risk of death in the high-risk *APOL1* group was related to differences in achieved clinic-based mean arterial pressures during the trial, we used linear mixed models to assess for the presence of any interaction between BP goal assignment and *APOL1* genotype on achieved MAP values. These analyses were performed in unadjusted and adjusted models.

Finally, we sought to understand the differential mortality risk associated with strict versus usual BP control in participants with differing *APOL1* risk status by examining differences in BPs obtained at time of entry into AASK cohort. At the beginning of the cohort phase, BPs were available by both clinic and 24 hour ambulatory measurements, and hence we separately analyzed differences in BPs by both clinic and ABPM-derived measurements. Details of ambulatory BP monitor (ABPM) performance in AASK have been previously described.[46] Only the first ABPM performed within one year of baseline entry into AASK cohort with sufficient number of readings (at least 14 readings between 6 AM and midnight, and at least 6 readings between midnight and 6 AM) were included for analysis, (Figure 1). Clinic BPs obtained at the closest visit to ABPM performance were used for comparison to ABPM values. Kruskal-Wallis tests were used to test for differences between mean clinic and ABPM-based SBP and DBP values, comparing high- versus low-risk *APOL1* genotype groups in separate analyses for the assigned BP strategy.

Stata 13 was used for the performance of all statistical analyses. P-values <0.05 were considered statistically significant for all analyses, including interaction terms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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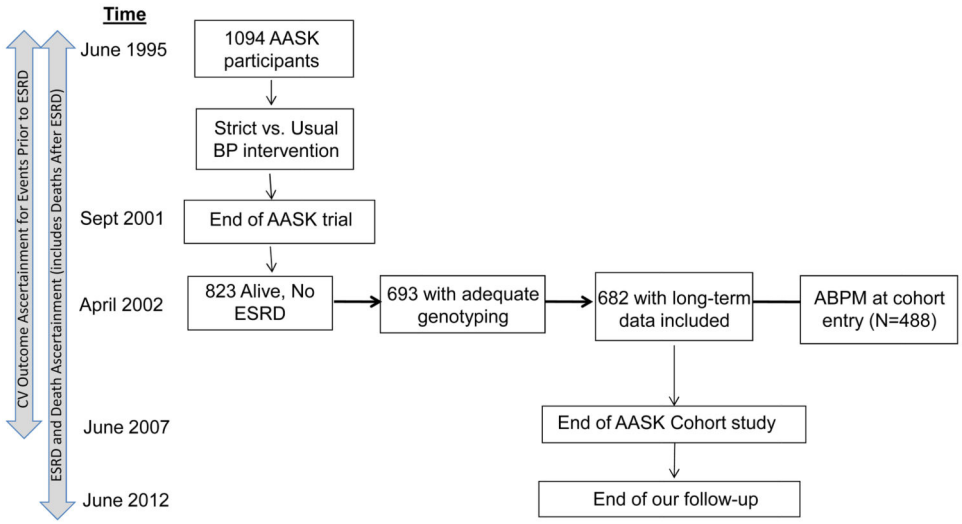

Figure 1.

Derivation of cohort included for study and timeline of events during long-term AASK follow-up.

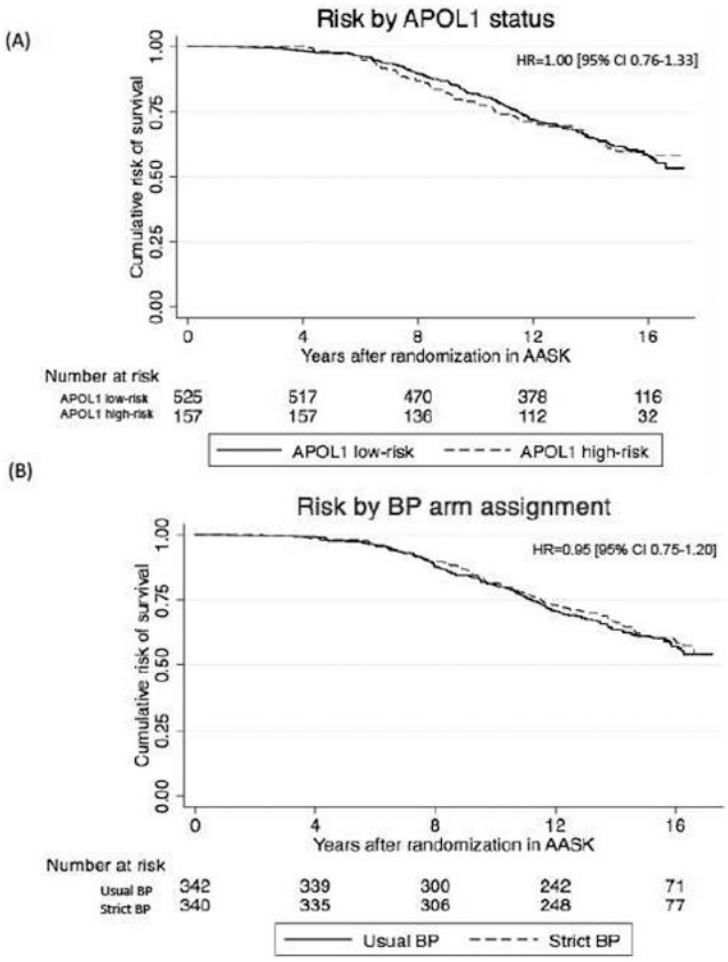

Figure 2.

Risk of death by (a) *APOL1* risk group or (b) BP arm assignment.

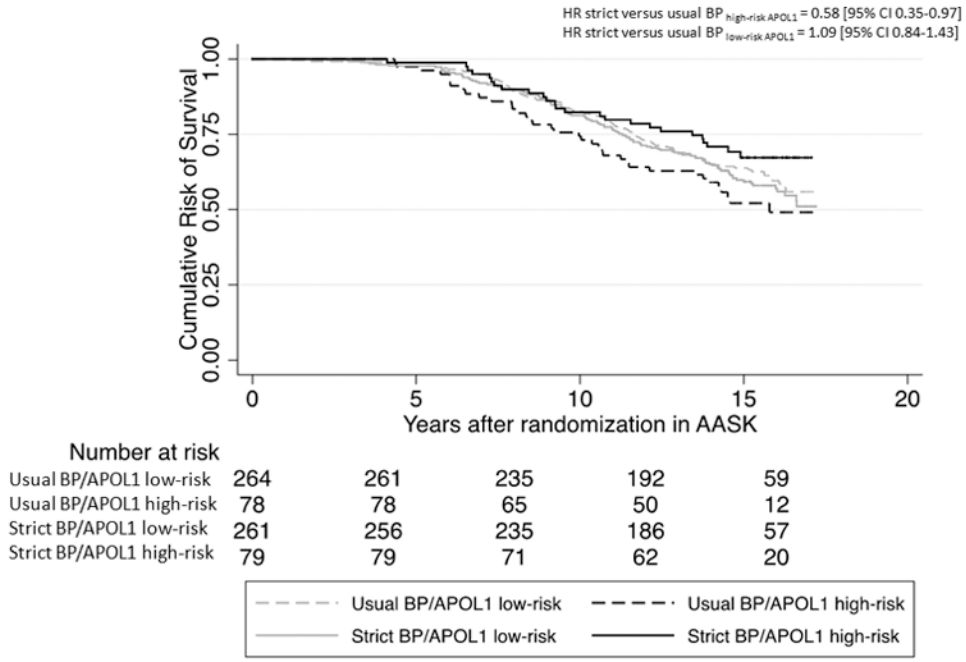

Figure 3.
Risk of death in strict versus usual BP control arms by *APOL1* status.

Table 1

Baseline characteristics of AASK participants included for analysis by *APOL1* risk group.

Characteristic N (%)	High-risk APOL1 (N=157)	Low-risk APOL1 (N=525)	P-value
Mean Age (y) ± SD	51.2 ± 11.8	54.5 ± 10.0	0.003
Men	88 (56.1)	319 (60.8)	0.29
Mean body mass index (kg/m^2) ± SD	31.7 ± 7.2	30.9 ± 6.5	0.30
Mean systolic BP, mm Hg ± SD	146.1 ± 22.0	151.6 ± 24.7	0.01
Mean diastolic BP, mm Hg ± SD	93.6 ± 13.6	96.5 ± 14.9	0.03
Median glomerular filtration rate (mL/min/1.73 m^2) [interquartile range]	44.7 [32.5, 55.5]	51.1 [38.0, 59.0]	<0.001
Median proteinuria (g/d) [interquartile range]	0.25 [0.06-0.89]	0.09 [0.04-0.31]	<0.001
Baseline heart disease	66 (42.0)	279 (53.1)	0.02
Strict BP arm	79 (50.3)	261 (49.7)	0.89
Drug assignment			
Angiotensin-converting enzyme inhibitor	63 (40.1)	218 (41.5)	0.69
Beta-blocker	66 (42.0)	202 (38.5)	
Calcium-channel blocker	28 (17.8)	105 (20.0)	
Current smoker	44 (28.0)	146 (27.8)	0.62

Table 2

Baseline characteristics of AASK participants included for analysis by BP goal assignment.[1]

Characteristic N (%)	***APOL1* high-risk group[2]**		***APOL1* low-risk group[3]**	
	Strict Blood Pressure N=79	**Usual Blood Pressure N=78**	**Strict Blood Pressure N=261**	**Usual Blood Pressure N=264**
Mean Age (y) ± SD	50.6 ± 11.8	51.8 ± 11.8	54.3 ± 10.1	54.7 ± 9.9
Men	41 (51.9%)	47 (60.3%)	166 (63.6%)	153 (58.0%)
Mean body mass index (kg/m^2) ± SD	32.1 ± 7.4	31.3 ± 7.0	30.6 ± 6.6	31.1 ± 6.3
Mean systolic BP, mm Hg ± SD	147.7 ± 23.5	144.6 ± 20.4	152.8 ± 27.0	150.5 ± 22.3
Mean diastolic BP, mm Hg ± SD	94.3 ± 14.3	92.9 ± 12.8	97.8 ± 15.9	95.1 ± 13.6
Median glomerular filtration rate (mL/min/1.73 m^2) [IQR]	44.7 [32.8-57.1]	44.3 [29.5-55.2]	51.1 [38.4-58.1]	51.1 [37.7-59.4]
Median proteinuria (g/d) [interquartile range]	0.27 [0.06, 0.89]	0.25 [0.06,0.89]	0.09 [0.04, 0.29]	0.08 [0.04,0.34]
Baseline heart disease	35 (44.3)	31 (39.7)	147 (56.3)	132 (50.0)
Drug assignment				
Angiotensin-converting enzyme inhibitor	31 (39.2)	32 (41.0)	112 (42.9)	106 (40.2)
Beta blocker	33 (41.8)	33 (42.3)	97 (37.2)	105 (39.8)
Calcium channel blocker	15 (19.0)	13 (16.7)	52 (19.9)	53 (20.1)
Current smoker	26 (32.9)	18 (23.1)	86 (33.0)	60 (22.7)

[1] All values are provided as N (%) unless otherwise specified

[2] All p > 0.05 for comparison of strict versus usual BP control strategies except for smoking (p=0.048)

[3] All p> 0.05 for comparison of strict versus usual BP control strategies except for smoking (p=0.03).

IQR = interquartile range

Table 3

Risk of death in AASK participants comparing strict versus usual BP control strategies by *APOL1* risk group.

Risk of death during long-term follow-up (N=682)					
	***APOL1* low-risk Hazard ratio (95% CI)**	**P-value**	***APOL1* high-risk Hazard ratio (95% CI)**	**P-value**	**Test for interaction[2]**
Unadjusted overall mortality risk comparing strict versus usual BP control	1.09 (0.84-1.43)	0.52	0.58 (0.35-0.97)	0.03	0.03
Adjusted[1] overall mortality risk comparing strict versus usual BP control	0.98 (0.74-1.28)	0.87	0.48 (0.28-0.84)	0.01	0.03
Risk of CV events during AASK trial and cohort (N=682)					
Unadjusted overall risk comparing strict versus usual BP control	1.07 (0.74-1.55)	0.73	0.86 (0.43-1.72)	0.67	0.68
Adjusted[1] overall risk comparing strict versus usual BP control	0.96 (0.66-1.40)	0.83	0.72 (0.34-1.53)	0.40	0.76

[1]Adjusted for age, sex, GFR, logarithmic of proteinuria, smoking status, and heart disease, all determined at time of enrollment.

[2]Compares high- versus low-risk *APOL1* groups.