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Risk of Variceal Hemorrhage in Patients With Cirrhosis Taking Calcium-Channel Blockers

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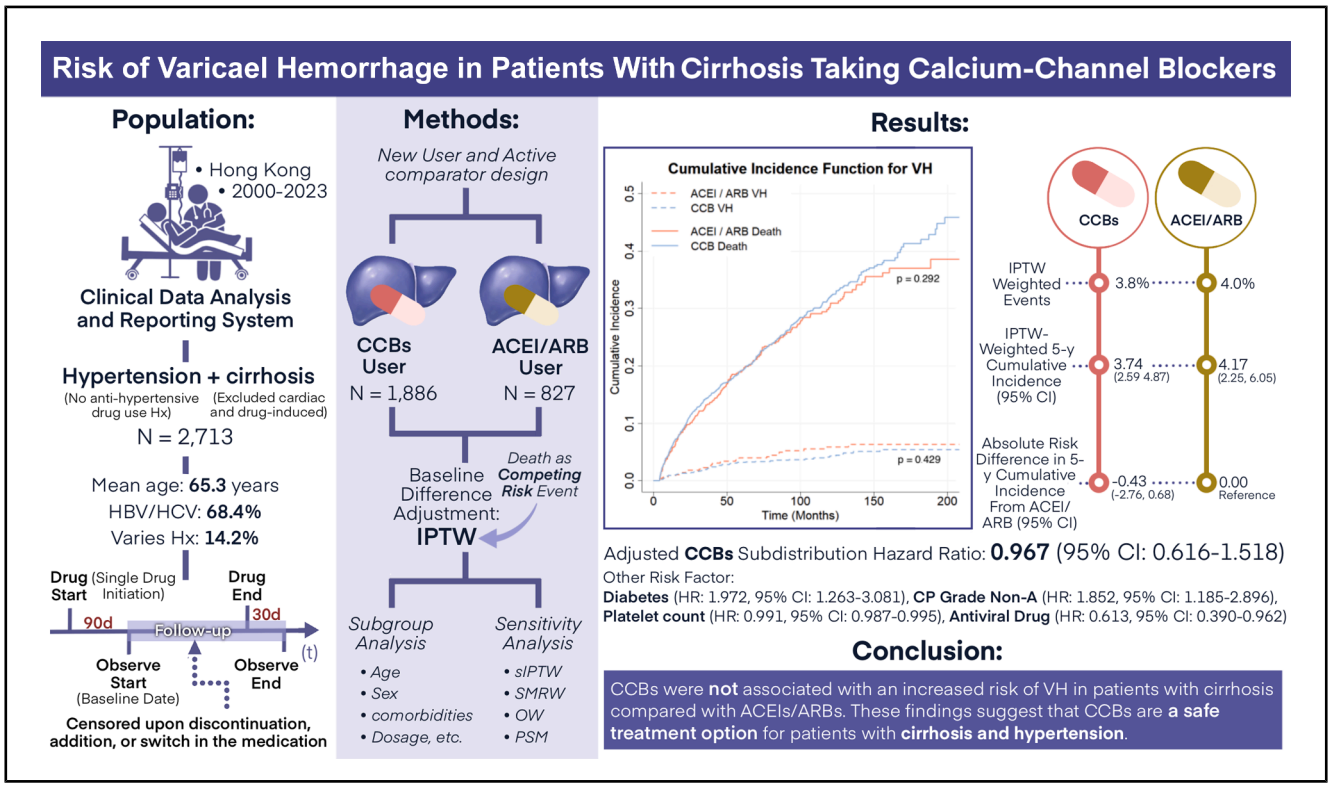

BACKGROUND & AIMS: **Calcium-channel blockers (CCBs) are widely prescribed for arterial hypertension. However, it remains uncertain whether CCBs, through their vasodilatory effects, influence the risk of variceal hemorrhage (VH) in cirrhosis patients. This study aimed to investigate the association between CCB use and VH risk in cirrhosis patients.**

METHODS: **This territory-wide retrospective cohort study included patients with cirrhosis and no prior history of VH identified from the Clinical Data Analysis and Reporting System of the Hospital Authority, Hong Kong between 2000 and 2023. An active comparator new-user design was**

Abbreviations used in this paper: **ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CDARS, Clinical Data Analysis and Reporting System; CCB, calcium-channel blocker; CI, confidence interval; DDD, defined daily dose; HBV, hepatitis B virus; ICD-9-CM, International Classification of Diseases–Ninth Revision–Clinical Modification; IPTW, inverse probability of treatment weighting; NOAC, novel oral anticoagulant; NSBB, nonselective beta-blocker; PS, propensity score; SHR, subdistribution hazard ratio; VH, variceal hemorrhage.**

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adopted, with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) as active comparators. Either CCB or ACE inhibitor/ARB were initiated as monotherapy for hypertension. Patients were censored at discontinuation, addition, or switching of the medication.

RESULTS: **A total of 1886 CCB and 827 ACE inhibitor/ARB users were included. After inverse probability of treatment weighting, VH incidence rates were comparable between CCB and ACE inhibitor/ARB users (7.42 vs 10.50 cases per 1000 person-years; $P = .116$). The 5-year cumulative incidence was 3.74% (95% confidence interval [CI], 2.59%–4.87%) and 4.17% (95% CI, 2.25%–6.05%) for CCB and ACE inhibitor/ARB users, respectively. No significant association between CCB use and VH risk was observed (adjusted subdistribution hazard ratio 0.967; 95% CI, 0.616–1.518; $P = .880$).**

CONCLUSIONS: **CCBs were not associated with an increased risk of VH in patients with cirrhosis compared with ACE inhibitors/ARBs. These findings suggest that CCBs are a safe treatment option for patients with cirrhosis and hypertension, providing valuable guidance on medication selection in this vulnerable population.**

Keywords: Variceal Hemorrhage; Cirrhosis; Calcium-Channel Blockers.

The prevalence of metabolic diseases, including arterial hypertension, is rising in patients with cirrhosis.[1] According to the World Health Organization's Global Hypertension Report, the age-standardized prevalence of hypertension among individuals 30 to 79 years of age was approximately one-third in 2019.[2] With changing dietary patterns, decreasing physical inactivity, and the growing prevalence of sedentary lifestyles, an increasing proportion of patients with cirrhosis have metabolic comorbidities. In fact, a recent prospective study reported that approximately 60% of out-patients with cirrhosis at an Italian center had a history of hypertension.[3]

Calcium-channel blockers (CCBs) are one of the commonly used first-line medications for managing hypertension, with a well-established safety profile. However, in patients with cirrhosis and portal hypertension, the impact of CCB-induced vasodilation on portal hemodynamics remains uncertain. On one hand, CCBs may cause splanchnic vasodilation, increasing organ blood flow and portal pressure,[4] and consequently increase the risk of variceal hemorrhage (VH). On the other hand, they may reduce intrahepatic vascular resistance, potentially lowering portal pressure and VH risk.[5] This ambiguity is particularly concerning, as many patients with cirrhosis and hypertension require long-term CCB therapy. This raises the question of their potential impact on bleeding risk and overall long-term safety in cirrhosis.

VH is a severe complication of cirrhosis and portal hypertension which carries a significant mortality risk. Survivors also face a high risk of rebleeding, with approximately 60% experiencing recurrent VH within 1 year.[6] Despite advancements in therapeutics, the mortality rate remains significant. As one of the most severe and life-threatening decompensating events in cirrhosis, any factors influencing VH risk should garner significant attention from clinicians. However, little is known on whether CCBs would impact VH from current evidence, leaving a major knowledge gap in this important topic. Thus, in this real-world, territory-wide cohort study, we aimed to evaluate the impact of CCBs on VH in patients with cirrhosis.

Materials and Methods

Study Design and Data Source

This retrospective cohort study was conducted using data from the Clinical Data Analysis and Reporting System (CDARS), a comprehensive electronic healthcare database managed by the Hospital Authority in Hong Kong. CDARS integrates a wide range of healthcare data, including demographic information, mortality records, medical diagnoses, procedures, medication prescribing and dispensing history, and laboratory test results. It captures data from all public hospitals and clinics in Hong Kong, which cover around 80% of the local population. To ensure confidentiality, all patient information in CDARS is de-identified. Medical diagnoses in CDARS are coded using the International Classification of Diseases–Ninth Revision–Clinical Modification (ICD-9-CM). Validation against electronic medical records, encompassing clinical, laboratory, imaging, and endoscopy data, has demonstrated a 99% accuracy rate for ICD-9-CM–coded diagnoses,[7] affirming the reliability of the database for research purposes.

Participants

Consecutive patients with cirrhosis of any etiology between January 2000 and June 2023 were identified (Figure 1). Supplemental Tables 1 and 2 present the baseline characteristics of the entire population. Patients included in the study were those who initiated CCB or ACE inhibitor/ARB treatment between 2004 and 2020, with data extracted in June 2023 to ensure an adequate follow-up period and avoid misclassification during the early

years of CDARS establishment. The baseline date was defined as the initiation of antihypertensive treatment following a confirmed diagnosis of cirrhosis (Supplemental Figure 1). Patients were excluded if they met any of the following criteria: incomplete demographic data; age <18 years at baseline; co-infection with human immunodeficiency virus as identified by ICD-9-CM diagnosis codes; history of hepatic decompensation including VH, liver transplantation before baseline, VH at or within 3 months of baseline, or cirrhosis due to nonhepatic causes (eg, cardiac cirrhosis and drug-induced hepatitis). Patients were followed until the occurrence of VH, death, or the last follow-up date (June 30, 2023). Follow-up was censored at the time of liver transplantation, discontinuation of the current antihypertensive medication, or switching to or adding other antihypertensive drugs.

This study adhered to the ethical principles outlined in the 1975 Declaration of Helsinki and the study protocol was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee. Informed consent was exempted due to the retrospective nature of the study.

What You Need to Know

Background

The safety of calcium-channel blockers (CCBs) in cirrhotic patients, particularly regarding variceal hemorrhage (VH) risk, remains uncertain due to limited real-world evidence.

Findings

In this territory-wide cohort study, CCB use was not associated with an increased risk of VH compared with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers use among patients with cirrhosis.

Implication for patient care

These findings support the safe use of CCBs in patients with cirrhosis, providing reassurance regarding VH risk in clinical decision making.

Definitions

The primary endpoint was VH, which was defined by a combination of ICD-9-CM diagnosis codes and positive findings in endoscopy records. A particular strategy to identify varices and VH in endoscopy records combined with its own diagnosis codes, procedure codes, indication text, and hemoglobin results for this study is described in Supplemental Figures 2 and 3. Cirrhosis, underlying liver disease etiology (such as chronic hepatitis B and C, metabolic dysfunction–associated steatotic liver disease, alcohol-associated liver disease, autoimmune causes, and others), related hepatic conditions (eg, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome), hypertension, and other comorbidities were identified using diagnosis codes (Supplemental Table 3). All comorbidities in this study were defined by having a corresponding diagnostic record on or before the index date of drug initiation. Concomitant medication use was identified through filled prescriptions for selective and nonselective beta-blockers (NSBBs), nitrates, diuretics, antiplatelets, anticoagulants (eg, warfarin, novel oral anticoagulants), hypoglycemic agents, statins, and antiviral treatments for hepatitis B and C. To assess a dose-response relationship, CCB doses were categorized as <1 defined daily dose (DDD) or ≥1 DDD based on the maximum DDD (Supplemental Table 4).

Statistical Analysis

Data was analyzed using R software (version 4.3.1; R Foundation for Statistical Computing). Continuous variables were presented as mean ± SD or median (interquartile range [IQR]), depending on their distribution, while categorical variables were reported as count and percentage. Differences between subgroups were evaluated using the chi-square test or Fisher's exact test for categorical variables, and Student's *t* test or the Mann-Whitney *U* test for continuous variables, as appropriate.

We employed an active-comparator and new-user design by selecting medications with indications similar to CCBs as potential comparators.[8] Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) were chosen as active comparators due to their similar indications and frequency of use compared with CCBs. The new-user design ensured that all patients had not received any antihypertensive medications, including diuretics, selective beta-blockers, alpha-blockers, or direct vasodilators, prior to initiating CCBs or ACE inhibitor/ARBs. To avoid selection bias arising from excluding patients who had taken NSBBs due to more severe liver disease under the new user design, patients with prior NSBB use were not removed in the main analysis. However, in the sensitivity analysis, we applied a stricter new user design criterion by excluding all patients with prior NSBB use to assess the robustness of the results.

To ensure adequate observation, a landmark analysis excluded patients with <90 days of follow-up after treatment initiation.[9] This approach minimizes time-dependent bias (eg, patients with more severe conditions being more likely to initiate CCB treatment earlier) and survivor bias (eg, patients who die early being unable to complete treatment).[10] Patients were subsequently followed until the occurrence of a study outcome, censoring event, or the end of the study period.

Clinical covariates were assessed prior to medication initiation. To mitigate the potential biases introduced by missing data, single imputation was employed, using the mean or median for continuous variables and appropriate measures for categorical variables.

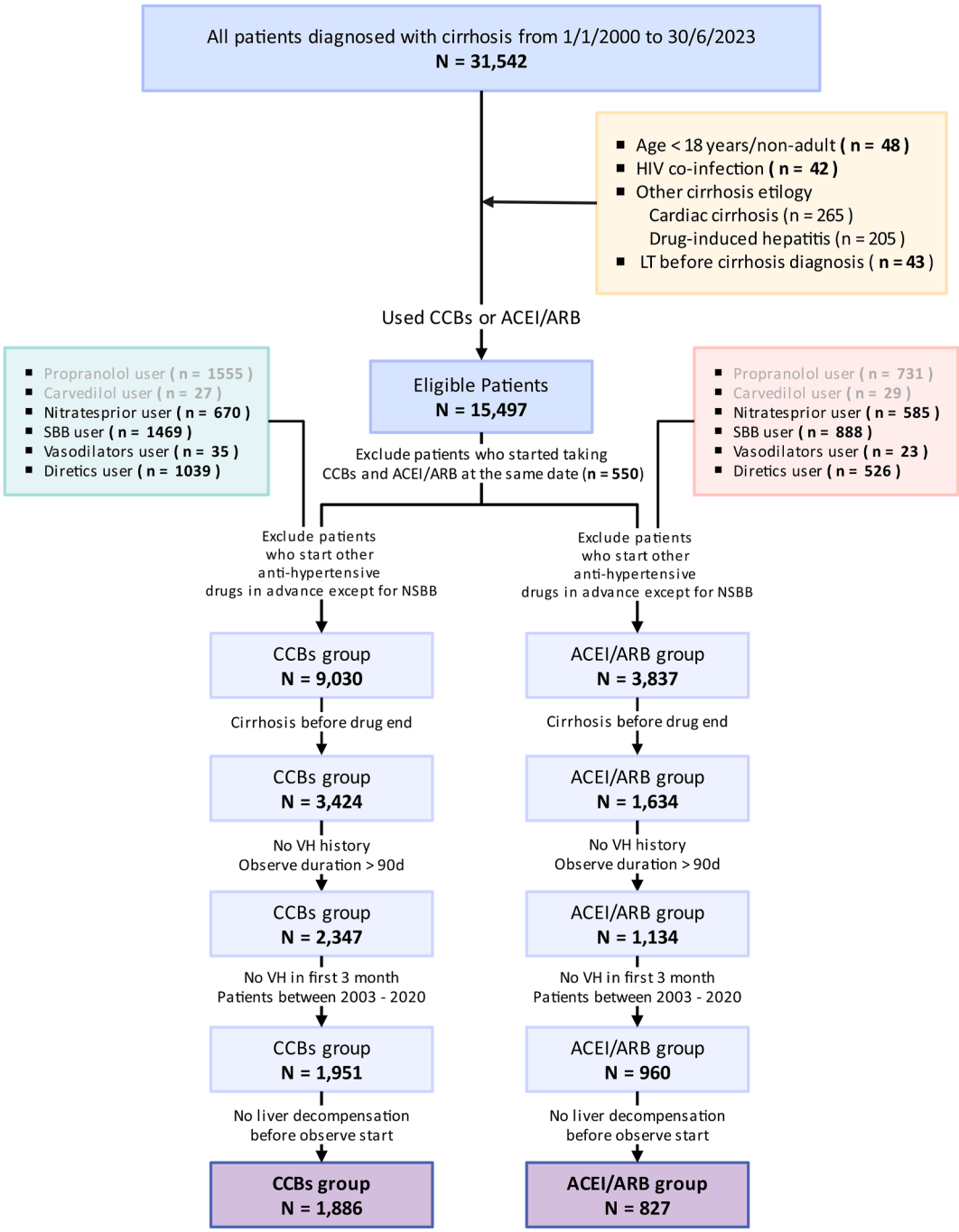

Figure 1. Patient selection flowchart. ACEI, angiotensin-converting enzyme inhibitor; LT, liver transplantation; SBB, selective beta-blocker.

To account for potential confounders associated with hypertensive drug allocation, a propensity score (PS) model was developed to estimate the probability of receiving CCBs and to minimize selection bias. Twelve baseline covariates selected a priori, based on theory and literature, were included in estimating the PS: age, sex, Child-Pugh (CP) grade, international normalized ratio, diabetes, cardiovascular diseases, kidney diseases, use of antiplatelet agents, anticoagulants, oral hypoglycemic agents, insulin, and antiviral medications.[11] Logistic regression was applied to estimate the PS of receiving CCB for calculating inverse probability of treatment weighting (IPTW).[12] Subjects in the CCB and ACE inhibitor/ARB groups were assigned a weight of 1/PS and 1/(1 – PS), respectively, to balance baseline covariates and estimate the average treatment effect, ensuring comparable distributions between groups.[13] Covariate balance was assessed using absolute standardized mean differences, with values exceeding 0.1 indicating imbalance. To improve the robustness of the estimates, PS truncation was applied in the sensitivity analysis. If the PS of an individual is below 0.01 or above 0.99, it is considered an

extreme weight and is trimmed. Additionally, different weighting methods, such as overlap weighting and standardized mortality ratio weighting, were included as supplementary analyses beyond the primary analysis (Supplemental Tables 5–7).[14]

Cumulative incidence and competing risk-adjusted cumulative incidence function curves were constructed using IPTW-weighted Kaplan-Meier method and Fine-Gray competing risks models, respectively, with 95% confidence intervals (CIs) to compare CCB users with ACE inhibitor/ARB users.[15] Subdistribution hazard ratios (SHRs) were calculated using Fine-Gray's competing risks regression model in both univariable and multivariable analyses, accounting for competing risks.[16] An SHR >1 indicated an increased risk of VH. The proportional hazards assumption was verified using Schoenfeld's test. Event rates, 5-year cumulative incidences by cumulative incidence function, absolute risk differences with bootstrapped 95% CIs, and proportional hazards ratios by IPTW-weighted Cox model were calculated. Additionally, to explore the factors influencing bleeding in these patients overall, a multivariable weighted Cox proportional hazards model was further used in the supplementary analysis. Differences between cohorts were assessed using Gray's test. To further enhance the robustness of the conclusions, matching was also considered using the nearest neighbor matching method, with a 1:1 ratio between the CCB group and the ACE inhibitor/ARB group.[17] This approach was applied as a sensitivity analysis to complement the competing risks model in assessing the risk of VH. Subgroup analyses were conducted based on baseline demographic (age, sex) and other clinical characteristics (etiology, liver function, comorbidities, and drug dosage). Statistical significance was defined as a 2-sided P value <.05 for all tests.

Results

Demographic Characteristics

We identified 2713 eligible patients from 31,542 patients with cirrhosis, including 1886 CCB users and 827 ACE inhibitor/ARB users. Baseline clinical characteristics are summarized in Table 1. The median follow-up duration was longer for CCB users compared with ACE inhibitor/ARB users (44.0 months vs 35.4 months). CCB users were older than ACE inhibitor/ARB users (mean age 66.0 years vs 63.9 years), and male patients predominated in both groups (64.8% vs 68.9%). Chronic hepatitis B was the most common etiology (63.3% vs 61.9%). CCB users had a lower prevalence of diabetes (13.8% vs 46.3%) and cardiovascular disease (10.1% vs 22.1%). Baseline liver function parameters were generally comparable. After IPTW, balance was achieved across all measured variables, with standardized mean differences reduced to within ±0.1.

Events

The clinical events and long-term outcomes between CCB and ACE inhibitor/ARB users are summarized in Table 2. During the follow-up period, the incidence of varices was similar between CCB and ACE inhibitor/ARB users (12.6% vs 15.0%; $P = .107$). The occurrence of VH was also comparable (3.4% vs 4.2%; $P = .374$). For other hepatic events, the rates of jaundice, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and hepatorenal syndrome also did not differ significantly between the CCB and ACE inhibitor/ARB groups.

The overall mortality rate was similar in CCB users compared with ACE inhibitor/ARB users (42.1% vs 39.7%; $P = .254$). Liver-related deaths occurred in 33.2% of CCB users and 32.2% of ACE inhibitor/ARB users ($P = .803$). Similarly, the incidence of hepatocellular carcinoma was comparable between the CCB and ACE inhibitor/ARB users.

Risk of VH in CCB vs ACE Inhibitor/ARB Users

The VH cumulative incidence was similar between the two groups over the follow-up period (Supplemental Figure 4). The weighted incidence of VH was 3.8% for CCB users and 4.0% for ACE inhibitor/ARB users ($P = .672$). The IPTW-adjusted cumulative incidence of VH over 5 years was similar in CCB users (3.74%; 95% CI, 2.59% to 4.87%) and ACE inhibitor/ARB users (4.17%; 95% CI, 2.25% to 6.05%) (Table 3). In weighted multivariable analysis, CCB use was not associated with an increased risk of VH compared with ACE inhibitor/ARB use (hazard ratio, 0.822; 95% CI, 0.503 to 1.345; $P = .436$). Rather, Child-Pugh grade (non-A) and lower platelet count were the independent factors associated with a higher risk of VH (Supplemental Table 8).

Figure 2 illustrates the cumulative incidence of VH and death with competing risks over time for patients treated with ACE inhibitor/ARB or CCB. There was no significant difference between the two groups for VH ($P = .429$) or death ($P = .292$). Table 4 shows the results of the Fine-Gray competing risks regression. In the multivariable analysis, diabetes (adjusted SHR, 1.972; 95% CI, 1.263 to 3.081; $P = .003$), Child-Pugh B/C (adjusted SHR, 1.852; 95% CI, 1.185 to 2.896; $P = .007$), platelet count (adjusted SHR, 0.991; 95% CI, 0.987 to 0.995; $P < .001$), and antiviral drugs (adjusted SHR, 0.613; 95% CI, 0.390 to 0.962; $P = .033$) were significant predictors of VH. Other factors, including CCB use (adjusted SHR, 0.967; 95% CI, 0.616 to 1.518; $P = .880$), were not associated with VH.

Subgroup and Sensitivity Analyses

Subgroup analyses stratified by age (<60 years vs ≥60 years), sex, etiology of liver disease (viral vs nonviral hepatitis), liver function (CP grade A vs non-A),

Table 1. Baseline Clinical Characteristics of the Study Cohort

Clinical characteristics	CCB user (n = 1886)	ACE inhibitor/ ARB user (n = 827)	SMD before IPTW	SMD after IPTW
Drug application				
Follow-up, *mo*	44.0 (17.1–81.4)	35.4 (12.5–66.5)	—	—
Use before diagnosis	1057 (56.0)	482 (58.3)	–0.0224	0.0154
Initiation year				
2003–2005	174 (9.2)	107 (12.9)	–0.0371	–0.0255
2006–2008	188 (10.0)	128 (15.5)	–0.0551	–0.0790
2009–2011	412 (21.8)	199 (24.1)	–0.0222	–0.0010
2012–2014	354 (18.8)	115 (13.9)	0.0486	0.0651
2015–2017	325 (17.2)	136 (16.4)	0.0079	–0.0046
2018–2020	433 (23.0)	142 (17.2)	0.0579	0.0450
Demographic parameters				
Age, *y*	66.0 ± 11.4	63.9 ± 11.3	0.1837	–0.0463
Male	1222 (64.8)	570 (68.9)	–0.0413	0.0066
Liver disease etiology				
CHB	1194 (63.3)	512 (61.9)	0.0140	0.0295
CHC	157 (8.3)	69 (8.3)	–0.0002	–0.0002
MASH	59 (3.1)	36 (4.4)	–0.0122	–0.0019
Alcohol consumption	454 (24.1)	194 (23.5)	0.0061	0.0554
Autoimmune	1 (0.1)	1 (0.1)	–0.0007	0.0004
PBC	216 (11.5)	71 (8.6)	0.0287	–0.0206
Varices before drug use	272 (14.4)	112 (13.5)	0.0088	0.0002
Comorbidities				
Diabetes	261 (13.8)	383 (46.3)	–0.3247	0.0102
Cardiovascular disease	191 (10.1)	183 (22.1)	–0.1200	0.0167
Chronic kidney disease (eGFR <60 mL/min/1.73 m^2)	56 (3.0)	45 (5.4)	–0.0247	0.0016
Laboratory parameters				
Hemoglobin, *g/dL*	13.0 ± 2.1	13.0 ± 2.1	0.0188	0.0389
Platelet ($\times 10^9$/L)	152.0 (108.0–207.0)	148.0 (103.8–204.0)	0.0221	0.0074
Albumin, *g/L*	37.3 ± 6.8	36.7 ± 7.0	0.0871	0.0433
Total bilirubin, *μmol/L*	14.0 (9.9–21.5)	15.7 (10.0–23.0)	–0.0954	–0.0673
Alanine aminotransferase, *U/L*	30.0 (20.0–51.5)	31.2 (20.0–53.2)	0.0233	0.0255
Prothrombin time (s)	12.3 ± 2.1	12.7 ± 3.5	–0.1316	0.0834
International normalized ratio	1.1 ± 0.2	1.1 ± 0.3	–0.1504	0.0548
Creatinine, *μmol//L*	78.0 (66.0–93.0)	80.0 (68.0–96.0)	0.0664	0.0239
Liver function				
Child-Pugh class (A/non-A)			–0.0506	0.0034
A	1387 (77.6)	544 (71.5)	—	—
B	358 (20.0)	194 (25.5)	—	—
C	43 (2.4)	23 (3.0)	—	—
MELD score	8.0 (6.9–10.1)	8.3 (7.0–10.7)	–0.0903	–0.0056
Medications				
Concomitant drugs				
Nonselective beta-blocker	756 (40.1)	373 (45.1)	–0.0502	–0.0221
Propranolol				
Prior use	296 (15.7)	141 (17.0)	—	—
Concomitant use	394 (20.9)	168 (20.3)	—	—
Subsequent use	224 (11.9)	135 (16.3)	—	—
Carvedilol				
Prior use	3 (0.2)	2 (0.2)	—	—
Concomitant use	62 (3.3)	57 (6.9)	—	—
Subsequent use	46 (2.4)	20 (2.4)	—	—
Antiplatelet			–0.0887	0.0105
Aspirin	182 (9.7)	154 (18.6)	—	—
Clopidogrel/ticagrelor/prasugrel	37 (2.0)	48 (5.8)	—	—

Table 1. Continued

Clinical characteristics	CCB user (n = 1886)	ACE inhibitor/ ARB user (n = 827)	SMD before IPTW	SMD after IPTW
Anticoagulants			–0.0302	0.0089
Warfarin	14 (0.7)	25 (3.0)	—	—
NOACs	3 (0.2)	7 (0.8)	—	—
Oral hypoglycemic agent	302 (16.0)	450 (54.4)	–0.3840	0.0136
Insulin	95 (5.0)	174 (21.0)	–0.1600	0.0165
Statin	204 (10.8)	198 (23.9)	–0.1313	–0.0622
Antiviral agents			0.0059	0.0033
HBV	641 (34.0)	279 (33.7)	—	—
HCV	11 (0.6)	2 (0.2)	—	—

NOTE. Values are median (interquartile range), n (%), or mean ± SD.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker; CHB, chronic hepatitis B; CHC, chronic hepatitis C; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; MASH, metabolic dysfunction-associated steatohepatitis; MELD, Model for End-Stage Liver Disease; NOAC, novel oral anticoagulant; NSBB, nonselective beta-blocker; PBC, primary biliary cholangitis; SBB, selective beta-blocker; SMD, standardized mean difference; VH, variceal hemorrhage.

comorbidities, and drug use characteristics consistently showed no significant association between CCB use and VH risk across all examined subgroups (Supplemental Table 9 and Supplemental Figures 5–13).

Sensitivity analyses using different weighting methods, including truncated IPTW (99%), overlap weighting, and standardized mortality ratio weighting consistently showed comparable cumulative incidence rates of VH between CCB and ACE inhibitor/ARB users (Supplemental Figure 14*A*–*C*). The weighted 5-year cumulative incidence of VH ranged from 3.55% to 4.39% for the CCB group and from 4.04% to 4.18% for the ACE inhibitor/ARB group (Supplemental Table 10). Weighted hazard ratios across all methods ranged from 0.83 to 1.10, which depicted the absence of a significant association between CCB use and increased VH risk. PS matching further confirmed the comparability of VH risk between CCB and ACE inhibitor/ARB users, with cumulative incidence rates at 5 years being 5.13% (95% CI, 3.13% to 7.09%) and 4.18% (95% CI, 2.26% to 6.06%), respectively (Supplemental Tables 11 and 12 and Supplemental Figure 15). After strictly excluding all patients with prior NSBB use, there were 1468 and 626 patients in the CCB and ACE inhibitor/ARB groups, respectively (Supplemental Figure 16). Using the same parameters as in the main analysis for weighting and achieving balance,

Table 2. Comparison of Number of Clinical Events and Long-Term Outcomes Between CCB and ACE Inhibitor/ARB Users

Characteristics	CCB user (n = 1468)	ACE inhibitor/ARB user (n = 626)	*P* value
Varices			
Events during drug using	238 (12.6)	124 (15.0)	.107
VH			
Events during drug using	65 (3.4)	35 (4.2)	.374
Crude incidence (per 1000 person-years)	7.42	10.50	.116
Other hepatic events			
Jaundice	14 (0.7)	4 (0.5)	.612
Ascites	735 (88.9)	92 (11.1)	.982
Spontaneous bacterial peritonitis	23 (1.2)	15 (1.8)	.301
Hepatic encephalopathy	143 (7.6)	63 (7.6)	1.000
Hepatorenal syndrome	20 (1.1)	5 (0.6)	.355
Long-term outcomes			
Death	348 (42.1)	748 (39.7)	.254
Liver-related death	248 (33.2)	112 (32.2)	.803
Liver transplantation	4 (0.2)	2 (0.2)	1.000
HCC	542 (28.7)	219 (26.5)	.247

NOTE. Values are n (%), unless otherwise indicated. These comparisons were based on counts without time-to-event analysis. VH incidence rates were comparable between CCB and ACE inhibitor/ARB users (7.42 vs 10.50 cases per 1000 person-years; $P = .116$).
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker; HCC, hepatocellular carcinoma; VH, variceal hemorrhage.

Table 3. Association Between CCB Use and Risk of VH

Treatment group	IPTW-weighted events	IPTW-weighted 5-y cumulative incidence (95% CI)	Absolute risk difference in 5-y cumulative incidence from ACE inhibitor/ARB (95% CI)	IPTW-weighted HR (95% CI)
All				
CCB	105/2784 (3.8)	3.74 (2.59–4.87)	–0.43 (–2.76 to 0.68)	0.91 (0.55–1.51)
ACE inhibitor/ARB	107/2667 (4.0)	4.17 (2.25–6.05)	0.00 (Reference)	1.00 (Reference)

NOTE. Values are n/n (%), unless otherwise indicated.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; VH, variceal hemorrhage.

no statistically significant difference between the 2 groups was observed in either the Fine-Gray model or the weighted Cox regression model (Supplemental Tables 13–16, Supplemental Figures 17 and 18).

Discussion

This territory-wide retrospective cohort study included 1886 CCB users and 827 ACE inhibitor/ARB users to evaluate the impact of these antihypertensive agents on the risk of VH in patients with cirrhosis and arterial hypertension. After IPTW adjustment, the incidence rates of VH were comparable between the CCB and ACE inhibitor/ARB groups (weighted event rates 3.8% vs 4.0%). The 5-year cumulative incidence was 3.74% in the CCB group and 4.17% in the ACE inhibitor/ARB group, resulting in an absolute risk difference of –0.43% (95% CI: –2.76% to 0.68%). Additionally, multivariable weighted Cox regression analysis and Fine-Gray competing risk models demonstrated no significant association between CCB use and an increased risk of VH. These findings support that CCBs have a neutral effect on VH risk in this population and provide reassurance regarding the safety of CCB use in patients with cirrhosis and hypertension.

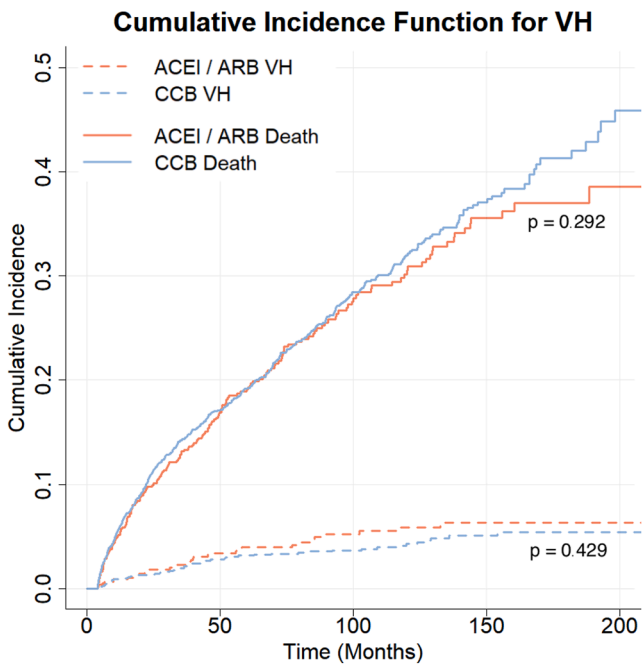

Figure 2. Cumulative incidence of variceal hemorrhage and death by treatment group cumulative incidence of variceal hemorrhage (*dashed lines*) and death (*solid lines*) for ACE inhibitor (ACEI)/ARB vs CCB users, accounting for competing risks. The *P* values indicate the statistical comparison between the groups ($P = .429$ for VH and $P = .292$ for death).

CCBs exert their vasodilatory effects by inhibiting voltage-dependent L-type calcium channels, reducing calcium ion influx into cells, and consequently lowering peripheral resistance and blood pressure.[18] Although the vasodilatory effects of CCBs could theoretically increase splanchnic blood flow, elevate portal pressure, and raise hydrostatic load-factors that may increase VH risk, these effects may be counterbalanced by the reduction in intrahepatic vascular resistance and improved intrahepatic blood flow, which can mitigate portal hypertension. Furthermore, the impact of CCBs on the gastrointestinal mucosa appears dual-faceted.[19] Moderate blood pressure reduction may relieve vascular stress, improve microcirculation, and reduce the risk of mucosal ischemia. Conversely, excessive blood pressure reduction could impair mucosal perfusion, weaken barrier function, and increase the risk of bleeding. This balance between risk and protection may partially explain the neutral effect of CCBs on VH risk observed in this study. Additionally, the primary target of CCBs is the arterial vessel wall, which is rich in smooth muscle, whereas their direct effects on the portal venous system are relatively weak.[20] The neutral effect of CCBs on VH incidence may reflect an adaptive response to these complex pathophysiological interactions.

Previous studies have shown contradictory results. In a study by Merkel et al[21] involving 8 patients with alcohol-associated liver disease, hemodynamic parameters were measured 10, 20, and 30 minutes after verapamil administration. While mean arterial pressure and systemic vascular resistance decreased significantly (–9% and –14%, respectively), there were no notable changes in wedged hepatic venous pressure or hepatic venous

Table 4. SHRs for Risk Factors Associated With Variceal Hemorrhage Using Fine and Gray's Competing Risks Regression Model

	Univariate analysis		Multivariable analysis	
Parameters	SHR (95% CI)	*P* value	Adjusted SHR (95% CI)	*P* value
Drug CCB (ACE inhibitor/ARB as reference)	0.799 (0.530–1.206)	.290	0.967 (0.616–1.518)	.880
Age	0.997 (0.979–1.015)	.710		
Male	0.997 (0.979–1.015)	.730		
Diabetes	2.071 (1.386–3.095)	<.001	1.972 (1.263–3.081)	.003
Cardiovascular disease	1.058 (0.601–1.862)	.850		
Chronic kidney disease	1.038 (0.385–2.794)	.940		
CP non class A (A as reference)	2.192 (1.462–3.285)	<.001	1.852 (1.185–2.896)	.007
Platelet	0.990 (0.986–0.994)	<.001	0.991 (0.987–0.995)	<.001
ALT	1.000 (0.998–1.002)	1.000		
INR	1.691 (1.087–2.631)	.020	0.469 (0.168–1.314)	.150
Creatinine	1.001 (0.999–1.002)	.460		
NSBB	1.768 (1.092–2.862)	.020	1.425 (0.863–2.352)	.170
Antiplatelet	0.687 (0.348–1.356)	.280		
OHA	1.951 (1.313–2.899)	<.001		
Insulin	0.938 (0.474–1.857)	.850		
Statin	0.520 (0.252–1.071)	.076	0.593 (0.282–1.243)	.170
Antiviral agents	0.686 (0.438–1.076)	.100	0.613 (0.390–0.962)	.033

NOTE. To avoid collinearity, laboratory variables that overlapped with components of the Child-Pugh classification were not included in this analysis.
ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker; CI, confidence interval; CP, Child-Pugh; INR, international normalized ratio; OHA, oral hypoglycemic agent; SHR, subdistribution hazard ratio.

pressure gradient (fluctuations not exceeding 0.2 kPa). Meanwhile, hepatic blood flow increased significantly by 12%, which partly supports the proposed pathophysiological mechanism behind the neutral effects of CCBs on VH. However, another study by Dinç et al[22] showed different results. They investigated the hemodynamic parameters of major vessels, including the portal vein and splenic vein, in 14 patients with posthepatic cirrhosis before and after oral administration of 80 mg verapamil using duplex Doppler ultrasound. The results showed that verapamil significantly dilated the portal vein and reduced intravascular resistance (with vessel diameter increasing by 8%, blood flow velocity and flow increasing by 20%, and resistance index decreasing by 17%), suggesting the feasibility of using verapamil to reduce the incidence of VH. However, Dinç et al also noted the lack of further clinical observations to support the reliability of their findings. In addition to VH, our study also found no significant difference in all-cause mortality between CCB and ACE inhibitor/ARB users among patients with cirrhosis. This is consistent with a recent large-scale study on patients with metabolic dysfunction–associated steatotic liver disease, which reported a survival benefit of ACE inhibitor/ARB over CCB in the overall population but not in the cirrhosis subgroup.[23] Moreover, that study also observed no significant difference in variceal bleeding risk (hazard ratio, 0.95; 95% CI, 0.48 to 1.89), further supporting our findings.

A clinical trial by Li et al[5] compared several CCBs in 321 cirrhotic patients with VH history from 23 hospitals. After 2 years of treatment, patients treated with tetrandrine were less likely to have recurrent gastrointestinal bleeding than those treated with nifedipine, verapamil, or cinnarizine. This suggests a potential benefit of CCBs for cirrhotic patients with esophageal varices. However, the study did not assess the impact of CCBs on patients without a history of variceal hemorrhage, who represent a more common subset of cirrhotic patients in clinical practice. Moreover, the observed benefit was limited to a single CCB subgroup, restricting the generalizability of these findings to all calcium-channel blockers. As a result, the overall effect remains uncertain. Another systematic review and meta-analysis on CCBs reported opposite findings: the study by He et al[24] found that CCB users had an increased risk of gastrointestinal bleeding compared with nonusers (relative risk, 1.17; 95% CI, 1.01 – 1.36). Subgroup analysis indicated that CCB use was associated

with a slightly higher risk of lower gastrointestinal bleeding (relative risk, 1.83; 95% CI, 1.17 – 2.84), but not upper gastrointestinal bleeding. However, this study did not differentiate between cirrhotic patients, and whether the findings are applicable to this high-risk population remains to be explored.

This study benefits from a large sample size and the use of hard clinical outcomes, enhancing the reliability of the results. Additionally, the CDARS database has been well validated in many of our previous studies, ensuring the robustness and accuracy of the data.[25,26] Incorporating multiple covariates with multiple sensitivity analyses to conclude a neutral effect of CCB use on VH risk reinforced the study's robustness. An active-comparator new-user design was applied to minimize confounding by indication and healthy user bias.[27] We also accounted for shorter life expectancy and higher mortality in vulnerable populations using landmark analysis and competing risk models. However, the study has limitations. First, all patients in our study had compensated cirrhosis, and thus caution is warranted when extrapolating our conclusions to patients with decompensated cirrhosis. Second, the retrospective design introduced the potential for variable coding times by different doctors. To mitigate this, we also used endoscopy records, which were updated in real time following endoscopy procedures, reducing the risk of coding delays. The study may also be influenced by biases, such as indication biases including the indication and optimization of NSBB treatment. To address this, we employed rigorous statistical methods, including the active comparator new-user design and PS weighting. The sensitivity analyses also consolidated our findings. Last, we were unable to compare dihydropyridine and nondihydropyridine CCBs due to the limited sample size and low event rate (only 41 [2.2%] patients took nondihydropyridine CCBs alone).

In conclusion, this study provides valuable evidence regarding the association between CCBs and the incidence of VH in patients with cirrhosis, offering insights into the potential risks and benefits of CCB use. While the findings suggest a neutral effect on the risk of VH associated with CCBs, we recommend that future research focuses on larger, prospective studies with more diverse cohorts to confirm these findings and explore the impact of different subgroups. Ultimately, these efforts will contribute to the development of more precise clinical guidelines and help optimize the safe use of antihypertensives in cirrhosis.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2025.11.010.

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Conflicts of interest

These authors disclose the following: Terry Cheuk-Fung Yip has served on the advisory committee for, as a speaker for, and received research grant support from Gilead Sciences. Grace Lai-Hung Wong has served on the advisory committee for AstraZeneca, Gilead Sciences, and Janssen; served as a speaker for Abbott, AbbVie, Ascletis, Bristol Myers Squibb, Echosens, Gilead Sciences, Janssen, and Roche; and received research grant support from Gilead Sciences. Vincent Wai-Sun Wong has served as a consultant or on the advisory committee for AbbVie, Boehringer Ingelheim, Echosens, Intercept, Inventiva, Novo Nordisk, Pfizer, and TARGET PharmaSolutions; has served as a speaker for Abbott, AbbVie, Gilead Sciences, and Novo Nordisk; has received research grant support from Gilead Sciences; and is a cofounder of Illuminatio Medical Technology Limited. Jimmy Che-To Lai has served as a speaker for Gilead Sciences and Abbott; and on the advisory board for Gilead Sciences and Boehringer Ingelheim. The remaining authors disclose no conflicts.

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