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Original Article

The comparison of losartan and ramipril on the incidence of hyperkalaemia among hypertensive patients with chronic kidney disease

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ABSTRACT

Background and Aims: The Joint National Committee 8th guideline recommends the initiation of renin angiotensin aldosterone system (RAAS)-linked drugs for hypertensive patients with chronic kidney disease (CKD). Losartan, an angiotensin receptor blocker (ARB), and ramipril, angiotensin converting enzyme (ACE) inhibitors, are widely utilized antihypertensive agents with sound efficacy and safety. The study compared the hyperkalemia incidences in CKD patients exposed to losartan and ramipril.

Methods: A prospective observational study was conducted for 12 months in the nephrology outpatient setting of a private tertiary care referral hospital in the Malabar region of Kerala. CKD patients with hypertension who were on ACE inhibitors or ARB therapy constituted our study population. Their demographic details, serum creatinine and potassium and urine protein were documented for three consecutive patient consultations.

Results: There were an equal number of samples (n=186) in each of the losartan and ramipril administered groups. Losartan and ramipril doses preferred by the nephrologist were 1.25, 25, 50 & 100 mg and 0.625, 1.2, 2.5, 5 and 10 mg, respectively. The Mann-Whitney U test showed statistical significance ($p \geq 0.05$) between RAAS-related drugs and patients' total daily doses. We noticed more frequency of hyperkalemia in the losartan group (n=11, 5.9%) than in the ramipril group (n=4, 2.2%). Initially, the mean serum potassium was low in the ACE inhibitor (4.35±0.55) subset, and then there was augmentation in the second (4.46±0.52) and third (4.52±0.55) patient consultations. The repeated measures ANOVA tests depicted the samples to be different ($p<0.05$) in the serum potassium measurements within the losartan group ($p-= 0.018$) and ramipril group ($p<0.001$).

Conclusion: Losartan gave favorable clinical effects in CKD patients with regards to serum creatinine and potassium. However, the frequency in reduction of proteinuria was profound in ramipril understudies.

Keywords: Ramipril, Losartan, Hyperkalemia, Serum creatinine, Urine Protein

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INTRODUCTION

The prevalence of chronic kidney disease (CKD) is increasing enormously and the impairment is responsible for pathophysiological changes in the serum electrolyte levels (Coresh et al., 2007). The incidence of hyperkalemia in such patients can lead to cardiovascular complications (Esposito et al., 2004; Mandal, 1997). The distorted glomerular filtration rate (GFR) with lack of dietary control can aggravate dyselectrolytemia. The extracellular potassium shift is further sensitized by antihypertensive agents, mainly, renin angiotensin aldosterone system (RAAS) blockers (Palmer, 2004; Reardon & Macpherson, 1998; Weir, 1999).

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) are commonly administered renoprotective agents. The persistent increment in the serum potassium observed in patients can be an impact of CKD progression. End stage renal disease (ESRD) without serum potassium homeostasis, even after optimal pharmaco-therapeutic management and dietary restriction, warrants renal transplantations. It is the responsibility of the clinical pharmacist to prevent and treat at the earliest any drug-induced dyselectrolytemia. Thus, we assessed the impact of losartan and ramipril, the commonly prescribed ACE inhibitor and ARBs, on the patients' serum potassium in CKD with co-existing hypertension.

MATERIAL AND METHODS

Ethical approval

The prospective observational study was conducted in KIMS Al Shifa tertiary care referral Hospital, Kerala, India, from 2018 to 2019. The study was approved by the ethics committee of KIMS Al Shifa Hospital as per the letter KAS/EC/2018-29 (dated 30-04-2018), and written informed consent was obtained from each patient.

Patient selection and study design

The sample size was statistically determined using the equation of estimation of prevalence.

$$N = (Z^2_{\alpha/2} \times p \times (1- p) \times D)/ E^2$$

Where, $Z_{\alpha/2}$ = normal deviate for two tailed hypothesis, P = proportion from previous studies, D = design effect, E = margin of error.

A total of 375 subjects were enrolled in the study based on the selection criteria. All the patients who consulted the nephrologist during the research period, and those on ramipril or losartan therapy and diagnosed with CKD and hypertension were included. Patients who were hypertensive but did not have CKD, unconscious and mentally ill patients, pregnant patients, and those with combination antihypertensive therapy were excluded from the study. However, we could not properly follow up with a few patients and there were 3 dropouts. Thus, 372 patients were finally considered for results analysis.

The patient's demographic details, such as age, gender, CKD stages, and duration of CKD were retrieved from their medical case file and direct patient interview, along with information regarding the nephrologist's clinical decision. Serum creatinine and serum potassium levels were noted on three consecutive specialist consultations. The adverse drug reactions pointed out were reported, and their causality assessment was performed with the Naranjo scale.

Statistical analysis

The data was put into Microsoft Excel 2007 version and exported into SPSS version 26. The chi-square test was employed to associate the variables. Mann-Whitney U and repeated ANOVA tests were computed to identify the difference between urine protein values and serum creatinine at different consultations. Spearman's ratio was analyzed to correlate the serum creatinine with the total daily dose and duration of CKD. The Bonferroni test was instituted for the pair wise comparison of serum potassium across consultations. The significance level (*p*) was fixed at 0.05 with a confidence interval of 95%.

RESULTS

We obtained 372 samples according to our inclusion criteria. Among them, the losartan group (n=186) and ramipril group (n=186) constituted equal proportions. Patients aged between 60 and 70 years were more common among both the ramipril- and the losartan-administered groups (Table 1). CKD patients in stages 3 and 4 were significant in our study. Losartan prescribing predominated in stage 3 but less so in stage 4 when compared with the ramipril group.

The losartan doses preferred by the nephrologist were 12,5 mg, 25 mg, 50 mg, and 100 mg (Table 2). There were more patients who were administered with the 50 mg tablet (n=84). Few patients were prescribed 12.5 mg (n=1) and 100 mg (n=3). On the other hand, the chosen ramipril doses were 0.625 mg, 1.2 mg, 2.5 mg, 5 mg, and 10 mg. Limited participants had 0.625 mg (n=2) and 10 mg (n=2). The abundance of the 1.25

Table 1. The frequency distribution of patient's age and CKD stages (years) observed in ramipril and losartan groups.

Age of the patients	Ramipril (n=186)	Losartan (n=186)
less than 50 years	29 (15.6%)	46 (24.7%)
50 to 60 (years)	34 (18.3%)	42 (22.6%)
60 to 70 (years)	62 (33.3%)	53 (28.5%)
70 above (years)	61 (32.8%)	45 (24.2%)
Total	186 (100%)	186 (100%)
CKD	**Ramipril (n=186)**	**Losartan (n=186)**
Stage 1	7 (3.7%)	8 (4.3%)
Stage 2	10 (5.4%)	21 (11.3%)
Stage 3	85 (45.7%)	93 (50%)
Sage 4	83 (44.6%)	63 (33.9%)
Stage 5	1 (0.5%)	1 (0.5%)
Total	186 (100%)	186 (100%)

Table 2. The frequency of the distribution of doses of losartan and ramipril groups.

Losartan (n=186)				
Dose (mg)	**Once daily**	**Twice daily**	**Thrice daily**	**Total**
12.5	1 (0.5%)	0 (0%)	0 (0%)	1 (0.5%)
25	60 (32.3%)	38 (20.4%)	0 (0%)	98 (52.7%)
50	40 (21.5%)	43 (23.1%)	1 (0.5%)	84 (45.2%)
100	1 (0.5%)	2 (1%)	0 (0%)	3 (1.6%)
Total	102 (54.8%)	83 (44.7%)	**1 (0.5%)**	**186 (100%)**
Ramipril (n=186)				
Dose (mg)	**Once daily**	**Twice daily**	**Total**	
0.625	2(1%)	0 (0%)	2 (1%)	
1.25	88 (47.3%)	15 (8.1%)	103 (55.4%)	
2.5	38 (20.4%)	8 (4.3%)	46 (24.7%)	
5	22 (11.8%)	11 (5.9%)	33 (17.7%)	
10	1 (0.5%)	1 (0.5%)	2 (1%)	
Total	**151 (81.2%)**	**35 (18.8%)**	**186 (100%)**	

(n = 372)		**Median**	**IQR**	**"Z"**	**P value**
Total daily dose Losartan	**Ramipril**	2.50	1.25 to 2.50	-16.951	< 0.001*
	50	25 to 100			

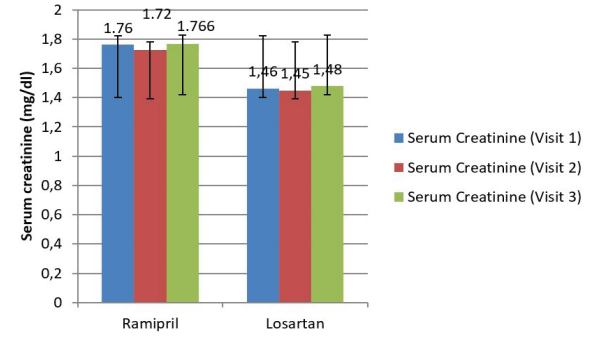
mg prescriptions was noticed. The Mann-Whitney U test was used to compare the patients' total daily dose according to the RAAS drug groups. There was a difference in the samples ($p<0.05$) concerning the two variables.

We found that ramipril (n=86) decreased proteinuria better than losartan (n=61). However, the losartan group (n=74) dominated in the patient set with same proteinuria throughout the three consultations (Table 3). The chi-square test was used to compare the change in patients' urine protein across the two drug groups and observed to have a relation with a *p* value <0.05. Similarly, the Mann Whitney U test found a difference ($p<0.05$) in urine protein between the losartan and ramipril groups for the first, second, and third consultations. There was one substantial patient with abnormal serum creatinine in both the ramipril and losartan populations observed in their first consultations. The serum creatinine of most CKD patients in the ramipril (first visit mean=1.76) and losartan (first visit mean=1.46) groups decreased initially (second visit: ramipril, mean=1.72; second visit: losartan, mean=1.45) and then increased slightly (third visit: ramipril, mean=1.77; second visit: losartan, mean=1.48) (Figure 1). The independent sample "t" test was employed for the patient's serum creatinine in each of the three consultations and each sample was identified to be different ($p<0.05$). The changes in mean serum creatinine between the first and second consultations and the second and third showed that the ramipril group had a decrease followed by a mild increase. But the losartan group showed a drastic increase in the serum creatinine observed in the middle and then sloped down in the end (Figure 2). The Spearman's ratio was calculated and there was a negative correlation (Ramipril group: Spearman's ratio=-0.154, $p=0.036$; Losartan: Spearman's

Table 3. Change in proteinuria preceding 3 consultations in ramipril and losartan groups.

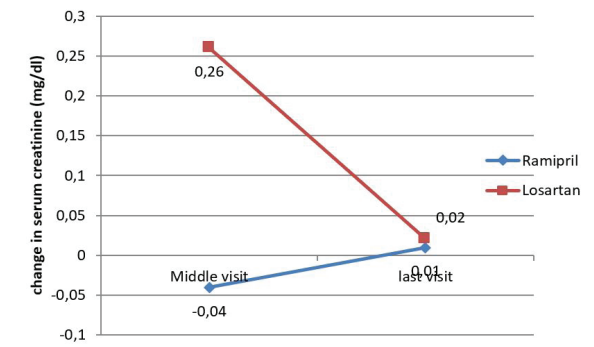
Proteinuria					**Chi square**	**P value**
	Ramipril (n=186)		**Losartan (n=186)**			
Same	74 (39.8%)		99 (53.2%)			
Decreased	86 (46.2%)		61 (32.8%)		7.864	0.020*
Increased	26 (14%)		26 (14%)			

Consultations	**Ramipril**		**Losartan**		**"Z"**	**P value**
	Median	**IQR**	**Median**	**IQR**		
1st	3	2 to 3	2	2 to 3	-4.166	<0.001*
2nd	2	2 to 3	2	2 to 2	-4.033	<0.001*
3rd	2	2 to 3	2	2 to 2	-2.307	0.021*



Independent t test, p<0.05

Figure 1. The bar diagram shows the mean and standard deviation of serum creatinine on 1st, 2nd and 3rd consultation, administered with ramipril and losartan.

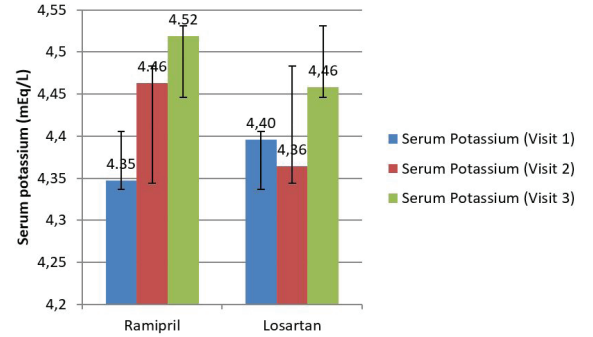


Independent t test, p<0.05

Figure 2. The line diagram plotted against the change in mean serum creatinine level of patients on 2nd and 3rd consultation with respect to the 1st.

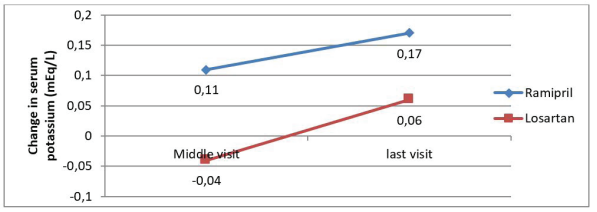
ratio=-207, p value=0.005) between serum creatinine with the total daily doses of RAAS drugs. A positive correlation (Spearman's ratio=0.182, *p*=0.013) was noted among the patients treated with losartan and the duration of their CKD.

From our study, the initial mean serum potassium (4.35) was low in the ACE inhibitor group. However, a drastic shift was observed in the second (4.46) and third (4.52) consultations. However, the losartan group had a lesser increase in mean serum potassium (Figure 3). The repeated measures ANOVA test portrayed difference ($p<0.05$) in the measurements of serum potassium within losartan group ($p=0.018$) and ramipril group ($p<0.001$). When we closely examined the change in mean serum potassium of each group, the ramipril group had a further increase in value. In the losartan group, even though the second consultation showed a decrease, there was a slight increase in later consultation (Figure 4). The Bonferroni test was computed for the pair wise comparison of serum potassium across consultations. There was a difference in serum potassium between the measurements of first and second consultations (mean difference=-0.116, $p=0.001$) and first and third consultations (mean difference=-0.172, $p=<0.001$) among the ramipril group, and second and third consultations (mean difference= -0.094, $p=0.014$) in the losartan group.



ANOVA, Losartan: p<0.05, Ramipril: p<0.01

Figure 3. The bar diagram shows the mean and standard deviation of serum potassium on 1st, 2nd and 3rd consultation, administered with ramipril and losartan.



Bonferronic test, Ramipril: Middle visit-p<0.05, Last visit- p<0.01, Losartan: p<0.05

Figure 4. The line diagram plotted against the change in mean serum potassium level of patients on 2nd and 3rd consultation with respect to the 1st.

Table 4. The frequency distribution of serum creatinine and potassium of losartan group and ramipril group.

Serum creatinine		
Losartan (n=186)	**Male**	**Female**
Normal	23 (12.4%)	38 (20.4%)
Abnormal	87 (46.8%)	38 (20.4%)
Total	**110 (59.1%)**	**76 (40.9%)**
Ramipril (n=186)	**Male**	**Female**
Normal	17 (9.1%)	24 (12.9%)
Abnormal	101 (54.3%)	44 (23.7%)
Total	**118 (63.4%)**	**68 (36.6%)**
Serum Potassium		
	Ramipril (n=186)	**Losartan (n=186)**
Normal	182 (97.8%)	175 (94.1%)
Abnormal	4 (21.5%)	11 (5.9%)
Total	**186 (100%)**	**186 (100%)**

The reported ADRs were classified as probable according to Naranjo's scale and are represented in Table 5. Ramipril had more cases of hypercreatinemia (n=93) and lesser patients with hyperkalemia (n=4). The Likelihood Ratio test inferred the adverse events can occur equally among ACE inhibitor or ARBs-administered patients ($p>0.05$).

Table 5. Frequency of the distribution of adverse drug reactions encountered with ramipril and losartan.

	(n=412)	Ramipril		Losartan		Likelihood Ratio	P value
		Frequency	%	Frequency	%		
Adverse Events	Cough	9	4.33	9	4.41	11.884	0.104
	Dizziness	2	0.96	4	1.96		
	Fatigue	18	8.65	17	8.33		
	Headache	7	3.37	4	1.96		
	Hypotension	1	0.48	0	0.00		
	Hypercreatinemia	93	44.71	65	31.86		
	Hyperkalemia	4	1.92	5	2.45		
	No Adverse Event	74	35.58	100	49.02		

DISCUSSION

ACE inhibitor or ARBs are the best antihypertensive agents preferred for CKD patients (Zhang et al., 2020). The study had a higher geriatric population, constituted to be significant in the ramipril group. The epidemiology status of CKD has changed and expanded to the adult population (Hallan et al., 2006). The misuse of medicines, genetic susceptibilities, and sedentary lifestyle influence patients, aggravating CKD's prevalence (Baker & Perazella, 2020). Poly-pharmacy and the irrational administration of medicine during pregnancy can bring insult to kidney for both mother and offspring.

The proportion of end stage renal disease (ESRD) patients who were on ramipril or losartan was negligible. This is because preferred antihypertensive agents may not be a RAAS-related agent in advanced kidney disease. On the other hand, a study of patients in Karnataka district showed that the results of a huge number of patients in stage 3 coincided with our results (Duan et al., 2019).

The oral bioavailability of losartan is 33%, with significant first-pass metabolism utilizing cytochrome P450 system. The CYP2C9 and CYP3A4 are specifically involved in the biotransformation, which is 10 to 40 times more potent by weight than the parent molecule (Ripley & Hirsch, 2010). The L losartan dose ranged from 1.25 to 100 mg in our samples. This variation was intended to normalize the blood pressure (BP) and reduce proteinuria (Maione, Annemans, & Strippoli, 2009). A study that compared the efficacy of losartan with amlodipine concluded that there was considerable decrease in urine protein excretion after a year of therapy (Praga et al., 2003). Thus, we can label the drug to be an excellent renoprotective agent among ARBs (Ono, Sanai, Miyahara, & Noda, 2013).

The initial dose for ramipril among renal impaired patients is 1.25mg and can be titrated to an effective dose not exceeding 5 mg/day. For a patient without CKD, the antihypertensive dose can be increased up to 20mg per day in divided doses (James et al., 2014). The drug generates action for 24 hours, and as the creatinine clearance decreases less than 40 ml/ minute/ 1.73m^2, the peak levels of its metabolite are approximately doubled. This is the reason behind restricting the maximum dose to 5 mg/day. Our study depicted prescription pattern of ramipril to be between 0.625 and 10 mg for CKD patients. The clinical trial conducted to assess the efficacy of ramipril in kidney disease patients showed that even though a small dose of ramipril (1.25 mg daily therapy) had a limited effect on improving hypertensive symptoms, it could preserve the kidney function (Doggrell, 2001). It's the pharmacist's duty to select a brand that imparts the dose according to the prescription and if not possible, breaking the tablets into halves should be their duty.

The main advantage of ACE inhibitors and ARBs is their ability to decrease the proteinuria in CKD patients. This is also a determinant that quantifies kidney function improvement. Here, we found that ramipril decreased the proteinuria among CKD patients more than the losartan group. This was supported by Kahvecioglu et al. where they conducted a 12-month follow up and observed 1% more reduction in the former group (Kahvecioglu et al., 2007).

Reno-protection happens with adequate BP control, which slows progression of CKD. Alone and in combination with other antihypertensive agents, losartan tends to normalize blood pressure (Chan et al., 1995; Tikkanen, Omvik, & Jensen, 1995). Researchers claimed that the antihypertensive and renoprotective effects of ARBs are similar to ACE inhibitors. The Optimal Anti-proteinuric Doses (ROAD) trial concluded that losartan can reduce the risk of doubling serum creatinine concentration and ESRD after titrating the dose beyond usual antihypertensive ranges (Hou et al., 2007).

The normal values of serum creatinine are slightly different for males and females. It is approximately 0.6 to 1.2 mg/dl in males whereas it is 0.5 to 1.1 mg/dl in females. CKD patients should monitor serum creatinine and serum potassium from 3 days to a week after initiation of the RAAS-related agent. Hypercreatinemia is observed within a few days after beginning the therapy, as angiotensin II levels are rapidly reduced or blocked from binding. This would result in efferent arteriolar dilatation and a decline in effective glomerular filtration rate (GFR). Our patients reported with abnormal serum creatinine in both the ramipril- and losartan-administered groups. However, an increase up to 20 to 30 percent is acceptable (Council on Credentialing in

Pharmacy, Albanese, & Rouse, 2010; Whelton et al., 2018), but the therapy should be withdrawn if creatinine levels rise above 30% after 6 to 8 weeks (Bakris & Weir, 2000). A cohort study in a primary care population showed an increased adverse incidence of cardio-renal outcomes even with a small creatinine increase after initiating the ACE inhibitor or ARB (Schmidt et al., 2017). The decrease in renal functions other than introduction of the drug was more likely to lead to serum creatinine elevation at higher systolic blood pressure targets (Collard, Brouwer, Peters, Vogt, & van den Born, 2018).

The normal serum potassium is 3.5 to 5.5 mEq/L in healthy adults. A fully functioning kidney would not abnormalize serum potassium level after a RAAS drug. The decline in GFR to 20 ml/min/1.73m^2 would sensitize the body to hyperkalemia, as ACE inhibitors or ARBs would reduce serum aldosterone (Palmer, 2004). Moreover, the prevalence of hyperkalemia is approximately 10 percent in outpatients within a year of ACE inhibitor consumption (Bakris & Weir, 2000; Reardon & Macpherson, 1998). This increase in serum potassium would lead to discontinuation of the antihypertensive therapy in CKD patients. The study found that more patients encountered hyperkalemia in the losartan group compared to the ramipril group (Sadjadi, McMillan, Jaipaul, Blakely, & Hline, 2009).

The hypercreatinemia was significant in the ramipril group and was reported as ADR. Few patients had RAAS drug induced hyperkalemia. When considering the normal physiology, angiotensin II and increased serum potassium can elevate aldosterone secretion. Further, they can lead to the elimination of the excess potassium from the body. In a normal person, studies pointed out that RAAS-related medicine only increases the blood potassium level less than 0.5 mEq/L 37. However, there would be more prominent increase in this electrolyte level in CKD patients (Magvanjav et al., 2019). The risk is greater in ACE inhibitors or ARBs-treated patients who are on dialysis (Knoll et al., 2008). In ESRD patients, the inefficiency of the kidney and colon in pushing potassium out of the body can be the prime reason for hyperkalemia.

The American Heart Association (AHA) also recommends the initiation of ACE inhibitors or ARBs to patients in early stages and in advanced CKD. This is based on the fact that the reduction in proteinuria can slow the progression of kidney damage. Thus, we should focus on the two major factors that slow kidney damage when treating CKD patients. The first one is treatment of the underlying disease, and the second is treatment that is predictive of progression, such as elevated blood pressure. We observed that ARBs influence the renal function more than ACE inhibitors concerning serum creatinine, urine protein and serum potassium.

CONCLUSION

Losartan was found to impart display favorable clinical effects in CKD patients. This was evident from their its lesser incidence of hyperkalemia and abnormal serum creatinine. However, reduction in proteinuria reflects the efficacy of antihypertensive agents in CKD patients, which was observed with ramipril.

Abbreviations

ACE – Angiotensin Converting Enzyme

AHA- American Heart Association

ARB – Angiotensin Receptor Blocker

ESRD- End Stage Renal Disease

CKD – Chronic Kidney Disease

RAAS- Renin Angiotensin Aldosterone System

Peer-review: Externally peer-reviewed.

Informed Consent: Written consent was obtained from the participants.

Ethics Committee Approval: This study was approved by the Kims Al Shifa Ethics Committee (Date: 30.04.2018 No: KAS/EC/2018-29).

Author Contributions: Conception/Design of Study- M.S.K., R.T.S.K., D.C.; Data Acquisition- M.S.K., R.T.S.K., D.C.; Data Analysis/Interpretation- M.S.K., R.T.S.K., D.C.; Drafting Manuscript- M.S.K., D.C., R.T.S.K.; Critical Revision of Manuscript- M.S.K., D.C., R.T.S.K.; Final Approval and Accountability- M.S.K., R.T.S.K., D.C.

Conflict of Interest: The authors have no conflict of interest to declare.

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