

The Use of Renin-Angiotensin System Blockades Among Patients with Chronic Kidney Disease

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Abstract

Background and objectives: Hypertension is common in adult patients with chronic kidney disease with a prevalence that depends on the stage and etiology of chronic kidney disease and has been reported to range from 60-90%. The aim of this study was to evaluate the clinical use of renin angiotensin system blockers in chronic kidney disease patients and to identify their potential indications, contraindications and side effects amongst different clinical specialties in relation to their clinical outcomes.

Methods: This study was a descriptive cross sectional based on self-administered online questionnaire, 133 medical doctors from different specialties including nephrologists, internists, urologists, general practitioners responded to the questionnaire and filled it up, which was composed of three main parts including the socio-demographic data of the participants, data about CKD and its stages and finally the RAS blockades. The study extended from June until July 2021.

Results: The mean age \pm standard deviation of respondents was 44.65 ± 6.89 years. Nearly one third of the respondents were internist, 12.8% nephrologist, 7.5% urologist and 45.9% from other different specialties. The vast majority (98.5%) of the physicians thought that renin angiotensin system inhibitors are effective anti-hypertensive agents even for chronic kidney disease patients. Most of the nephrologists and other specialties would continue the renin angiotensin system inhibitors while most of the internists and urologists would either stop or change the renin angiotensin system inhibitors, this was statistically significant and p -value was 0.010.

Conclusions: Clinicians use renin-angiotensin-system blockers for patients with caution fearing of its negative impacts like hyperkalaemia and renal artery stenosis. Creating clinical guidelines concerning renin-angiotensin system inhibitors for patients with chronic kidney disease is necessary.

Key words: Angiotensin-converting enzyme inhibitors; Chronic kidney disease; End-stage renal disease.

Introduction

Hypertension is common in adult patients with chronic kidney disease (CKD) with a prevalence that depends on the stage and etiology of CKD and has been reported to range from 60% to 90%.¹ Hypertension and high blood pressure (BP) are considered independent risk factor for end-stage renal disease (ESRD)² and they account for approximately 25% of the new

ESRD cases diagnosed annually in the United States.² Hypertension and CKD are two pathophysiologic conditions that are closely interlinked with each condition affecting the other; for instance, a sustained hypertension and elevation of BP would lead to worsening of kidney functions whereas a progressive decline in kidney functions on the other hand would

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conversely lead to worsening of BP control.² Although it is evident that progression of CKD is accelerated by uncontrolled HT and elevated BP, existing evidence have illustrated that the currently recommended BP target of <130/80 mmHg does not stop the progression of CKD but only slows it. In patients with CKD, removal of volume overload has been associated with consistent reduction of BP which suggest that achieving and maintaining euvolemia could be a key strategy in achieving the recommended target blood-pressure levels.⁴ The main therapeutic approaches for managing HT in patients with CKD include dietary salt restriction, initiation of pharmacological treatment with antihypertensive agents like angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and diuretics. Antihypertensive medications that inhibit the renin angiotensin- aldosterone system (RAS), such as angiotensin-converting enzyme inhibitors and angiotensin receptors blockers, have been proven to be more effective in reducing proteinuria and slowing the progression of renal diseases. The ACEIs and ARBs' mechanism of delaying the development of renal diseases is similar to that of calcium channels blockers.⁵ The ACEIs/ARBs are often considered the drug of first choice in pre-dialysis CKD patients unless there is a compelling indication for another antihypertensive medication.⁶ Recommendations from recent guidelines for the management of CKD patients have indicated RAS drugs as first line of treatment as they provide additional renoprotection independent of their BP lowering effect as well as their effectiveness in counteracting the adverse effects of diuretics.⁷ Compared to other antihypertensive agents, early ACEIs treatment in CKD patients was associated with a 30% reduction in incidence of ESRD development.⁸ Moreover, ACEIs and ARBs are the first-line choice of treatment in diabetic patients with

albuminuria as they reduce proteinuria by 20% due to their renoprotective effect. However, in hypovolemic patients, ACEIs/ARBs might cause acute renal failure as they cause vasoconstriction of the efferent arteriole; hence, careful attention is required in this group of patients.^{9,10} Compared to ACEIs, ARBs (also called sartans) have additional nephroprotective effects and fewer side effects (mainly dry cough) as, unlike ACEIs, they directly block Angiotensin II receptors. Evidence from clinical studies have demonstrated that irbesartan therapy was associated with 18-30% and 23% reduction in CKD progression and mortality, respectively, among diabetic patients when compared to amlodipine [A]. Although both ACEIs and ARBs have inhibitory effect on the RAS, ACEIs may not completely inhibit the RAS when given as monotherapy at conventional doses.¹¹ Several studies have started to investigate the long-term renal protective effects of ACEIs versus other antihypertensive agents but with conflicting findings. For instance, in patients with established diabetic nephropathy, enalapril therapy for an average of 2.2 years resulted in a slower reduction in GFR when compared with metoprolol for the same BP reduction level.¹² On the other hand, non-significant differences in renal protective effects between captopril and nifedipine were observed among non-diabetic CKD patients.¹³ The researcher was interested in investigating in-depth the theoretical background and knowledge, clinical attitudes and daily practices of the physicians from different specialties in Iraq regarding the use of RAS blockers in CKD patients. The objectives of this study were to evaluate the clinical use of RAS blockers in CKD patients from clinicians' point of view and to identify their potential indications, contraindications and side effects amongst different clinical specialties in relation to their clinical outcomes.

Patients and methods

This study was a descriptive cross sectional based on self-administered online questionnaire. The questionnaire was sent to 153 medical doctors from different specialties including nephrologists, internists, urologists, general practitioners. The respondents were distributed over most provinces of Iraq with majority from the three governorates of Kurdistan region namely Erbil, Duhok and Sulaymaniyah. Among all doctors only 20 of them did not reply to our request and did not send back the questionnaire. The questionnaire was distributed online and the response rate was higher than 87%. This study used an online questionnaire survey which was composed of three main parts including the socio-demographic data of the participants, data about CKD and its stages and finally the ACE/ARB inhibitors comprising the use, side effects and importance of prescribing those medications in the management of patients with CKD/ESRD. The study was

commenced at the beginning of June 2021 and extended till the end of July 2021. The data were collected and entered in the computer via Microsoft Excel worksheet (Excel 2010) and then analyzed using appropriate data system which is called Statistical Package for Social Sciences (IBM SPSS Statistics, IBM Company, USA) version 25 and the results were compared between patients with different variables, with a statistical significance level of ≤ 0.05 . The results presented as rates, ratio, frequencies, percentages in tables and figures and analyzed using Chi square test or Fisher's exact tests if necessary. Ethical approval was obtained from the Research Ethics Committee at Kurdistan Board of Medical Specialties. The purpose of the study and questionnaire was explained to all participants and consent was obtained from all of them. Confidentiality and anonymity of data were ensured.

Results

A total of 133 physicians from different specialties responded to our online questionnaire. The mean age \pm standard deviation of respondents was 44.65 ± 6.89 years; their age was ranging from 27-67 years with average experience of 13.77 years at public and private sectors. About one third (33.8%) of the respondents were internist, 12.8% nephrologist, 7.5% urologist and 45.9% from other different specialties. Most of the participants were male (69.2%), and the majority of the study sample were from Erbil governorate (85.7%). The vast majority (98.5%) of the physicians thought that RAS inhibitors are

effective anti-hypertensive agents even for CKD patients. Most of them were thinking that diabetes mellitus and hypertension are the main and most common causes of ESRD. Majority of the respondents (75.2%) were referring CKD patients to a nephrologist on regular basis, while the rest only sometimes or did not refer the patients at all. Nearly two thirds of them believed that if RAS inhibitors were stopped due to any reason, the calcium channel blockers were the best alternative anti-hypertensive and were Sending CKD patients for S. PTH before giving one alpha tablets.

Table (1): Sociodemographic and basic characteristics of the sample size.

Variables	Categories	Frequency	Percent
Specialty	nephrologist	17	12.8
	internist	45	33.8
	urologist	10	7.5
	others	61	45.9

Gender	male	92	69.2
	female	41	30.8
Governorate	Erbil	114	85.7
	Duhok	6	4.5
	Sulaymaniyah	9	6.8
	non-KRG	4	3.0
RAS inhibitors are effective anti-hypertensive agents even for CKD patients	yes	131	98.5
	no	2	1.5
Most common causes of ESRD	diabetes mellitus	32	24.1
	hypertension	17	12.8
	diabetes mellitus and hypertension	51	38.3
	glomerulonephritis	5	3.8
	polycystic kidney dis.	3	2.3
	combined causes	25	18.8
Referring CKD patient to a nephrologist	yes	100	75.2
	no	6	4.5
	sometimes	27	20.3
If RAS inhibitors are withheld, the alternative anti-hypertensive will be:	calcium channel blockers	87	65.4
	beta blockers	15	11.3
	calcium channel blockers & beta blockers	20	15.0
	combination of drugs	11	8.3
Sending CKD patients for S. PTH before giving one alpha tablets	yes	88	66.2
	no	45	33.8
Total		133	100

The results of Table 2 show that there was a significant statistical association between specialties and their actions when they have diabetic patients on RAS inhibitors who developed renal impairment. Most of the nephrologists and other specialties would continue the RAS inhibitors while most of the internists and urologists would either stop or change the RAS inhibitors. Pearson Chi square test was done and p-value was 0.010.

Table (2): What will be the actions when you have a diabetic patient on RAS inhibitors who developed renal impairment.

Specialty	continue the medications No. (%)	continue the RAS inhibitors No. (%)	adjust the type and the dose No. (%)	stop the RAS inhibitors No. (%)	change the RAS inhibitors No. (%)	p-value
nephrologist	1 (5.9%)	9 (52.9%)	6 (35.3%)	1 (5.9%)	0 (0%)	0.010
internist	0 (0%)	8 (17.8%)	10 (22.2%)	14 (31.1%)	13 (28.9%)	
urologist	0 (0%)	1 (10%)	0 (0%)	6 (60%)	3 (30%)	

others	2 (3.3%)	19 (31.1%)	9 (14.8%)	16 (26.2%)	15 (24.6%)	
Total	3 (2.3%)	37 (27.8%)	25 (18.8%)	37 (27.8%)	31 (23.3%)	

There were many reasons to make the doctors afraid and cautious in using RAS inhibitors for patients with CKD. Most of the physicians considered a combination of decline of RFT, hyperkalemia, renal artery stenosis and angioedema as the main reasons that make them afraid of using such medications, while (30%) urologists

mentioned that renal artery stenosis was the main cause in reverse most of the nephrologists, internists and others regarded hyperkalemia as the main cause of being cautious in prescribing RAS inhibitors for patients with CKD. Pearson Chi square test was done and p-value was 0.020 (Table 3).

Table (3): Reasons make physicians cautious in using RAS inhibitors for CKD patients.

Specialty	Decline of RFT No. (%)	Hyperkalemia No. (%)	renal artery stenosis No. (%)	angioedema No. (%)	combined reasons No. (%)	p-value
nephrologist	0 (0%)	2 (11.8%)	0 (0%)	0 (0%)	15 (88.2%)	0.020
internist	7 (15.6%)	12 (26.7%)	2 (4.4%)	0 (0%)	24 (53.3%)	
urologist	0 (0%)	5 (50%)	3 (30%)	0 (0%)	2 (20%)	
others	7 (11.5%)	20 (32.8%)	4 (6.6%)	2 (3.3%)	28 (45.9%)	
Total	14 (10.5%)	39 (29.3%)	9 (6.8%)	2 (1.5%)	69 (51.9%)	

The findings from Table 4 indicate that there was a significant statistical association between specialties and calculation of eGFR. While most of the internists were only sometimes calculating

the eGFR CKD patients, in contrast majority of nephrologists, urologists and others were always calculating the eGFR CKD patients. Chi square test was significant (p: 0.001).

Table (4): Calculation of eGFR for suspected CKD patients.

Specialty	Yes	No	Sometimes	p-value
nephrologist	16 (94.1%)	0 (0%)	1 (5.9%)	0.001
internist	19 (42.2%)	5 (11.1%)	21 (46.7%)	
urologist	8 (80%)	1 (10%)	1 (10%)	
others	35 (57.4%)	13 (21.3%)	13 (21.3%)	
Total	78 (58.6%)	19 (14.3%)	36 (27.1%)	

Although the prescription of medical treatment for CKD patients is the main responsibility of nephrologists (100%), yet most of the internists, urologists and other

specialties were prescribing medical treatment sometimes. Chi square test was significant (p: < 0.001).

Table (5): Prescription of medical treatment for CKD patients.

Specialty	Yes	No	Sometimes	p-value
nephrologist	17 (100%)	0 (0%)	0 (0%)	<0.001
internist	14 (31.1%)	6 (13.3%)	25 (55.6%)	
urologist	4 (40%)	2 (20%)	4 (40%)	
others	15 (24.6%)	19 (31.1%)	27 (44.3%)	
Total	50 (37.6%)	27 (20.3%)	56 (42.1%)	

The results of Table 6 indicate that there was a significant statistical association between specialties and PTH investigation. The majority of nephrologists, urologists and other specialties were sending the

patients for PTH before giving one alpha tablets in CKD patients, in contrary most of the internists did not send the patients for this investigation. Chi square test was significant and p-value was 0.005.

Table (6): Investigation of PTH before giving one alpha tablets in CKD patients.

Specialty	Yes	No	p-value
Nephrologist	16 (94.1%)	1 (5.9%)	0.005
Internist	22 (48.9%)	23 (51.1%)	
Urologist	8 (80%)	2 (20%)	
Others	42 (68.9%)	19 (31.1%)	
Total	88 (66.2%)	45 (33.8%)	

Discussion

The current study aimed to evaluate the clinicians' use of renin-angiotensin-system blockers for CKD patients as CKD is considered to be a public health concern globally. One of the important finding was that respondents stated that, for CKD patients, RAS inhibitors are effective anti-hypertensive agents. This finding is in accordance with Leon and Tangri who reported that clinical guidelines recommend renin-angiotensin system inhibitors as the antihypertensive medication of choice for patients with CKD.¹⁴ Momoniat and colleagues reported that apart from the RAS blockers' advantages, these drugs are under-prescribed due to the concern of their side effects after use such as an increase in serum creatinine and potassium; and consequently, they are under-used in the patients who may get great benefit from them.¹⁵ Likewise, our analysis revealed that clinicians prescribed RAS inhibitors for CKD patients with caution having concern about emerging adverse effects of the drug such as elevated RFT, hyperkalemia, renal artery stenosis and angioedema among CKD patients using such medications. In a review conducted by Loutradis and colleagues who reported that in patients with advanced CKD, RAS blockers are commonly less prescribed and discontinued due to the fear of hyperkalemia or acute renal decline.¹⁶

However, our analysis indicated statistically significant association among the specialties concerning the main reason for using RAS medications with caution as it was varied among the different specialties. For instance, renal artery stenosis was primarily cited among urologists and hyperkalemia was mainly mentioned by nephrologists, internists and others. This might be due to their clinical experience with regard to the treatment of CKD patients. The current study also uncovered that there were some discrepancies with regard to the clinicians' actions when they have a diabetic patient on RAS blockers who developed renal impairment, as some of them would continue to prescribe RAS inhibitors and others would either stop or change the RAS inhibitors. Hence, in order to tackle the issues of this inconsistency in the treatment of CKD patients, establishing clinical guidelines addressing the management and treatment of CKD patients in the Kurdistan region of Iraq (KRI) is essential. The findings of the current study highlighted that although the prescription of medical treatment for CKD patients is the main responsibility of nephrologists, yet most of the other specialties sometimes prescribed such medical treatments. Again, establishing clinical guidelines clarifying the roles of different specialties in treating CKD

patients is important in the KRI. Since the RAS blocker drugs lead to decrease the GFR and increase the serum potassium level, it is therefore essential to monitor the GFR and the serum creatinine and potassium levels (Momoniat).¹⁵ Our results showed that the majority of respondents (nephrologists, urologists and others) always calculated the eGFR for CKD patients. It is of considerable importance that the clinicians in our study adhered to what the clinical guidelines recommend concerning the use of RAS inhibitors for CKD patients as they always calculated the eGFR and most of the specialties sent their patients for the PTH investigation (NICE).¹⁷ Regardless of baseline potassium level, “The 2012 Kidney Disease: Improving Global Outcomes (KDIGO)” guideline on CKD evaluation and management recommends that GFR along with potassium should be assessed within 1 week once introducing or increasing the ACE-I or ARB dose. In addition, in a large study evaluating hyperkalemia in 69 426 ARB/ACE-I therapy new users in Sweden, it was found that within the first year of ARB/ACE-I therapy, hyperkalemia was reasonably uncommon among people with eGFR >60mL/min per 1.73m² nevertheless, the rates remained much higher among people with lower eGFR according to Bandak et al.¹⁸ Recently, in a large cohort study in the UK which aimed to evaluate the “real-world” association of RAS inhibitors dose and adverse clinical outcomes among patients with ‘new-onset’ CKD or heart failure, it was found that there were

undesirable effects of under-prescribing RAS inhibitors than what is recommended in the clinical guidelines. For example, it was found that the cumulative incidence of death (over 10 years) was consistently highest in CKD patients who received lesser doses than the guideline-recommended dose, while it was lowest among patients who received $\geq 50\%$ of the recommended during their follow-up. Subsequently, there is a need for policies that allow patients to be continued on appropriate therapy (Linde et al).¹⁹ In a retrospective study conducted in Thailand to evaluate the efficacy of RAS blockers on CKD progression, it was reported that 15.6% of the sample (15,032 diabetic patients) developed ESRD and 68.5% died after ESRD. The clinicians in our study believed that diabetes mellitus and hypertension are the main and most common causes of ESRD. Studies shown that using RAS blockers for one year or longer could stop CKD from progressing into both ESRD and premature mortality (Vejakama et al).²⁰ Although this study shed light on an important issue of the management of CKD patients as it evaluated the clinicians’ use of renin-angiotensin-system blockers for CKD patients, it has some limitations. The sample size was considerably small and the respondents were mostly from Erbil governorate, therefore it is essential that further studies to be conducted involving more clinicians and from different governorates in order to assure the generalisability of the findings.

Conclusions

Clinicians use renin-angiotensin-system blockers for CKD patients with caution fearing of its negative impacts like hyperkalaemia and renal artery stenosis.

Conflicts of interest

The author reports no conflicts of interest.

Developing clear clinical guidelines concerning renin-angiotensin system blockades for patients with CKD in Iraq is mandatory.

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