Hypertension

KIDNEY

Association of Apparent Treatment-Resistant Hypertension With Differential Risk of End-Stage Kidney Disease Across Racial Groups in the Million Veteran Program

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ABSTRACT: Apparent treatment-resistant hypertension (ATRH) has been linked to end-stage kidney disease (ESKD) and cardiovascular disease. We tested the hypothesis that the effect of ATRH on ESKD is greater in Black patients than in White patients and investigated the effect of ATRH on ESKD independent of *APOL1* genotype. In a retrospective cohort of 139 685 hypertensive veterans (22% Black, 5% women) in the Million Veteran Program, ATRH was defined as failure to achieve outpatient blood pressure <140/90 mmHg with 3 antihypertensives including a thiazide or use of ≥4. Outcomes included incident ESKD, myocardial infarction, and stroke. Poisson models were used to test effect modification by race. Over a median follow-up of 10.3 years (interquartile range, 5.8–11.7), 17 521 incident ATRH cases were observed. Compared with nonresistant hypertension, patients with ATRH had higher incidence rates (per 1000-person-years) of ESKD (4.7 versus 1.6), myocardial infarction (6.7 versus 3.4), and stroke (16.7 versus 8.5). A greater attributable risk of ESKD because of ATRH was observed among Black patients (44.4/1000) compared with White patients (25.5/1000). Black patients with ATRH had a 2.3-fold higher risk of ESKD compared with Black patients with nonresistant hypertension; 3-fold the risk of White patients with ATRH, and 9-fold the risk of White patients with nonresistant hypertension (*P*-interaction<0.001). Among Black patients, ATRH remained associated with a 98% (95% CI, 1.66–2.75) higher risk of ESKD after adjustment for *APOL1* genotype. Patients with ATRH experienced excess ESKD and cardiovascular disease risk. This excess ATRH-related ESKD risk was magnified among Black patients independently of *APOL1* genotype. Targeted treatment of ATRH could curtail ESKD and cardiovascular disease incidence.
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Key words: Treatment-resistant hypertension ■ end-stage kidney disease ■ race ■ apolipoprotein L1 variants ■ stroke ■ myocardial infarction.

Black individuals have a 3-fold higher incidence of end-stage kidney disease (ESKD) compared with White individuals.[1] Hypertension is one of the leading causes of ESKD among Black persons, and it affects over 100 million adults in the United States.[2] Apparent-treatment resistant hypertension (ATRH) is a severe form of hypertension characterized by failure to respond to therapy despite the concurrent use of ≥3 antihypertensive agents of different classes, at maximally tolerated dose, or reaching goal with ≥4.[3] ATRH is

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‡A list of study participants of the VA Million Veteran Program is given in the Data Supplement.

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Novelty and Significance

What Is New?

- In this multiethnic cohort of US veterans with hypertension, the adverse effect of apparent treatment-resistant hypertension on end-stage kidney disease (ESKD) risk was greater among Black patients compared with White patients. Importantly, this effect was independent of *APOL1* genotype.

What Is Relevant?

- Previous studies suggest apparent treatment-resistant hypertension is a strong risk factor for cardiovascular disease and ESKD.
- Whether the impact of apparent-treatment resistant hypertension on the risk of ESKD differs by race and is independent of *APOL1* genotype is not known.

Summary

There was a considerably high population risk of ESKD, myocardial infarction, and stroke that could be attributable to apparent treatment-resistant hypertension. The excess risk of ESKD attributable to apparent treatment-resistant hypertension was greater among Black patients and was independent of *APOL1* genotype. Targeted interventions to treat apparent treatment-resistant hypertension could curtail the incidence of ESKD and adverse cardiovascular outcomes in this high-risk population.

Nonstandard Abbreviations and Acronyms

AASK	African American Study of Kidney Disease and Hypertension
APOL1	Apolipoprotein L1
ACE	angiotensin-converting enzyme
AHD	antihypertensive drug
ALLHAT	Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial
ATRH	apparent treatment-resistant hypertension
CHF	congestive heart failure
CKD	chronic kidney disease
CRIC	Chronic Renal Insufficiency Cohort
eGFR	estimated glomerular filtration rate
ESKD	end-stage kidney disease
MI	myocardial infarction
REGARDS	Reasons for Geographic and Racial Differences in Stroke
SPRINT	Systolic Blood Pressure Intervention Trial
VA	Veterans Affairs

independently associated with an elevated risk of adverse renal[4,5] and cardiovascular outcomes.[6] The estimated prevalence of ATRH varies between 9% and 17% among persons with hypertension, with ATRH being reportedly more common among Black individuals.[7,8] The reasons for the racial differences are unclear, and data regarding variations in ATRH-related outcomes by race are scarce. One likely contributing factor is chronic kidney disease (CKD), which may exacerbate ATRH risk among Black individuals.[9,10] Identifying groups at high risk of renal and cardiovascular end-organ damage could foster targeted approaches to mitigate the adverse effects of ATRH at the population level.

Our primary aim was to investigate the interaction between ATRH and both race and baseline kidney function on the risk of ESKD. Given that apolipoprotein L1 (*APOL1*) risk alleles are key contributors to the elevated risk of ESKD among Black individuals,[11] we also investigated whether any potential excess risk of ESKD conferred by ATRH is independent of *APOL1* risk alleles among Black patients. Our secondary aim was to quantify the risk of ESKD and cardiovascular outcomes (myocardial infarction and stroke) attributable to ATRH, to inform the potential health impact among US Veterans.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Design and Study Population

The Million Veteran Program is a large observational cohort and mega biobank designed to investigate the genetic underpinnings of common conditions among US veterans.[12] Full details of the Million Veteran Program design and methods have been published elsewhere.[12] Briefly, participants were recruited from 63 Veterans Affairs (VA) clinics beginning in 2011. At enrollment, participants provided blood samples for genotyping and biomarker studies and completed baseline questionnaires. Participants also agreed for medical records to be accessed. The study was approved by the VA Central Institutional Review Board and patients signed informed consent.

For the current study, we assembled a retrospective cohort of 139 685 hypertensive veterans, enrolled in the Million Veteran Program who were active users of the VA health care system, between January 1, 2004 and December 31, 2015 (Figure S1 in the Data Supplement). Hypertension was defined as the presence of International Classification of Diseases,

Ninth Revision, Clinical Modification codes for hypertension in the electronic health record and the prescription of antihypertensive medication before cohort entry. Patients entered the cohort on the date of their first available serum creatinine in the electronic health record and were followed up until they experienced an event of interest, died, or were censored on the date of their last VA visit. "Active VA use" was defined as having 2 clinic visits the year before cohort entry or one visit in each of the 2 years before cohort entry. This approach was used to include patients with continuity of care within the VA Healthcare System, thereby mitigating ascertainment bias for patient-level outcomes. Patients who had a prior history of ESKD at baseline or an entry estimated glomerular filtration rate (eGFR) <30 mL/minute per 1.73 m2 were excluded from this cohort.

Ascertainment of ATRH

During the 12-year follow-up period between January 1, 2004 and December 31, 2015, we identified 17 521 patients with ATRH using clinical data defined as: failure to achieve outpatient BP <140/90 mmHg[7] with 3 antihypertensive drugs (AHDs), including a thiazide diuretic, or use of 4 or more AHDs of different classes.[3,13] We excluded BP measurements associated with a pain score >5 or when interfering medications were prescribed. Additionally, patients with documented cocaine use or a history of secondary causes of hypertension at baseline were excluded (Table S1). A multistage algorithm based on pharmacy refill data was used to ascertain ATRH (Methods in the Data Supplement). Briefly, after intensification of patients' antihypertensive regimen with a fourth drug, refill data for all 4 drugs was required to distinguish treatment intensification versus drug switching. For patients on 3 drugs, a maximum BP>140/90 mm Hg within 15 to 180 days after treatment intensification with the third drug was additionally required to rule-in ATRH. For patients who met ATRH criteria based on the use of 4 drugs, the date of change of exposure classification from NRH to ATRH was the date of the refill of the 4 drugs after 3 to 6 months of overlapping days' supply. For patients who met ATRH criteria based on uncontrolled BP on 3 drugs, the date of change of exposure classification was the date the elevated BP (>140/90 mmHg) was documented after treatment intensification with the third drug. Intensification with a third drug also required a refill of the 3 drugs after 3 to 6 months of overlapping days' supply to confirm intensification of treatment. Participants who met the criteria for ATRH before cohort entry were excluded. Individuals with nonresistant hypertension (NRH) were patients who were taking 1 or 2 AHDs, regardless of BP values, or those that were controlled on 3 AHDs. Once participants met the criteria for ATRH and were classified as such, they could not revert back to NRH.

Covariates

Baseline covariates were obtained from within 730 days before cohort entry. Physiological covariates (eg, baseline BP) were the closest to, and before, cohort entry. We defined each comorbid condition at baseline using a combination of clinical, laboratory, and administrative criteria: 2 outpatient codes on 2 different dates or 1 inpatient code (Table S2). The Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) equation was used to calculate eGFR.[14] Information on race and ethnicity were based on a combination of self-report through centralized VA data collection methods or the Observational Medical Outcomes Partnership data (Methods in the Data Supplement).

Outcomes

Incident ESKD, stroke, and myocardial infarction (MI) were ascertained using validated algorithms based on physician administrative diagnostic codes (International Classification of Diseases, Ninth Revision, Clinical Modification/CPT, Table S2). ESKD was defined by a procedure or diagnosis code indicating dialysis, renal transplant, or an eGFR<15 mL/minute per 1.73 m2. Except for renal transplant, a second confirmatory event (dialysis code or eGFR<15 mL/minute per 1.73 m2), at least ≥90 days apart was required to confirm ESKD. Incident MI was defined as a primary discharge diagnosis for fatal or nonfatal acute MI (ICD9-CM 410.x).[15] The positive predictive value for this algorithm was up to 95%.[16] The algorithm for stroke (positive predictive value=97%) included discharge codes for ischemic stroke (433.x1, 434, or 436), intracerebral hemorrhage (431), and subarachnoid hemorrhage (430).[17] Death was ascertained using National Death Index or Observational Medical Outcomes Partnership data.

APOL1 Genotype

APOL1 variants, including rs73885319 and rs60910145, missense mutations in near absolute linkage disequilibrium, which form haplotype G1, and rs71785313 (deletion of p.N388/Y389 amino acids, denoted G2), were directly genotyped on the Affymetrix Axiom Biobank Array chip using DNA extracted from whole blood.[18] Participants were defined as 2 risk allele carriers if they were homozygotes for G1/G1, homozygotes for G2/G2, or compound G1/G2 heterozygotes.

Statistical Analysis

ATRH was modeled as a time-varying exposure with every patient being ATRH-free at baseline. Poisson regression with robust standard errors was used to estimate incidence rates and incidence rate ratios for ATRH versus NRH. Additive interaction between ATRH and race or eGFR categories (eGFR ≥60 versus 30–59.9 mL/minute per 1.73 m2) were tested using the relative excess risk due to interaction, the attributable proportion due to interaction (AP) and the synergy index (S).[19,20] For each outcome of interest, we computed the cumulative incidence, attributable risk, number needed to harm, attributable fraction in the exposed (patients with ATRH) and population attributable fraction.

Kaplan-Meier plots for each outcome were constructed for patients with ATRH and NRH, overall and stratified by race. We further examined the independent associations of ATRH with each outcome using sequential multivariable Cox proportional hazard models. Covariates in model 1 included age, sex, and race. Model 2 further adjusted for baseline eGFR and calendar year of entry. Model 3 added smoking, diabetes, chronic obstructive pulmonary disease, malignancy, coronary artery disease, peripheral artery disease, stroke, body mass index, serum lipids, and statin use. In sensitivity analyses, we further adjusted for (1) systolic and diastolic BP (at baseline and time of ATRH ascertainment) and (2) time from first hypertension code in the

electronic health record to cohort entry, to examine the effect of ATRH beyond nominal BP values or duration of exposure to hypertension. Further sensitivity analyses were performed by excluding ATRH ascertainment occurring within 6 months of cohort entry or incident events occurring within 1 or 2 years of cohort entry. We also performed competing-risks analysis for ESKD, MI, and stroke using Fine and Gray sub-distribution hazard models with death as the competing event.[21]

Among Black patients, we investigated whether the excess risk of ESKD conferred by ATRH was independent of the presence of *APOL1* risk alleles by additionally adjusting for *APOL1* genotype in Cox models already comprising all aforementioned covariates and 10 principal components of ancestry. We also tested for additive interaction between ATRH and *APOL1* genotype using Poisson models. Interaction analyses were restricted to Black patients with 0 or 2 *APOL1* risk alleles since the presence of 1 risk allele does not confer any excess risk of ESKD.

We computed the proportion of missing values for each covariate and examined missingness patterns using hierarchical cluster analysis of variables usually missing together.[22] The observed patterns were suggestive of data being missing at random. Multiple imputation of missing data was performed using Harrell's *aregImpute* algorithm.[22] The algorithm uses different bootstrap resamples for each of the multiple imputations. Details are presented in the Data Supplement. Five imputations were performed, creating 5 complete data sets. The regression models (containing all covariates included in the imputation model) were fitted on each complete data set, and the regression coefficients were averaged over the multiple imputations.

Statistical significance for 2-sided *P* was set at 0.05. All analyses were performed using Stata v15.1 and R v3.2 in the VA informatics and computing environment.

RESULTS

Patient Characteristics

Among the 139 685 hypertensive patients included in this study, 22% were Black; and 5% were women. The median (interquartile range) age at baseline was 60 (54–67) years. Compared with patients with NRH, patients who developed ATRH (n=17 521 [12.5%]) during follow-up were more likely to be male and Black. Incident ATRH patients also had a higher baseline systolic BP and body mass index as well as a higher prevalence of cardiometabolic comorbidities at baseline (Table 1). Black patients were younger, more likely to be female, and had higher systolic BP, eGFR and higher baseline prevalence of stroke and diabetes. Conversely, they had lower baseline prevalence of coronary artery disease and peripheral artery disease (Table S3 in the Data Supplement). Among patients who developed ATRH, the median number of AHDs at the time of incident ATRH was similar by race. The top 4 AHDs used by patients at the time of ATRH ascertainment were thiazides (100%), RAAS inhibitors (88.7%), β-blockers (67.8%), and calcium-channel blockers (59.4%; Table S4).

Table 1. Baseline Characteristics of Veterans in the MVP with Nonresistant Hypertension and Those Who Developed Apparent Treatment-Resistant Hypertension During Follow-Up From 2004 to 2015

Baseline characteristics*	Nonresistant HTN, n=122 164	Apparent treatment-resistant HTN, n=17 521
Age, y; IQR	60 (54–67)	59 (55–66)
Women, %	5.1	3.9
Hispanic, %	4.4	4.8
Race, %		
Non-Hispanic Whites	75.0	70.3
Non-Hispanic Blacks	21.9	26.6
Others†	3.1	3.08
Body mass index, kg/m^2 (IQR)	30.2 (27.0–34.1)	31.0 (27.7–35.0)
Systolic BP, mm Hg (IQR)	136 (125–147)	140 (130–154)
Diastolic BP, mm Hg (IQR)	79 (71–87)	80 (72–89)
eGFR, mL/min per 1.73 m2 (IQR)	79.2 (65.8–93.1)	79.0 (65.2–93.0)
Serum lipids, mg/dL		
Total cholesterol	182 (157–209)	180 (157–208)
HDL cholesterol	41 (35–50)	40 (34–49)
LDL cholesterol	107 (86–131)	105 (85–129)
Triglycerides	137 (93–205)	145 (98–218)
Smoking history, %		
Never	24.6	22.7
Former	51.4	53.9
Current	24.1	23.4
Comorbidities, %		
Diabetes	28.1	38.4
Cerebrovascular disease	3.3	4.0
Coronary artery disease	28.2	29.5
Peripheral artery disease	5.7	7.0
COPD	11.8	12.0
All malignancies	9.5	9.7
Anti-hypertensive drugs‡, %		
ACE-inhibitors/ARBs	61.4	68.4
Beta blockers	37.5	42.4
Alpha blockers	14.8	15.9
Calcium channel blockers	26.7	35.1
Thiazide diuretics	31.9	44.1
Loop diuretics	7.5	6.6
Potassium-sparing diuretics	6.9	6.4
Vasodilators	0.7	0.9
Number of AHDs at cohort entry (IQR)	2 (1–2)	2 (1–3)

ACE indicates angiotensin-converting enzyme; AHD, antihypertensive drugs; ARB, angiotensin II receptor blocker; ATRH, apparent treatment resistant hypertension; BP, blood pressure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; and HTN, Hypertension.

*Most between-group comparisons were statistically significant ($P<0.01$ for all other baseline variables) except for age, ethnicity, baseline eGFR, COPD, and malignancy.

†Others: Asian, Pacific Islanders/Hawaiian, Native American, and unspecified.

‡Tabulated values for medication usage (and other variables) represent baseline values (at or before cohort entry) not time of ATRH ascertainment. At the time of ATRH ascertainment, 100% of ATRH participants were on ≥3 drugs including a Thiazide (Table S1 in the Data Supplement).

Population Health Impact of ATRH on ESKD, MI, Stroke, and All-Cause Mortality

Over 12 years of follow-up, the cumulative incidence of ESKD, MI, and stroke were 2.5%, 4.7%, and 10.8% respectively. Median follow-up time for the primary outcome (ESKD) was 10.3 years (interquartile range, 5.8–11.7). Compared with patients with NRH, those with ATRH had higher incidence rates of ESKD (4.7 versus 1.6/1000 person-years), MI (6.7 versus 3.4),and stroke (16.7 versus 8.5; Table S5). The population attributable fraction of ESKD, MI, and stroke due to ATRH was 12.8, 6.8, and 7.6%, respectively (Table S6). The numbers needed-to-harm for the aforementioned outcomes were 32, 25, and 8, respectively. In stratified analyses, a greater attributable risk of ESKD due to ATRH was observed among Black patients (44.4 per 1000) compared with White patients (25.5 per 1000; Table S7).

Multivariable Models for Primary and Secondary Outcomes

In fully adjusted Cox models, ATRH was associated with a 1.85 (95% CI, 1.67–2.04), 1.65 (95% CI, 1.52–1.78), and 1.81 (95% CI, 1.72–1.91) higher risk of incident ESKD, MI and stroke respectively, compared with patients with NRH (Figure 1). Further adjustment for systolic and diastolic BP (at baseline and time of ATRH) or duration of hypertension resulted in some attenuation of the hazard ratios (Table S8). Estimates from competing-risks analyses were similar to those obtained from the Cox models, (Table S9) minimizing concerns about informative censoring by death.

Race-Stratified Incidence of ESKD and Effect Modification by Race

In race-stratified nonparametric survival analysis, Black patients with ATRH had the highest probability of incident ESKD ([8.4% [95% CI, 7.4–9.5]) compared with Black patients with NRH (4.2% [95% CI, 3.9–4.5]), White patients with ATRH (4.1% [95% CI, 3.7–4.6]), and White patients with NRH (1.6% [95% CI, 1.5–1.7]; Figure S2). Similar patterns were observed for eGFR-adjusted incidence rates of ESKD (Table 2). Figure 2A shows the excess incidence of ESKD due to the interaction between ATRH and race. In Poisson models, Black patients with ATRH had a 2.3-fold (95% CI, 1.96–2.59) higher risk of ESKD compared with Black patients with NRH; 3-fold (95% CI, 2.53–3.53) the risk of White patients with ATRH, and 9-fold (95% CI, 7.88–10.38) the risk of White patients with NRH (*P*-interaction <0.001). Compared with the common referent group (White patients with NRH), the eGFR-adjusted incidence rate ratios were 3-fold higher in White patients with ATRH, 4-fold higher in Black patients with NRH and over 9-fold higher in Black patients with ATRH (Table 2). The relative excess risk due to interaction was 3.00 (95% CI, 1.79–4.21, *P*-interaction <0.001). Up to 33.2% (95% CI, 23.6–42.7) of the risk of ESKD among Black patients with ATRH was attributable to the interaction between Black race and ATRH (Figure 2B; Table 2). The additive interaction patterns remained consistent in fully adjusted Poisson models (Figure S4). Interactions patterns for stroke were modest, and there were none for incident MI (Tables S10 and S11).

Effect Modification by Baseline Kidney Function

Patients with reduced baseline eGFR (30–59.9 mL/minute per 1.73 m2) and ATRH had a 2.3-fold (95% CI, 2.01–2.60) higher risk of ESKD compared with patients reduced eGFR and NRH, a 4-fold (95% CI, 3.39–4.66) higher risk compared with patients with preserved eGFR (>60 mL/minute per 1.73 m2) and ATRH, and a 13.5-fold (95% CI, 11.87–15.43) higher risk compared with patients with preserved eGFR and NRH (*P*-interaction <0.001; Table 2). The test for additive interaction remained significant in fully adjusted models.

Independent Effects of ATRH and *APOL1* Genotype on Incident ESKD Among Black patients

Among Black patients with ATRH and NRH, we observed similar prevalence of 0 (42.2% versus 41.2%), 1 (45.9% versus 46.1%), and 2 (11.9% versus 12.7%) *APOL1* risk allele carriers (Table S12). Compared with Black patients with no *APOL1* risk alleles, those with 2 *APOL1* risk alleles showed no significant difference in the odds of developing ATRH (odds ratio, 0.92 [95% CI, 0.81–1.02]). ATRH was associated with a 97% (incidence rate ratio, 1.97 [95% CI, 1.65–2.34]) higher risk of incident ESKD in models adjusted for demographics and clinical variables. Further adjustment for *APOL1* genotype showed no attenuation of the effect estimates (incidence rate ratio, 1.98 [95% CI, 1.66–2.35]; Tables 3 and 4). In addition, among patients with no *APOL1* risk alleles, ATRH was associated with an adjusted 2.44-fold (95% CI, 1.74–3.14) higher risk of incident ESKD (Tables 3 and 4). There was no evidence of additive interaction between ATRH and *APOL1* genotype for the association with ESKD (Tables 3 and 4).

DISCUSSION

In a large multiethnic cohort of US veterans with hypertension, we found that the adverse effect of incident ATRH on ESKD incidence was greater among Black patients compared with White patients. Importantly, this effect was independent of *APOL1* risk alleles. Furthermore, the population risk of ESKD, MI, and stroke that was attributable to ATRH alone was substantial, highlighting the major health implications for the affected population. Additionally,

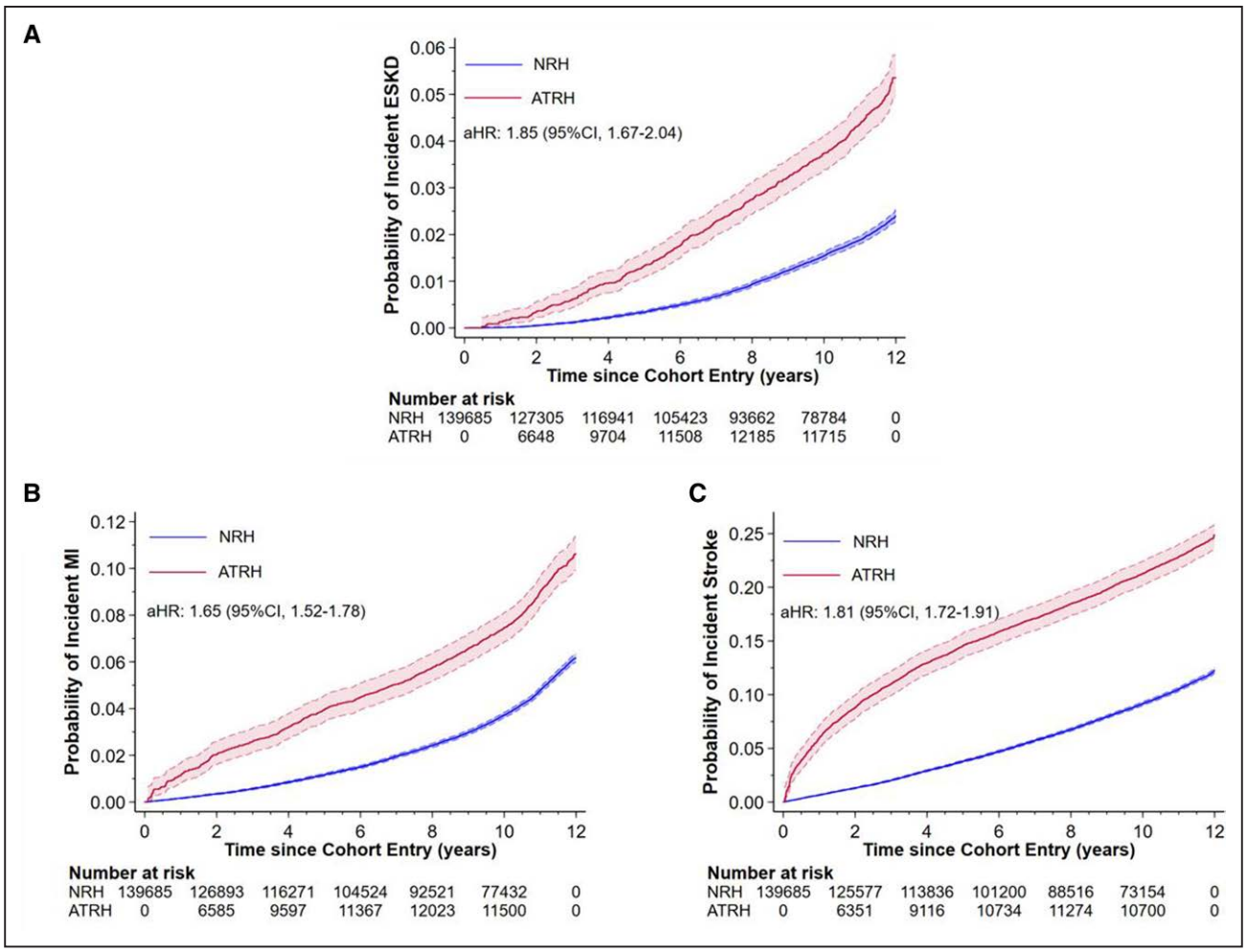

Figure 1. Effect of apparent treatment resistant hypertension (ATRH) on the risk of incident end-stage kidney disease (ESKD), myocardial infarction (MI), and stroke among hypertensive Veterans in the Million Veteran Program.
After full adjustment for baseline covariates, compared with nonresistant hypertension (NRH), ATRH was associated with an 85%, 65%, and 81% higher risk of incident ESKD, MI, and stroke, respectively.

reduced kidney function potentiated the ATRH effect on the risk of ESKD.

Apparent-treatment resistant hypertension is found in 10% to 20% of treated hypertensive patients and is an established risk factor for adverse renal and cardiovascular outcomes.[23,24] We found an appreciably high population risk of incident MI, stroke, and ESKD attributable to ATRH with correspondingly small numbers-needed-to harm (ranging from 8 for stroke to 32 for ESKD), which underscores the enormous population health relevance of ATRH and our findings. Importantly, our findings also suggest an early spike in the risk of incident stroke among persons with ATRH that may be related to extreme values of systolic BP observed among some patients in this group underscoring the importance of stringent BP control to curb the risk of adverse cerebrovascular events.

Prior studies—including REGARDS (Reasons for Geographic and Racial Differences in Stroke), ALLHAT (Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial), MASTERPLAN (Multifactorial Approach and Superior Treatment Efficacy in Renal Patients With the Aid of Nurse Practitioners) and others—have reported increased risk of ESKD in patients with ATRH.[4,5,25] The current study further extends these findings reporting an excess incidence of ESKD in Black patients compared with patients among patients with ATRH—which is synonymous with a synergistic interaction between race and ATRH in the association with ESKD. In this study, we chose to assess the interaction of ATRH and race on the additive scale as this is more indicative of an underlying mechanistic interaction[26–28] and provides a more useful framework to assess the potential public health benefit of an intervention (to mitigate the effect of a causal factor) across different populations, including racial groups.[20,26,27] These observed racial disparities in the consequences of ATRH on ESKD incidence underscore the need for further research into the underlying factors that explain these findings and need for novel therapeutics to mitigate the effect of this risk factor among Black patients. While our

Table 2. Additive Interaction Between Apparent Treatment-Resistant Hypertension and Both Race and eGFR for the Association With Incident ESKD Among Hypertensive Veterans in the Million Veteran Program

Interaction with race (*P*-interaction <0.001)				
Parameters/models	**White patients with no ATRH (n=86 959)**	**White patients with ATRH (n=11 621)**	**Black patients with no ATRH (n=26 362)**	**Black patients with ATRH (n=4588)**
Incident ESKD cases	1049	309	864	251
PY	958 674	87 690	289 066	33 689
Incidence rate*/1000 PY (95% CI)	0.63 (0.58–0.68)	1.90 (1.69–2.14)	2.53 (2.35–2.72)	5.69 (5.01–6.47)
Incidence rate ratio* (95% CI)	1.00 (ref)	3.02 (2.66–3.43)	4.02 (3.67–4.40)	9.05 (7.88–10.38)
Hazard ratios (95% CI)				
Model 1	1.00 (ref)	2.56 (2.25–2.91)	2.65 (2.42–2.91)	5.17 (4.49–5.94)
Model 2	1.00 (ref)	2.27 (2.00–2.58)	2.77 (2.52–3.04)	5.31 (4.26–6.11)
Model 3	1.00 (ref)	1.98 (1.72–2.28)	2.64 (2.37–2.94)	4.68 (4.01–5.46)
Interaction with eGFR (*P*-interaction <0.001)				
Parameters/models	Patients with eGFR ≥60 and No ATRH (n=102 526)	Patients with eGFR ≥60 and ATRH (n=14 507)	Patients with eGFR <60 but no ATRH (n=19 638)	Patients with eGFR <60 and ATRH (n=3014)
Incident ESKD cases	1004	325	1134	288
PY	1 128 157	107 304	215 177	23 906
Incidence rate*/1000 PY (95% CI)	0.89 (0.84–0.95)	3.03 (2.72–3.38)	5.27 (4.97–5.59)	12.05 (10.73–13.52)
Incidence rate ratio (95% CI)	1.00 (ref)	3.40 (3.00–3.86)	5.92 (5.43–6.45)	13.54 (11.87–15.4)
Hazard ratios (95% CI)				
Model 1	1.00 (ref)	2.55 (2.25–2.89)	10.20 (9.31–11.57)	17.22 (15.04–19.70)
Model 2	1.00 (ref)	2.54 (2.24–2.88)	10.22 (9.33–11.19)	17.23 (15.06–19.72)
Model 3	1.00 (ref)	2.33 (2.03–2.68)	9.99 (9.03–11.05)	14.63 (12.60–16.98)

Model 1: adjusted for age, sex and race (omitted when testing the interaction with race but included for models testing eGFR interaction). Model 2: adjusted for age (restricted cubic splines with 4 knots), sex, race, calendar year of cohort entry and baseline eGFR (omitted when testing the interaction with eGFR but included for models testing interaction with race). Model 3: Model 2+smoking+BMI (restricted cubic splines with 4 knots)+serum lipids (total cholesterol, triglycerides, LDL cholesterol and HDL cholesterol)+history of cancer, COPD, diabetes, CAD, PAD, and stroke. ATRH indicates apparent treatment resistant hypertension; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAD, peripheral artery disease; and PY, person-years.

*Incidence rates are adjusted for baseline eGFR (adjusted to the mean baseline eGFR: 80.4 mL/min per 1.73 m^2).

†Overall Incidence rates of ESKD among (1) patients with eGFR ≥60=1.08 (1.02–1.13) per 1000 PY and (2) patients with eGFR<60=5.95 (5.64–6.27) per 1000 PY.

findings emphasize a greater severity of ATRH among Black patients compared with White patients with respect to ESKD risk, the observed adverse effect of ATRH on kidney function remained significant after adjustment for blood pressure at time of ATRH diagnosis. Therefore, an approach emphasizing more intensive BP control may be less efficacious in the reduction of ESKD risk among hypertensive patients with reduced and preserved kidney function hence more specific interventions may be required. This interpretation is corroborated by the findings of the landmark SPRINT (Systolic Blood Pressure Intervention Trial)[29] and the AASK (African American Study of Kidney Disease and Hypertension) Trial.[30] In AASK, 1094 Black patients with hypertensive CKD were randomized to either intensive BP-control (mean BP≈130/81) or standard BP-control (mean BP≈141/86) and followed up for 4.6 years during the trial phase and up to 12 years during the cohort phase. In both phases, there was no significant between-group difference in the risk of the primary kidney outcome (doubling of serum creatinine, incident ESKD, or death).[31] However, Wright et al[30] found that ramipril did portend a greater benefit on the composite kidney outcome than metoprolol and amlodipine suggesting ACE (angiotensin-converting enzyme) inhibitors may be first-line treatment for patients with hypertensive CKD. Perhaps, for ATRH as well, more appropriate drug choices would help to mitigate adverse kidney outcomes. Recently, several studies have shown that mineralocorticoid excess or subclinical hyperaldosteronism seems to be involved as a common pathophysiological mechanism underlying ATRH.[32] Spironolactone has been shown to be effective and safe in Black patients[33] and patients with CKD.[34] Meanwhile, <5% of patients with ATRH in our study were on a mineralocorticoid inhibitor. Studies elucidating the molecular mechanisms involved in these physiological pathways, including among Black patients, as well as research into novel therapeutic targets would be pertinent.

ESKD risk has been shown to cluster in families and to be partially mediated by the presence of *APOL1* risk variants in Black individuals.[11,35] Using data from the AASK and CRIC (Chronic Renal Insufficiency Cohort) studies, Parsa et al[11] found that Black

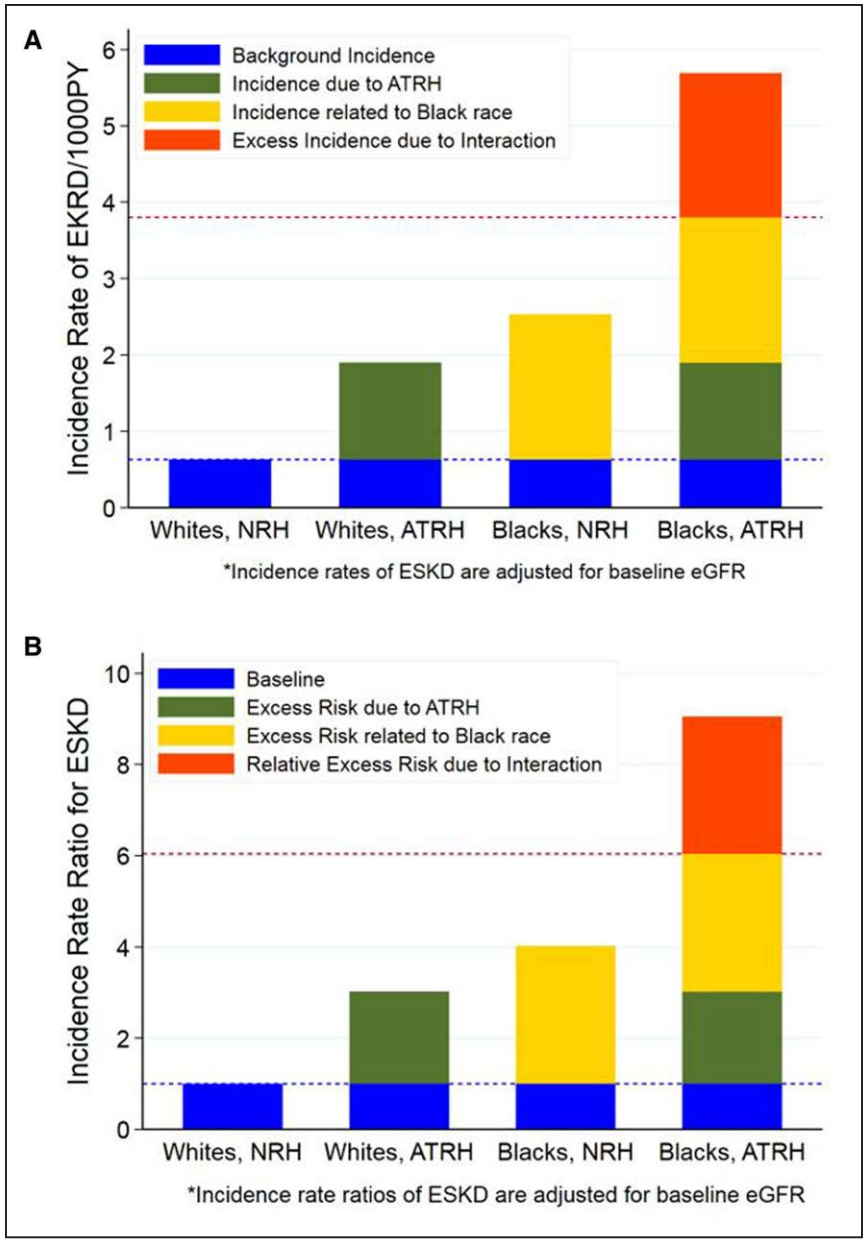

Figure 2. A, Excess incidence of incident end-stage kidney disease (ESKD) because of interaction between apparent treatment resistant hypertension (ATRH) and race. In the absence of interaction, the expected incidence rate (per 1000 person-years [PY]) among Black patients with ATRH would be the sum of the background incidence (0.63), incidence due to ATRH alone (1.27), and incidence related to black race (1.90). However, the observed incidence (5.69) was greater than the expected (3.80); which is suggestive of synergistic additive interaction between ATRH and black race for the association with incident ESKD. The excess incidence due to interaction (dark orange bar) represents an excess of 189 incident ESKD cases per 100 000 PY among Black patients with ATRH. **B**, Relative excess risk of incident ESKD because of interaction between ATRH and race. The *y* axis represents the incidence rate ratio (IRR) for ESKD comparing White patients with ATRH, Black patients with nonresistant hypertension (NRH), Black patients with ATRH to the referent group (White patients with NRH). The relative excess risk due to interaction (RERI) between ATRH and race=$IRR_{11}-IRR_{10}-IRR_{01}+1$=3.00 (95% CI, 1.79–4.21) and is represented by the dark orange bar as in **A**. The attributable proportion (AP)=RERI/IRR_{11}=33.2 (95% CI, 23.6–42.7) suggesting that 33.2% of the risk of incident ESKD among Black patients with ATRH is due to the synergistic interaction between ATRH and race.

patients in the *APOL1* high-risk group (2 *APOL1* risk variants) had higher rates of ESKD and CKD progression (50% decline in eGFR or doubling of serum creatinine) compared with Black patients in the *APOL1* low-risk group (0 or 1 *APOL1* risk variant) and White patients. In the current study, we found that while both ATRH and *APOL1* high risk genotype were significant predictors of ESKD, the ATRH effect on ESKD incidence was independent of *APOL1* genotype. Whether the greater ATRH-related ESKD risk observed among Black patients compared with White patients is due to other genetic variants or environmental factors needs to be investigated further. If the genetic underpinnings underlying the occurrence of ATRH differ across racial groups, then perhaps these differential molecular mechanisms may also produce differential effects on renal outcomes. Furthermore, differential patterns of genotype-by-environment interactions among racial groups could be involved. In addition, differences in socioeconomic status (known to associate with racial disparities in ESKD incidence)[36]; and potential differential efficacy of antihypertension medication across racial groups could also play a role.

Previous studies—including the Jackson Heart Study, CRIC, MASTERPLAN study and others—have reported an increased risk of ATRH in populations with CKD.[9,10,25] In our study, we emphasize the joint effect of reduced kidney function and ATRH on ESKD incidence compared with the effect of each exposure taken singly. We observed a 13.5-fold higher risk of incident ESKD in the group with both exposures (eGFR=30–59.9 and ATRH), which was greater than the sum of each individual effect suggesting a synergistic additive interaction between lower eGFR and ATRH on the risk of incident ESKD.

Table 3. Effect of ATRH and *APOL1* Risk Alleles on Incident ESKD Among Black patients With Hypertension

Risk categories	IR* per 1000 PY (95% CI)	IRR model 1a* (95% CI)	IRR model 2a† (95% CI)
2 *APOL1* risk alleles, ATRH	9.99 (6.76 to 13.23)	5.25 (3.41 to 7.08)	3.18 (1.83 to 4.53)
2 *APOL1* risk alleles, NRH	4.80 (4.11 to 5.50)	2.53 (2.03 to 3.00)	2.00 (1.55 to 2.44)
0 *APOL1* risk alleles, ATRH	7.05 (5.60 to 8.50)	3.71 (2.81 to 4.59)	2.44 (1.74 to 3.14)
0 *APOL1* risk alleles, NRH	1.90 (1.67 to 2.14)	1.00 (ref)	1.00 (ref)
P value for additive interaction=0.63			
Relative excess risk due to interaction, RERI (95% CI)=$IRR_{11}-IRR_{10}-IRR_{01}+1$=−0.26 (−1.69 to 1.18).			
Attributable proportion due to interaction, AP (95% CI)=$RERI/IRR_{11}$=0.0 (−0.56 to 0.40).			

ATRH indicates apparent treatment resistant hypertension; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HDL, high-density lipoprotein; IR, incidence rate; IRR, incidence rate ratio; LDL, low-density lipoprotein; NRH, nonresistant hypertension; PAD, peripheral artery disease; PY, person-years; and RERI, relative excess risk due to interaction.

*IRs were adjusted for age, sex, and 10 PCs. IRRs in model 1a are adjusted for age (restricted cubic splines with 4 knots), sex (M/F), and 10 PCs.

†Model 2a includes model 1a+baseline eGFR (restricted cubic splines with 4 knots), calendar year of cohort entry (4 categories of 3 consecutive years), smoking (never, former, current), BMI (restricted cubic splines with 4 knots), serum lipids (total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol; all restricted cubic splines with 4 knots), history of cancer, COPD, diabetes, CAD, PAD, and stroke (all yes/no).

This suggests that while better management of blood pressure is beneficial in patients with ATRH with both preserved and reduced kidney function, a significantly greater number of incident ESKD cases could potentially be prevented by optimal and targeted interventions of ATRH among patients with reduced kidney function. The 2017 American College of Cardiology/American Heart Association clinical practice guidelines for the prevention, detection, evaluation, and management of high blood pressure suggested a lower target of <130/80 mmHg for all patients with CKD given that most patients with CKD die from cardiovascular complications.[13] This lower target was supported by the overwhelming evidence of cardiovascular benefit in the intensive SBP lowering arm, SBP<120 mm Hg (versus the routine management arm, SBP<140 mm Hg) of the SPRINT trial—25% reduction in the risk of the primary cardiovascular outcome comprising MI, acute coronary syndrome, stroke, congestive heart failure (CHF), and cardiovascular death.[37]

Table 4. Effect of ATRH on Incident ESKD Among Black patients With HTN in Models Adjusted for *APOL1* Risk Alleles

Parameters/models	Nonresistant HTN	Apparent treatment-resistant HTN
Incident ESKD cases	675	199
Hazard ratios (95% CI)		
Model 1b	1.00 (ref)	2.27 (1.92–2.64)
Model 2b	1.00 (ref)	1.97 (1.65–2.34)
Model 3b	1.00 (ref)	1.98 (1.66–2.35)

Model 1b: adjusted for age (restricted cubic splines with 4 knots), sex (M/F), 10 principal components of ancestry (PCs), baseline eGFR (restricted cubic splines with 4 knots) and calendar year of cohort entry (4 categories of 3 consecutive years). Model 2b includes model 1b+smoking (never, former, current)+BMI (restricted cubic splines with 4 knots)+serum lipids (total cholesterol, triglycerides, LDL cholesterol and HDL cholesterol; all restricted cubic splines with 4 knots)+history of cancer, COPD, diabetes, CAD, PAD and stroke (all yes/no). Model 3b includes model 2b+APOL1 risk alleles (2 dummy variables for patients with 1 and 2 risk alleles; with the no risk allele group as the referent). APOL1 indicates apolipoprotein L1; ATRH, apparent treatment-resistant hypertension; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; and PAD, peripheral artery disease.

Our study has several limitations. Our cohort included predominantly male veterans, and findings should be generalized to other populations with caution. As with any observational study that relies on administrative/physician diagnostic codes for exposure and outcome ascertainment, there is the risk of potential misclassification. The potential for survival bias is acknowledged. That said, we controlled for several known predictors of survival in the VA population including history of any malignancy, chronic obstructive pulmonary disease, coronary artery disease, stroke, and diabetes to mitigate this bias. We used antihypertensive medication refill data (which was similar across racial groups) as a proxy for medication adherence (Figure S4). This may obscure cases of pseudoresistance and result in some misclassification of ATRH. However, this approach is virtually free of recall bias and has good concordance with self-reported medication use.[38] Some patients with CHF who were classified as ATRH because they were taking 4 antihypertensive drugs may actually have been misclassified. Given the overlap between treatment for CHF and hypertension, even when a drug is prescribed for CHF as the primary indication, it may treat coexisting hypertension. It may be infeasible to parse these with 100% accuracy, so some degree of misclassification is unavoidable in some patients with CHF. The main findings remain similar after excluding patients with concurrent CHF from the ATRH subgroup in sensitivity analyses (data not shown). We also acknowledge the potential for ascertainment bias for nonfatal outcomes in the ATRH group as these patients may have had greater interaction with the VA health care system, which could in turn increase the

likelihood of documenting data for nonfatal outcomes in their electronic health record. Another limitation is the potential for residual confounding related to not adjusting for individual socioeconomic status and insurance coverage, which are data we did not have access at the time of these analyses.

There are several strengths to our study. The large size and multiethnic nature of our cohort with over 20% Black representation ensured that we had sufficient power for our interaction analyses. Our ATRH definition was constructed using pharmacy files that documented initiation of a third or fourth drug, drug classes and refill data, to accurately define treatment intensification and not switching of AHDs. Among patients with incident ATRH, a long median follow-up time of 7.0 (interquartile range, 4.1–9.7) years post-ATRH strengthened the validity of our findings. We performed several sensitivity analyses including additional adjustment for BP and hypertension duration, interaction analyses with *APOL1* genotype and competing-risks regression, which were consistent with the primary results, supporting the robustness of the study findings.

In conclusion, ATRH was associated with an elevated risk of adverse kidney and cardiovascular outcomes. Population attributable risks of kidney and cardiovascular outcomes related to ATRH were considerable. The effect of ATRH on incident ESKD was magnified among patients with reduced kidney function as well as Black patients, independently of *APOL1* genotype.

PERSPECTIVES

The substantial population risk of ESKD and cardiovascular outcomes attributable to ATRH observed in this study underscores the enormous population health relevance of ATRH. Interventions that improve reaching BP targets in patients with ATRH, including more appropriate drug choices, could have a major impact on ESKD incidence in this high-risk population. Studies deciphering the mechanisms and genetic underpinnings of this condition should be pursued to develop novel tools for risk stratification and identify new therapeutic targets.

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Disclosures

None.

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