Circulation Research

LETTER TO THE EDITOR

Response by Zhang et al to Letter Regarding Article, "Association of Inpatient Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Mortality Among Patients With Hypertension Hospitalized With COVID-19"

Peng Zhang, Lihua Zhu, Jingjing Cai, Fang Lei, Juan-Juan Qin, Yibin Wang, Yufeng Yuan, Rohit Loomba, Peter P. Liu, Hongliang Li

In Response:

We thank Cohen et al for their letter on our recent report on the association of inpatient use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) with mortality among the hospitalized coronavirus 2019 (COVID-19) patients with hypertension from Hubei, China.[1]

As Cohen et al pointed out, and clearly discussed in our original report, the inherent limitations of such retrospective study must be carefully considered in interpreting the results. Indeed, we had a great deal of concerns about potential bias and implemented 3 different models to cross-validate the key conclusions. First, a mixed-effect Cox model was used by adjusting for confounding variables. Second, we applied a stricter propensity score-matched analysis, followed by adjusting imbalanced variables. Finally, to further minimize the potential bias resulting from patients who did not receive antihypertensive drugs, we conducted a subgroup propensity score-matched analysis by including only the patients who received antihypertensive medication during hospitalization. We did not find an association for harm with those on ACEI/ARB in all 3 models. Cohen et al stated that "sicker patients will almost invariably be less likely to receive ACEIs/ARBs." As we reported, after matching, the baseline characteristics of the ACEI/ARB group and nonuser group were largely comparable, while the remaining imbalanced variables were further adjusted. We agree with Cohen et al that there might be some unmeasured confounders. As such, we performed an E-value and 2 other sensitivity analyses to further assess the robustness of the conclusion. The results remained consistent and statistically significant in these sensitivity analyses for both mixed-effect Cox and propensity score-matched models.

Regarding the proportion of ACEI/ARB users, however, the calculation by Cohen et al was inappropriate. In China, the therapeutic ratio of hypertension was only 40.7%, and ACEI/ARB was used only in 25% to 30% among those patients.[2] In our study, this proportion was 25.2%, which was consistent with that for the general hypertensive patients in China. Thus, the concern from Cohen et al regarding the lower-than-expected number of patients taking ACEI/ARB was not correct. About the immortal time bias mentioned by Cohen et al, we agree that a longer-term and stable exposure to ACEI/ARB would further solidify their association with COVID-19 mortality. Unfortunately, as we clearly acknowledged in our original article, prehospital medications were not available in the in-hospital electronic record systems due to the urgent circumstance of the COVID-19 pandemic. We agree that this potential immortal time-related bias may still exist as an inherent limitation of an observational study even after rigorous matching and adjustment.

More recently, Rentsch et al[3] reported a retrospective study including 2 026 227 veterans from the United States but did not find a significant association between ACEI/ARB use and the need for intensive care in patients with COVID-19.[3] However, they did not analyze whether the use of ACEI/ARB was associated with mortality. The complex composition and obvious confounders (eg, ethnicity, comorbidities, severity, and in-hospital medications) of this large-scale cohort may have significant impact on this conclusion, which, however, was not matched or rigorously adjusted. Another recent *JAMA* report including 5700 patients with COVID-19 in the New York City also included the data of ACEI/ARB usage.[4] The mortality rates for patients with hypertension taking ACEI (32.7%), or taking ARB (30.6%), or not taking ACEI or ARB (26.7%) were calculated. Unfortunately,

For Disclosures, see page e143.

Circulation Research is available at www.ahajournals.org/journal/res

such simple calculation without a minimal level of multivariate analysis to adjust for the evident confounders would not be interpretable. Furthermore, the overall length of stay and postdischarge follow-up duration was very short, with only 4.1 and 4.4 days, respectively. These may be the major reasons for the apparent discrepancies between our report and the above 2 studies.

We certainly agree with Cohen et al about the importance and the critical need to conduct randomized controlled trials to address the impact of ACEI/ARB on COVID-19 patients with hypertension. While our results imply no harm by following current recommendations from several medical societies regarding continuous application of ACEI/ARB in COVID-19 patients with hypertension, the ongoing randomized controlled trials conducted by Cohen's team and others can provide further evidence to guide clinical practice for COVID-19 patients with hypertension. We look forward to the early release of these data.

ARTICLE INFORMATION

Affiliations

From the Department of Cardiology, Renmin Hospital of Wuhan University, China (P.Z., L.Z., J.-J.Q., H.L.); Medical Science Research Center (P.Z., H.L.) and Department of Hepatobiliary and Pancreatic Surgery (Y.Y.), Zhongnan Hospital of Wuhan University, China; Institute of Model Animal of Wuhan University, China (P.Z., L.Z., F.L., J.-J.Q., H.L.); Department of Cardiology, The Third Xiangya Hospital, Central South University, Changsha, China (J.C.); Department of Anesthesiology, Cardiovascular Research Laboratories, David Geffen School of Medicine, University of California, Los Angeles (Y.W.); NAFLD Research Center, Division of Gastroenterology and Epidemiology, University of California San Diego (R.L.); and Division of Cardiology, Department of Medicine, University of Ottawa Heart Institute, ON, Canada (P.P.L.).

Disclosures

None.

REFERENCES

1. Zhang P, Zhu L, Cai J, Lei F, Qin J-J, Xie J, Liu Y-M, Zhao YC, Huang X, Lin L, et al. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circ Res*. 2020;126:1671–1681. doi: 10.1161/CIRCRESAHA.120.317134
2. Wang Z, Chen Z, Zhang L, Wang X, Hao G, Zhang Z, Shao L, Tian Y, Dong Y, Zheng C, et al; China Hypertension Survey Investigators. Status of hypertension in China: results from the China Hypertension Survey, 2012-2015. *Circulation*. 2018;137:2344–2356. doi: 10.1161/CIRCULATIONAHA.117.032380
3. Rentsch CT, Kidwai-Khan F, Tate JP, Park LS, King JT, Skanderson M, Hauser RG, Schultze A, Jarvis CI, Holodniy M, et al. Covid-19 testing, hospital admission, and intensive care among 2,026,227 United States veterans aged 54-75 years. *medRxiv*. 2020.
4. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, Northwell C-RC, Barnaby DP, Becker LB, Chelico JD, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area [published online April 22, 2020]. *JAMA*. doi: 10.1001/jama.2020.6775