Supplemental Material

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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Methods

Multi-stage Algorithm for ascertaining apparent treatment resistant hypertension

Starting with the premise that patients primarily refilled their medication on a 90 to 180-day basis, we scanned the entire 12 years (01/01/04 – 12/31/2015) of follow-up in consecutive blocks of 3, then 6 months, in a longitudinal fashion, to ascertain medication refills (for each patient) from pharmacy data in a given time interval. We documented the number of antihypertensive drugs a patient was refilling at any given interval during the study based on the refill dates of all the drugs in the patient's regimen. For example, once a patient was identified as intensifying their antihypertensive regimen with a 4th drug, regardless of blood pressure (BP), a refill for all 4 drugs was required to be documented in the next 3 to 6-month refill window to ascertain ATRH. This choice was made to prevent capturing someone who was switching drugs rather than intensifying their regimen. Next, medication use among patients taking three drugs was examined. The date of the 3rd drug was ascertained was noted and the maximum BP within 15-180 days thereafter were examined, with patients with maximum BP greater than 140/90 mmHg considered to have ATRH.

Antihypertensive medication classes were defined using the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[1] One-pill combinations were classified into multiple medication classes. Participants (n = 5360) who met the criteria for ATRH prior to cohort entry (first creatinine in the EHR) or who had been diagnosed with secondary causes of HTN were excluded leaving a total of 17,521 patients with incident ATRH. Individuals with non-resistant hypertension (NRH) were defined as patients taking 1 or 2 classes of antihypertensive medications regardless of BP values and patients that were controlled on 3 antihypertensive medications.

Race/ethnicity

Information on race (White, African-American, Asian, Hawaiian/Pacific Islander and Native American) and ethnicity (Hispanic/Latino) were based on a combination of self-report through centralized VA data collection methods (using standardized survey forms), or through the use of information from the CDW, or Observational Medical Outcomes Partnership (OMOP) data, in case of missing self-report data. Ethnicity and race categories were merged to form the following: non-Hispanic white, non-Hispanic black (African-Americans/black), non-Hispanic Asian (Asian), non-Hispanic Native American and Hispanic.

Measures of additive interaction

These include the relative excess risk due to interaction (RERI) or interaction contrast ratio (ICR), the attributable proportion due to interaction (AP) and the synergy index (S).[2, 3] The RERI or ICR was calculated as:

$$RR_{11} - RR_{10} - RR_{01} + 1 \quad [\textbf{equation 1}]$$

In equation 1, RR_{11} is the rate ratio for the "doubly exposed" group (for example: African-Americans with ATRH) compared to the doubly unexposed group (Whites with NRH). RR_{10} and RR_{01} are the rate ratios for each "exposure" or predictor separately in the absence of the other (namely African-Americans with NRH and Whites with ATRH) when compared to the doubly unexposed group (Whites with NRH). The AP is calculated as: $RERI/RR_{11}$; and $S = RR_{11} - 1/(RR_{10} - 1) + (RR_{01} - 1)$. A p-value <0.05 for the null hypothesis of RERI = 0 (equivalent to testing for AP = 0 and S = 1) was considered significant for additive interaction. This would indicate that the rate of ESKD attributable to the combination of 2 exposures (having ATRH and being of African-American race) was greater than the sum of the of the rate of disease that would be caused by each exposure (ATRH and African-American race) separately.

Modeling continuous covariates in multivariable models

All continuous covariates were modeled using restricted cubic splines with 4 knots. Knots were placed at quantiles of the covariate's distribution, equally spaced in sample size.[4]

Multiple imputation of missing data

The proportion of missing values was computed for each covariate and the missingness patterns were examined using hierarchical cluster analysis of variables usually missing together.[4] Serum lipids had the highest proportion of missing values (15%). The proportion of missing values for BMI, smoking, baseline systolic BP and diastolic BP in our MVP cohort was 10, 1.1, 0.1, and 0.1% respectively. Multiple imputation of the missing values was performed using the *aregImpute* algorithm in the Hmisc package in R. Details of the *aregImpute* algorithm have been described elsewhere.[4] Briefly, the algorithm accounts for all aspects of uncertainty in the imputations by using bootstrap resamples to approximate the process of drawing predicted values from a full Bayesian predictive distribution. Different bootstrap resamples are used for each of the multiple imputations that are performed by the algorithm. A flexible additive model is fit on a sample with replacement from the original data and this model is used to predict all of the original missing as well as the non-missing values for the target variable, then the imputation models are run. In the imputation model, linearity is assumed for the variables being imputed while continuous predictors on the right-hand side of the model are transformed using restricted cubic splines with 5 knots. The algorithm uses predictive mean matching with weighted probability sampling of donors to fill-in the missing data.[4] Five imputations were performed, creating 5 complete data sets. The final multivariable Cox model (containing all covariates included in the imputation model) was fitted on each complete data set, and the regression coefficients were averaged over the multiple imputations.

Supplemental References

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Table S1. List of interfering medications and diagnostic codes used to exclude secondary causes of hypertension at the time of ATRH ascertainment

ICD-9 Code	Clinical conditions
	Parathyroid disease
252	Hyperparathyroidism
252	Hyperparathyroidism, unspecified
252.01	Primary hyperparathyroidism
252.02	Secondary hyperparathyroidism, non-renal
252.08	Other hyperparathyroidism
252.1	Hypoparathyroidism
252.8	Other specified disorders of parathyroid gland
252.9	Unspecified disorder of parathyroid gland
	Sleep apnea
327.2	Organic sleep apnea, unspecified
327.21	Primary central sleep apnea
327.22	High altitude periodic breathing
327.23	Obstructive sleep apnea (adult) (pediatric)
327.24	Idiopathic sleep related non-obstructive alveolar hypoventilation
327.25	Congenital central alveolar hypoventilation syndrome
327.26	Sleep related hypoventilation/hypoxemia in conditions classifiable elsewhere
327.27	Central sleep apnea in conditions classified elsewhere
327.29	Other organic sleep apnea
	Secondary hypertension
405.01	Malignant renovascular hypertension
405.09	Other malignant secondary hypertension
405.11	Benign renovascular hypertension
405.19	Other benign secondary hypertension
405.91	Unspecified renovascular hypertension
405.99	Other unspecified secondary hypertension
	Cortico-adrenal disorders
227.0	Benign neoplasm of adrenal gland
255.0	Cushing's Syndrome
255.1	Hyperaldosteronism
255.3	Other corticoadrenal overactivity
255.6	Medulloadrenal hyperfunction
	Urinary obstruction
599.60	Urinary obstruction, unspecified
599.69	Urinary obstruction, not elsewhere classified
	Thyroid disorders
240	Goiter, specified as simple
240.9	Goiter, unspecified
241	Nontoxic 6nimodular goiter
241.1	Nontoxic multinodular goiter
241.9	Unspecified nontoxic nodular goiter

ICD-9 code	Clinical Conditions
242	Toxic diffuse goiter without mention of thyrotoxic crisis or storm
242.01	Toxic diffuse goiter with mention of thyrotoxic crisis or storm
242.1	Toxic 7nimodular goiter without mention of thyrotoxic crisis or storm
242.11	Toxic 7nimodular goiter with mention of thyrotoxic crisis or storm
242.2	Toxic multinodular goiter without mention of thyrotoxic crisis or storm
242.21	Toxic multinodular goiter with mention of thyrotoxic crisis or storm
242.3	Toxic nodular goiter, unspecified type, without mention of thyrotoxic crisis or storm
242.31	Toxic nodular goiter, unspecified type, with mention of thyrotoxic crisis or storm
242.4	Thyrotoxicosis from ectopic thyroid nodule without mention of thyrotoxic crisis or storm
242.41	Thyrotoxicosis from ectopic thyroid nodule with mention of thyrotoxic crisis or storm
242.8	Thyrotoxicosis of other specified origin without mention of thyrotoxic crisis or storm
242.81	Thyrotoxicosis of other specified origin with mention of thyrotoxic crisis or storm
242.9	Thyrotoxicosis without mention of goiter or other cause, and without mention of thyrotoxic crisis or storm
242.91	Thyrotoxicosis without mention of goiter or other cause, with mention of thyrotoxic crisis or storm
243	Congenital hypothyroidism
244	Postsurgical hypothyroidism
244.1	Other postablative hypothyroidism
244.2	Iodine hypothyroidism
244.3	Other iatrogenic hypothyroidism
244.8	Other specified acquired hypothyroidism
244.9	Unspecified acquired hypothyroidism
245	Acute thyroiditis
245.1	Subacute thyroiditis
245.2	Chronic lymphocytic thyroiditis
245.3	Chronic fibrous thyroiditis
245.4	Iatrogenic thyroiditis
245.8	Other and unspecified chronic thyroiditis
245.9	Thyroiditis, unspecified
246	Disorders of thyrocalcitonin secretion
246.1	Dyshormonogenic goiter
246.2	Cyst of thyroid
246.3	Hemorrhage and infarction of thyroid
246.8	Other specified disorders of thyroid
246.9	Unspecified disorder of thyroid
	Interfering medications that motivated exclusions in the ATRH arm
1.	Erythropoiesis-stimulating agents (Epoetin and Dabepoetin)
2.	Calcineurin inhibitors (Cyclosporine and Tacrolimus).
3.	Corticosteroids (Prednisone, Prednisolone, Methylprednisolone and Dexamethasone).
4.	Amphetamines (Amphetamine, Dextroamphetamine and Methylphenidate).

Abbreviations: ATRH, apparent treatment-resistant hypertension; BP, blood pressure.

Table S2: Diagnostic and procedure codes used to identify comorbidities, exposures and outcomes

	Definition
Past Medical History	
Diabetes Mellitus	ICD-9 codes : 249.x, 250.x, 357.2x, 362.0x, 366.41 ; ICD-9 CM codes V45.85, V53.91
Hypertension	ICD-9 codes: 401.x-405.x, 437.2
Coronary Artery Disease	ICD-9 codes : 410.x-413.x, 414.0x, 414.2-414.9, V45.81, V45.82
Stroke	ICD9-CM diagnosis codes: ischemic stroke (433.x1, 434 [excluding 434.x0], or 436), intracerebral hemorrhage (431), and subarachnoid hemorrhage (430) but excluded traumatic brain injury (800–804, and 850–854).
Chronic Obstructive Pulmonary Disease	ICD9-CM diagnosis codes : 491.x-492.x, 493.2x, 496.x
Malignancy	Cancer excluding non-melanoma skin cancer: ICD9-CM codes: 140.x-208.x (excluding 173.x)
Peripheral Vascular Disease	ICD-9 codes : 440.x, 441.x, 442.x, 444.2x, V43.4
Inpatient Diagnoses	
Acute Myocardial Infarction	ICD-9 codes: 410.x
Dialysis	Dialysis ICD-9 procedure codes : 39.93, 39.95, 54.98, V39.27, V39.42, V38.43, V45.1, V56.0, V56.2, V56.31, V56.32, V56.8 ICD-9 Diagnosis codes : 585.6 CPT codes: 90921, 90925, 90935, 90937, 90945, 90947, 90960, 90961, 90962, 90966, 90989, 90993, 90999, G8956
Renal transplant	ICD-9 codes : 55.69, 996.81, V42.0 ICD-9 inpatient procedure codes : 00.91, 00.92, 00.93 outpatient CPT codes: 50360, 50365
Hospice care	ICD-9 outpatient or inpatient discharge codes : V66.7 CPT code: 99377

Table S3. Baseline characteristics of White and African-American hypertensive veterans in the MVP followed up at the Veteran Health Administration from 2004 to 2015

Baseline characteristics	Whites n = 98, 580	African-Americans n = 30, 950
Age, years	62 (56-69)	55 (50-61)
Women, %	4.1	97.9
Body Mass Index, kg/m^2	30.3 (27.1-34.2)	30.1 (26.7-34.1)
Systolic BP, mmHg	136 (125-147)	138 (127-150)
Diastolic BP, mmHg	78 (70-86)	82 (75-91)
eGFR, mL/min/1.73m^2	76.8 (63.9-90.5)	85.7 (71.7-100.8)
Serum Lipids, mg/dl		
Total Cholesterol	180 (156-208)	185 (160-213)
HDL Cholesterol	41 (34-49)	44 (37-54)
LDL Cholesterol	105 (85-129)	112 (89-136)
Triglycerides	146 (100-216)	112 (79-168)
Smoking history, %		
Never	24.1	23.4
Former	54.7	43.0
Current	21.2	33.6
Comorbidities, %		
Diabetes	28.3	30.0
Cerebrovascular disease	3.2	4.0
Coronary artery disease	31.6	19.4
Peripheral artery disease	6.3	4.7
COPD	12.9	9.2
All malignancies	10.1	8.4
Anti-hypertensive drugs, %		
ACE-Inhibitors/ARBs	63.4	58.1
Beta Blockers	41.0	29.7
Alpha Blockers	15.9	12.5
Calcium Channel Blockers	25.0	37.6
Thiazide diuretics	30.0	44.6
Loop diuretics	7.7	6.8
Potassium-sparing diuretics	6.4	8.6
Vasodilators	0.5	1.5

[a]All between-group comparisons were statistically significant ($P < 0.001$ for all other baseline variables).

[b]**Abbreviations:** ACE indicates angiotensin converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate.

Table S4. Clinical characteristics of veterans with hypertension in the MVP at the time they developed apparent treatment-resistant hypertension during follow-up from 2004 to 2015

Baseline characteristics	Apparent Treatment-Resistant HTN n = 17,521
Body Mass Index (IQR), kg/m^2	31.4 (27.8-35.6)
Systolic BP (IQR), mm Hg	144 (131-154)
Diastolic BP (IQR), mm Hg	79 (70-88)
eGFR (IQR), mL/min/1.73m^2	74.4 (59.8-89.9)
Current Smoking, %	18.4
Comorbidities, %	
Diabetes	51.1
Cerebrovascular disease	2.1
Coronary artery disease	26.3
Peripheral artery disease	6.7
COPD	13.2
All malignancies	2.5
Anti-hypertensive drugs, %	
ACE-Inhibitors/ARBs	88.7
Beta Blockers	67.8
Alpha Blockers	32.4
Calcium Channel Blockers	59.4
Thiazide diuretics	100.0
Loop diuretics	10.6
Potassium-sparing diuretics	5.1
Vasodilators	3.2
Number of antihypertensive drug classes (IQR)	4 (3-4)

Abbreviations: ACE indicates angiotensin converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HTN, Hypertension.

Table S5: Association of ATRH with incident ESKD and cardiovascular outcomes among hypertensive veterans in the MVP.

	Non-Resistant HTN	Apparent Treatment resistant HTN
Primary outcome:		
Incident ESKD cases	2138	613
Person-Years (PY)	1, 343, 334	131, 210
Incidence rate/1000PY (95 % CI)	1.59 (1.52-1.66)	4.68 (4.34-5.07)
Hazard ratios (95% CI)		
Model 1	1.00 (ref)	2.22 (2.02-2.43)
Model 2	1.00 (ref)	2.07 (1.89-2.27)
Model 3	1.00 (ref)	1.85 (1.67-2.04)
Secondary Outcomes:		
Incident MI cases	4517	872
Person-Years (PY)	1, 330, 911	129, 376
Incidence rate/1000PY (95 % CI)	3.39 (3.29-3.49)	6.74 (6.30-7.20)
Hazard ratios (95% CI)		
Model 1	1.00 (ref)	1.72 (1.60-1.85)
Model 2	1.00 (ref)	1.70 (1.58-1.83)
Model 3	1.00 (ref)	1.65 (1.52-1.78)
Incident cases of Stroke	10, 918	2033
Person-Years (PY)	1, 290, 739	121, 890
Incidence rate/1000PY (95 % CI)	8.46 (8.3-8.62)	16.68 (15.97-17.42)
Hazard ratios (95% CI)		
Model 1	1.00 (ref)	1.89 (1.80-1.98)
Model 2	1.00 (ref)	1.87 (1.78-1.96)
Model 3	1.00 (ref)	1.81 (1.72-1.91)

Model 1: Includes ATRH (modeled as a time-varying covariate versus non-resistant HTN), age (restricted cubic splines with 4 knots), race (Whites/Blacks/Other) and sex (M/F). **Model 2**: Model 1 + baseline eGFR (restricted cubic splines with 4 knots) and calendar year of cohort entry (4 categories of 3 consecutive years). **Model 3**: Model 2 + 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) + statin use + history of Cancer, COPD, diabetes, CAD, PAD and stroke (all yes/no). Abbreviations: ATRH, apparent treatment resistant hypertension; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; PAD, peripheral artery disease.

Abbreviations: ATRH, apparent treatment resistant hypertension; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HTN, hypertension; PAD, peripheral artery disease; SBP, systolic blood pressure.

Table S6: Cumulative incidence of ATRH-related outcomes and potential population health impact

	Non-Resistant HTN	Apparent Treatment resistant HTN
Incident ESKD		
Cumulative incidence, %	2.17	5.31
Attributable fraction, %	ref.	57.2
Population attributable fraction, %	ref.	12.8
Number Needed to Harm	ref.	32
Incident MI		
Cumulative Incidence, %	4.37	8.42
Attributable fraction, %	ref.	42.3
Population attributable fraction, %	ref.	6.8
Number Needed to Harm	ref.	25
Incident Stroke		
Cumulative Incidence, %	10.06	22.48
Attributable fraction, %	ref.	48.4
Population attributable fraction, %	ref.	7.6
Number Needed to Harm	ref.	8

Abbreviations: ATRH, apparent treatment-resistant hypertension; ESKD, end-stage kidney disease; HTN, Hypertension; MI, myocardial infarction.

Table S7: Race-stratified estimates of attributable risk of ESKD due to ATRH

	Non-Resistant HTN	Apparent Treatment resistant HTN
Whites		
Cumulative Incidence, %	1.60	4.15
Attributable risk, per 1000	ref.	25.5
Population attributable risk, per 1000	ref.	2.6
Number needed to harm	ref.	39
African-Americans		
Cumulative Incidence, %	4.05	8.49
Attributable risk, per 1000	ref.	44.4
Population attributable risk, per 1000	ref.	5.4
Number needed to harm	ref.	23

Abbreviations: ATRH, apparent treatment-resistant hypertension; ESKD, end-stage kidney disease; HTN, Hypertension.

Table S8. Effect of ATRH on incident ESKD and cardiovascular outcomes in a fully adjusted model[a] including time-varying[b] blood pressure, hypertension duration[c] or proteinuria[d]

Outcome	SBP and DBP	HTN duration	Proteinuria
Incident ESKD	1.63 (1.48-1.80)	1.84 (1.67-2.04)	1.62 (1.44, 1.82)
Incident MI	1.60 (1.48-1.74)	1.64 (1.51, 1.78)	1.64 (1.49, 1.80)
Incident Stroke	1.77 (1.68-1.86)	1.80 (1.71-1.90)	1.76 (1.65, 1.87)

[a] Covariates included age (restricted cubic splines with 4 knots), race (Whites/Blacks/Other), sex (M/F), 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), statin use, history of Cancer, COPD, diabetes, CAD, PAD and stroke (all yes/no).

[b] Time-varying blood pressure: Baseline BP values were updated at time of ATRH for persons who developed incident ATRH.

[c] HTN duration: Time (in years) from the date of the first HTN code in the medical record to the date of cohort entry.

[d]This analysis was conducted in the 65% of participants with available urine protein data at cohort entry.

Abbreviations: ATRH, apparent treatment resistant hypertension; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HTN, hypertension; PAD, peripheral artery disease; SBP, systolic blood pressure.

Table S9. Effect of ATRH on the risk of ESKD and cardiovascular outcomes among veterans in the MVP: Cox models versus competing-risks regression (Fine and Gray model)

	Cox PHM	Fine and Gray Model
	n = 139, 685	n = 139, 685
Incident ESKD cases	2751	2751
Model 1	2.22 (2.02-2.43)	2.22 (2.03-2.44)
Model 2	2.07 (1.89-2.27)	2.09 (1.90-2.29)
Model 3	1.85 (1.67-2.04)	1.86 (1.68-2.05)
Incident MI cases	5389	5389
Model 1	1.72 (1.60-1.85)	1.73 (1.60-1.86)
Model 2	1.70 (1.58-1.83)	1.71 (1.59-1.84)
Model 3	1.65 (1.52-1.78)	1.66 (1.52-1.79)
Incident cases of Stroke	12, 951	12, 951
Model 1	1.89 (1.80-1.98)	1.89 (1.80-1.99)
Model 2	1.87 (1.78-1.96)	1.88 (1.79-1.97)
Model 3	1.81 (1.72-1.91)	1.81 (1.72-1.92)

Model 1: Includes ATRH (modeled as a time-varying covariate versus non-resistant HTN), age (restricted cubic splines with 4 knots), race (Whites/Blacks/Other) and sex (M/F). **Model 2**: Model 1 + baseline eGFR (restricted cubic splines with 4 knots) and calendar year of cohort entry (4 categories of 3 consecutive years). **Model 3**: Model 2 + 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) + Statin use + history of Cancer, COPD, diabetes, CAD, PAD and stroke (all yes/no).

Abbreviations: ATRH, apparent treatment resistant hypertension; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; MVP, million veteran program; PAD, peripheral artery disease; PHM, proportional hazards model.

Table S10. Additive interaction between ATRH and both race and eGFR for the association with incident MI among hypertensive veterans in the Million Veteran Program

Interaction with race (p-interaction = 0.41)				
	Whites with NRH (n= 86, 891)	Whites with ATRH (n = 11, 621)	Blacks with NRH (n = 26, 349)	Blacks with ATRH (4588)
Incident MI cases	3360	616	835	201
Person-Years (PY)	946, 998	85788, 160	288, 947	33, 778
Incidence rate*/1000PY (95 % CI)	3.49 (3.37-3.61)	7.04 (6.51-7.63))	3.00 (2.80-3.21)	(6.12 (5.33-7.03)
Incidence rate ratio* (95% CI)	1.00 (ref)	2.02 (1.85-2.20)	0.86 (0.80-0.93)	1.75 (1.52-2.02)
Hazard ratios (95% CI)				
Model 1	1.00 (ref)	1.76 (1.61-1.91)	0.88 (0.81-0.95)	1.52 (1.32-1.76)
Model 2	1.00 (ref)	1.73 (1.58-1.88)	0.88 (0.82-0.95)	1.52 (1.31-1.75)
Model 3	1.00 (ref)	1.68 (1.53-1.84)	0.95 (0.87-1.03)	1.62 (1.39-1.89)
Interaction with eGFR (p-interaction = 0.13)				
	Patients with eGFR ≥ 60 and NRH (n = 102, 450)	Patients with eGFR ≥ 60 and ATRH (n = 14, 507)	Patients with eGFR < 60 and NRH (19, 625)	Patients with eGFR < 60 and ATRH (n = 3014)
Incident MI cases	3534	661	983	211
Person-Years (PY)	1, 115, 145	105, 336	215, 766	24, 040
Incidence rate*/1000PY (95 % CI)	3.19 (3.09-3.30)	6.31 (5.58-6.81)	4.33 (4.05-4.63)	8.41 (7.34-9.64)
Incidence rate ratio* (95% CI)	1.00 (ref)	1.98 (1.82-2.15)	1.36 (1.26-1.46)	2.63 (2.29-3.03)
Hazard ratios (95% CI)				
Model 1	1.00 (ref)	1.70 (1.57-1.85)	1.39 (1.29-1.50)	2.38 (2.07-2.74)
Model 2	1.00 (ref)	1.70 (1.56-1.85)	1.40 (1.30-1.51)	2.40 (2.08-2.76)
Model 3	1.00 (ref)	1.66 (1.52-1.82)	1.29 (1.29-1.50)	2.04 (1.75-2.39)

Model 1: adjusted for age, sex and race (omitted when testing the interaction with race but included for models testing GFR interaction). **Model 2**: adjusted for age, sex, race, calendar year of cohort entry and eGFR (omitted when testing the interaction with GFR but included for models testing interaction with race). **Model 3**: Model 2 + smoking + BMI + serum lipids (total cholesterol, triglycerides, LDL cholesterol and HDL cholesterol;) + Statin use + history of Cancer, COPD, diabetes, CAD, PAD and stroke. Abbreviations: ATRH, apparent treatment resistant hypertension; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; MVP, million veteran program; PAD, peripheral artery disease.

*Incidence rates are age-adjusted (adjusted to the mean age at cohort entry: 60 years).

Table S11. Additive interaction between ATRH and both race and eGFR for the association with incident stroke among hypertensive veterans in the Million Veteran Program

Interaction with race (p-interaction = 0.02)[§]				
	Whites with NRH (n= 86, 959)	Whites with ATRH (n = 11, 621)	Blacks with NRH (n = 26, 362)	Blacks with ATRH (4588)
Incident cases of stroke	7514	1278	2616	581
Person-Years (PY)	921, 225	81, 618	277, 625	31, 257
Incidence rate*/1000PY (95 % CI)	7.81 (7.63-7.99)	14.95 (14.15-15.80)	10.15 (9.76-10.55)	19.56 (18.03-21.21)
Incidence rate ratio* (95% CI)	1.00 (ref)	1.91 (1.80-2.03)	1.30 (1.24-1.36)	2.50 (2.30-2.73)
Hazard ratios (95% CI)				
Model 1	1.00 (ref)	1.86 (1.75-1.98)	1.31 (1.23-1.38)	2.45 (2.25-2.67)
Model 2	1.00 (ref)	1.84 (1.74-1.96)	1.30 (1.24-1.36)	2.41 (2.21-2.62)
Model 3	1.00 (ref)	1.77 (1.66-1.90)	1.20 (1.14-1.27)	2.18 (1.99-2.39)
Interaction with eGFR (p-interaction = 0.65)				
	Patients with eGFR ≥ 60 and NRH (n = 102, 305)	Patients with eGFR ≥ 60 and ATRH (n = 14, 507)	Patients with eGFR < 60 and NRH (19, 574)	Patients with eGFR < 60 and ATRH (n = 3014)
Incident cases of stroke	8591	1589	2327	444
Person-Years (PY)	1, 083, 925	99, 405	206, 814	22, 485
Incidence rate*/1000PY (95 % CI)	8.02 (7.85-8.19)	16.10 (15.33-16.92)	10.26 (9.82-10.72)	18.26 (16.62-20.06)
Incidence rate ratio* (95% CI)	1.00 (ref)	2.01 (1.90-2.12)	1.28 (1.22-1.34)	2.28 (2.07-2.51)
Hazard ratios (95% CI)				
Model 1	1.00 (ref)	1.92 (1.82-2.03)	1.32 (1.26-1.38)	2.26 (2.05-2.48)
Model 2	1.00 (ref)	1.92 (1.82-2.03)	1.33 (1.26-1.39)	2.27 (2.06-2.50)
Model 3	1.00 (ref)	1.99 (1.79-2.21)	1.22 (1.15-1.28)	1.99 (1.79-2.21)

Model 1: adjusted for age, sex and race (omitted when testing the interaction with race but included for models testing GFR interaction). **Model 2**: adjusted for age, sex, race, calendar year of cohort entry and eGFR (omitted when testing the interaction with GFR but included for models testing interaction with race). **Model 3**: Model 2 + smoking + BMI + serum lipids (total cholesterol, triglycerides, LDL cholesterol and HDL cholesterol) + Statin use + history of Cancer, COPD, diabetes, CAD, PAD and stroke. Abbreviations: ATRH, apparent treatment resistant hypertension; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease.

*Incidence rates are age-adjusted (adjusted to the mean age at cohort entry: 60 years).

[§]Excess stroke incidence among blacks with ATRH due to interaction between ATRH and race = IR_{11} - [IR_{00} + (IR_{01} - IR_{00}) + (IR_{10} - IR_{00})] = 19.56 - [7.81 + (14.95 - 7.81) + (10.15 - 7.81)] = 2.27 which represents an excess of 227 cases/100,000PY among blacks with ATRH. The relative excess risk due to interaction (RERI) between ATRH and race = IRR_{11} - IRR_{10} - IRR_{01} + 1 = 0.29 (95%CI: 0.05-0.53). The attributable proportion (AP) = RERI/IRR_{11} = 11.6 (3.0, 20.2) suggesting that up to 11.6% of the risk of incident stroke among blacks with ATRH is due to the synergistic interaction between ATRH and race.

Table S12. Prevalence of 0, 1 and 2 *APOL1* risk allele carriers among patients with ATRH and NRH in the Million Veteran Program.

Number of *APOL1* risk alleles	Overall n (%)	NRH n (%)	ATRH n (%)
0	10740 (41.7)	9266 (41.2)	1474 (42.2)
1	11993 (45.9)	10390 (46.1)	1603 (45.9)
2	3275 (12.4)	2862 (12.7)	413 (11.9)

Abbreviations: APOL1, apolipoprotein L1; ATRH, apparent treatment resistant hypertension; NRH, non-resistant hypertension.

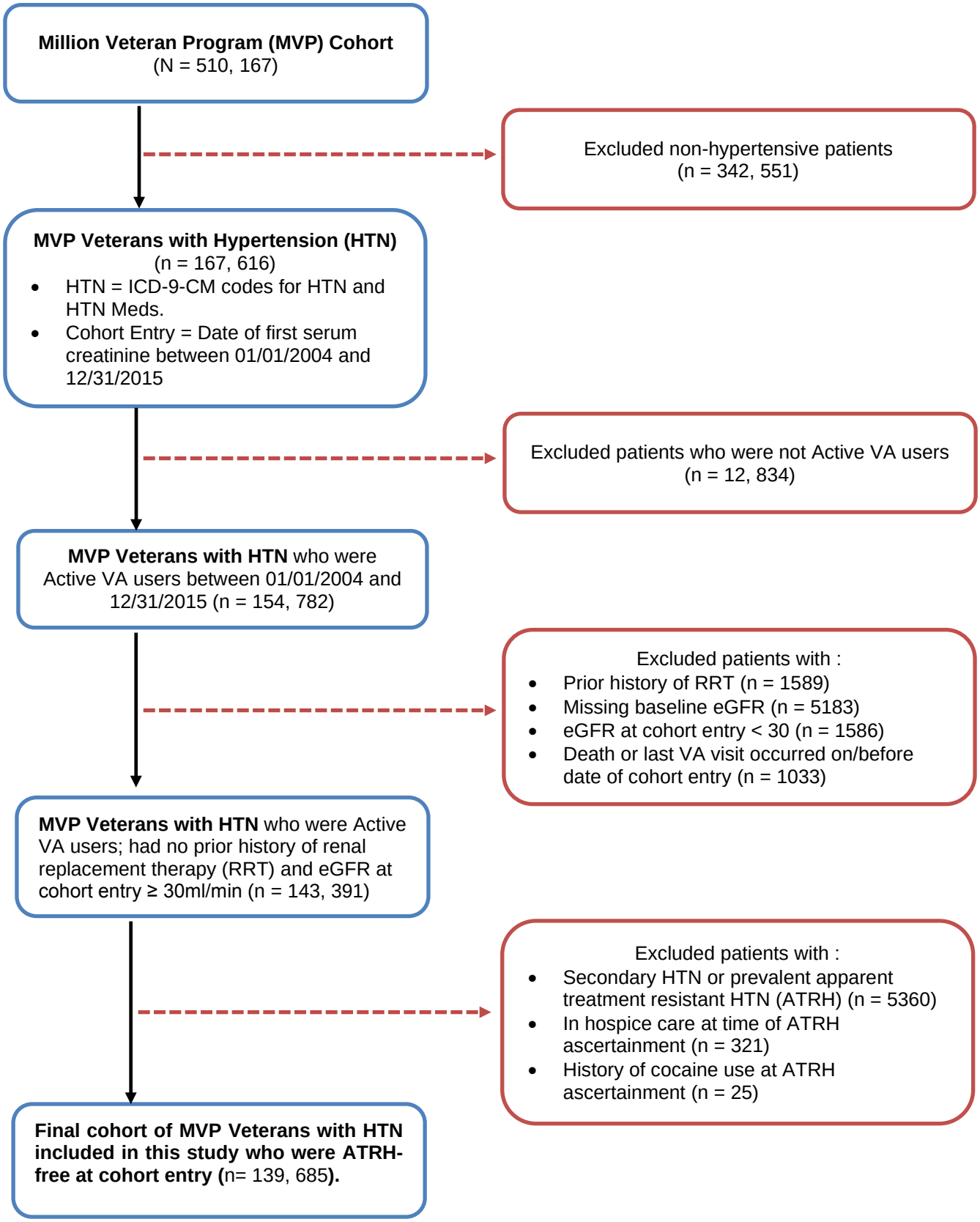


Figure S1: Flow chart for retrospective cohort study of 139,685 hypertensive veterans enrolled in the Million Veteran Program who were active VHA users between 01/01/2004 and 12/31/2015.

Abbreviations: ATRH, apparent treatment resistant hypertension; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; VHA, Veterans Health Administration.

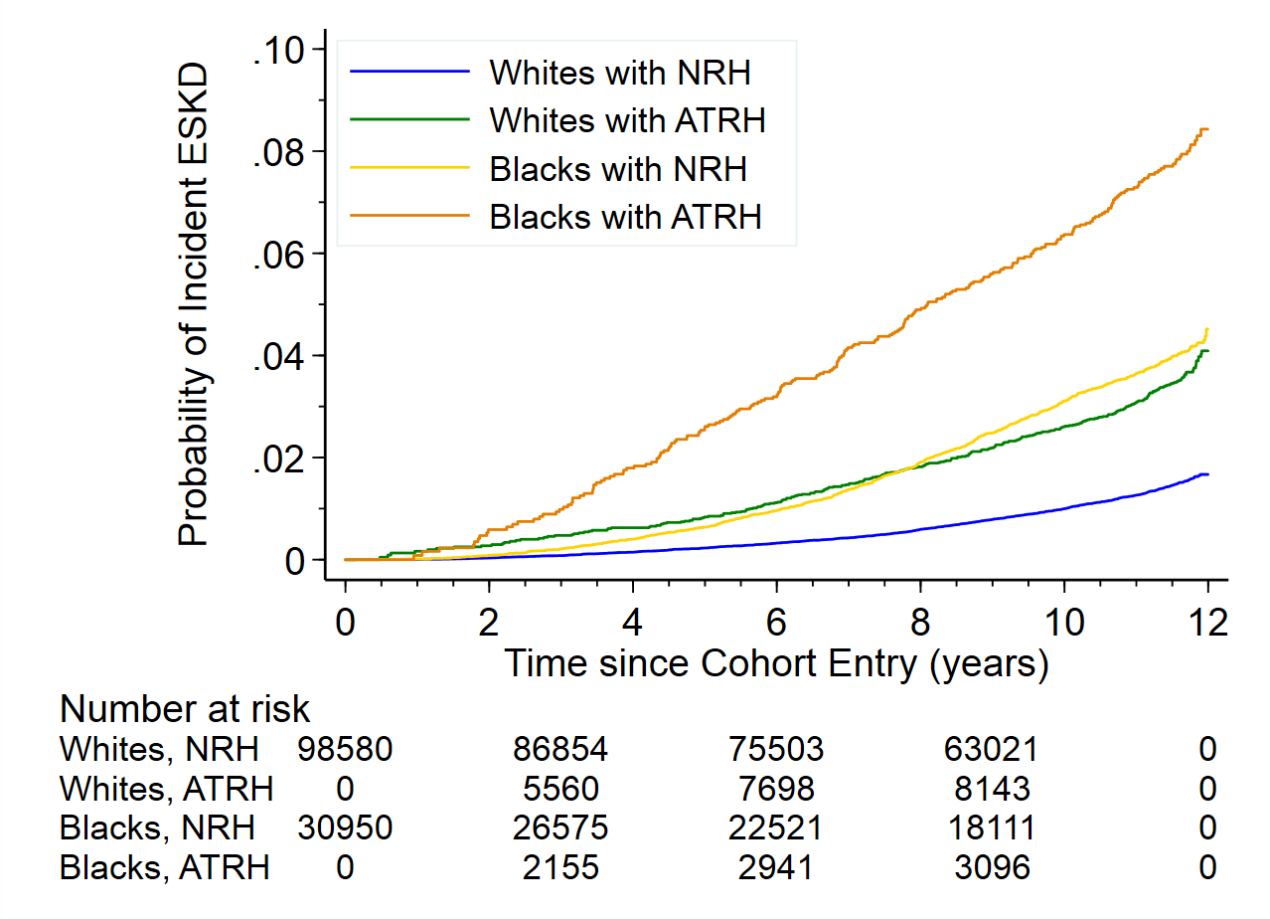
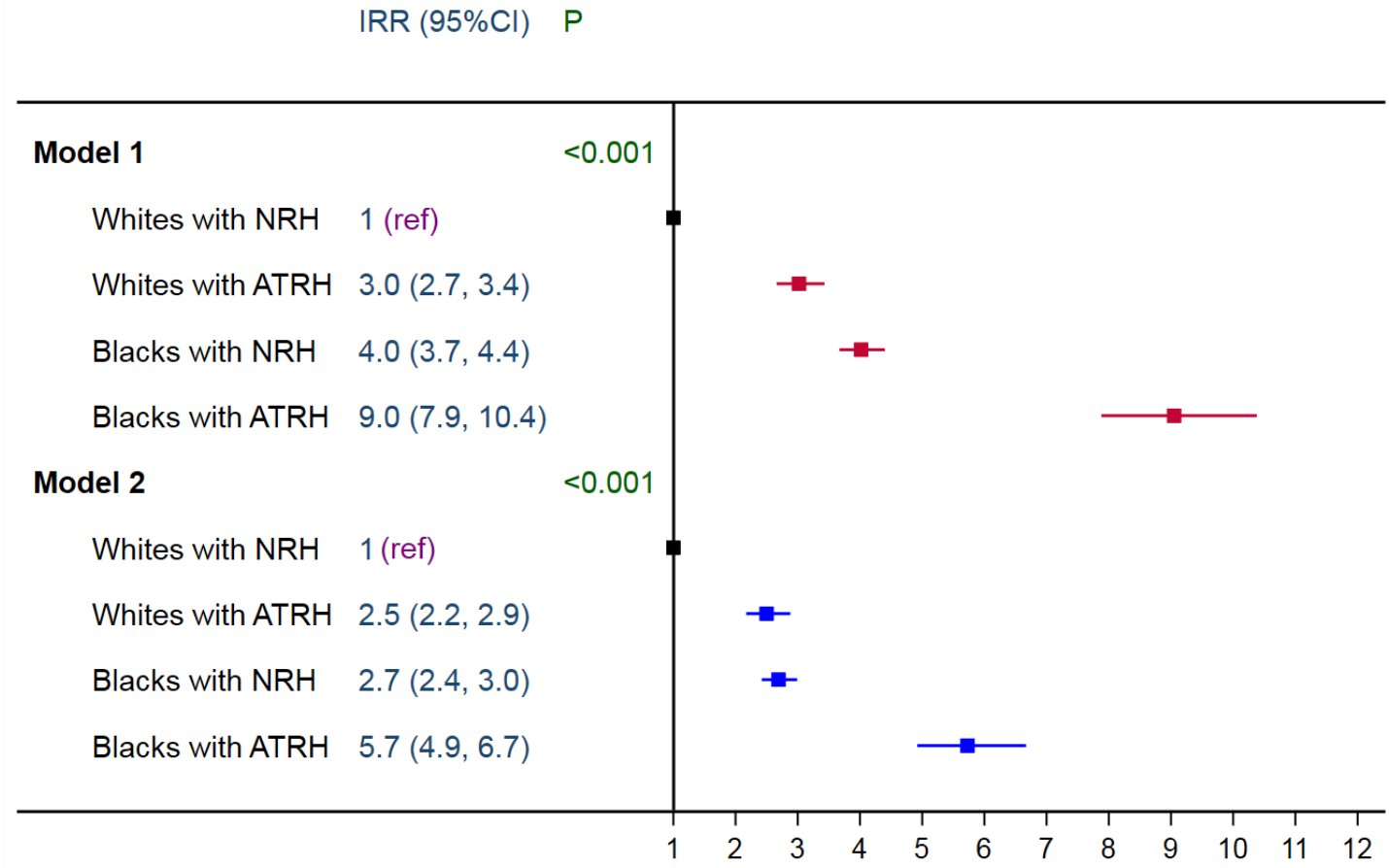


Figure S2. Probability of incident ESKD in patients with ATRH and NRH by race

Abbreviations: ATRH, apparent treatment resistant hypertension; ESKD, end-stage kidney disease; NRH; Non-resistant hypertension.



IRR: Incidence rate ratio for ESKD. P: p-values for additive interaction from Poisson regression
Model 1: Adjusted for eGFR. Model 2: Full adjustment for baseline covariates

	RERI (95% CI)	AP (85%CI)	S (95% CI)	P
Model 1	3.00 (1.79-4.21)	33.2 (23.6-42.7)	1.60 (1.33-1.86)	<0.001
Model 2	1.59 (0.76-2.42)	28.5 (17.0-40.0)	1.53 (1.22-1.84)	< 0.001

Model 1 is adjusted for eGFR. **Model 2** covariates included demographics (age, sex and race), smoking, body mass index, baseline eGFR, serum lipids (total cholesterol, triglycerides, LDL cholesterol and HDL cholesterol;) + Statin use + history of Cancer, COPD, diabetes, CAD, PAD and stroke. **RERI** = IRR_{11} - IRR_{10} - IRR_{01} + 1. **AP** = RERI/ IRR_{11}. **S** = IRR_{11}-1/(IRR_{10}-1) + (IRR_{01}-1)

Figure S3. Adjusted Incidence rate ratios for ESKD and indices of interaction

Abbreviations: AP, attributable proportion due to interaction; 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; HTN, hypertension; NRH; Non-resistant hypertension; RERI, relative excess risk due to interaction; S, synergy index.

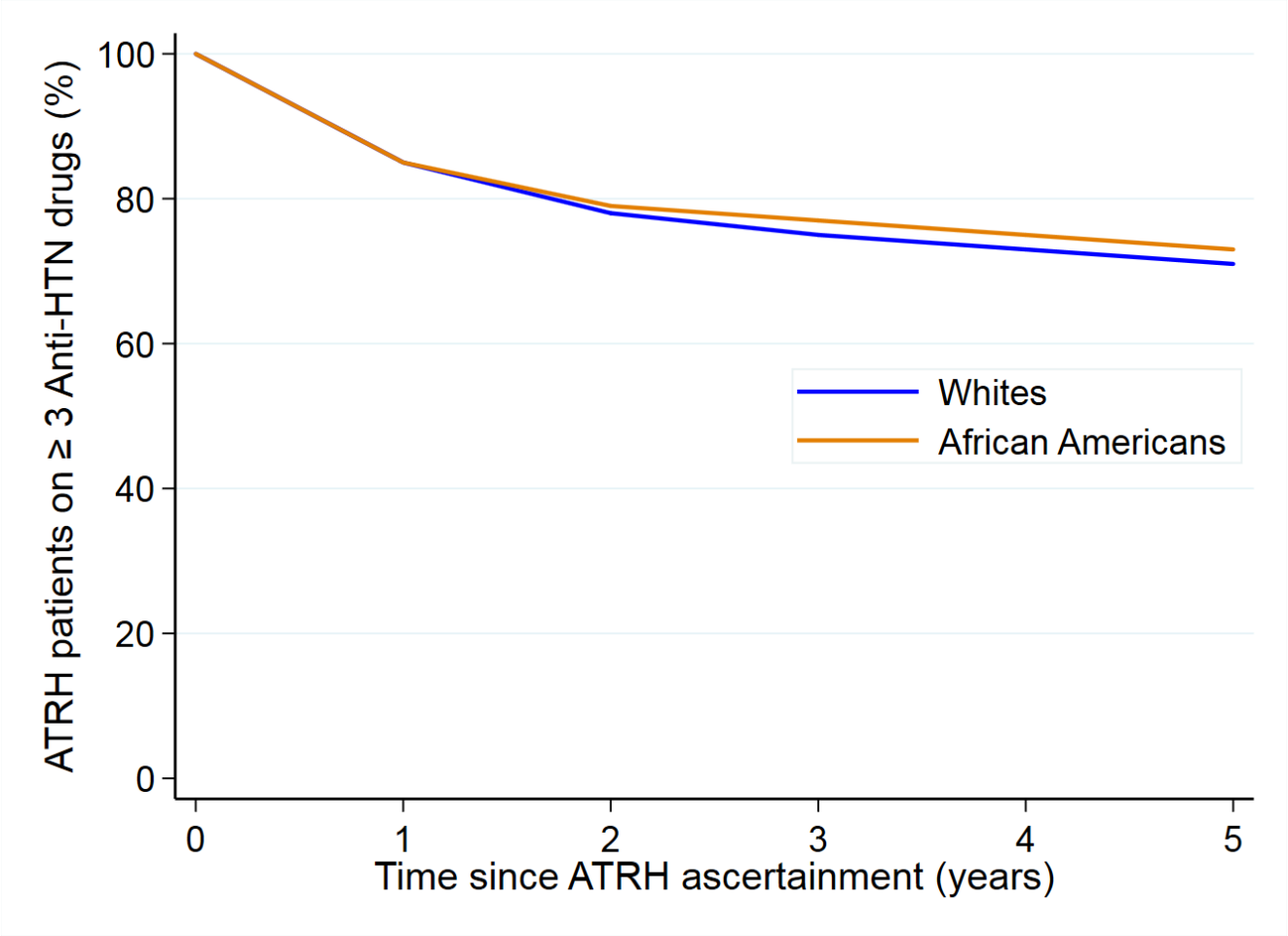


Figure S4: Proportion of patients with ATRH taking 3 or more antihypertensive drugs during the 5 years following ATRH ascertainment

Abbreviations: ATRH, apparent treatment resistant hypertension; HTN, hypertension.

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