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RESPONSE TO LETTER

Association Between Long-Term ACEI/ARB Use and Postoperative Pain in Hypertensive Patients: A Retrospective Cohort Study and Genetic Validation [Response to Letter]

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Dear editor

We appreciate Drs. Ke, Wang, and Liu[1] for their careful reading of our work[2] and their constructive comments, which provide a valuable opportunity for further scholarly discussion on this topic. We address their points below.

First, regarding the residual imbalance in ASA physical status, we acknowledge this as a limitation of the weighting approach. To minimize the influence of the residual imbalance, we estimated the primary outcome by multivariable logistic regression model with potential confounders adjusted, including ASA physical status, based on the result of IPTW. This two-step analytical strategy improved the robustness of effect estimate for our primary outcome.

Second, we fully agree with the commentators' point that an observed effect size below the MDE requires careful interpretation, even in the presence of statistical significance. We have also mentioned this limitation in Discussion section. Crucially, we explicitly positioned the work not as a definitive outcome study, but as a hypothesis-generating analysis whose primary value is to identify a signal for future investigation. Therefore, we fully agree that the result should be seen as preliminary and expect further validation in larger, prospective studies. The commentators' emphasis usefully reinforces this key message.

Third, we recognize that there is a typographical error in the 95% CI of ARR and NNT in main text. The correct 95% CI for the 6.87% Absolute Risk Reduction is 6.86%-6.88%, and correct 95% CI for a number needed to treat of 14.6 is 14.5–14.6.

Fourth, we appreciate the insightful comment on the conceptual interpretation of our Mendelian Randomization results. We agree that acute postoperative pain and multisite chronic pain involve distinct, though potentially overlapping, pathophysiological mechanisms. We used this proxy approach because of the absence of large-scale GWAS for acute pain and mentioned this as a limitation of our study. Our intention was not to equate the two phenotypes but to use genetic evidence to explore the shared biological plausibility of the renin-angiotensin system pathway in pain modulation.

Finally, we concur that our combination of ACEIs and ARBs may mask the heterogeneity of them. Our decision to combine them in this hypothesis-generating study was based on two primary considerations. Firstly, these drug classes are often considered and used interchangeably as renin-angiotensin system inhibitors for hypertension management in real-world clinical practice. Secondly, the number of patients using ACEIs alone in our cohort was limited, so analyzing them separately would have resulted in an underpowered comparison. We fully agree that investigating the potential distinct analgesic effects of ACEIs versus ARBs is a crucial and logical next step, and we explicitly highlight this as an important direction for future research.

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We are grateful again to Drs. Ke, Wang, and Liu for their engaging comments, which enhances the precision and interpretation of our work.

Disclosure

The authors report no conflicts of interest in this communication.

Reference

1. Ke S, Wang Z, Liu Q. Association between long-term ACEI/ARB use and postoperative pain in hypertensive patients: a retrospective cohort study and genetic validation [Letter]. *J Pain Res*. 2026;19:616233. doi:10.2147/JPR.S616233
2. Li X, Che L, Shen L. Association Between Long-Term ACEI/ARB Use and Postoperative Pain in Hypertensive Patients: A Retrospective Cohort Study and Genetic Validation. *J Pain Res*. 2026;19:549864. doi:10.2147/JPR.S549864

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