Title

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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 (ACEi) and angiotensin II receptor blockers (ARB) 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 de-identified national electronic health record data from the Optum Labs Data Warehouse, we examined ACEi/ARB dosing among adults with proteinuria, defined as either urine albumin/creatinine ratio (UACR) ≥30 mg/g or protein/creatinine ratio ≥150 mg/g, who were prescribed an ACEi/ARB medication between January 1, 2017 and December 31, 2018. Among 100,238 included patients (mean age 65 years; 49.4% female), 29.8% (n=29,883) were on maximal ACEi/ARB doses. Among patients (n=74,287) without potential contraindications to dose escalation (systolic blood pressure <120 mmHg, estimated glomerular filtration rate <15 ml/min/1.73m^2, serum potassium >5.0 mEq/L, or acute kidney injury [AKI] within the prior year), the frequency of maximal ACEi/ARB dosing was 32.3%. In adjusted analyses, age <40 years, female sex, Hispanic ethnicity, lower UACR, lack of diabetes, heart failure, lower blood pressure, higher serum potassium, and prior AKI 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.

Introduction

Angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) 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-

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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] as suboptimal ACEi/ARB dosing is associated with greater CKD progression.[8,9] In addition, trials of new therapies with a demonstrated kidney-protective benefit, including sodium-glucose cotransporter 2 inhibitors and nonsteroidal mineralocorticoid inhibitors, have required participants to be on 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 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, e.g., 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.

Methods

We conducted a cross-sectional study using the Optum Labs Data Warehouse, a longitudinal, real-world dataset with deidentified electronic health record data. Our study population comprised adults age ≥18 years who were prescribed an ACEi/ARB medication between 1/1/2017 and 12/31/2018 and who had abnormal proteinuria, defined as either urine albumin/creatinine ratio (UACR) ≥30 mg/g or protein/creatinine ratio (UPCR) ≥150 mg/g, 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 transplantation identified using *International Classification of Diseases* (ICD) and *Current Procedural Terminology* codes. We also excluded patients receiving dual blockade with both ACEi and ARB therapy, as this 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 lookback 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 CKD-Epidemiology Collaboration creatinine equation.[14] Clinical characteristics, including diabetes, heart failure, and history of acute kidney injury (AKI) were based on ICD codes documented from all encounters over the 1-year lookback. Prior nephrology care was defined as having at least one outpatient encounter with a nephrologist during the 1-year lookback.

We calculated the proportion 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 1). We then determined the proportion on maximal ACEi/ARB therapy among patients without any apparent contraindications to ACEi/ARB dose escalation: systolic BP <120 mmHg, eGFR <15 ml/min/1.73m^2, serum potassium >5.0 mEq/L, 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 were modeled as categorical variables (age <40, 40-49, 50-59, 60-69, 70-79, and ≥80 years; systolic BP <100, 100-119, 120-129, 130-139, and ≥140 mmHg; serum potassium <3.5, 3.6-4.0, 4.1-4.5, 4.6-5.0, >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 (KFRE), a widely validated model for predicting the need for dialysis or kidney transplantation within 5 years using age, sex, eGFR, and UACR as inputs.[16] 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 version 4.0.2 (R Project for Statistical Computing). The University of California, San Francisco Institutional Review Board considered this study exempt from review as it involved deidentified, pre-existing data.

Results

Derivation of the study population is shown in Supplemental Figure 1. Among the included study participants (n=100,238), mean (SD) age was 65 (14) years; 49.4% were female (Table 1). The most common ACEi/ARB drug was lisinopril (55.2%; n=55,356), followed by losartan (28.1%; n=28,188). In the prior year, 8,374 patients (8.4%) had a visit with a nephrologist.

In total, 29.8% (n=29,883) were on maximal ACEi/ARB doses. Among 74,287 patients without any apparent contraindication to dose escalation, 32.3% (n=24,025) were prescribed maximal ACEi/ARB therapy, compared with 22.6% (5,858/25,951) 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). Serum potassium >5.0 mEq/L was associated with less maximal dosing compared with 4.1-4.5 mEq/L (adjusted OR 0.92; 95% CI 0.86, 0.98). Prior AKI was associated with less maximal dosing (aOR 0.64; 95% CI 0.61, 0.68). Compared with eGFR ≥60 ml/min/1.73m^2, lower eGFR

categories were associated with increased odds of maximal dosing, with the exception of the eGFR 15-29 ml/min/1.73m^2 group. Other factors associated with maximal dosing included older age categories (compared with 18-40 years), female sex, Black race (compared with White), non-Hispanic ethnicity, greater albuminuria (UACR >300 compared with 30-300 mg/g), diabetes, and use of diuretics. History of heart failure was associated with less maximal dosing (aOR 0.74; 95% CI 0.71, 0.78). Prior nephrology care was not associated with maximal therapy (aOR 1.00; 95% CI 0.95, 1.06; p=0.91).

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<0.001), although maximal dosing was similar in the two highest risk groups.

Discussion

Among persons with proteinuria receiving ACEi/ARB therapy in a large national US population, approximately 70% were on submaximal doses. Even among those without apparent contraindications to dose escalation, 68% were on submaximal doses. Among common barriers to ACEi/ARB uptitration, 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 30-300 versus >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 on maximal doses, suggesting that a large opportunity remains for optimizing cardiovascular and kidney 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 demonstrated mortality benefit in randomized clinical trials.[18] However, our data are consistent with 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 on ACEi/ARB therapy were receiving maximal doses, compared with 27% for patients without heart failure. Heart failure patients are often treated with low doses of multiple antihypertensives as part of guideline-directed medical therapy (e.g., beta 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 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 uptitrate guideline-indicated

medications for heart failure or CKD once initiated. This 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 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 significant 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 be titrated 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 demonstrated proteinuria, which is the specific CKD population for which ACEi/ARB therapy has been shown 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 uptitration and the cross-sectional design limiting interpretation of factors affecting ACEi/ARB dose. Additionally, our analysis likely included some patients newly on ACEi/ARB treatment without sufficient time for uptitration. 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 a single definition will fully reflect how clinicians view, integrate, and act on BP measurements. We chose 120/80 mmHg as the threshold below which to defer ACEi/ARB uptitration in a subgroup analysis, but this threshold may be subject to significant 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 uptitration if they received concomitant reduction of other antihypertensive medications.

Conclusion

In conclusion, among adults with proteinuria prescribed ACEi/ARBs, a majority were on submaximal doses, even among patients lacking apparent contraindications to ACEi/ARB uptitration. 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Financial support and conflict of interest disclosure:

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Abbreviations

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
ESKD	end-stage kidney disease
ICD	International Classification of Diseases
KFRE	Kidney Failure Risk Equation
SD	standard deviation
UACR	urine albumin/creatinine ratio
UPCR	urine protein/creatinine ratio

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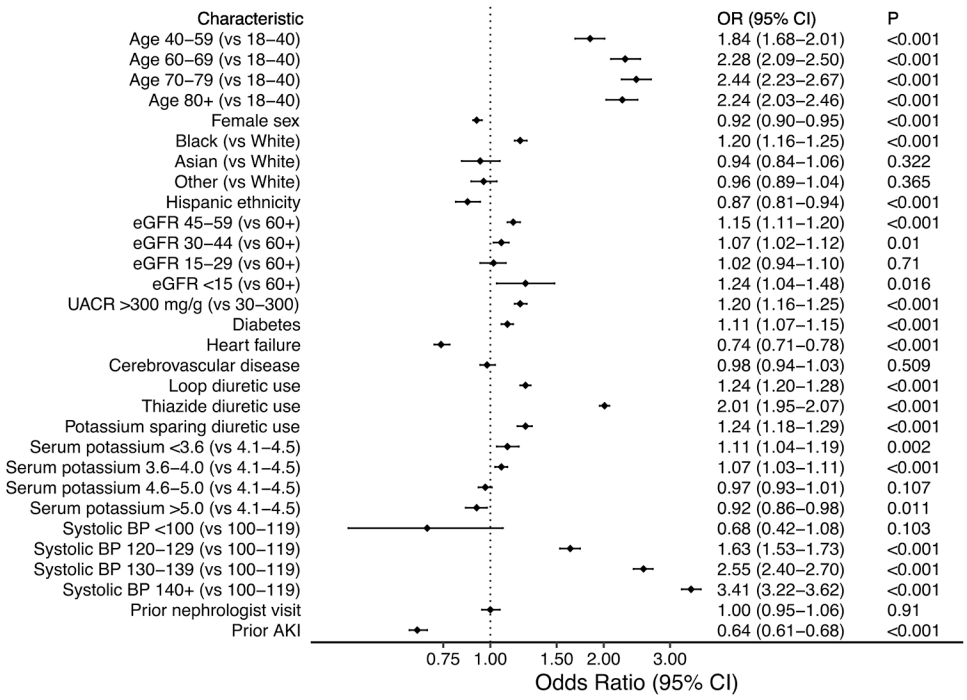

Figure 1. Adjusted Odds Ratios (95% CI) for Maximal ACEi/ARB Dose (N=100,238)

Data are adjusted for all variables shown. Abbreviations: ACEi, angiotensin converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; UACR, urine albumin/creatinine ratio.

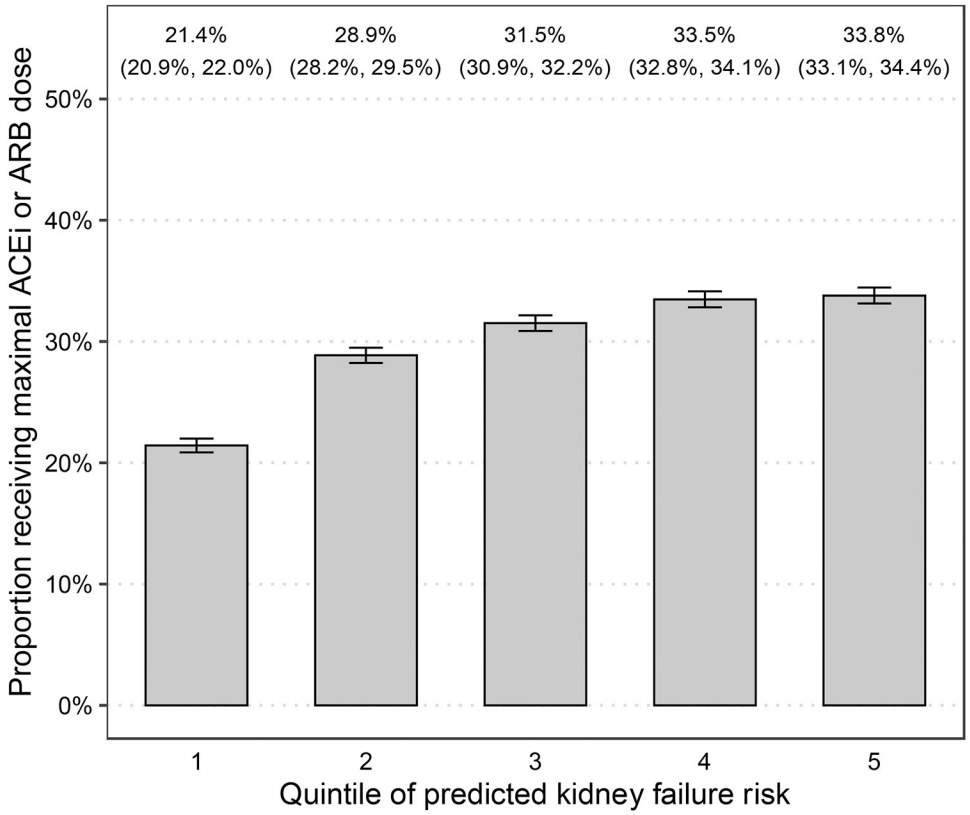

Figure 2. Proportion Receiving Maximal ACEi/ARB Dose by Kidney Failure Risk (N=100,238)

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/creatinine ratio as inputs. Error bars represent 95% confidence intervals. Proportions on maximal ACEI/ARB dose (95% confidence intervals) are shown above each quintile bar. Test for trend p value is <0.001. Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Table 1.

Study Population Characteristics

Characteristic	Overall	Submaximal dose[b]	Maximal dose[b]
N	100,238	70,355	29,883
Age in years, mean (SD)	65.1 (13.5)	64.3 (14.0)	66.8 (12.1)
Female sex, n (%)	49,523 (49.4)	34,878 (49.6)	14,645 (49.0)
Race, n (%)			
Asian	1,775 (1.8)	1,337 (1.9)	438 (1.5)
Black	16,135 (16.1)	10,372 (14.7)	5,763 (19.3)
White	78,539 (78.4)	55,817 (79.3)	22,722 (76.0)
Other/Unknown	3,789 (3.8)	2,829 (4.0)	960 (3.2)
Hispanic ethnicity, n (%)	4,587 (4.6)	3,489 (5.0)	1,098 (3.7)
Hypertension, n (%)	86,136 (85.9)	58,401 (83.0)	27,735 (92.8)
Systolic blood pressure (mmHg), mean (SD)	134 (19)	133 (19)	138 (20)
Diabetes mellitus, n (%)	83,404 (83.2)	58,136 (82.6)	25,268 (84.6)
Cerebrovascular disease, n (%)	9,294 (9.3)	6,443 (9.2)	2,851 (9.5)
eGFR (ml/min/1.73m^2), mean (SD)	74 (26)	76 (26)	71 (25)
eGFR category, n (%)			
≥60 ml/min/1.73m^2	69,161 (69.0)	49,653 (70.6)	19,508 (65.3)
45-59 ml/min/1.73m^2	16,085 (16.0)	10,637 (15.1)	5,448 (18.2)
30-44 ml/min/1.73m^2	10,595 (10.6)	7,132 (10.1)	3,463 (11.6)
15-29 ml/min/1.73m^2	3,777 (3.8)	2,540 (3.6)	1,237 (4.1)
<15 ml/min/1.73m^2	620 (0.6)	393 (0.6)	227 (0.8)
Albuminuria category, n (%)			
30-299 mg/g	81,459 (81.3)	58,204 (82.7)	23,255 (77.8)
≥300 mg/g	18,779 (18.7)	12,151 (17.3)	6,628 (22.2)
Thiazide-type diuretic use, n (%)	36,336 (36.2)	21,273 (30.2)	15,063 (50.4)
Loop diuretic use, n (%)	33,304 (33.2)	22,378 (31.8)	10,926 (36.6)
Potassium sparing diuretic use, n (%)	12,956 (12.9)	8,136 (11.6)	4,820 (16.1)
Serum potassium (mEq/L), mean (SD)	4.3 (0.5)	4.3 (0.5)	4.2 (0.5)
Prior acute kidney injury, n (%)	8,571 (8.6)	6,413 (9.1)	2,158 (7.2)
Prior nephrology encounter, n (%)	8,374 (8.4)	5,733 (8.1)	2,641 (8.8)

[a] Abbreviations: eGFR, estimated glomerular filtration rate; SD, standard deviation.

[b] All comparisons of characteristics between submaximal and maximal dose groups are statistically significant to p <0.001 except for sex (p=0.102) and cerebrovascular disease (p=0.058).