CORRESPONDENCE

Reply

We thank Dr. Panigrahi and colleagues for their comments on our paper. They referred to two review articles and inquired on the reasons for a differential effect between angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers on liver-related outcomes in patients with NAFLD. During the period of the study, a number of angiotensin-receptor blocker preparations were removed from the market because of possible contamination by carcinogens.[1] In addition, because of the price difference, most patients were initially on ACEIs, only to switch to angiotensin-receptor blockers when they developed side effects such as coughing. It is therefore difficult to discern the independent effects of angiotensin-receptor blockers. Data on liver histology or transient elastography were not available in this database.

Among the 183 patients without cirrhosis at baseline, 162 had liver cancer, and 26 had cirrhotic complications during follow-up. Compared with nonusers, patients without cirrhosis who used ACEIs had subdistribution HRs of 0.43 (95% CI 0.26–0.72) and 0.43 (95% CI 0.26–0.71) for liver cancer and cirrhotic complications, respectively.

Dr. Panigrahi et al. also discussed the risk of angiotensin-receptor blockers during pregnancy. Although we do not have information on pregnancy, please note that the mean baseline age of angiotensin-receptor blocker users was 61.6 years (Table S3 of our paper), so it is unlikely that there were many pregnant women in this cohort. In any case, such interruption would have been transient.

Finally, we agree with Dr. Panigrahi et al. that prospective studies, preferably randomized controlled trials, would provide definitive proof for the effect of ACEIs on liver-related events. Nonetheless, because ACEIs have already become generic and it would take thousands of patients being followed for 5 to 10 years to demonstrate a difference in clinical events, we doubt if such a study will ever materialize. As for mechanistic work, a number of studies have already demonstrated an effect of ACEIs on liver fibrosis and hepatocarcinogenesis.[2,3] In such situations, sometimes the best evidence has to come from adequately powered retrospective studies with a sufficient duration of follow-up.

CONFLICT OF INTEREST

Dr. Yip consults for and is on the speakers’ bureau for Gilead Sciences. Dr. V. Wong consults for and received grants from Gilead. He consults for AbbVie, Boehringer Ingelheim, Echosens, Intercept, Inventiva, Merck, Novo Nordisk, Pfizer, and ProScierto. He is the cofounder of Illumina Medical Technology Limited.

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REFERENCES

1. Rudolph UM, Enners S, Kieble M, Mahfoud F, Böhm M, Laufs U, et al. Impact of angiotensin receptor blocker product recalls on antihypertensive prescribing in Germany. J Hum Hypertens. 2021;35:903–11.
2. Reza HM, Tabassum N, Sagor MA, Chowdhury MR, Rahman M, Jain P, et al. Angiotensin-converting enzyme inhibitor prevents oxidative stress, inflammation, and fibrosis in carbon tetrachloride-treated rat liver. Toxicol Mech Methods. 2016;26:46–53.

3. Noguchi R, Yoshiji H, Kuriyama S, Yoshii J, Ikenaka Y, Yanase K, et al. Combination of interferon-beta and the angiotensin-converting enzyme inhibitor, perindopril, attenuates murine hepatocellular carcinoma development and angiogenesis. Clin Cancer Res. 2003;9(16 Pt 1):6038–45.