

A comparative study of the prevalence of hyperkalemia with the use of angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers

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Background and objectives: Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are increasingly used in a variety of settings including heart failure, renal failure, arterial hypertension, and diabetic nephropathy. The objective of this study was to investigate the prevalence of hyperkalemia with ACEI and ARB use, in a population of the United States veterans.

Design, settings, material, and measurements: Retrospective observational cohort study of 1163 patients on ACEIs and 1168 patients on ARBs in a single Veterans Affairs Medical Center. Electronic medical records were reviewed over a 12-month period with data collected on various demographic, laboratory, comorbidity, and medication related variables.

Results: Hyperkalemia (>5 mEq/L) was observed in 20.4% of patients on ACEIs and 31.0% on ARBs. Severe hyperkalemia (6 mEq/L or higher), was observed in 0.8% of ACEI and 2.8% of ARB users. In univariate logistic regression analyses, diabetes mellitus; serum glucose, total carbon dioxide content, creatinine, and estimated glomerular filtration rate (GFR) were significantly associated with hyperkalemia. ARB use, when compared to ACEI, was associated with a 42% increase in odds of hyperkalemia (odds ratio [OR] = 1.42; $p = 0.001$) in a model including adjustment for GFR and a 56% increase in odds of hyperkalemia (OR = 1.56; $p < 0.001$) in a model including adjustment for serum creatinine.

Conclusions: Hyperkalemia, associated with the use of ACEIs and ARBs, is usually mild and severe hyperkalemia is rare. Hyperkalemia is more common with ARBs than ACEIs. ARB use, when compared to ACEI use, may significantly and independently be associated with increased odds of hyperkalemia.

Keywords: hyperkalemia, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers

Introduction

Over the past four decades, many advances have taken place in the management of heart failure, diabetic nephropathy, arterial hypertension, and chronic kidney disease. These advances have included use of angiotensin-converting enzyme inhibitors (ACEIs),¹ angiotensin receptor blockers (ARBs), and more recently, renin blockers. Use of ACEIs² and ARBs³ has contributed to better outcomes in heart failure with less need for hospitalization, improved functional class, and decreased mortality. Similarly, ACEIs and ARBs have shown efficacy in decreasing proteinuria, and slowing the progression of diabetic nephropathy. Their use, however, is sometimes complicated

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by hyperkalemia that may necessitate their discontinuation. It is also estimated that as many as 5% to 10% of patients with congestive heart failure (CHF) may not tolerate ACEIs due to hypotension or azotemia, but do better with ARBs.⁴ Some studies,⁵ have shown a reduced prevalence of hyperkalemia with ARBs possibly due to less suppression of aldosterone secretion,⁶ but others have not confirmed this effect.⁷ If confirmed, substituting ARBs for ACEIs becomes a plausible alternative in patients who desperately need the beneficial effects of renin–angiotensin–aldosterone system blockade. Therefore, we decided to examine and compare the prevalence of hyperkalemia in a large veteran population receiving ACEIs and ARBs to explore factors that increase the risk of hyperkalemia.

Methods

We investigated the prevalence, magnitude, and independence of the association of ACEI and ARB use with hyperkalemia in a population of the United States veterans after receiving approval from our local institutional review board. The pharmacy service provided a list of several thousand patients receiving these medications. Through randomized selection, 1,163 patients receiving ACEIs and 1,168 patients receiving ARBs were included in the study. Using a computerized patient record system (CPRS), serum potassium over a 12-month period was reviewed, the highest value identified, and concurrent laboratory values recorded. Information was collected on various demographic, comorbid, and laboratory variables including age, body mass index (BMI), presence or absence of ICD-9-CM classified heart failure (CHF), diabetes mellitus (DM), arterial hypertension (HTN), chronic kidney disease (CKD), serum sodium, potassium, chloride, total carbon dioxide content (CO₂), blood urea nitrogen (BUN), serum creatinine (Cr), and GFR estimated by a four-variable modification of diet in renal disease formula (MDRD). Information was also collected on medication usage: ACEI type and dose, ARB type and dose, and concomitant nonsteroidal anti-inflammatory drug (NSAID), diuretic, and potassium supplement use. Patients who were on ACEIs or ARBs with missing clinical and laboratory variables were excluded. This accounted for 11% of screened patients. Hyperkalemia was defined as serum potassium level higher than 5 mEq/L that was observed on at least one occasion during the 12-month period preceding the analysis. Comparison of groups was done by Student's *t*-test for normally distributed continuous variables and Pearson's chi-squared test for categorical variables. A *p*-value less than 0.05 was considered significant. Univariate logistic regression was used to

determine the association of each variable of interest with hyperkalemia. For each variable significantly associated with hyperkalemia, bivariate logistic regression was performed to determine which of these factors resulted in a greater than 10% change in the odds of hyperkalemia for ARB use when compared to ACEI use. To achieve optimal model stability, these factors were then included in a multivariate logistic regression analysis to determine the adjusted odds of hyperkalemia for ARB use in reference to ACEI use.

Results

Comparison of ACEI and ARB users

Table 1 details demographics, associated medical conditions, simultaneous medication use, and CKD stage of the two groups. There were no significant differences between the two groups with regard to age, gender, BMI, diabetes mellitus, or hypertension; but CHF was more common in ARB users (17.1 vs 9.5%). Serum creatinine (1.47 ± 1.03 vs 1.25 ± 0.64 mg/dL; *p* < 0.001) was significantly higher and

Table 1 Patient demographics, associated conditions, and medication use

	ACEI	ARB	P Value
Number	1163	1168	
Mean age, years	67.5 ± 10.9	67.2 ± 10.7	0.439
BMI, kg/m ²	30.7 ± 6.9	31.3 ± 7.3	0.025
Diabetes mellitus (%)	51.5	52.1	0.649
Hypertension (%)	91.7	92.9	0.326
Heart failure (%)	9.5	17.1	0.001
Creatinine mg/dL	1.25 ± 0.64	1.47 ± 1.03	<0.001
eGFR ml/min/1.73 m ²	69.0 ± 21.4	60.9 ± 20.7	<0.001
Glucose mg/dL	130.9 ± 57.8	141.0 ± 76.4	0.809
Total CO ₂ meq/L	27.4 ± 2.9	27.7 ± 3.9	0.001
Loop diuretics (%)	14.7	24.4	<0.001
Thiazides (%)	26.7	28.4	0.379
Potassium-sparing diuretics (%)	6.1	11.1	<0.001
Potassium chloride (%)	6	13.1	<0.001
NSAIDs (%)	17	17.5	0.784
CKD stage 1 (%)	16.2	8.2	<0.001
CKD stage 2 (%)	51.4	46.0	<0.009
CKD stage 3 (%)	30.1	39.9	<0.001
CKD stage 4 (%)	1.7	4.6	<0.001
CKD stage 5 (%)	0.6	1.3	<0.089

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; CKD, chronic kidney disease; GFR, glomerular filtration rate; NSAIDs, nonsteroidal anti-inflammatory drugs.

GFR was significantly lower in ARB users (60.0 ± 20.7 vs 69.0 ± 21.4 mL/min/1.73 m² body surface area [BSA]; $p = 0.001$). Use of loop diuretics (24.4% vs 14.7%, $p < 0.001$), potassium-sparing diuretics (11.1% vs 6.1%; $p < 0.001$), and potassium supplements (13.1% vs 6.0%; $p < 0.001$) was significantly higher in ARB compared to ACEI users. When grouped according to CKD stage, the distribution of GFR was significant for more advanced kidney disease among ARB users: 39.9% vs 30.1% for stage III, 4.6% vs 1.7% for stage IV, and 1.3% vs 0.6% for stage V.

Of the 1,136 patients on ACEI, 831 (71.0%) were on lisinopril, 225 (19.3%) on benazepril, 84 (7.2%) on fosinopril, 12 (1.0%) on enalapril, and 11 (0.8%) on captopril. Among ARB users, 1126 (96.4%) were on irbesartan and 42 (3.5%) on losartan (ARB use was restricted by hospital formulary). Mean daily dosage of these medications were as follows: lisinopril 29.4 ± 13.8 mg, benazepril 31.2 ± 12 mg, fosinopril 34 ± 12.1 mg, enalapril 9.5 ± 3.9 mg, captopril 68.7 ± 47.8 mg, irbesartan 202.3 ± 87.4 mg, and losartan 66.6 ± 33.3 mg.

Comparison of hyperkalemic ACEI and ARB Users

Hyperkalemia, serum potassium >5.0 mEq/L on at least one occasion and over a one-year period, was observed in 238 (20.4%) of ACEI users vs 361 (31.0%) of ARB users. Serum potassium, when stratified by the level of hyperkalemia from 5.0 to 5.50, 5.6 to 5.9, and 6.0 mEq/L or higher was seen in 16.6%, 4.9%, and 0.8% of ACEI users vs 22.3%, 5.8%, 2.8% of ARB users, respectively. Among diabetics, 143 (24%) on ACEI therapy and 229 (37.7%) on ARB therapy were hyperkalemic, with mean GFR of 68.7 ± 22.9 in ACEI vs 58.7 ± 21.3 ml/min in ARB users. Hyperkalemia was seen in 30.6% of patients on irbesartan or losartan, 27.2% on captopril, 21.7% on fosinopril, 21.5% on lisinopril, and 16.5% on benazepril. One hundred seventy five patients were on combined ACEI and ARB. Of these, 48 (27.4%) had a serum potassium >5.0 , 14 (8.0%) had a serum potassium >5.5 , and 4 (2.2%) had a serum potassium of 6 mEq/L or higher. Table 2 shows comparison of hyperkalemic patients on ACEIs and ARBs. Among hyperkalemic patients, ARB users had significantly higher mean BUN and serum creatinine, but a lower GFR. Concomitant use of potassium sparing diuretics (17.5% vs 8.0%) and nonpotassium-sparing diuretics (48.0% vs 38.0%) was significantly higher among hyperkalemic ARB users.

Logistic regression analysis

Of the demographic-, comorbidity-, laboratory-, and medication-related variables studied, we identified four

Table 2 Comparison of hyperkalemic patients receiving ACEI or ARBs

	ACEI	ARB	p value
	238	361	
Age, years	68.6 ± 10.8	68.2 ± 10.5	NS
BMI, Kg/m ² BSA	30.3 ± 6.3	30.4 ± 5.8	NS
Glucose mg/dL	142.3 ± 79.4	148.7 ± 81.0	NS
BUN mg/dL	23.8 ± 14.8	30.2 ± 16.9	<0.001
Creatinine mg/dL	1.44 ± 0.79	1.82 ± 1.35	<0.001
CO ₂ content	26.89 ± 3.42	26.73 ± 3.58	NS
DM %	60.0	63.0	NS
Potassium-sparing diuretic %	8.0	17.5	0.001
Nonpotassium-sparing diuretic %	38.0	48.0	0.016
eGFR ml/min/1.73 m ² BSA	60.88 ± 21.2	51.5 ± 21.2	<0.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; BSA, body surface area; BUN, blood urea nitrogen; DM, diabetes mellitus; GFR, glomerular filtration rate; NS, Not significant.

factors significantly associated with hyperkalemia, which in bivariate logistic regression analysis were found to result in greater than 10% change in the odds ratio (OR) of hyperkalemia for ARBs in reference to ACEIs. Specifically, these included serum glucose, BUN, Cr, and GFR. Notably, none of the other variables we studied, including diabetes, CHF, CO₂, nonpotassium-sparing and potassium-sparing diuretic use, NSAID use, or potassium supplement use significantly affected the odds of hyperkalemia for ARBs in reference to ACEIs. Blood glucose, BUN, and Cr were positively correlated, while GFR was negatively correlated with hyperkalemia ($p < 0.001$). Due to collinearity between three of these variables, (BUN, Cr, and GFR), we developed two separate multiple logistic regression models to determine the adjusted odds of hyperkalemia for ARBs in reference to ACEIs. In the first model, we included the GFR, and in the second model, we included the serum Cr. In univariate logistic regression analysis, ARB use was associated with a 73% increase in crude OR for hyperkalemia (OR = 1.739; $p < 0.001$). After adjusting for blood glucose and GFR, there was still an increased risk of hyperkalemia with ARBs (OR = 1.43; $p = 0.001$). Even after adjusting for blood glucose and serum Cr, risk of hyperkalemia with ARBs (OR = 1.56; $p < 0.001$) compared to ACEIs persisted.

Discussion

ACEIs, along with beta blockers,⁸ spironolactone,⁹ and eplerenone¹⁰ have proven themselves to be of great benefit in the management of patients with left ventricular dysfunction.

Their use has become part of accepted regimens of treatment and a yardstick of quality of care provided to these patients.¹¹ ACEI s and ARBs have also been found to be effective in preserving renal function¹² in patients with diabetes mellitus and also in nondiabetic conditions like polycystic kidney disease,^{13,14} idiopathic nephrotic syndrome and Ig A nephropathy.^{15,16} Combined use of ACEI and ARB has been advocated by some studies¹⁷⁻¹⁹ but not all to be more effective in preserving renal function.²⁰

Every patient with heart failure and diabetes mellitus, even those that are not hypertensive are expected to receive these medications unless there is an untoward reaction to their use, like, angioedema, progressive renal failure, or hyperkalemia.

Hyperkalemia, because of its serious consequences, like cardiac arrhythmia and death,^{21,22} frequently compels physicians to discontinue these medications, especially in those with kidney disease. Opinions vary as to what level of hyperkalemia requires action. Some would advocate a level of 8 mEq/L or higher²³ as grounds for hospitalization, while others feel very uneasy leaving a patient with a serum potassium level higher than 5 mEq/L on these agents. In our study we found that although hyperkalemia (serum potassium >5 mEq/L) can be seen in as many as 30% of patients, severe hyperkalemia (>6 mEq/L), is observed only in about 1% to 3% of patients. Higher prevalence of hyperkalemia with ARBs (31% vs 20.4%) in our study may be due to higher prevalence of CHF in this group, higher use of potassium-sparing diuretics and potassium replacement therapy, and the switching of hyperkalemic patients from ACEI to ARBs due to the widely held belief among physicians that ARBs cause less hyperkalemia than ACEIs. However, even after accounting for all the above mentioned factors, and although the association weakened, ARB use was still associated with a significant increase in odds risk for hyperkalemia.

In our study hyperkalemia was more common, compared to controlled studies, where ARBs were used primarily for the treatment of heart failure or nephropathy in patient populations with normal or near normal kidney function and where hyperkalemia was not the primary study focus (Table 3). Bakris and colleagues⁶ and Preston and colleagues⁷ compared the effect of ACEIs and ARBs on serum potassium concentration. In the former study, there were 35 patients with a mean GFR of 65 ± 5 mL/min and there was less increase in serum potassium with valsartan than with lisinopril (0.12 vs 0.28 mEq/L). In the latter study, 24 diabetic patients who had normal renal function (Cr clearance 109 mL/min),

were treated with candesartan and lisinopril. No difference in fractional excretion of potassium or serum potassium concentration was observed. However, in posthoc analyses of RENAAL study, Winklemayer and colleagues²⁴ and Appel and colleagues²⁵ reported hyperkalemia (value not reported) in 24.3% of losartan treated patients vs 12.3% of controls and discontinuation of treatment in 1.3% of patients because of hyperkalemia. The prevalence rate of hyperkalemia in this randomized controlled study is very similar to the results of our study.

Some of the hyperkalemia observed in our study may be artifactual, related to the technique of blood drawing²⁶ and some due to the fact that most of our patients had moderate to advanced renal and heart failure where there is more likelihood of renal dysfunction and hyperkalemia.^{27,28} However, as previously noted, the observed associations between hyperkalemia and ARB use in reference to ACEI use persisted even after adjustment for renal function.

Our study has some limitations. First is the fact that it was retrospective and observational in nature and it can not provide any information on the time frame of development of hyperkalemia after the start of ACEIs or ARBs. Second, it was limited to a veteran population at a single center and may not be generalizable to other populations. Third, there may have been a tendency among practitioners to preferentially prescribe ARBs over ACEIs to patients with a higher disease severity, introducing the possibility for confounding by indication, a type of selection bias. Lastly, causal inference regarding the effect of ARB use in reference to ACEIs use cannot be drawn from this study due to its observational nature. Nevertheless, the validity of our study findings are supported by the detection of other well established associations between other study variables and hyperkalemia, which occurred in the direction and magnitude expected based on previous reports in the literature.

In conclusion, use of ACEIs and ARBs is associated with a high prevalence of hyperkalemia, but more so with ARBs. Most patients can and should benefit from the beneficial effects of these agents, but caution should be exercised especially in those with advanced kidney disease, heart failure, on renal replacement therapy, on potassium sparing diuretics and KCl replacement therapy.²⁹ We agree with Palmer³⁰ that ACEIs or ARBs should be discontinued once serum potassium exceeds 5.5 mEq/L, unless it can be controlled with diet, diuretics or sodium polystyrene sulfonate. As it has been recommended by others, we would advise checking of serum potassium level in one week after any change in ACEI or ARB dosing.

Table 3 Prevalence of hyperkalemia with ARBs in published literature

Author/Study type	No of patients	Serum Cr, Cr Cl or GFR	Patient type	Medication	Hyperkalemia, % or increase meq/L	Definition of hyperkalemia
Cohn and colleagues: randomized controlled trial ³	5,010	<2 mg/dL	CHF	Valsartan	0.12 mEq/L increase	NR*
Granger and colleagues: randomized single-blind trial ⁴	270	<2.5 mg/dL	CHF EF < 35%	Candesartan	2.20%	> 5.5
Bakris and colleagues: randomized double-blind trial ⁶	35	1.6 mg/dL	CKD	Lisinopril vs valsartan	0.12 mEq/L increase vs none	5.5
Preston and colleagues: randomized open-label cross over ⁷	24	120 mL/min	HTN/DM	Candesartan	no difference with placebo	NR
Lewis and colleagues: randomized double-blind trial ¹²	1,715	1.67 mg/dL	DM	Irbesartan	1.90%	NR
The ONTARGET investigators: randomized double-blind trial ²⁰	25,620	1.1 mg/dL	DM/vascular disease	Ramipril vs Telmisartan	Ramipril 3.3%, Telmisartan 3.4%, both 5.6%	> 5.5
Winkelmayer and colleagues: Randomized double-blind trial ²⁴	1,513	1.9 mg/dL	DM	Losartan	24.3%	NR
Takaichi and colleagues: Retrospective ³¹	9,117	>2 mg/dL	DM/HTN	ACEI/ARB	DM 4%, non-DM 10%	> 5.0
Pfeffer and colleagues: Randomized double-blind trial ³²	14,626	1.1 mg/dL	CAD/CHF	Captopril vs Valsartan	Valsartan 1.4%, Captopril 1%, both 1.4%	NR
Present study: Retrospective	2,331	1.47 mg/dL	DM/HTN/CHF	ACEI/ARB	ACEI 20.4% ARB 31%	> 5.0

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CHF, coronary heart failure; CKD, chronic kidney disease; Cr, creatinine clearance; DM, diabetes mellitus; EF, ejection fraction; HTN, hypertension; NR, not reported.

Disclosure

The authors report no conflicts of interest in this work.

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