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CLINICAL STUDY

Major Barriers against Renin–Angiotensin–Aldosterone System Blocker Use in Chronic Kidney Disease Stages 3–5 in Clinical Practice: A Safety Concern?

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Abstract

Renin–angiotensin–aldosterone system (RAAS) blockers are underutilized in patients with chronic kidney disease (CKD). We aimed to determine barriers against the use of RAAS blockers in these patients. Patients with stage 3–5 CKD referred to Hacettepe University Hospital Nephrology Unit during a 1 year period were evaluated for RAAS blocker use. Two hundred and seventy-nine patients (166 male, 113 female) were analyzed. The mean age of the patients was 56.7 ± 15.2 years, mean serum creatinine was 2.45 ± 1.44 mg/dL, and mean glomerular filtration rate was 33.3 ± 15.1 mL/min. The mean follow-up time was 22.0 ± 21.9 months and the clinical visit number was 4.0 ± 3.5. Angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers were used by 68.8% of all patients and 67.7% of diabetic patients at the time of analysis. In 82.1% of patients, RAAS blockers had either been used earlier or were being used. Hyperkalemia was the principal reason for both not starting and also discontinuing these drugs in patients with CKD. In 37.4% of patients, reasons for not starting RAAS blockers were unclear. This study showed that hyperkalemia is the major barrier against the use of RAAS blockers in patients with CKD. There was, however, a subset of patients who did not receive RAAS blockers even without clear contraindications.

Keywords: angiotensin converting enzyme inhibitors, angiotensin receptor blockers, barriers, chronic kidney disease, renin-angiotensin-aldosterone system

INTRODUCTION

Chronic kidney disease (CKD) is a public health problem with high morbidity and mortality.[1] There are common factors affecting the progression rate of CKD toward end-stage renal disease irrespective of the underlying cause. Systemic and glomerular hypertension, proteinuria, hyperlipidemia, metabolic acidosis, smoking, daily protein intake, and glycemic control for diabetic patients are the major determinants of rate of progression of CKD.[2,3] Control of blood pressure and proteinuria are the most important interventions in order to slow the rate of deterioration in renal functions.[4–6] The activation of renin–angiotensin–aldosterone system (RAAS) had been shown to play a key role in both systemic and glomerular hypertension and also proteinuria. RAAS blockers are effective in slowing the progression of CKD independent of their antihypertensive effects. These effects are observed both in diabetic and nondiabetic proteinuric CKD patients.[7–15]

Positive results of randomized controlled trials affected the guideline recommendations. The Kidney Disease Outcome Quality Initiative (K/DOQI) guideline recommends using RAAS blockers in all diabetic CKD patients irrespective of their blood pressure. For nondiabetic CKD patients, K/DOQI recommends using RAAS blockers if proteinuria level is >200 mg/day.[16] The seventh report of the Joint National Committee (JNC) recommends using RAAS blockers in all hypertensive CKD patients independent of proteinuria level.[17]

Despite these recommendations, there were reports indicating that these drugs were not widely adopted due to concerns about potential side effects such as cough, hyperkalemia, and possible deterioration in renal functions.[18] The aim of this study was to determine the prevalence of CKD patients using RAAS blockers in a

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real-life setting and the main barriers against using them despite guideline recommendations.

MATERIALS AND METHODS

We conducted a retrospective review of our medical records with the purpose of evaluating the medical treatments of patients with stage 3–5 CKD regularly followed at Department of Nephrology, Hacettepe University Medical Faculty Hospital, during a calendar year for 12 months. All adult patients (>18 years) with an estimated glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for more than 3 months were included. Patients who had a confirmed diagnosis of CKD were also included in this study even if they had a single creatinine measurement in our hospital. Patients already receiving renal replacement therapy, using immunosuppressive treatments, or having incomplete data were excluded. Patients with a single GFR value less than 60 mL/min/1.73 m^2 were also excluded if they did not have a previously confirmed diagnosis of CKD. Two hundred and seventy-nine patients (166 males, 113 females) were available for the analysis. This study was conducted in accordance with the principles outlined in the declaration of Helsinki and was approved by the Hacettepe University Local Ethics Committee.

The age, sex, and underlying cause of CKD for all patients were recorded. Patients' blood pressure, serum creatinine, serum potassium, 24-h urinary protein excretion, the total number and classes of antihypertensive medications that the patients had used before the nephrology visits, and the antihypertensive medications recommended by physicians after the visits were recorded. These details were also collected for all previous nephrology visits from their medical records. GFR was calculated by using the Modification of Diet in Renal Disease formula [$175 \times \text{standardized } S_{cr}^{-1.154} \times \text{age}^{-0.203} \times 1.212$ (black race) $\times$ 0.742 (women) (www.mdrd.com)]. The first visit was defined as the visit in which the first-time patient's GFR was detected to be less than 60 mL/min/1.73 m^2. All patients had home blood pressure monitoring for five consecutive days (two measurements per day), and ambulatory blood pressure monitoring was done whenever possible. We investigated whether RAAS blockers were started to the patients during nephrology visits, and if not, we had recorded the reasons. The reasons necessitating the discontinuation of these drugs were also recorded for all visits. The percentage of patients using RAAS blockers after their first and last visits and the percentage of patients ever and never having used RAAS blockers were determined.

SPSS, version 16, was used for statistical analysis (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to define the demographic characteristics of the patients. Wilcoxon signed-rank test was used to determine the significance of blood pressure difference between the first and last visits of patients.

RESULTS

Demographic Characteristics of Patients

There were 279 patients (166 males, 113 females, mean age 56.7 ± 15.2) who met the inclusion criteria. Of these patients, 222 had been admitted to the clinic more than once. The demographic characteristics and laboratory values of patients based on stages of CKD at first visit are shown in Table 1. The average number of visits was

Table 1. Demographic characteristics and laboratory values of patients at first visit.

Variable	All patients ($n = 279$)	Stage 3 CKD ($n = 151$)	Stage 4 CKD ($n = 103$)	Stage 5 CKD ($n = 25$)
Age (Mean ± SD)	56.7 ± 15.2	58.7 ± 14.9	54.7 ± 14.7	53.6 ± 18.0
Male (number/%)	166/59.5	106/70.2	49/47.6	11/44.0
Female (number/%)	113/40.5	45/29.8	54/52.4	14/56.0
Systolic blood pressure (mmHg)	142.8 ± 29.4	139.1 ± 26.9	146.9 ± 33.0	148.8 ± 26.3
Diastolic blood pressure (mmHg)	87.0 ± 15.3	85.3 ± 14.5	88.5 ± 15.9	91.0 ± 16.7
Proteinuria (mg/day)	1469.7 ± 2088.1	1082.6 ± 2052.0	2004.3 ± 2142.8	1673.8 ± 1467.5
24-h urinary sodium (mmol/L)	169.0 ± 86.5	180.6 ± 85.1	150.2 ± 82.7	176.5 ± 111.5
Glomerular filtration rate (mL/min)	33.3 ± 15.1	44.7 ± 10.2	22.1 ± 4.5	10.5 ± 2.6
Serum creatinine (mg/dL)	2.45 ± 1.44	1.62 ± 0.31	2.88 ± 0.69	5.71 ± 2.28
Serum potassium (mg/dL)	4.73 ± 0.58	4.64 ± 0.58	4.80 ± 0.54	4.94 ± 0.66
Past medical history (number/%)				
Hypertension	197 (70.6)	108 (71.0)	76 (73.7)	13 (52.0)
Diabetes mellitus	65 (23.3)	35 (23.17)	23 (22.3)	7 (28.0)
Coronary heart disease	46 (18.6)	27 (17)	15 (16.4)	4 (16.0)
Nephrolithiasis	32 (11.5)	19 (12.0)	12 (11.7)	1 (4.0)
Glomerulonephritis	21 (7.5)	14 (9.0)	6 (5.8)	1 (4.0)
Malignancy	19 (7.3)	11 (7.0)	5 (4.8)	3 (12.0)
Polycystic kidney disease	14 (5.0)	8 (5.0)	4 (3.8)	2 (8.0)
Pyelonephritis	13 (4.6)	6 (7.5)	5 (4.8)	2 (8.0)
Solitary kidney	12 (4.3)	6 (7.5)	4 (3.8)	2 (8.0)
Congestive heart failure	13 (4.6)	7 (8.1)	4 (3.8)	2 (8.0)
Chronic lung disease	7 (2.5)	4 (2.5)	3 (2.9)	0 (0)
Familial mediterranean fever	1 (0.4)	0 (0)	1 (0.9)	0 (0)

4.0 ± 3.5 and the average follow-up time was 22.0 ± 21.9 months for the 222 patients who were admitted to the clinic more than once.

RAAS Blocker Use in Patients

We recorded the percentage of patients recommended RAAS blockers after the last visit. One hundred and ninety-two patients (68.8%) were using RAAS blockers after their last visit. For diabetic patients, RAAS blocker use was not more common, and 44 of the 65 diabetic patients (67.7%) were using RAAS blockers. We investigated all visits of the patients from their medical files and found that 229 of 279 patients (82.1%) had used RAAS blockers in the past or were still using these drugs.

RAAS blockers were recommended in 177 patients (63.4%) after their first visits (75 patients started on and 102 patients were already using these drugs). A number of patients (22 patients, 7.9%), who were using RAAS blockers on admission, were recommended to stop these drugs due to acceptable reasons. The main reasons for discontinuation were hyperkalemia in 12 patients and acute deterioration in kidney functions in 4 patients. The other reasons for discontinuation were renal artery stenosis and hypotension in two patients and a very low GFR and cough in one patient. The remaining 80 patients (28.7%) were not using RAAS blockers on admission and had not started on these drugs. Table 2 shows the reasons for not starting RAAS blockers in these 80 patients. There were no clear contraindications for not starting these drugs in a considerable percentage of these patients (30 patients, 37.4%). During follow-up visits, RAAS blockers were started in 15 of these 30 patients. We investigated the remaining 15 patients who were never started on RAAS blockers. While 4 of these 15 patients were not admitted for another visit, the remaining 11 patients had been admitted more than once. Four of these 11 patients had no hypertension and their proteinuria level was less than 200 mg/day. However, for the remaining seven patients who had clear indications for RAAS blocker use and with no contraindications, there were several missed opportunities to start these drugs during the following visits.

When all visits were considered, RAAS blocker therapy was discontinued in 51 patients. Hyperkalemia was the main reason (34 patients, 66.6%). The second most common reason was acute deterioration in renal functions (9 patients, 17.6%). Table 3 shows the reasons for discontinuation of RAAS blockers in these 51 patients.

Table 2. Reasons for not starting renin–angiotensin–aldosterone system blockers in the first visit.

	$n = 80$	%
No clear reason	30	37.4
Past or current hyperkalemia	11	13.8
Suspicion of renal artery stenosis	11	13.8
Acute deterioration of renal function	10	12.5
Hypotension	10	12.5
Very low glomerular filtration rate	8	10.0

Table 3. Reasons for discontinuation of renin–angiotensin–aldosterone system blockers.

	$n = 51$	%
Hyperkalemia	34	66.6
Acute deterioration of renal function	9	17.6
Hypotension	3	5.9
Renal artery stenosis	2	3.9
Very low glomerular filtration rate	1	2
Angioedema	1	2
Cough	1	2

Blood Pressure Control

Blood pressure values could be collected for 221 of 222 patients who were admitted more than once. On comparing blood pressure values of the first and last visits, there was a statistically significant decrease in the mean systolic blood pressure in the last visits when compared with first visits (131.9 ± 29.5 mmHg vs. 143.1 ± 29.4 mmHg respectively, $p = 0.001$). There was a similar decrease in the mean diastolic blood pressure (81.8 ± 11.2 mmHg vs. 87.3 ± 15.2 mmHg, $p = 0.001$). Blood pressure values less than 130/80 mmHg were observed in 119 (53.8%) patients, and the average number of antihypertensive drugs used by patients after the last visit was 1.9 ± 1.0.

DISCUSSION

This study showed that 63.4% of CKD patients were prescribed RAAS blockers after their first visit. This percentage increased to 68.8% by the last visit. RAAS blockers were being used by 82.1% of the patients at any time during their follow-up period. Confirmed or suspected renal artery stenosis, hyperkalemia, hypotension, very low GFR, and acute deterioration in kidney functions were the major barriers against prescribing RAAS blockers during first visit and each had similar frequencies.

CKD patients and diabetic CKD patients who were using RAAS blockers after their last visit constituted 68.8% and 67.7%, respectively. These drugs are not indicated for all patients with CKD. K/DOQI, in the *hypertension and antihypertensive drugs in chronic kidney disease guideline,* recommends using RAAS blockers for all diabetic CKD patients and for nondiabetic CKD patients with proteinuria level > 200 mg/day, independent of blood pressure.[16] There were 204 patients with an indication for RAAS blockers according to K/DOQI guidelines [diabetic or nondiabetic but proteinuric (>200 mg/day)], and 71.1% of these patients (145 patients) were using these drugs. This means that nearly one-third of CKD patients were not prescribed RAAS blockers in spite of a clinical indication.

We observed slightly higher rates of RAAS blocker use in this study when compared to previous studies. Philipneri and colleagues observed that 50% of CKD patients followed by nephrologists and 30% of patients followed by physicians other than nephrologists were using RAAS blockers.[19] Bailie et al.[20] reported in their trial that 44% of patients with stage 2–5 CKD were using angiotensin-converting-enzyme inhibitor (ACEI) and 13% were using angiotensin receptor blocker (ARB). In another study, the prevalence of RAAS blocker use was found to be 64.5% in patients with GFR <75 mL/min. Advanced age, male gender, chronic obstructive lung disease, depression, and dementia were found to be the main factors for underuse of these drugs.[21]

The reason for higher use of RAAS blockers in this study may be explained by several factors. First, the increasing reports about underutilization of these drugs may reinforce physicians to use them more. Another probable reason is the delivery of treatment to all patients by nephrologists in our study. Previously, it has been shown that patients treated by nephrologists were more likely to be started RAAS blockers.[22]

This study has showed that nearly one-third of CKD patients were not prescribed RAAS blockers. The main reasons for not prescribing these drugs were very low GFR, known or suspected renal artery stenosis, hyperkalemia, acute deterioration of kidney functions, and hypotension, each with similar frequencies. There is only one report in literature about the barriers against RAAS blocker use in CKD patients. In this study, physicians filled a questionnaire and indicated reasons for not starting these drugs in CKD patients.[21] The main reasons were physicians' opinions that patients will not have any benefit (22.9%) and will have severe side effects (12.0%), unstable kidney functions (3.3%), and cough (1%). It was not clear why physicians thought some patients will not benefit from therapy. Individual frequencies of each severe side effect were also not available.

Since this was a retrospective study, we could not talk over with physicians about reasons for their treatment choices. It was therefore not possible to find out all reasons for not using these drugs if these were not reported clearly in the medical files. In some of these cases, obvious causes such as hyperkalemia could be easily estimated although not recorded in medical files by physicians. However, there may be some other concerns like polypharmacy. The average number of drugs used by CKD patients was shown to be 8 ± 4 in a study.[20] Physicians may have concerns that adding another drug, in this case a RAAS blocker, especially to elderly patients whose blood pressure is under control, may decrease compliance.

The percentage of patients using RAAS blockers increased from 63.4% after the first visit to 68.8% after the last visit. There were 80 patients who were not recommended RAAS blockers at their first visit. There was no clear contraindication for 30 patients (37.4%). Half of these patients were started on RAAS blockers during following visits. This is probably due to concerns about probable renal artery stenosis or acute renal failure in the first visit. When these concerns are excluded in the following visits, physicians possibly felt comfortable to prescribe these drugs.

The main reason for stopping these drugs in this trial was hyperkalemia (66.6%). The second reason was acute deterioration in kidney functions (17.6%), similar to previous studies. Studies have shown that 5–10% of patients using ACEI or ARB had to stop these drugs due to worsening renal functions or hyperkalemia.[9,22] This number may be higher in clinical practice.[23]

Blood pressure control is one of the main factors in slowing progression of kidney disease. Reaching blood pressure goals is extremely difficult in CKD patients. We observed that 53.8% of patients' blood pressure was under control (< 130/80 mmHg) at the last visit, which was higher than previous reports. This value changed between 12% and 37% in previous studies.[20,24]

The limitations of this trial are that it is a single center study with a small sample size and uses a single creatinine value for determining the stage of patients. Since this was a retrospective study, the reasons for not using RAAS blockers may not be correctly determined in some cases.

In conclusion, although there is an increase in the usage of RAAS blockers, they are still underutilized in CKD patients. Hyperkalemia is the main barrier against the use of these drugs. Unless there is a contraindication, these drugs should be used to slow the progression of CKD by closely monitoring potassium and creatinine levels.

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