SUPPLEMENTAL MATERIAL

Supplemental Methods:

The Health Improvement Network (THIN): Additional Information.

This data source represents a large sample (5.7%) of the general population of the UK in an outpatient setting with diverse representation of age, sex, socioeconomic status, and geography (1). Every patient in the UK must be registered with a general practitioner who coordinates all care, writes all prescriptions, including those recommended by specialists, and is informed of events in the patient's care. The data contain demographics (excluding race), diagnoses, procedures, laboratory and radiology results, blood pressure, BMI, prescription data, hospitalization data, socioeconomic status, and death certificate data (see Supplemental Methods for additional information) (1). Completeness of the medical record is now tied to reimbursement through a pay-for-performance program, which corresponds to improved adherence to quality measures including ambulatory blood pressure monitoring for confirmation of the diagnosis of hypertension, waist circumferences measurements in obese patients, and screening for proteinuria (2, 3). *With regard to prescribing data, the database captures prescriptions as they are issued to patients (4, 5). The date associated with each medication reflects the date in which the actual prescription was ordered. The accuracy and completeness of the prescribing data have been well-validated previously (6, 7).* The database also includes free text of supplemental information such as kidney biopsy results and descriptive information related to death data. Medications use to define patient exposures were identified using the British formulary to identify a comprehensive list of drug codes in the THIN database.

In order to be eligible for initial inclusion in the study, we required that patients be registered with a THIN practice for a minimum of 6 months. This 6 month post-registration index date was based on protocols developed in previous studies using THIN, intended to ensure that data collected did not capture incorporation of preceding medical events and diagnoses into the health record (8). With regard to exit from the cohort, patients were censored at the time of transfer out of the practice or loss to follow up (defined as 18 months with no physician visits or prescriptions). UK general practitioners routinely record when patients transfer out of their practices, and transfer date is reliably captured as part of the THIN dataset (9). Transfer date in THIN has been used in many previous studies for defining the end of follow up or exit from the cohort (10-16). Additionally, the UK's National Institute for Health and Care Excellence (NICE) recommends that all patients in the UK with hypertension be seen a minimum of once annually (3), and prescriptions in the UK expire after a maximum of six months (17). Thus, we selected 18 months of inactivity in the medical record as a conservative estimate of loss to follow up.

Statistical Power:

There was 90% power to detect a hazard ratio of 0.91 at a 0.05 significance level among patients who met eligibility criteria for the primary analyses (18, 19), indicating sufficient power to detect a very small statistically significant effect.

Supplemental Table 1. Baseline and Time-Updated Covariates Incorporated into each Model.

	Traditional Cox Model	Marginal Structural Model
Baseline Covariates	Age	Age
	Gender	Gender
	Townsend Deprivation Index (20)	Townsend Deprivation Index (20)
	Cardiovascular Disease Diagnosis	Cardiovascular Disease Diagnosis
	Congestive Heart Failure Diagnosis	Congestive Heart Failure Diagnosis
	Hepatitis B Virus Diagnosis	Hepatitis B Virus Diagnosis
	Hepatitis C Virus Diagnosis	Hepatitis C Virus Diagnosis
	Body Mass Index	Body Mass Index
	Systolic Blood Pressure	
	Number of Antihypertensive Medications	
	Treatment with Mineralocorticoid Antagonist	
	Treatment with Diuretic	
	eGFR (CKD-EPI)	
Time-Updated Covariates		Systolic Blood Pressure
		Number of Antihypertensive Medications
		Treatment with Mineralocorticoid Antagonist
		Treatment with Diuretic
		Development of Diabetes Diagnosis
		eGFR (CKD-EPI)

Supplemental Table 2. Effect of Exposure to RAS Blockade on Mortality Using Multivariable Cox Model vs. Marginal Structural Modeling.

		Multivariable Cox Model*		Marginal Structural Model†	
	Patients (n)	HR (95% CI)	p-value	HR (95% CI)	p-value
Overall	219,701	1.03 (0.99-1.07)	0.105	0.91 (0.81-1.02)	0.112
+ CKD	52,637	1.07 (1.01-1.13)	0.024	0.94 (0.79-1.12)	0.479
- CKD	167,064	1.00 (0.95-1.06)	0.937	0.90 (0.76-1.06)	0.189
Overall proteinuria subgroup	55,963	1.03 (0.95-1.11)	0.451	0.96 (0.76-1.21)	0.716
+ Proteinuria and + CKD	564	0.77 (0.33-1.82)	0.558	0.69 (0.16-2.97)	0.621
- Proteinuria and + CKD	16,141	1.02 (0.91-1.13)	0.747	0.86 (0.62-1.19)	0.362
- Proteinuria and - CKD	39,258	1.04 (0.93-1.16)	0.489	1.12 (0.83-1.52)	0.463

Supplemental Table 3. Effect of Exposure to RAS Blockade on Development of Diabetes Using Multivariable Cox Model vs. Marginal Structural Modeling.

		Multivariable Cox Model*		Marginal Structural Model†	
	Patients (n)	HR (95% CI)	p-value	HR (95% CI)	p-value
Overall	219,701	0.944 (0.92-0.97)	< 0.001	0.847 (0.81-0.88)	< 0.001
+ CKD	52,637	0.952 (0.90-1.00)	0.068	0.855 (0.79-0.93)	< 0.001
- CKD	167,064	0.942 (0.92-0.97)	< 0.001	0.824 (0.79-0.86)	< 0.001
Overall proteinuria subgroup	55,963	0.921 (0.88-0.96)	< 0.001	0.831 (0.77-0.90)	< 0.001
+ Proteinuria and + CKD	564	1.048 (0.74-1.48)	0.789	0.946 (0.49-1.84)	0.871
- Proteinuria and + CKD	16,141	0.893 (0.82-0.98)	0.012	0.874 (0.75-1.01)	0.073
- Proteinuria and - CKD	39,258	0.929 (0.88-0.98)	0.004	0.813 (0.74-0.89)	< 0.001

Supplemental Table 4. Effect of Exposure to RAS Blockade on Death-Censored Renal Outcomes (50% Reduction in eGFR or ESRD) Using Multivariable Cox Model vs. Marginal Structural Modeling.

		Multivariable Cox Model*		Marginal Structural Model†	
	Patients (n)	HR (95% CI)	p-value	HR (95% CI)	p-value
Overall	219,701	1.18 (1.10-1.26)	< 0.001	1.17 (1.08-1.27)	< 0.001
+ CKD	52,637	1.25 (1.13-1.38)	< 0.001	1.22 (1.08-1.38)	0.001
- CKD	167,064	1.14 (1.05-1.25)	< 0.001	1.24 (1.12-1.38)	< 0.001
Overall proteinuria subgroup	55,963	1.21 (1.07-1.39)	0.004	1.25 (1.09-1.44)	0.001
+ Proteinuria and + CKD	564	1.01 (0.53-1.93)	0.974	1.02 (0.47-2.22)	0.955
- Proteinuria and + CKD	16,141	1.28 (1.05-1.57)	0.013	1.12 (0.91-1.38)	0.285
- Proteinuria and - CKD	39,258	1.16 (0.97-1.39)	0.112	1.38 (1.14-1.66)	0.001

Supplemental Table 5. Effect of Exposure to RAS Blockade on Composite Renal Endpoint (Single eGFR Value with 50% Reduction from Baseline, ESRD, or Death) Using Multivariable Cox Model vs. Marginal Structural Modeling.

		Multivariable Cox Model*		Marginal Structural Model†	
	Patients (n)	HR (95% CI)	p-value	HR (95% CI)	p-value
Overall	219,701	1.10 (1.07-1.14)	< 0.001	1.19 (1.10-1.28)	< 0.001
+ CKD	52,637	1.15 (1.10-1.21)	< 0.001	1.21 (1.07-1.36)	0.002
- CKD	167,064	1.06 (1.02-1.11)	0.007	1.20 (1.09-1.33)	< 0.001
Overall proteinuria subgroup	55,963	1.09 (1.02-1.16)	0.006	1.26 (1.10-1.45)	0.001
+ Proteinuria and + CKD	564	1.15 (0.72-1.85)	0.551	1.48 (0.68-3.23)	0.325
- Proteinuria and + CKD	16,141	1.12 (1.03-1.23)	0.010	1.11 (0.90-1.36)	0.321
- Proteinuria and - CKD	39,258	1.04 (0.95-1.14)	0.392	1.42 (1.18-1.70)	< 0.001

Supplemental Table 6. Effect of Exposure to RAS Blockade on Composite Renal Endpoint (Single eGFR Value with 50% Reduction from Baseline, ESRD, or Death) Using Multivariable Cox Model vs. Marginal Structural Modeling; <u>Incident User Design</u>.

		Multivariable Cox Model*		Marginal Structural Model†	
	Patients (n)	HR (95% CI)	p-value	HR (95% CI)	p-value
Overall	121,738	1.21 (1.16-1.26)	< 0.001	1.48 (1.34-1.64)	< 0.001
+ CKD	29,867	1.17 (1.10-1.02)	< 0.001	1.46 (1.25-1.70)	< 0.001
- CKD	91,871	1.24 (1.18-1.31)	< 0.001	1.54 (1.35-1.75)	< 0.001
Overall proteinuria subgroup	30,753	1.21 (1.12-1.31)	< 0.001	1.47 (1.22-1.77)	< 0.001
+ Proteinuria and + CKD	273	1.22 (0.65-2.29)	0.532	0.48 (0.17-1.40)	0.178
- Proteinuria and + CKD	8,754	1.14 (1.02-1.28)	0.024	1.16 (0.89-1.53)	0.276
- Proteinuria and - CKD	21,726	1.26 (1.13-1..40)	< 0.001	1.86 (1.42-2.38)	< 0.001

Supplemental Table 7. Lowest Quintile of Black Population Density: Effect of Exposure to RAS Blockade on Modified Composite Renal Endpoint by Baseline Multivariable Cox Model vs. Marginal Structural Modeling.[‡]

		Multivariable Cox Model*		Marginal Structural Model[†]	
	Patients (n)	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Overall	21,132	1.03 (0.93-1.13)	0.603	0.98 (0.83-1.14)	0.763
+ CKD	5,039	0.99 (0.86-1.14)	0.870	0.89 (0.72-1.11)	0.303
- CKD	16,093	1.05 (0.93-1.20)	0.418	1.11 (0.87-1.41)	0.392

Supplemental Table 8. Highest Quintile of Black Population Density: Effect of Exposure to RAS Blockade on Modified Composite Renal Endpoint by Baseline Multivariable Cox Model vs. Marginal Structural Modeling.[§]

		Multivariable Cox Model*		Marginal Structural Model[†]	
	Patients (n)	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Overall	45,432	0.99 (0.92-1.06)	0.742	1.04 (0.92-1.18)	0.558
+ CKD	11,046	0.94 (0.84-1.04)	0.177	0.93 (0.78-1.11)	0.435
- CKD	34,386	1.06 (0.95-1.18)	0.273	1.19 (0.99-1.42)	0.067

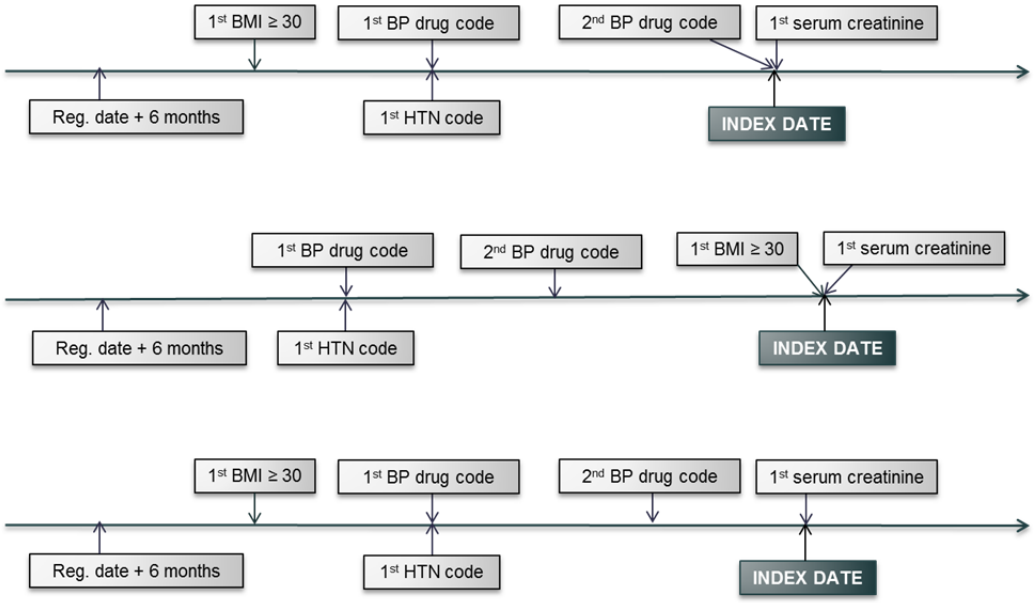
* RAS blockade usage and all other covariates are defined at the index date.

† RAS blockade usage and covariates are time-updated. Marginal structural modeling uses stabilized inverse probability of treatment weighting, taking into account important time-updated confounders with regard to the likelihood of treatment at each time-point (21, 22).

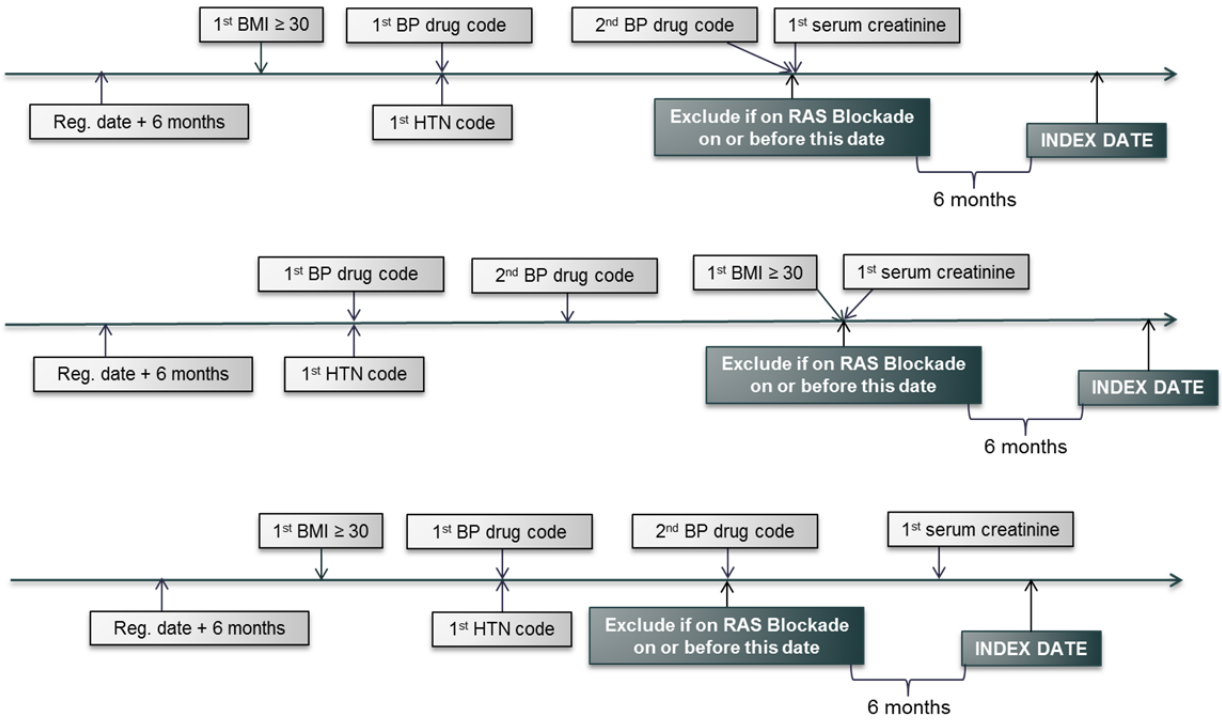
‡ 43.5% of patients in the lowest black population density quintile were on RAS blockade at baseline.

§ 43.0% of patients in the highest black population density quintile were on RAS blockade at baseline (p=0.248).

Supplemental Figure 1. Primary Cohort Assembly Timeline



Supplemental Figure 2. Incident-User Cohort Assembly Timeline



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