Research

Renin–angiotensin system inhibitors and risk of hepatocellular carcinoma among patients with hepatitis B virus infection

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Abstract

Background: Hepatitis B virus (HBV) infection is a common cause of liver-related morbidity and mortality. Evidence suggests that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) decrease liver fibrosis, an intermediate step between liver injury and hepatocellular carcinoma (HCC). Our aim was to investigate the association between the use of ACEIs and ARBs on incident HCC and liver-related mortality among patients with HBV infection.

Methods: We conducted a population-based study on a new-user cohort of patients seen at 24 hospitals across China. We included adult patients with HBV infection who started ACEIs or ARBs (ACEIs/ARBs), or calcium channel blockers or thiazide diuretics (CCBs/THZs) from January 2012 to December 2022. The primary outcome was incident HCC; secondary outcomes were liver-related mortality and new-onset cirrhosis. We used propensity score matching and Cox proportional hazards regression to estimate the hazard ratio (HR) and 95% confidence intervals (CIs) of study outcomes.

Results: Among 32 692 eligible patients (median age 58 [interquartile range (IQR) 48–68] yr, and 18 804 male [57.5%]), we matched 9946 pairs of patients starting ACEIs/ARBs or CCBs/THZs. During a mean follow-up of 2.3 years, the incidence rate of HCC per 1000 person-years was 4.11 and 5.94 among patients who started ACEIs/ARBs and CCBs/THZs, respectively, in the matched cohort. Use of ACEIs/ARBs was associated with lower risks of incident HCC (HR 0.66, 95% CI 0.50–0.86), liver-related mortality (HR 0.77, 95% CI 0.64–0.93), and new-onset cirrhosis (HR 0.81, 95% CI 0.70–0.94).

Interpretation: In this cohort of patients with HBV infection, new users of ACEIs/ARBs had a lower risk of incident HCC, liver-related mortality, and new-onset cirrhosis than new users of CCBs/THZs.

Chronic hepatitis B virus (HBV) infection is a global public health concern, affecting about 296 million people.[1,2] Despite recent advances in treatment — notably, tenofovir disoproxil fumarate and entecavir — HBV remains a common cause of liver-related morbidity and mortality. Hepatitis B virus infection accounts for 42% of cases of liver cirrhosis, 60% of cases of hepatocellular carcinoma (HCC), and 63% of liver-related deaths.[2–6] Deaths from viral hepatitis, including hepatitis B, have increased by 22% since 2000, accompanied by a rising incidence of liver cancer.[7] Thus, an urgent need exists to develop effective treatments in addition to current anti-HBV drugs, to prevent liver disease progression and decrease liver-related mortality in patients with HBV infection.

The renin–angiotensin–aldosterone system (RAS) is believed to play a key role in liver fibrosis, the condition from which liver cirrhosis develops.[8–11] The interaction between angiotensin II and the angiotensin II type 1 receptor can induce proliferation of mesangial cells and hepatic stellate cells, stimulate the synthesis of extracellular matrix proteins, and promote liver fibrosis.[8,10] Research in well-established animal models has shown that blocking RAS has potent antifibrogenic effects in the liver.[8,10,12–14] Renin–angiotensin–aldosterone system inhibitors (RASi), which include angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), are among the most commonly used antihypertensive medications. Previous studies of the association between RASi and risk of HCC differed in their study populations, outcomes studied, and results.[15–17] Two studies explored the potential protective effect of RASi on liver-related outcomes in patients with HBV infection in real-world settings.[18,19] One study[18] found a significant reduction in mortality associated with ACEIs among patients with viral hepatitis, but another[19] reported no significant effect. Whether treatment with ACEIs or ARBs can slow disease progression in patients with HBV infection remains unclear.

Using data from a large, population-based cohort and a new-user, active comparator study design, we aimed to evaluate the association between the use of ACEIs or ARBs and the risk of new-onset HCC and liver-related mortality among patients with HBV infection, compared with the use of calcium channel blockers (CCBs) or thiazide diuretics (THZs).

Methods

Study design and data source

We performed a propensity score–matched cohort study using a new-user active comparator design to compare the risk of incident HCC in patients with HBV infection started on ACEIs/ARBs versus CCBs/THZs between Jan. 1, 2012, and Dec. 31, 2022. Previous studies found no association between CCBs and incident cancer.[20,21] A potential protective effect of THZs on reducing HCC was reported by a Mendelian randomization study,[22] but there is not convincing evidence that THZs protect against HCC. We selected the study population from a nationwide cohort[23] of more than 8 million Chinese inpatients and outpatients seen at 24 urban academic hospitals; this was a joint initiative of the National Clinical Research Center and the China Center for Disease Control and Prevention. The data included patients' demographic characteristics, vital signs, diagnostic codes at admission and discharge, medications, surgical information, and laboratory measurements. This database has been used to conduct many research studies.[24–26] The study conformed to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.[27]

Study population

We included patients with HBV infection prescribed ACEIs/ARBs or CCBs/THZs while they were being treated in the institutions whose data are included in the database. We enrolled patients with a confirmed diagnosis of HBV infection, identified by the presence of diagnosis codes B18.0 or B18.1 using the *International Classification of Diseases, 10th Revision* (ICD-10).[28] Additionally, we required a positive hepatitis B surface antigen test result to validate the diagnosis. We defined cohort entry (index date) as the date of the first prescription of a study drug of interest (Appendix 1, Supplementary Figure 1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.240003/tab-related-content). To be included in the study, all patients needed to have at least 6 months of prescription records before cohort entry. We excluded patients who initiated both ACEIs/ARBs and CCBs/THZs concurrently. We also excluded patients younger than 16 years, those with a previous diagnosis of HCC, and patients with any prescription of a study drug (ACEIs, ARBs, CCBs, or THZs) at any time before cohort entry to ensure that both groups were new users. Finally, we excluded patients without any medical records after the index date. We outline the specific look-back periods for the eligibility criteria in Appendix 1, Supplementary Figure 2.

Exposure

We defined cohort entry as the time of first prescription of ACEIs, ARBs, CCBs, or THZs. Prescriptions for the study drugs were recorded in the database by Anatomical Therapeutic Chemical code with the starting and stopping date, units, administration method, dose, and frequency of administration. We selected CCBs or THZs as the active comparator to reduce confounding by indication, as both drug classes are widely prescribed first-line antihypertensive drugs.

Outcomes

The primary outcome was incident HCC, which we defined as ICD-10 code C22.0[28,29] in any medical record after the index date. The diagnosis and corresponding ICD-10 code was recorded by the most responsible clinician. The diagnosis of new-onset HCC was confirmed by 2 experienced oncologists with access to all available medical records, including imaging, laboratory and pathologic data, and notes on hospital admission. The secondary outcome was liver-related mortality (defined as ICD-10 code K70-K77 or C22.0).[30] We collected the date and cause of death from the national electronic cause-of-death reporting system of the China Center for Disease Control and Prevention, which we linked to our database. We followed all patients from the index date until incident HCC, death, or the end of the study period (Dec. 31, 2022), whichever came first.

Covariates

We identified potential confounding factors based on existing literature and clinical and methodological expertise. These variables included demographic characteristics such as age and sex, comorbidities, other medications, and clinical assessments (Appendix 1, Supplementary Table 1). The comorbidities were cirrhosis, diabetes, heart failure, hepatitis C virus (HCV) infection, HIV infection, history of alcohol liver disease, myocardial infarction, and chronic kidney disease. Medications included antiviral therapies, statins, acetylsalicylic acid (ASA), and β-blockers. Clinical assessments included systolic and diastolic blood pressure, estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), α fetoprotein (AFP), serum albumin, platelet count, proteinuria, and serological measures such as HBV DNA and hepatitis B e antigen (HBeAg). We estimated the eGFR using the Chronic Kidney Disease Epidemiology Collaboration equation.[31] Additionally, we used the Fibrosis-4 Index (FIB-4) to measure the degree of liver fibrosis based on age, ALT, AST, and platelet count.[32]

Statistical analysis

To control for baseline confounding factors, we employed the propensity score matching (PSM) of "greedy nearest neighbour" algorithm in a 1:1 ratio (caliper = 0.2 times the standard deviation of logit of propensity score) using logistic regression models with confounders at baseline predicting both initiation of 1 of the study drugs and the outcomes. Propensity score matching calculated the average treatment effect in those who started ACEIs/ARBs compared with what would have happened if they had started CCBs/THZs. We used descriptive statistics to summarize baseline characteristics

before and after matching, and assessed covariate balance using standardized mean differences, with an absolute value of less than 0.10 indicative of good balance. We estimated incidence rates of HCC and liver-related mortality per 1000 person-years with 95% confidence intervals (CIs), using the Poisson distribution for both the ACEIs/ARBs and CCBs/THZs groups. We plotted Kaplan–Meier curves to visualize the cumulative incidence of HCC and liver-related mortality in each group within the matching cohorts and compared them using the stratified log-rank test. After matching, we conducted a univariate Cox proportional hazards regression with a robust variance estimator[33] to account for clustering within matched sets to assess the association between ACEIs/ARBs versus CCBs/THZs and the risk of HCC and liver-related mortality. Using the matched data set, we fitted a multivariable-adjusted model that included the baseline confounding factors, which were also added in the propensity matching process, to obtain the adjusted hazard ratio. To address missing data for covariates with a missing proportion less than 20% (all covariates except for smoking status), we assumed the missing pattern to be random and then conducted multiple imputations by chained equations using 5 imputed data sets with 20 iterations. We treated smoking status as a multilevel categorical variable (people who did not smoke, currently smoked, and unknown).

In post hoc subgroup analyses, we conducted stratified analyses to examine potential effect modification by age (< 60 and ≥ 60 yr), sex, cirrhosis, diabetes, chronic kidney disease, heart failure, antiviral therapy, use of β-blockers, statins, and ASA on incident HCC. We assessed effect modification on a multiplicative scale by including interaction terms between the exposure variable and the baseline characteristics in the regression model based on the matched cohort.

We conducted 4 prespecified additional analyses. First, we separately compared ACEI and ARB initiators with the CCBs/THZs group. Second, we repeated the analysis examining initiators of CCB and THZ monotherapy or combination therapy. Third, considering that cirrhosis is an important risk factor and mediation factor for progression of hepatitis to HCC, we repeated our analyses in people free of cirrhosis at baseline and assessed incident cirrhosis after the initiation of ACEIs/ARBs versus CCBs/THZs. Fourth, we used restricted mean time lost, which is the area above the survival curve, to quantify the treatment effect. We reported the differences in restricted mean time lost among the 2 groups with 3-, 5-, and 10-year follow-up separately.

We conducted several sensitivity analyses to evaluate the robustness of our findings. First, we censored data from patients who subsequently initiated another antihypertensive medication. Second, we used other methods to adjust for confounders, including propensity score overlap weighting and inverse probability of treatment weighting. Third, we treated death as a competing risk using Fine–Gray subdistribution hazard regression. Fourth, given that drug treatment might change during follow-up (e.g., the initiation or discontinuation of antiviral therapy), we treated other medications as time-varying confounders and further adjusted for them in Cox regression. Fifth, we repeated the analyses in patients with at least 1 year of follow-up to mitigate the potential impact of reverse causality. Sixth, we limited the study population to patients at relatively low risk, excluding those with FIB-4 > 3.25, HBV DNA > 1000 IU/L, ALT > 120 U/mL, or AFP > 100 μg/L. Last, we repeated the analyses using incident dermatitis (ICD-10 code L20) as a negative control outcome to assess the impact of residual confounding. This outcome has been associated with HBV but not with the drugs of interest. We based this analysis on the cohorts used in the primary analysis but excluded patients with dermatitis before cohort entry. To account for the bias introduced by unmeasured confounders, we calculated the E-value for the study outcomes (the E-value estimates the minimum magnitude of association required for an unmeasured confounder to reverse the observed association toward a null. In brief, if the relative risk between unmeasured confounders, outcome, and treatment is greater than the estimated E-value, residual confounders may be sufficient to explain the identified association).[34]

We conducted all statistical analyses using R (version 4.1.2) and GraphPad Prism (version 8.0.1). We considered a 2-sided $p < 0.05$ to be statistically significant.

Ethics approval

The study was approved by the China Office of Human Genetic Resources for Data Preservation Application (approval no. 2021-BC0037). The protocol was approved by the Medical Ethics Committee of Nanfang Hospital, Southern Medical University (approval no. NFEC2019–213), and the requirement for informed consent was waived.

Results

Study population

We identified a total of 32 692 patients with HBV infection who initiated ACEIs/ARBs or CCBs/THZs during the study period (Figure 1). Their median age was 58 (interquartile range [IQR] 48–68) years, 18 804 (57.5%) were male, and median systolic and diastolic blood pressure were 135 (IQR 121–151) mm Hg and 80 (IQR 72–90) mm Hg, respectively. Of these, 10 364 (31.7%) patients started ACEIs/ARBs and 22 328 (68.3%) patients started CCBs/THZs. Compared with those who started CCBs/THZs, those who started ACEIs/ARBs had a lower blood pressure; were more likely to have heart failure, myocardial infarction, and chronic kidney disease; and were more likely to be taking a β-blocker (Table 1). After propensity matching, we matched 7171 patients who started ACEIs/ARBs with 7171 who started CCBs/THZs. The distribution of propensity scores before and after matching is shown in Appendix 1, Supplementary Figure 3. All covariates were well balanced (standardized mean difference < 0.1) in the matching cohorts. Blood pressure in the ACEIs/ARBs group was slightly lower than that in the CCBs/THZs group and remained stable during follow-up (Appendix 1, Supplementary Figure 4).

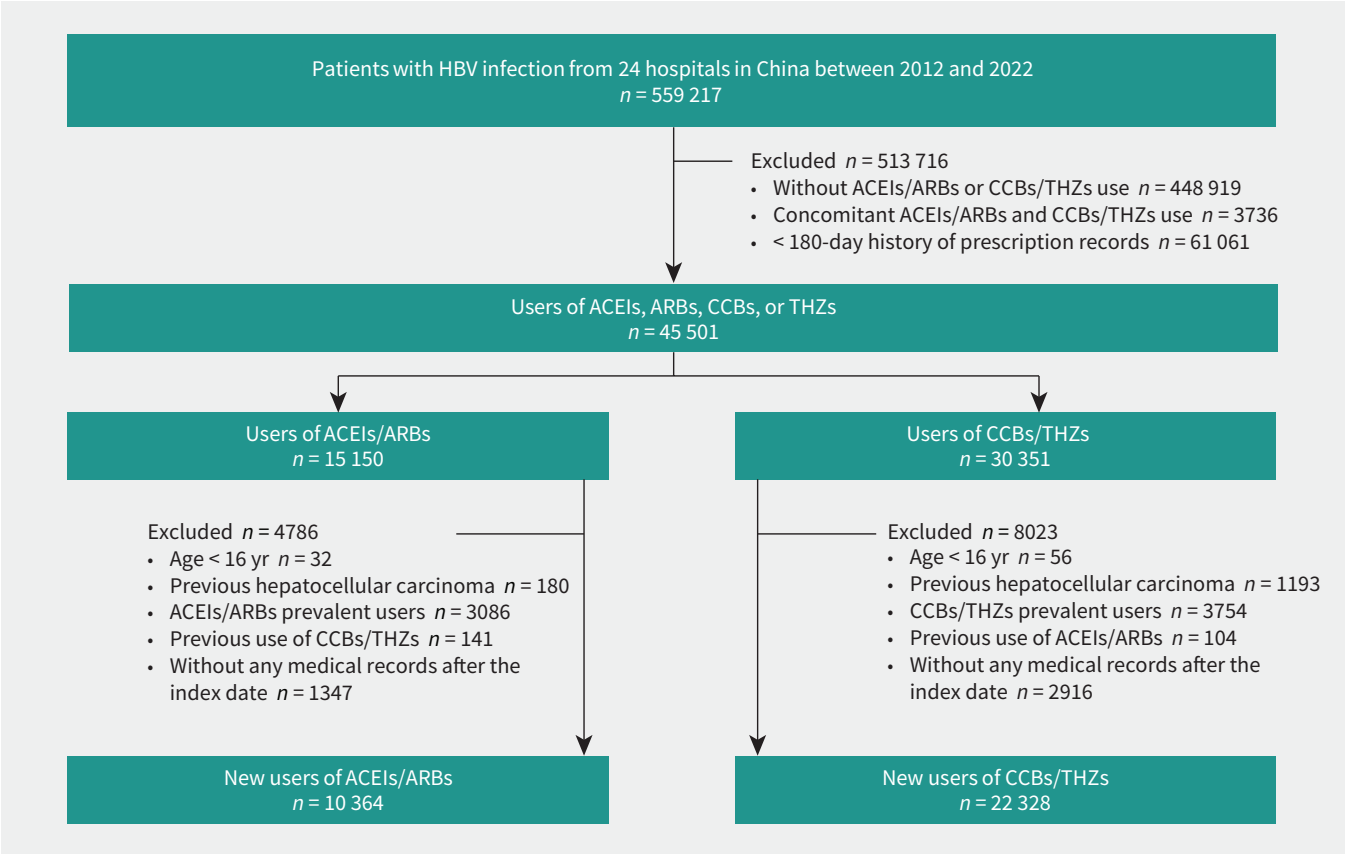

Figure 1: Study flow diagram of patients starting angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEIs/ARBs) or calcium channel blockers or thiazide or thiazide-like diuretics (CCBs/THZs) in the China Renal Data System between 2012 and 2022. Note: HBV = hepatitis B virus.

Risk of HCC and liver-related mortality in patients with ACEIs/ARBs versus CCBs/THZs

During a mean follow-up of 2.3 years, the incidence rate of HCC was 4.11 (95% CI 3.34–5.05) per 1000 person-years in the ACEIs/ARBs group and 5.94 (95% CI 5.01–7.04) per 1000 person-years in the CCBs/THZs group in the matched cohort (Table 2). The start of ACEIs/ARBs was associated with a 31% lower risk of developing incident HCC compared with CCBs/THZs starters (HR 0.69; 95% CI 0.53–0.90) (Figure 2 and Table 2). After we adjusted for multiple variables, the association between starting ACEIs/ARBs and risk of HCC remained significant (HR 0.66; 95% CI 0.50–0.86). In subgroup analyses (Figure 3), we did not find any substantial modification effect for age, sex, cirrhosis, diabetes, chronic kidney disease, heart failure, antiviral therapy, β-blockers, statins, and ASA (p for interaction > 0.05).

A total of 485 liver-related deaths occurred during 89 471 person-years of follow-up (Table 2), yielding a crude incidence rate of 4.75 per 1000 person-years among the ACEIs/ARBs group and 6.04 per 1000 person-years among the CCBs/THZs group. Starting ACEIs/ARBs was associated with a lower risk of liver-related mortality than starting CCBs/THZs (HR 0.77; 95% CI 0.64–0.93).

Additional analyses

Both ACEIs and ARBs were associated with reduced risk of HCC and liver-related mortality compared with CCBs/THZs (Appendix 1, Supplementary Table 2). Initiating ACEIs/ARBs was associated with lower risks of HCC and liver-related mortality than either initiating combination therapy with CCBs and THZs or monotherapy of CCBs or THZs (Appendix 1, Supplementary Table 3). After we excluded patients with cirrhosis at baseline (Appendix 1, Supplementary Table 4), those who started ACEIs/ARBs had a 19% lower risk of incident liver cirrhosis than those who started CCBs/THZs (HR 0.81; 95% CI 0.70–0.94). The results of restricted mean time lost analysis also favoured patients who started ACEIs/ARBs, indicating that those who started CCBs/THZs lost an additional 29 days of disease-free time due to HCC and 26 days of life due to liver-related events within 10 years of follow-up, compared with patients who started ACEIs/ARBs (Appendix 1, Supplementary Table 5).

Sensitivity analyses

The results remained consistent after we censored data from patients who subsequently started another antihypertensive medication (Appendix 1, Supplementary Table 6). Findings were similar in sensitivity analyses using different methods of adjustment, such as propensity score overlap weighting and inverse probability of treatment weighting (Appendix 1, Supplementary Table 7), accounting for death as a competing risk using the Fine–Gray subdistribution hazard regression, or adjusting the time-varying comedications (antiviral therapy, statins, ASA, and β-blockers) (Appendix 1, Supplementary Table 8). Restricting the

analysis to patients with at least 1-year follow-up also produced consistent results (Appendix 1, Supplementary Table 9). Excluding patients with known risk factors and focusing on a population with relatively low risk of HCC showed a consistent association between the start of ACEIs/ARBs and the outcomes (Appendix 1, Supplementary Table 10). Furthermore, starting ACEIs/ARBs was not significantly associated with incident dermatitis (negative control) compared with CCBs/THZs (Appendix 1, Supplementary Table 11). The E-values for all-cause and liver-related mortality were 2.40 and 1.92 in the primary analyses. Overall, the results from multiple sensitivity analyses were consistent with the primary analysis.

Interpretation

In this nationwide real-world cohort of patients with HBV infection in China, the use of ACEIs/ARBs was associated with significantly lower risks of being diagnosed with HCC and liver-related death, compared with the use of CCBs/THZs. This association held after adjusting for many confounding factors and remained consistent across subgroup and sensitivity analyses. Patients who started ACEIs/ARBs were also 20% less likely to develop liver cirrhosis than those who started CCBs/THZs. These findings suggest that ACEIs/ARBs were more effective than CCBs/THZs in improving liver-related outcomes and may be a potential new approach for preventing HCC and liver-related deaths in patients with HBV infection.

Our results extend the previous evidence linking RASi to the prevention of HCC among patients with HBV infection by showing the association between the use of RASi and reduced risk of incident HCC in a real-world setting. The incidence rate of HCC in patients with HBV infection was 4.11 to 5.94 per 1000 person-years in our study, which is comparable with previous studies in patients with chronic liver diseases.[15,17,35,36] Although a previous meta-analysis found an association between RASi administration and decreased risk of HCC, the studies that were included were heterogeneous in the study populations (e.g., HCC patients after curative therapy, patients with hypertension, or patients with diabetes) and the definition of outcomes.[17] Two of the studies focused on patients with previous HCC and assessed HCC recurrence as an outcome,[37,38] and none was specific to HBV-infected patients. These limitations make it challenging to generalize the results of the meta-analysis to patients with HBV infection.

Table 1 (part 1 of 2): Baseline characteristics of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers and calcium channel blocker/thiazides or thiazide-like diuretics exposure groups before and after propensity score weighting*

	Before PSM				After PSM		
Characteristics	Overall no. (%)* of patients *n* = 32 692	No. (%)* of patients starting ACEIs/ARBs *n* = 10 364	No. (%)* of patients starting CCBs/THZs *n* = 22 328	SMD	No. (%)* of patients starting ACEIs/ARBs *n* = 9946	No. (%)* of patients starting CCBs/THZs *n* = 9946	SMD
Median age, yr (IQR)	58 (48–68)	58 (47–68)	58 (48–68)	0.064	58 (47–68)	57 (46–68)	0.010
Sex, male	18 804 (57.5)	6050 (58.4)	12 754 (57.1)	0.025	5720 (57.5)	5641 (56.7)	0.016
Smoking status				0.059			0.042
Did not smoke	10 640 (32.5)	3288 (31.7)	7352 (32.9)	–	3160 (31.8)	3207 (32.2)	–
Currently smoked	8881 (27.2)	3002 (29.0)	5879 (26.3)	–	2833 (28.5)	2648 (26.6)	–
Unknown	13 171 (40.3)	4074 (39.3)	9097 (40.7)	–	3953 (39.7)	4091 (41.1)	–
BMI (IQR)	21.8 (21.0–24.2)	21.8 (21.0–24.8)	21.7 (20.9–23.9)	0.119	21.8 (21.0–24.6)	21.8 (21.0–24.6)	0.006
Clinical characteristics							
SBP, mm Hg (IQR)	135 (121–151)	132 (120–147)	137 (122–153)	0.217	131 (120–146)	132 (120–148)	0.018
DBP, mm Hg (IQR)	80 (72–90)	80 (71–89)	81 (73–91)	0.168	80 (71–88)	80 (71–89)	0.015
ALT, U/L (IQR)	22 (15–34)	22 (15–34)	22 (15–34)	0.025	21 (15–32)	21 (14–32)	0.002
AST, U/L (IQR)	24 (19–35)	24 (19–33)	24 (19–36)	0.061	23 (18–31)	23 (18–32)	0.001
AFP, ng/mL (IQR)	2.6 (1.70–4.40)	2.5 (1.60–4.0)	2.60 (1.70–4.80)	0.077	2.4 (1.6–3.9)	2.5 (1.6–4.0)	0.005
Albumin, g/L (IQR)	39 (35–43)	40 (36–43)	39 (34–43)	0.144	40 (36–44)	40 (36–44)	0.010
Platelets, × 10^9/L (IQR)	191 (143–240)	195 (152–242)	189 (138–240)	0.075	196 (151–244)	197 (151–245)	0.016
FIB-4 > 3.25	4793 (14.7)	1110 (10.7)	3683 (16.5)	0.169	1065 (10.7)	1009 (10.1)	0.018
HBV DNA > 1000 IU/L	3361 (10.3)	1032 (10.0)	2329 (10.4)	0.058	1003 (10.1)	975 (9.8)	0.009
HBeAg-positive	1509 (4.6)	405 (3.9)	1104 (4.9)	0.187	398 (4.0)	367 (3.7)	0.030
eGFR, mL/min/1.73^2 (IQR)	86.5 (63.5–100.7)	86.0 (65.6–99.8)	86.80 (62.40–101.0)	0.098	88.6 (68.0–102.4)	90.9 (69.9–104.1)	< 0.001
Proteinuria	4924 (15.1)	1656 (16.0)	3268 (14.6)	0.037	1582 (15.9)	1565 (15.7)	0.005

Table 1 (part 2 of 2): Baseline characteristics of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers and calcium channel blocker/thiazides or thiazide-like diuretics exposure groups before and after propensity score weighting*

	Before PSM				After PSM		
Characteristics	Overall no. (%)* of patients *n* = 32 692	No. (%)* of patients starting ACEIs/ARBs *n* = 10 364	No. (%)* of patients starting CCBs/THZs *n* = 22 328	SMD	No. (%)* of patients starting ACEIs/ARBs *n* = 9946	No. (%)* of patients starting CCBs/THZs *n* = 9946	SMD
Comorbidities							
Charlson Comorbidity Index score (IQR)	4 (2–6)	4 (2–6)	4 (3–6)	0.105	4 (2–5)	4 (2–6)	0.016
Cirrhosis	2874 (8.8)	617 (6.0)	2257 (10.1)	0.153	606 (6.1)	589 (5.9)	0.007
Child–Pugh–Turcotte score				0.226			0.037
1	2154 (74.9)	505 (81.8)	1649 (73.1)	–	494 (81.5)	473 (80.3)	–
2	676 (23.5)	101 (16.4)	575 (25.5)	–	101 (16.7)	103 (17.5)	–
3	44 (1.5)	11 (1.8)	33 (1.5)	–	11 (1.8)	13 (2.2)	–
Diabetes	6083 (18.6)	2267 (21.9)	3816 (17.1)	0.121	2136 (21.5)	2123 (21.3)	0.003
Heart failure	2721 (8.3)	1440 (13.9)	1281 (5.7)	0.277	1193 (12.0)	1002 (10.1)	0.061
HCV infection	923 (2.8)	653 (6.3)	270 (1.2)	0.270	437 (4.4)	263 (2.6)	0.095
Alcoholic liver disease	68 (0.2)	21 (0.2)	47 (0.2)	0.002	20 (0.2)	24 (0.2)	0.009
HIV infection	227 (0.7)	64 (0.6)	163 (0.7)	0.014	63 (0.6)	60 (0.6)	0.004
Myocardial infarction	9 (0.0)	5 (0.0)	4 (0.0)	0.017	4 (0.0)	3 (0.0)	0.005
CKD	6359 (19.5)	2270 (21.9)	4089 (18.3)	0.090	2157 (21.7)	2121 (21.3)	0.009
Co-medications							
Antiviral therapy	5249 (16.1)	1522 (14.7)	3727 (16.7)	0.055	1482 (14.9)	1471 (14.8)	0.003
β-blocker	8674 (26.5)	3797 (36.6)	4877 (21.8)	0.330	3445 (34.6)	3196 (32.1)	0.053
ASA	7569 (23.2)	3398 (32.8)	4171 (18.7)	0.327	3072 (30.9)	2954 (29.7)	0.026
Statins	10 334 (31.6)	4721 (45.6)	5613 (25.1)	0.437	4320 (43.4)	4176 (42.0)	0.029

Note: ACEI = angiotensin-converting enzyme inhibitor, AFP = α fetoprotein, ALT = alanine aminotransferase, ARB = angiotensin II receptor blocker, ASA = acetylsalicylic acid, AST = aspartate aminotransferase, BMI = body mass index, CCB = calcium channel blocker, CKD = chronic kidney diseases, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, FIB-4 = Fibrosis-4 Index, HBeAg = hepatitis B e antigen, HBV = hepatitis B virus, HCV = hepatitis C virus, IQR = interquartile range, PSM = propensity score matching, SBP = systolic blood pressure, SMD = standardized mean difference.
*Unless otherwise specified.

A cohort study of 7724 patients with HBV and 7873 patients with HCV infection reported nonsignificant associations between the use of RASi and the incidence of HCC,[18] and suggested a positive association between the use of RASi and HCC development that was not statistically significant. Similarly, a nationwide nested case–control study from South Korea also found nonsignificant differences in the incidence of HCC between RASi users and nonusers.[39] These inconsistencies may arise from heterogeneity in the study populations; that is, confounding by treatment indication and bias caused by inclusion of prevalent users.

Renin–angiotensin–aldosterone system inhibitors are widely used to treat hypertension, heart failure, and chronic kidney disease, and are generally safe and well tolerated. Our findings suggest that RASi may be the preferred antihypertensive medications for patients with HBV infection, particularly those at high risk for HCC or liver-related events. However, studies are needed to confirm our findings. Randomized controlled trials assessing the impact of RASi on HCC would be ideal but challenging to conduct because of the large sample size and long follow-up required, although studying a relatively high-risk population might make such a trial feasible.

Limitations

Because this was a retrospective study, residual confounding is possible, despite the use of an active comparator and propensity score matching to balance confounding variables. Although we were unable to adjust for unmeasured confounders such as lifestyle factors and family history of HCC, given the E-values for study outcomes in the primary analyses (2.40 and 1.92), the robustness of the study results did not appear to be substantially affected by the presence of unassessed confounders. We did not examine the association between specific RASi drugs or their dose and outcomes. Further investigations are needed to evaluate the appropriate intensity and duration of treatment. Some patients dropped out of the study because they relocated or changed health care providers, which may have introduced bias. We conducted a sensitivity analysis that included only patients with at

Table 2: Crude and adjusted hazard ratios for association between angiotensin-converting enzyme inhibitors/angiotensin receptor blockers versus calcium channel blockers/thiazides or thiazide-like diuretics and risk of hepatocellular carcinoma and liver-related mortality in the 9946 matching cohorts

Outcomes by drug	No. of events	No. of person-years	Incidence rate*	Crude HR (95% CI)	Adjusted HR (95% CI)†
Risk of HCC					
CCBs or THZs	137	23 053	5.94 (5.01–7.04)	1.00 (Ref.)	1.00 (Ref.)
ACEIs or ARBs	93	22 636	4.11 (3.34–5.05)	0.69 (0.53–0.90)	0.66 (0.50–0.86)
Risk of liver-related mortality					
CCBs or THZs	282	46 709	6.04 (5.36–6.79)	1.00 (Ref.)	1.00 (Ref.)
ACEIs or ARBs	203	42 762	4.75 (4.13–5.46)	0.75 (0.63–0.90)	0.77 (0.64–0.93)

Note: ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, CCB = calcium channel blocker, CI = confidence interval, HCC = hepatocellular carcinoma, HR = hazard ratio, Ref. = reference category, THZ = thiazide-like diuretic.
*Per 1000 person-years.
†Adjusted for age, sex, body mass index, smoking status, systolic blood pressure, diastolic blood pressure, alanine aminotransferase, aspartate aminotransferase, estimated glomerular filtration rate, α fetoprotein, albumin, platelets, Fibrosis-4 Index, hepatitis B virus DNA, hepatitis B e antigen, proteinuria, Charlson Comorbidity Index score, cirrhosis, Child–Pugh–Turcotte score, diabetes, heart failure, myocardial infarction, HIV, hepatitis C virus, alcohol liver disease, chronic kidney diseases, antiviral therapy, β-blocker, statins, and acetylsalicylic acid.

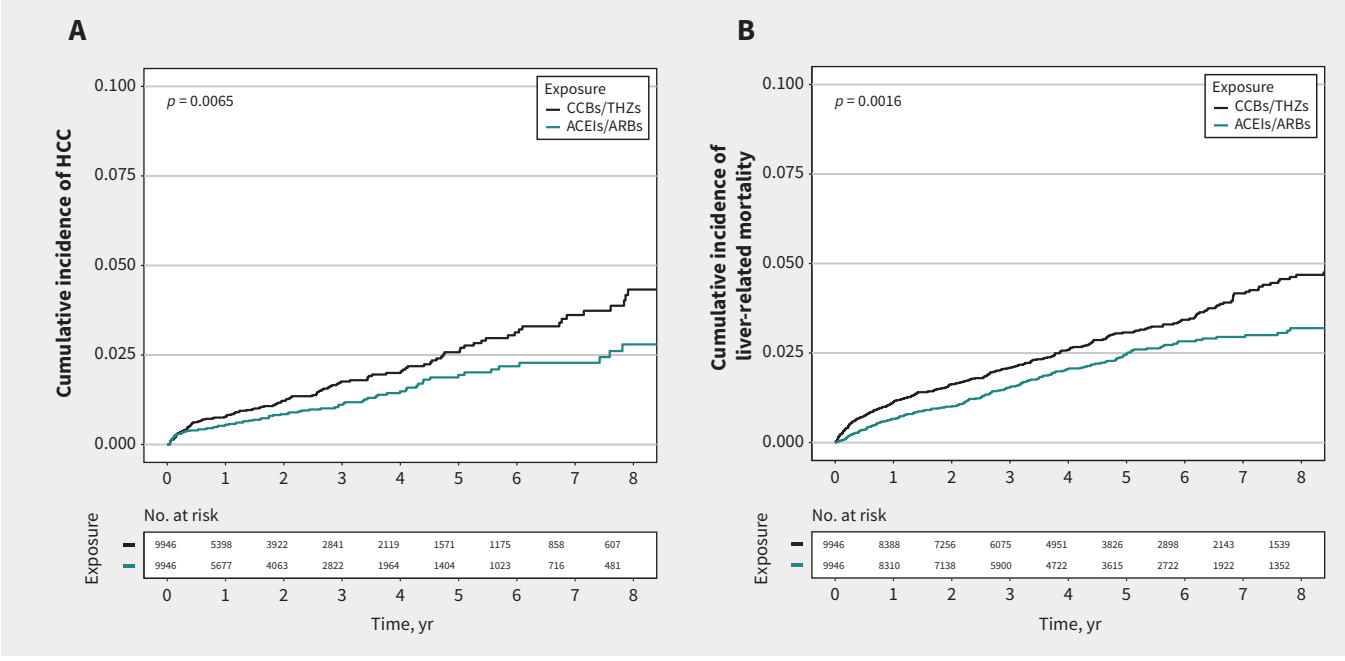

Figure 2: Cumulative incidence of hepatocellular carcinoma (HCC) and liver-related mortality among patients who started angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEIs/ARBs) and those who started calcium channel blockers or thiazide or thiazide-like diuretics (CCBs/THZs).

least 1-year follow-up and observed a similar association between the use of RASi and study outcomes. All patients with baseline HCC may not have been excluded. In China, screening for HCC — such as measuring HBV DNA, liver function, and AFP — combined with abdominal ultrasound is recommended for participants with HBV infection 1–4 times annually, depending on risk stratification.[40] Hence, we performed a sensitivity analysis to extend the lag period to 1 year. In this population, the median follow-up was 3.9 years and the results remained consistent. The absolute reduction in the risk of HCC with the use of ACEIs/ARBs was small (1.83 per 1000 person-years). However, given the large number of people with HBV infection in China (> 70 million), even a slight reduction would lead to a large public health benefit.[40] The generalizability of our findings may be limited by the predominantly Chinese ethnicity of our study population and the focus on patients with HBV. Whether the protective association of RASi in patients with HBV infection varies by ethnicity or genotypes remains uncertain, and will require study in other populations. Additionally, the retrospective period for defining new users was 180 days from the index date, which may not completely exclude all prevalent users. Finally, the number of outcome events in some secondary analyses, such as those stratifying on individual drugs, were small and the CIs around measures of association were wide. Thus, these results should be interpreted with caution.

Subgroups	ACEIs/ARBs N	ACEIs/ARBs Incidence rate*	CCBs/THZs N	CCBs/THZs Incidence rate*	HR (95% CI)†	p for interaction
Age, yr						
≥ 60	4496	6.09	4346	8.32	0.63 (0.44–0.90)	0.874
< 60	5461	2.71	5611	4.13	0.66 (0.43–1.00)	
Sex						
Female	4214	2.04	4271	2.21	0.87 (0.48–1.60)	0.226
Male	5743	5.58	5686	8.54	0.57 (0.42–0.78)	
Cirrhosis						
No	9351	3.01	9318	4.08	0.67 (0.49–0.93)	0.349
Yes	606	25.52	639	45.76	0.51 (0.30–0.84)	
Diabetes						
No	7825	3.47	7837	5.40	0.56 (0.41–0.77)	0.191
Yes	2132	6.81	2120	7.08	0.85 (0.49–1.47)	
CKD						
No	7796	4.05	7827	5.47	0.67 (0.50–0.91)	0.282
Yes	2161	4.10	2130	6.86	0.46 (0.24–0.87)	
Heart failure						
No	8751	4.06	8948	5.61	0.61 (0.46–0.82)	0.683
Yes	1206	4.00	1009	6.67	0.76 (0.28–2.07)	
Antiviral therapy						
No	8485	2.51	8455	3.36	0.66 (0.46–0.96)	0.646
Yes	1472	13.64	1502	21.02	0.58 (0.39–0.87)	
β-blocker						
No	6505	4.38	6742	5.37	0.65(0.47–0.90)	0.647
Yes	3452	3.36	3215	6.36	0.56 (0.34–0.94)	
Statins						
No	5634	4.45	5749	6.97	0.54 (0.39–0.75)	0.101
Yes	4323	3.43	4208	3.44	0.90 (0.54–1.51)	
ASA						
No	6879	4.30	7047	6.45	0.56 (0.41–0.76)	0.134
Yes	3078	3.43	2910	3.56	0.93 (0.51–1.70)	

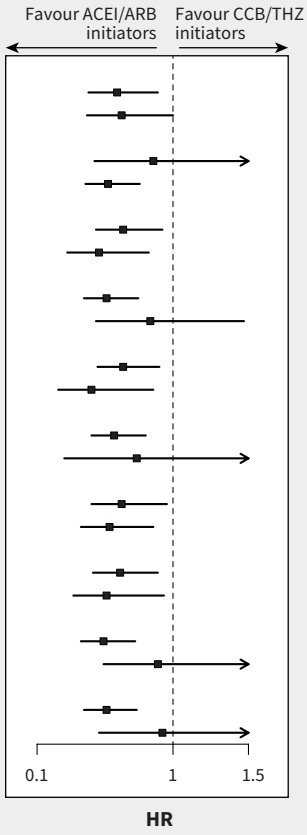

Figure 3: Hazard ratio (HR) for the association between patients who started angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEIs/ARBs) versus those who started calcium channel blockers or thiazide or thiazide-like diuretics (CCBs/THZs) and risk of hepatocellular carcinoma among different subgroups. Note: ASA = acetylsalicylic acid, CI = confidence interval, CKD = chronic kidney disease. *Per 1000 person-years. †Adjusted for age, sex, smoking status, systolic blood pressure, diastolic blood pressure, alanine aminotransferase, aspartate aminotransferase, estimated glomerular filtration rate, α fetoprotein, albumin, platelets, Fibrosis-4 Index, hepatitis B virus DNA, hepatitis B e antigen, proteinuria, Charlson Comorbidity Index score, cirrhosis, Child–Pugh–Turcotte score, diabetes, heart failure, myocardial infarction, HIV, hepatitis C virus, alcohol liver disease, chronic kidney diseases, antiviral therapy, β-blocker, statins, and ASA.

Conclusion

In a multicentre study of patients with HBV infection in China, we found that use of ACEIs/ARBs was associated with a reduced risk of incident HCC and liver-related deaths, compared with use of CCBs/THZs. Studies are needed to confirm these effects and the underlying mechanisms require further investigation.

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