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BRIEF REPORT

Submaximal Angiotensin-Converting Enzyme Inhibitor and Angiotensin Receptor Blocker Dosing Among Persons With Proteinuria

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Abstract

For persons with proteinuria, angiotensin-converting enzyme inhibitors (ACEis) and angiotensin II receptor blockers (ARBs) are treatment mainstays for reducing kidney disease progression. Guidelines for managing hypertension and chronic kidney disease recommend titrating to the maximum ACEi/ARB dose tolerated. Using deidentified national electronic health record data from the Optum Labs Data Warehouse, we examined ACEi/ARB dosing among adults with proteinuria—defined as either a urine albumin to creatinine ratio of 30 mg/g or greater or a protein to creatinine ratio of 150 mg/g or greater—who were prescribed an ACEi/ARB medication between January 1, 2017, and December 31, 2018. Among 100,238 included patients (mean age, 65.1 years; 49,523 [49.4%] female), 29,883 (29.8%) were taking maximal ACEi/ARB doses. Among 74,287 patients without potential contraindications to dose escalation (systolic blood pressure <120 mm Hg, estimated glomerular filtration rate <15 mL/min per 1.73 m^2, serum potassium level greater than 5.0 mEq/L, or acute kidney injury within the prior year), the frequency of maximal ACEi/ARB dosing was 32.3% (24,025 patients). In adjusted analyses, age less than 40 years, female sex, Hispanic ethnicity, lower urine albumin to creatinine ratio, lack of diabetes, heart failure, lower blood pressure, higher serum potassium level, and prior acute kidney injury were associated with lower odds of maximal ACEi/ARB dosing. Having a prior nephrologist visit was not associated with maximal dosing. Our results suggest that greater attention toward optimizing the dose of ACEi/ARB therapy may represent an opportunity to improve chronic kidney disease care and reduce excess morbidity and mortality associated with disease progression.

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Angiotensin-converting enzyme inhibitors (ACEis) and angiotensin II receptor blockers (ARBs) are cornerstone treatments for reducing the progression of chronic kidney disease (CKD) with albuminuria.[1] Underutilization of ACEi/ARB therapy in CKD is a well-documented quality of care gap,[2-5] but there are limited data on whether persons with albuminuria receiving ACEi/ARB therapy are receiving the optimal doses of these medications for reducing CKD progression. Clinical practice guidelines for CKD with albuminuria recommend that ACEi/ARB therapy be titrated to the maximum approved dose that is tolerated[6,7] because suboptimal ACEi/ARB dosing is associated with greater CKD progression.[8,9] In addition, trials of new therapies with a documented kidney-protective benefit, including sodium-glucose cotransporter 2 inhibitors and nonsteroidal mineralocorticoid inhibitors, have required participants to be taking the maximal tolerated doses of ACEi/ARB therapy at baseline.[10,11]

Prior studies examining ACEi/ARB dosing in routine clinical practice settings have found that less than half of patients

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with CKD were receiving maximal doses.[9,12] These studies were limited by the use of diagnostic codes to define CKD and the lack of data on albuminuria. Critically, ACEi/ARB therapy is not indicated for all persons with CKD; rather, it is specifically indicated when albuminuria is present (although there may be indications for comorbidities, eg, heart failure with reduced ejection fraction).[6,7,13] Among persons with albuminuria, submaximal dosing represents an opportunity to optimize CKD care and prevent disease progression. To examine the extent of this gap in care with more relevant and accurate clinical information, we used a large national database to examine dosing of ACEi/ARB medications among patients with proteinuria receiving ACEi or ARB therapy.

PATIENTS AND METHODS

We conducted a cross-sectional study using the Optum Labs Data Warehouse, a longitudinal, real-world data set with deidentified electronic health record data. Our study population comprised adults aged 18 years or older who were prescribed an ACEi/ARB medication between January 1, 2017, and December 31, 2018, and who had abnormal proteinuria—defined as either a urine albumin to creatinine ratio (UACR) of 30 mg/g or greater or urine protein to creatinine ratio (UPCR) of 150 mg/g or greater—at any time preceding the ACEi/ARB prescription. We excluded patients with end-stage kidney disease, defined as any prior receipt of dialysis or kidney transplant identified using *International Classification of Diseases* and Current Procedural Terminology codes. We also excluded patients receiving dual blockade with both ACEi and ARB therapy because it may be a reason for submaximal dosing of either agent. We excluded patients receiving sacubitril-valsartan, given that it is primarily prescribed and titrated for heart failure with reduced ejection fraction.

Additional variables were defined as follows based on a 1-year look-back period from each patient's "index" ACEi/ARB prescription, the initial ACEi/ARB prescription identified in the 2017-2018 study period. Blood pressure (BP) was defined as the median of outpatient readings over the preceding year, and laboratory values were based on the most recent values in this period. Estimated glomerular filtration rate (eGFR) was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine equation.[14] Clinical characteristics, including diabetes, heart failure, and history of acute kidney injury (AKI) were based on *International Classification of Diseases* codes documented from all encounters over the 1-year look back. Prior nephrology care was defined as having at least one outpatient encounter with a nephrologist during the 1-year look back.

We calculated the proportion of patients taking the maximal dose of ACEi or ARB medications, based on the Lexicomp database maximum recommended oral dose for adults for treatment of hypertension (Supplemental Table, available online at http://www.mayoclinicproceedings.org). We then determined the proportion receiving maximal ACEi/ARB therapy among patients without any apparent contraindications to ACEi/ARB dose escalation: systolic BP, less than 120 mm Hg; eGFR, less than 15 mL/min per 1.73 m^2; serum potassium, less than 5.0 mEq/L (to convert value to mmol/L, multiply by 1.0); and AKI (within the prior year). We used multivariable logistic regression to assess independent associations between demographic or comorbidity-related factors and maximal dosing, including demographic characteristics (age, sex, race, ethnicity) and clinical parameters (systolic BP, eGFR, UACR, serum potassium, diabetes mellitus, heart failure, cerebrovascular disease, use of potassium-modulating medications [loop, thiazide-type, and potassium-sparing diuretics], and prior nephrology care). For patients who only had a UPCR, we used a validated conversion to calculate UACR.[15] The linearity of associations between maximal ACEi/ARB dosing and other variables was explored using restricted cubic splines. To simplify presentation and interpretation of results, statistically significant nonlinear relationships with age, systolic BP, and serum potassium

TABLE. Study Population Characteristics[a,b,c]

Characteristic	Overall (N=100,238)	Submaximal dose (n=70,355)[d]	Maximal dose (n=29,883)[d]
Age (y), mean ± SD	65.1±13.5	64.3±14.0	66.8±12.1
Female sex	49,523 (49.4)	34,878 (49.6)	14,645 (49.0)
Race			
Asian	1775 (1.8)	1337 (1.9)	438 (1.5)
Black	16,135 (16.1)	10,372 (14.7)	5763 (19.3)
White	78,539 (78.4)	55,817 (79.3)	22,722 (76.0)
Other/unknown	3789 (3.8)	2829 (4.0)	960 (3.2)
Hispanic ethnicity	4587 (4.6)	3489 (5.0)	1098 (3.7)
Hypertension	86,136 (85.9)	58,401 (83.0)	27,735 (92.8)
Systolic blood pressure (mm Hg), mean ± SD	134±19	133±19	138±20
Diabetes mellitus	83,404 (83.2)	58,136 (82.6)	25,268 (84.6)
Cerebrovascular disease	9294 (9.3)	6443 (9.2)	2851 (9.5)
eGFR (mL/min/1.73 m^2), mean ± SD	74±26	76±26	71±25
eGFR category (mL/min/1.73 m^2)			
≥60	69,161 (69.0)	49,653 (70.6)	19,508 (65.3)
45-59	16,085 (16.0)	10,637 (15.1)	5448 (18.2)
30-44	10,595 (10.6)	7132 (10.1)	3463 (11.6)
15-29	3777 (3.8)	2540 (3.6)	1237 (4.1)
<15	620 (0.6)	393 (0.6)	227 (0.8)
Albuminuria category (mg/g)			
30-299	81,459 (81.3)	58,204 (82.7)	23,255 (77.8)
≥300	18,779 (18.7)	12,151 (17.3)	6628 (22.2)
Thiazide-type diuretic use	36,336 (36.2)	21,273 (30.2)	15,063 (50.4)
Loop diuretic use	33,304 (33.2)	22,378 (31.8)	10,926 (36.6)
Potassium-sparing diuretic use	12,956 (12.9)	8136 (11.6)	4820 (16.1)
Serum potassium (mEq/L), mean ± SD	4.3±0.5	4.3±0.5	4.2±0.5
Prior acute kidney injury	8571 (8.6)	6413 (9.1)	2158 (7.2)
Prior nephrology encounter	8374 (8.4)	5733 (8.1)	2641 (8.8)

[a]eGFR, estimated glomerular filtration rate.
[b]Data are presented as No. (percentage) of patients unless indicated otherwise.
[c]SI conversion factors: To convert potassium values to mmol/L, multiply by 1.0.
[d]All comparisons of characteristics between submaximal and maximal dose groups are statistically significant to $P<.001$ except for sex ($P=.102$) and cerebrovascular disease ($P=.058$).

were modeled as categorical variables (age <40, 40 to 49, 50 to 59, 60 to 69, 70 to 79, and ≥80 years; systolic BP <100, 100 to 119, 120 to 129, 130 to 139, and ≥140 mm Hg; serum potassium <3.5, 3.6 to 4.0, 4.1 to 4.5, 4.6 to 5.0, and >5.0 mEq/L).

In a secondary analysis, to examine whether maximal ACEi/ARB dosing varied by risk of kidney failure, we computed the predicted kidney failure risk for each patient using the Kidney Failure Risk Equation, a widely validated model for predicting the need for dialysis or kidney transplant within 5 years using age, sex, eGFR, and UACR as inputs.[16,17] We then determined the proportion of patients receiving maximal ACEi/ARB dose by quintile of kidney failure risk.

All statistical analyses were conducted using R statistical software, version 4.0.2 (R Project for Statistical Computing). The University of California, San Francisco Institutional Review Board considered this study exempt from review because it involved deidentified, preexisting data.

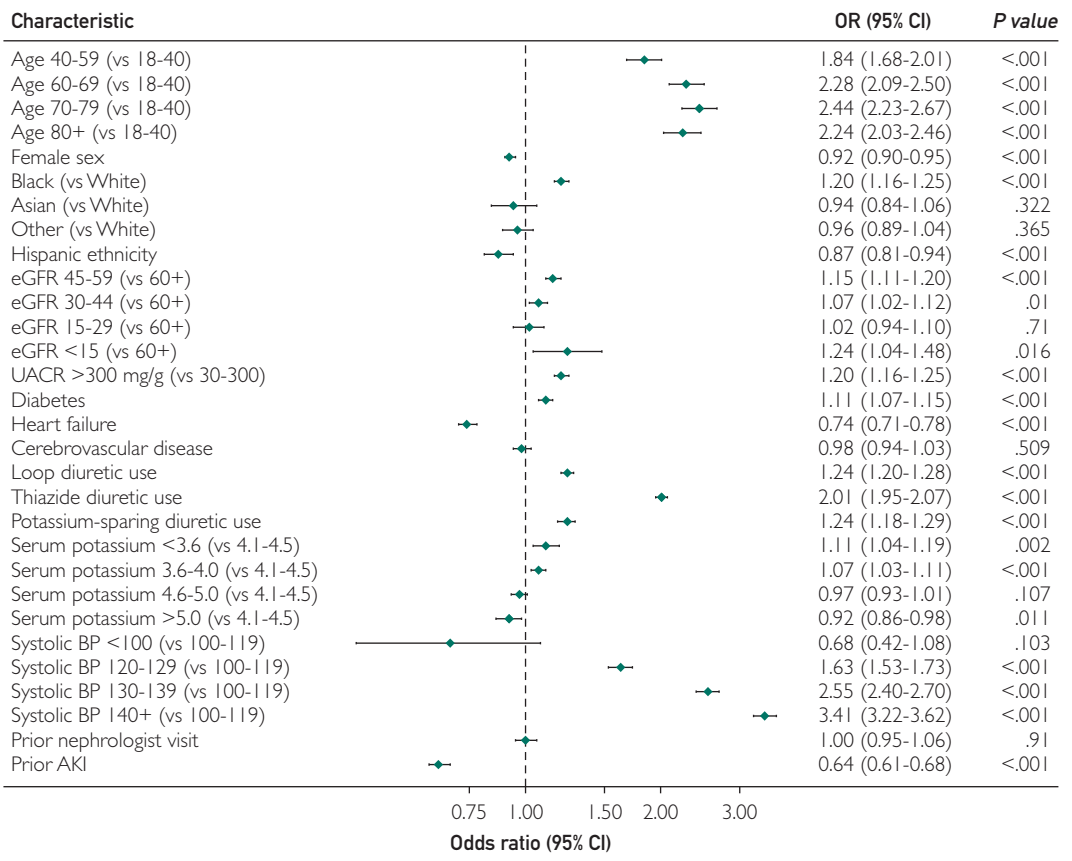

FIGURE 1. Adjusted odds ratios (ORs) and 95% CIs for maximal angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker dose in 100,238 study patients. Data are adjusted for all variables shown. AKI, acute kidney injury; BP, blood pressure (mm Hg); eGFR, estimated glomerular filtration rate (mL/min per 1.73 m^2); UACR, urine albumin to creatinine ratio. Serum potassium levels shown as mEq/L

RESULTS

Derivation of the study population is shown in the Supplemental Figure (available online at http://www.mayoclinicproceedings.org). Among the 100,238 study participants, the mean ± SD age was 65.1±13.5 years; 49,523 (49.4%) were female (Table). The most common ACEi/ARB drug was lisinopril (in 55,356 patients [55.2%]), followed by losartan (28,188 patients [28.1%]). In the prior year, 8374 patients (8.4%) had a visit with a nephrologist.

In total, 29,883 patients (29.8%) were taking maximal ACEi/ARB doses. Among 74,287 patients without any apparent contraindication to dose escalation, 24,025 (32.3%) were prescribed maximal ACEi/ARB therapy, compared with 22.6% (5858 of 25,951) among patients having at least one contraindication. In fully adjusted analyses, higher systolic BP categories were associated with progressively greater odds of maximal dosing (Figure 1). A serum potassium level of greater than 5.0 mEq/L was associated with less maximal dosing compared with 4.1 to 4.5 mEq/L (adjusted odds ratio [aOR], 0.92; 95% CI, 0.86 to 0.98). Prior AKI was associated with less maximal dosing (aOR, 0.64; 95% CI, 0.61 to 0.68). Compared with an eGFR level of 60 mL/min per 1.73 m^2 or higher, lower eGFR categories were associated with increased odds of maximal dosing, with the exception of the group with an eGFR level of 15 to 29 mL/min per 1.73 m^2. Other factors associated with maximal dosing included older age categories

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(compared with 18 to 40 years), female sex, Black race (compared with White), non-Hispanic ethnicity, greater albuminuria (UACR >300 compared with 30 to 300 mg/g), diabetes, and use of diuretics. A history of heart failure was associated with less maximal dosing (aOR, 0.74; 95% CI, 0.71 to 0.78). Prior nephrology care was not associated with maximal therapy (aOR, 1.00; 95% CI, 0.95 to 1.06; P=.91).

Figure 2 shows the proportions of patients receiving maximal ACEi/ARB dosing by quintiles of predicted 5-year kidney failure risk. With higher kidney failure risk, there was a monotonic increase in the proportion of patients receiving maximal ACEi/ARB treatment, from 21.4% in the lowest risk quintile to 33.8% in the highest risk quintile (test for trend, P<.001), although maximal dosing was similar in the 2 highest risk groups.

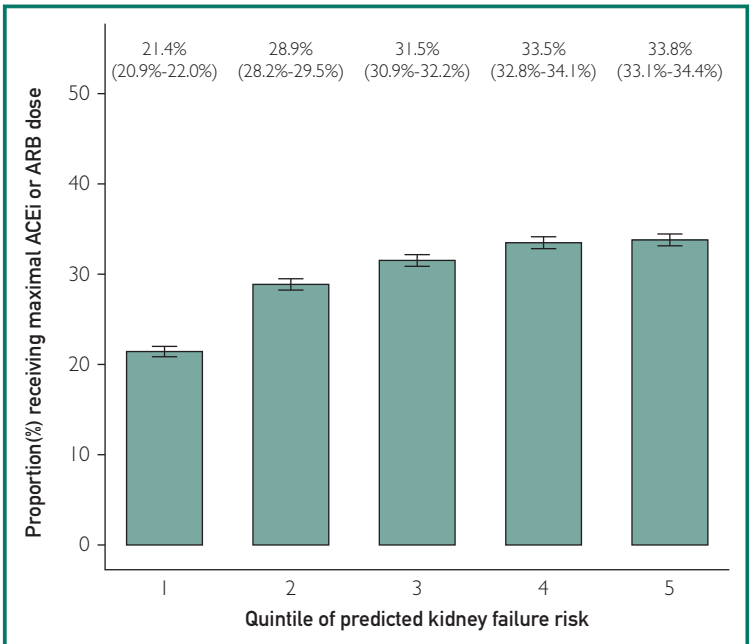

FIGURE 2. Proportion of 100,238 study patients receiving maximal angiotensin-converting enzyme inhibitor (ACEi)/angiotensin II receptor blocker (ARB) dose by kidney failure risk. Quintile of predicted kidney failure risk is ordered from lowest risk (1) to highest risk (5). Risk thresholds delineating the quintiles are 0.006%, 0.03%, 0.2%, and 1.3%. Predicted kidney failure risk was obtained using the Kidney Failure Risk Equation with age, sex, estimated glomerular filtration rate, and urine albumin to creatinine ratio as inputs. Error bars represent 95% CIs. Proportions taking maximal ACEI/ARB dose (95% CIs) are shown above each quintile bar. Test for trend P value is less than .001.

DISCUSSION

Among persons with proteinuria receiving ACEi/ARB therapy in a large national US population, approximately 70% were taking submaximal doses. Even among those without apparent contraindications to dose escalation, 68% were taking submaximal doses. Among common barriers to ACEi/ARB up-titration, we found that lower BP and prior AKI were strongly associated with less maximal dosing. Other notable factors associated with less maximal dosing included female sex, Hispanic ethnicity, younger age, lack of diabetes, heart failure, and lower albuminuria (UACR, 30 to 300 vs >300 mg/g). The positive association between kidney failure risk and maximal dosing was an encouraging finding given the kidney-protective benefit of ACEi/ARB therapy, despite the study population having low absolute kidney failure risk. However, even in the highest risk quintile, only about 34% of individuals were taking maximal doses, suggesting that a large opportunity remains for optimizing cardiovascular and kidney failure preventive care in CKD with proteinuria.

The finding that heart failure was associated with reduced odds of maximal therapy was surprising given that heart failure with reduced ejection fraction is a well-recognized indication for ACEi/ARB treatment independent of proteinuria, with documented mortality benefit in randomized clinical trials.[18] However, our data are consistent with those of a previous study examining electronic health record data of patients with indications for ACEi/ARB therapy.[12] In that population, only 23% of patients with heart failure receiving ACEi/ARB therapy were receiving maximal doses, compared with 27% for patients without heart failure. Patients with heart failure are often treated with low doses of multiple antihypertensives as part of guideline-directed medical therapy (eg, β-blockers, mineralocorticoid antagonists), which may leave insufficient BP "room" for ACEi/ARB maximization. Although we adjusted for potentially confounding factors, residual or

unmeasured confounding may still be explanations for the association of heart failure with less maximal dosing.

We found that higher systolic BP was associated with greater maximal dosing. Clinicians may intensify ACEi/ARB therapy more actively for patients with uncontrolled hypertension, as elevated BP is monitored and recognized frequently in routine clinical practice. Meanwhile, there may be less immediate impetus to up-titrate guideline-indicated medications for heart failure or CKD once initiated. This issue suggests that greater emphasis and guidance on ACEi/ARB dosage should be included in educational or quality improvement interventions seeking to optimize guideline-recommended care for kidney failure and cardiovascular risk reduction, beyond recording any use of ACEi/ARB therapy as sufficient for achieving quality metric goals.

Higher serum potassium level was associated with less maximal dosing. Concerns about hyperkalemia may contribute to submaximal dosing, but hyperkalemia is modifiable with novel potassium-binding agents and concomitant diuretic use, which may facilitate continuation and dose optimization of ACEi/ARB therapy.[19] As an alternative to treatment discontinuation due to hyperkalemia or AKI, nephrology consultation could play a role in providing individualized strategies to help maintain and optimize ACEi/ARB therapy. We did not find that a prior nephrology encounter was associated with more maximal dosing, although the lack of a notable association may be subject to confounding by indication. Patients referred to nephrologists may have greater risk for AKI or hyperkalemia for reasons not captured in the models and therefore be less likely to have up-titration to maximal ACEi/ARB doses. Nevertheless, the importance of optimizing ACEi/ARB therapy dosing for reducing cardiovascular and CKD progression risk should be emphasized for both primary care and subspecialty clinicians.

Our study had several strengths. We examined ACEi/ARB therapy among patients with documented proteinuria, which is the specific CKD population for which ACEi/ARB therapy has been found to be beneficial and is guideline-recommended. We were able to identify patients with proteinuria using direct laboratory measurements rather than administrative billing codes for CKD, which often do not specify the presence of proteinuria. We examined a subgroup without apparent contraindications to ACEi/ARB dose escalation to best quantify the actionable gap in care constituting a realistic opportunity for improvement.

Limitations of our study include imperfect assessment of contraindications to ACEi/ARB up-titration and the cross-sectional design limiting interpretation of factors affecting ACEi/ARB dose. Additionally, our analysis likely included some patients newly receiving ACEi/ARB treatment without sufficient time for up-titration. Given the infrequency of proteinuria ascertainment in clinical practice,[20] we defined proteinuria based on a single UACR or UPCR measurement, rather than averages or trends over time. Thus, we could not account for longitudinal factors, such as proteinuria trajectories or treatment response, which could influence ACEi/ARB titration decisions. We defined BP using the median outpatient reading over the preceding year, but it is unlikely that a single definition will fully reflect how clinicians view, integrate, and act on BP measurements. We chose 120/80 mm Hg as the threshold below which to defer ACEi/ARB up-titration in a subgroup analysis, but this threshold may be subject to substantial variability across clinical practice patterns. For patients with well-controlled BP, we could not reliably assess the possibility that these patients could be candidates for ACEi/ARB up-titration if they received concomitant reduction of other antihypertensive medications.

CONCLUSION

Among adults with proteinuria prescribed ACEi/ARBs, a majority were taking submaximal doses, even among patients lacking apparent contraindications to ACEi/ARB up-titration. Our results suggest that greater attention toward optimizing the dose of ACEi/ARB therapy may represent an

opportunity to improve CKD care and reduce excess morbidity and mortality associated with CKD progression.

POTENTIAL COMPETING INTERESTS

Dr Chu has received research funding from Bayer AG, outside the submitted work (funds paid to his institution). Dr Estrella has received research funding from Bayer AG and Booz Allen Hamilton Inc, outside the submitted work (funds paid to her institution); has received consulting fees from Boehringer Ingelheim GmbH; and has had a leadership or fiduciary role with Milken Institute (unpaid). Dr Shlipak has received research support from Bayer AG, outside the submitted work (funds paid to his institution). The other authors report no competing interests.

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Author Contributions: Dr Chu—Conceptualization, data curation, formal analysis, methodology, writing/original draft; Dr Powe—Methodology, supervision, writing/review, editing; Dr Estrella—Methodology, writing/review, editing; Dr Shlipak—Methodology, writing/review, editing; Dr McCoy—Methodology, writing/review, editing; Dr Tuot—Conceptualization, methodology, supervision, writing/review, editing.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **ACEi**, angiotensin-converting enzyme inhibitor; **AKI**, acute kidney injury; **aOR**, adjusted odds ratio; **ARB**, angiotensin II receptor blocker; **BP**, blood pressure; **CKD**, chronic kidney disease; **eGFR**, estimated glomerular filtration rate; **UACR**, urine albumin to creatinine ratio; **UPCR**, urine protein to creatinine ratio

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