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ACE inhibition or angiotensin receptor blockade: Impact on potassium in renal failure

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Background. Inhibition of the renin-angiotensin system is known to raise serum potassium [K^+] levels in patients with renal insufficiency or diabetes. No study has evaluated the comparative effects of an angiotensin-converting enzyme (ACE) inhibitor versus an angiotensin receptor blocker (ARB) on the changes in serum [K^+] in people with renal insufficiency.

Methods. The study was a multicenter, randomized, double crossover design, with each period lasting one month. A total of 35 people (21 males and 14 females, 19 African Americans and 16 Caucasian) participated, with the mean age being 56 ± 2 years. Mean baseline serum [K^+] was 4.4 ± 0.1 mEq/L. The glomerular filtration rate (GFR) was 65 ± 5 mL/min/1.73 m^2, and blood pressure was 150 ± 2/88 ± 1 mm Hg. The main outcome measure was the difference from baseline in the level of serum [K^+], plasma aldosterone, and GFR following the initial and crossover periods.

Results. For the total group, serum [K^+] changes were not significantly different between the lisinopril or valsartan treatments. The subgroup with GFR values of ≤60 mL/min/1.73 m^2 who received lisinopril demonstrated significant increases in serum [K^+] of 0.28 mEq/L above the mean baseline of 4.6 mEq/L ($P = 0.04$). This increase in serum [K^+] was also accompanied by a decrease in plasma aldosterone ($P = 0.003$). Relative to the total group, the change in serum [K^+] from baseline to post-treatment in the lisinopril group was higher among those with GFR values of ≤60 mL/min/1.73 m^2. The lower GFR group taking valsartan, however, demonstrated a smaller rise in serum [K^+], 0.12 mEq/L above baseline ($P = 0.1$), a 43% lower value when compared with the change in those who received lisinopril. This blunted rise in [K^+] in people taking valsartan was not associated with a significant decrease in plasma aldosterone ($P = 0.14$).

Conclusions. In the presence of renal insufficiency, the ARB valsartan did not raise serum [K^+] to the same degree as the ACE inhibitor lisinopril. This differential effect on serum [K^+] is related to a relatively smaller reduction in plasma aldosterone by the ARB and is not related to changes in GFR. This study provides evidence that increases in serum [K^+] are less likely with ARB therapy compared with ACE inhibitor therapy in people with renal insufficiency.

Drug-induced hyperkalemia, that is, serum potassium >5.5 mEq/L, is an important but often overlooked problem encountered commonly in clinical practice. Medications generally produce hyperkalemia either by causing redistribution of potassium (β_2-adrenergic blockers, succinylcholine, digitalis overdose, hypertonic mannitol) or by impairing renal potassium excretion. Drugs such as nonsteriodal anti-inflammatory drugs (NSAIDs), inhibitors of the renin-angiotensin-aldosterone (RAA) system, heparin, and cyclosporine impair renal potassium excretion by interfering with the production and/or secretion of aldosterone [1]. Renal insufficiency, defined by a glomerular filtration rate (GFR) of <30 mL/min, is generally required to predispose someone to hyperkalemia [1]. Thus, an elevated serum potassium concentration in a person with normal or mildly impaired renal function should not be attributed to renal insufficiency alone.

One of the more common settings in which hyperkalemia appears to limit treatment of hypertension is in people who have pre-existing elevations of serum potassium and/or renal insufficiency. Unfortunately, this frequently necessitates discontinuation of angiotensin-converting enzyme (ACE) inhibitors in the people in whom they have been shown to provide the greatest benefit

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with regard to slowing the progression of renal disease [2]. In six separate clinical trials of more than 1500 people with renal insufficiency, elevations in serum potassium of between 0.3 and 0.6 mEq/L occurred in those randomized to an ACE inhibitor [3–8]. This increase in serum potassium necessitated discontinuation of the ACE inhibitor in between 1.2 and 1.6% of people in any given trial.

Further support for hyperkalemia limiting antihypertensive therapy with ACE inhibitors in people with renal insufficiency stems from the results of a case-controlled study of patients followed in a General Medicine Clinic with baseline serum potassium levels of greater than 5.1 mEq/L while on ACE inhibitor therapy [9]. Of 1818 patients reviewed, 194 (11%) developed further increases in serum potassium when placed on ACE inhibitor therapy. Moreover, 19% of the 11% (37 of 194) had potassium levels elevated to levels ≥5.6 mEq/L, with only 3 of the 194 (1.5%) reaching potassium levels of ≥6 mEq/L. The most relevant factor for predicting hyperkalemia in this study was a baseline serum creatinine level of ≥1.6 mg/dL. It should be noted that in this study, as in clinical practice, the incidence of hyperkalemia was higher than appreciated in the more controlled setting of the aforementioned clinical trials, thus making it a very important and clinically relevant issue.

A separate dose–response study in people with chronic renal insufficiency reported a low incidence of hyperkalemia with angiotensin receptor blockers (ARBs) [10]. In this study, no increase in serum potassium was noted following one month of treatment with low doses of the ARB losartan. However, an increase in serum potassium (0.3 mEq/L above baseline) did occur following an additional month of therapy at the highest doses of the ARB. Additional data to support potential differences between ACE inhibitors and ARBs on serum potassium concentrations come from clinical trials that compare an ACE inhibitor to an ARB on renal function in people with heart failure [11, 12]. These trials demonstrated a significantly lower incidence of hyperkalemia (serum potassium ≥6 mEq/L) at one year in the more than 1000 people randomized to an ARB compared with those randomized to the ACE inhibitor [11, 12].

To date, there has been no clinical study that examines the possible mechanisms to account for this differential effect on serum potassium between ACE inhibitors and ARBs. The current study was designed to test the hypothesis that an ARB compared with ACE inhibitor fails to increase the serum potassium concentration significantly in people with pre-existing renal insufficiency caused by a lesser effect on aldosterone production. To test this hypothesis, a multicenter, randomized, crossover design was implemented. The study assessed the effects of an ARB and an ACE inhibitor on GFR, plasma aldosterone, plasma renin activity, and angiotensin II, as well as serum potassium levels in people with hypertension and varying degrees of renal insufficiency.

METHODS

The participants were selected from screening through chart review of laboratory data, medical history, recent physical exam findings, and current medical status. Eighty-four men and women were screened for the study, 37 of whom met the inclusion and exclusion criteria. The inclusion criteria included the following: age between 18 and 75 years, a serum potassium level between 4.3 and 5.5 mEq/L, a history of hypertension, and a calculated creatinine clearance between 30 and 80 mL/min, as estimated by the Cockcroft and Gault equation and verified by a 24-hour urine collection for creatinine clearance. The exclusion criteria included unstable renal function or active renal disease, patients who require diuretics for edema management, those who required three or more drugs to control blood pressure, a recent history or evidence of drug or alcohol abuse, known allergies to ACE inhibitor, angiotensin II antagonists, or iodine, known positive for human immunodeficiency virus disease (HIV), significant hepatic disease [serum glutamic-oxaloacetic transaniminase (SGOT) or serum glutamic-pyruvic transaminase (SGPT) greater than three times the upper limit of normal or total bilirubin or alkaline phosphatase greater than 2.5], an average sitting blood pressure of greater than 200/115 mm Hg, unstable angina pectoris on treatment or history of a myocardial infarction or coronary artery bypass surgery or angioplasty within three months of study entry, a history of a stroke within three months of study entry, transient ischemic attack within six months of study entry, ventricular tachyarrhythmias requiring therapy, congestive heart failure, NYHA Class II, III, or IV, pregnancy, lactation, or women of childbearing potential, daily required use of intake of non-steroidal anti-inflammatory agents, excluding aspirin, more than 20 days per month (aspirin up to 325 mg/day was permissible), and finally, a history of significant malabsorption or gastrointestinal surgery.

Thirty five of the 37 participants (95%) completed the study. All of the individuals were scheduled for a screening visit. At this visit, all participants were given an informed consent that was read to the participant and given to him/her in order to discuss the study participation with their primary health care provider. Additionally, a complete medical history and physical examination were completed as well as a review of the inclusion/exclusion criteria. Participants were also informed about salt substitutes and instructed to avoid all such substances during the study. Finally, they were instructed and encouraged to follow a <120 mEq/day sodium diet.

The individual then returned for the baseline examination within two weeks. At this time, any questions regard-

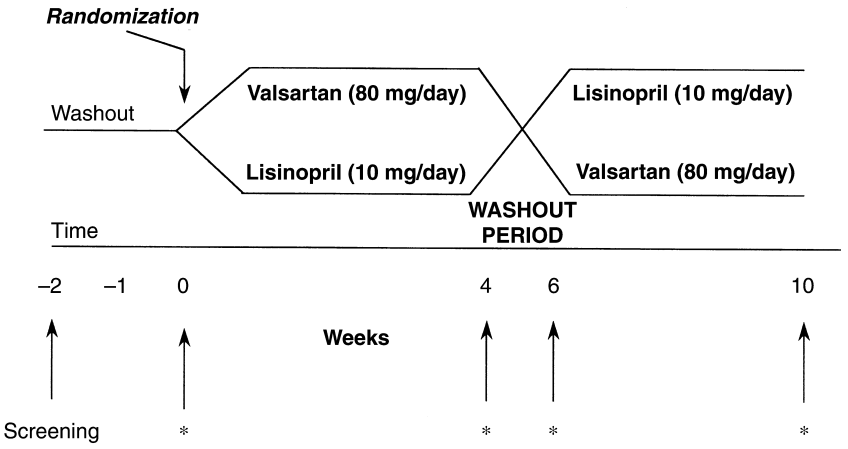

Fig. 1. Illustrated protocol of study. Measurements of plasma renin, angiotensin II, aldosterone, serum [K^+] 24-hour urine for sodium, potassium and aldosterone, and GFR are by the iohexol method.

ing the study were addressed. All participants then signed the Institutional Review Board-approved consent form and entered into the study.

The study implemented a randomized, crossover, multicentered, open-label design that involved the ACE inhibitor lisinopril (10 mg/day) and the ARB valsartan (80 mg/day). The illustrated protocol (Fig. 1) outlines the study design and procedures carried out during the study. In brief, all participants had their antihypertensive medication stopped. Those who had a diastolic blood pressure above 115 mm Hg within the two-week washout period were excluded from the study. The remaining participants were randomized in a 1:1 fashion to either lisinopril 10 mg/day or valsartan 80 mg/day. Participants were maintained on this medication for one month, after which it was terminated, and a two-week washout period ensued. Following the second washout period, individuals were crossed over to the other medication and followed for an additional period of one month. Follow-up visits from randomization to washout were conducted at the discretion of the investigator. Any serum potassium value that was greater than or equal to 6.0 mEq/L was considered a stop point. Participants were also dropped from the study if their systolic blood pressure could not be reduced to less than 180 mm Hg or their diastolic blood pressure to below 100 mm Hg while on randomized drug.

The GFR was measured using iohexol clearance at the end of the washout periods and at the end of one month of therapy with each agent (Fig. 1). Thus, in total, four GFRs were performed on each participant over the duration of the study. The methodology for these GFR measurements has been previously described [13]. During each of the GFR periods, plasma renin activity, angiotensin II levels, as well as plasma aldosterone activity were also measured. Serum electrolytes such as potassium and sodium as well as bicarbonate were also measured during each of these periods. Twenty-four–hour urine specimens for potassium, sodium, and aldosterone were collected in the 24-hour period immediately before GFR determination. Methodology for these measurements has also been previously described [14].

Statistical analyses

This study was designed as an AB/BA crossover trial. Each patient was treated with both lisinopril and valsartan, each for one month. However, patients were randomized to one of two groups, defined by whether lisinopril was taken first [15]. The primary analysis involved a comparison of the average percentage change from baseline in serum potassium levels between the two antihypertensive drugs. Secondary analyses involved a comparison of the average differences from baseline in the levels of plasma renin, angiotensin II, as well as urinary values of potassium, aldosterone, sodium, and others.

Comparisons were made using the paired *t*-test, in which the paired observation for each patient consisted of the percentage change under lisinopril use and the percentage change under valsartan. Sample size calculations were based on the primary analysis.

Previous studies demonstrate that ACE inhibitors generally raise serum potassium levels an average of 15% above baseline after a one-month period [2–9]. Conversely, ARBs raise serum potassium levels an average of 5% above baseline over the same period [10–12]. This represents a 10% difference in the increase from baseline between the two types of drugs. Thus, conservatively assuming an overall standard deviation of 15 for the percentage increase from baseline, a within-patient correlation of 0.20 between the percentage increase under the ACE inhibitor and the ARB, and 80% power to detect a 10% point difference in the average percentage increase between the two types of drug, 29 patients were required [16]. Allowing an additional 15% for loss of data, such as due to attrition, 35 patients were required.

Baseline characteristics were compared between the

Table 1. Baseline and post-treatment values over all randomized participants, by drug

Variable	Drug	*N*	Baseline	Post-treatment	*P*
Systolic blood pressure *mm Hg*	L	35	150 ± 4	139 ± 5	0.002
	V	35	149 ± 3	139 ± 5	0.002
Diastolic blood pressure *mm Hg*	L	35	85 ± 2	80 ± 2	0.012
	V	35	90 ± 2	83 ± 2	0.009
Glomerular filtration rate *mL/min/1.73 m²*	L	34	62 ± 4	65 ± 5	0.37
	V	35	66 ± 5	64 ± 5	0.53
Serum potassium *mEq/L*	L	34	4.47 ± 0.07	4.59 ± 0.10	0.19
	V	35	4.42 ± 0.07	4.42 ± 0.11	0.94
Fractional excretion of potassium *%*	L	33	17.5 ± 2	19.8 ± 3	0.61
	V	35	20.0 ± 3	21.6 ± 2.6	0.53
Plasma renin activity *ng/mL/hour*	L	34	1.63 ± 0.39	4.42 ± 1.55	0.06
	V	35	1.81 ± 0.76	2.94 ± 0.56	0.19
Plasma angiotensin II *pg/mL*	L	32	26.2 ± 2.5	22.2 ± 1.74	0.06
	V	30	24.7 ± 2.8	33.3 ± 3.7	0.02
Plasma aldosterone *pg/mL*	L	34	6.73 ± 0.65	4.96 ± 0.61	0.01
	V	35	6.31 ± 0.62	5.2 ± 0.65	0.07
Urinary aldosterone *pg/mL*	L	33	4.5 ± 0.48	3.71 ± 0.48	0.08
	V	35	4.67 ± 0.52	4.36 ± 0.52	0.37

Data are expressed as mean ± SE of the mean. *P* values reflect statistical comparison of mean values. Abbreviations are: L, lisinopril; V, valsartan.

two randomized groups using chi-square tests and Wilcoxon signed-rank tests, as appropriate. Nonparametric tests, such as Wilcoxon rank tests, were used any time the relevant sample size was less than 30. Individual effects of the two drugs were assessed by testing whether mean post-treatment values were significantly different from mean pretreatment values using paired *t*-tests. Comparisons between the two drugs were made by comparing mean post-treatment and pretreatment differences. Linear relationships between variables were examined using multiple regression analyses. Because a crossover design was used, study data were also analyzed using the methods of Senn, both as an alternative analysis and to test the assumption of no carryover effect from the first treatment to the second [15]. Finally, because renal insufficiency can significantly influence many of the metabolic and hemodynamic variables under study, these analyses were also performed stratified by low-GFR status (baseline GFR ≤60 mL/min/1.73 m^2) versus high-GFR status (baseline GFR >60 mL/min/1.73 m^2). These values were selected since they reflect a greater than 50% loss in renal function and clinically have been associated with a higher probability for developing hyperkalemia [4, 9].

RESULTS

Initial randomization

The mean ± age of the participants was 56 ± 2 years. Of the 35 people who completed the study, 19 were African Americans, and 16 were Caucasian. Twenty-one were males, and 14 were female. The group was obese with a body mass index of 31 ± 1 kg/cm^2 and a weight of 91 ± 4 kg.

The baseline systemic, renal hemodynamic, and hormonal characteristics of all randomized patients are shown in Table 1. The primary analysis demonstrated no significant difference between the effect of lisinopril or valsartan on serum potassium levels over all patients at the 0.05 level.

Individual and comparative drug effects

In comparing the effects between the two drugs on the other specified variables, only the mean change, from baseline, in plasma angiotensin II levels was significantly different ($P = 0.005$, Wilcoxon). The analyses proposed by Senn yielded similar results. The Senn analyses also showed no evidence of a carryover effect from the first to the second drug.

The changes in blood pressure, GFR, plasma renin, angiotensin II, plasma, and urinary aldosterone as well as serum and urinary potassium over all people studied, by drug, are shown in Table 1. A marginal increase in plasma renin activity ($P = 0.06$), a marginal decrease in plasma angiotensin II ($P = 0.06$), and a significant decrease in plasma aldosterone ($P = 0.01$) were noted with lisinopril use. However, with valsartan use, the patients experienced a significant increase in plasma angiotensin II ($P = 0.02$) and a lesser fall in plasma aldosterone ($P = 0.07$).

Analysis by level of renal function

To evaluate further the trends in hormone profiles and serum potassium responses between the two agents, we analyzed the groups based on level of renal function at baseline. The baseline characteristics of those participants stratified by level of GFR are shown in Table 2. Those with baseline GFR values of ≤60 mL/min/1.73 m^2 were significantly younger, more obese, and with higher plasma levels of renin and angiotensin II but not aldoste-

Table 2. Baseline characteristics of the study participants based on GFR stratification demographic characteristics

	< 60 mL/min/1.73 m^2	> 60 mL/min/1.73 m^2	*P* value
N	18	17	
Age *years*	52 ± 3	60 ± 2	0.05
Race *AA/C*	7/11	12/5	NS
Sex *M/F*	11/7	10/7	NS
Weight *kg*	101 ± 7	81 ± 2	0.01
Body mass index *kg/cm^2*	34 ± 1	29 ± 1	0.02
Metabolic and hemodynamic characteristics			
Systolic blood pressure *mm Hg*	146 ± 4	153 ± 4	NS
Diastolic blood pressure *mm Hg*	87 ± 2	89 ± 2	NS
Serum creatinine *mg/dL*	1.6 ± 0.1	1.1 ± 0.1	<0.0005
Glomerular filtration rate *mL/min/1.73 m^2*	43 ± 2	88 ± 5	<0.0005
Serum potassium *mEq/L*	4.6 ± 0.1	4.3 ± 0.1	0.04
Plasma renin activity *ng/mL/hour*	2.4 ± 0.7	0.5 ± 0.1	0.01
Plasma angiotensin II *pg/mL*	31 ± 4	22 ± 2	0.05
Plasma aldosterone *pg/mL*	6.3 ± 0.8	7.1 ± 1	NS

Values are expressed as mean ± SE of the mean. Abbreviations are: AA, African American; C, Caucasian, M, Male; F, female.

Table 3. Metabolic and hemodynamic changes noted in the group with renal insufficiency (GFR <60 mL/min)

	Baseline		Post Treatment	
	Valsartan	Lisinopril	Valsartan	Lisinopril
Systolic blood pressure *mm Hg*	146 ± 4	148 ± 5	138 ± 3[a]	139 ± 4[a]
Diastolic blood pressure *mm Hg*	87 ± 2	88 ± 2	83 ± 2[a]	84 ± 2[a]
Serum creatinine *mg/dL*	1.6 ± 0.1	1.5 ± 0.1	1.6 ± 0.1	1.5 ± 0.1
Glomerular filtration rate *mL/min/1.73 m^2*	43 ± 2	42 ± 2	43 ± 2	43 ± 2
Serum potassium *mEq/L*	4.5 ± 0.1	4.6 ± 0.1	4.6 ± 0.2	4.9 ± 0.1[a]
Plasma renin activity *ng/mL/hour*	3 ± 1.4	3 ± 0.7	11 ± 3.9[a]	7 ± 3[a]
Plasma angiotensin II *pg/mL*	30 ± 5	31 ± 5	39 ± 6	23 ± 4[a]
Plasma aldosterone *pg/mL*	5.9 ± 0.8	6.8 ± 0.7	4.4 ± 0.6	3.6 ± 0.4[a]

Values are expressed as mean ± SE of the mean.
[a] $P < 0.05$ compared to respective baseline value

rone (Table 2). They also had modestly higher mean baseline serum potassium levels when compared with the higher GFR group (Table 2). The mean change in GFR in both groups was not significantly changed from baseline. In the low GFR group, the difference between the two agents was clearly not significant (1 ± 2 ΔmL/min/1.73 m^2, lisinopril vs. 1 ± 2 ΔmL/min/1.73 m^2, valsartan, $P > 0.5$).

In people with a baseline GFR of ≤60 mL/min/1.73 m^2, lisinopril significantly increased serum potassium levels ($P = 0.047$) as well as plasma renin activity (Table 3). It decreased plasma angiotensin II and plasma aldosterone compared with the change in people with better renal function (Fig. 2). Moreover, in this low GFR group, the correlation between plasma aldosterone and serum potassium was higher with the ACE inhibitor than with the ARB (Fig. 3). Note also that while valsartan, like lisinopril, significantly increased plasma renin activity, it only marginally increased plasma angiotensin II levels (Table 3). This marginal increase in angiotensin II levels in the valsartan group corresponded to a blunted reduction in plasma aldosterone levels ($P = 0.21$). This change in plasma aldosterone levels was more marked in those randomized to lisinopril (−3.2 ± 0.9 Δpg/mL, lisinopril vs. −1.1 ± 0.8 Δpg/mL, valsartan, $P < 0.003$). These differential effects on plasma aldosterone and serum potassium between these two inhibitors of the RAA system could not be explained by differences in blood pressure or GFR (Fig. 4). Importantly, these relationships between plasma aldosterone and serum potassium were present regardless of which agent was given first. This further supports the notion that the washout process was effective.

Among the people whose baseline GFR was >60 mL/min/1.73 m^2, both lisinopril ($P = 0.004$) and valsartan ($P = 0.002$) significantly increased plasma renin activity, while only valsartan significantly increased plasma angiotensin II ($P = 0.04$). All *P* values reported above in this subsection are based on the use of Wilcoxon signed-rank tests.

Regression analyses showed that the change in serum potassium from baseline to post-treatment with lisinopril was significantly correlated with the same change in plasma aldosterone. This correlation was even higher among those with GFR values at or below 60 mL/min/1.73 m^2 (Fig. 3). A similar correlation, however, was not

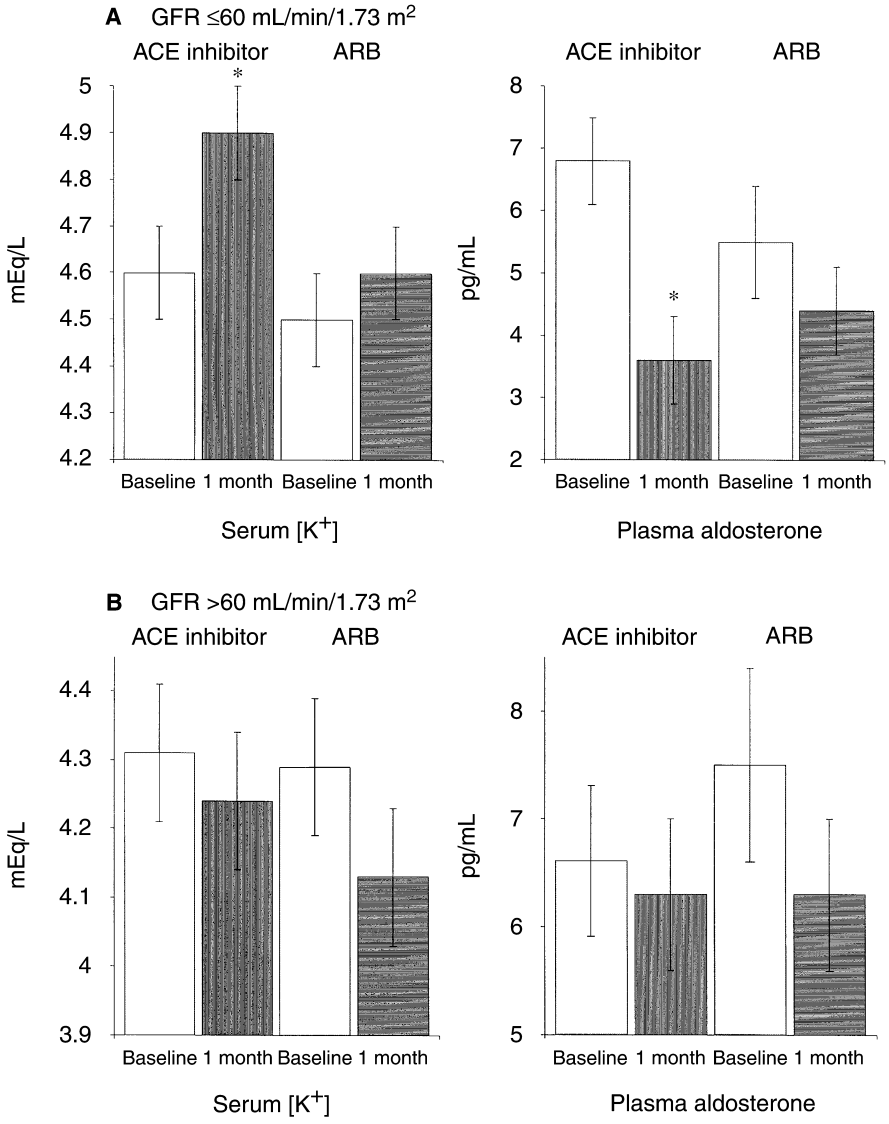

Fig. 2. Comparative effects of lisinopril and valsartan on changes in serum potassium and plasma aldosterone in people with two different levels of renal function (*A* and *B*). *$P <$ 0.05 compared with baseline value.

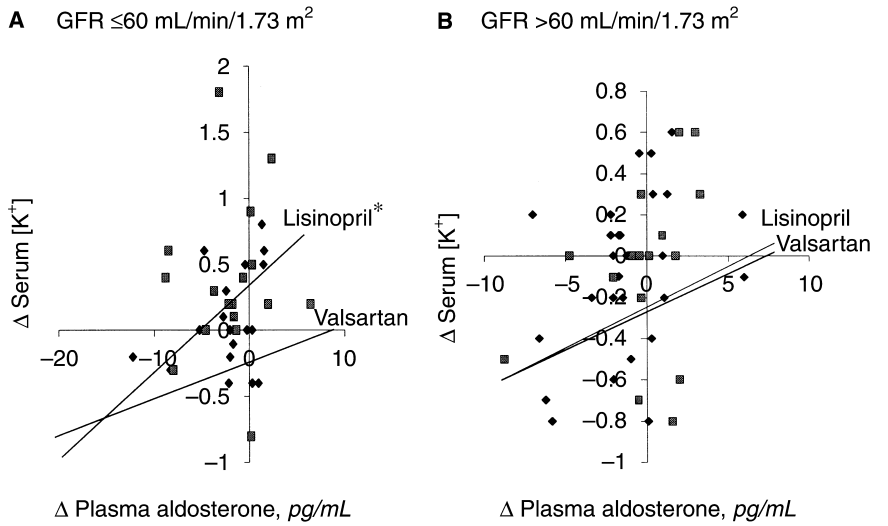

Fig. 3. Association between changes in serum potassium as a function of change in plasma aldosterone in people with two different levels of renal function: (*A*) GFR ≤ 60 mL/min/1.73 m² (r = 0.35 lisinopril, r = 0.14 valsartan), and (*B*) GFR > 60 mL/min/1.73 m² (r = 0.43 lisinopril, r = 0.33 valsartan). *$P <$ 0.02 compared with valsartan for those with GFR < mL/min/1.73 m². Symbols are: (■) lisinopril; (◆) valsartan.

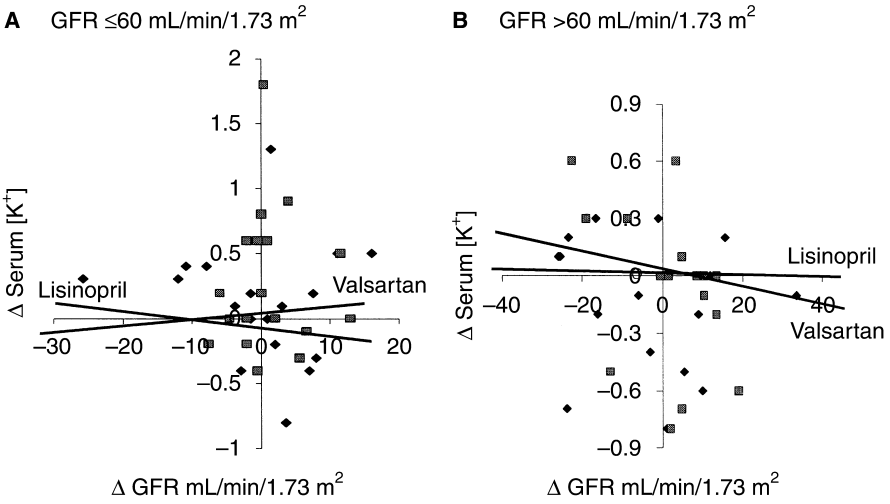

Fig. 4. Association between the change in serum potassium as a function of change in glomerular filtration rate in people with two different levels of renal function: (*A*) GFR ≤ 60 mL/min/1.73 m² (r = 0.12 lisinopril, r = 0.05 valsartan; *P* = 0.12), and (*B*) GFR > 60 mL/min/1.73 m² (r = 0.12 lisinopril, r = 0.41 valsartan; P = 0.16). Symbols are: (■) lisinopril; (◆) valsartan.

observed in those with comparable GFR values treated with valsartan (Fig. 3).

DISCUSSION

The results of this trial demonstrate that there is a clear difference in the degree of serum potassium increase from baseline between the ACE inhibitor and ARB studied in those with a GFR below 60 mL/min/1.73 m². Specifically, the ACE inhibitor lisinopril significantly increased the serum potassium concentration from a baseline of 4.6 mEq/L to levels between 4.9 and 5.3 mEq/L at study end. This is compared with the ARB valsartan that increased potassium from 4.6 mEq/L at baseline to levels between 4.6 and 4.8 mEq/L at study end. The degree of serum potassium rise correlated with the degree of aldosterone reduction. A significant reduction in plasma aldosterone was noted in those taking lisinopril and was independent of blood pressure reduction, baseline serum potassium, or change in GFR. The magnitude of aldosterone reduction was much less in those who received the ARB.

While studies have been performed in normal subjects to compare the effects of an ARB with an ACE inhibitor on changes in the renin-angiotensin system and serum potassium, no studies have been carried out in people with moderate to severe renal insufficiency to evaluate the relative differences between these agents in the context of changes in the renin-angiotensin system. Patient-oriented, clinical studies confirm our observation of no substantive reductions in aldosterone with an ARB or ACE inhibitor in people with relatively normal renal function. Goldberg et al compared the chronic effects of an ARB to an ACE inhibitor in normal subjects and found no difference in the aldosterone effect [17]. Other investigators, however, have described a low-sodium dependency of an ARB to reduce aldosterone in normal volunteers [18]. This latter observation was also observed in 25 normotensive people with normal renal function placed on a low-sodium diet [19]. This latter study, however, noted a relatively greater aldosterone reduction by the ACE inhibitor compared to the ARB [19]. Our study participants were not placed on a sodium-restricted diet. They were instructed, however, to ingest <150 mEq/L of sodium per day. Sodium intake for the group ranged from 120 to 215 mEq/day at the end of each crossover period, with no differences between those taking either agent. These data are consistent with those placed on non–sodium-restricted diets.

Conversely, clinical trials in people with moderate to severe renal insufficiency have noted differences in the incidence of hyperkalemia between these two drug classes [2, 9–12]. To our knowledge, however, this is the first multicentered study that compares the effects of these two classes of agents in the same patients with variable degrees of renal insufficiency. Taken together with previous studies, these data support the concept that ARBs reduce the risk of hyperkalemia in people at high risk for such an event compared with ACE inhibition.

Several possible reasons could account for the observed differences in degree of potassium elevation between these two agents. One potential explanation is that the group with a lower GFR had a higher baseline potassium level, a factor known to increase plasma aldosterone levels. Serum potassium elevation above its normal range, that is, >5.5 mEq/L, enhances the kaliuretic action of aldosterone [20]. However, there were no differences in baseline plasma aldosterone levels between the two groups, thus making this an unlikely explanation to account for the differences in potassium response. Moreover, only 3 of our 35 (8.5%) participants achieved this level of serum potassium. Thus, the meaningfulness

of this aforementioned mechanism to account for the difference between these agents is not testable.

Another important reason for this difference in serum potassium elevation may relate to a blunted stimulation by angiotensin II of aldosterone in older people who have lost a certain amount of renal function. While there are no data to support a blunted role of angiotensin II stimulation on aldosterone production in such individuals, there are data to support reduced levels of aldosterone and a blunted response to increased potassium. Earlier studies in people with renal insufficiency support the concept of lower baseline levels of plasma aldosterone as well as a blunted response in potassium excretion to aldosterone loading [21]. More recently, studies by Mulkerrin, Epstein, and Clark evaluated the response of aldosterone to increase serum potassium in people over age 64 years with baseline serum potassium values of 4.3 mEq/L [22]. These individuals manifested lower baseline levels of plasma aldosterone as well as a blunted increase in response to potassium loading compared with young controls. Our data confirm the observation of lower baseline plasma aldosterone levels in older individuals. However, in our study, only those with low GFR values give ACE inhibitor-manifested significant differences in aldosterone and potassium changes from baseline.

Additional factors that may help explain these differential effects include dosage of drug and/or its tissue penetrability, effects on GFR, effects on other hormonal systems affecting potassium homeostasis such as prostaglandin or bradykinin, relative effects on the angiotensin II type 2 receptor versus the angiotensin II type 1 receptor, and finally, effects on aldosterone itself. The dosage of the drug administered would clearly have an impact on the degree of potassium rise and suppression of aldosterone production. All clinical trials performed to date have used moderate to high doses of ACE inhibitors to achieve blood pressure control. A recent study by Keilani et al, however, demonstrated that even very low doses of an ACE inhibitor could increase serum potassium by as much as 0.25 mEq/L [23]. While this was not statistically significant in this study, it may be clinically significant in a different clinical setting. Additionally, Davidson et al noted a significantly greater lowering of plasma aldosterone concentration and rise in potassium at high versus low doses of lisinopril in patients with heart failure [24]. In our study, we used comparable blood pressure lowering doses of both agents, as evidenced by a similar reduction in blood pressure between groups, regardless of randomization order of the drugs. Moreover, tissue penetrability of both agents is low, especially in the adrenal gland [25, 26]. Thus, differences in dosing would not likely explain our results.

Another possible explanation for the difference in potassium balance between these two agents may relate to prostaglandin levels [27]. Gomez-Martino et al examined the contribution of prostaglandins in diabetic patients with renal insufficiency on potassium excretion. Much like our low GFR group, participants in this study had an average GFR of 34 mL/min. Prostaglandin administration significantly increased plasma potassium when compared with controls and plasma aldosterone decreased. This effect of prostaglandins on neurohumoral systems has also been described in heart failure [28]. While we did not measure prostaglandins in our study, it is well established that ACE inhibitors increase prostaglandins of the E series and prostacyclin; this has not yet been demonstrated for ARBs [28, 29].

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