Journal of Pain Research

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LETTER

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

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Dear editor

We read with great interest the recent mixed-design study by Li et al, which combined a retrospective cohort study with Mendelian randomization. This study explored the potential benefits of ACEIs/ARBs in perioperative analgesia, offering new insights for optimizing perioperative management in patients with hypertension; the topic has clear clinical value.[1] However, the paper contains several methodological and statistical issues, which we hereby raise for discussion and consideration.

First, the balance of key covariates after inverse probability weighting (IPTW) did not meet the predefined criteria. In the Methods section, the authors explicitly set a standardized mean difference (SMD) < 0.10 as the threshold for adequate balance. However, as shown in Table 1, the weighted SMD for ASA classification was 0.127, significantly exceeding the 0.10 threshold. ASA classification is an important confounding factor in predicting postoperative pain and complications; its residual imbalance suggests that the IPTW model failed to fully correct for selection bias.[2] This methodological flaw may introduce bias into the effect estimate for the primary outcome (OR 0.74), thereby undermining the internal validity of the study's conclusions.

Second, there is a discrepancy between the statistical significance of the primary outcome and the study's power. The sensitivity analysis report indicates that the minimum detectable effect (MDE) detectable by this study at an 80% power level is 8%, whereas the actual observed absolute risk reduction was only 6.87%. When the observed effect size falls below the study's own predefined detection threshold, the robustness of the results warrants cautious interpretation even if the p-value is less than 0.05. Characterizing results where the effect size fails to meet the MDE threshold as a positive finding may increase the risk of Type I errors.[3]

Third, there are obvious data entry errors in the results section. On page 6 of the main text, the absolute risk reduction (ARR) is stated as "absolute risk reduction of 6.87% (95% CI 6.88–6.86%)"; the lower limit of this confidence interval (6.88%) is higher than the point estimate (6.87%), which may be an oversight during typesetting or proofreading. We recommend correcting this to avoid misleading interpretations of the ARR and NNT.

Fourth, the conclusion of the Mendelian randomization (MR) analysis contains a conceptual overstep. The authors describe the MR results for multisite chronic pain (MCP) as "genetic validation" of observational findings regarding acute postoperative pain. However, acute postoperative pain and chronic pain differ fundamentally in their pathophysiological mechanisms; the former is primarily characterized by nociceptive and inflammatory pain, while the latter involves central sensitization and neural remodeling processes.[4] Equating evidence of genetic susceptibility to chronic pain directly with validation of acute perioperative analgesia constitutes a logical leap in phenotypic extrapolation.

https://doi.org/10.2147/JPR.S616233
Received: 12 April 2026
Accepted: 18 April 2026
Published: 22 April 2026

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Furthermore, the study combined ACEIs and ARBs into a single exposure group. While this improved statistical power, it may have introduced non-differential classification bias from a pharmacological perspective, thereby masking the heterogeneous effects of the drugs.[5] Future studies should perhaps evaluate the independent analgesic effects of each class separately.

Conclusion

In summary, Li et al employ an innovative hybrid design to investigate the analgesic potential of ACEI/ARB in hypertensive surgical patients. Clarification of the methodological and statistical concerns raised herein would strengthen the validity of the findings and provide a more robust foundation for future prospective research in this clinically important area.

Disclosure

The authors have no conflicts of interest to disclose in this communication.

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https://doi.org/10.2147/JPR.S616233