

ORIGINAL ARTICLE

Association of Aspirin with Hepatocellular Carcinoma and Liver-Related Mortality

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ABSTRACT

BACKGROUND

More information is needed about the long-term effects of low-dose aspirin (≤ 160 mg) on incident hepatocellular carcinoma, liver-related mortality, and gastrointestinal bleeding in persons with chronic hepatitis B or hepatitis C virus infection.

METHODS

Using nationwide Swedish registries, we identified all adults who received a diagnosis of chronic hepatitis B or hepatitis C from 2005 through 2015 and who did not have a history of aspirin use (50,275 patients). Patients who were starting to take low-dose aspirin (14,205 patients) were identified by their first filled prescriptions for 90 or more consecutive doses of aspirin. We constructed a propensity score and applied inverse probability of treatment weighting to balance baseline characteristics between groups. Using Cox proportional-hazards regression modeling, we estimated the risk of hepatocellular carcinoma and liver-related mortality, accounting for competing events.

RESULTS

With a median of 7.9 years of follow-up, the estimated cumulative incidence of hepatocellular carcinoma was 4.0% among aspirin users and 8.3% among nonusers of aspirin (difference, -4.3 percentage points; 95% confidence interval [CI], -5.0 to -3.6 ; adjusted hazard ratio, 0.69; 95% CI, 0.62 to 0.76). This inverse association appeared to be duration-dependent; as compared with short-term use (3 months to <1 year), the adjusted hazard ratios were 0.90 (95% CI, 0.76 to 1.06) for 1 to less than 3 years of use, 0.66 (95% CI, 0.56 to 0.78) for 3 to less than 5 years of use, and 0.57 (95% CI, 0.42 to 0.70) for 5 or more years of use. Ten-year liver-related mortality was 11.0% among aspirin users and 17.9% among nonusers (difference, -6.9 percentage points [95% CI, -8.1 to -5.7]; adjusted hazard ratio, 0.73 [95% CI, 0.67 to 0.81]). However, the 10-year risk of gastrointestinal bleeding did not differ significantly between users and nonusers of aspirin (7.8% and 6.9%, respectively; difference, 0.9 percentage points; 95% CI, -0.6 to 2.4).

CONCLUSIONS

In a nationwide study of patients with chronic viral hepatitis in Sweden, use of low-dose aspirin was associated with a significantly lower risk of hepatocellular carcinoma and lower liver-related mortality than no use of aspirin, without a significantly higher risk of gastrointestinal bleeding. (Funded by the National Institutes of Health and others.)

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WORLDWIDE, MORE THAN 500,000 cases of incident hepatocellular carcinoma are diagnosed each year,¹ related primarily to chronic infection with hepatitis B or hepatitis C virus.² Since the 1990s, the incidences of cirrhosis and hepatocellular carcinoma have increased dramatically in the United States and Europe, and mortality from hepatocellular carcinoma is increasing faster than that from any other cancer.^{1,3} Although the incidences of hepatocellular carcinoma and liver-related death are reduced with hepatitis B viral suppression or hepatitis C eradication, they nonetheless persist in high-risk patients, including those with advanced fibrosis.² Thus, an urgent need remains to develop effective strategies to prevent hepatocellular carcinoma and reduce mortality from cirrhosis.

Experimental⁴⁻⁸ and clinical⁹⁻¹² data suggest that aspirin may prevent progression of liver disease and hepatocarcinogenesis through diverse potential mechanisms including prevention of platelet degranulation, modulation of bioactive lipids, and inhibition of the proinflammatory cyclooxygenase-2 (COX-2) enzyme.⁴⁻⁸ However, epidemiologic data from the United States and Europe remain limited. Three prior observational studies of this issue lacked detailed data regarding key determinants of hepatic outcomes, including underlying viral hepatitis, cirrhosis, and use of antiviral medication.⁹⁻¹¹ Moreover, information about aspirin-related bleeding events from an unselected population of patients with established chronic viral hepatitis would be valuable.

We examined the use of low-dose aspirin (≤ 160 mg) in relation to incident hepatocellular carcinoma, liver-related mortality, and gastrointestinal bleeding among Swedish adults with confirmed chronic hepatitis B or hepatitis C infection. This nationwide population with well-validated and prospectively updated data permits a more comprehensive examination of the potential benefits and risks of aspirin in patients with chronic viral hepatitis.

METHODS

DATA SOURCES

The nationwide Swedish Register for Surveillance of Communicable Diseases maintains a validated database of all cases of acute and chronic hepatitis B (since 1967) and hepatitis C (since 1990)

infection.¹³ Cases are confirmed by both clinicians and serologic testing (i.e., testing for hepatitis B surface antigen and hepatitis B DNA and for hepatitis C virus antibodies and hepatitis C RNA).¹³ Using the unique personal identity number assigned to all Swedish residents, we linked this database to additional validated registries: the Patient Register, Cause of Death Register, Cancer Register, and Prescribed Drug Register. The Patient Register contains prospectively updated data regarding hospitalizations (including liver transplantations), discharge diagnoses (since 1964), and specialty outpatient care (since 2001). Diagnoses are recorded with codes from the International Classification of Diseases (ICD), which have positive predictive values of 85 to 95%.¹⁴ This study was approved by the regional ethics review board in Stockholm.

POPULATION

We identified all adults 18 years of age or older in Sweden with confirmed chronic hepatitis B or hepatitis C monoinfection who began taking low-dose aspirin between July 1, 2005, and December 31, 2013, and for whom follow-up data were available from Statistics Sweden and the National Board of Health and Welfare through December 31, 2015. (Additional information about the patients, data sources, outcome measures, covariates, development of the propensity score model, and sensitivity analyses is provided in the Supplementary Appendix text and Fig. S1A and S1B, available with the full text of this article at NEJM.org.) To ensure a new-user design,¹⁵ patients who initiated aspirin had to complete an entry period of at least 180 days between the date they were notified of their hepatitis B or hepatitis C diagnosis and the date of their first filled prescription for aspirin (the index date). Nonusers similarly were required to complete the same 180-day entry period without any filled aspirin prescriptions.¹⁶ We excluded from the study any patients who had received a previous diagnosis of human immunodeficiency virus (4334 patients) or hepatocellular carcinoma (338 patients) or who filled prescriptions for aspirin or other antiplatelet agents before the end of the 180-day entry period (1112 patients).¹⁷

ASPIRIN EXPOSURE

The Prescribed Drug Register prospectively records, with high validity, accuracy, and complete-

ness, all prescriptions dispensed from Swedish pharmacies (since July 1, 2005).¹⁸ In Sweden, low-dose aspirin (75 mg or 160 mg), rather than higher-dose aspirin, is recommended for primary cardiovascular prevention or secondary risk reduction; low-dose aspirin is available only by prescription and cannot be purchased over the counter. Accordingly, prescription low-dose aspirin constitutes more than 95% of all aspirin used in Sweden, whereas less than 1% is obtained over the counter (at any dose) and 4% is received in acute-care settings.^{18,19} Prescriptions for low-dose aspirin are recorded by Anatomical Therapeutic Chemical (ATC) code B01AC06, with the date, number of pills, and defined daily dose (a measure of the average daily consumption of a prescribed medication). (Additional information about exposures and covariates is available in Table S1.) One defined daily dose of aspirin equals 1 tablet (i.e., 75 mg or 160 mg). The cumulative dose and duration (termed the cumulative defined daily dose) can be calculated by summing the defined daily doses over monthly intervals.^{17,20}

We identified 17,592 new aspirin users at the index date. To reduce misclassification, we further selected 14,205 new aspirin users who filled a prescription for 90 or more consecutive cumulative defined daily doses after the index date without receiving other antiplatelet therapy. Similarly, we identified 37,784 nonusers at the end of the 180-day entry period and then further excluded anyone who used aspirin or another antiplatelet agent during the subsequent 90 days (1714 patients), resulting in 36,070 nonusers at the study baseline.

Our primary analysis applied an intention-to-treat design, with aspirin use defined by 90 or more consecutive cumulative defined daily doses after the index date. In further analyses, we modeled aspirin use as a time-varying exposure. To assess duration, we summed the duration of all filled prescriptions (in months), and updated these data at each monthly interval of follow-up. Furthermore, we identified 11,932 consistent aspirin users (i.e., ≥ 290 consecutive cumulative defined daily doses filled within 1 year after the first prescription), and compared outcomes between persons who subsequently continued aspirin beyond 1 year and persons who discontinued aspirin after 1 year.²¹ We selected 290 cumulative

defined daily doses because this number corresponds to 1 year of daily use with 80% or greater adherence, which in turn correlates with long-term consistent use.^{21,22} In addition, we compared outcomes for consistent users ($\geq 80\%$ adherence) with those for inconsistent users ($< 80\%$ adherence).

OUTCOMES

The two primary outcomes were incident hepatocellular carcinoma and liver-related mortality, ascertained from the Cancer and Cause of Death registries.^{23,24} The Cancer Register contains data on more than 96% of incident cancers,²³ with hepatocellular carcinoma cases confirmed by specialists with established pathological or radiographic criteria. The Cause of Death Register is more than 99% complete, and liver-related mortality, gastrointestinal bleeding, and major gastrointestinal bleeding were defined by their primary ICD codes.

STATISTICAL ANALYSIS

Using a propensity score approach, we applied inverse probability of treatment weighting to balance baseline characteristics between exposure groups. Each observation was weighted by the inverse of the probability of a patient receiving aspirin, given observed confounders identified to the index date. This approach created a pseudopopulation in which the exposure was independent of measured confounders.²⁵ Weights were derived to obtain estimates representing population-average treatment effects, with optimal balance between groups. The two primary prespecified analyses focused on aspirin use in relation to the risk of incident hepatocellular carcinoma and liver-related mortality.

Follow-up began at baseline and continued to the date of incident hepatocellular carcinoma, a competing event, or December 31, 2015, whichever occurred first. For analyses of hepatocellular carcinoma, competing events included death, liver transplantation, and emigration; for liver-related mortality, they included death from another cause, liver transplantation, and emigration (Table S3). Using Cox proportional-hazards regression models adjusted for inverse probability of treatment weighting, we estimated cumulative incidence, absolute risk differences, and adjusted subhazard ratios,²⁶ which specifically

estimate the effect of covariates on the cumulative incidence function while accounting for competing risks. The multivariable-adjusted model included 14 prespecified prognostic covariates. Combining outcome regression after propensity score weighting is called “doubly robust” estimation²⁷ and produces effect estimates robust to potential misspecification of the model based on inverse probability of treatment weighting or the regression model. We also repeated the analyses after censoring data from persons who subsequently initiated another antiplatelet agent. We observed no heterogeneity between the hepatitis B cohort and the hepatitis C cohort regarding aspirin use and risk of hepatocellular carcinoma or liver-related mortality ($P=0.40$ and $P=0.27$, respectively, for heterogeneity); therefore, data for these cohorts were pooled. Schoenfeld residual tests identified no violations of the proportional-hazards assumption.

We assessed whether the associations varied by prespecified risk factors. We evaluated the relationship between duration of aspirin use and outcomes using time-varying aspirin exposures. We also examined the influence of subsequent discontinuation of aspirin on study outcomes among 11,932 consistent aspirin users in whom follow-up started 1 year after the first prescription.^{11,21,28}

We conducted several sensitivity analyses. First, we limited the analysis to 10,946 persons with detailed data regarding underlying severity of liver disease; second, we excluded any person with a history of alcohol abuse; third, we repeated our analysis without inverse probability of treatment weighting, without competing risks, and with gastrointestinal bleeding as a competing risk; fourth, we excluded hepatocellular carcinoma diagnosed within 4 years after the baseline date, to minimize reverse causation¹¹; fifth, we applied an alternative 1:1 propensity score–matched design²⁹; and sixth, we evaluated alternative end points, including incident liver decompensation,³⁰ all-cause mortality, and a negative control outcome (incident diabetes). We conducted exploratory analyses focused on non-aspirin antiplatelet agents. Finally, we estimated the potential effect of unobserved confounders, using an array-approach analysis.³¹ Two-tailed P values are reported for analyses of the two primary outcome measures, with $P<0.025$ considered to indicate statistical significance. For

all other analyses, 95% confidence intervals are reported without P values; confidence intervals have not been adjusted for multiplicity. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute).

RESULTS

STUDY POPULATION

The study population consisted of 50,275 adults (13,276 with hepatitis B and 36,999 with hepatitis C), including 14,205 aspirin users and 36,070 nonusers (Table 1). After adjustment for inverse probability of treatment weighting, all covariates were well balanced (i.e., standardized mean differences were <0.1).³² Among aspirin users, 7955 (56%) had coronary artery disease and 12,358 (87%) had at least one cardiovascular risk factor (i.e., diabetes, dyslipidemia, obesity, or hypertension); 11,932 (84%) filled prescriptions for 290 or more consecutive cumulative defined daily doses after the initial prescription. Follow-up was similar in the two groups (median, 7.9 years; range, 2.0 to 9.8). Overall, we recorded 1612 incident cases of hepatocellular carcinoma and 5017 liver-related deaths.

HEPATOCELLULAR CARCINOMA

The 10-year cumulative incidence of hepatocellular carcinoma was 4.0% (95% confidence interval [CI], 3.6 to 4.4) among aspirin users and 8.3% (95% CI, 8.1 to 8.5) among nonusers (a difference of -4.3 percentage points; 95% CI, -5.0 to -3.6 ; $P<0.001$) (Fig. 1 and Table 2). Aspirin users had a 31% lower risk of hepatocellular carcinoma than nonusers after multivariable adjustment (adjusted subhazard ratio, 0.69; 95% CI, 0.62 to 0.76). The results were similar after data from patients who subsequently initiated another antiplatelet agent were censored (adjusted subhazard ratio, 0.65; 95% CI, 0.59 to 0.71), and they were consistent across all prespecified subgroups (Table S4).

LIVER-RELATED MORTALITY

The 10-year liver-related mortality was 11.0% (95% CI, 10.8 to 11.2) among aspirin users and 17.9% (95% CI, 17.8 to 18.0) among nonusers (risk difference, -6.9 percentage points; 95% CI, -8.1 to -5.7 ; $P<0.001$) (Table 2 and Fig. 2). Aspirin users had a 27% lower adjusted risk of liver-

Table 1. Characteristics of the Pooled Study Population of 50,275 Persons, According to Aspirin-Use Status.*

Characteristic (%)†	No Aspirin Use (N=36,070)	Aspirin Use (N=14,205)	Standardized Mean Difference before IPTW	Standardized Mean Difference after IPTW
Type of chronic viral hepatitis — no. (%)‡			0.41	0.0007
HBV	10,278 (28.5)	2,998 (21.1)		
HCV	25,792 (71.5)	11,207 (78.9)		
Age at notification of HBV or HCV infection — yr	39.6±13.5	50.5±13.0	0.45	0.004
Female sex — no. (%)	12,949 (35.9)	4,034 (28.4)	0.39	0.002
Compensated cirrhosis — no. (%)	3,959 (11.0)	1,535 (10.8)	0.06	0.0001
Decompensated cirrhosis — no. (%)	1,162 (3.2)	397 (2.8)	0.19	0.005
Diabetes — no. (%)	3,246 (9.0)	3,864 (27.2)	0.63	−0.0003
Hypertension — no. (%)	3,896 (10.8)	5,497 (38.7)	0.55	0.001
Obesity — no. (%)	1,767 (4.9)	2,585 (18.2)	0.26	−0.0002
Coronary artery disease — no. (%)	3,102 (8.6)	7,955 (56.0)	0.88	−0.006
Cardiac arrhythmia — no. (%)	902 (2.5)	1,492 (10.5)	0.67	0.0001
Vascular disease — no. (%)	613 (1.7)	1,179 (8.3)	0.35	0.005
Congestive heart failure — no. (%)	794 (2.2)	1,974 (13.9)	0.40	0.008
Alcohol abuse — no. (%)	6,276 (17.4)	1,705 (12.0)	0.38	0.003
Metformin use — no. (%)	2,272 (6.3)	3,054 (21.5)	0.44	−0.0006
Insulin use — no. (%)	1,226 (3.4)	1,108 (7.8)	0.21	−0.0001
Statin use — no. (%)	3,463 (9.6)	7,443 (52.4)	0.78	−0.009
ACE inhibitor use — no. (%)	3,282 (9.1)	5,952 (41.9)	0.52	0.0005
Nonaspirin NSAID — no. (%)§	6,673 (18.5)	3,082 (21.7)	0.19	0.0002
Anti-HBV therapy — no./total no. with HBV (%)¶	919/10,278 (8.9)	386/2,998 (12.9)	0.27	0.0001
Anti-HCV therapy — no./total no. with HCV (%)¶	5,882/25,792 (22.8)	1,718/11,207 (15.3)	0.33	0.0008

* Aspirin use was identified by the validated Anatomic Therapeutic Chemical code B01AC06 and defined as a filled prescription for 90 or more consecutive cumulative defined daily doses after the index date (the date on which a patient filled the first aspirin prescription after an 180-day entry period). Nonuse was defined as fewer than 90 cumulative defined daily doses — or no use — during the same 90-day period after the 180-day entry period. Plus-minus values are means ±SD. ACE denotes angiotensin-converting enzyme, HBV hepatitis B virus, HCV hepatitis C virus, IPTW inverse probability of treatment weighting, and NSAID nonsteroidal antiinflammatory drug.

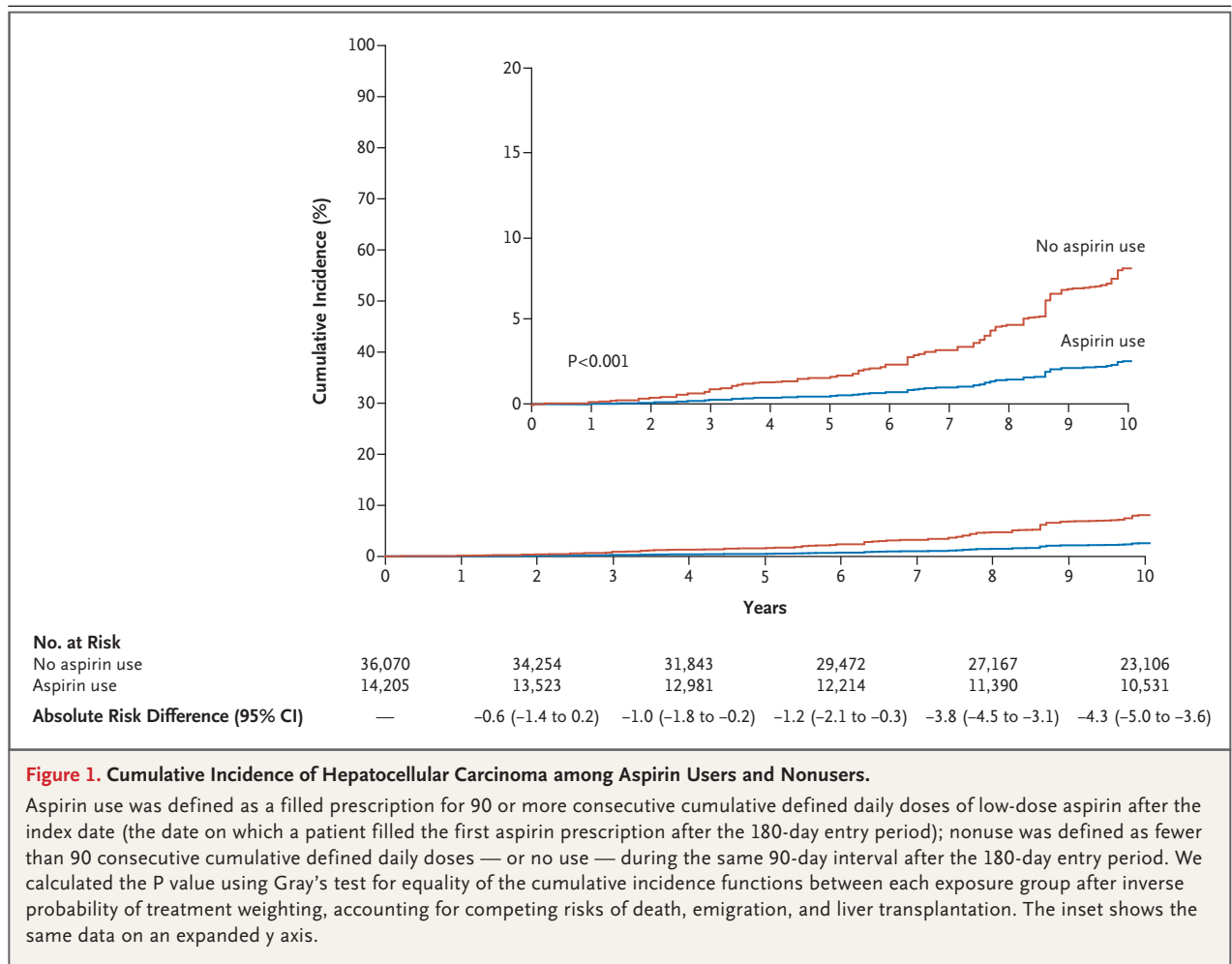
† Clinical characteristics of the patients were defined according to validated diagnoses in the International Classification of Diseases coding system (Table S1).

‡ Included are patients who had mono-infection with either HBV or HCV.

§ Nonaspirin NSAIDs include apazone, diclofenac, etodolac, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, nabumetone, naproxen, phenylbutazone, piroxicam, proquazone, sulindac, tenoxicam, tiaprofenic acid, tolfenamic acid, and tolmetin, as described in Table S1, with use defined as a filled prescription for more than 30 cumulative defined daily doses.

¶ Use of antiviral therapy was assessed separately in each cohort. Use of HBV therapy was defined as a filled prescription for more than 30 cumulative defined daily doses of interferon or a nucleoside reverse transcriptase inhibitor. Use of HCV therapy was defined as dispensation of a prescription for more than 30 cumulative defined daily doses of interferon or direct-acting antiviral therapy.

related death than nonusers (adjusted subhazard ratio, 0.73; 95% CI, 0.67 to 0.81); the difference in risk was similar after data from patients who subsequently initiated another antiplatelet agent were censored (adjusted subhazard ratio, 0.70; 95% CI, 0.64 to 0.79).



DURATION OF USE

The inverse relationship between aspirin use and the risk of hepatocellular carcinoma appeared to be duration-dependent, even after the population was restricted to aspirin users (Table 3). The risk of hepatocellular carcinoma was not significantly lower with use of aspirin from 1 year up to 3 years than with short-term use (3 months to <1 year) (risk difference, -1.8; [95% CI -3.8 to 0.2]; adjusted subhazard ratio, 0.90 [95% CI, 0.76 to 1.06]); however, the risk was significantly lower with use of aspirin from 3 years up to 5 years than with short-term use (risk difference, -3.7 [95% CI, -5.1 to -2.3]; adjusted subhazard ratio, 0.66 [95% CI, 0.56 to 0.78]) and with use of aspirin for 5 years or more than with short-term use (risk difference, -5.6 [95% CI, -7.3 to -3.9]; adjusted subhazard ratio, 0.57 [95% CI, 0.42 to 0.70]).

We also evaluated the effect of discontinuation of aspirin among 11,932 consistent aspirin users (Table S5). Among persons who discontinued aspirin, the risk of hepatocellular carcinoma was 22% greater (subhazard ratio, 1.22; 95% CI, 1.10 to 1.33) and the risk of liver-related death was 31% greater (subhazard ratio, 1.31; 95% CI, 1.17 to 1.45) than the risks among persons who continued aspirin. These findings were similar after exclusion of any person who had an outcome in the first 4 years of follow-up (adjusted subhazard ratio for hepatocellular carcinoma, 1.19 [95% CI, 1.08 to 1.35]; adjusted subhazard ratio for liver-related death, 1.37 [95% CI, 1.24 to 1.50]). This relationship appeared to be duration-dependent; as compared with current aspirin users, the risk of incident hepatocellular carcinoma among persons who discontinued aspirin

Table 2. Effect of Aspirin Use on Risk of Incident Hepatocellular Carcinoma (HCC) and Liver-Related Death.*

Event and Treatment Group	No. with Event/ Total No.	10-Yr Cumulative Incidence	Hazard Ratio (95% CI)	
			Unadjusted	Adjusted†
Incident HCC				
No aspirin use	1274/36,070	8.3%	1.00 (reference)	1.00 (reference)
Aspirin use	338/14,205	4.0%	0.67 (0.61 to 0.73)	0.69 (0.62 to 0.76)
Absolute risk difference (95% CI)		−4.3 (−5.0 to −3.6) percentage points		
Liver-related death				
No aspirin use	4298/36,070	17.9%	1.00 (reference)	1.00 (reference)
Aspirin use	719/14,205	11.0%	0.70 (0.63 to 0.75)	0.73 (0.67 to 0.81)
Absolute risk difference (95% CI)		−6.9 (−8.1 to −5.7) percentage points		

* Aspirin use was defined as a filled prescription for 90 or more consecutive cumulative defined daily doses of aspirin after the index date. Use of all other medications was defined by more than 30 cumulative defined daily doses. Ten-year cumulative incidence, absolute risk differences, and hazards estimates were obtained with the use of a proportional subdistribution hazards regression model fit to the inverse probability of treatment weighted cohort that accounted for competing risks; the model was conditioned on age at study entry, calendar year, and cohort (hepatitis B vs. hepatitis C). The bootstrap method was used to calculate 95% confidence intervals for risk differences. CI denotes confidence interval.

† A multivariable-adjusted model further accounted for the following prognostic covariates: sex; continuous years since diagnosis of hepatitis B or hepatitis C; liver disease severity (defined in three categories as no cirrhosis, compensated cirrhosis, or decompensated cirrhosis or liver failure [in a person with established cirrhosis]); use of antihepatitis B therapy (i.e., >30 cumulative defined daily doses of filled prescriptions for interferon or a nucleoside reverse transcriptase inhibitor) or antihepatitis C therapy (defined as >30 cumulative defined daily doses of filled prescriptions for interferon or a direct-acting antiviral) as compared with nonuse; duration of use (in months) of antiviral therapy; presence or absence of diabetes, hypertension, obesity, or alcohol abuse or misuse; and use of insulin, metformin, and statins.

increased in magnitude with the passage of time after the last use of aspirin (Table S6). The risk was also influenced by consistency of aspirin use: the overall incidence of hepatocellular carcinoma was 5.9% (95% CI, 5.2 to 6.6) among inconsistent users and 1.1% (95% CI, 0.4 to 1.8) among consistent users (Fig. S2).

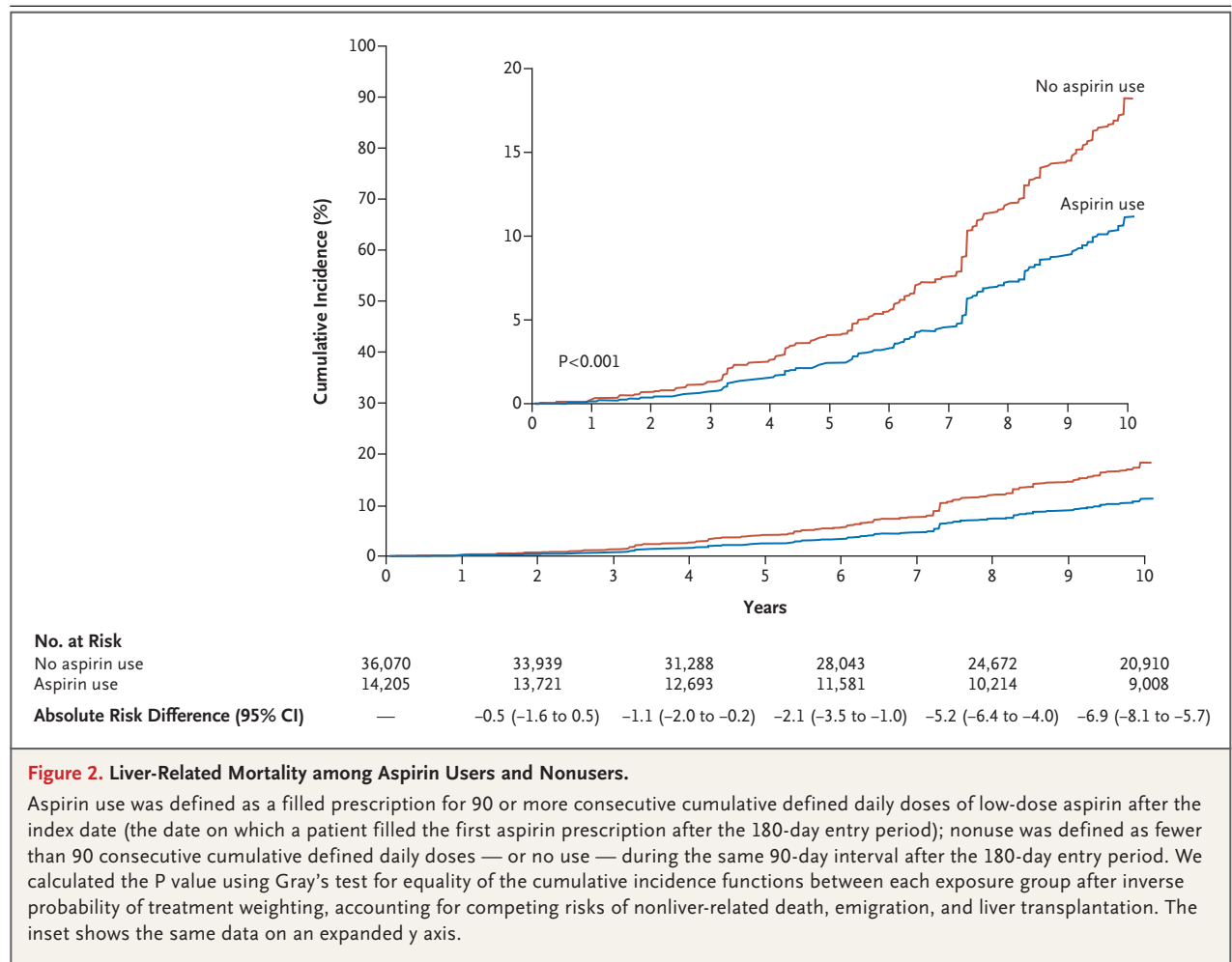
BLEEDING

Aspirin users did not have a significantly higher 10-year cumulative incidence of gastrointestinal bleeding than nonusers (7.8% and 6.9%, respectively; risk difference, 0.9 percentage points [95% CI, –0.6 to 2.4]) or of major gastrointestinal bleeding than nonusers (1.8% and 1.3%, respectively; risk difference, 0.5 percentage points [95% CI, –1.6 to 2.6]) (Table S7). Among aspirin users, the risks of any gastrointestinal bleeding were similar among those with compensated cirrhosis and those without cirrhosis (8.3% and 7.5%, respectively; risk difference, 0.8 percentage points [95% CI, –1.0 to 2.6]), as were the risks of major gastrointestinal bleeding (3.6% and 2.4%, respectively; risk difference, 1.2 percentage points [95% CI, –0.5 to 2.9]). These

findings were similar across subgroup strata (Table S8); however, given the small size of certain subgroups, the findings should be interpreted with caution.

SENSITIVITY ANALYSES

Our results were consistent across all sensitivity analyses, including those performed when we limited the analysis to persons with more detailed data regarding severity of liver disease (Table S9); after we excluded persons with prior alcohol abuse (adjusted subhazard ratio for hepatocellular carcinoma, 0.63 [95% CI, 0.55 to 0.70]; adjusted subhazard ratio for liver-related death, 0.73 [95% CI, 0.68 to 0.88]); after we repeated the analyses without inverse probability of treatment weighting or competing risks, with gastrointestinal bleeding as a competing risk, or with an alternative model for inverse probability of treatment weighting (Table S10); after we excluded persons with hepatocellular carcinoma diagnosed within the first 4 years of follow-up (246 persons excluded; adjusted subhazard ratio, 0.70; 95% CI, 0.64 to 0.83); after we matched propensity scores (Table S11A and S11B); and



after we focused on incident liver decompensation (adjusted subhazard ratio, 0.71; 95% CI, 0.64 to 0.80) (Table S12), all-cause mortality (adjusted subhazard ratio, 0.82; 95% CI, 0.71 to 0.95), and a negative control outcome (Table S13). In exploratory analyses of the use of non-aspirin antiplatelet agents, the adjusted subhazard ratio for hepatocellular carcinoma was 0.94 (95% CI, 0.69 to 1.86); however, because the confidence intervals are wide, this finding merits cautious interpretation. Finally, we observed that an unmeasured confounder would have to be very strongly associated with hepatocellular carcinoma and highly imbalanced between aspirin users and nonusers (i.e., hazard ratio <0.50 or >2.0, with >40% difference in prevalence) to fully attenuate the relationship with aspirin (Table S14A and S14B).

DISCUSSION

In a nationwide population with chronic viral hepatitis, use of low-dose aspirin (75 mg or 160 mg) was associated with a substantially lower risk of incident hepatocellular carcinoma and lower liver-related mortality than no use of aspirin. The apparent benefits of aspirin were duration-dependent, with a significantly lower risk of hepatocellular carcinoma after 3 to 5 years of use than with short-term use. In addition, the benefits were not accompanied by a substantially higher incidence of gastrointestinal bleeding. Our results were consistent regardless of sex, cause of hepatitis, or underlying compensated cirrhosis, which suggests that the benefits of aspirin may apply to a broad at-risk population.

Our findings extend previous data linking

Table 3. Effect of Duration of Aspirin Use on Risk of Incident Hepatocellular Carcinoma (HCC) and Liver-Related Death among 14,205 Aspirin Users.*

Event and Duration of Low-Dose Aspirin	10-Yr Cumulative Incidence	Absolute Risk Difference (95% CI)	Hazard Ratio (95% CI)	
			Unadjusted	Adjusted†
	%	percentage points		
Incident HCC				
3 mo to <1 yr	7.6	—	1.00 (reference)	1.00 (reference)
1 to <3 yr	5.8	−1.8 (−3.8 to 0.2)	0.87 (0.72 to 1.03)	0.90 (0.76 to 1.06)
3 to <5 yr	3.9	−3.7 (−5.1 to −2.3)	0.62 (0.50 to 0.71)	0.66 (0.56 to 0.78)
≥5 yr	2.0	−5.6 (−7.3 to −3.9)	0.52 (0.48 to 0.55)	0.57 (0.42 to 0.70)
Liver-related death				
3 mo to <1 yr	16.1	—	1.00 (reference)	1.00 (reference)
1 to <3 yr	14.3	−1.8 (−3.5 to −0.1)	0.91 (0.85 to 0.97)	0.94 (0.88 to 0.99)
3 to <5 yr	10.5	−5.6 (−7.8 to −3.4)	0.72 (0.63 to 0.84)	0.77 (0.65 to 0.89)
≥5 yr	8.1	−8.0 (−10.5 to −5.5)	0.60 (0.50 to 0.71)	0.63 (0.53 to 0.75)

* Aspirin use was defined as a filled prescription for 90 or more consecutive cumulative defined daily doses after the index date. The cumulative duration of aspirin use was determined prospectively at each monthly interval of follow-up by summing the total number of months of filled aspirin prescriptions up to that interval and was modeled as a time-varying exposure. Ten-year cumulative incidence, absolute risk differences, and hazards estimates were obtained with the use of a proportional subhazards regression model fit to the unweighted study population with accounting for competing risks; the model was conditioned on age at study entry, calendar year, and cohort (hepatitis B or hepatitis C). The bootstrap method was used to calculate 95% confidence intervals for risk differences.

† A multivariable-adjusted model further accounted for the following prognostic covariates: sex; continuous years since diagnosis of hepatitis B or hepatitis C; liver disease severity (defined in three categories as no cirrhosis, compensated cirrhosis, or decompensated cirrhosis or liver failure [in a person with established cirrhosis]); use of antihepatitis B therapy (i.e., >30 cumulative defined daily doses of filled prescriptions for interferon or a nucleoside reverse transcriptase inhibitor) or antihepatitis C therapy (defined as >30 cumulative defined daily doses of filled prescriptions for interferon or a direct-acting antiviral) as compared with nonuse; duration of use (in months) of antiviral therapy; presence or absence of diabetes, hypertension, obesity, or alcohol abuse or misuse; and use of insulin, metformin, and statins.

aspirin to a reduced risk of hepatocellular carcinoma,^{9,12,33} including studies focused on duration of therapy.^{9,11,34} However, previous U.S. and European observational studies have been limited by the inclusion of selected populations, imbalanced exposure groups, or lack of detailed data regarding key determinants of hepatic outcomes.⁹⁻¹¹ Specifically, failure to balance treatment groups can introduce confounding by indication, and poor accounting for viral hepatitis, cirrhosis, or antiviral therapy can lead to residual confounding. By applying inverse probability of treatment weighting approaches to an unselected population with confirmed viral hepatitis and detailed clinical and medication use data, the current study provides more compelling evidence of the potential hepatoprotective benefits of aspirin. The consistent duration–response associations

lend further credence to a potential causal relationship.

Preclinical evidence also supports a role for aspirin in the prevention of liver disease progression and hepatocellular carcinoma. The proinflammatory COX-2 enzyme is overexpressed in activated hepatic stellate cells³⁵ and inflammatory cancers, including hepatocellular carcinoma.⁴⁻⁶ COX-2 overexpression activates profibrotic and proliferative signaling cascades, including protein kinase 3, mammalian target of rapamycin, and nuclear factor κ B pathways,⁴ which are inhibited by aspirin.^{5,36,37} In preclinical models, selective COX-2 inhibition reduces liver fibrosis,^{35,38} portal hypertension,³⁹ and proliferation of liver cancer cells.⁵ Aspirin also blocks proinflammatory lipids such as sphingosine-1-phosphate⁷ while triggering the biosynthesis of pro-

resolution lipid mediators.⁴⁰ Finally, aspirin may prevent fibrosis and hepatocellular carcinoma through glycoprotein 1b α -mediated inhibition of intrahepatic platelet activation, degranulation, and immune cell trafficking.⁸

Recently, two retrospective, observational studies that evaluated aspirin-related risks of bleeding in patients with chronic hepatitis B in Korea³³ and Taiwan¹² showed that gastrointestinal bleeding events were not significantly more common among users of aspirin as monotherapy than among nonusers. In the current study, low-dose aspirin monotherapy was not associated with a substantially higher risk of gastrointestinal bleeding than no aspirin therapy, even among persons with compensated cirrhosis. Although this finding is noteworthy, before aspirin can safely be incorporated into guidelines for prevention of hepatocellular carcinoma, further research is needed to define its potential hazards across the complete spectrum of liver diseases.

Strengths of this study include the unselected population with validated and prospectively updated data regarding low-dose aspirin and confounding variables, accompanied by strict definitions of viral hepatitis and outcomes. The specificity and near-complete follow-up of the Swedish registries address selection bias, and accounting for ranges of time between exposure assessment and outcomes minimizes reverse causation. We applied numerous analytic approaches to address potential biases, including a direct comparison of current and former aspirin users. Furthermore, utilizing time-varying exposures minimized misclassification and bias related to immortal time (i.e., a follow-up period in which study outcomes cannot occur).

We acknowledge several limitations to our study. First, we lacked information regarding smoking, hepatitis B DNA levels, hepatitis C eradication, specific fibrosis stages, hepatocellular carcinoma screening, aflatoxin exposure, and coffee consumption. Furthermore, most of the people in the Swedish hepatitis C cohort are white, and we lacked data regarding actual adherence; both these factors underscore the need for future research to understand the appropriate timing of aspirin initiation, minimum necessary duration, and durability of response in diverse populations. However, the incidence of hepatocellular carcinoma that we observed ac-

cords with that from published hepatitis B and hepatitis C cohort studies,^{12,17} which supports the generalizability of our findings. Second, although residual confounding is possible, our sensitivity analyses indicate that an unmeasured confounder would need to both have a strong association with the outcomes and be highly imbalanced between aspirin users and nonusers to fully attenuate the relationship with aspirin. Third, temporal trends or concerns regarding bleeding or future disease progression could affect utilization of aspirin and outcomes; however, all models were stratified according to index year, and findings were similar in analyses that accounted for severity of liver disease and in analyses limited to aspirin users. Fourth, the aspirin ATC code does not distinguish between 75 mg and 160 mg, which prevented our performing a comparison of treatment effects between low doses. In addition, we lacked information about over-the-counter use of 325-mg aspirin tablets or other aspirin-containing medications; however, prior studies indicate that use of those over-the-counter medications is very low in Sweden. Fifth, our study focused on viral hepatitis, and future studies of other causes of liver disease are needed. Finally, despite the completeness of the Prescribed Drug Register, misclassification of exposure is possible; however, any nondifferential misclassification would most likely have underestimated a true association.

In conclusion, in a nationwide population of persons with chronic viral hepatitis, low-dose aspirin use was associated with a duration-dependent significantly lower risk of incident hepatocellular carcinoma and liver-related death than no use of aspirin, without a significantly higher risk of gastrointestinal bleeding. Our findings support the need for randomized clinical trials designed to test the benefits of aspirin for primary prevention of hepatocellular carcinoma.

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