RESEARCH LETTER

Intensive Blood Pressure Control, *APOL1* Genotype, and Kidney Outcomes in Individuals With Type 2 Diabetes: A Post Hoc Analysis of the Action to Control Cardiovascular Risk in Diabetes-Blood Pressure (ACCORD-BP) Trial

To the Editor:

African ancestry–specific variation in the apolipoprotein L1 gene (*APOL1*) is associated with faster progression of chronic kidney disease (CKD) in Black individuals.[1] While there is preliminary evidence from the African American Study of Kidney Disease and Hypertension Study (AASK) trial that intensive blood pressure (BP) control may improve mortality in Black individuals with *APOL1* high-risk (but not low-risk) genotypes, the AASK trial excluded individuals with diabetes.[2] Whether intensive BP control confers additive kidney benefits in individuals with high-risk genotypes and type 2 diabetes is unknown.[1,3] To test the hypothesis that intensive BP control confers less risk of adverse kidney outcomes by *APOL1* risk status in patients with type 2 diabetes, we performed a retrospective analysis of the Action to Control Cardiovascular Risk in Diabetes-Blood Pressure (ACCORD-BP) trial.

Details of the ACCORD trial were previously published.[4] *APOL1* genotyping was performed on samples from Black ACCORD participants who consented to storage of blood for genetic studies (see supplementary methods in Item S1).[5] High-risk genotypes were defined by presence of 2 copies of *APOL1* risk alleles. Low-risk genotypes were defined by presence of 0-1 *APOL1* risk alleles.

We included 3,289 ACCORD-BP participants (2,777 White, 451 Black *APOL1* low-risk, and 61 Black *APOL1* high-risk participants; see Table S1). We excluded 1,444 participants; details are provided in Item S1. Cox proportional hazards models (primary analysis) were used to test for the hazard of intensive versus standard BP control stratified by *APOL1* risk categories for the kidney outcome (doubling of serum creatinine or estimated glomerular filtration rate (eGFR) decline >20 mL/min/1.73 m^2) as defined by ACCORD.[6] In these models we tested for interaction between BP target and *APOL1* risk categories for the kidney outcome. In secondary analysis, we added glycemic control assignment, age, sex, eGFR, and albuminuria in adjusted models.

During mean follow-up of 4.9 years, the kidney outcome occurred in 53% of low-risk participants, 48% of high-risk participants, and 52% of Whites (Table S2). Overall, intensive (vs standard) BP control was associated with a 69% (95% CI 1.53-1.86) higher hazard of the kidney outcome.

In primary analysis, an interaction was present between intensive BP control and *APOL1* genotype for the kidney outcome (*P* interaction = 0.054). In our primary models stratified by race and *APOL1* risk status, intensive BP control in Whites led to a 77% higher hazard of the kidney outcome (95% CI 1.60-1.97) compared with standard BP control (Table 1). Low-risk Black participants receiving intensive versus standard BP control had a 33% higher hazard of the kidney outcome (95% CI 1.03-1.71). In contrast, for high-risk Black participants, intensive (vs standard) BP control was not statistically significantly associated with the kidney outcome (HR 1.05, 95% CI 0.51-2.18) (Fig 1). Similar findings were noted using adjusted models.

Current guidelines recommend targeting a systolic BP of <140 mm Hg overall but a lower systolic BP target of <130 mm Hg in patients with diabetes and at high risk of cardiovascular disease, though individualization of treatment is recommended.[7] While prior post hoc analyses of the ACCORD trial suggested that targeting a systolic BP <120 mm Hg associates with an increased risk of CKD in patients with type 2 diabetes,[6] we found that Black participants with high-risk *APOL1* genotypes receiving intensive (vs standard) BP control were not at a statistically significantly increased risk of the kidney outcome. This finding in Black participants with high-risk genotypes contrasts with observations in low-risk Black participants and Whites, where we observed a higher risk of the kidney outcome in those receiving intensive BP control. Although findings require confirmation, our data suggest the potential for individualizing BP targets when treating hypertension in patients with diabetes.

It is unclear why intensive BP control increased the risk of eGFR decline in the overall ACCORD-BP population. One hypothesis is that in individuals with type 2 diabetes, intensive (vs standard) BP control may have led to larger hemodynamic shifts with subsequent eGFR decline through mechanisms of impaired glomerular autoregulation (which is thought to particularly affect individuals with diabetic nephropathy).[8]

The strengths of this study include the ability to leverage a trial intervention and its interaction with genetic makeup of individuals to examine a kidney outcome. Our study also has several limitations. There were fewer participants with baseline CKD in the ACCORD trial and many trial participants may have been older and at lower risk for progression of CKD by the time they were enrolled into ACCORD study, so the applicability of these findings to other CKD populations with *APOL1* high-risk genotype and

Table 1. Primary and Adjusted Hazard of Kidney Outcome With Intensive Blood Pressure Control Target Compared to Standard Blood Pressure Target Stratified by Race and *APOL1* Genotype

Group	Primary Model HR (95% CI)	*P*	Adjusted Model HR (95% CI)	*P*
White	1.77 (1.60–1.97)	<0.001	1.81 (1.63–2.02)	<0.001
Black *APOL1* low-risk genotype	1.33 (1.03–1.71)	0.03	1.40 (1.08–1.81)	0.01
Black *APOL1* high-risk genotype	1.05 (0.51–2.18)	0.89	1.00 (0.48–2.07)	0.99

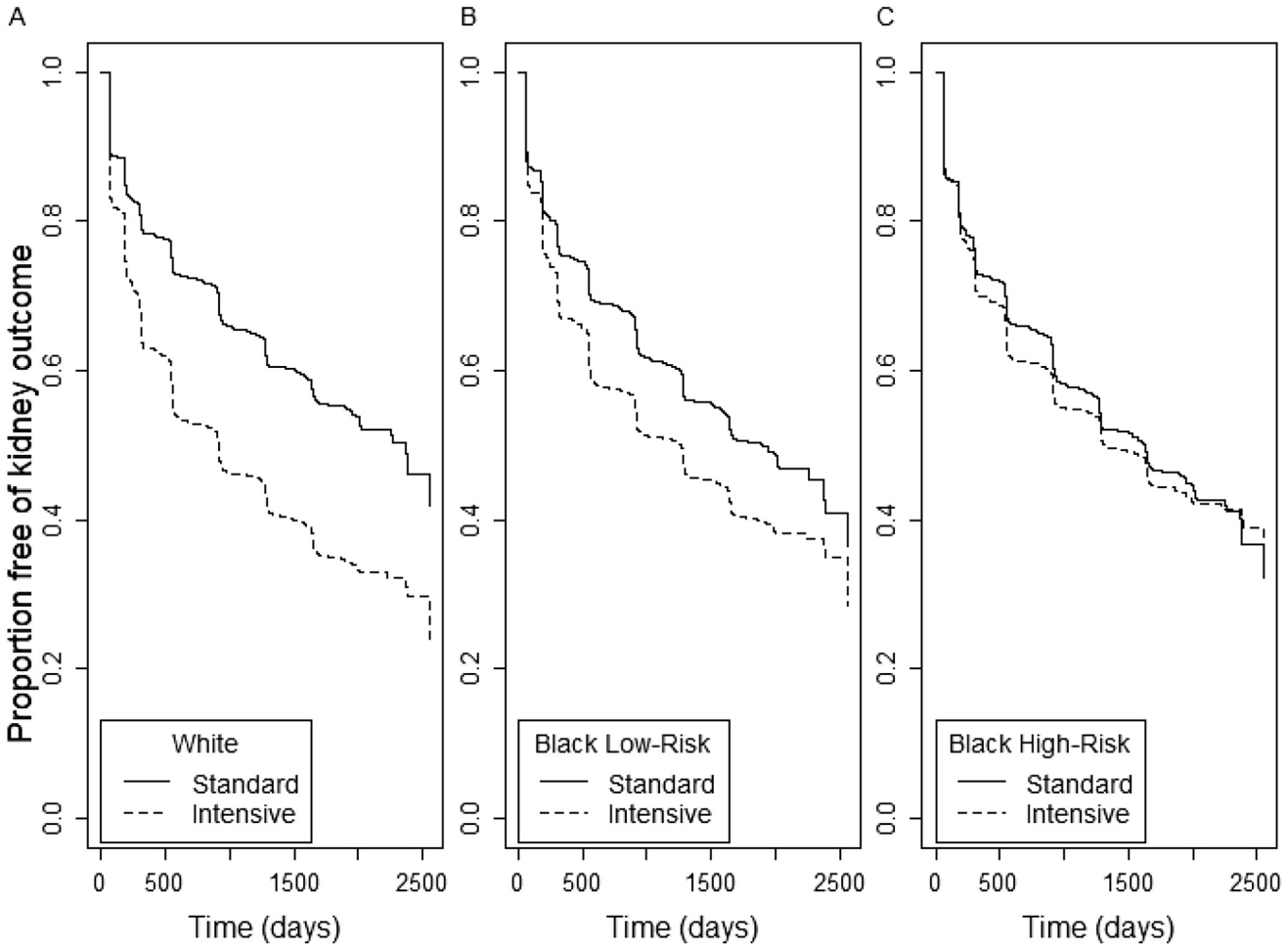

Figure 1. Kaplan-Meier curves for cumulative incidence of kidney function decline by assignment to intensive or standard blood pressure target in (A) White participants, (B) Black *APOL1* low-risk participants, and (C) Black *APOL1* high-risk participants. HR = hazard ratio.

diabetes is unknown. While the percentage of ACCORD participants with 2 *APOL1* risk alleles is representative of the expected prevalence in the general population, the overall number of participants in ACCORD-BP with high-risk *APOL1* genotypes was low. This may have contributed to imprecise estimates and wide confidence intervals. Further studies to understand how to individualize BP targets in patients with type 2 diabetes (potentially with consideration of *APOL1* high-risk genotypes) are needed.

Alex Dinh, MD, Timothy Copeland, PhD, Barry I. Freedman, MD, Charles E. McCulloch, PhD, Elaine Ku, MD, MAS

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Item S1: Detailed Methods

Table S1: Baseline Characteristics by Race and *APOL1* Risk Genotype Group

Table S2: Kidney Outcome Events by Race, APOL1 Genotype, and Blood Pressure Target Assignment

ARTICLE INFORMATION

Authors' Affiliations: Division of Nephrology, Department of Medicine (AD, TC, EK), Department of Epidemiology & Biostatistics (CEM, EK), and Division of Pediatric Nephrology, Department of Pediatrics (EK), University of California, San Francisco, San Francisco, California; and Department of Internal Medicine, Section on Nephrology, Wake Forest School of Medicine, Winston-Salem, North Carolina (BIF).

Address for Correspondence: Alex Dinh, MD, Division of Nephrology, Department of Medicine, University of California, San Francisco, 500 Parnassus Ave, MUW 418, Box 0532, San Francisco, CA 94143. Email: Alex.Dinh@ucsf.edu

Authors' Contributions: Research idea and study design: AD, EK; data acquisition: BIF, EK; data analysis/interpretation: AD, TC, BIF, CEM, EK; statistical analysis: AD, TC; supervision or mentorship: EK, CEM. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Support: This study was supported by K23 HL131023. The funders of this study had no role in the study design, collection, analysis, interpretation of data, writing of the report, or the decision to submit the report for publication.

Financial Disclosure: Wake Forest University Health Sciences and Dr Freedman have rights to a US patent regarding *APOL1* gene testing. Dr Freedman is a consultant for and receives research support from AstraZeneca and RenalytixAI. The remaining authors declare that they have no relevant financial interests.

Disclaimer: This manuscript was prepared using ACCORD research materials obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the ACCORD study or the NHLBI.

Peer Review: Received February 18, 2021. Evaluated by 1 external peer reviewer, with direct editorial input by a Statistical Editor and the Editor-in-Chief. Accepted in revised form April 18, 2021.

REFERENCES

1. Parsa A, Kao WH, Xie D, et al. APOL1 risk variants, race, and progression of chronic kidney disease. *N Engl J Med*. 2013;369(23):2183-2196.
2. Ku E, Lipkowitz MS, Appel LJ, et al. Strict blood pressure control associates with decreased mortality risk by APOL1 genotype. *Kidney Int*. 2017;91(2):443-450.
3. Foster MC, Coresh J, Fornage M, et al. APOL1 variants associate with increased risk of CKD among African Americans. *J Am Soc Nephrol*. 2013;24(9):1484-1491.
4. Group AS, Cushman WC, Evans GW, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362(17):1575-1585.
5. Langefeld CD, Divers J, Pajewski NM, et al. Apolipoprotein L1 gene variants associate with prevalent kidney but not prevalent cardiovascular disease in the Systolic Blood Pressure Intervention Trial. *Kidney Int*. 2015;87(1):169-175.
6. Mottl AK, Buse JB, Ismail-Beigi F, et al. Long-term effects of intensive glycemic and blood pressure control and fenofibrate use on kidney outcomes. *Clin J Am Soc Nephrol*. 2018;13(11):1693-1702.
7. American Diabetes A. 9. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2018. *Diabetes Care*. 2018;41(Suppl 1):S86-S104.
8. Christensen PK, Hansen HP, Parving HH. Impaired autoregulation of GFR in hypertensive non-insulin dependent diabetic patients. *Kidney Int*. 1997;52(5):1369-1374.