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Barriers to ACEi/ARB use in proteinuric chronic kidney disease: an observational study

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Abstract

Objective—To assess present angiotensin converting enzyme inhibitor (ACEi) and angiotensin receptor blocker (ARB) use among patients with proteinuric CKD and examine barriers limiting this guideline-concordant care.

Patients and Methods—Using a nationwide database containing patient-level claims and integrated clinical information through the end of 2017, we examined current ACEi/ARB prescriptions on the index date (April 15th, 2017) as well as prior ACEi/ARB usage in 41,743 insured adults with proteinuric CKD. Using multivariable logistic regression, we estimated adjusted associations between current ACEi/ARB use and putative barriers including past AKI, hyperkalemia, advanced CKD, and lack of nephrology care.

Results—Only 49% of patients had an active ACEi/ARB prescription on the index date, but 87% had been previously prescribed an ACEi/ARB. Usage was lower in patients with past AKI, hyperkalemia, CKD stages 4 or 5, and a lack of nephrology care (adjusted odds ratios and 95% confidence intervals were 0.61(0.58–0.64), 0.76 (0.72–0.80), 0.48 (0.45–0.51), and 0.85 (0.81–0.89), respectively).

Conclusions—Discontinuing, rather than never initiating, ACEi/ARB limits guideline-concordant care in proteinuric CKD. Past AKI, hyperkalemia, advanced CKD, and lack of nephrology care were associated with lower use of ACEi/ARB, but these putative barriers may in many instances be inappropriate (AKI, advanced CKD) or modifiable (hyperkalemia, lack of nephrology care).

Keywords

clinical practice guideline; chronic kidney diseases; angiotensin-converting enzyme inhibitors; angiotensin receptor blockers

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INTRODUCTION

Inhibitors of the renin angiotensin aldosterone system (RAAS) slow the progression of proteinuric chronic kidney disease (CKD), providing patients with additional years free from dialysis[1–4]. Guidelines from the Kidney Disease Improving Global Outcomes (KDIGO)[5], the National Quality Forum[6], and others[7] recommend that an angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACEi) be used in patients with proteinuric CKD. Recently this metric was endorsed by the American Society of Nephrology Quality Committee and rated as highly valid[8].

Yet in this population, ACEi/ARB use remains the exception rather than the rule. In 2008, the Centers for Medicare and Medicaid Services (CMS) Physician Quality Reporting Initiative (PRQI) claims option indicated that 45% of patients failed to receive an ACEi/ARB, and significant variations in performance were noted across the program[6,9]. Data from the National Ambulatory Medical Care Survey (NAMCS) showed that ACEi/ARB use in CKD defined by ICD-9/10 codes decreased from 45% in 2006–2008 to 36% in 2012–2014[10]. An analysis of National Health and Nutrition Examination Survey (NHANES) data defining CKD by estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 or urinary albumin to creatinine ratio (UACR) ≥30 mg/g similarly found prevalence of ACEi/ARB use 39–40% during this period[11]. Reasons for this disconnect between guideline recommendations and practice are unclear.

Barriers to RAAS inhibition may include fear of acute kidney injury (AKI) or hyperkalemia, concerns for higher risk in the presence of other medications such as non-steroidal anti-inflammatory drugs (NSAIDs), or other unrecognized barriers such as clinician training. Many of these barriers may be modifiable, such as treating hyperkalemia with diuretics or oral binding resins. In this study, we investigated modern ACEi/ARB use in adults with proteinuric CKD and possible barriers to therapy in a nationwide claims and integrated database.

METHODS

The Clinformatics Data Mart, OptumInsight Life Sciences dataset (OptumInsight, Eden Prairie, MN) is a single-payer, closed data system that consists of patient-level administrative and demographic information, including but not limited to type of insurance plan, age, sex, income, medical and prescription claims, laboratory values, and unique identifiers for linking patients. We used fully de-identified data from this large claims and integrated database that included employed and commercially insured patients in the United States. This study was approved by the Institutional Review Board of Stanford University.

We studied adults (age ≥18 years) with proteinuric CKD, defined as a UACR ≥300 mg/g or a urine protein to creatinine ratio (UPCR) ≥500 mg/g[12] using the maximums of all values prior to the index date of April 15, 2017 (Figure 1). We sequentially removed patients without at least one year of continuous enrollment, patients without medication information, and patients without data required for eGFR calculation (race and serum creatinine within

five years of the index date) using the four-variable Chronic Kidney Disease Epidemiology Collaboration formula[13].

ACEi/ARB Use Outcome

Our primary outcome was current use of an ACEi or ARB on the index date, operationalized as the prescription date + the number of days prescribed including April 15, 2017. We also described past ACEi/ARB use defined as any prescription before the index date.

Putative Barriers

We hypothesized that patients with histories of AKI or hyperkalemia, or current NSAID use would be prescribed ACEi/ARB less frequently. AKI was defined as any prior International Classification of Diseases, 9th or 10th Edition (ICD-9/10) codes for AKI (584.x/N17.x). Hyperkalemia was defined as either a prior ICD-9/10 code (276.7/E87.5), or laboratory serum potassium value >5.5 mmol/L, or past prescription of patiromer sorbitex calcium or sodium polystyrene sulfonate. NSAID use was defined by prescription including the index date (use of over-the-counter NSAIDs could not be assessed).

Covariate Definitions

We defined the following comorbidities by inpatient and/or outpatient ICD-9/ICD-10 codes (Supplemental Material) recorded before the index date: hypertension, diabetes mellitus, ischemic heart disease, heart failure (all types), cerebrovascular disease, and peripheral arterial/vascular disease. We obtained sociodemographic variables from the Optum SES Member file (SES data file, v. 7.0). We defined moderate to heavy proteinuria as UACR ≥700 mg/g or UPCR ≥1000 mg/g[12,14], which approximated median values in our cohort. We also examined concurrent prescriptions for other medications which might be expected to modify the risks of selected complications of ACEi/ARB use, including loop diuretics, thiazide and thiazide-type agents, and mineralocorticoid receptor antagonists (MRA; spironolactone and eplerenone). Finally, we defined nephrology care as a visit with a nephrologist within the year prior to the index date.

Statistical Analysis

We report raw proportions of patients with current and past ACEi/ARB use. We performed multivariable logistic regression to assess associations among putative barriers to ACEi/ARB prescription (hyperkalemia, AKI, NSAID use) and current ACEi/ARB use, and adjusting for the following covariates using backwards variable selection with $p < 0.05$ to stay: age, sex, race, comorbidities, CKD stage, concurrent diuretic use, moderate to heavy proteinuria, and lack of nephrology care. The residual association of age with ACEi/ARB use (after accounting for eGFR) was modeled as a cubic spline. We repeated the regression in the subset with a history of hyperkalemia to look for distinct associations.

Finally, we performed several sensitivity analyses. To examine the possibility that some patients may have had a short lapse in ACEi/ARB prescriptions due to running out for a few days or having extra pills, we examined looser outcome definitions looking for ACEi/ARB prescriptions within 30 days and 90 days prior to the index date. To investigate the possibility that patients with CKD who were excluded from our cohort for missing

UACR/UPCR information have a different prevalence of ACEi/ARB use, we examined the proportion of patients with ACEi/ARB use in the larger Optum cohort of patients with CKD 3–5 defined by eGFR without any requirement for urinary albumin/protein measurements. To investigate the possibility that patients with CKD who were excluded from our cohort for missing eGFR (missing race or creatinine data) have a different prevalence of ACEi/ARB use, we examined the proportion of patients with ACEi/ARB use in patients with CKD defined by UACR/UPCR alone (no requirement for CKD stage). We performed all statistical analyses using SAS, v. 9.4 software (SAS Institute, Cary, NC).

RESULTS

We examined 41,743 adults with proteinuric CKD and available eGFR, UACR/UPCR, and prescription drug information. Clinical characteristics around the index date are shown in Table 1. The median age was 72 years, about half were female, and 15% were reported as Black. Almost all had hypertension (96%) and most had diabetes (81%). Most had CKD stage 3 (39%), but substantial proportions had stages 1 or 2 (36%) and stages 4 or 5 (25%).

In the cohort with complete eGFR and proteinuria data, 49% were currently on an ACEi/ARB (26% ACEi; 24% ARB) on the index date (Figure 2). This result was substantively unchanged in our sensitivity analyses looking at alternative CKD definitions (49% among 56,983 patients with proteinuric CKD without requirement for an eGFR measurement; and 44% among 339,673 patients with CKD 3–5 defined by eGFR alone). In the sensitivity analysis evaluating recent prescriptions that may not have included the index date, ACEi/ARB prescriptions were found for 52% and 61% of patients within 30 days and 90 days prior to the index date respectively (Supplemental Table 1).

The proportion of patients with at least one ACEi/ARB prescription in the past was much higher: 87%. Past ACEi/ARB use occurred a mean of 22 months prior to the index date, with mean enrollment in the database of 6.1 years prior to the index date.

Factors independently associated with ACEi/ARB use included history of AKI, history of hyperkalemia, CKD stage, and lack of nephrology care in the prior year (Table 2). Despite being an independent indication for ACEi/ARB use, systolic heart failure was paradoxically associated with lower odds of ACEi/ARB use, even after controlling for confounding variables, including history of AKI and hyperkalemia. All concurrent medication usages were associated with higher ACEi/ARB use, with thiazide and thiazide-type agents having the highest odds ratio (adjusted OR 5.10, 95% CI 4.75–5.47). Results were substantially unchanged in the subset of patients with a history of hyperkalemia (Supplemental Table 2).

DISCUSSION

We found that fewer than half (49%) of adult patients with proteinuric CKD were currently prescribed ACEi/ARBs, but most (87%) had been prescribed ACEi/ARBs in the past. This finding suggests that clinicians are aware that these medications are indicated in this patient population, but that barriers hinder continued use (“persistence”). Our results parallel those of a recent analysis of real-world clinical data that found that a majority of ACEi/ARB users discontinue treatment within five years[15].

A history of AKI was associated with 39% lower odds of ACEi/ARB use. Mild increases in serum creatinine are common after ACEi/ARB treatment, but the increases are usually <10% and increases >30% above baseline are uncommon[16,17]. This finding led to clinical practice guidelines recommending dose reduction or discontinuation of ACEi/ARBs in patients with >30% increase in serum creatinine[5,18,19], though this recommendation has been increasingly called into question[16,20,21]. While the odds of a modest rise in serum creatinine are higher at more advanced stages of CKD, the benefits of RAAS inhibition are not diminished in patients who experience a modest rise in serum creatinine[16,22,23]. In fact, several reports have found greater benefits of RAAS inhibition in patients who experience these modest rises in serum creatinine after treatment initiation[22,24,25]. Our finding that seeing a nephrologist increased the odds of ACEi/ARB use may reflect a more nuanced understanding of changes in serum creatinine that often occur following initiation or dose titration of ACEi/ARB. Changes to clinical practice guidelines moving away from creatinine-based cutoffs and towards individualized ACEi/ARB use based on a lack of hypotension or progressive creatinine rise may allow ACEi/ARB utilization to increase substantially.

Hyperkalemia was also associated with less frequent use of ACEi/ARB, and has been cited as the main reason for discontinuation by others[26]. Data from clinical trials and observational series suggest that up to 6–10% of patients develop hyperkalemia while on these medications[27], with most patients experiencing a 0.1–0.3 mmol/L rise in serum potassium after ACEi/ARB initiation[28]. However, there are numerous approaches that can be used to manage hyperkalemia in this setting. For example, in patients who require additional antihypertensive effect, the addition of a thiazide or thiazide-type agent to ACEi/ARB typically improves control of hypertension and corrects hyperkalemia. Oral sodium bicarbonate or other alkalinizing agents may help to correct hyperkalemia in patients with metabolic acidosis. Finally, several oral potassium binding resins (sodium and calcium polystyrene sulfonate, patiromer sorbitex calcium, and sodium zirconium cyclosilicate) have been widely used in moderate to advanced CKD. Indeed, we found that diuretic use and oral potassium binding resin use were associated with higher ACEi/ARB use. The recent AMBER trial demonstrated the ability of oral potassium binders to enable continued spironolactone treatment in resistant hypertension[29], and ongoing trials are evaluating their ability to enable ongoing RAAS blockade and improve cardiovascular outcomes in heart failure (PRIORITIZE HF;NCT03532009 and DIAMOND;NCT03888066, scheduled for completion by the end of 2021). Psychologically, clinicians may be predisposed to omit therapy due to unconsciously weighing potential harms more heavily than benefits of the same magnitude[30,31]. In this case, clinicians may be less prone to prescribe ACEi/ARB due to a fear of inducing hyperkalemia or a rise in serum creatinine (a harm), without due consideration of the benefits to CKD progression (a foregone gain). Concerns for harm from ACEi/ARB-induced hyperkalemia must be balanced against the harms of ACEi/ARB discontinuation, which has been associated with poorer outcomes in patients in whom ACEi/ARB was discontinued due to hyperkalemia[32,33].

Patients with CKD stages 4 and 5 were less than half as likely to be prescribed ACEi/ARB compared with patients with CKD stages 1 and 2, after adjusting for other putative barriers including hyperkalemia and AKI. Discontinuing ACEi/ARB therapy in advanced CKD is

not evidence-based. Although these patients may have greater risk of harm from ACEi/ARBs, they may also have greater benefit since the risk of progression to kidney failure is higher in this group. Clinical equipoise remains, although the ongoing STOP-ACEi trial (ISRCTN 62869767) may provide evidence to guide ACEi/ARB prescription in this population by 2022.

Prescription NSAID use was paradoxically associated with increased ACEi/ARB use, in contrast with our a priori hypothesis. We should note that most NSAID use is over-the-counter[34]. The presence of a prescription for NSAIDs may be a marker for clinician perception that the patient is at low risk for adverse effects from ACEi/ARB due to health factors not captured here. Mineralocorticoid receptor antagonists may have been associated with increased ACEi/ARB use for similar reasons.

Clinical practice guidelines recommend ACEi/ARB treatment for patients with ischemic heart disease or heart failure with reduced ejection fraction, where they have been consistently shown to reduce mortality and other cardiovascular events in large-scale, event-driven clinical trials[6,35,36]. The finding that the additional indication for ACEi/ARBs of systolic heart failure was associated with less ACEi/ARB use, independent of the examined barriers, suggests that other barriers are involved (e.g., lack of recognition of the additional indication, increased perceived risks, low blood pressure, etc.). Diabetes was associated with 44% higher odds of ACEi/ARB use, suggesting that clinicians may be especially cognizant of ACEi/ARB use in their proteinuric CKD patients with diabetes. Higher proteinuria (UACR ≥700 mg/g or UPCR ≥1000 mg/g) was associated with 10% higher odds of ACEi/ARB use, perhaps reflecting provider recognition of the stronger indication for ACEi/ARB use.

Our study has several strengths including real-world ACEi/ARB use data in a contemporary nationwide cohort and the integration of laboratory, claims, and prescription information that allows up to explore possible barriers to ACEi/ARB use. We were able to select proteinuric CKD, the population in which ACEi/ARB use has been shown to delay the need for dialysis, by laboratory measurements rather than administrative codes. Limitations include the use of single maximum proteinuria measurements rather than trends over time, and the possibility that we underestimated the prevalence of previous ACEi/ARB use since we do not have prescription information before enrollment in Optum (mean enrollment duration of 6.1 years prior to the index date). Hypotension can be a barrier to ACEi/ARB use[26]; although 96% of the primary cohort were diagnosed with hypertension, Optum lacks measured blood pressure and the presence of other indicated antihypertensives (e.g., beta-blockers for secondary prevention in ischemic heart disease or loop diuretics for volume control in heart failure) may result in insufficient blood pressure room to add an ACEi/ARB. The temporal relationship between ACEi/ARB and concurrent medications (i.e., which came first) cannot be assessed from these data. Finally, we cannot know the reasons why clinicians prescribed or did not prescribe ACEi/ARB for particular patients, and associations with putative barriers may not be causal.

CONCLUSION

In summary, we found that fewer than half of adults with proteinuric CKD were prescribed ACEi/ARB therapy, but most had been trialed on an ACEi or ARB in the past. Acute kidney injury, hyperkalemia, advanced CKD, and lack of nephrology care were associated with less ACEi/ARB use, but these barriers may be inappropriate (AKI, advanced CKD) or modifiable (hyperkalemia, lack of nephrology care). Further work is needed to overcome barriers to ACEi/ARB use in order to attenuate progression and abrogate complications of proteinuric CKD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Financial Support and Conflict of Interest Disclosure

This work was supported by National Institutes of Health grant numbers 5T32DK007357 (Dr. McCoy) and 2K24DK085446 (Drs. Chertow and Montez-Rath). Dr. Chertow serves on the Board of Directors of Satellite Healthcare, a non-profit dialysis provider, and serves on the Executive Committee of the PRIORITIZE HF trial, sponsored by AstraZeneca. There were no other relevant conflicts of interest.

ABBREVIATIONS

ACEi	Angiotensin converting enzyme inhibitor
AKI	acute kidney injury
ARB	Angiotensin receptor blocker
CKD	chronic kidney disease
eGFR	estimated glomerular filtration rate
MRA	mineralocorticoid receptor antagonist
NSAID	non-steroidal anti-inflammatory drug
RAAS	renin angiotensin aldosterone system
UACR	urinary albumin to creatinine ratio
UPCR	urinary protein to creatinine ratio

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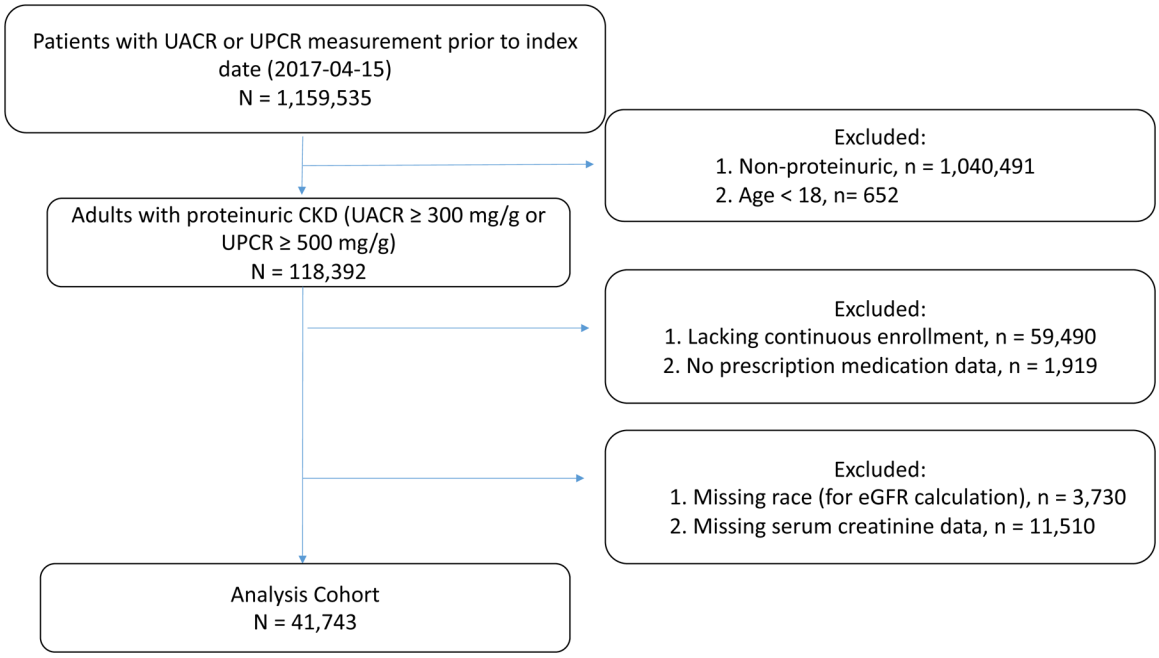

Figure 1.

Cohort assembly

UACR: urine albumin to creatinine ratio; UPCR: urine protein to creatinine ratio; eGFR: estimated glomerular filtration rate.

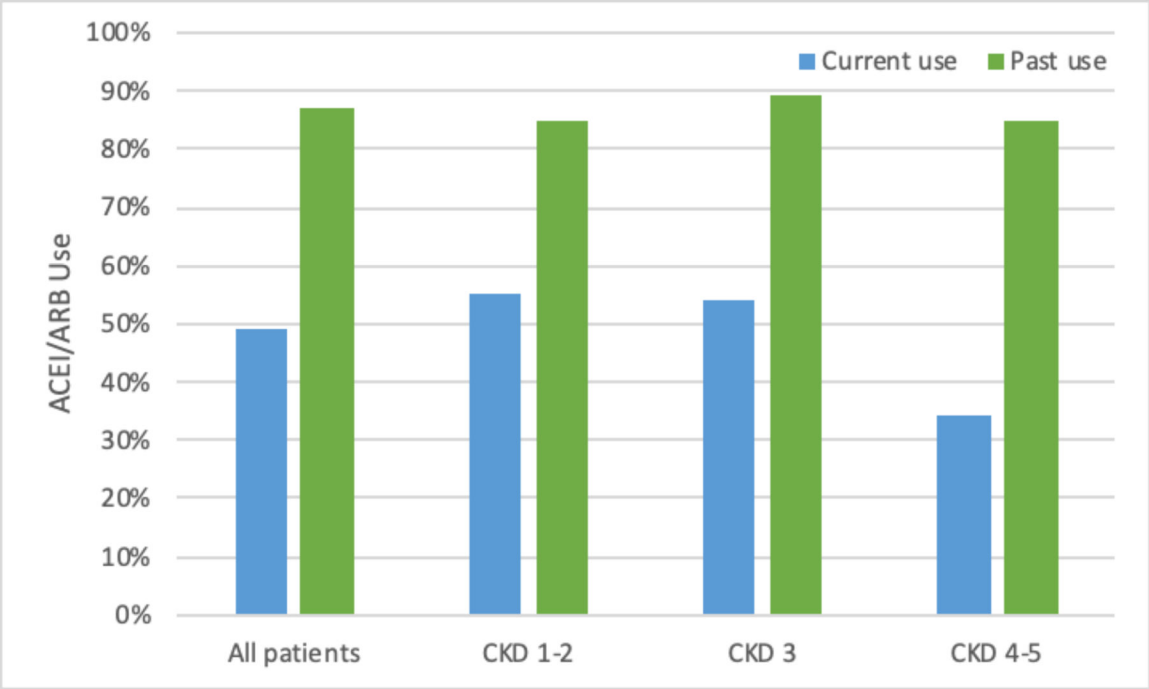

Figure 2.

Current and Past ACEi/ARB use by CKD stage.

ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Table 1.

Demographic and clinical characteristics of patients at baseline

Baseline Characteristics	All patients N = 41,743	CKD 1/2 N = 15,043	CKD 3 N = 16,361	CKD 4/5 N = 10,339
Age (yrs)	72 (62–79)	67 (55–75)	75 (68–81)	74 (66–81)
Female sex	47%	46%	46%	49%
Black race	15%	14%	14%	17%
Comorbidities				
Hypertension	96%	93%	98%	99%
Ischemic heart disease	50%	38%	54%	61%
Cerebrovascular disease	37%	27%	41%	46%
Peripheral vascular disease	39%	30%	42%	46%
Heart failure	39%	24%	42%	57%
Systolic heart failure	16%	8%	17%	26%
Diabetes mellitus	81%	79%	83%	82%
Laboratory data				
eGFR (ml/min/1.73 m^2)	48 (30–72)	81 (69–94)	44 (37–51)	20 (13–25)
UACR (mg/g)*	726 (401–1573)	611 (392–1128)	688 (383–1446)	1414 (564–3125)
UPCR (mg/g)*	1333 (714–3107)	983 (620–2066)	1082 (654–2242)	2326 (1047–5060)
History of hyperkalemia	33%	14%	34%	57%
History of AKI	42%	18%	47%	70%
Current prescription NSAID use	3%	4%	2%	1%
Current loop diuretic use	20%	11%	22%	30%
Current thiazide diuretic use	14%	17%	16%	9%
History of oral potassium binder use	6%	1%	5%	15%
Current MRA use	3%	3%	4%	2%
Lack of nephrology care in the last year	51%	76%	49%	19%

AKI: acute kidney injury; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; MRA: mineralocorticoid receptor antagonist; NSAID: non-steroidal anti-inflammatory drug; UACR: urinary albumin to creatinine ratio; UPCR: urinary protein to creatinine ratio. Binary variables presented as proportions. Continuous variables shown as median (25^{th}–75^{th} percentiles). UACR and UPCR had 24% and 47% missingness respectively, but all patients had either a UACR or a UPCR.

Table 2.

Factors independently associated with ACEi/ARB prescription

Characteristic	Adjusted OR	95% CI
History of AKI	0.61	(0.58–0.64)
History of hyperkalemia	0.76	(0.72–0.80)
Lack of nephrology care	0.85	(0.81–0.89)
CKD Stage (ref. stage 1/2)		
Stage 3	0.99	(0.94–1.04)
Stage 4/5	0.48	(0.45–0.51)
Hypertension	2.81	(2.47–3.19)
Systolic heart failure	0.77	(0.72–0.82)
Diabetes mellitus	1.39	(1.31–1.47)
High proteinuria	1.10	(1.05–1.14)
Loop diuretic use	1.80	(1.70–1.90)
Thiazide diuretic use	5.10	(4.75–5.47)
MRA use	1.36	(1.20–1.53)
Oral potassium binder use	1.43	(1.05–1.94)
NSAID use	1.53	(1.35–1.75)

ACEi: angiotensin converting enzyme inhibitor; AKI: acute kidney injury; ARB: angiotensin receptor blocker; CI: confidence interval; CKD: chronic kidney disease; MRA: mineralocorticoid receptor antagonist; OR: odds ratio; Medication usages refers to current use on the index date. Results are also adjusted for age, race, peripheral vascular disease, and cerebrovascular disease.