J Prev Epidemiol. 2024;9(x):e35244 Letter to Editor

doi 10.34172/jpe.2024.35244 Journal of Preventive Epidemiology http jprevepi.com

Lorundrostat may cause a clinically significant decline in renal function; a letter to the editor

Farzad Safari[1#], Ali Noursina[1#], Yasaman Vahdani[2*], Rohollah Valizadeh[1], Hamid Nasri[1*]

[1]Nickan Research Institute, Isfahan, Iran
[2]Department of Biochemistry and Molecular Medicine, University of Montreal, Montreal, Canada
[#]These authors contributed equally as the first author.

Correspondence to:
Prof. Hamid Nasri, Email: hamidnasri@med.mui.ac.ir, Email: hamidnasri@yahoo.com
And Yasaman Vahdani, Email: yasaman.vahdani@umontreal.ca

Received: 21 Dec. 2023
Accepted: 23 Feb. 2024
ePublished: 4 Apr. 2024

Keywords: Lorundrostat, Renal function, eGFR, AKI, CKD

Abstract

Lorundrostat is an aldosterone synthase inhibitor that can be used in patients with uncontrolled hypertension. It effectively lowers blood pressure, but there are concerns about the limited renal safety data available for lorundrostat. In order to address this issue, it is recommended that future research should incorporate more detailed kidney assessments, which would include monitoring for conditions such as proteinuria and acute kidney injury (AKI). This paper discusses the effects of lorundrostat on the estimated glomerular filtration rate (eGFR) and highlights the significant variability in these effects among individuals. The research shows that lorundrostat may cause a decline in eGFR exceeding one standard deviation above the mean change in approximately 16% of patients. In severe cases, 0.2% of patients may experience eGFR declines of ≥42 mL/min/1.73 m². These declines in eGFR could increase chronic kidney disease (CKD) stages, even in those with baseline eGFR >60 or 90 mL/min/1.73 m². In conclusion, while most lorundrostat patients do not experience severe eGFR declines, there is still a risk of clinically meaningful declines and CKD progression, particularly among susceptible individuals. Further research is needed to confirm these findings and identify renal risk factors in uncontrolled hypertension patients who receive aldosterone synthase inhibition.

Citation: Safari F, Noursina A, Vahdani Y, Valizadeh R, Nasri H. Lorundrostat may cause a clinically significant decline in renal function; a letter to the editor. J Prev Epidemiol. 2024;9(1):e35244. doi: 10.34172/jpe.2024.35244.

Dear Editor,

Aldosterone synthase inhibitors are a type of medication that can aid in reducing blood pressure by decreasing the production of aldosterone, a hormone that contributes to hypertension. Lorundrostat is a specific aldosterone synthase inhibitor that is currently being studied for its potential to lower blood pressure in people with uncontrolled hypertension (1).

In a recent study conducted by Laffin et al, it was found that lorundrostat can help lower blood pressure in patients with uncontrolled hypertension. They also noted that lorundrostat use does not have any renal side effects(2). We should express our concern about the limited renal safety data for lorundrostat in Laffin and colleagues' study. The study should have included more detailed kidney assessments, such as monitoring for proteinuria and acute kidney injury (AKI). The authors should have reported the number of patients who experienced estimated glomerular filtration rate (eGFR) declines exceeding 15 and 30 mL/min/1.73 m², as these decreases could exacerbation chronic kidney disease (CKD) stages (3).

Key point

Although lorundrostat appears to be a promising treatment for uncontrolled hypertension, it is essential to carefully monitor renal function due to the risk of significant eGFR declines in some patients. Further research is necessary to verify these findings and identify potential renal risk factors. Medical professionals should be adequately informed about this treatment's potential benefits and risks to make informed decisions.

Although the mean eGFR decrease was relatively small at all doses, the large standard deviations indicate significant interindividual variability in lorundrostat's effects. This finding suggests that lorundrostat may cause some patients to experience more significant eGFR declines than others. Assuming a normal distribution of eGFR changes, we estimate that lorundrostat may cause approximately 16% of patients to experience an eGFR decline exceeding one standard deviation above the mean change. Lorundrostat may cause about 2.5% of patients to see declines surpassing two standard deviations, while 0.2% could experience changes beyond three standard deviations.

According to Table 1, lorundrostat may

Table 1. Estimated mean of decrease in eGFR based on normal distribution diagram

Dose	Mean	SD	Mean+1SD	Mean+2SD	Mean+3SD
100 mg daily	7.83	11.62	19.45	31.07	42.69
50 mg daily	4.64	9.87	14.51	24.38	34.25
25 mg BID	5.55	9.22	14.77	23.99	33.21
12.5 mg BID	6.66	7.92	14.58	22.5	30.42
12.5 mg daily	3.67	8.10	11.77	19.87	27.97
100 mg daily, Cohort 2	7.95	9.13	17.08	26.21	35.34

BID, Twice daily; SD, Standard deviation.

cause roughly 16% of patients to undergo meaningful eGFR declines of ≥11 mL/min. Approximately 2.5% could experience considerable 19+ mL/min/1.73 m^2 declines, while 0.2% may see marked 27+ mL/min/1.73 m^2 decreases. The 50 and 100 mg doses are associated with more pronounced eGFR effects. For these doses, around 16% of patients may encounter clinically relevant 14+ and 19+ mL/min/1.73 m^2 eGFR decreases, respectively. In severe cases, 0.2% of 100 mg patients may experience eGFR plummets of ≥42 mL/min/1.73 m^2.

These eGFR declines could increase CKD stages, even in those with baseline eGFR >60 or 90 mL/min/1.73 m^2 (3). Patients with some albuminuria face exceptionally high risks from notable decreases in eGFR (4). In summary, while most lorundrostat patients avoided severe eGFR decreases, susceptible individuals may still experience clinically meaningful declines and CKD progression. Further research should confirm these findings and identify renal risk factors in uncontrolled hypertension patients receiving aldosterone synthase inhibition.

Authors' contribution

Conceptualization: Farzad Safari, Ali Noursina, Rohollah Valizadeh, Hamid Nasri, Yasaman Vahdani.
Data curation: Farzad Safari, Ali Noursina, Rohollah Valizadeh, Hamid Nasri.
Formal analysis: Farzad Safari, Ali Noursina, Rohollah Valizadeh, Hamid Nasri.
Funding acquisition: Farzad Safari, Ali Noursina, Rohollah Valizadeh, Hamid Nasri.
Investigation: Farzad Safari, Ali Noursina, Rohollah Valizadeh, Hamid Nasri.
Methodology: Farzad Safari, Ali Noursina, Rohollah Valizadeh, Hamid Nasri.
Project administration: Farzad Safari, Ali Noursina, Rohollah Valizadeh, Hamid Nasri.
Resources: Farzad Safari, Ali Noursina, Rohollah Valizadeh, Hamid Nasri.
Software: Farzad Safari, Ali Noursina, Rohollah Valizadeh, Hamid Nasri.
Supervision: Farzad Safari, Ali Noursina, Rohollah Valizadeh, Hamid Nasri.
Validation: Farzad Safari, Ali Noursina, Rohollah Valizadeh, Hamid Nasri.
Visualization: Farzad Safari, Ali Noursina, Rohollah Valizadeh, Hamid Nasri.
Writing–original draft: Farzad Safari, Ali Noursina, Rohollah Valizadeh, Hamid Nasri.
Writing–review & editing: Farzad Safari, Ali Noursina, Rohollah Valizadeh, Hamid Nasri, Yasaman Vahdani.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

References

1. Irfan H, Ahmed A, Nawani KD. Hypertension and lorundrostat: key discoveries from the target-HTN trial. Curr Probl Cardiol. 2024;49:102144. doi: 10.1016/j.cpcardiol.2023.102144.
2. Laffin LJ, Rodman D, Luther JM, Vaidya A, Weir MR, Rajicic N, et al. Aldosterone synthase inhibition with lorundrostat for uncontrolled hypertension: the target-HTN randomized clinical trial. JAMA. 2023;330:1140-50. doi: 10.1001/jama.2023.16029.
3. Sun L, Hua RX, Wu Y, Zou LX. Acute kidney injury in hospitalized adults with chronic kidney disease: comparing cROCK, KDIGO, and combined criteria. Kidney Res Clin Pract. 2023;42:639-548. doi: 10.23876/j.krcp.22.161.
4. Lo KB, Essa H, Wattoo A, Gulab A, Akhtar H, Sudani HA, et al. Representation of chronic kidney disease in randomized controlled trials among patients with heart failure with reduced ejection fraction: a systematic review. Curr Probl Cardiol. 2023;48:101047. doi: 10.1016/j.cpcardiol.2021.101047.