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НИРКИ KIDNEYS

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Current and Emerging Nephroprotective Strategies in Chronic Kidney Disease: From RAAS Inhibition to Novel Therapeutics

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ABSTRACT

Multidimensional nephroprotection is necessary for chronic kidney disease (CKD) as haemodynamic, metabolic, inflammatory and fibrotic mechanisms play key roles in disease progression. The objective of this study was to assess the use of known and new nephroprotective drugs in adults who had CKD in a cross-sectional, population-based study design. Studies with persons 20 years of age or older were considered. CKD was defined as urine albumin creatinine ratio ≥ 30 mg/g and/or estimated glomerular filtration rate < 60 mL/min/1.73 m². Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter-2 inhibitors were the categories of prescription drugs. Multivariable logistic regression and survey-weighted descriptive analyses were carried out. Angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors were used by 43.4% of the 1,003 persons with CKD. Mineralocorticoid receptor antagonists and sodium-glucose cotransporter-2 inhibitors were utilised by just 3.6% and 2.0% of individuals, respectively. The prevalence of use of RAAS inhibitors was 77.2% among persons with diabetes and hypertension. There was a positive association between increasing age, diabetes, and hypertension and increasing use of RAAS inhibitors, with hypertension having the greatest association. In summary, fewer that half of adults with the CKD received this therapy, and generally RAAS inhibition was the most widely used nephroprotective modality. The low adoption of emerging agents shows that there is still a chance to bridge the gap between therapeutic progress and actual deployment.

Keywords: Chronic kidney disease; nephroprotection; RAAS inhibitors; SGLT2 inhibitors; mineralocorticoid receptor antagonists.

1. Introduction

Minimal change disease (MCD) is a leading cause of idiopathic nephrotic syndrome in adults, accounting for

Abstract

Chronic Kidney Disease (CKD) is a advanced condition of more than 3 months' duration defined by the presence of increased risk of cardiovascular disease, structural renal damage, albuminuria and progressive decline in renal function. Long-term renoprotection is a multidimensional therapeutic challenge, as it is determined by interactions between various haemodynamic, metabolic, inflammatory, oxidative and fibrotic mechanisms(1). In conventional management, efforts have been directed towards optimizing blood pressure, lowering intraglomerular pressure, controlling diabetes, and blocking the renin angiotensin aldosterone system (RAAS)(2). However, even with standard treatment, renal and cardiovascular risks persist, underscoring the importance of more comprehensive treatment regimens (3). Because they lower intraglomerular pressure and albuminuria, angiotensin receptor blockers and angiotensin-converting enzyme inhibitors are essential treatments for chronic kidney disease.

Adverse events, however, including hyperkalaemia, hypotension, and a decrease in estimated GFR at the start of treatment, may lead to discontinuation or insufficient doses of RAAS blockade (4). The use of RAAS inhibitors remains a cornerstone of treatment

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and individualised monitoring and combinations that can enhance kidney protection without worsening treatment effects continue to be supported by recent evidence (5). Cardiovascular and renal therapies in the future could be further improved by small-molecule development targeting components of the RAAS (6). There has been a shift in the therapeutic options from traditional RAAS blockade. Renal benefits of sodium–glucose cotransporter-2 inhibitors include restoration of tubuloglomerular feedback, reduction of intraglomerular hypertension, natriuresis and favourable metabolic effects (7).

They are an important step towards multidrug nephroprotection in diabetic and non-DKD (8). The mineralocorticoid receptor pathway is implicated in inflammation, oxidative stress, endothelial dysfunction, and fibrosis, which are important processes to curb CKD progression (9). Other new cardiovascular and renal therapies could also be beneficial for decreasing vascular ageing and cardiovascular complications in individuals with diabetes and impaired kidney function (10). With the advancements in DKD, there are also novel promising therapies that target four key pathological processes, namely, inflammation, fibrosis, mitochondrial dysfunction, cellular stress, and metabolic injury (11). New targets have been identified through molecular investigations that could be used in combination with haemodynamic therapies and could offer more personalised nephroprotection (12).

Kidney-specific proteins are also being studied as targets for therapeutic intervention, which could make them more effective with fewer side effects throughout the body (13). Likewise, new biomarkers can be used as complementary tools to facilitate timely diagnosis, risk stratification, therapeutic decision making, and personalized therapeutic monitoring (14). Anti-inflammatory drugs, antifibrotic drugs, endothelin receptor antagonists, hypoxia-inducible factor modulators, incretin-based drugs and cellular senescence and oxidative stress inhibitors are some of the investigational strategies (15). Molecular mediators of renal fibrosis represent great targets for drug development, as it is a final common pathway of progressive CKD (16). Repurposing of drugs could help identify existing drugs that have not been previously studied for renal protection, which can then be used for a new purpose in a new disease (17). Other natural compounds have also exhibited antioxidant and anti-inflammatory properties, which warrant further support from controlled studies for clinical use (18).

The objective of the present study was to investigate the use of existing and novel nephroprotective therapies in adult patients with CKD. This included the use of sodium–glucose cotransport-2 inhibitors, RAAS inhibitors, mineralocorticoid receptor antagonists, kidney function tests, and albuminuria. The aims were to describe the treatment patterns, to compare the clinical characteristics of treated and non-treated patients, to identify factors associated with the use of RAAS inhibitors, and to evaluate potential gap in the use of newer kidney-protective drugs.

2. Materials and Methods

2.1 Study Design and Study Population

A cross-sectional analytical study was carried out with the use of available data on population-based health surveys, which were based on a complex, multistage probability sampling design. Details from the survey included demographic information, clinical questionnaires, lab tests, and records of prescription medications. The age of 20 years and above for adults was the criterion for the analysis (19). Participants were selected when there was enough information to evaluate kidney function or albuminuria. Any patient for whom age, sex, serum creatinine, urinary albumin or urinary creatinine were missing were excluded from analyses that required these variables. This involved having a study population of individuals who fulfilled the criteria for chronic kidney disease.

2.2 Definition and Assessment of Chronic Kidney Disease

Reduced estimated glomerular filtration rate (eGFR<60 mL/min/1.73 m2) and/or urine albumin-to-creatinine ratio (ACR≥30 mg/g) were indicators of chronic kidney disease. The race-free CKDEpidemiology was used to calculate the estimated glomerular filtration rate. collaboration creatinine calculation based on age and sex and derived from a serum creatinine test. Kidney function was classified into the following categories: G1, estimated glomerular filtration rate of at least G2 is 60–89 mL/min/1.73 m²; G3a is 45–59 mL/min/1.73 m²; G3b is 30–44 mL/min/1.73 m²; G4 is 15–29 mL/min/1.73 m²; and G5 is less than 15 mL/min/1.73 m². Three categories have been established for the urine albumin-to-creatinine ratio: albuminuria A1 (less than 30 mg/g), albuminuria A2 (30 to 299 mg/g), and albuminuria A3 (equal to or greater than 300 mg/g). Serum creatinine, blood urea nitrogen, serum albumin, and serum uric acid were other laboratory measures associated with renal activity.

2.3 Assessment of Nephroprotective Therapies

The main exposure was the use of nephroprotective pharmacotherapy. Prescription medication records were examined and sorted by the active ingredient. Established renin–angiotensin–aldosterone system inhibition included angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. A new treatment class, mineralocorticoid receptor antagonists (MRAs), such as spironolactone or eplerenone, was tested. The new emerging nephroprotective drugs were Sodium–glucose cotransporter-2 inhibitors. To prevent misclassification, combination medications were identified by each of the active ingredients. The main groups of participants were angiotensin-converting enzyme (ACE) inhibitors users and non-users of angiotensin receptor blockers (ARBs). The effects of mineralocorticoid receptor antagonists and sodium–glucose cotransporter-2 inhibitors were evaluated individually. Because not many patients were treated with emerging therapies, these were primarily assessed by descriptive and exploratory analyses, and not directly through comparative effectiveness models.

2.4 Study Variables and Outcomes

The main outcome measured was the use of renin–angiotensin–aldosterone system inhibitors in adults with chronic kidney disease. Secondary outcomes were the use of mineralocorticoid receptor antagonists, sodium–glucose cotransporter-2 inhibitors, decreased kidney function, neuroprosthetic medication use differences among clinical subgroups, and albuminuria severity. Age, sex, race/ethnicity, education level, household income, diabetes, hypertension, serum creatinine, blood urea nitrogen, serum albumin, serum uric acid, estimated glomerular filtration rate, and number of prescription drugs were the covariates. Self-reported physician diagnosis or current use of glucose-lowering medication was used to diagnose diabetes. Self-reported physician diagnosis of hypertension and/or reported antihypertensive medication use were used to define hypertension.

2.5 Statistical Analysis

Participants' characteristics are summarized overall and by nephroprotective medication use. When the variable was normally distributed, it was displayed as a weighted mean and standard error. Medians with interquartile ranges were used to report skewed variables, notably urinary albumin-to-creatinine ratio. Unweighted frequencies and survey-weighted percentages were used to describe categorical variables. Survey-adjusted statistical tests were used to determine differences among users and non-users of renin–angiotensin–aldosterone system inhibitors. Categorical variables were analyzed with the Rao–Scott chi-square test and permanent variables were analyzed with survey-weighted linear regression. As urinary albumin-to-creatinine ratio is likely to be right skewed, it was log transformed prior to regression analysis. Survey-weighted logistic regression was conducted to determine factors accompanying with the use of ACEI or ARB. The following factors were added to the models for adjustment: age, sex, race/ethnicity, diabetes, hypertension, estimated glomerular filtration rate category, albuminuria category, serum albumin, blood urea nitrogen, and prescription medication count. Odds ratio (OR) with 95% confidence interval (CI) was reported. Subgroup analyses were performed based on diabetes status, hypertension status, kidney function category, and albuminuria severity. The descriptive analyses of emerging therapies were used when the number of exposed participants was too small for reliable multivariable estimates. All analyses were adjusted for the complicated survey design using sampling weights, strata, and primary sampling units. The values of missing variables were not included in the analyses performed. A two-side p value < 0.05 was regarded as statistically significant. Due to the cross-sectional design, outcomes were interpreted as associations, and not as causal treatment effects.

3. Results

3.1 Study Population and Clinical Characteristics

One thousand and three adults met the operational definition of CKD on the basis of either an eGFR < 60 mL/min/1.73 m² or an uACR ≥ 30 mg/g. Of these, 440 were taking an ACE inhibitor or ARB. The age of the CKD population was 60.5 ± 17.1 years, with 55.5% being female. The occurrence of diabetes and hypertension were 32.4% and 63.1% respectively. The age of the participants in RAAS inhibitor users group was greater, and the prevalence of diabetes and hypertension was higher among them, associated to the non-user group. They also had a lower mean eGFR and higher blood urea nitrogen and serum uric acid levels. The clinical features of 1003 adults with CKD are summarized in Table 1, according to whether they used RAAS inhibitors. The prevalence of diabetes and hypertension was higher, eGFR was lower, and BUN and SUA were higher in the RAAS inhibitor users than in the non-users.

Table 1. Clinical characteristics of adults with chronic kidney disease according to RAAS inhibitor use

Characteristic	Overall, n = 1,003	RAAS inhibitor users	Non-users
Age, years	60.5 ± 17.1	66.7 ± 11.6	55.8 ± 19.0
Female, %	55.5	50.3	59.4
Diabetes, %	32.4	51.4	17.9
Hypertension, %	63.1	92.1	40.8
eGFR, mL/min/1.73 m²	76.5 ± 29.2	69.2 ± 25.3	82.2 ± 30.7
UACR, median (IQR), mg/g	50.6 (25.5–129.8)	51.2 (17.9–131.9)	50.5 (30.8–129.5)
Blood urea nitrogen, mg/dL	19.0 ± 8.5	21.2 ± 8.3	17.2 ± 8.2
Serum albumin, g/dL	3.99 ± 0.33	3.99 ± 0.33	3.99 ± 0.33
Serum uric acid, mg/dL	5.89 ± 1.72	6.15 ± 1.70	5.69 ± 1.71

Values are survey-weighted means ± standard deviations or weighted percentages, except UACR, which is presented as the unweighted median and interquartile range.

3.2 Distribution of Kidney Function and Albuminuria

35.9%, 28.7% and 20.1% of the CKD population fell into the largest weighted eGFR categories, G1, G3a and G2, respectively. G1 and G2 category participants were indicative of identification of CKD based on elevated albuminuria with normal eGFR. Moderately increased albuminuria (A2) was the most common category among those who had urinary albumin data available and made up 59.0% of all those with CKD. Eleven and one-third (11.7%) had a very high rate of albuminuria. Participants in each eGFR and albuminuria category are shown in Table 2. G1 was the most common eGFR category, and A2 albuminuria was the largest albuminuria group, suggesting that many subjects had had some degree of albuminuria despite normal eGFR. The distribution of CKD patients by eGFR is weighted

as shown in Figure 1. The most abundant were G1, G3a and G2, while the more advanced stages G4 and G5 were comparatively rare.

Table 2. Distribution of CKD participants according to eGFR and albuminuria categories

CKD category	Unweighted n	Weighted %
eGFR categories		
G1: ≥90 mL/min/1.73 m²	288	35.9
G2: 60–89 mL/min/1.73 m²	224	20.1
G3a: 45–59 mL/min/1.73 m²	281	28.7
G3b: 30–44 mL/min/1.73 m²	113	8.7
G4: 15–29 mL/min/1.73 m²	33	2.2
G5: <15 mL/min/1.73 m²	16	1.0
Albuminuria categories		
A1: UACR <30 mg/g	253	26.9
A2: UACR 30–299 mg/g	591	59.0
A3: UACR ≥300 mg/g	127	11.7

Percentages may not total 100% because eGFR or UACR information was unavailable for a small proportion of participants.

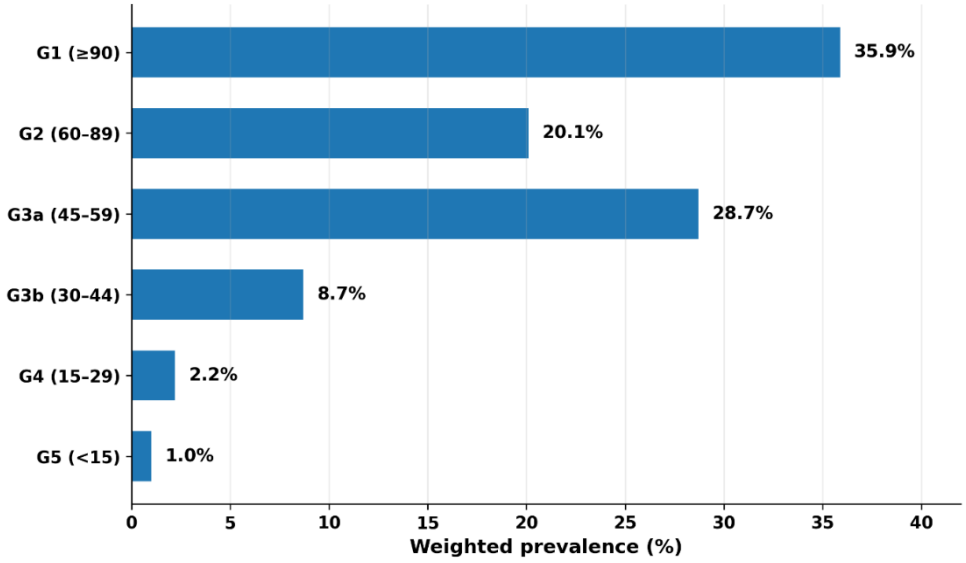

Figure 1. Distribution of CKD participants by eGFR category

3.3 Utilization of Current and Emerging Nephroprotective Therapies

Overall, 43.4% of adults with CKD were taking an ACE inhibitor or ARB. Twenty-three percent used ACE inhibitors and 20.4% used ARBs. The rates of use of RAAS inhibitors were significantly higher in those with diabetes, as well as in those with hypertension. Nephroprotective therapies (emerging and adjunctive) were used rarely. Only 3.6% of participants used mineralocorticoid receptor antagonist and 2.0% used SGLT2 inhibitor. For those who had diabetes and hypertension, the use of RAAS inhibitors (77.2%) was more common, but SGLT2 inhibitors (7.4%) were less common.

Table 3 illustrates the use of existing and new nephroprotective therapies. While mineralocorticoid receptor antagonists and SGLT2 inhibitors were used less frequently (3.6% and 2.0%, respectively), ACE-inhibitors and ARBs were utilised frequently (43.4% of all individuals). The comparative use of nephroprotective drugs is depicted in Figure 2. The use of RAAS-based therapies was significantly higher than mineralocorticoid receptor antagonists and SGLT2 inhibitors. Use of RAAS inhibitors and SGLT2 inhibitors among the major clinical subgroups is shown in Figure 3. The usage of the RAAS inhibitors was highest in the subgroup of participants with diabetes and hypertension, and the use of the SGLT2 inhibitors was low across all subgroups.

Table 3. Utilization of nephroprotective pharmacotherapies in the CKD population

Therapy	Unweighted n	Overall weighted %	Diabetes, %	Hypertension, %	Diabetes and hypertension, %
ACE inhibitor	245	23.3	41.6	33.2	45.3
Angiotensin receptor blocker	198	20.4	27.3	30.5	32.2
ACE inhibitor or ARB	440	43.4	68.8	63.4	77.2
Mineralocorticoid receptor antagonist	28	3.6	3.9	5.4	4.2
SGLT2 inhibitor	10	2.0	6.2	3.1	7.4

Medication categories were identified from active ingredients. Combination products were included in the corresponding therapeutic classes.

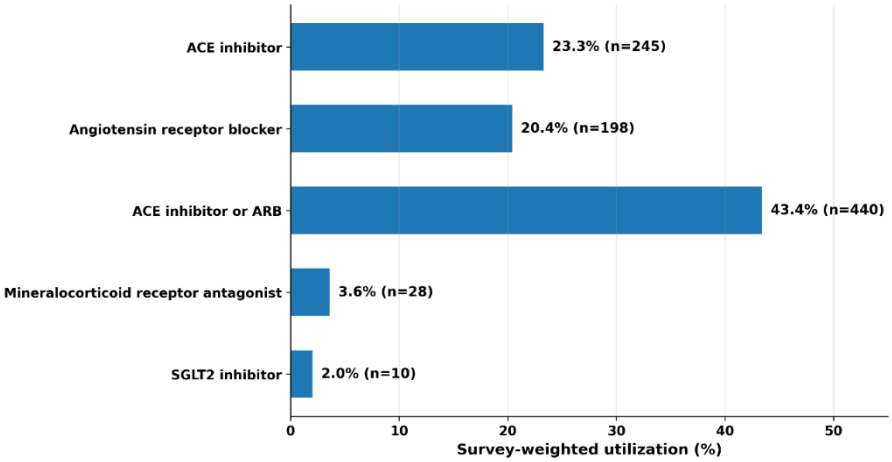

Figure 2. Utilization of established and emerging nephroprotective therapies

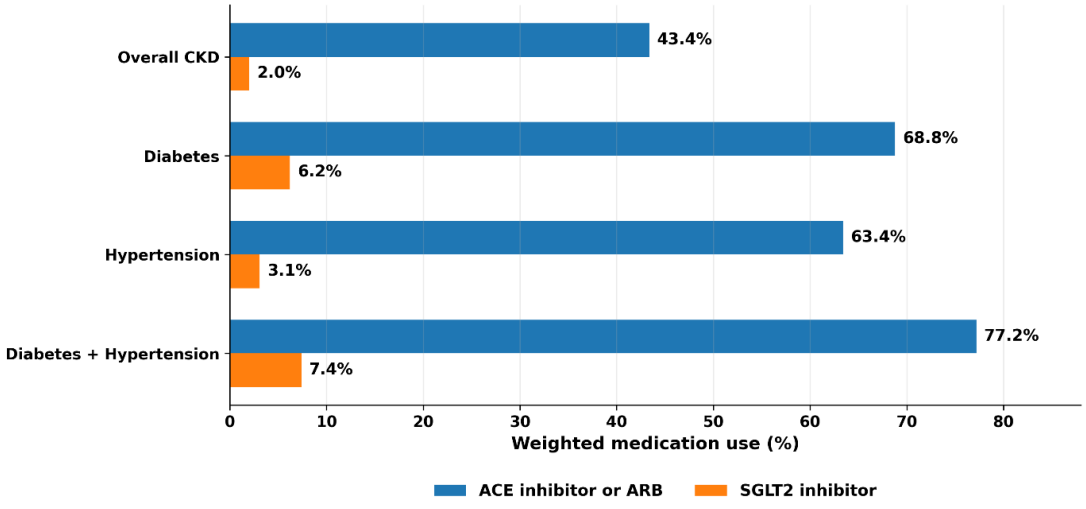

Figure 3. RAAS inhibitor use across major clinical subgroups

3.4 Factors Associated with RAAS Inhibitor Use

The age, diabetes, and hypertension were unrelated risk factors for the use of RAAS inhibitors in the adjusted weighted logistic regression analysis. There was a corresponding increase in odds of receiving an ACE inhibitor or ARB with each 10-year increment in age (+31% for each 10 years). The odds of RAAS inhibitor use were nearly four times superior in participants with diabetes than in those without diabetes. The strongest association was with hypertension, where the participants with hypertension had over 14 times the odds of receiving RAAS inhibition. Neither female sex

nor eGFR was independently associated with use of RAAS inhibitors after adjustment. There was a modest decrease in the odds for treatment with each increment of the log-transformed UACR.

The adjusted factors of RAAS inhibitors use are presented in Table 4. Female sex and eGFR were not statistically significant predictors, with hypertension showing the strongest association and diabetes and increasing age showing a less strong association. The odds ratios for the various factors associated with the use of RAAS inhibitors were adjusted for these other factors as shown in Figure 4. The strongest positive predictors were hypertension and diabetes, and the lower the log transformed UACR, the lower the odds of treatment.

Table 4. Weighted multivariable logistic regression of factors associated with RAAS inhibitor use

Predictor	Adjusted OR	95% CI	p-value
Age, per 10-year increase	1.31	1.11–1.55	0.002
Female sex	0.74	0.43–1.26	0.265
Diabetes	4.00	2.22–7.22	<0.001
Hypertension	14.11	7.95–25.03	<0.001
eGFR, per 10 mL/min/1.73 m² increase	1.04	0.95–1.13	0.421
Log-transformed UACR	0.84	0.72–0.98	0.026

OR: odds ratio; CI: confidence interval; eGFR: estimated glomerular filtration rate; UACR: urinary albumin-to-creatinine ratio. The model included 923 participants with complete information for all included variables.

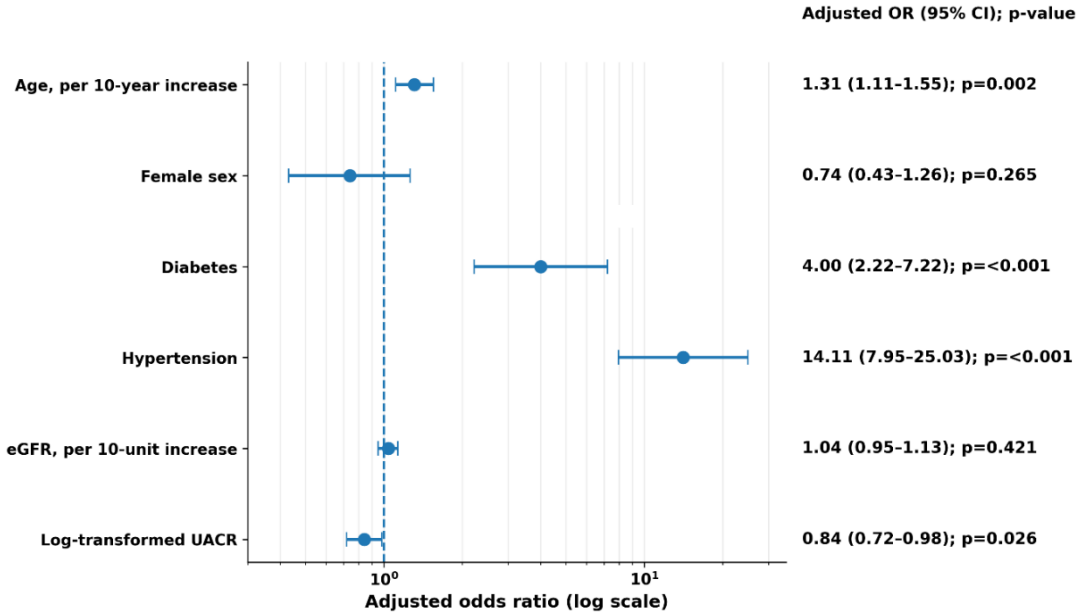

Figure 4. Adjusted factors associated with RAAS inhibitor use

3.5 Summary of Major Findings

The results showed that the nephroprotective treatment strategy that was still predominant was the use of RAAS inhibitors, especially in patients with diabetes and hypertension. However, only half of the total CKD population were on an ACE inhibitor or ARB, which may suggest a large treatment gap. Adoption of novel treatment was low compared with the use of traditional RAAS inhibitors. Only 10 participants had CKD for whom SGLT2 inhibitors were identified and 28 participants had CKD for whom mineralocorticoid receptor antagonists were identified. These were so small that they did not allow for any meaningful comparative effectiveness analyses to be conducted. In general, treatment use seemed to be primarily related to hypertension and diabetes, and not to kidney-function testing alone. Due to the concurrent exposure to treatment and assessment of kidney outcomes, the associations observed should not be seen as evidence that RAAS inhibitors led to a decrease in eGFR or to changes in albuminuria.

4. Discussion

This analysis demonstrated that the renin–angiotensin–aldosterone system (RAS) inhibitors continue to be the leading nephroprotective strategy in adults with CKD(CKD)(20). Less than half of the identified CKD population was on an angiotensin receptor blocker or angiotensin-converting enzyme inhibitor, indicating a substantial therapeutic gap. From a clinical perspective, since the blockade of this axis remains a cornerstone in the treatment of CKD, the results are pertinent as they involve the reduction of intraglomerular pressure, proteinuria, and cardiovascular risk (5). However,

hyperkalaemia, hypotension, acute decrease in estimated GFR, intolerance, and advanced kidney dysfunction are possible limitations to treatment (4).

most strongly associated with hypertension, and diabetes was significantly associated with the highest odds of medicine with an ACE inhibitor or ARB. These trends indicate that, perhaps, only cardiovascular and metabolic disease was enough to justify treatment initiation, not renal disease(21). Patients with diabetes are especially dependent on conventional management to avoid further haemodynamic and metabolic injury, which in turn increases the damage to the glomeruli and progression of CKD (11). But some patients with albuminuria but normal eGFR may not receive treatment because the treatment is based on their comorbid conditions. There was a significant number of participants in the G1 and G2 categories despite having elevated albuminuria and meeting the definition of CKD. This observation supports the need to measure the urinary ACR, in addition to eGFR. Early renal injury does not preclude preserved filtration and albuminuria may serve as a means of identifying patients that may benefit from preventive therapy before significant renal functional loss has occurred. New biomarkers can further enhance early risk stratification, disease phenotyping and targeted interventions (14). In addition, molecular markers specific to the kidney could be helpful to discriminate the various biological pathways leading to progression (13).

Those who were taking RAAS inhibitors tended to be older, and had a higher mean blood urea nitrogen level, and a higher prevalence of diabetes and hypertension; their mean eGFR was lower. It should be noted that such differences did not document an adverse effect on renal function by RAAS inhibition(22). This cross-sectional design will not be able to determine when medications were initiated in relation to renal decline. However, more advanced disease and/or other comorbidities could have enhanced the probability of treatment, which could lead to confounding by indication(23). Longitudinal studies are needed with repeated measures of kidney function in order to establish the effect of treatment on progression of kidney disease (24). New nephroprotective therapies were very sparsely used. Although SGLT2 inhibitors are known to restore tubuloglomerular feedback, reduce intraglomerular hypertension and have cardiovascular and renal benefits, they were only prescribed to a small proportion of the population with CKD (7). The low use may be due to the timing of the survey data, which were based on a time when there was still growth in indications for kidney protection.

The next step in the evolution of the use of SGLT2 inhibitors in the treatment of CKD is a significant paradigm shift from glucose-lowering treatment alone (8). Also of low prevalence was the use of a mineralocorticoid receptor antagonist. Along with its role as a key therapeutic target, mineralocorticoid receptor activation is linked to inflammation, oxidative stress, endothelial dysfunction and renal fibrosis (9). However, hyperkalaemia concerns may restrict the use of steroidal agents especially in combination with RAAS inhibitors. There may be more selective protection with newer non-steroidal mineralocorticoid

The prevalence of use of RAAS inhibitors was drastically higher in the diabetes and hypertension group. Treatment was receptor antagonists, but monitoring is still important. The results also underscore the disconnect between innovation and implementation, as well as the need for more routine monitoring(25). Today, the focus of therapeutic research is shifting to fibrosis, inflammation, mitochondrial dysfunction, oxidative stress, cellular senescence, endothelin signalling and metabolic injury (12). It is particularly important to note antifibrotic pathways as these are especially relevant because renal fibrosis is a common final pathway of progressive CKD (16). When there are no suitable treatment options, drug repurposing and small molecule development can be used to generate new treatment possibilities (17).

Limitations of the study include the cross-sectional design, patient self-report of medication exposure, lack of adherence and dose information, and lack of repeated measurements to confirm the chronicity of the CKD. Due to the limited number of participants on emerging therapies, reliable comparative-effectiveness analysis was not possible. The results therefore reflect the characteristics of the treated patients rather than the therapeutic effects. Overall, the results validate ongoing optimization of RAAS inhibition and underscore the importance of more widespread and evidence-based use of newer nephroprotective drugs.

5. Conclusion

This study confirms that RAAS inhibition is the main nephroprotective treatment in adults with chronic kidney disease, especially in patients with hypertension and diabetes. Less than half of identified CKD had been treated with an ACEi or ARB, suggesting a clinically significant treatment gap. It also revealed that patients with established comorbidities were more likely to receive treatment than those with only renal function parameters, indicating that some patients with albuminuria or preserved renal eGFR might be undertreated. However, the uptake of emerging nephroprotective therapies was significantly less. Comparative assessment of the use of newer drugs was limited, as very few participants used SGLT2 inhibitors and antagonists of the mineralocorticoid receptor. The allocation of CKD in both reduced and preserved eGFR categories further supports that combining eGFR with urinary albumin-to-creatinine ratio could be used to identify risk and plan treatment. The overall message is that the standard RAAS-based therapy should be pursued and expanded use of newer, evidence-based kidney protection therapy should be encouraged. Treatment effectiveness, adherence, safety, and effects on progression of CKD and cardiovascular outcomes should be assessed by longitudinal studies.

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