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Does Angiotensin-Converting Enzyme Inhibitor and β -Blocker Use Reduce the Risk of Primary Liver Cancer? A Case-Control Study Using the UK Clinical Practice Research Datalink

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Abstract

Study Objective—It has been suggested that use of the antihypertensive drugs, angiotensin-converting enzyme (ACE) inhibitors and β -blockers, may decrease the risk of primary liver cancer; thus, the objective of this study was to evaluate whether use of ACE inhibitors and/or β -blockers is associated with a lower risk of liver cancer.

Design—Nested case-control study.

Data Source—United Kingdom Clinical Practice Research Datalink.

Patients—We identified 490 cases with hypertension and a first-time (incident) diagnosis of primary liver cancer between 1988 and 2011. To account for an induction period, the index date was defined as the date of the first recorded liver cancer diagnosis minus one year. Controls were selected from patients with hypertension in the CPRD during the study period with a recorded diagnosis of hypertension who had no diagnosis of liver cancer and were free of any other cancer (except nonmelanoma skin cancer) prior to the index date; they were matched up to a 4:1 ratio to cases based on index date (same index date as that of their matched case), age (same year of birth), sex, general practice, and number of years of recorded history in the CPRD prior to the index date (1909 controls). Both cases and controls were required to have at least 2 years of recorded activity in the database before the index date.

Measurements and Main Results—Exposure was defined as receipt of two or more prescriptions for ACE inhibitors and/or β -blockers before the index date; the reference group was nonuse (0-1 prescription) of ACE or β -blocker prescriptions before the index date. We also examined the effect duration of use and, separately, the effect of individual drugs within each medication class on risk of liver cancer, and conducted analyses restricted to patients without liver disease or diabetes mellitus. Conditional logistic regression analysis was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs). No association was found between use of ACE inhibitors and/or β -blockers and the risk of liver cancer compared with nonuse (adjusted OR 1.14,

95% CI 0.85–1.55). No significant differences were noted in risk duration of use or by individual drugs, or after restricting the analyses to patients without diabetes or liver disease.

Conclusion—Use of ACE inhibitors and/or β -blockers was not associated with reduced risk of primary liver cancer compared with nonuse of these drugs in persons with hypertension.

Keywords

angiotensin-converting enzyme inhibitors; ACE inhibitors; β -blockers; antihypertensives; liver cancer

Introduction

Liver cancer is the sixth most frequently occurring cancer worldwide and the second most common cause of cancer mortality¹. Established risk factors for liver cancer include infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), excessive alcohol consumption, aflatoxin consumption, obesity, and diabetes mellitus^{2–3}. Studies have also indicated that hypertension may be a risk factor for liver cancer⁴. Evidence from experimental models has suggested that angiotensin-converting enzyme (ACE) inhibitors and β -blockers have antineoplastic (e.g., antiangiogenic, proapoptotic, and antiproliferative) properties^{5–8}. Despite promising laboratory findings, results from human studies of these drugs have been mixed^{9–11}. A review of secondary analyses of randomized clinical trials of both ACE inhibitors and β -blockers reported slight increases in risk of malignancy⁹, whereas observational studies have reported no association or decreases in cancer risk^{10–13}. Few studies have specifically evaluated the association between use of ACE inhibitors and/or β -blockers and the risk of liver cancer, and data from the studies that have are sparse and inconsistent^{10, 14–16}. Two small randomized controlled trials in patients with cirrhosis reported a lower frequency of hepatocellular carcinoma in the β -blocker-treated group than band ligation-treated groups^{17–18}; however, cancer incidence was not the main outcome under study. We also found no evidence of other antihypertensive medications being associated with the risk of liver cancer.

We conducted a nested case-control study using the United Kingdom (UK) Clinical Practice Research Datalink (CPRD) to evaluate whether use of ACE inhibitors and/or β -blockers lowers the risk of primary liver cancer. We restricted the study population to patients with hypertension to control for confounding by indication.

Methods

Data Source

This nested case-control study was conducted using data from the CPRD, a large, population-based, medical record database covering approximately 10 million people whose age and sex distributions are representative of the UK population¹⁹. The database includes demographic data, medical diagnoses, prescriptions, details of hospital stays, and deaths. Diagnoses, physical findings, symptoms, and administrative events such as referrals to specialists are recorded by using Read codes. Detailed information is available for all medications prescribed by the general practitioner. Several validation studies have been

published on the CPRD,^{20–22} which have indicated that the data are reasonably complete and accurate with regard to clinical diagnoses and that approximately 95% of all computer-identified primary cancer cases were confirmed as incident cancer²³.

Cases and Controls

The population from which cases and controls were selected was all persons present in the CPRD from 1988 through 2011 (end of data collection) who were between the ages of 18 and 90 years and had a recorded diagnosis of hypertension. Cases were persons with a first-time (incident) diagnosis of primary liver cancer. To account for an induction period, the index date was defined as the date of the first recorded liver cancer diagnosis minus one year. To be eligible, cases had to have at least 2 years of recorded activity in the database before the index date and a diagnosis of hypertension recorded at any time before the index date. Cases were excluded if they had a prior cancer diagnosis (except nonmelanoma skin cancer) or if they had a code for liver metastases at any time.

Controls were selected from persons in the study population (patients with hypertension) who had no diagnosis of liver cancer, matched up to a 4:1 ratio to cases based on index date (same index date as that of their matched case, which was defined as the case's liver cancer diagnosis date minus 1 year), age (same year of birth), sex, general practice, and number of years of recorded history in the CPRD prior to the index date. All controls were required to have a hypertension diagnosis recorded before the index date, to have at least 2 years of history in the database prior to the index date, and to be free of any cancer (except nonmelanoma skin cancer) prior to the index date.

Exposure Definition

To evaluate whether ACE inhibitors and β -blockers were protective against liver cancer, we assessed use of all antihypertensive medications before the index date among cases and controls. A patient was considered to be exposed if they had received two or more prescriptions for either an ACE inhibitor and/or a β -blocker before the index date, and the last prescription was received less than a year prior to the index date. Gaps in prescription coverage were allowed. We categorized exposure by type of antihypertensive medication received: both an ACE inhibitor and a β -blocker, an ACE inhibitor but no β -blocker, and a β -blocker but no ACE inhibitor. The reference group was nonuse of either ACE inhibitors or β -blockers, defined as receipt of 0 or 1 prescription for ACE inhibitors or β -blockers before the index date. We considered that one prescription would confer too little exposure to have an effect on cancer risk. Also, as these are prescriptions written by a general practitioner, patients who only receive one prescription may not have filled it at the pharmacy, whereas patients who receive more than one prescription are likely to have taken the medication. Patients in both the exposed and nonuse reference group may or may not have also received prescriptions for other antihypertensive medications.

Duration of use of ACE inhibitors or β -blockers, defined as the number of years between the first and last prescription received, was categorized as < 5 years, 5 years, and unknown duration (those who had antihypertensive prescriptions at the start of their record and had duration of use of < 5 years). Number of prescriptions received was categorized as 2–4, 5–9,

and 10 or more prescriptions. We also evaluated the effects of individual ACE inhibitors (enalapril, lisinopril, ramipril, or other ACE inhibitors) and β -blockers (atenolol, propranolol, bisoprolol fumarate, or other β -blockers).

Covariates

We assessed presence of known or suspected liver cancer risk factors in cases and controls prior to the index date, including diagnoses recorded in the patient's electronic medical record, identified by using Read codes, indicating history of alcohol abuse, infection with HBV and/or HCV, rare metabolic disorders (hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, porphyrias), liver disease, diabetes, use of statins and acetaminophen (paracetamol; defined as receipt of one or more prescriptions prior to the index date), body mass index (BMI), and smoking status. BMI and smoking status was determined based on the last record before the index date. Duration of hypertension was defined as the time from the first hypertension diagnosis through the index date, categorized 0-4 years, 5-9 years, 10 years, and unknown (those whose first hypertension diagnosis was recorded < 6 months after the start of their record and who had duration of hypertension of < 10 years).

Statistical Analyses

We conducted conditional logistical regression analyses using SAS statistical software, version 9.2 (SAS Institute, Inc., Cary, NC), to calculate crude and adjusted odd ratios (ORs) and 95% confidence intervals (CIs). Age, sex, calendar time, and general practice were controlled through matching. We adjusted for known or suspected liver cancer risk factors in the analyses (BMI, smoking status, alcohol abuse, HBV and/or HCV, rare metabolic disorders, liver disease, diabetes, and use of statins and acetaminophen), as well as duration of hypertension. Diabetes, an important risk factor for liver cancer, is a key mediator of the association between antihypertensive drugs and development of liver cancer. Confounding by indication or contraindication is a concern for some patients with hypertension who have diabetes or are at risk of diabetes since they should either be prescribed certain antihypertensive medications preferentially (e.g., ACE inhibitors prevent development of diabetes or diabetes-related complications²⁴) or not be prescribed some antihypertensive medications (e.g., β -blockers, which increase risk and complications of diabetes²⁵). To address this, we repeated the analysis restricted to cases and controls without diabetes. We also restricted the analysis to cases and controls without liver disease and repeated the analysis.

We conducted two stratified analyses to assess effect modification: by sex and by age group (< 60 and $\geq$ 60 years). We also conducted four sensitivity analyses. We first redefined the reference exposure restricted to patients who did not receive any prescriptions for either an ACE inhibitor or a β -blocker. The second sensitivity analysis assessed potential misclassification of liver cancer cases by restricting the analysis to cases with clinical codes that indicated either a diagnostic examination (liver biopsies), treatment (chemotherapy, radiotherapy, or surgery), palliative care, and/or referrals to specialty care, and their matched controls. The third and fourth sensitivity analyses evaluated the accuracy of the latency period: by using used an index date of 2 years prior to the case's date of liver cancer

diagnosis, and by using an index date equal to the case's liver cancer diagnosis date, rather than 1 year.

The protocol for this study was reviewed and approved by the Independent Scientific Advisory Committee of the CPRD.

Results

We identified 490 cases of liver cancer and 1909 matched controls among people with hypertension in the CPRD who met all eligibility criteria. The majority of the cases (434 [88.6%]) had clinical codes in their record that supported the presence of liver cancer, whereas 56 cases (11.4%) had no supporting clinical codes recorded because they either died shortly after their liver cancer diagnosis or had the cancer diagnosis recorded at the time of their death. Table 1 displays the characteristics of the cases and matched controls. Cases were more likely than controls to be obese; be current or former smokers; have alcohol-related disorders, HBV and/or HCV infection, liver disease, rare metabolic disorders, or diabetes; or have received prescriptions for acetaminophen. A higher proportion of cases (43.9%) had 10 or more years of hypertension history before the index date compared with 38.3% of controls.

Table 2 provides the ORs for liver cancer in users of ACE inhibitors and β -blockers compared with nonusers (reference group). The adjusted OR for use of ACE inhibitors or β -blockers was 1.14 (95% CI 0.85-1.55) compared with nonuse. When we analyzed type of antihypertensive medication prescribed, the adjusted OR for use of both ACE inhibitors and β -blockers was 1.27 (95% CI 0.88-1.82), whereas the adjusted OR for use of ACE inhibitors was 1.13 (95% CI 0.79-1.60) and for use of β -blockers was 1.08 (95% CI 0.75-1.55) compared with nonuse. There was no significant difference in risk when we further categorized type of antihypertensive by duration of use, or by individual ACE inhibitors and β -blockers. A similar proportion of patients in the exposed and nonuse categories had prescriptions for other antihypertensive drugs (85.2% of exposed patients compared with 79.3% of nonusers).

In the secondary analysis restricted to the population of 277 cases and 876 matched controls without diabetes (Table 3), the adjusted OR for use of ACE inhibitors or β -blockers was 1.21 (95% CI 0.84–1.74) compared with nonuse. When we evaluated exposure by type of antihypertensive medication prescribed, the adjusted ORs for use of ACE inhibitors was 0.96 (95% CI 0.60–1.53) and for use of β -blockers was 1.20 (95% CI 0.79–1.83) compared to nonuse, whereas the adjusted OR for use of both ACE inhibitors and β -blockers was elevated (OR 1.60, 95% CI 1.02–2.52).

In the analysis restricted to the population of 435 cases and 1693 matched controls without a diagnosis of liver disease, the adjusted OR for use of ACE inhibitors or β -blockers was 1.15 (95% CI 0.84–1.56) compared to nonuse (Table 4). When we evaluated type of antihypertensive medication prescribed, the adjusted OR for use of both ACE inhibitors and β -blockers was 1.25 (95% CI 0.87–1.80), whereas the adjusted OR for use of ACE inhibitors

was 1.13 (95% CI 0.79–1.62) and for use of β -blockers was 1.10 (95% CI 0.76–1.58) compared with nonuse.

The vast majority of cases were aged 60 years or older (88%) and 72% were male; no cases under age 35 years met our study criteria. Stratification by age yielded no differences in results. The results were also not materially different when stratified by sex (adjusted OR among males for use of ACE inhibitors or β -blockers was 1.03 [95% CI 0.71–1.49], whereas the adjusted OR was 1.40 [95% CI 0.81–2.42] for females).

We conducted four sensitivity analyses. In the first, we redefined our reference to the 74 cases and 368 controls who did not receive any prescriptions for either ACE inhibitors or β -blockers, and the results did not differ from the main analysis (adjusted OR 1.20, 95% CI 0.87–1.65). In the second sensitivity analysis restricted to the 434 cases with codes supporting the liver cancer diagnosis and their 1692 matched controls, the adjusted OR for use of ACE inhibitors or β -blockers was 1.04 (95% CI 0.75–1.44) compared with nonuse. When we analyzed type of antihypertensive medication prescribed, the adjusted OR for use of both ACE inhibitors and β -blockers was 1.14 (95% CI 0.78–1.68), whereas the adjusted OR for use of ACE inhibitors was 1.04 (95% CI 0.71–1.52) and for use of β -blockers was 0.97 (95% CI 0.66–1.43) compared with nonuse. The results were also similar to those of the full analysis when we changed the index date in the third and fourth sensitivity analyses to evaluate the appropriateness of the induction period window. When we moved the index date back to 2 years before the liver cancer diagnosis date, the adjusted OR for use of ACE inhibitors or β -blockers was 1.08 (95% CI 0.81–1.43) compared with nonuse. The results were not materially changed when we moved the index date to equal the case's liver cancer diagnosis date, thereby removing the induction period: adjusted OR 0.96 (95% CI 0.71–1.30).

Discussion

In this large, nested case-control study of liver cancer in persons with hypertension, use of ACE inhibitors and/or β -blockers was not associated with reduced risk of primary liver cancer in comparison to nonuse of these medications. Our study is the first to evaluate this association in a population of people with hypertension and to restrict the analysis to patients without liver disease or diabetes.

Two prior studies also reported on the association between ACE inhibitors and liver cancer. A cohort study conducted by Friis et al in Denmark, which compared the rates of cancer to expected rates in the general population, reported a nonsignificant decreased standardized incidence ratio (SIR) of 0.7 (95% CI 0.2–1.5) for liver cancer, based on five liver cancer cases.¹⁰ In a case-control study conducted using data from the GPRD (former version of the CPRD), Walker et al identified 224 cases of liver cancer diagnosed between 1987–2002, with 2313 matched controls, and reported an OR adjusted for alcohol use, smoking, cirrhosis, and liver disease of 1.29 (95% CI 0.88–1.88) for use of ACE inhibitors compared with nonuse of the drug, where exposure status was confined to the window of time between 24 and 12 months before the index date.¹⁴ Our findings for ACE inhibitors were similar to these findings; however, our analysis included more cases, considered patient's exposure during

the entire period before the index date, and made statistical adjustments for BMI, HBV and/or HCV, rare metabolic disorders, liver disease, statin and acetaminophen use, diabetes, and duration of hypertension in the analysis.

Similar to our findings with β -blockers, in a hospital-based study of patients with cirrhosis conducted by Kim et al, no significant difference was noted in the incidence of hepatocellular carcinoma between the 138 users of β -blockers and the 135 patients who did not use β -blockers (17.4% vs 17.0%, $p=0.938$) (median follow-up of 45 months).¹⁵ In contrast, Nkontchou et al conducted a cohort study of HCV-positive patients with cirrhosis who were attending a screening program for hepatocellular carcinoma and reported a hazard ratio of 0.31 (95% CI 0.12–0.83) for use of the β -blocker propranolol ($n=50$) compared to patients who received the alternative treatment of band ligation ($n=241$) (mean 54 months of follow-up).¹⁶ In their study, no significant differences in the rates of hepatocellular carcinoma were noted between propranolol-treated patients compared with those who did not receive propranolol for durations of use of less than 5 years; however, the 5-year incidence rates of hepatocellular carcinoma were 10% among propranolol-treated patients compared with 20% among those who did not receive propranolol treatment ($p=0.03$). Our findings did not support a reduction in risk of liver cancer with longer duration of β -blocker use. Prescribing bias may have accounted for the association observed in the Nkontchou et al study,¹⁶ as β -blockers are contraindicated for patients with diabetes, a strong risk factor for liver cancer; therefore, cirrhotic patients with diabetes, who are at a higher baseline risk for liver cancer, may have preferentially received the band ligation (the comparator treatment) over propranolol.

Our population-based study has a number of strengths. We used the CPRD, a large, longitudinal primary care database known for high accuracy of diagnoses and completeness of drug prescribing data. As all information on diseases and drug exposures is recorded in the absence of a study hypothesis, there is no risk of recall bias. The mean length of medical record before the index date, during which covariate and exposure information was assessed, was greater than 12 years for both cases and controls. We further controlled our analyses for a range of potential confounders, including duration of hypertension, BMI, smoking status, and liver cancer risk factors (alcohol abuse, HBV and/or HCV, chronic liver disease, statin and acetaminophen use). By excluding cases and controls who had less than 2 years of history in their medical record before the index date, we reduced the risk of including prevalent (preexisting), rather than incident, liver cancer cases. We also conducted separate analyses restricted to persons without diabetes and those without liver disease in attempt to address any mediating effect due to these precursor conditions of liver cancer. Finally, we also examined the independent effect of angiotensin II receptor blockers (ARBs) because of their potential inhibitory effect on tumor growth, and no additional protective effect of ARBs was noted in users of ACE inhibitors, β -blockers, or ACE inhibitors and β -blockers (data not shown).

Despite these strengths, there are limitations to consider. We may have missed some cases of liver cancer; however, it is unlikely that any missed cases would have had a differential use of antihypertensive medications, and thus it would not have affected our results. It is possible that some cases were secondary or metastatic liver cancers and not primary liver

cancers. To minimize misclassification, we excluded patients with any prior diagnosis of cancer (except nonmelanoma skin cancer) before the index date as well as patients whose clinical records indicated that their liver cancer diagnosis was a metastasis. The results were not materially different in the sensitivity analysis restricted to cases with supporting clinical codes in their records (88.6%) and their matched controls, which provides evidence that case misclassification did not impact our results and provides confidence in liver cancer diagnoses recorded in the CPRD. We restricted our study population to patients with a diagnosis of hypertension; thus, our study is only generalizable to these patients. The CPRD does not adequately capture information on race-ethnicity, so we were not able to evaluate differences due to race-ethnicity in this study. As the majority of UK residents are Caucasian, these results are mainly generalizable to Caucasians; thus, caution should be exercised when extrapolating the results to non-Caucasian populations. It is possible that we missed a history of viral hepatitis if the infection occurred before a patient registered with their current practice and it was not recorded by the general practitioner as a historical diagnosis. Thus, information on history of viral hepatitis status may be incomplete, which would result in an underascertainment of the number of patients with these risk factors in the analysis, although it is unlikely that this would differentially affect the results. It is also possible that we missed history of alcohol abuse if it was not recorded by the general practitioner, but this is also unlikely to differentially affect the results. Finally, there were a limited number of exposed patients in this study, and therefore the results should be interpreted with caution. However, it is important to note that the CPRD is one of the few data sources in the world in which 490 liver cancer cases with hypertension could be identified, the largest number studied to date.

Conclusion

These data suggest that use of ACE inhibitors and/or β -blockers was not associated with reduced risk of primary liver cancer compared with nonuse of these drugs in persons with hypertension.

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TABLE 1

Characteristics of Cases and Controls and Univariable Effects in Relation to Liver Cancer

Characteristic	No. (%) of Cases (n=490)	No. (%) of Controls (n=1909)	Univariable OR ^a (95% CI)
Index year			
1991–1994	17 (3.5)	67 (3.5)	†
1995–1999	37 (7.5)	141 (7.4)	†
2000–2004	106 (21.6)	415 (21.7)	†
2005–2010	330 (67.4)	1286 (67.4)	†
Age at index date (yrs)			
< 50	9 (1.8)	35 (1.8)	†
50 – 59	50 (10.2)	192 (10.1)	†
60 – 69	142 (29.0)	548 (28.7)	†
70 – 79	204 (41.6)	803 (42.1)	†
80 – 89	85 (17.4)	331 (17.3)	†
Mean ± SD age	70.9 ± 9.0	70.9 ± 8.9	†
Sex			
Male	354 (72.2)	1383 (72.4)	†
Female	136 (27.8)	526 (27.6)	†
Length of Medical Record Before Index Date (yrs)			
Mean ± SD	12.1 ± 5.3	12.2 ± 5.2	†
Median (Interquartile Range)	12.8 (7.8–16.4)	12.8 (7.8–16.6)	†
BMI category			
< 18.5 (Underweight)	6 (1.2)	19 (1.0)	1.67 (0.64–4.35)
18.5 – 24.9 (Normal)	90 (18.4)	475 (24.9)	1.0 (Reference)
25 – 29.9 (Overweight)	163 (33.3)	726 (38.0)	1.20 (0.90–1.59)
30 (Obese)	185 (37.8)	491 (25.7)	2.02 (1.52–2.69)
Unknown	46 (9.4)	198 (10.4)	1.17 (0.77–1.79)
Mean ± SD	29.1 ± 5.3	28.0 ± 5.2	—
Smoking status			
Nonsmoker	148 (30.2)	799 (41.9)	1.0 (Reference)
Smoker	98 (20.0)	265 (13.9)	2.07 (1.53–2.80)
Ex-smoker	226 (46.1)	764 (40.0)	1.68 (1.32–2.13)
Unknown	18 (3.7)	81 (4.2)	1.18 (0.63–2.20)
Alcoholism	75 (15.3)	99 (5.2)	3.51 (2.51–4.92)
Hepatitis B or C	19 (3.9)	0 (0.0)	**
Liver Disease	55 (11.2)	5 (0.3)	42.13 (16.86–105.29)
Rare Metabolic Disorder	10 (2.0)	3 (0.2)	12.53 (3.44–45.59)
Acetaminophen Use	352 (71.8)	1205 (63.1)	1.58 (1.25–2.00)
Diabetes mellitus	213 (43.5)	372 (19.5)	3.26 (2.62–4.05)

Characteristic	No. (%) of Cases (n=490)	No. (%) of Controls (n=1909)	Univariable OR ^a (95% CI)
Length of Hypertension History (yrs)			
0–4	138 (28.2)	601 (31.5)	1.0 (Reference)
5–9	115 (23.5)	483 (25.3)	1.05 (0.79–1.39)
10	215 (43.9)	731 (38.3)	1.31 (1.02–1.68)
Unknown	22 (4.5)	94 (4.9)	0.99 (0.59–1.65)
Mean ± SD	11.0 ± 8.5	9.7 ± 8.1	—

OR = odds ratio; CI = confidence interval; BMI = body mass index.

^{**} There were too few cases/controls to make meaningful comparisons.

[†] Matching variables.

^a Conditional on matching variables.

TABLE 2

Odds Ratios for Liver Cancer in Users of ACE Inhibitors and β -Blockers

	No. (%) of Cases (n=490)	No. (%) of Controls (n=1909)	Crude OR ^a (95% CI)	Adjusted OR ^b (95% CI)
Exposure				
Nonuse (0–1 prescription of ACE inhibitor or β -blocker)	89 (18.2)	428 (22.4)	1.0 (Reference)	1.0 (Reference)
Exposed (≥ 2 prescriptions of ACE inhibitor or β -blocker)	401 (81.8)	1481 (77.6)	1.34 (1.03–1.75)	1.14 (0.85–1.55)
Type of Antihypertensive				
Unexposed (0–1 ACE Inhibitor or β -blocker)	89 (18.2)	428 (22.4)	1.0 (Reference)	1.0 (Reference)
ACE inhibitor + β -blocker (≥ 2 prescriptions)	176 (35.9)	574 (30.1)	1.60 (1.18–2.18)	1.27 (0.88–1.82)
ACE inhibitor (No β -blocker) (≥ 2 prescriptions)	124 (25.3)	483 (25.3)	1.30 (0.95–1.77)	1.13 (0.79–1.60)
β -Blocker (No ACE inhibitor) (≥ 2 prescriptions)	101 (20.6)	424 (22.2)	1.17 (0.85–1.61)	1.08 (0.75–1.55)
Type and Duration of Use				
Nonuse (0–1 ACE inhibitor or β -blocker)	89 (18.2)	428 (22.4)	1.0 (Reference)	1.0 (Reference)
ACE inhibitor + β -blocker (≥ 2 prescriptions)				
< 5 years	28 (5.7)	104 (5.5)	1.32 (0.81–2.15)	1.03 (0.59–1.83)
2–4 prescriptions	0 (0.0)	0 (0.0)	†	†
5–9 prescriptions	1 (0.2)	9 (0.5)	0.56 (0.07–4.49)	0.33 (0.03–3.21)
10 prescriptions	27 (5.5)	95 (5.0)	1.38 (0.84–2.26)	1.12 (0.62–2.01)
5 years	141 (28.8)	440 (23.1)	1.65 (1.18–2.29)	1.29 (0.87–1.93)
2–4 prescriptions	0 (0.0)	0 (0.0)	†	†
5–9 prescriptions	1 (0.2)	5 (0.3)	†	†
10 prescriptions	140 (28.6)	435 (22.8)	1.65 (1.19–2.30)	1.29 (0.86–1.92)
Unknown Duration	7 (1.4)	30 (1.6)	1.27 (0.50–3.22)	0.87 (0.28–2.76)
ACE inhibitor (No β -blocker) (≥ 2 prescriptions)				
< 5 years	60 (12.2)	292 (15.3)	1.02 (0.71–1.48)	0.88 (0.58–1.33)
2–4 prescriptions	13 (2.7)	43 (2.3)	1.50 (0.77–2.94)	1.38 (0.63–3.02)
5–9 prescriptions	12 (2.5)	50 (2.6)	1.24 (0.63–2.43)	1.12 (0.54–2.33)
10 prescriptions	35 (7.1)	199 (10.4)	0.86 (0.55–1.33)	0.71 (0.43–1.17)
5 years	45 (9.2)	153 (8.0)	1.46 (0.97–2.22)	1.16 (0.71–1.89)
2–4 prescriptions	1 (0.2)	1 (0.1)	†	†
5–9 prescriptions	0 (0.0)	1 (0.1)	†	†
10 prescriptions	44 (9.0)	151 (7.9)	1.46 (0.96–2.22)	1.17 (0.72–1.92)
Unknown Duration	19 (3.9)	38 (2.0)	2.50 (1.32–4.74)	2.78 (1.37–5.66)
β -Blocker (No ACE inhibitor) (≥ 2 prescriptions)				
< 5 years	33 (6.7)	135 (7.1)	1.17 (0.75–1.84)	1.09 (0.65–1.85)
2–4 prescriptions	7 (1.4)	29 (1.5)	1.15 (0.48–2.77)	0.74 (0.25–2.20)
5–9 prescriptions	4 (0.8)	24 (1.3)	0.81 (0.27–2.39)	1.29 (0.41–4.08)

	No. (%) of Cases (n=490)	No. (%) of Controls (n=1909)	Crude OR ^a (95% CI)	Adjusted OR ^b (95% CI)
10 prescriptions	22 (4.5)	82 (4.3)	1.28 (0.75–2.17)	1.20 (0.64–2.24)
5 years	50 (10.2)	233 (12.2)	1.04 (0.70–1.53)	0.90 (0.58–1.42)
2–4 prescriptions	0 (0.0)	6 (0.3)	[†]	[†]
5–9 prescriptions	50 (10.2)	227 (11.9)	1.06 (0.72–1.57)	0.92 (0.58–1.44)
10 prescriptions	18 (3.7)	56 (2.9)	1.63 (0.85–3.15)	1.77 (0.86–3.67)
Unknown Duration	18 (3.7)	56 (2.9)	1.68 (0.87–3.25)	1.80 (0.87–3.73)
Individual ACE inhibitor^{**}				
Nonuse (0–1 prescription of ACE inhibitor or β -blocker)	89 (18.2)	428 (22.4)	1.0 (Reference)	1.0 (Reference)
Enalapril (2 prescriptions)	57 (11.6)	166 (8.7)	1.54 (0.90–2.62)	0.99 (0.48–2.02)
Lisinopril (2 prescriptions)	98 (20.0)	376 (19.7)	1.25 (0.80–1.94)	0.98 (0.55–1.73)
Ramipril (2 prescriptions)	105 (21.5)	399 (20.9)	1.05 (0.65–1.68)	0.63 (0.34–1.21)
Other ACE inhibitors (2 prescriptions)	85 (48.9)	268 (38.5)	1.46 (0.92–2.31)	1.42 (0.81–2.49)
Individual β-blocker^{**}				
Nonuse (0–1 prescription of ACE inhibitor or β -blocker)	89 (18.2)	428 (22.4)	1.0 (Reference)	1.0 (Reference)
Atenolol (2 prescriptions)	201 (41.0)	789 (41.3)	1.23 (0.90–1.69)	1.21 (0.83–1.76)
Propranolol (2 prescriptions)	50 (10.2)	92 (4.8)	3.08 (1.57–6.03)	1.27 (0.53–3.06)
Bisoprolol Fumarate (2 prescriptions)	53 (10.8)	172 (9.0)	1.49 (0.76–2.95)	0.82 (0.34–1.97)
Other β -blockers (2 prescriptions)	36 (7.3)	121 (6.3)	0.97 (0.50–1.90)	0.55 (0.21–1.41)

^a Conditional on matching variables.

^b Adjusted for body mass index, smoking, alcohol-related disorders, statin, other antihypertensive medications, and acetaminophen use, rare metabolic disorders, liver disease, diabetes, and duration of hypertension, conditional on matching variables.

^{**} Some persons received prescriptions for more than 1 individual drug and therefore were counted more than once.

[†] There were too few cases/controls to make meaningful comparisons

TABLE 3

Odds Ratios for Liver Cancer in Users of ACE Inhibitors and β -Blockers, Restricted to Cases and Controls without Diabetes Mellitus

Variable	No. (%) of Cases (n=277)	No. (%) of Controls (n=876)	Crude OR ^a (95% CI)	Adjusted OR ^b (95% CI)
Exposure				
Nonuse (0–1 prescription of ACE inhibitor or β -blocker)	69 (24.9)	239 (27.3)	1.0 (Reference)	1.0 (Reference)
Exposed (≥ 2 prescriptions of ACE inhibitor or β -blocker)	208 (75.1)	637 (72.7)	1.09 (0.79–1.52)	1.21 (0.84–1.74)
Type of Antihypertensive				
Nonuse (0–1 prescription of ACE inhibitor or β -blocker)	69 (24.9)	239 (27.3)	1.0 (Reference)	1.0 (Reference)
ACE inhibitor + β -blocker (≥ 2 prescriptions)	85 (30.7)	216 (24.7)	1.33 (0.89–1.99)	1.60 (1.02–2.52)
ACE inhibitor (No β -blocker) (≥ 2 prescriptions)	48 (17.3)	193 (22.0)	0.84 (0.55–1.29)	0.96 (0.60–1.53)
β -Blocker (No ACE inhibitor) (≥ 2 prescriptions)	75 (27.1)	228 (26.0)	1.13 (0.77–1.65)	1.20 (0.79–1.83)

OR = odds ratio; CI = confidence interval; ACE = angiotensin-converting enzyme.

^aConditional on matching variables.

^bAdjusted for body mass index, smoking, alcohol-related disorders, other antihypertensive medications, statin and acetaminophen use, rare metabolic disorders, liver disease, and duration of hypertension, conditional on matching variables.

TABLE 4

Odds Ratios for Liver Cancer in Users of ACE Inhibitors and β -Blockers, Restricted to Cases and Controls without Liver Disease

Variable	No. (%) of Cases (n=435)	No. (%) of Controls (n=1693)	Crude OR ^a (95% CI)	Adjusted OR ^b (95% CI)
Exposure				
Nonuse (0–1 prescription of ACE inhibitor or β -blocker)	80 (18.4)	378 (22.3)	1.0 (Reference)	1.0 (Reference)
Exposed (≥ 2 prescriptions of ACE inhibitor or β -blocker)	355 (81.6)	1315 (77.7)	1.31 (0.99–1.74)	1.15 (0.84–1.56)
Type of Antihypertensive				
Nonuse (0–1 prescription of ACE inhibitor or β -blocker)	80 (18.4)	378 (22.3)	1.0 (Reference)	1.0 (Reference)
ACE inhibitor + β -blocker (≥ 2 prescriptions)	157 (36.1)	523 (30.9)	1.54 (1.11–2.13)	1.25 (0.87–1.80)
ACE inhibitor (No β -Blocker) (≥ 2 prescriptions)	112 (25.8)	408 (24.1)	1.37 (0.98–1.90)	1.13 (0.79–1.62)
β -Blocker (No ACE inhibitor) (≥ 2 prescriptions)	86 (19.8)	384 (22.7)	1.08 (0.77–1.52)	1.10 (0.76–1.58)

OR = odds ratio; CI = confidence interval; ACE = angiotensin-converting enzyme.

^aConditional on matching variables.

^bAdjusted for body mass index, smoking, alcohol-related disorders, statin, other antihypertensive medications, and acetaminophen use, rare metabolic disorders, diabetes, and duration of hypertension, conditional on matching variables.